Varicella-Zoster Virus Pneumonitis*

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Varicella-zoster virus (VZV) infection occurs primarily as chickenpox or herpes zoster. The VZV infection is generally considered self-limiting, with little associated morbidity and mortality. Fatal infections due to VZV were reported in the latter years of the 19th century and early in the 20th century. It was not until 1942 that VZV pneumonitis was recognized as a clinical entity with potentially lethal effects in otherwise healthy adults. Today, this complication is regarded as the most serious manifestation of disseminated VZV infections. Reviewed herein is the epidemiology, pathology, clinical features (including radiographic hallmarks), complications, treatment, and prevention of VZV pneumonitis.

EPIDEMIOLOGY

In 1953, a few years after the introduction of steroid compounds into clinical medicine, a corticosteroid-treated patient with acute rheumatic fever developed fatal hemorrhagic varicella. Over the next four decades, VZV pneumonitis became recognized as a relatively common disorder in patients with compromised immunity (Table 1). Bone marrow transplant recipients and children with cancer are at the highest risk for this complication, as illustrated by the 32 percent and 20 percent incidence rate in children with leukemia and solid tumors, respectively. Among transplant recipients with primary varicella or varicellalike eruptions (positive pretransplant serologic findings or history and a diffuse rash lacking a dermatome distribution), dissemination to the lungs approaches 50 percent. Severe and often fatal varicella has also been reported in recipients of renal and liver transplants, as well as in patients with HIV infection.

The risk of herpes zoster is highest in patients who have received bone marrow transplants and individuals with Hodgkin’s disease (approximately 50 percent), but it is considerably lower in those with acute leukemia or solid tumors (20 percent and 10 percent, respectively). It is important to note that dissemination to the lungs is rare in immunocompromised patients with herpes zoster (5 percent to 10 percent).

The VZV-related mortality among neonates born to mothers who develop varicella within 4 days of delivery or 2 days postdelivery, or neonates developing infection at 5 to 10 days of age, is 25 percent. By contrast, infants with VZV infection during the first 4 days of life (as a result of maternal transfer of VZV antibody 5 or more days before delivery) rarely die of the infection. Brunell hypothesized that the early production and placental transfer of VZV antibody modify the infection in newborns. Thus, newborns who lack maternal VZV antibody are at high risk for fatal infection during the first 5 to 10 days of life. Otherwise healthy full-term infants who contract varicella after 2 weeks of life have sufficient immune responses to prevent dissemination of the infection. Hospitalized small premature infants (≤28 weeks’ gestation or birth weight ≤1,000 g), irrespective of maternal history, and hospitalized premature infants (>28 weeks’ gestation) with a negative history of maternal varicella are also considered at high risk for severe varicella.

Although varicella in adults accounts for only 2 percent of the estimated 3 to 4 million annual cases in the United States, 25 percent of the fatalities occur in this age group, reflecting a higher complication rate as compared with children. The incidence of varicella pneumonia in otherwise healthy adults has been estimated to range from 10 percent to 50 percent. However, several very recent studies suggest that the incidence in adults may be much lower: 5 percent or less. Interestingly, some reports have indicated that 50 percent of cigarette smokers with varicella develop pneumonia, in contrast to only 3 percent (or fewer) of their nonsmoking counterparts. Untreated adult varicella pneumonia is fatal in approximately 10 percent of cases. Although pregnant and postpartum women have an increased risk of VZV pneumonitis, the incidence rates in these subgroups are unknown. However, the mortality rate is approximately 40 percent, exceeding estimates for otherwise normal healthy adults while corresponding to rates reported for patients with cancer and bone marrow transplant recipients.

Corticosteroid therapy as administered to patients with underlying renal, collagen-vascular, or other disorders (Table 1) has been associated with an increased risk of VZV pneumonitis. Several recent

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Table 1—Factors Contributing to an Increased Risk for Development of VZV Pneumonitis

