Epidemiology, clinical manifestations, and diagnosis of herpes zoster

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Literature review current through: Feb 2023. | **This topic last updated:** Jun 20, 2022.

Introduction

Varicella-zoster virus (VZV) infection causes two clinically distinct diseases. Primary infection with VZV results in varicella (chickenpox), which is characterized by vesicular lesions on an erythematous base in different stages of development; lesions are most concentrated on the face and trunk. Herpes zoster, also known as shingles, results from reactivation of latent VZV that gained access to sensory ganglia during varicella. Herpes zoster is characterized by a painful, unilateral vesicular eruption, which usually occurs in a single or two contiguous, dermatomes (picture 1A-J).

This topic will address the epidemiology, clinical manifestations, and diagnosis of herpes zoster. The treatment and prevention of herpes zoster, and the epidemiology, pathogenesis, diagnosis, and treatment of varicella, are discussed elsewhere. (See "Treatment of herpes zoster in the immunocompetent host" and "Diagnosis of varicella-zoster virus infection" and "Clinical features of varicella-zoster virus infection: Chickenpox".)

Pathogenesis

During the initial phase of varicella, varicella-zoster virus (VZV) infects the nasopharyngeal lymphoid tissue through airborne droplets in a susceptible host. This results in a viremia consisting of VZV-infected T cells that traffic through these tissues and subsequently throughout the body [1-3].

VZV enhances infection by inhibiting multiple host defenses, such as downregulation of major histocompatibility complex (MHC) class I expression and inhibition of interferon

response genes [1,3,4]. This enables the virus to partially evade the immune response. The prolonged incubation period prior to the onset of skin lesions in varicella reflects the time required for VZV to overcome local immune-mediated defenses, such as alpha interferon (IFN-a) production by epidermal cells [1,4,5]. VZV DNA (primarily in T-lymphocytes) is detected 11 to 14 days before rash [6]; VZV viremia is detected six to eight days before rash appears and ceases one to two days later [6].

Once the rash develops, cell-free virus, which is present only in skin vesicles, is postulated to infect nerve endings in skin and move retrograde along sensory axons to establish life-long latency in neurons within the regional ganglia [3,7-9]. VZV may also infect neurons as a consequence of the viremia [1,6]. VZV-specific cell-mediated immune responses that develop during varicella are required to end the infection. These responses also play a critical role in controlling VZV latency and limiting the potential for reactivation to cause herpes zoster [10].

During latency, one or a small number of VZV genes are transcribed, but infectious virus cannot be found in ganglia [11]. If reactivation occurs and is not limited, infectious VZV can spread within the ganglion to involve multiple sensory neurons and subsequently spread antegrade down the sensory nerve to establish infection in the skin and cause the typical rash [12-14].

Following VZV reactivation and if VZV replication continues, the involved sensory ganglion typically exhibits intense inflammation, accompanied by hemorrhagic necrosis of nerve cells [15,16]. This neuronal damage is the source of the typical neuropathic pain of herpes zoster. The ganglion undergoes eventual neuronal loss with subsequent fibrosis of afferent nerve fibers, particularly type C nociceptors [17].

Epidemiology

Incidence — In the United States, herpes zoster occurs in more than 1.2 million individuals annually, causing substantial morbidity [18]. The United States Centers for Disease Control and Prevention (CDC) estimates that approximately 30 percent of persons in the United States will experience herpes zoster during their lifetime [19,20]. Incidence rates progressively increase with age, presumably due to the decline in virus (VZV)-specific cell-mediated immunity [18,21-25]. The epidemiology is similar worldwide (figure 1).

The incidence of herpes zoster has been increasing throughout the world [18,23,26-28]. As an example, in a population-based cohort study of 8017 patients with herpes zoster in Minnesota, the incidence rate was 0.76 per 1000 person-years from 1945 to 1949, and increased to 3.15 per 1000 person-years from 2000 to 2007 [27,29]. In a large database analysis that evaluated trends in herpes zoster cases from 1993 to 2016 in over 27 million persons aged ≥35 years, the incidence of herpes zoster increased from 2.5 per 1000 person-

years in 1993 to 7.2 per 1000 person-years in 2016 [30]. In this study, the incidence continued to increase in a relatively steady manner among those aged 35 through 55 years over this period. Among those aged >55 years, there was a similar rise in herpes zoster incidence through 2006, but this rate subsequently decelerated. The reason for the overall increase in herpes zoster incidence, as well as these age-specific findings, is unclear.

Some experts raised the possibility that widespread varicella immunization in childhood may increase the age-specific incidence of herpes zoster in adults [31]. Their concern was based on evidence that exposure to endemic varicella boosts VZV-specific immunity in adults and that cessation of varicella in the community would result in a decline in the T cell-mediated immunity required to maintain latency of VZV in neurons [32]. However, numerous epidemiologic studies have failed to document this effect [27,31,33,34]. In addition, the rise in herpes zoster incidence has occurred equally in countries without varicella immunization, and in the United States, the rise in incidence occurred equally in states with or without good uptake of the varicella vaccine.

There have also been concerns that varicella immunization might lead to an increased risk of vaccine-associated herpes zoster, particularly in immunocompromised children. The incidence of post-vaccination herpes zoster was examined in a study of 346 children with acute lymphocytic leukemia who received the Oka live attenuated varicella vaccine. Herpes zoster developed in five subjects (1.45 percent) after 10,878 months of observation [35]. In a substudy that matched 84 vaccinated subjects to those who had prior natural varicella infection, herpes zoster was less frequent in the immunized group (3 versus 11 cases). Reductions in herpes zoster among children have also been reported in a population-based study evaluating persons vaccinated in a community-based setting [36,37]. In a database analysis of 13.08 million children aged <18 years from 1998 to 2016, there was an initial increase in incidence of herpes zoster among those aged 6 to 17 years, but this was followed by a dramatic reduction, with the incidence declining from peak values by about 70 to 80 percent in children of all ages [38]. (See "Vaccination for the prevention of chickenpox (primary varicella infection)".)

Risk factors — The natural history of herpes zoster is influenced by the immune status of the host. Reactivation is influenced by age-related immunosenescence, disease-related immunocompromise, or iatrogenic immunosuppression, with age being the major risk factor for 90 percent of cases of herpes zoster.

Age — Age is the most important risk factor for the development of herpes zoster (figure 1) [18,19,23,39]. A dramatic increase in the age-specific incidence of herpes zoster begins at approximately 50 years of age. Twenty percent of cases occur between ages of 50 and 59 years, and 40 percent occur in people at least 60 years of age. It is estimated that approximately 50 percent of persons who live to 85 years of age will have had an episode of

herpes zoster [21]. Globally, older patients account for the majority of medical consultations and hospitalizations for herpes zoster [40-44].

The severity of disease and the likelihood of complications, including postherpetic neuralgia (PHN), also increase with age (figure 1) [18]. In one study, the risk for experiencing PHN increased 27-fold among patients aged >50 years compared with those <50 years [45]. In another study, PHN occurred in 18 percent of adult patients with herpes zoster overall but in more than one-third of those aged ≥79 years [18]. (See "Postherpetic neuralgia".)

Immunocompromised patients — Immunocompromised patients are at increased risk of VZV reactivation because of reduced T cell-mediated immunity. This includes transplant recipients [46-53], patients receiving selected immunomodulator therapies [52,54-61], patients treated with chemotherapy and/or corticosteroids, and patients with HIV [52,61-64]. The rate of complications is also significantly higher in immunocompromised patients [18].

Transplant patients — The risk of developing herpes zoster is increased in hematopoietic stem cell (HCT) and organ transplant recipients compared with the general population [52,53,65,66]. The risk is higher in those undergoing HST [67].

In a large database analysis that evaluated data from 51 million individuals between 2005 and 2009, the incidence of herpes zoster in the total study population was 4.82 per 1000 person-years, compared with a very high incidence among bone marrow or stem cell transplant recipients (43 per 1000 person-years) [52]. Among HCT recipients, the risk of developing herpes zoster remained increased even with reduced-intensity regimens. The risk of developing herpes zoster in those who underwent solid organ transplant was 17 per 1000 person-years.

In patients undergoing HCT, disseminated VZV remains one of the most frequent late infections of allogeneic bone marrow transplant recipients [68,69]. In one study, herpes zoster occurred in 35 percent of allogeneic HCT recipients at one year, and almost 50 percent of those patients developed disseminated VZV [70]. Concurrent graft versus host disease (GVHD), which usually requires additional immune suppression, is a major risk factor for dissemination [69]. However, when antiviral therapy is used in transplant settings, it can prevent herpes zoster [71,72]. Topic reviews that discuss the use of antiviral prophylaxis in transplant recipients are found elsewhere. (See "Prevention of viral infections in hematopoietic cell transplant recipients", section on 'Varicella-zoster virus' and "Prophylaxis of infections in solid organ transplantation", section on 'Herpes simplex and varicella-zoster'.)

Autoimmune disease — The incidence of herpes zoster is increased in patients with autoimmune diseases (eg, rheumatoid arthritis, inflammatory bowel disease), primarily related to the use of immunosuppressive therapies such as glucocorticoids, nonbiologic

disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor (TNF)-alpha inhibitors, sphingosine 1-phosphate (S1P) receptor inhibitors, and Janus kinase (JAK) inhibitors [55-59,61,73-80].

In a nested retrospective case-control study that included 18,000 patients with inflammatory bowel disease treated with glucocorticoids and/or the nonbiologic DMARDs azathioprine or 6-mercaptopurine, the incidence of herpes zoster was significantly increased with both glucocorticoids and azathioprine/6-mercaptopurine (adjusted odds ratio 1.5 and 3.1, respectively) [74]. In a retrospective Veterans Affairs cohort study involving 20,357 patients with rheumatoid arthritis, those who received treatment for either moderate disease (eg, methotrexate, azathioprine, cyclosporin) or severe disease (eg, TNF-alpha inhibitors) were at increased risk of developing herpes zoster [81].

There are conflicting data regarding the question of whether biologic agents confer a greater risk of herpes zoster compared with nonbiologic therapies for autoimmune diseases. In one study, the rate of herpes zoster associated with tofacitinib, a JAK inhibitor, was approximately double that observed in patients using the selective T-cell costimulation blocker, abatacept (hazard ratio 2.01; 95% CI 1.40-2.88) [77]. By contrast, no difference in risk was seen in a multicenter cohort study that compared the incidence of herpes zoster in 25,742 patients with rheumatoid arthritis or another autoimmune disease initiating nonbiologic DMARDs with 33,324 patients initiating a TNF-alpha inhibitor [76]. In this study, baseline use of glucocorticoids at a dose of ≥10 mg per day prednisone equivalents was associated with an increased risk of herpes zoster (adjusted hazard ratio 2.13, 95% CI 1.64-2.75) compared with no baseline use, but patients who initiated a TNF-alpha inhibitor were not at higher risk for herpes zoster than patients initiating nonbiologic DMARDs. No differences in risk were observed among infliximab, etanercept, and adalimumab recipients [76,77].

More detailed information on the risk of developing herpes zoster in patients receiving TNF-alpha inhibitors is presented elsewhere. (See "Tumor necrosis factor-alpha inhibitors: Bacterial, viral, and fungal infections", section on 'Herpes zoster'.)

HIV infection

- **Adults** – Adults with HIV are at greater risk of developing herpes zoster compared with those without HIV [62,63]. This was most evident prior to the introduction of potent antiretroviral therapy (ART), when a prospective study of 966 men who have sex with men found a higher incidence of herpes zoster in men with versus men without HIV (51.51 per 1000 person-years versus 3.31 per 1000 person-years), and second cases were only documented in individuals with HIV (26 percent) [63]. In this study, the incidence of herpes zoster increased with decreasing CD4 cell counts (31.2 per 1000 person-years for CD4 count >500 cells/microL, 47.2 per 1000 person-years for CD4

count 200 to 499 cells/microL, and 97.5 per 1000 person-years for CD4 count <200 cells/microL), demonstrating the importance of T cell-mediated immunity in maintaining latency. (See 'Pathogenesis' above.)

With the widespread availability of potent ART, the incidence of herpes zoster has decreased in persons with HIV, but remains greater than the general population. In adults, this was illustrated in a study evaluating 7167 cases of herpes zoster among 91,044 individuals [82]. Although there was an overall decline in the incidence of herpes zoster that was attributed to ART (2955 cases per 100,000 person-years between 1992 and 1996 versus 628 cases per 100,000 person-years between 2009 and 2011), the incidence of herpes zoster remained significantly higher in patients with HIV compared with the general population (overall standardized incidence ratio 2.7, 95% CI 2.6-2.9).

- **Children** – The incidence of herpes zoster in children with prior varicella is estimated to be 2.6 per 1000 person-years [83]. However, the incidence is higher in children with HIV. Prior to the availability of effective ART, the natural history of varicella infection was observed in 30 children, of whom 8 developed herpes zoster [64]. The incidence of herpes zoster was 467 cases per 1000 person-years in those with CD4 cells <15 percent at the time they developed chickenpox. Half of the children who developed herpes zoster had a recurrence

  Similar to adults, herpes zoster is less common in children after the introduction of potent ART. One study evaluated 536 perinatally infected children with HIV and a history of prior varicella over a 13-year period (from 1993 to 2006) [84]. Although the incidence of herpes zoster increased from 1993 to 1996 (prior to the introduction of potent ART) and then declined by more than half through 2006, an incidence rate of 14 to 31 herpes zoster episodes per 1000 person-years persisted from 2001 to 2006. The incidence of herpes zoster declined significantly after more than 90 days of potent ART.

Other risk factors — Other risk factors for developing herpes zoster include**:**

- **Sex** – Age-specific rates of herpes zoster are greater in women, even when controlling for age [85].

- **Race** – The incidence of herpes zoster is significantly lower in Black Americans compared to White Americans [86].

- **Physical trauma** – Physical trauma may be a risk factor for herpes zoster, particularly cranial herpes zoster [87]. As an example, in an age-matched case-control study that used Medicare data, patients ≥65 years of age who developed herpes zoster were 3.4 times more likely than controls to have experienced trauma during the week prior to herpes zoster onset [88]. Patients who had cranial herpes zoster were more than 25

times as likely as controls to have had cranial trauma during the week prior to herpes zoster onset.

