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Herpes Zoster in Diverse Situations: A Review

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Abstract

Herpes zoster occurred when the suppressive ability of immune system failed to prevent the reactivation of initial varicella-zoster virus infection. Its frequency is higher among immune compromised individuals. Herpes zoster presents with characteristic painful grouped vesicles on erythematous background along the dermatome area and could be complicated by post-herpetic neuralgia. The current review examined the risk factors and discussed herpes zoster in different situations, treatment and concluded by discussing the future research trend of herpes zoster.

Keywords

Herpes Zoster, Post Herpetic Neuralgia, Immunocompromised, Malignancy, HIV

1. Introduction

Herpes zoster (HZ) typically occurs when suppressed varicella-zoster virus (VZV) in the neuronal cell bodies is reactivated after resolution of the initial occurrence of chicken pox. Usually, after the occurrence of chicken pox, immune system eliminates the VZV and suppresses its reactivation, but sometimes, the suppressive ability of the immune system fails leading to the reactivation of the VZV [1]. Although the concept of reactivation of suppressed VZV has been established since the 1950's [2], the exact causes of the suppression and subsequent reactivation of VZV leading to HZ remain unclear. Herpes zoster is also called shingles and frequently occurs in immune-compromised individuals as a result of aging, psychological stress and infections such as human immunodeficiency virus (HIV) [1]. Herpes zoster is clinically characterized by painful grouped vesicles on erythematous rash along the dermatome area with clinical symptoms which could include headache, photophobia, malaise, localized abnormal skin

sensations and rarely fever [3]. Herpes zoster can also lead to post-herpetic neuralgia mostly in elderly individuals [4] [5]. Although, the occurrence of HZ in children and young adults is rare, HZ has been reported among sub-Saharan Africa young adults where it has been considered as one of the most influential predictors of HIV [1] [6].

2. Epidemiology

Varicella-zoster virus causes two different diseases *i.e.* the primary infection and reactivated disease known as HZ. The primary infection*:* usually present as a contagious but benign disease called chickenpox among vulnerable children aged between 2 - 7 years [7]. The mode of transmission is via droplet inhalation into the respiratory system [7]. After about 10 - 23 days of incubation period, small pus filled-vesicles break out on the face or upper trunk which get busted and become covered by skin with intense itching. Individuals who recover from chicken pox become subsequently immune to this disease; however, they are not free of the VZV as the viral DNA remains in a latent state in the dorsal root ganglia [8].

The reactivated disease: immunosuppression may occur following immunosuppressive illness or medical treatments or naturally through aging in individuals previously infected with chickenpox [9]. In this context, the VZV may become reactivated and migrate along the afferent sensory nerves to the skin and eye where they replicate and cause characteristic lesions [10]. This subsequent reactivation of latent VZV in dorsal root ganglia results in a localized cutaneous eruption called "herpes zoster."

The global annual incidence rate of HZ ranges from 1.2 - 3.4 cases per 1000 healthy individuals [11] [12]. Since increasing age is a crucial risk factor for the development of HZ; there is an increase of the annual incidence to 3.9 - 11.8 per 1000 individuals among those older than 65 years [11] and exceeds 10 cases per 1000 persons among individuals older than 75 years of age. The lifetime risk of herpes HZ is estimated to be 10 to 20 percent [12].

Several risk factors for herpes zoster have been identified. These include altered cell-mediated immunity, human immunodeficiency virus infection, neoplastic diseases, patients on immunosuppressive drugs and organ-transplant recipients. A study has shown an incidence of 29.4 cases of HZ per 1000 individuals who were HIV-seropositive, compared to 2 cases per 1000 individuals among HIV-seronegative [13]. In the context of HIV infection, HZ may occur in asymptomatic HIV-positive individuals. Therefore, HZ might be an indication for HIV serology testing in patients with high risk of HIV infection due to its ability to cause early alteration in cell-mediated immunity and there are also several studies showing that individuals with HZ are more likely to have HIV [14] [15].