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Cancer</td>
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<td>Bone marrow transplant</td>
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<td>Solid organ transplant</td>
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<td>Prolonged treatment with corticosteroids, cytotoxic or radiation therapy</td>
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<tr>
<td>Limited corticosteroid therapy for acute asthma</td>
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<tr>
<td>Topical nasal corticosteroids for sinusitis</td>
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<tr>
<td>Prolonged use of inhaled steroids for asthma</td>
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<tr>
<td>Acquired immunodeficiency syndrome</td>
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<tr>
<td>Congenital immunodeficiencies</td>
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<tr>
<td>Cigarette smokers</td>
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<tr>
<td>Pregnancy and postpartum period</td>
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<tr>
<td>Premature births and newborn status</td>
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reports have indicated that conventional “low-dose” corticosteroid therapy (<2 mg/kg/d or 5 to 20 mg/d), topical nasal corticosteroids for chronic sinu-
sitis, and short-course corticosteroid therapy for acute attacks of asthma (when administered during the incubation period of varicella) may predispose to disseminated varicella. Although cystic fibrosis has not been associated with severe varicella, it does appear that the viral infection exacerbates the underlying pulmonary condition.

PATHOLOGY

On gross pathologic examination, the lungs are firm, heavy, and plum colored. There are numerous scattered necrotic and hemorrhagic foci in a distribution resembling the poxlike lesions of the skin (Fig 1). Microscopically, the necrotic foci involve the alveolar walls, blood vessels, and small bronchioles. In the most recently affected areas, eosinophilic intranuclear inclusions (Cowdry’s type A) and syncytial giant cells are identified. Electron microscopy of these areas reveals herpes virus particles. Other findings include interstitial pneumonia, mononuclear cell infiltrates with intra-alveolar fibrous exudates, hemorrhage, and hilar membranes. In some instances, there is early interstitial fibrosis. Occasionally, there are features of necrotizing bronchitis/bronchiolitis.

RADIOPHIC FEATURES

Chest radiographs of VZV pneumonitis typically show ill-defined nodular or reticular densities of various sizes scattered throughout both lung fields (Fig 2). Initially, the nodules are 2 to 5 mm in diameter and are best visualized in the periphery of the lung, away from the normal vascular markings, or in the lateral view of the chest radiograph. With progressive disease, the nodules enlarge and coalesce, forming extensive infiltrates. In the milder cases, the infiltrates may resolve in 3 to 5 days; however, in

FIGURE 1. Gross appearance of the lung in varicella pneumonia. Scattered throughout the lungs are necrotic and hemorrhagic foci, resembling poxlike lesions of the skin. Blood in the trachea and larynx is indicative of massive pulmonary hemorrhage, a frequent terminal event. (Reprinted with permission.)

FIGURE 2. Chest roentgenogram showing diffuse “fluffy” nodular infiltrates of varicella pneumonia. (Reprinted with permission.)
widespread severe disease, the radiographic abnormalities may persist for several weeks.

**Clinical Features**

Fever, cough, dyspnea, tachypnea, chest pain, and hemoptysis are the hallmarks of severe VZV infection in the lungs. Early clues to pneumonia in subjects at risk are continued eruption of new lesions, persistent fever, and new-onset cough. The development of varicella pneumonia in the absence of fever and after the cessation of new lesion formation is exceedingly rare. In 50 percent to 75 percent of subjects, pneumonia is accompanied or preceded (for 1 to 2 days) by severe and often unremitting abdominal and/or back pain. These complaints are not related to overlying skin lesions or specific organ invasion by the virus but likely represent neuralgia, either virologic or immunologic in origin.

In two large studies of varicella in immunocompromised hosts, new lesions appeared for 7 to 14 days, usually accompanied by fever. The mean (±SE) time to onset of pneumonia was 5.8 ± 1.9 days. There was no indication that the degree of risk for pneumonia was related to either the onset or duration of immunosuppressive therapy during the month preceding infection. Moreover, the course of varicella was uncomplicated in children who had completed anticancer therapy a month or more before infection. The best predictor of pneumonitis was the absolute lymphocyte count (ALC) at the onset of infection. Varicella-zoster virus pneumonia developed in 48 percent of children with cancer and an ALC of less than 500 cells per microliter, compared with only 21 percent in children with cancer and an ALC of greater than 500 cells per microliter. As the ALC declined, the risk for lung dissemination increased, reaching 71 percent at an ALC of less than 100 cells per microliter. Similarly, the risk of mortality increased from 7 percent in children with an ALC of greater than 500 cells per microliter to 29 percent in those with an ALC of less than 100 cells per microliter. Viremia often accompanies pneumonia in immunocompromised patients and may persist for as long as 10 days before death from respiratory failure and pulmonary hemorrhage (S.F., unpublished data, 1975).