- **Comorbid conditions** – Certain conditions other than those described above (eg, transplant, autoimmune disease, HIV) may be associated with herpes zoster. These include underlying malignancy and chemotherapy, disorders of cell-mediated immunity, and chronic lung or kidney disease [81,89,90]. Some studies indicate that depression is a risk factor [91], but this was not observed in another study [92].

Transmission

People with herpes zoster can transmit varicella-zoster virus (VZV), causing varicella (chickenpox) in contacts who are varicella naïve (ie, never had varicella or the varicella vaccine). VZV is spread by direct contact with the active herpes zoster lesions or via airborne transmission from individuals with localized herpes zoster [93-96]. The lesions are considered non-infectious after crusting [94-96]. A more detailed discussion of VZV transmission is found elsewhere. (See "Prevention and control of varicella-zoster virus in hospitals".)

VZV DNA can be detected in saliva during herpes zoster. In a study of 54 patients with herpes zoster who were treated with valacyclovir, VZV DNA was identified in saliva of all patients on the first day of treatment, and resolved in 82 percent of patients by day 15 [97]. However, attempts to isolate infectious virus from the saliva of these patients have failed.

Clinical manifestations

Common findings — The presenting clinical manifestations of herpes zoster are usually rash and acute neuritis. Fewer than 20 percent of patients who develop a rash have significant systemic symptoms, such as headache, fever, malaise, or fatigue [2].

Rash — The rash starts as erythematous papules, typically in a single dermatome or several contiguous dermatomes (figure 2A-B and picture 1A-B, 1K-L). The dermatomal distribution of the vesicular rash of herpes zoster corresponds to the sensory fields of the ganglion (or neighboring ganglia) involved.

Within several days, grouped vesicles or bullae are the predominant manifestation (picture 1C-F, 1M). Within three to four days, the rash becomes pustular (picture 1G). The rash can be hemorrhagic in immunosuppressed people and people of advanced age (picture 2).

In immunocompetent hosts, the lesions crust by 7 to 10 days and are no longer considered infectious (picture 1J). Scarring and hypo- or hyperpigmentation may persist months to years after herpes zoster has resolved (picture 3) [98]. The development of new lesions more than a week after presentation should raise concerns regarding possible underlying immunodeficiency [2]. (See 'Approach to diagnosis' below.)

Although the rash can occur in any dermatome, the thoracic and lumbar dermatomes are most commonly involved (figure 2A) [18]. Herpes zoster occurs on the face in 10 percent or more of cases. Some patients may also have a few scattered vesicles located at some distance away from the involved dermatome, probably reflecting the presence of varicella-zoster virus (VZV) viremia early in herpes zoster [2,12].

Herpes zoster keratitis or herpes zoster ophthalmicus can result from involvement of the ophthalmic branch of the trigeminal cranial nerve [98,99]. These complications can be sight-threatening. (See 'Complications' below.)

Acute neuritis — Pain is the most common symptom of herpes zoster [100]. Most patients describe a deep "burning," "throbbing," or "stabbing" sensation [44,101]. In a study of 1669 patients with confirmed herpes zoster, 18 percent had pain in the area of rash for at least 30 days, and the duration of pain increased with age [18]. Acute neuritis should not be confused with postherpetic neuralgia (PHN), which is discussed below. (See 'Postherpetic neuralgia' below.)

Approximately 75 percent of patients have prodromal pain that precedes the rash in the affected dermatome [2]. Prodromal pain may be constant or intermittent and typically precedes the rash by two to three days, but this interval can be longer [101]. Prior to the development of rash, the prodromal pain is often misinterpreted as another disease, such as angina, cholecystitis, appendicitis, spinal disc diseases, or renal colic, depending on the involved dermatome [18,102].

The concept that some atypical pain syndromes may be related to herpes zoster without rash, or "zoster sine herpete," has been raised. Clinical data paired with serologic and polymerase chain reaction (PCR) evidence of concurrent VZV reactivation support this theory [103,104]. (See "Varicella zoster virus vasculopathy".)

Complications — The most common complication of herpes zoster is PHN. Other complications include ocular, neurologic, and bacterial superinfection of the skin [18,98,99,105,106].

Postherpetic neuralgia — Postherpetic neuralgia (PHN) is frequently defined as significant pain persisting for 90 days after the onset of rash. Significant pain is considered a pain level 3 or higher on a pain scale of 1 to 10. Sensory symptoms can also include numbness,

dysesthesias, pruritus, and allodynia in the affected dermatome. A more detailed discussion of the clinical manifestations and diagnosis of PHN is presented in a separate topic review. (See "Postherpetic neuralgia".)

Approximately 10 to 15 percent of patients with herpes zoster will develop PHN [107,108]; individuals older than 60 years of age account for 50 percent of these cases [45]. In one study, the percentage of patients with herpes zoster who developed PHN increased from 5 percent in those younger than 60 years to 20 percent in those aged 80 years or older [109]. Immunosuppressed patients also have a higher incidence. By contrast, patients who receive either the live attenuated or recombinant herpes zoster vaccines are less likely to develop PHN, even if herpes zoster occurs. (See "Vaccination for the prevention of shingles (herpes zoster)".)

Herpes zoster ophthalmicus — Herpes zoster ophthalmicus (HZO) (picture 1H-I, 1N), a potentially sight-threatening condition, is defined as herpes zoster involvement of the ophthalmic division of the fifth cranial nerve [110]. Incidence rates of HZO complicating herpes zoster in various surveys have ranged from 8 to 20 percent [110-112]. Approximately 50 percent of patients with HZO experience direct ocular involvement if antiviral therapy is not used [110,111].

- HZO begins with a prodrome of headache, malaise, and fever. Unilateral pain or hypesthesia in the affected eye, forehead, and top of the head may precede or follow the prodrome.
- With the onset of the rash, hyperemic conjunctivitis, uveitis, episcleritis, and keratitis may occur [105,111,113,114]; ptosis is rare.
- Acute keratitis typically involves the epithelial, stromal, or endothelial layers of the cornea [115]. Patients who develop epithelial or stromal keratitis are most at risk for vision loss.

Vesicular lesions on the side or tip of the nose correlate highly with eye involvement (picture 1N) [116]. Lesions in this area of the face signify involvement of the nasociliary branch of the trigeminal nerve, which also innervates the globe [117].

Early diagnosis and treatment is critical to prevent progressive corneal involvement and potential loss of vision [118]. The treatment of HZO is discussed separately. (See "Treatment of herpes zoster in the immunocompetent host", section on 'Herpes zoster ophthalmicus'.)

Acute retinal necrosis — VZV is the leading cause of acute retinal necrosis (ARN) [119-122]. ARN occurs in both immunocompetent and immunocompromised hosts [123-125]. In one study, VZV DNA was detected in aqueous humor in seven of nine patients with necrotizing retinopathies of suspected viral origin and in four of six patients with ARN [123]. Herpes

simplex virus (HSV) is another cause of ARN and has been described in patients with a history of herpes encephalitis [126]. (See "Retinal vasculitis associated with systemic disorders and infections".)

The clinical features of ARN are acute iridocyclitis, vitritis, necrotizing retinitis, occlusive retinal vasculitis with rapid loss of vision, and eventual retinal detachment [105,120,123-125]. Blurred vision is characteristic and pain is present in the affected eye due to progressive necrotizing retinitis.

Initial disease is usually unilateral, but can subsequently involve the other eye in 33 to 50 percent of patients [120]. The mechanism of bilateral involvement is not clear, but one study found a diminished or absent VZV-specific delayed hypersensitivity reaction in patients with ARN compared with patients with herpes zoster involving only the skin [127]. This is suggested by the frequency of bilateral disease in patients with advanced AIDS.

Patients with advanced AIDS and ARN are subject to rapid progression and severe disease. In one report of ARN in patients with AIDS prior to the introduction of potent ART, only 4 of 20 involved eyes retained useful vision at two-month follow-up, and 70 percent had no light perception at the conclusion of the study [125]. In addition, 82 percent of patients had bilateral eye involvement, and 73 percent had accompanying central nervous system (CNS) disease (eg, confusion, encephalopathy), presumably due to VZV. ARN is now rare in patients with HIV, reflecting the near normal immune status of patients receiving ART.

The management of ARN is discussed in a separate topic review. (See "Treatment of herpes zoster in the immunocompetent host", section on 'Acute retinal necrosis'.)

Ramsay Hunt syndrome (herpes zoster oticus) — The major otologic complication of VZV reactivation is the Ramsay Hunt syndrome, which typically includes the triad of ipsilateral facial paralysis, ear pain, and vesicles in the auditory canal or on the auricle (picture 4) [128,129]. Ipsilateral altered taste perception and tongue lesions, hearing abnormalities (decreased hearing, tinnitus, hyperacusis), and lacrimation occur in some patients; vestibular disturbances (vertigo) are also frequently reported [129].

Ramsay Hunt syndrome reflects reactivation of latent VZV in the geniculate ganglion [130,131], with subsequent spread of the infection to the eighth cranial nerve. Ramsay Hunt syndrome may rarely occur as a component of multiple cranial nerve involvement, especially cranial nerves V, IX, and X [128].

The facial paralysis seen in Ramsay Hunt syndrome is often more severe than Bell's palsy attributed to HSV, with increased rates of late neural denervation and a decreased probability of complete recovery [132,133]. Antiviral therapy is prescribed, although there

are few data on the management of this complication [134]. (See "Treatment of herpes zoster in the immunocompetent host", section on 'Ramsay Hunt syndrome'.)

Other neurologic complications — Herpes zoster is not always limited to a spinal nerve distribution; it may also extend centrally, which can result in meningeal inflammation and clinical meningitis. Occasionally, VZV reactivation affects motor neurons in the spinal cord and brainstem, resulting in motor neuropathies .

Aseptic meningitis — A subset of immunocompetent patients with herpes zoster develop clinically evident aseptic meningitis [135]; lumbar puncture typically confirms a brisk cerebrospinal fluid (CSF) pleocytosis and an elevated protein concentration [136,137]. Most patients will have a rash at the time of diagnosis, although in some cases, the rash can appear after the onset of meningitis. In a Finnish epidemiologic study of 144 patients with aseptic meningitis without an obvious cause, 8 percent had VZV infection [135].

Aseptic meningitis differs from subclinical meningeal irritation, evidenced by a reactive CSF pleocytosis, which occurs in 40 to 50 percent of cases [138,139]. Patients with subclinical meningeal irritation can also have VZV DNA detected in the CSF.

Encephalitis — Herpes zoster-associated encephalitis typically presents with delirium within days following the vesicular eruption, but may occur prior to the onset of rash or following an episode of herpes zoster [138,140]. Although VZV encephalitis is a more common complication in immunocompromised patients, it is also seen in previously healthy hosts [105,138,140-142]. Major risk factors identified for the development of zoster encephalitis include cranial or cervical dermatomal involvement, two or more prior episodes of herpes zoster, disseminated herpes zoster, and impaired cell-mediated immunity [138,141].

Patients with AIDS may develop a leukoencephalitis associated with CNS white matter demyelination and cerebral vasculopathy due to ongoing VZV replication within the brain parenchyma [138,143]. CSF PCR assays, in conjunction with magnetic resonance imaging (MRI) brain imaging studies, provide rapid diagnosis of VZV encephalitis [144,145].

Peripheral motor neuropathy — Segmental motor paresis develops in approximately 3 percent of patients with herpes zoster [138,146]. Peripheral motor weakness results from spread of VZV from the dorsal root ganglia to the anterior root/horn of the spinal cord. Although the onset is typically coincident with the development of pain and cutaneous eruption in a dermatomal distribution [138,146,147], there are reports of delayed onset with neurologic symptoms presenting two to three weeks after the onset of rash [148,149]. Muscle atrophy may result in the affected region, but approximately 75 percent of patients experience gradual recovery of motor strength [138]. Involvement of sacral sensory ganglia may cause bladder or bowel dysfunction.

Myelitis — Transverse myelitis is a rare complication of herpes zoster (usually involving thoracic dermatomes (figure 2A)) and typically occurs within days to weeks following the initial onset of the vesicular rash [138,150]. There are several reports of myelitis occurring in untreated persons with HIV [151,152]. One report described herpes zoster myelitis in the absence of rash, but with documented VZV DNA in spinal cord specimens at autopsy [151].

Guillain-Barré syndrome — There is an association between herpes zoster and Guillain-Barré Syndrome (GBS). Data from a Taiwan health registry indicated an increased risk of GBS in people with herpes zoster within the prior two months of GBS [153]. Of 315,595 patients with herpes zoster, 0.03 percent developed GBS. Although GBS was a relatively rare event, the risk of developing this syndrome was significantly higher among patients with a recent history of herpes zoster compared with controls, who were matched by age and sex. (See "Guillain-Barré syndrome in adults: Pathogenesis, clinical features, and diagnosis".)

Stroke syndromes — VZV infection can produce stroke syndromes secondary to infection of cerebral arteries. In a series of 30 patients with VZV vasculopathy, diagnosed by either VZV-specific antibodies or VZV DNA in the CSF, rash occurred in 19 (63 percent), and CSF pleocytosis occurred in 20 (67 percent) [154]. Angiography demonstrated the involvement of both large and small arteries in approximately half of the patients. HZO can be complicated by contralateral thrombotic stroke syndrome [138,155,156]. A more detailed discussion of stroke syndromes and other forms of vasculopathy associated with VZV is presented in a separate topic review. (See "Varicella zoster virus vasculopathy".)

Bacterial infections — Patients with localized herpes zoster are at risk for developing soft tissue infection with bacterial pathogens, particularly if they are immunocompromised. Common pathogens include *Staphylococcus* and *Streptococcus* [157,158]. In addition to antiviral therapy, antibiotic therapy targeting these bacterial pathogens is indicated when this complication occurs. (See "Acute cellulitis and erysipelas in adults: Treatment".)

