Varicella-zoster virus (VZV)

Varicella-zoster virus (VZV) causes primary, latent, and recurrent infections. The primary infection is manifested as varicella **(chickenpox)** and results in establishment of a lifelong latent infection of sensory ganglion neurons. Reactivation of the latent infection causes

herpes zoster **(shingles).** Although often a mild illness of childhood, varicella can cause substantial morbidity and mortality in otherwise healthy children. Morbidity and mortality are higher in immunocompetent infants, adolescents, and adults as well as in immunocompromised

persons. Varicella predisposes to severe group A *Streptococcus* and *Staphylococcus aureus* infections. A clinically modified disease can occur among vaccinated persons (breakthrough varicella), usually with milder presentation.

ETIOLOGY

VZV is a **neurotropic** double-stranded DNA herpesvirus with similarities to herpes simplex virus.

EPIDEMIOLOGY

Persons with varicella are **contagious 1-2 day before the rash and until vesicles are crusted**, usually 3-7 days after onset of rash. VZV is transmitted by contact **with oropharyngeal secretions and the fluid of skin lesions** of infected individuals, either by airborne spread or through direct contact.

Herpes zoster is caused by the reactivation of latent VZV. It is not common in childhood and shows no seasonal variation in incidence. Zoster is not caused by exposure to a patient with varicella; in fact, exposures to varicella boost the cell-mediated immune response to VZV in individuals with prior infection, decreasing the likelihood of reactivation of latent virus.

PATHOGENESIS

VZV is transmitted by contact with oropharyngeal secretions and the fluid of skin lesions of infected individuals, either by airborne spread or through direct contact. Primary infection (varicella) results from inoculation of the virus onto the mucosa of the upper respiratory tract

and tonsillar lymphoid tissue. During the early part of the 10-21 day incubation period, virus replicates in the local lymphoid tissue, and then a brief subclinical viremia spreads the virus to the reticuloendothelial system. Widespread cutaneous lesions occur during a 2nd viremic phase that lasts 3-7 days. Peripheral blood mononuclear cells carry infectious virus, generating new crops of vesicles during this period of viremia. VZV is also transported back to the mucosa of the upper respiratory tract and oropharynx during the late incubation period, permitting spread to susceptible contacts 1-2 days before the appearance of rash.

CLINICAL MANIFESTATIONS

I.P. is 10-21 days. Prodromal symptoms begin 24-48 hr before the rash as **fever, malaise, anorexia, headache,** and occasionally mild abdominal pain; these symptoms usually resolve within 2-4 days after the rash.

Varicella lesions often appear first on the scalp, face, or trunk. Initial exanthem consists of intensely pruritic erythematous macules that evolve through the papular stage to form clear, fluid-filled vesicles. While the initial lesions are crusting, new crops form on the trunk and then the extremities; the simultaneous presence of lesions in various stages of evolution is characteristic of varicella. The distribution of the rash is predominantly central or **centripetal** with the greatest concentration on the trunk and proximally on the extremities.

Ulcerative lesions involving the mucosa of the oropharynx and vagina are also common. The exanthem may be much more extensive in children with skin disorders e.g. eczema or recent sunburn. Hypopigmentation or hyperpigmentation of lesion sites persists for days to weeks in some children.

Note: *Varicelliform rashes or "breakthrough varicella" is a mild disease in vaccinated individuals.*

differential diagnosis of varicella includes vesicular rashes caused by other infectious agents, such as herpes simplex virus, enterovirus, monkey pox, rickettsial pox, and *S. aureus;* drug reactions; disseminated herpes zoster; contact dermatitis; and insect bites (especially

for breakthrough varicella). Severe varicella was the most common illness confused with smallpox before the eradication of smallpox.

COMPLICATIONS

The complications of VZV infection occur with varicella or with reactivation of infection, more commonly in immunocompromised patients.

1.Secondary bacterial infections of the skin usually caused by group A *Streptococcus* and *S. aureus*. These range from impetigo to cellulitis, lymphadenitis, subcutaneous abscesses…etc. Bacterial toxin–mediated diseases e.g. toxic shock syndrome may also occur.