3. Clinical Manifestations of Herpes Zoster

The prodrome of HZ could include a report of a headache, photophobia, ma-

laise, and rarely fever. Most patients present with localized abnormal skin sensations, ranging from itching or tingling to severe pain, which precedes the typical skin lesions by 1 - 5 days. The pain in HZ is of variable severity, and virtually all patients with acute HZ complain of pain. Following these, the patient developed erythematous macule and papular rash which progresses to clusters of clear vesicles which continue to form for about 3 - 5 days and evolve through stages of pustulation, ulceration, and crusting [**Figure 1**, **Figure 2**]. The cutaneous eruption is usually unilateral and does not cross the midline. Healing occurs over a period of 2 - 4 weeks and often results in scarring and permanent changes in pigmentation of the affected area [**Figures 3-5**]. The involvement of multiple noncontiguous dermatomes almost never occurs in immune-competent patients, although in 20% of cases, lesions overlap adjacent dermatomes. Presence of few skin lesions outside the main or contiguous dermatomes is not rare in immune-competent patients [3].

4. Diagnosis of Herpes Zoster

The diagnosis of HZ is essentially clinical when the presentation is typical. However, the manifestations may be bizarre or unusual particularly in immune-compromised individuals, and laboratory confirmation may be necessary. Available confirmatory investigations may include viral culture, polymerase-chain-reaction, and direct immunofluorescence assay. The lability of VZV makes it relatively hard to recover the virus from swabs of cutaneous lesions. Direct immunofluorescence assay is a more sensitive laboratory technique and has the additional advantages of a lower cost [16]. Like culture, the direct immunofluorescence assay can also distinguish herpes simplex virus infections from VZV infections. Polymerase-chain-reaction techniques are also useful for detecting VZV DNA in fluid and tissues [17].

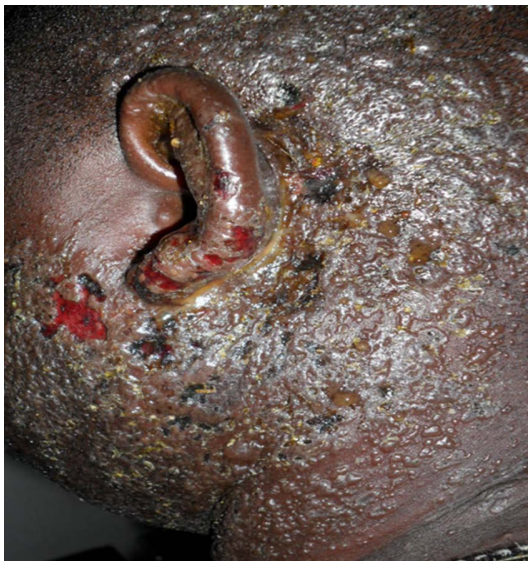

Figure 1. Vesiculation, ulceration and crusting of Acute Herpes Zoster.

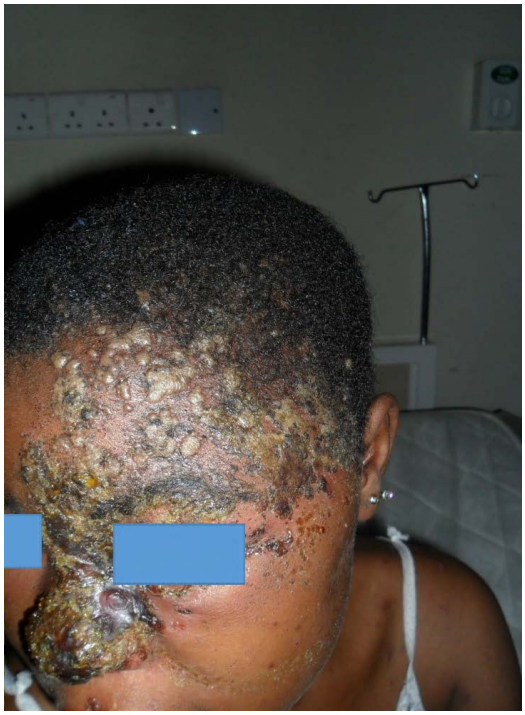

Figure 2. Hutchinson's sign, pustulation, crusting and swelling of in herpes zoster ophthalmicus in HIV patient