Special considerations in immunocompromised hosts — Immunocompromised hosts are at risk of having more frequent episodes of herpes zoster and/or severe VZV-related complications [105,138,151,152,159-162]. Severe complications include cutaneous dissemination and visceral involvement.

- Cutaneous dissemination is defined by multiple vesicular skin lesions in a generalized distribution distant from the dermatomes affected by the herpes zoster rash (picture 5A-B). This has been reported in solid organ and hematopoietic cell transplant recipients and in patients with hematologic malignancies undergoing chemotherapy [68,70,160]. Cutaneous dissemination may be accompanied by visceral involvement [70,163]. Patients with cutaneous dissemination are at high risk of transmitting VZV to nonimmune patients.

- Visceral organ involvement may present as a fulminant and rapidly evolving syndrome with pneumonia, hepatitis, or encephalitis and may occasionally develop in the absence of rash [164]. When cutaneous lesions are present, they may be delayed or atypical with hemorrhage [46]. In hematopoietic stem cell transplant patients, reactivation of VZV typically occurs later than cytomegalovirus or HSV (>3 months after immune compromise) [165].

  Hematopoietic stem cell and organ transplant recipients can have acute, severe abdominal pain as the initial manifestation of visceral reactivated VZV in the absence of antecedent cutaneous rash, hepatitis, or pneumonitis [68,166]. The appearance of a herpes zoster rash as long as 10 to 14 days after the abdominal pain begins delays the diagnosis, which results in a poor outcome despite the institution of appropriate antiviral therapy.

  Visceral dissemination is a life-threatening emergency [46]. VZV pneumonitis in transplant recipients has been associated with a high mortality despite prompt diagnosis and the empiric institution of antiviral therapy [167].

Approach to diagnosis

In immunocompetent individuals, the diagnosis of herpes zoster is usually based solely on the clinical presentation (unilateral, usually painful vesicular eruption with a well-defined dermatomal distribution) (picture 1M and picture 1A). (See 'Rash' above.)

However, herpes zoster may occasionally present with atypical skin lesions (eg, hemorrhagic), especially in immunocompromised individuals. In addition, patients with herpes simplex virus infection may develop vesicular lesions in a distribution that can be confused with herpes zoster ("zosteriform herpes simplex"); this is most likely to occur on the face or genital/buttock areas, which are characteristic locations for herpes simplex reactivation, and there is often a history of prior episodes in the same area. (See "Approach to the patient with cutaneous blisters".)

When the clinical presentation is uncertain, laboratory confirmation is indicated. Diagnostic techniques include polymerase chain reaction (PCR) testing, direct fluorescent antibody (DFA) testing, and viral culture [168].

- PCR testing is preferred since PCR is the most sensitive laboratory test to diagnose herpes zoster (>95 percent) and is more rapid (≤1 day) compared with conventional culture techniques [169,170]. PCR testing can be used to test lesions of all stages, including late-stage (ulcers and crusts) lesions. PCR is also useful for CSF, blood, and

other non-cutaneous specimens, such as vitreous humor, and bronchoalveolar lavage [169,171,172].

In a study that evaluated 1479 clinical specimens from 1220 patients with suspected herpes zoster, real-time PCR testing was highly sensitive compared with culture (92 versus 53 percent) [170]. In addition, PCR-based testing was highly specific, and no cross-reactivity was identified when tested against several other viruses.

- When PCR testing is not available, we try to do DFA testing on scrapings from vesicular skin lesions that have not yet crusted and viral culture. Both of these tests are best done from unroofed or recently ruptured vesicles. Viral culture can also be performed on sterile body fluid, such as CSF. DFA testing can provide results in approximately two hours. However, specific VZV culture isolation typically requires prolonged incubation with a turnaround time of about one week [173].

  The sensitivity of DFA and viral culture are significantly lower than PCR testing [106,170,174,175]. In one study, the sensitivity of DFA was approximately 55 percent compared with PCR testing [174]. DFA is often limited by the quality of the specimen since sufficient infected skin cells must be present on the slide to ensure a valid test. Virus isolation by culture is associated with a yield of 50 to 75 percent in PCR-positive samples [170,175,176]. The sensitivity of culture is very dependent on the age of the lesion (the closer a lesion is to healing, the less likely there will be culturable virus in the lesion); in addition, culture can be falsely negative if antiviral therapy has been initiated.

- Viral cultures must be performed if testing an isolate for antiviral drug resistance is required to guide treatment decisions. (See "Treatment of herpes zoster in the immunocompetent host".)

Assessing for comorbid conditions

Although herpes zoster is seen with increased frequency in immunocompromised individuals, an episode of herpes zoster itself should not prompt a detailed evaluation for an underlying disease (eg, occult cancer) in an otherwise healthy individual. However, a careful history and physical examination should be performed. In addition, HIV serologic testing should be performed on patients who have never had routine testing, as well as on those with significant risk factors for HIV acquisition [177]. (See "Screening and diagnostic testing for HIV infection", section on 'Whom to test'.)

Recurrent herpes zoster

Approximately 1 to 6 percent of individuals will experience a second episode of herpes zoster [18,41,178-180]. Recurrent herpes zoster is more frequent in women. Three or more episodes recurring in the same individual are very rare [168]. If recurrent herpes zoster is suspected, laboratory confirmation may be reasonable to rule out other etiologies [181], such as recurrent zosteriform herpes simplex, or a non-infectious etiology, such as contact dermatitis.

Recurrences are more common in immunocompromised hosts [178,182]. In one study of patients with HIV (mean age 41 years), 282 episodes of herpes zoster were identified in 239 patients. Of these episodes, 158 were new occurrences of herpes zoster and 124 were recurrent herpes zoster events [182].

Society guideline links

Links to society- and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Varicella-zoster virus".)

Information for patients

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Shingles (The Basics)")
- Beyond the Basics topic (see "Patient education: Shingles (Beyond the Basics)")

Summary and recommendations

- **Infections caused by varicella-zoster virus (VZV)** – Varicella-zoster virus (VZV) infection causes two distinct diseases. Primary infection with VZV results in varicella (chickenpox), characterized by vesicular lesions in different stages of development on the face, trunk, and extremities. Herpes zoster, also known as shingles, results from reactivation of latent VZV infection within the sensory ganglia. (See 'Introduction' above and 'Pathogenesis' above.)

- **Risk factors for herpes zoster infection** – The incidence of herpes zoster is influenced by the immune status of the host, age-related immunosenescence, disease-related immunocompromise, or iatrogenic immunosuppression, with age being the major risk factor for 90 percent of cases of herpes zoster in adults. (See 'Epidemiology' above.)

- **Risk of transmitting VZV to others** – People with herpes zoster can spread VZV to those who have not had varicella and have never received the varicella vaccine. The virus can spread through direct contact with herpes zoster lesions (the lesions are considered infectious until they dry and crust over). Airborne transmission of VZV from individuals with localized herpes zoster also occurs. (See 'Transmission' above.)

- **Clinical manifestations of herpes zoster** – The presenting clinical manifestations of herpes zoster are usually characterized by rash and acute neuritis (picture 1A-J). The thoracic and lumbar dermatomes are the most commonly involved sites of herpes zoster (figure 2A), although any dermatome can be affected. (See 'Common findings' above.)

  Immunocompromised hosts are at risk for cutaneous and visceral dissemination. (See 'Special considerations in immunocompromised hosts' above.)

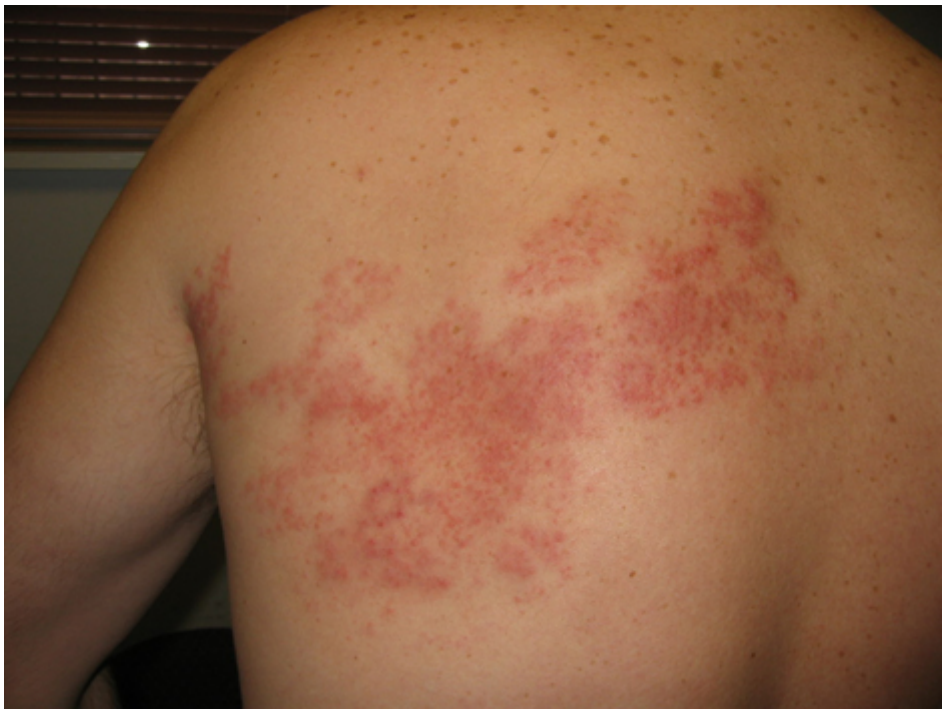
- **Complications of herpes zoster** – The most common complication of herpes zoster is postherpetic neuralgia. Other complications include herpes zoster ophthalmicus or oticus, and less commonly acute retinal necrosis, aseptic meningitis, and encephalitis. (See 'Complications' above.)

- **Approach to diagnosis** – In immunocompetent individuals, the diagnosis of herpes zoster is usually based on the clinical presentation (ie, unilateral, usually painful, vesicular eruption with a well-defined dermatomal distribution). However, when the diagnosis is uncertain, laboratory confirmation is indicated. Diagnostic techniques include the polymerase chain reaction (PCR) assay (which is the most sensitive test), direct fluorescent antibody testing, and viral culture. (See 'Approach to diagnosis' above.)

Topic 8327 Version 28.0

GRAPHICS

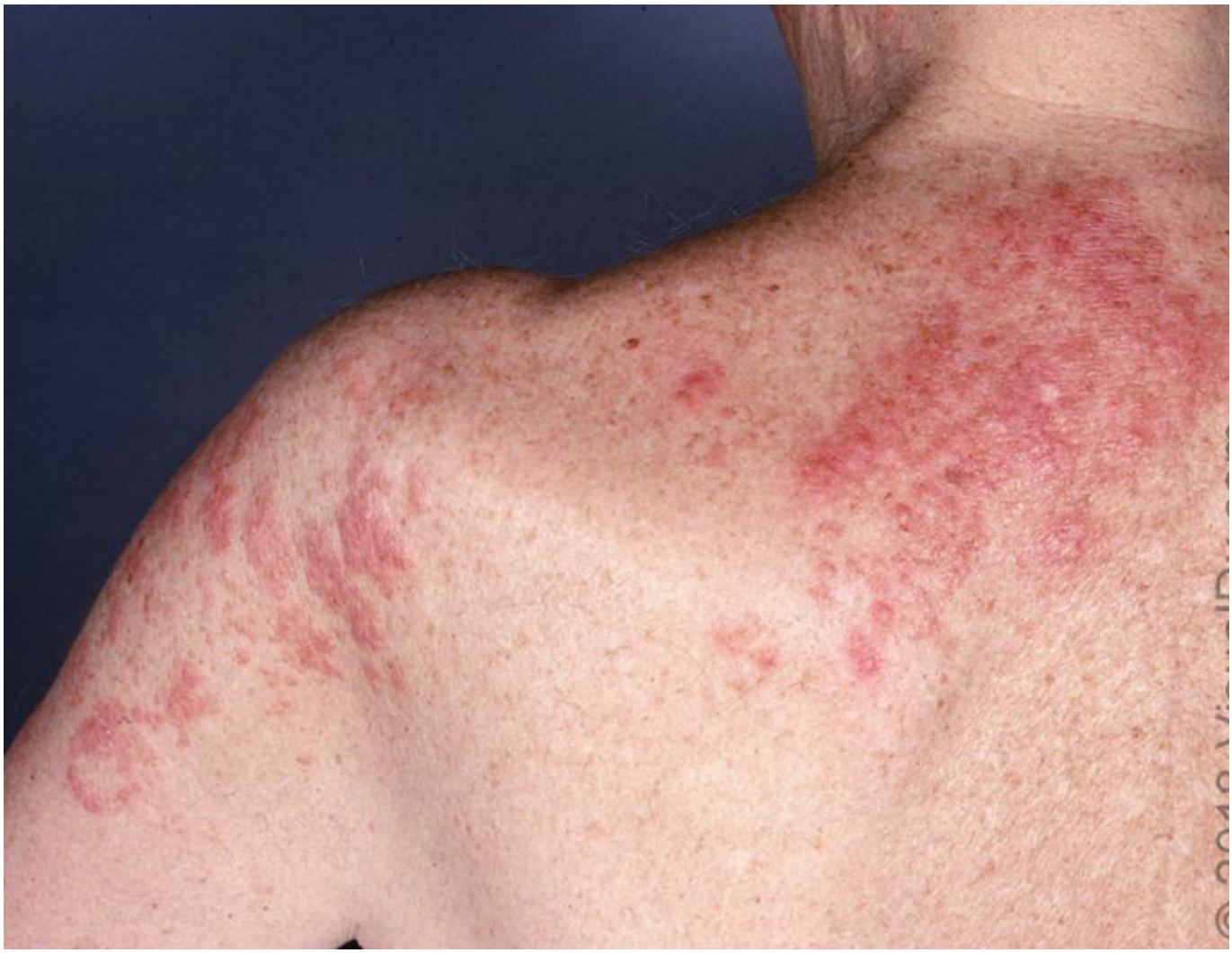
Herpes zoster



Courtesy of Vaibhav Parekh, MD, MBA.