2.Encephalitis and Cerebellar Ataxia are well-described neurologic Cxs that are highest among patients <5 yr and >20 yr. Clinical recovery is typically rapid. Nuchal rigidity,

altered consciousness, and seizures characterize meningoencephalitis. Patients with cerebellar ataxia have a gradual onset of gait disturbance, nystagmus, and slurred speech. Neurologic symptoms usually begin 2-6 days after the onset of the rash but may occur during the incubation

period or after resolution of the rash. Clinical recovery is typically rapid, occurring within 24-72 hr, and is usually complete.

Note: *Reye syndrome (hepatic dysfunction with hypoglycemia and encephalopathy) associated with varicella and other viral illnesses e.g. influenza is now rare because salicylates are no longer used as antipyretics in these situations.*

3.***Varicella pneumonia*** is a severe Cx that accounts for most of the increased morbidity and mortality from varicella. Respiratory symptoms, which may include cough,

dyspnea, cyanosis, pleuritic chest pain, and hemoptysis, usually begin

within 1-6 days after the onset of the rash.

4.***Progressive varicella*** with visceral organ involvement, coagulopathy, severe hemorrhage, and continued vesicular lesion development after 1 wk, is a severe Cx of primary VZV infection. Severe abdominal pain, which may reflect involvement of mesenteric lymph nodes or the liver. The appearance of hemorrhagic vesicles in otherwise healthy adolescents and adults, immunocompromised children, pregnant women, and newborns, may herald severe, and potentially fatal, disease.

5.***Other less common & rare Cxs*** include: mild hepatitis, mild thrombocytopenia, nephritis, nephrotic syndrome, HUS, arthritis, myo- carditis, pericarditis, pancreatitis, orchitis, and acute retinal necrosis.

Herpes zoster: VZV is transported in a retrograde manner through sensory axons to the dorsal root ganglia throughout the spinal cord. Herpes zoster is caused by the **reactivation** of latent VZV → vesicular rash that usually is **dermatomal** in distribution. HZ is **very rare** in healthy children <10 yr of age, with the exception of immunocompromised patients or those infected with VZV in utero or in the 1st yr of life. HZ in children tends to be milder than that in adults and postherpetic neuralgia generally does not occur in healthy children.

Neonatal Varicella: Mortality is particularly **high** in neonates born to susceptible mothers who contracted varicella around the time of delivery. Infants whose mothers demonstrate varicella in the period **from 5 days prior to delivery to 2 days afterward** are at high risk for severe varicella. Because the mother has not yet developed a significant antibody response, the infant receives a large dose of virus without the moderating effect of maternal anti-VZV antibody.

Congenital Varicella Syndrome: CVS occurs in ≈ 0.4% of infants born to women who have varicella during pregnancy before 13 wk of gestation and in ≈ 2% between **13 and 20 wk** of gestation; it is rare after 20 wk of pregnancy. CVS is characterized by **cicatricial skin scarring** in a zoster-like distribution; **limb hypoplasia**; and abnormalities of the **neurologic system** (e.g., microcephaly, cortical atrophy, seizures, and mental retardation), **eye** (e.g., chorioretinitis, microphthalmia, and cataracts), **renal system** (e.g., hydroureter and hydronephrosis), and **autonomic** nervous system (neurogenic bladder, swallowing dysfunction, and aspiration pneumonia).

DIAGNOSIS

Dx of varicella is mainly **clinical**; however tests are used for confirmation in atypical cases including:-

1.**CBP**: Leukopenia followed by a relative and absolute lymphocytosis.

2. **Liver** function tests mildly elevated.

3.**CSF** shows profile of viral meningoencephlitis in neurological Cx.

4. **Serology**: 4-fold or greater rise in VZV IgG antibodies is confirmatory of acute infection (but this requires a 2-3 wk delay to collect a convalescent specimen).

5. VZV can be identified ***quickly*** by **direct fluorescence assay** of cells from cutaneous lesions (vesicular fluid) in 15-20 min, by **PCR** amplification testing (vesicular fluid, crusts) in hours to days, and by **rapid culture** with specific immunofluorescence staining in2-3 days.