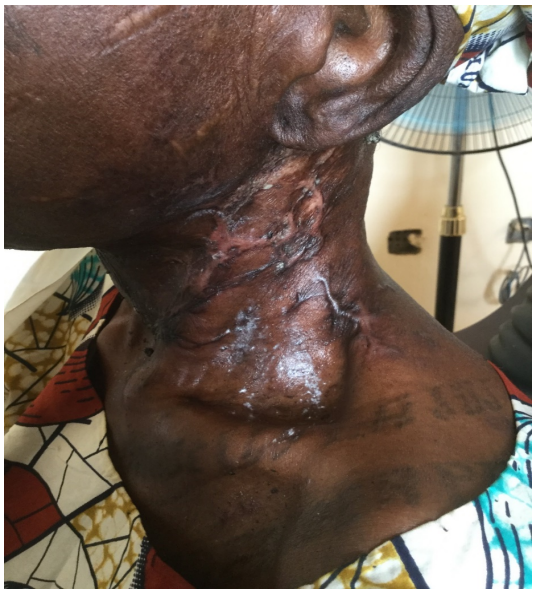

Figure 3. Cervical Post herpertic scarring and dyspigmentation in patient with Leucopenia.

5. Prognosis of Herpes Zoster

Herpes zoster rarely causes fatalities in immune-competent individuals; however, HZ can be life-threatening in individuals with compromised immunity. Ocular complications occur in about 50% to 90% of the HZ cases, resulting in either

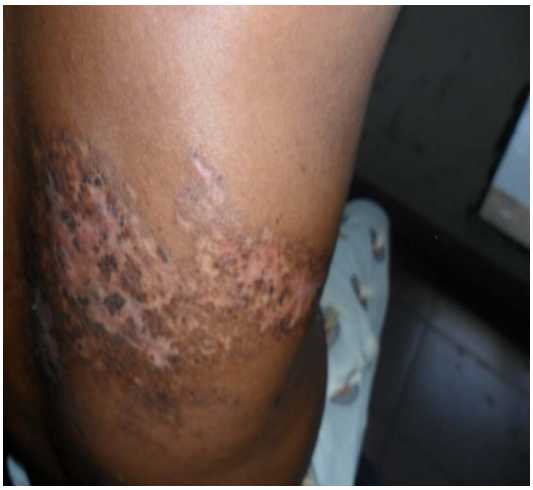

Figure 4. ThoracicPost herpertic scarring and dyspigmentation in patient with Leucopenia

Figure 5. Necrotic Herpes zoster in 75 year old woman with Chronic Lymphocytic Leukaemia.

temporary or permanently decreased visual acuity or total blindness if untreated [18] [19]. Other complications of HZ include sensory loss, peripheral nerve palsies, bacterial super-infections, and disseminated HZ [20].

6. Postherpetic Neuralgia and Other Complications

Post-herpetic neuralgia is defined as pain that persists more than 30 days after the onset of rash or after cutaneous healing. It is the most dreaded complication

in immune-competent individuals because both the incidence and duration of post-herpetic neuralgia are directly associated with the individuals' age [12] [21]. The reported incidence of post-herpetic neuralgia ranges from 8% - 70% and incidence increases with advancing age [12]. In addition to neuropathic pain, other sensory abnormalities within the affected dermatome could include allodynia, in which non-noxious stimuli is perceived as painful. Pain could continue for months and at times for years. Other complications of herpes zoster in immune-competent individuals include cranial and peripheral-nerve palsies, myelitis, encephalitis, and a syndrome of delayed contralateral hemiparesis [17].

Disseminated Herpes Zoster: Before the introduction of antiviral drugs, cutaneous spreading of VZV was reported in 6% - 26% of immune-compromised individuals [22] with the disseminated form of the disease restricted to the skin; however, there is visceral involvement like hepatitis, pneumonitis or encephalitis in about 10% - 50% of these patients. Even after the introduction of intravenous acyclovir therapy, the mortality rate from HZ with visceral dissemination reduced to about 5% - 15%, with most deaths caused by pneumonitis [22].