Graphic 52440 Version 1.0

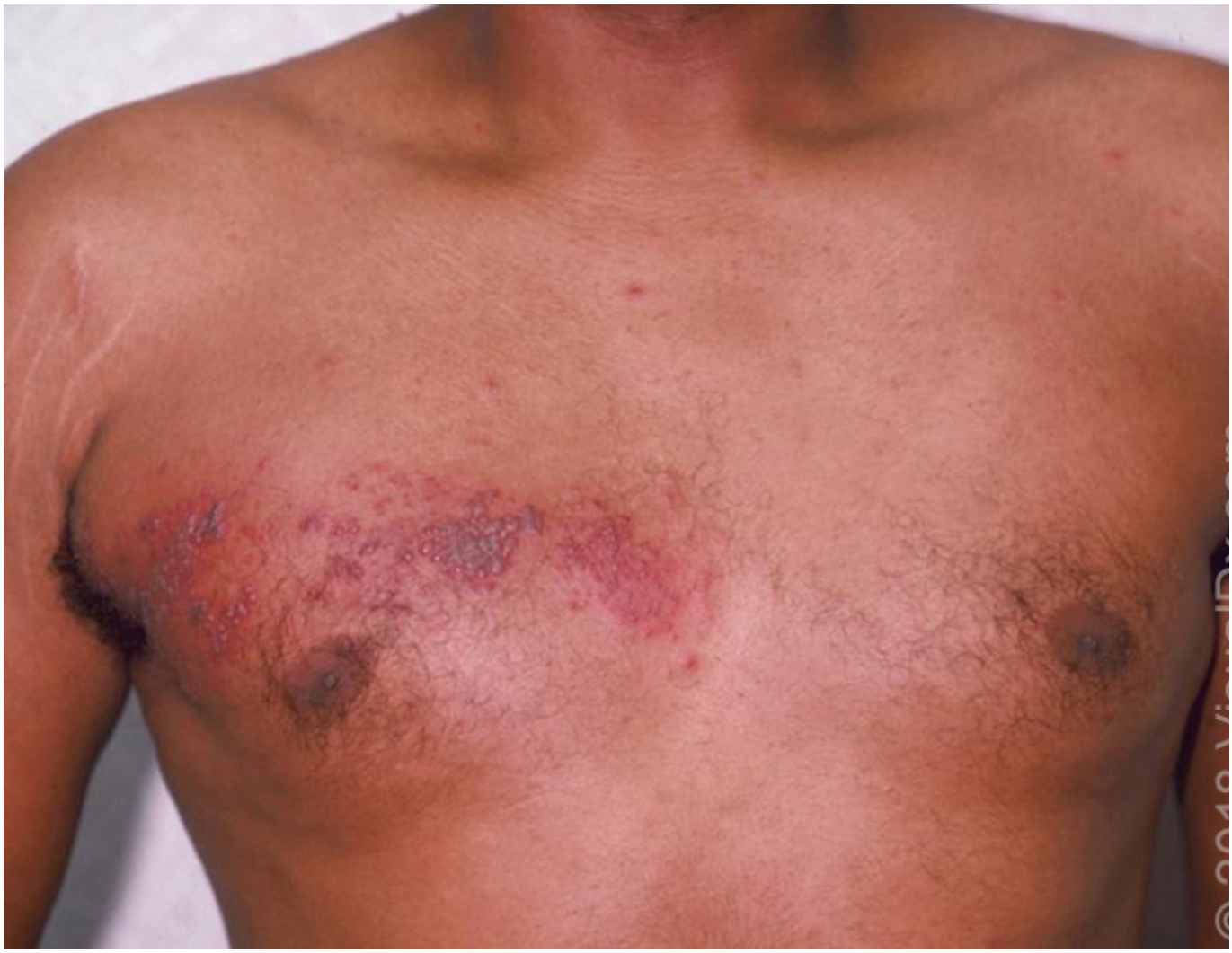
Herpes zoster



Grouped erythematous papules forming plaques in the C6 and C7 dermatomes.

Graphic 119544 Version 1.0

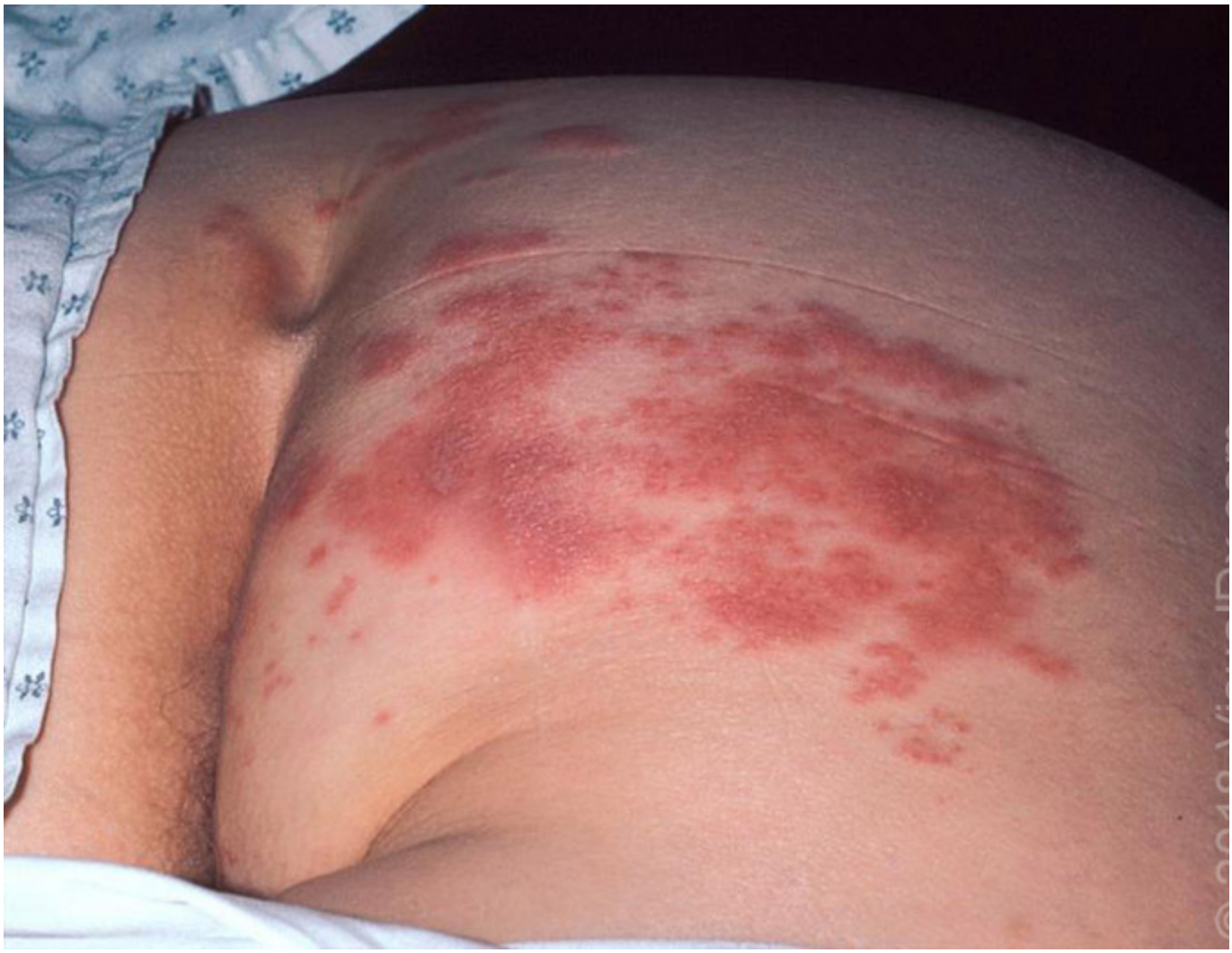
Herpes zoster



Grouped vesicles and erythema in a dermatomal distribution.

Graphic 119521 Version 1.0

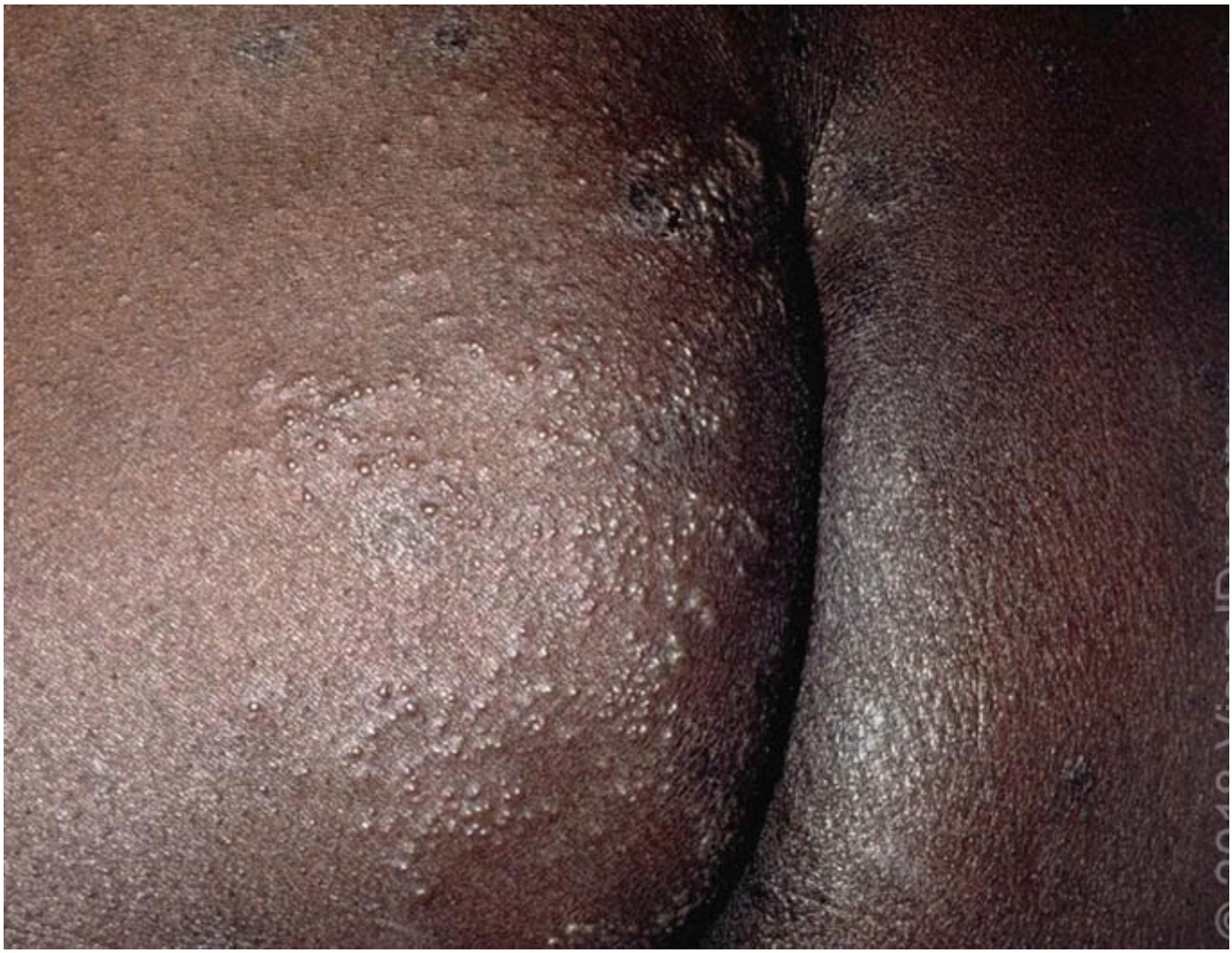
Herpes zoster



Grouped vesicles on an erythematous base in the S2 dermatome on the buttock.

Graphic 119546 Version 1.0

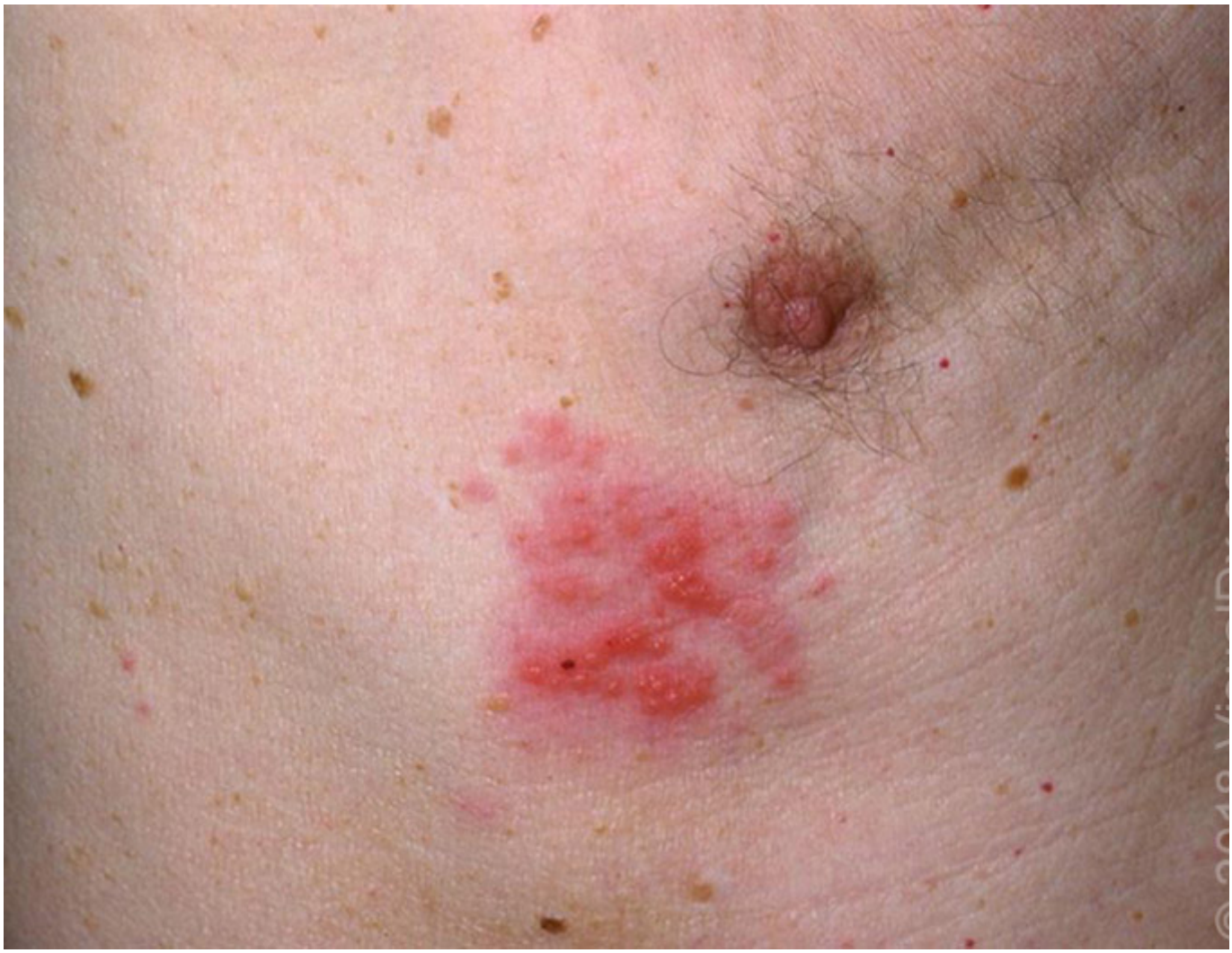
Herpes zoster



Discrete and grouped vesicles clustered in the S3 dermatome.

