Management of Smallpox Vaccine Adverse Events

Department of Health and Human Services
Centers for Disease Control and Prevention
February 2003

Today, Dr. Lane will be discussing the clinical management of the adverse events described in Dr. Rotz's segment.

Management of Smallpox Vaccine Adverse Events

- Learning Objectives:
  - Describe the treatment and management of vaccinia adverse events (AEs)
  - Describe the use of Vaccinia Immune Globulin (VIG) and Cidofovir

This segment is designed to discuss the treatment of adverse events as suggested by the MMWR article, as well as the appropriate use of VIG and Cidofovir.

Adverse Events Associated with Smallpox Vaccine

- Inadvertent inoculation
- Ocular vaccinia
- Generalized vaccinia
- Eczema vaccinatum
- Progressive vaccinia
- Post-vaccinial Encephalopathy
- Encephalomyelitis
- Fetal Vaccinia

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As discussed in the previous segment, adverse events associated with smallpox vaccination range from mild and self-limited to severe and life threatening. Vaccinia–specific complications may occur in vaccinees or their contacts that have been inadvertently inoculated with vaccinia.

We will look at the management of these and other common issues with vaccinia vaccine in the next few minutes.

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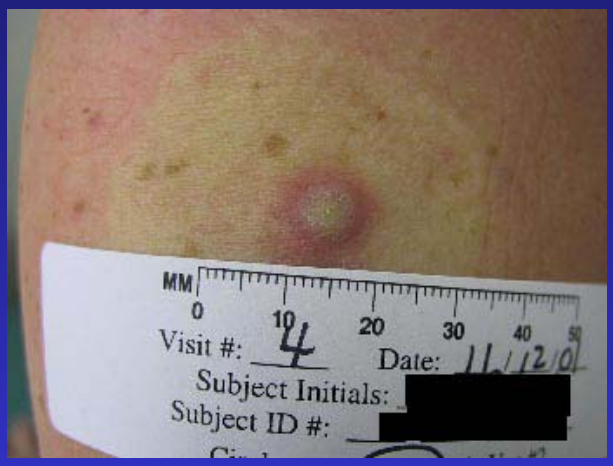
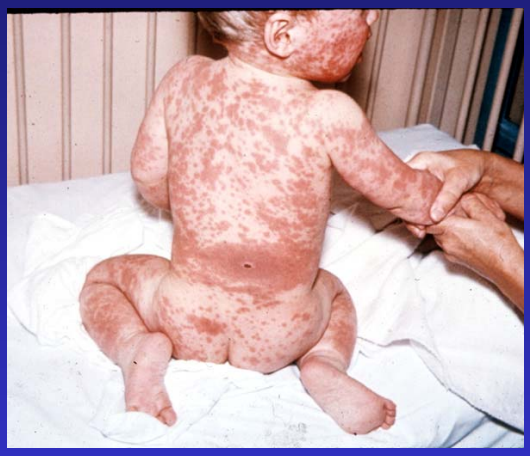
Local Skin Reactions
Irritation from Adhesive Dressing



Local skin reactions, while annoying, do not usually cause systemic symptoms and do not require much medical intervention.

Treatment includes oral nonsteroidal anti-inflammatory agents, or NSAIDS, and oral antipruritic agents. Frequent dressing changes, dressing holiday in other words, leaving the vaccination site open to air, or a change to paper tape may alleviate symptoms. Topical and oral steroid treatment for this reaction should be avoided since the site contains live vaccinia virus. Salves or ointments, including topical antibiotics, should not be applied to the vaccination site.

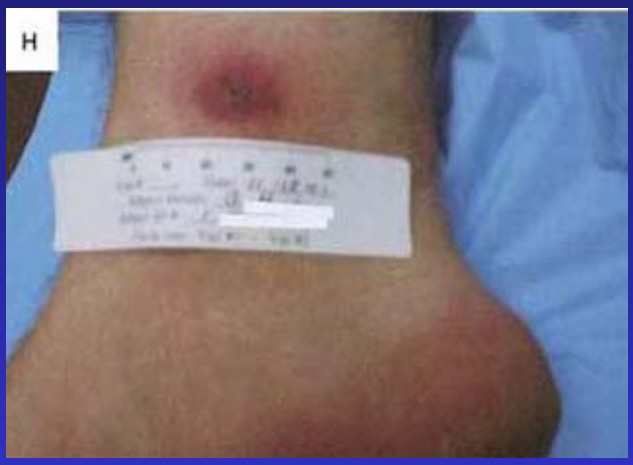
Non-Specific Rashes
Erythematous Patches