Although acute retinal necrosis caused by VZV rarely occurs in immune-competent individuals, recent reports have focused more on ocular disease in immune-compromised individuals particularly HIV-infected persons [23]. Visual changes start weeks or months after HZ have resolved and funduscopic examination shows characteristic granular, yellowish, non-hemorrhagic lesions. Usually, in HIV-infected patients, the lesions rapidly extend and coalesce, respond poorly to antiviral therapy, and almost inevitably cause blindness in the involved eye. Retinitis is less aggressive in immune-competent persons and can often be arrested with antiviral therapy than in immune-compromised persons [3].

7. Herpes Zoster in HIV

Human immunodeficiency virus (HIV) is a recognized risk factor for HIV. Other well documented immunosuppressive conditions include cancers and chronic medical conditions [24] [25] [26]. Numerous evidences have shown that the prevalence of HIV infection is very high among persons with highly threatening HZ [14] [27]. Other studies have also shown that HZ could be the first sign of undiagnosed HIV infection because of its role in cell-mediated immunity [14] [15].

The incidence of HZ in HIV infected individuals has been reported by several researchers to be between 8.4% - 26.7% [6] [13] [28], while in HIV seronegative patients are between 1% - 2% [5] [28]. The association between HZ and duration of HIV infection is still not clear. However, some literature has described HZ as the first indicator [29] and an important predictor of more rapid progression of HIV to acquired immunodeficiency syndrome (AIDS) [30], while others differ on this [31].

In the context of HIV infection, relapse of HZ is assumed to be an indication

of the more advanced stage of HIV infection. Cutaneous lesions in the majority of the cases of HZ have classical course, some have dispersed infection with more destructive and necrotic lesions. Systemic complications especially meningitis and encephalitis may also occur with dispersed or persistent eruptions [32]. While acute retinal necrosis caused by VZV occasionally occurs in immune-competent patients, it is frequent in HIV and a case of jaw osteonecrosis caused by HZ in HIV has also been reported [23] [33].

7.1. Herpes Zoster in HIV-Infected Adults on Combined Antiretroviral Therapy

Herpes zoster is mainly a disease of aged and immune-compromised individuals, likely due to impaired cell-mediated immunity [1]. Before the availability of combined antiretroviral therapy, the incidence of HZ in HIV infected individuals was about 10 to 30 times higher when compared to HIV-seronegative individuals [6] [13] [28] [29] with low CD4 cell counts being the most potent predictor of HZ [34].

Since the introduction of combined antiretroviral therapy (cART), studies opinion on prevalence of HZ varies. Several studies of both adults and children suggest that the incidence of HZ has not changed, whereas other studies have shown a significant decrease [34] [35] [36]. Also, numerous literature have reported a rise in the incidence of HZ during the first months following cART initiation, suggesting that HZ may be a feature of the immune reconstitution inflammatory syndrome (IRIS) [36].

7.2. Immune Reconstitution Herpes Zoster

Immune reconstitution inflammatory syndrome (IRIS) is an inflammatory reaction that ensues as a result of immune reconstitution after the start of highly active antiretroviral therapy (HAART) in HIV seropositive patients [37], giving way to deteriorating opportunistic infection like herpes zoster which is believed to be the most common manifestation of IRIS in spite of an increase in CD4+ cell count and a decrease in HIV viral load [38] [39]. HIV patients with CD4+ cell counts between 50 and 200 cells/mm^3 and those on HAART is believed to have the highest risk for HZ occurrence [40]. The IRIS can be classified into unmasking IRIS and paradoxical IRIS. Unmasking IRIS occurs when opportunistic diseases which are not present at the start of ART begin to manifest as a result of ART-induced immune reconstitution. However, paradoxical IRIS occurs when patients who are already on medication for an opportunistic disease, and in whom immune reconstitution after initiation of ART provokes the clinical worsening of that disease during the initial treatment [41]. The use of HAART in HIV management has led to a reduction in mortality rate; however, about 25% - 35% of patients on HAART have been reported to develop IRIS [42].

The period between onset of disease and commencement of HAART is so va-

riable that controversy exists when trying to define the interval which the disease must manifest for it to be termed IRIS. The duration between the start of HAART and the onset of an opportunistic disease has been reported to be greater than 90 days [38]. However, another report concluded that there was no difference in the risk of HZ occurrence before and after 90 days from the start of HAART [43]. Conversely, other authors believe that onset of IRIS-induced HZ tend to increase approximately after four weeks [44].