Note: *Although multinucleated giant cells can be detected with nonspecific stains (**Tzanck smear**), they have poor sensitivity and do not differentiate VZV from herpes simplex virus infections.*

In congenital varicella syndrome, VZV cannot be cultured from affected newborn!, but **viral DNA** may be detected in tissue samples by PCR.

TREATMENT

To be most effective, treatment of Varicella should be initiated **as early as possible**. Oral therapy with **acyclovir** (20 mg/kg/dose; maximum: 800 mg/dose) given as 4 doses/day for 5 daysto treat uncomplicated varicella in individuals at increased risk for moderate to severe

varicella: nonpregnant individuals older than 12 yr of age and individuals older than 12 mo of age with chronic cutaneous or pulmonary disorders; individuals receiving short-term, intermittent, or aerosolized corticosteroid therapy; individuals receiving longterm salicylate therapy; and possibly secondary cases among household contacts. To be most effective, treatment should be initiated as early as possible, preferably within 24 hr of the onset of the exanthem. There is less clinical benefit if treatment is initiated more than 72 hr after

onset of the exanthema. **Famciclovir** or **valacyclovir** in older children who can swallow tablets (these drugs are better absorbed by the oral route than acyclover).

Acyclovir therapy is not recommended routinely by the AAP for Rx of uncomplicated varicella in the otherwise healthy child.

IV therapy is indicated for severe disease and for varicella in immunocompromised patients. Any patient who has signs of disseminated VZV, including

pneumonia, severe hepatitis, thrombocytopenia, or encephalitis, should receive immediate treatment. IV acyclovir therapy (500 mg/m2 every 8 hr) initiated within 72 hr of development of initial symptoms decreases the likelihood of progressive varicella and visceral dissemination

in high-risk patients. Treatment is continued for 7-10 days or until no new lesions have appeared for 48 hr. Foscarnet and cidofovir may be useful for Rx of acyclovir- resistant VZV infections. Rx of Herpes Zoster is the **same** as VZV infection.

Neonates who exposed to maternal varicella 5 days prior to delivery to 2 days afterward should receive varicella-zoster immunoglobulin (**VZIG**) or **IVIG** (although less effective) with **IV acyclovir** (which may be delayed until the rash develop).

To prevent **congenital varicella syndrome**, VZIG has often been administered to the susceptible mother exposed to varicella to modify maternal disease severity. Similarly, acyclovir may be given to the mother with severe varicella.

Note: *Because the damage caused by fetal VZV infection does not progress in the postpartum period, antiviral Rx of infants with CVS is not indicated.*

PROGNOSIS

Primary varicella has a mortality rate of 2-3 per 100,000 cases, with the lowest case fatality rates among children 1-9 yr of age (~1 death per 100,000 cases). Compared with these age groups, infants have a 4 times greater risk of dying and adults have a 25 times greater risk of

dying. The most common complications among people who died from varicella were pneumonia, central nervous system complications, secondary infections, and hemorrhagic

conditions. The mortality rate of untreated primary infection is 7-14% in immunocompromised children and may approach 50% in untreated adults with pneumonia.

Herpes zoster among healthy children has an excellent prognosis and is usually self-limited. Severe presentation with complications and sometimes fatalities can occur in immunocompromised children.

PREVENTION

VZV transmission is difficult to prevent because a person with varicella is contagious for 24-48 hr before the rash.

Varicella vaccine can be administered as a monovalent vaccine or as MMRV vaccine as a 2 dose regimen at ages 12-15 mo and 4-6 yr. It is recommended that varicella and MMR vaccines either be administered simultaneously at different sites or be given at least 4 wk apart (because if given in <4 wk, it may be associated with higher risk for breakthrough varicella).

Postexposure Px: **Vaccine** given to healthy children **within 3 or 5 days** after exposure is effective in preventing or modifying varicella. Oral **acyclovir** administered late in the incubation period also may be of benefit. **VZIG** is recommended as postexposure Px for immunocompromised children, pregnant women, and newborns exposed to varicella.