In the era before antiviral therapy, the pulmonary course of VZV infection in asymptomatic or mildly symptomatic subjects did not persist beyond 3 to 5 days. For subjects with moderate or severe illness, death from pulmonary failure and/or other pulmonary complications occurs within 3 to 4 days of pneumonia onset. For the survivors who do not progress to frank pulmonary failure, clinical improvement is usually apparent by 5 to 7 days. In cases of respiratory failure, the mortality rate approaches 50 percent (S.F., unpublished data, 1975), despite intervention with assisted ventilation and intensive pulmonary management, including antiviral therapy.

Although the clinical course of varicella pneumonia in adults is similar to that in the immunocompromised host, there are notable exceptions. The eruption of new lesions in adults generally extends over 3 to 5 days, compared with 7 to 14 days in patients with inadequate immunity. Whereas pneumonia usually develops within the first 3 days of rash in adults, it requires 5 to 7 days in immunodeficient hosts. Pneumonia is symptomatic in about 10 percent of adults, in contrast to 75 percent of children with cancer (S.F., unpublished data, 1975). The adult smoker should be considered at increased risk for varicella pneumonia, especially for symptomatic and severe involvement.

**Treatment**

**Antiviral Therapy**

Acyclovir is preferred over vidarabine as treatment for VZV infections. It has been more effective in shortening the cutaneous course of VZV infection in the immunocompromised patient. In children with cancer and varicella, there was no evidence of VZV pneumonitis after 2 days of acyclovir therapy, whereas 30 percent of the vidarabine recipients developed the pulmonary complication pneumonitis. Other advantages of acyclovir are reduced hematopoietic and neurologic toxic reactions, shorter infusion time (1 h vs 12 h for vidarabine), and increased solubility (7 mg/ml vs 0.5 mg/ml for vidarabine). The preferred route of administration for acyclovir for the treatment of VZV pneumonitis is intravenous. To my knowledge, there is no information on the treatment of VZV pneumonitis with oral acyclovir.

The overall mortality for VZV pneumonitis in immunocompromised and immunocompetent hosts treated with acyclovir ranges from 10 percent to 20 percent. For patients in respiratory failure, the mortality approaches 50 percent (S.F., unpublished data, 1975). Pregnant women and cigarette smokers also appear to be at increased risk for fatal pneumonia. A recent study from the Acyclovir Registry of Burroughs Wellcome Co (Research Triangle Park, NC) found there was no indication of an increased risk for birth defects in the fatal wastage of 601 women who had received acyclovir during pregnancy for herpes infection.

Vidarabine and foscarnet have also been used to treat VZV infection, but with much less success than that reported with acyclovir. Recommended dosages of these drugs are listed in Table 2.
Table 2—Antiviral Therapy for VZV Infections*

<table>
<thead>
<tr>
<th>Infection</th>
<th>Drug</th>
<th>Dosage</th>
<th>Duration</th>
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<tbody>
<tr>
<td>VZV pneumonitis</td>
<td>Acyclovir, IV</td>
<td>30 mg/kg/d, divided every 8 h</td>
<td>Depends on clinical course</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1,500 mg/m²/d) divided every 8 h for children ≤12 yr</td>
<td></td>
</tr>
<tr>
<td>Varicella in the immunocompromised host</td>
<td>Vidarabine, IV</td>
<td>10 mg/kg/d infused over 12 h</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>Foscarnet, IV</td>
<td>40 mg/kg/d divided every 8 h</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>Acyclovir, IV</td>
<td>30 mg/kg/d, divided every 8 h</td>
<td>5-7 d (at least 2 d without fever and new lesions)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1,500 mg/m²/d) divided every 8 h for children &lt;12 yr</td>
<td></td>
</tr>
<tr>
<td>Varicella in the immunocompetent host</td>
<td>Vidarabine, IV</td>
<td>10 mg/kg/d infused over 12 h</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>Foscarnet, IV</td>
<td>40 mg/kg/d divided every 8 h</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>Acyclovir, PO</td>
<td>20 mg/kg per dose qid for children, 800 mg per dose qid for adolescents; 800 mg per dose five times a day for adults</td>
<td>5 d</td>
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</table>

*IV=intravenous; PO=oral; qid=four times daily.