Although HZ can occur at any CD4+ count in HIV-seropositive individuals, the occurrence is highest with CD4+ counts of < 200 cell/mm^3. The occurrence of IRIS after the initiation of HAART is rare in patients with CD4+ cell counts of >350 cell/mm^3 [45]. On the other hand, individuals with a baseline CD4+ cell percentage of < 10% has been reported to have a three-times increase in the risk of IRIS occurrence [37] [46].

Furthermore, the diagnostic value of CD8+ cells remains controversial. The number of circulating CD8+ cells does not necessarily show either their numbers in infected, inflamed tissues, or their functional competence [47]. Thus, CD8+ cells cannot be used as a laboratory marker for differentiation of HIV-IRIS from an opportunistic infection in immune-compromised patient. In spite of these reports, findings of some studies have established the significance of CD8+ cells in the pathogenesis of IRIS, but not its importance as a diagnostic tool. The percentage of CD8+ cells at baseline and the magnitude of their increase one month after initiation of antiretroviral therapy have shown a strong association with an increased risk for herpes zoster [48].

HAART has become a vital therapy in the management of HIV. Globally, numerous cases of IRIS are reported annually. However, many controversies still exist. While some literature has documented case definitions of IRIS [42], lack of agreement about the definition of IRIS makes differentiation of IRIS from recurrence or relapse of an infection a challenge. Also, a few risk factors, including CD4+ T-cell count, HIV-1 RNA level, and HAART regimen, have been reported. However, these are too complex to simplify as definite risk factors [42].

8. Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus (HZO) occurs due to reactivation of latent VZV in the ophthalmic division of the trigeminal nerve. Although HZO could damage the eye and surrounding structures through secondary perineural and intraneural inflammation of sensory nerves, it does not certainly affect the structures of the eye [49].

HZO accounts for about 10% - 25% of all cases of HZ and about 50% of persons diagnosed with HZO will develop complications [12]. While HZO usually produces a characteristic dermatomal rash, few of patients may have only ophthalmic findings, limited mainly to the cornea.

8.1. Extra-Ocular Manifestations of Herpes Zoster Ophthalmicus

HZO usually begins with an influenza-like illness with fatigue, malaise, and

low-grade fever for about one week before the appearance of rash over the forehead [50] with approximately 60% having varying degrees of dermatomal pain in the course of the ophthalmic nerve [51]. Later, erythematous macules, papules, vesicles containing serous fluid and pustules appear along the involved dermatome. These lesions rupture, crust heals over several weeks [52]. The risk of HZO is higher in immune-compromised individuals compared to immune-competent individuals [53]; with generalized vesicular rash and more serious visual complications occurring more in immune-compromised individuals [54].

8.2. Ocular Manifestations of Herpes Zoster Ophthalmicus

The affectation of the nose tip, also known as Hutchinson's sign [**Figure 2**] is believed to be a clinical predictor of ocular involvement. Although patients with Hutchinson's sign have double the occurrence of ocular manifestations, only one-third of patients without Hutchinson's sign develop ocular involvement [18]. Ocular manifestations in persons with HZO include the following:

a) Blepharitis and Conjunctivitis

The eyelids are frequently involved in HZO. Patients may develop blepharitis and present with ptosis secondary to edema and inflammation. Many of them usually have vesicular lesions on the eyelids which resolve with minimal scarring. Conjunctivitis is also a common manifestation of HZO wherein the conjunctiva appears injected, edematous, often with petechial hemorrhages [55] [56].

b) Corneal Disease

Corneal involvement occurs in almost 65% of HZO and can lead to varying degree of vision loss, pain, and light sensitivity [54]. Punctate epithelial keratitis, the first corneal finding [56] may occur between one or two days after the initial skin rash and may either resolve or progress to dendrite formation which appears at four to six days or even several weeks after [57]. In approximately 25% - 30% of persons with HZO, both punctate and dendritic lesions could cause anterior stromal corneal infiltrates which is characterized by multiple fine granular infiltrates in the anterior corneal stroma below the epithelial layer [57] [58]. Neurotrophic keratitis is the end consequence of decreased corneal sensation from HZO-mediated destruction, including susceptibility to mechanical trauma, decreased lacrimation, and delayed epithelial healing [54].