Graphic 119545 Version 1.0

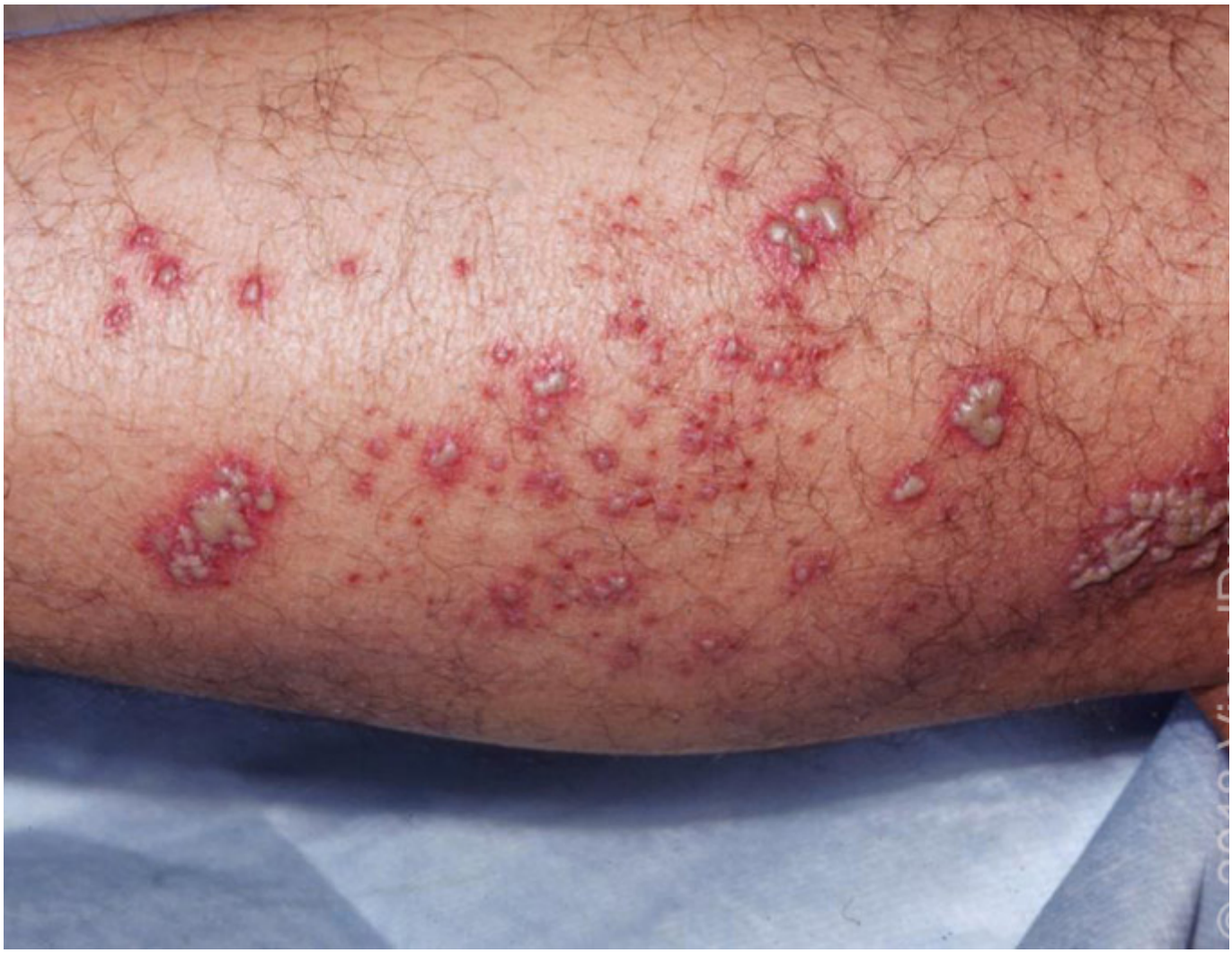
Herpes zoster



Grouped umbilicated vesicles on an erythematous base on the chest.

Graphic 119523 Version 1.0

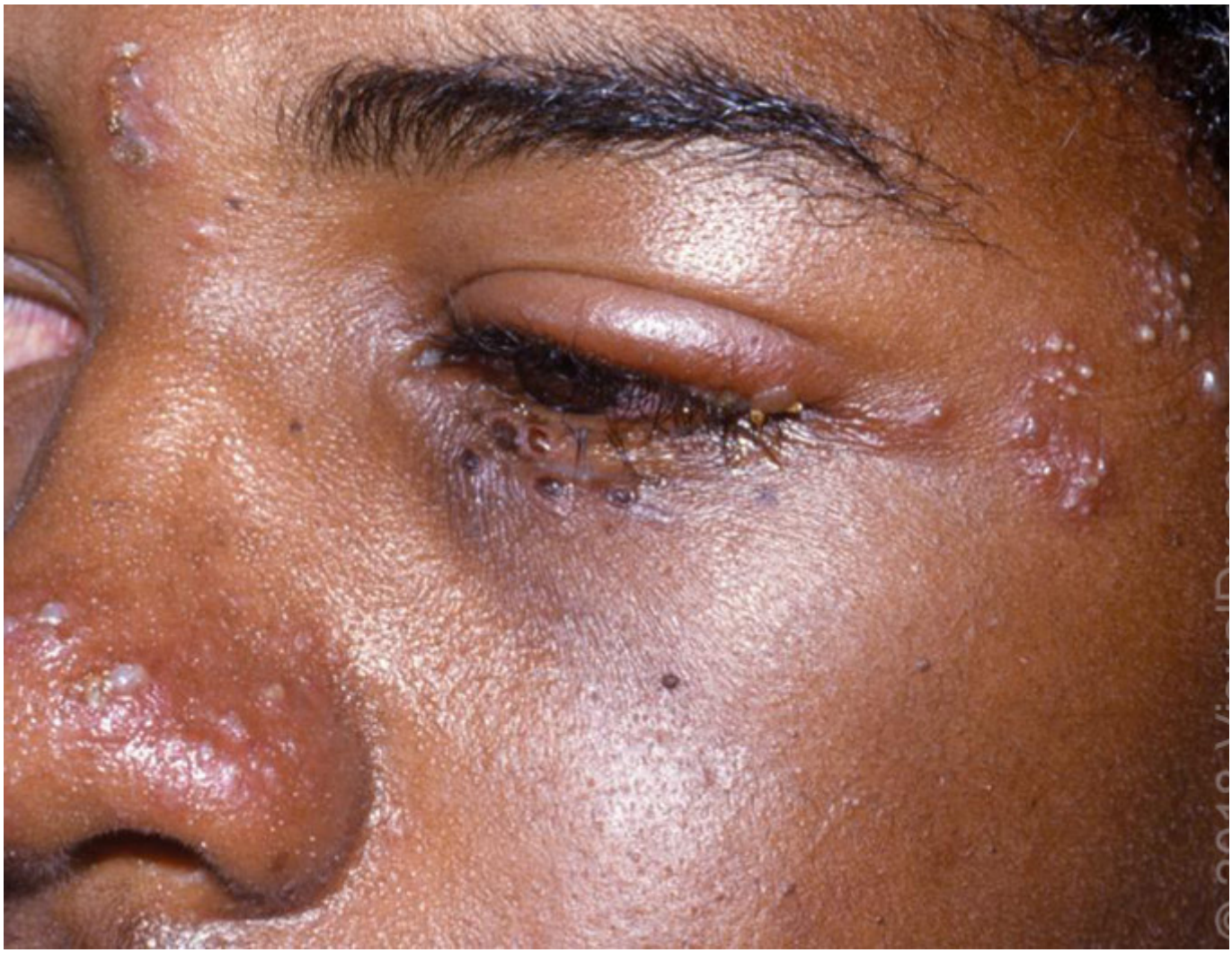
Herpes zoster



Grouped and confluent pustules on erythematous bases in a dermatomal distribution on the leg.

Graphic 119526 Version 1.0

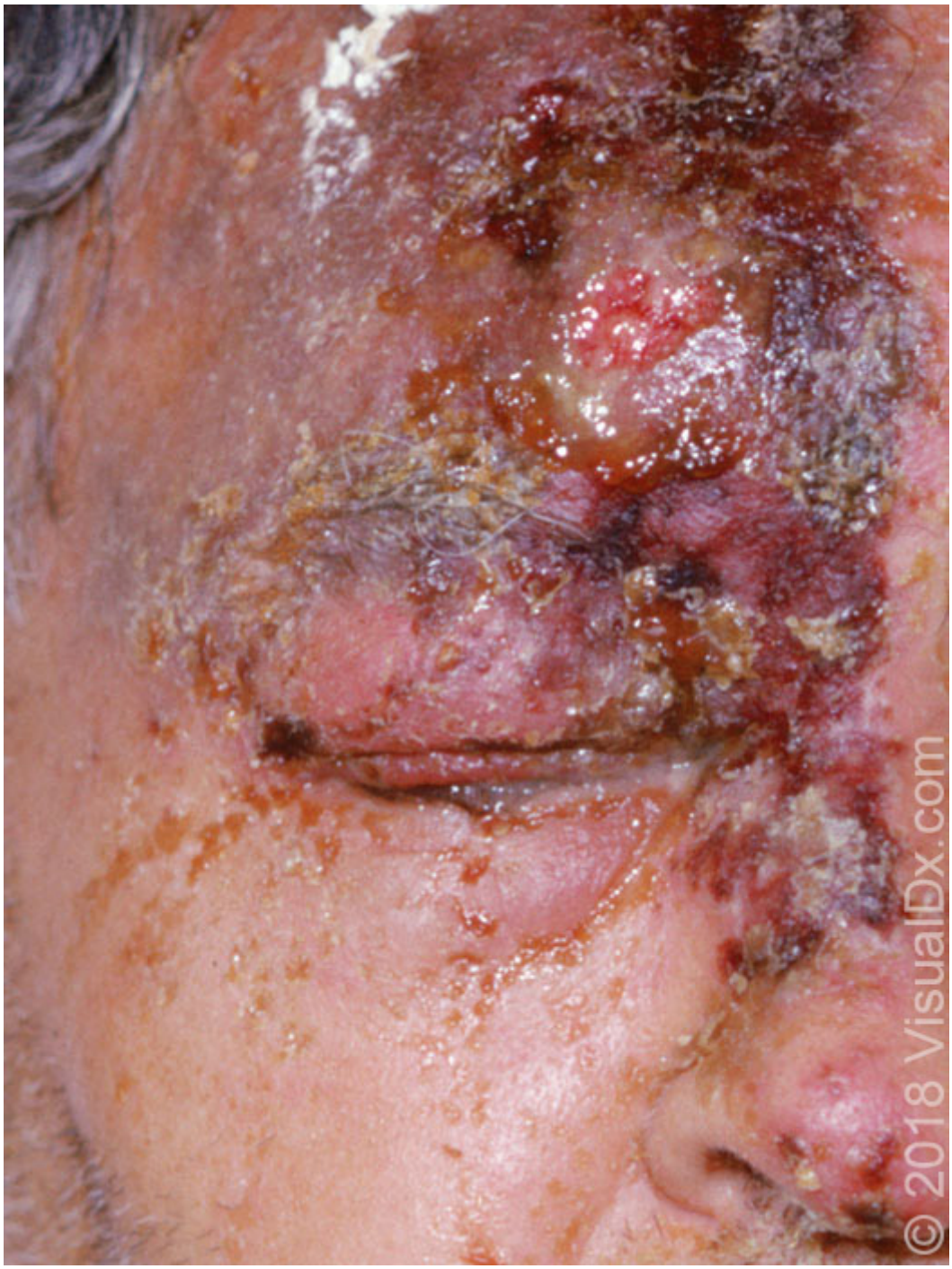
Herpes zoster ophthalmicus



Grouped vesicles and pustules in the V1 dermatome along with periorbital edema and hemorrhagic crusts on the lower eyelid.

