Smallpox Vaccination: The Risks for Patients With Atopic Dermatitis

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Because of recent threats of bioterrorism, smallpox vaccination was reinstated in the United States earlier this year. Since January 2003, more than 35,000 civilian and public health care workers in 54 jurisdictions have been vaccinated.

Despite its legacy of success, which culminated in the worldwide eradication of naturally occurring smallpox by 1980, smallpox vaccination has the potential to cause numerous adverse events, especially in the growing population of persons who are immunosuppressed as a result of transplantation, chemotherapy, HIV infection, or-most commonly-atopic dermatitis (AD). Young children with AD are at heightened risk for eczema vaccinatum, a potentially life-threatening complication of smallpox vaccine exposure. Because an estimated 7% to 17% of American children aged 5 to 9 years have AD, it is especially important to understand the risks smallpox vaccination poses to this population. Here we focus on eczema vaccinatum and discuss how to manage and prevent it.

NORMAL HOST RESPONSE TO THE SMALLPOX VACCINE
The smallpox vaccine does not contain the variola virus, the causative agent of smallpox; instead, it is derived from live vaccinia virus. All US vaccine formulations contain the New York City Board of Health vaccinia strain.

In the normal host response that follows primary vaccination, viral replication and shedding occurs at the vaccination site 2 to 5 days after vaccination and continues until the scab separates from the skin approximately 2 to 3 weeks after vaccination. Because the period of local viral shedding is prolonged, the virus can be inadvertently transmitted to distant sites on the vaccinee as well as to his or her close contacts.

DANGERS OF SMALLPOX VACCINATION IN PERSONS WITH AD
Exposure to the vaccinia virus contained in the smallpox vaccine is contraindicated in persons with a variety of health conditions. These include a history of AD, irrespective of disease severity or activity, and close contact with persons who have AD.

AD usually begins in infancy; this chronic inflammatory skin disease is characterized by severe itching, erythema, and excoriations. Lesions most commonly appear on the face, hands, and the flexural areas, such as the elbows and knees. Patients with AD have several immunologic defects that may contribute to their susceptibility to the development of adverse reactions to smallpox vaccination. First, atopic skin possesses type 2 helper T cells that produce higher levels of the cytokine interleukin-4 and lower levels of interferon-gamma. This cytokine profile is believed to permit the unchecked proliferation of viruses in vivo. Patients with AD also have a reduced ability to generate the cytotoxic T cells that are important in combating viral replication. Furthermore, investigators have recently discovered that the cytotoxic T cells in patients with AD appear to have depleted supplies of perforin granules, which play an important role in the antiviral cytolytic activity of these cells.

In addition to the abnormal cellular immunity of patients with AD, defects in these patients' innate immune response may also allow for uncontrolled viral replication and spread. AD keratinocytes express decreased levels of antimicrobial peptides that may play an important role in the innate immune response to viral infections.

It is important not to confuse AD with eczema. Eczema is a generic term that encompasses a wide variety of dermatologic conditions, including allergic contact dermatitis, xerotic dermatitis, nummular dermatitis, and many others-as well as AD. Patients with other types of eczema (eg, that...
caused by poison ivy) have no increased risk of serious complications of smallpox vaccination once the lesions associated with their condition have healed. Patients with AD, on the other hand, have a lifelong increased risk of eczema vaccinatum developing.

**ECZEMA VACCINATUM**

**Presentation and prognosis.** Eczema vaccinatum can develop in any person with active AD or with a history of the disease who is vaccinated against smallpox—or who has been inadvertently inoculated. Erythematous papules, vesicles, or pustules develop 5 to 19 days after suspected exposure—often in the areas of active dermatitis or in previously involved skin (Figure). Patients are often systemically ill with fever, lymphadenopathy, and fluid/electrolyte abnormalities; these symptoms are a result of exfoliative dermatitis skin loss similar to that seen in burn victims. Eczema vaccinatum can also lead to such complications as nosocomial bacterial and fungal infections.