c) Uveitis

Anterior uveitis frequently occurs in HZO and may be isolated or associated with keratitis. It causes a mild and transient inflammation with a mild rise in intraocular pressure. It could lead to atrophy of the iris, irregular pupil, glaucoma and cataract formation [19].

d) Retinal Necrosis

HZV is usually thought to be the causative agent in most cases of acute retinal necrosis and progressive outer retinal necrosis syndromes. Both conditions commonly cause retinal detachment. Acute retinal necrosisis characterized by peripheral patches and rapidly coalescing retinal necrosis, occlusive vasculitis,

and vitreous inflammation. However, progressive outer retinal necrosis is a more severe viral retinitis observed in immune-compromised individuals when compared with acute retinal necrosis. The severity of progressive outer retinal necrosis has been related to in ability immune incompetent individuals to mount a clear inflammatory response, leading to a rapid involvement of the macula. [19].

9. Herpes Zoster in Malignancy

It has been well established that immune suppression is the link between HZ and malignancy [59]; however, the outcomes of studies that investigated the relationship between HZ and malignancy have been conflicting. [60]-[65]. Some previous studies observed no link between HZ and occurrence of cancer [62] [63] [65]. One of the studies reported that HZ diagnosis did not increase the overall risk of cancer and the prevalence of cancer among patients with HZ was similar to the expected rate in the healthy population. However, HZ was reported to have increased the risk of multiple myeloma [65].

Conversely, studies that investigated the association between hematological malignancies such as multiple myeloma, non-Hodgkin's lymphoma, leukemia and the occurrence of HZ showed that there is a link between HZ and haematological malignancy [60] [61]. The factors associated with increase risk of cancer in patients with HZ include; age above 65 years and female gender. A certain prospective study that followed up patients with HZ showed that in the first year after HZ diagnosis, no difference was observed in the occurrence of cancer, suggesting that HZ may not be a sign of undiagnosed malignancy. Therefore, the study indicated that patients with HZ needed not to be screened for underlying malignancy [64].

Finally, a study concluded that there is an increased risk of malignancy development after HZ diagnosis, and this risk affects both gender and all age groups older than 18 years equally. The authors reported that the risk was greatest in the first six months after HZ and continued for about five years. They also concluded that though malignancy screening cannot be recommended because of the modest increase in risk and the lack of specificity regarding malignancy type, they suggested that clinicians should be observant for malignancy in HZ patients [66].

10. Herpes Zoster in Children

In children, HZ is a rare disease but could occur in children at any time after varicella infection or varicella vaccination. The HZ is less frequent after varicella vaccination compared to the higher frequency following natural progression from varicella infection. The prevalence of reactivated varicella is lower in children compared to adults. The incidence of HZ in children below 14 years is about 0.45 per 1000 persons, but the occurrence could rise to about 4.5 per 1000 persons in adults above 75 years [67] [68] [69]. Generally, the course HZ is relatively mild in children with a mean duration of 1 - 3 weeks. Although lesional pru-

ritus and pain may be present, the occurrence of postherpetic neuralgia or other common complications of HZ in adults is negligible [68] [69].

The presence of HZ in children is a marker of an underlying malignancy, particularly acute lymphatic leukemia. However, the increase in the prevalence of malignancy has not been shown in children with HZ, but about 3% of children with HZ had malignancies [70]. Increase incidence of HZ in immune-competent healthy children has been attributed to primary VZV infection *in-utero*, or in infancy when immunity was not fully developed. Immunologic findings associated with observed suppressed early life immunity include a low level of lymphocytes, cytokines, natural killer (NK) cells and virus-specific immunoglobulins, which may lead to an inability of preserving the dormancy of the VZV causing the early occurrence of HZ in children. To a lesser extent, vaccination with live attenuated varicella virus may also contribute [71]. The diagnosis of HZ in children is clinical but could be confirmed by viral culture [72].

11. Therapy for Herpes Zoster

The goals of effective HZ therapy include rapid healing, limitation of severity, limitation of the duration of acute/chronic pain, and reduction of complications. Furthermore, in immune-compromised persons, an additional therapeutic objective is to reduce the risk of spreading of VZV.