Corticosteroid Therapy

The role of corticosteroids in the treatment of severe VZV pneumonia remains controversial. Because of their impairment of the host response to infection, corticosteroids are contraindicated for most cases of herpes virus infection with pulmonary involvement. However, there are reports of improvement in severe pneumonitis following corticosteroid therapy. When used in conjunction with specific antiviral therapy, the role of corticosteroids in limiting lung damage during the resolution phase of pneumonia is uncertain.

PROPHYLAXIS

For more than two decades, high-titered VZV antibody preparations have been available for the prevention of varicella in persons at increased risk for severe or fatal infection. Varicella-zoster immune globulin (VZIG), the most widely used preparation, will reduce the incidence of clinical varicella by 50 percent if administered within 72 to 96 h of exposure. In the remaining subjects, the disease is usually subclinical or mild; however, small percentages of patients with childhood cancer who develop varicella after VZIG prophylaxis may also develop pneumonitis. This subgroup should be treated with acyclovir. Additional information on the use of VZIG in clinical settings can be obtained from previously published guidelines. A recent uncontrolled, nonrandomized study from Japan suggests that oral acyclovir, begun on or between days 7 through 9 of the incubation period and administered for 7 days, prevents varicella. Controlled studies to establish the prophylactic value of oral acyclovir are warranted.

It is anticipated that in the near future, a live attenuated varicella vaccine will be licensed for use in the United States. As recently reported by Gershon et al., the vaccine is safe, immunogenic, and efficacious in otherwise normal, healthy children, although in adults the results are less encouraging. For seroconversion rates of more than 90 percent, children require one dose while adults require two doses. Adverse reactions, such as generalized rashes, injection site rashes, and discomfort, are more frequent in adults than in children. Protection is approximately 70 percent in adults compared with 90 percent in children, and antibody persistence is found in only 75 percent of adult vaccinees after several years compared with more than 90 percent at 10 years for children.

COMPlications

Bacterial infection or sepsis due to superinfection of the lung or skin can be expected in about 25 percent of patients with VZV pneumonia. In the febrile patient with adequate neutrophils (>500 to 1,000 cells per microliter), Gram-positive cocci are the leading cause of infection. As neutrophil count declines below 500 cells per microliter, the risk for infection increases, as does the risk for enteric Gram-negative bacilli and fungi. Patients receiving ventilatory support are at very high risk for nosocomial infections. Although the thrombocytopenia accompanying varicella is usually mild and not associated with bleeding, a notable exception occurs in the host with simultaneous bone marrow failure and severe thrombocytopenia. Pulmonary hemorrhage, a common end-stage complication, can result from the diffuse injury and focal necrosis involving large blood vessels, and it is often accompanied by disseminated intravascular coagulopathy. Other complications include the syndrome of inappropriate antidiuretic hormone secretion and pulmonary embolus. In the ventilated patient, these complications include pneumomediastinum and pneumothorax.
LONG-TERM PULMONARY SEQUELAE

Limited information is available on the pulmonary status of patients who recover from VZV pneumonia. Mild diffusion defects and exercise intolerance have been found in some patients from several months to up to 2 years following the infection. Miliary pulmonary calcifications on chest radiographs have been noted in both children and adults. In many instances, these patients had no recollection of symp- tomatic VZV pneumonia complicating their chickenpox. In one case, histologic examination of residual pulmonary lesions apparent on chest radiographs revealed necrotizing granulomas with a mononuclear infiltrate and a fibrous capsule. Lung function and chest radiographs were evaluated in 11 children with acute lymphoblastic leukemia who survived VZV pneumonia in the era before effective antiviral therapy. Only one of the subjects had severe pneumonia requiring ventilatory assistance. This child and two others (27 percent of the series) had mild restrictive lung defects with normal gas exchange. The patient with severe pneumonitis had restrictive changes at 6 months postdiagnosis that had improved by 2 years. Serial chest radiographs revealed increased interstitial markings but no granulomas or calcifications. The other ten children had normal radiographic findings.

REFERENCES
2 Josserand P, de l'Hermitziere, Vacher. Varicella mortelle a forme hemorragique dans le decours d'un traitement par cortisones-ACTH. Pedriatrie 1953; 8:947-48