**Morbidity and mortality.** Eczema vaccinatum can develop in patients with AD who have either active or remitting disease. It occurs more frequently in younger children, through both accidental transmission and intentional vaccination, and it has a significant case-fatality rate. No cases of eczema vaccinatum were reported in the 32,644 Americans who received smallpox vaccinations between January 24 and April 13, 2003. However, toward the end of the period of routine vaccination of the general population in the United States, 123 cases of eczema vaccinatum were seen per million primary vaccinees, with a case fatality rate of about 1%. The disease was most common in younger children who had not been previously immunized; it has not resulted in a single adult death. Similar data from England show that eczema vaccinatum developed in 185 of 6.5 million Britons vaccinated, with a fatality rate of approximately 6%. Here, too, the disease was more common in children aged 1 to 5 years. It developed as a result of accidental inoculation from close contact with vaccinees in 65% of cases. Although the older US data did not contain information on the specific dermatologic condition of the patients with eczema vaccinatum (except to note that persons with "obvious and severe eczema" were rarely vaccinated), the data from England did. Of those Britons in whom eczema vaccinatum developed, 80% had a history of AD and about 67% of these persons had inactive skin disease at the time of exposure. Thus, the risk of eczema vaccinatum does not correlate with the severity or activity of AD.

Eczema vaccinatum mortality appears to be related to an inability to mount an effective neutralizing antibody response. Approximately 83% of patients with eczema vaccinatum whose neutralizing antibody titers were less than 1:2 died of the disease, whereas fewer than 2% of patients whose neutralizing antibody titers were greater than 1:4 died. It is not known whether a deficit of neutralizing antibodies is caused by a deficiency in B-cell immunity or whether it stems from an underlying defect in T-cell immunity that results in the loss of T-cell-dependent antibody production.

**Prevention and management.** If smallpox vaccination is being considered in a person who has an eczematous skin condition—or a history of such a condition—and there is any question about the diagnosis, refer him to a dermatologist. After the patient has been vaccinated, apply a semipermeable dressing to the vaccination site. To avoid transmission of the vaccinia virus from vaccinees to their close contacts—and to prevent accidental autoinoculation—instruct vaccinees to immediately wash their hands with warm soapy water or hand rubs containing more than 60% alcohol whenever they touch their vaccination sites. Used bandages should be placed in sealed plastic bags before disposal. Although no standard of therapy exists for adverse reactions to smallpox vaccination, patients in whom eczema vaccinatum develops generally require critical care that includes supportive skin care, antibiotics, antifungal medications, and vaccinia immunoglobulin therapy. Aside from supportive care, the use of vaccinia immunoglobulin and cidofovir offer the most favorable outcomes. Vaccinia immunoglobulin, first introduced in 1959 by Kempe, is a sterile solution of pooled immunoglobulin from the plasma of highly immune smallpox-vaccinated persons. Vaccinia immunoglobulin can be delivered intramuscularly (in a preparation that contains 0.01% thimerosal as a preservative) or intravenously (in a preparation that does not contain thimerosal). Contraindications to vaccinia immunoglobulin therapy include allergy to thimerosal, severe reaction to human immunoglobulin, and IgA deficiency (because of the increased risk of anaphylaxis). Pregnancy or breast-feeding are relative contraindications, because the effect of vaccinia immunoglobulin on a fetus or a newborn is unclear.

Cidofovir, a nucleotide analog of cytosine, has antiviral activity and is currently FDA-approved for the treatment of cytomegalovirus retinitis in AIDS patients. Because cidofovir's efficacy in vaccinia-specific complications is unknown, it is indicated only for patients in whom vaccinia immunoglobulin treatment fails, to whom vaccinia immunoglobulin is unavailable, or who have a...
likely fatal prognosis. The most common side effect of cidofovir is renal failure. Both vaccinia immunoglobulin and cidofovir can be requested under the "investigational new drug" protocol by calling the CDC's smallpox vaccinee adverse events clinician information line at 877-554-4625.

**References:**


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