11.1. Symptomatic Treatment

The skin lesion of HZ must be clean and dry to reduce the risk of superimposed bacterial infection. A sterile, non-occlusive and non-adherent dressing should be placed over the involved dermatome to prevent the lesions from contact with clothing. Clinicians should not underestimate neuralgic pain. Sympathetic-nerve blockade can provide rapid, temporary relief of severe pain [73]. For mild to moderate pain, scheduled short-acting narcotic analgesics could be prescribed, but for persistent pain, long-acting and controlled-release opioids (oral or transdermal) are preferred. Some studies of the pathogenesis of postherpetic neuralgia suggest that early reduction of acute pain may prevent central mechanisms of chronic pain initiation, thereby reducing the risk of post-herpetic neuralgia [74].

11.2. General Antiviral Therapy

In the United States, acyclovir, a prodrug of acyclovir, valacyclovir, and famciclovir are drugs that are approved for the treatment of HZ. The three drugs are very safe and well tolerated, and there are no contraindications to their use, although dosage adjustment is required in patients with renal insufficiency. However, none of these drugs are currently approved for use in pregnant women by the Food and Drug Administration, and there is no role for topical antiviral therapy in HZ management [13] [75].

A previous study using 800 mg of acyclovir five times daily reduced the extent

of viral shedding, stopped the rapid formation of new lesions, hastened to heal, and reduced acute pain severity [75]. However, the roles of acyclovir in the reduction of frequency and duration of post-herpetic neuralgia have been inconsistent [76]. Valacyclovir given as 1000 mg every 8 hours produced about 3 - 5 times higher serum levels of acyclovir levels than oral acyclovir therapy and resulted in equal degrees of cutaneous healing compared to acyclovir therapy [77]. In another study, famciclovir a pro-drug of penciclovir given 500 mg every 8 hours significantly reduced the extent of viral shedding, prevent and limits the formation of the new lesion and hasten to heal when compared with controls on placebo [78].

Valacyclovir and famciclovir have been shown to be both therapeutically equal in cutaneous healing and pain resolution [79]. The higher pharmacokinetic profiles and simpler dosing regimens of valacyclovir and famciclovir make them choice medication in the treatment of HZ.

11.3. Therapy for Herpes Zoster Ophthalmicus

Without antiviral treatment, approximately 50% of these individuals will have ocular complications such as keratopathy, episcleritis, iritis, or stromal keratitis, some of which are sight-threatening [50]. Oral antiviral therapy has been reported to also reduce the frequency of late ocular complications from about 50% to 20% [77].

11.4. Therapy for Herpes Zoster in HIV-Seropositive Patients

Although HZ seen in HIV-seropositive patients and immune-competent individuals is typically similar after adjustment for age, distinct features such as frequent recurrences and atypical lesions are well described [80]. Acyclovir is proven to be useful for HZ in HIV-infected patients [81] and cases of disease caused by acyclovir-resistant VZV in patients with advanced acquired immunodeficiency syndrome (AIDS) are rare [82]. Though famciclovir and valacyclovir have not been assessed systematically; anecdotal experience suggests that they are likely to be efficacious [82]. Also, because of the risk of relapsing infection in these patients, VZV disease should be treated until all lesions have resolved completely [3].

11.5. Corticosteroids Therapy

Previous clinical trials evaluating the role of corticosteroids in combination with acyclovir showed that individuals on corticosteroids had a moderate hastening in the rate of cutaneous healing and reduction of acute pain [83]. However, the use of corticosteroids without concomitant antiviral therapy is not recommended and should be avoided in patients at risk for corticosteroid-induced toxicity such as diabetes mellitus [3]. Also, combination therapy resulted in an improved quality of life, as measured by reductions in the use of analgesics, the time to uninterrupted sleep, and the time to resumption of usual activities [83]. Howev-

er, none of the studies established the influence of corticosteroids on the incidence or duration of post-herpetic neuralgia. Combination therapy using valacyclovir or famciclovir with corticosteroids is assumed to be equally effective, but it has not been examined in clinical trials [3].