Graphic 119527 Version 1.0

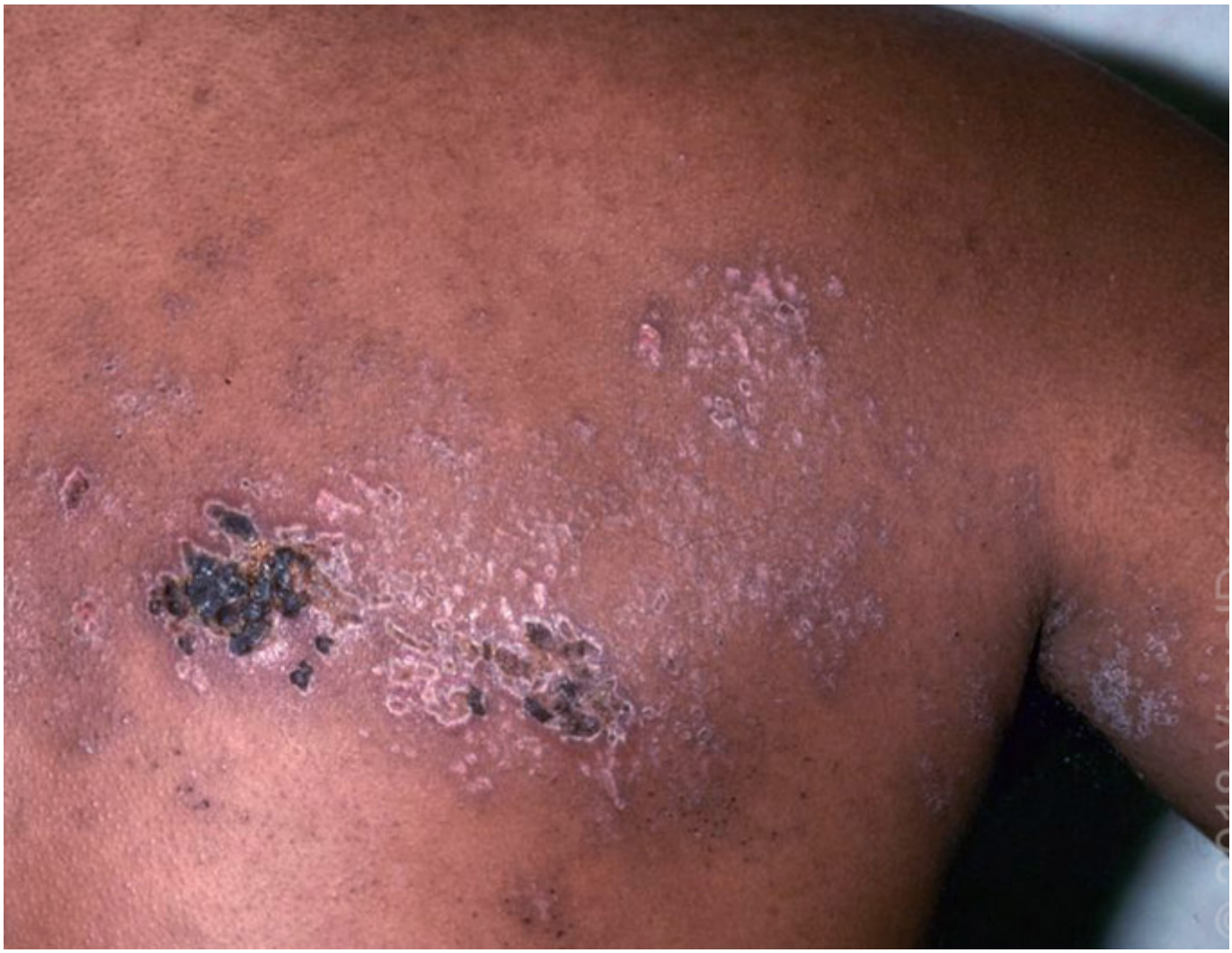
Herpes zoster ophthalmicus



Herpes zoster ophthalmicus in a patient with lymphoma displaying a large hemorrhagic crust with a sharp central cut-off, a weeping erosion, and periorbital edema. Note the involvement of the nasal tip as an indicator of eye involvement and the evident ocular discharge.

Graphic 119529 Version 1.0

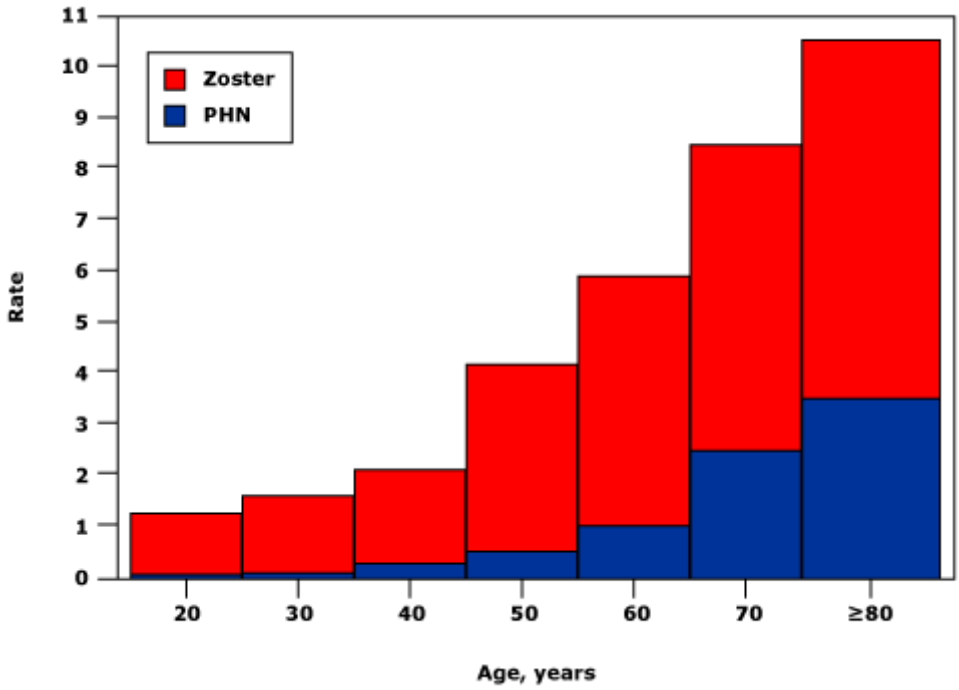
Herpes zoster



Healing zoster with a T5 distribution of grouped crusts and scars.

Graphic 119547 Version 1.0

Rates* of zoster and PHN¶ by age - United States



PHN: postherpetic neuralgia.

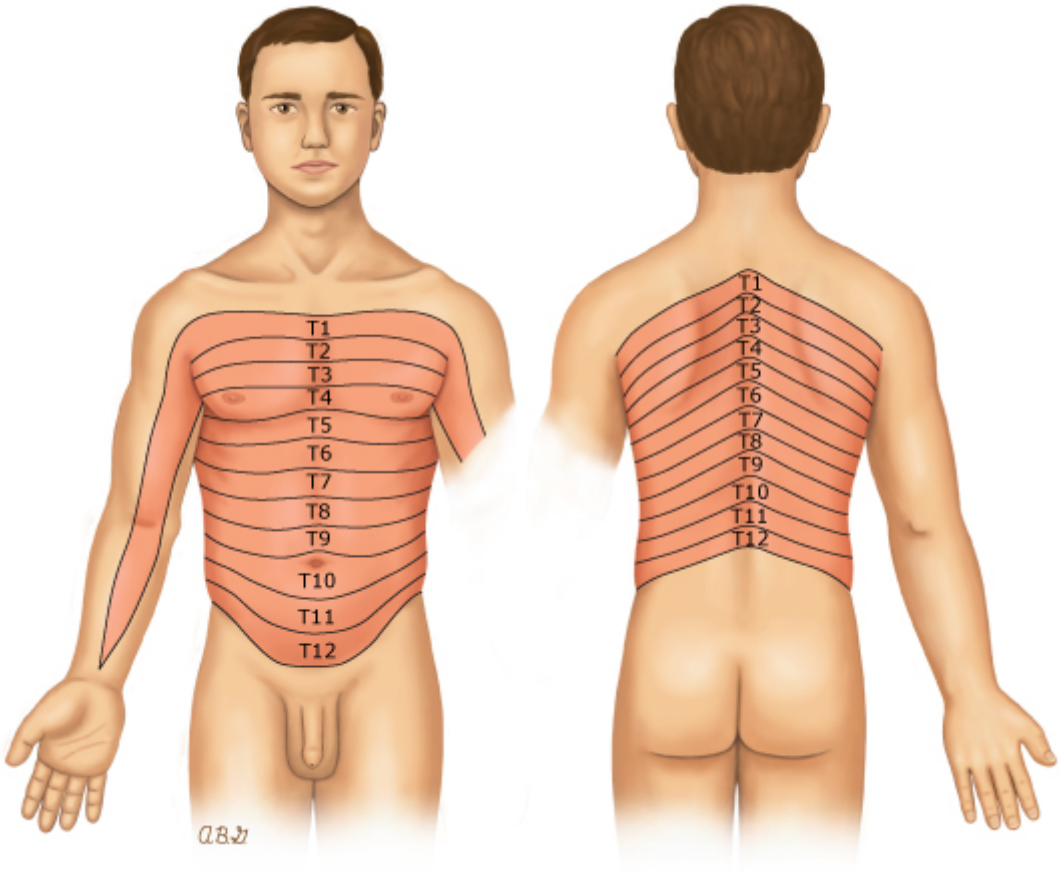
* Per 1000 person-years.

¶ Defined as ≥30 days of pain.

Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of Herpes Zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008; 57:1.