11.6. Therapy for Post-Herpetic Neuralgia

Treatment of post-herpetic neuralgia is complex since it usually requires a multifaceted approach [84] [85]. Although clinical trials have shown that opioids, tricyclic antidepressants, and gabapentin reduce the severity or duration of post-herpetic neuralgia, either as single agents or in combination [86], their adverse effects may, however, be additive, particularly in elderly individuals. Also, the topical use of lidocaine patches or capsaicin cream can provide relief for some individuals [84] [85]. A study has also shown that intrathecal injection of methylprednisolone acetate once every week for four weeks significantly reduced pain in individuals with intractable post-herpetic neuralgia [87]. However, because some patients still experience significant pain and intolerable side effects even after the use of the aforementioned therapies, further studies revealed that the use of topical peppermint oil (or menthol) [88], geranium oil [89] and adenosine monophosphate (AMP) [90] yielded great success rate with lessened pain and little or no side effect.

In the study conducted using topical peppermint oil (or menthol), it was reported that a 76-year-old woman who had tried numerous drug treatments such as tricyclic antidepressants amitriptyline and dosulepin; anticonvulsants carbamazepine and gabapentin for about three years had experienced no relief. She had also use intravenous lidocaine and capsaicin cream but has also been unhelpful. Surprisingly, the patient was successfully treated with topical peppermint oil, and after two months of follow-up, she has had only a little side effect with continuing analgesia [88]. Another study which assessed neuropathic pain relief and the timing of onset of the relief with the use of topical geranium oil showed that when compared to topical capsaicin which relieves neuropathic pain gradually over two weeks, topical use of geranium oil relieves pain in minutes and it's well tolerated with minimal side effect [89]. In the study using AMP for the treatment and prevention of post-herpetic neuralgia, it was documented that intramuscular injection of gel-sustained AMP thrice weekly for four weeks reduces pain, decreases desquamation time and virus shedding, and promoted faster skin healing with no side effect and toxicity during and after treatment. No pain or lesion reoccurrence was seen 3 - 18 months post-treatment [90].

12. Future Research Aspect

The most threatening future of HZ burden is the rising cost, driven primarily by demographic factors of increasing and aging population [91]. The pandemic of HIV/AIDS in sub-Sahara of Africa and other immunosuppression related dis-

eases are clinical related factors driving the burden of HZ. The availability of biologics and other immunosuppressant therapies in clinical use are also playing their roles. Varicella and HZ vaccines are safe and effective preventive tools that have made their inroads into the reducing the global burden of HZ. Vaccine reduces incident zoster in both immunocompetent and immunocompromised [92] [93]. Some live attenuated vaccine is bedeviled by chance of reactivation. Similarly, vaccine uptake is low especially among the blacks where it is available and not freely available for use in many African nations. Research should be directed towards ensuring wide availability of safe and efficient vaccines to reduce burden of HZ in every groups.

The Advisory Committee on Immunization Practices has suggested VZV Oka strain vaccine for universal childhood vaccination. This vaccine is also believed to induce immune enhancement in older seropositive individuals by increasing cytotoxic-lymphocyte responses specific for VZV [94]. However, further studies are required to be done to determine if the vaccine-induced immune enhancement could reduce the frequency or severity of HZ in elderly individuals.

13. Conclusion

Herpes zoster develops when there is a reactivation of suppressed VZV with increased incidence in older adults and immune-compromised individuals. The diagnosis of HZ is essentially clinical when the presentation is typical. However, laboratory confirmation such as viral culture, polymerase-chain-reaction, and direct immunofluorescence assay may be necessary in atypical cases. Although HZ is not usually fatal in immune-competent individuals, it could be life-threatening in individuals with compromised immunity. Apart from symptomatic treatment of HZ, acyclovir, valacyclovir, and famciclovir are very useful drugs that have been approved for HZ treatment. These drugs are very safe and well tolerated. Both valacyclovir and famciclovir are therapeutically equal, and because of their higher pharmacokinetic profiles and simpler dosing regimens, they are both preferred to acyclovir for the treatment of HZ. The possibility of the patients experiencing severe pain should never be underestimated or overlooked. Although, no single therapy has proven to be effective for post-herpetic neuralgia, however, strong analgesics will often be needed.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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