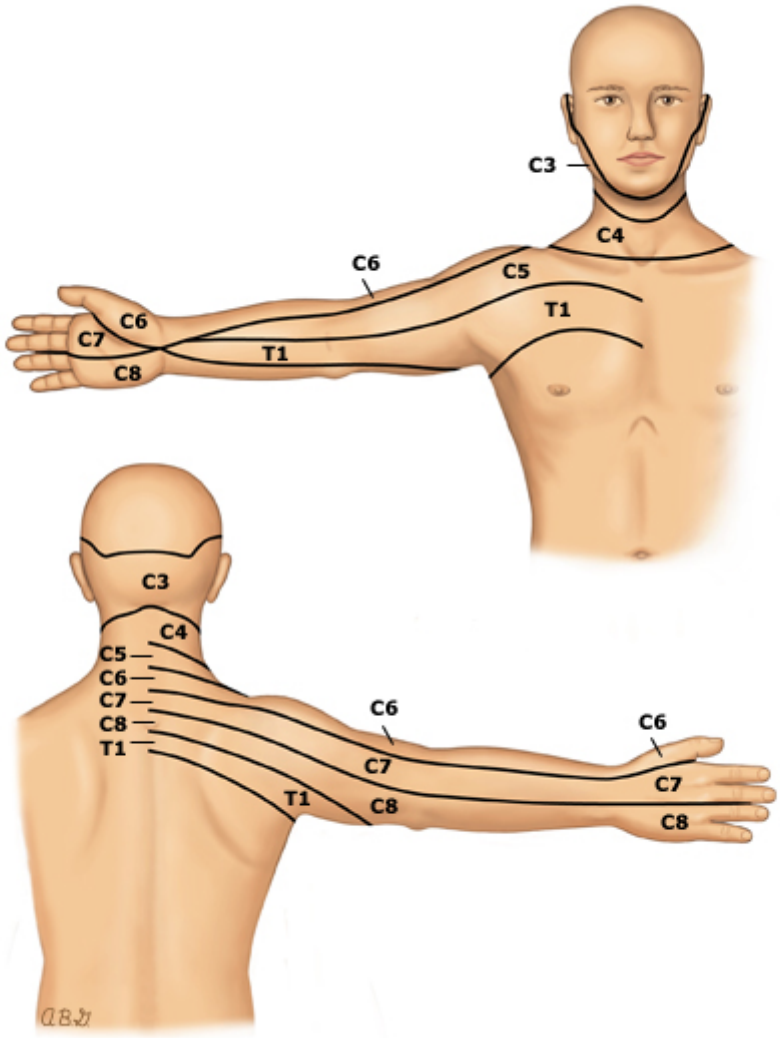
Graphic 79262 Version 3.0

Thoracic dermatomes



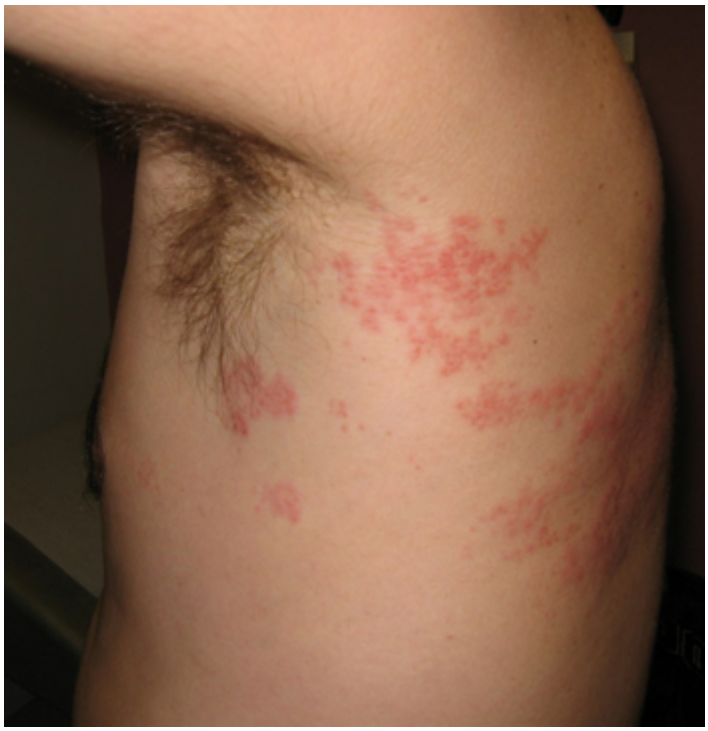
Graphic 64754 Version 2.0

Cervical dermatomes



Graphic 79158 Version 2.0

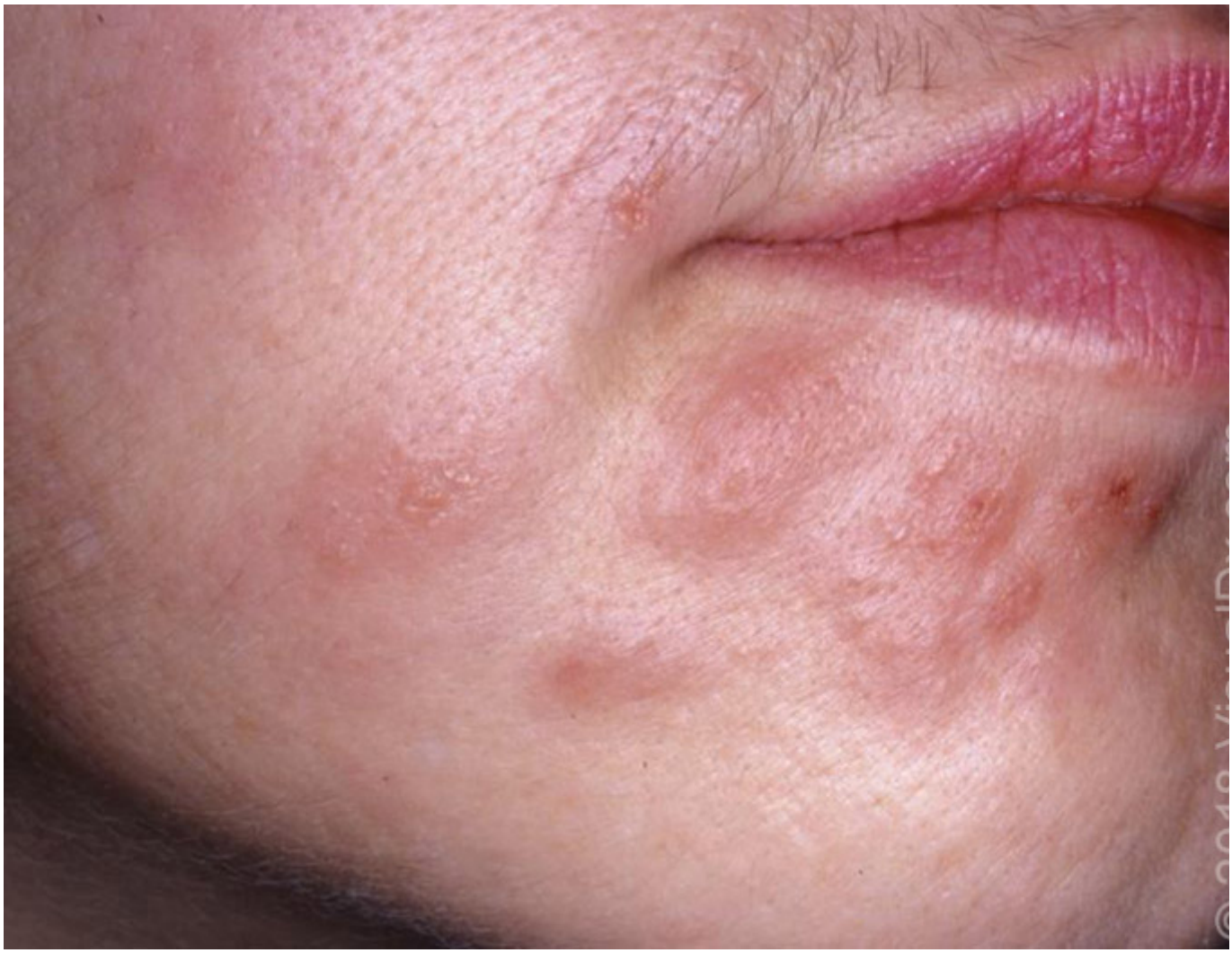
Herpes zoster



Courtesy of Vaibhav Parekh, MD, MBA.

Graphic 65213 Version 1.0

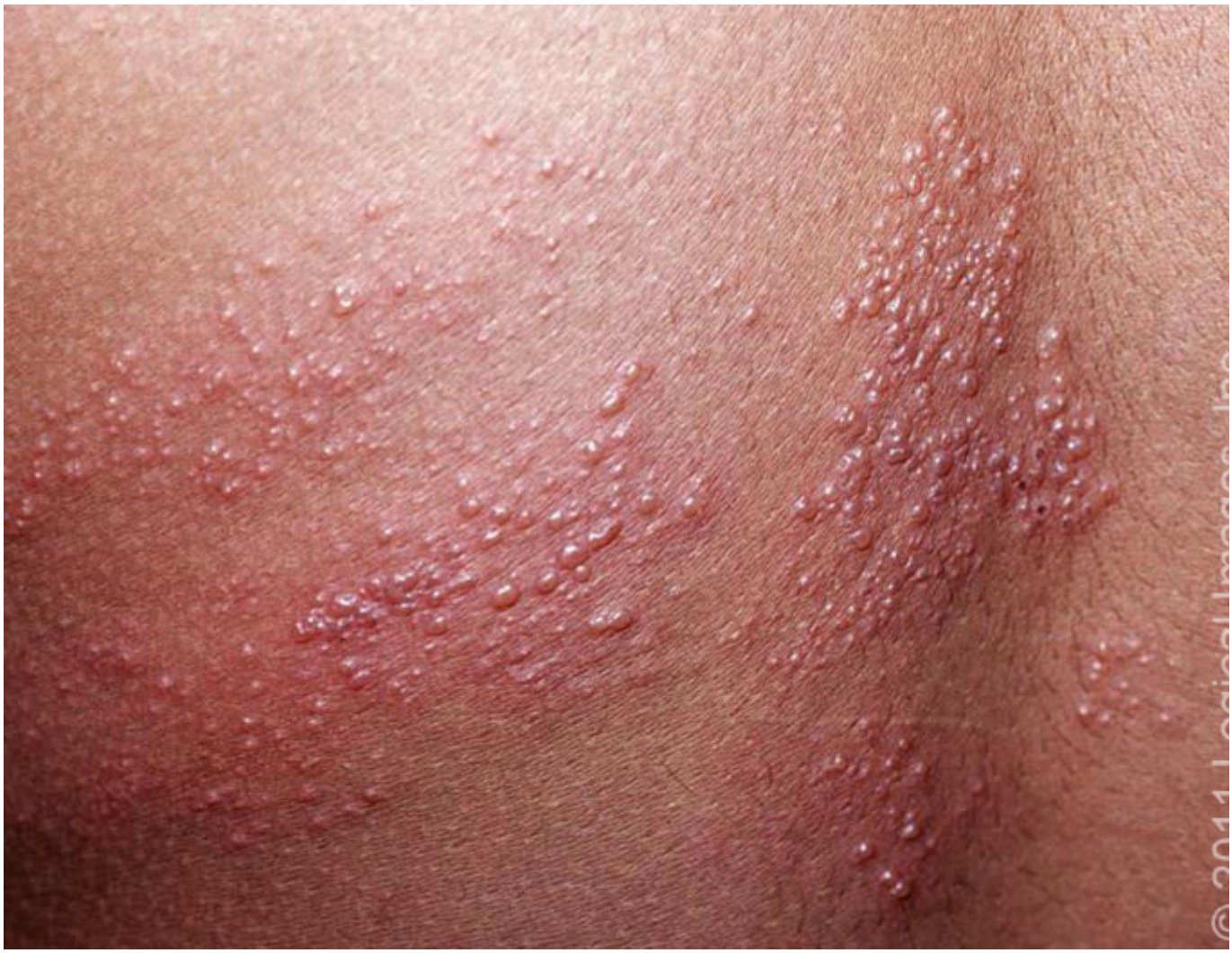
Herpes zoster



Grouped edematous pink papules and early vesicles in the V3 dermatome.

Graphic 119525 Version 1.0

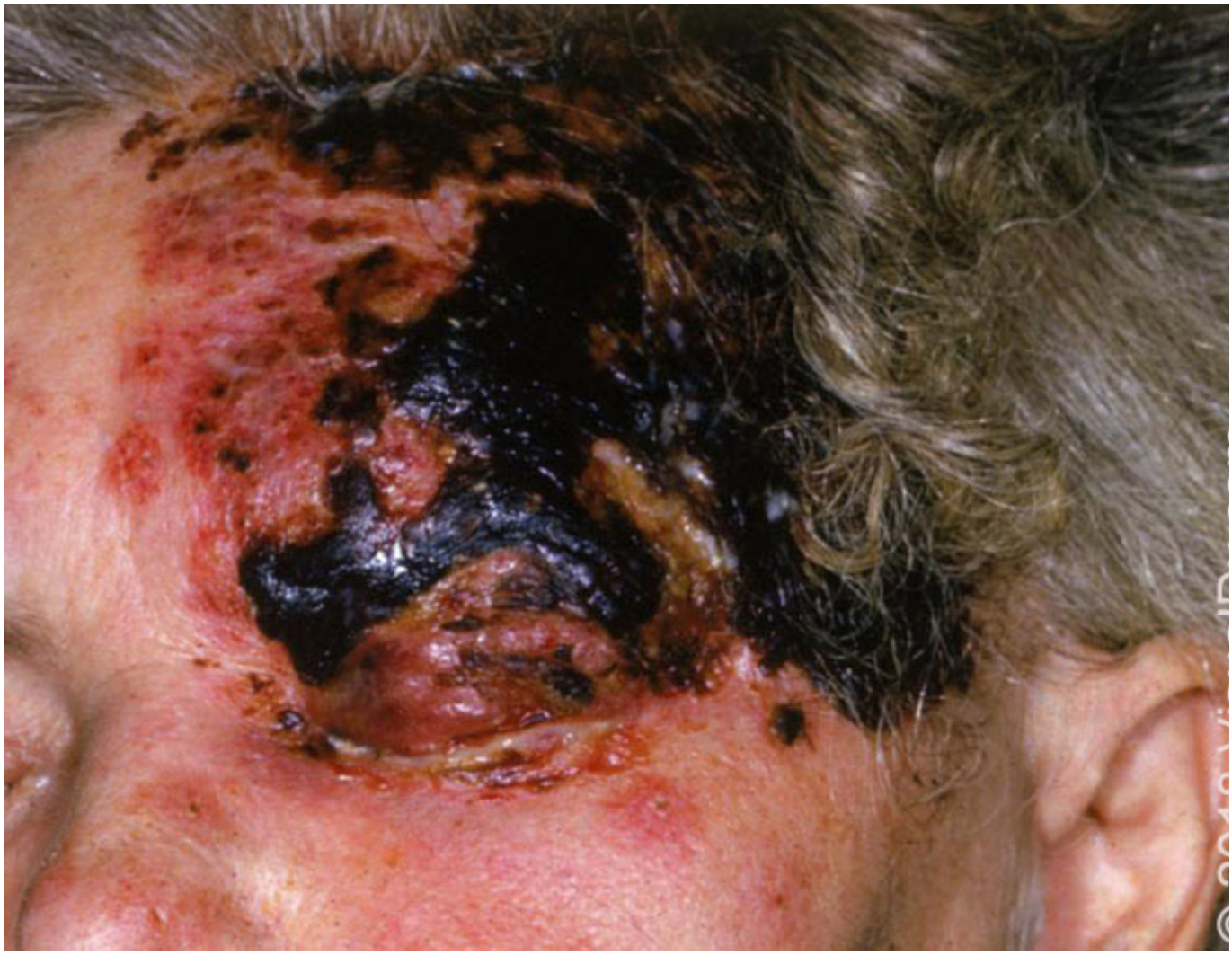
Herpes zoster



Grouped vesicles and underlying erythema are present on the back.

Graphic 58282 Version 6.0

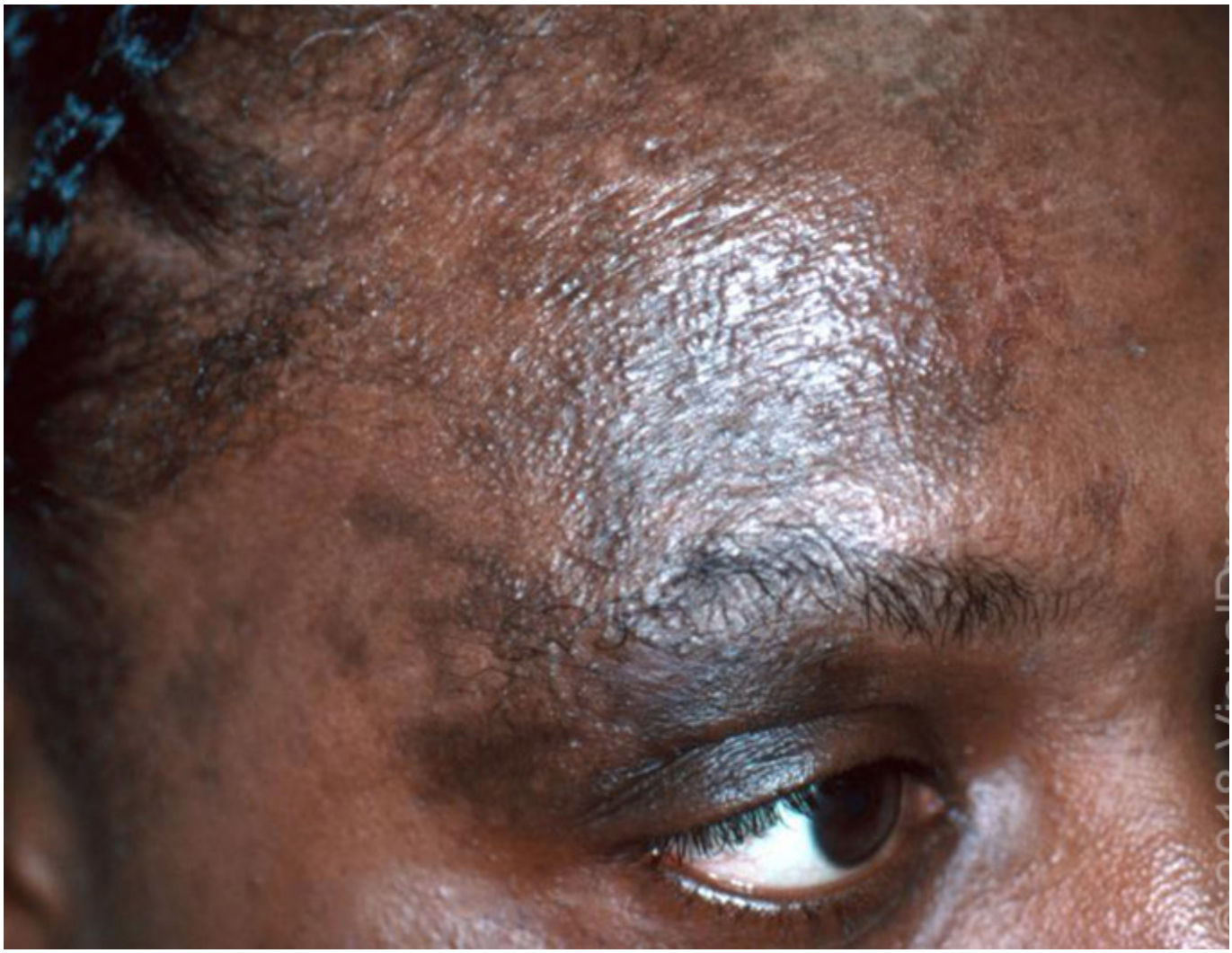
Herpes zoster



A large hemorrhagic crust and smaller surrounding crusts and erythema in the V1 distribution, with cloudy discharge at the eyelid margin signifying eye involvement, in a patient with lymphoma.

Graphic 119543 Version 1.0

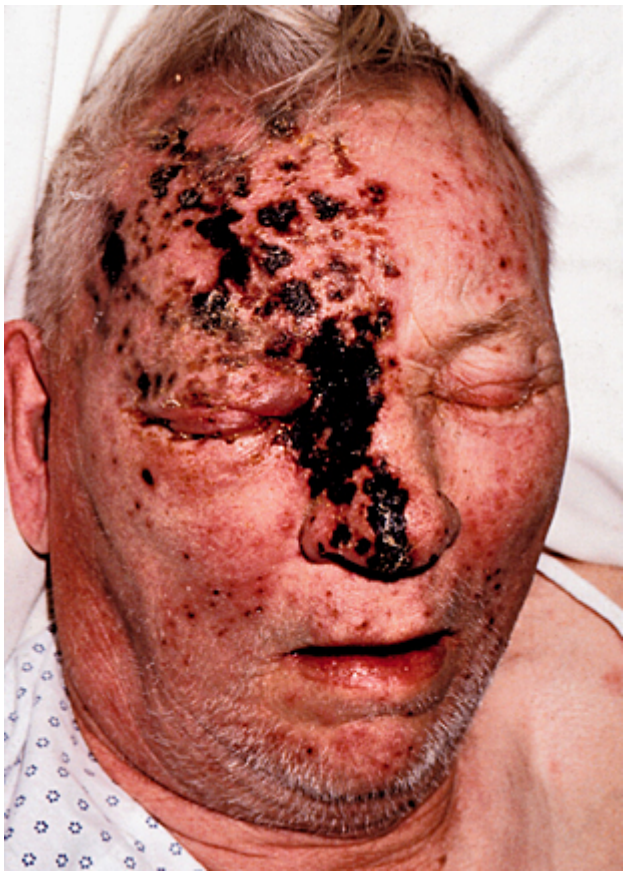
Postinflammatory hyperpigmentation secondary to herpes zoster



Postinflammatory hyperpigmentation in V1 distribution following resolution of herpes zoster.

Graphic 119542 Version 1.0

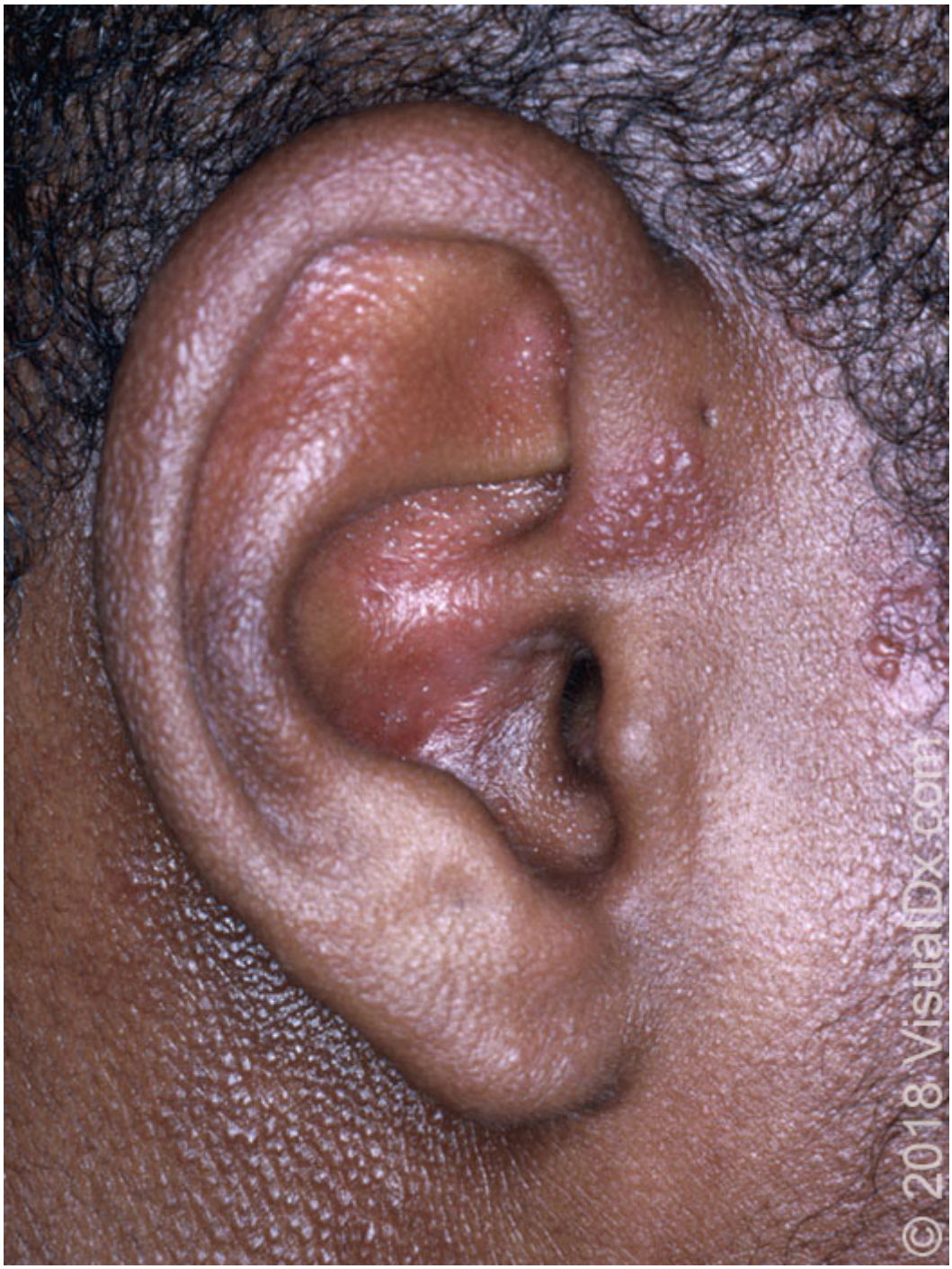
Herpes zoster ophthalmicus



The lesions of herpes zoster progress through stages, beginning as red macules and papules that, in the course of 7 to 10 days, evolve into vesicles and form pustules and crusts (scabs). A common site is the distribution of the ophthalmic division of the trigeminal nerve.

Graphic 74420 Version 10.0

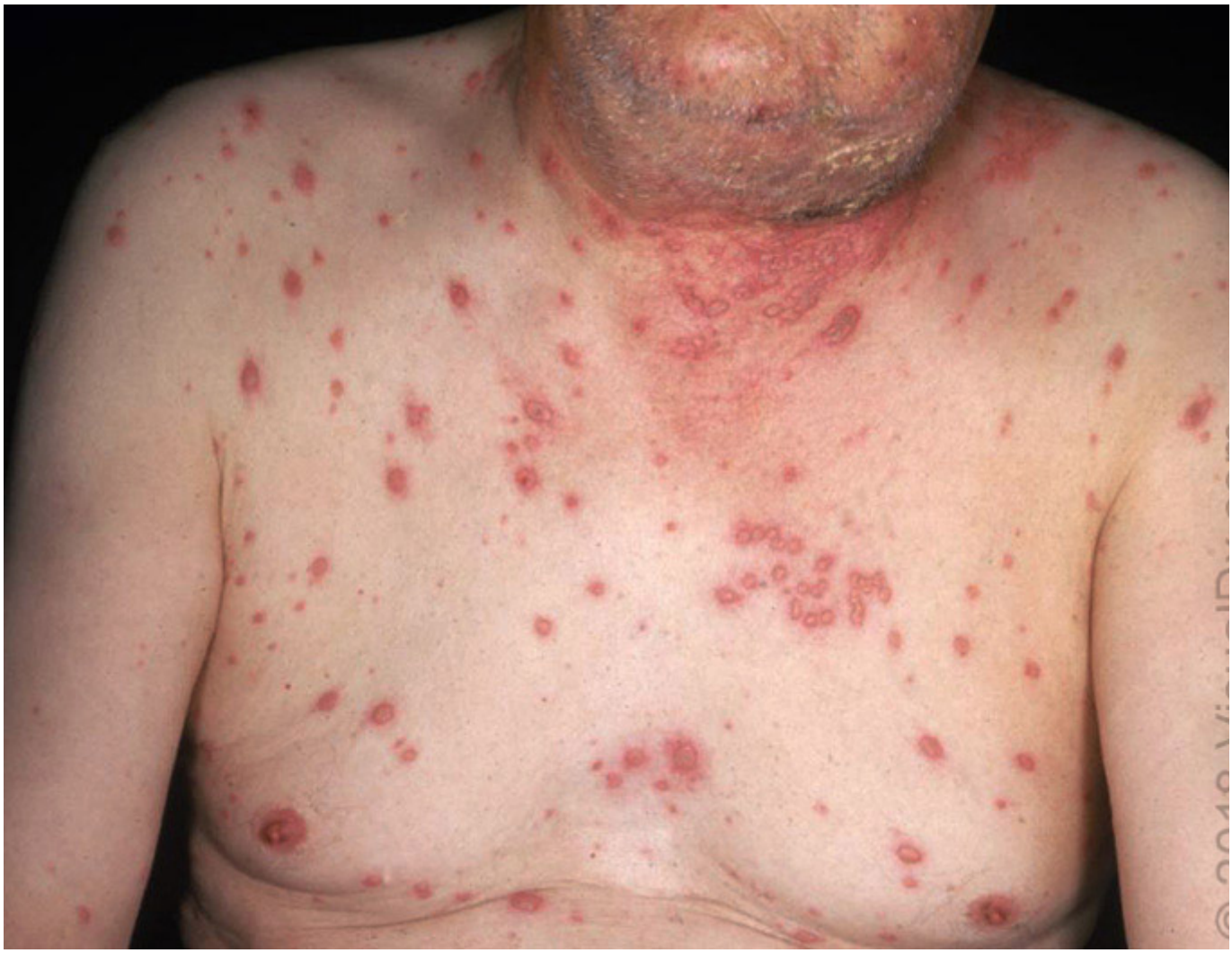
Ramsay Hunt syndrome (herpes zoster oticus)



Grouped vesicles on the auricle.

Graphic 119530 Version 1.0

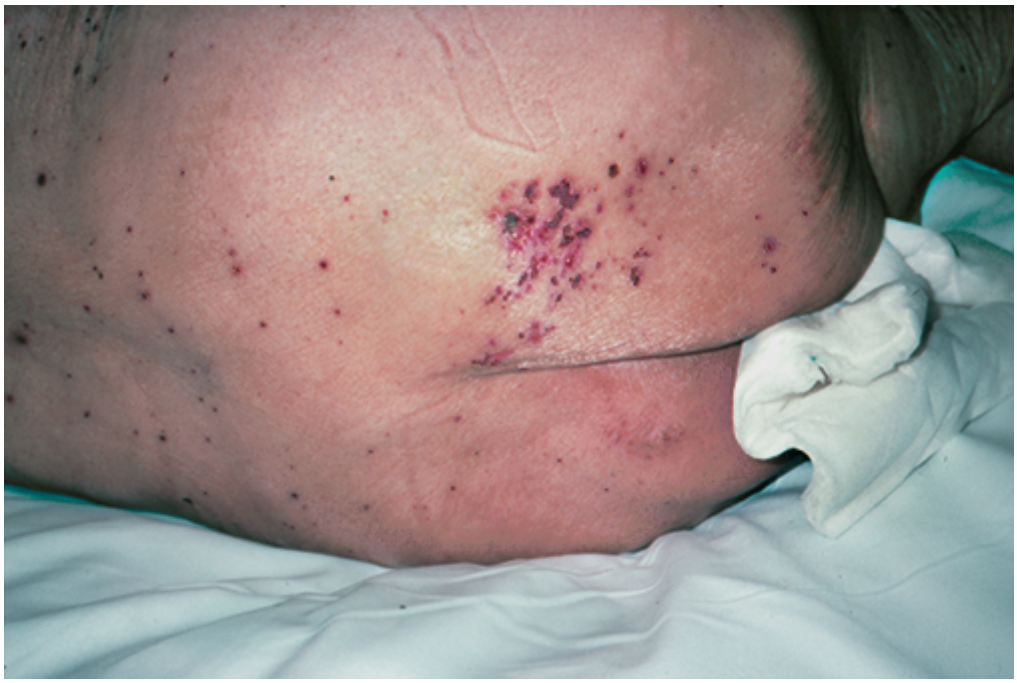
Disseminated herpes zoster



Disseminated zoster in a patient with lymphoma showing many scattered vesicles and crusted papules. Zoster is in the C3 dermatome on the patient's left.

Graphic 119541 Version 1.0

Disseminated herpes zoster



The multiple vesicles and crusts of herpes zoster are not limited to a dermatome.

Reproduced with permission from: Herbert A Hochman, MD. Originally published in Goodheart HP. Goodheart's Photoguide of Common Skin Disorders, 2nd Edition. Philadelphia: Lippincott Williams & Wilkins, 2003.

Graphic 77688 Version 1.0