Non-specific rashes are self-limited. Individuals with these rashes appear well and usually benefit from simple supportive care measures such as oral NSAIDS and oral anti-pruritic agents

Dermatologic Manifestations of Hypersensitivity Reactions

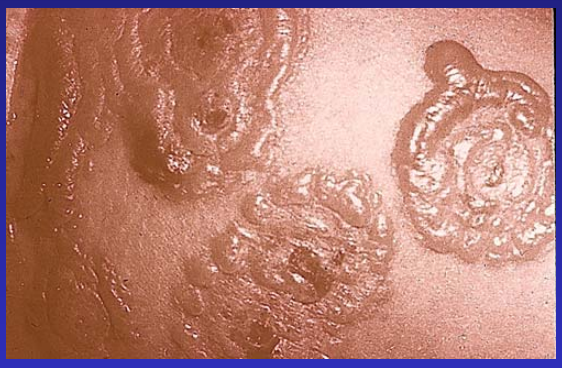
Erythema Multiforme

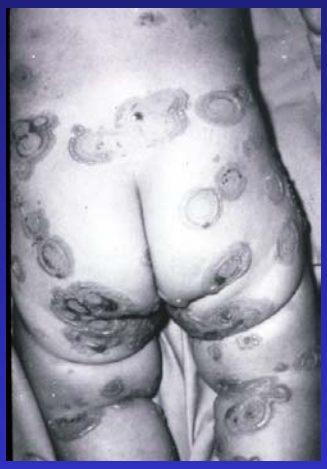


With erythema multiforme, the rash may be extremely pruritic, lasting up to 4 weeks, and patients benefit from administration of oral antipruritics.

Dermatologic Manifestations of Hypersensitivity Reactions

Stevens-Johnson Syndrome





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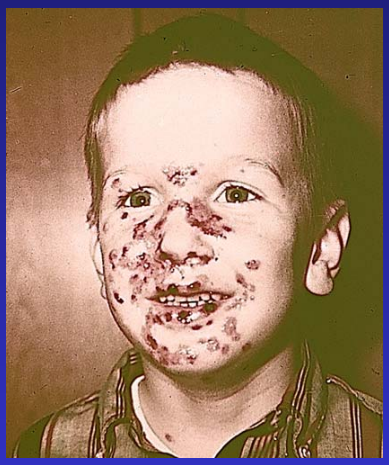
Much less commonly, erythema multiforme can progress to Stevens-Johnson syndrome or SJS. This typically requires hospitalization and supportive care.

The role of systemic steroids for treatment of SJS is controversial; therefore the decision to administer systemic steroids, Vaccinia immune globulin, or VIG, is not used to treat non-specific rashes, erythema multiforme or SJS, because these lesions are likely a manifestation of a hypersensitivity reaction and are not believed to contain vaccinia virus.

Vaccinia Specific Adverse Events
Inadvertent Inoculation

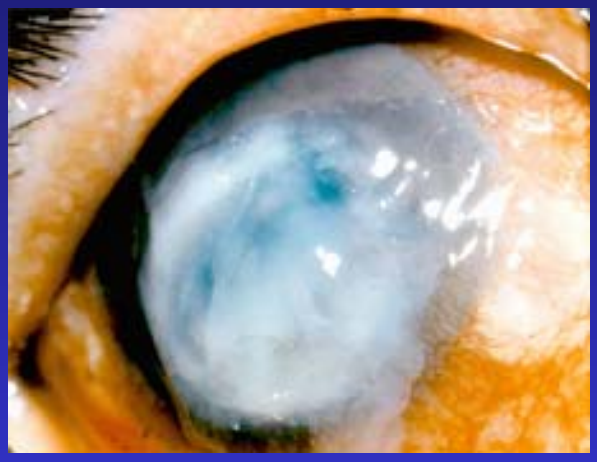


Uncomplicated inadvertent inoculation lesions are self-limited. They resolve in about 2 to 3 weeks, and require no therapy.

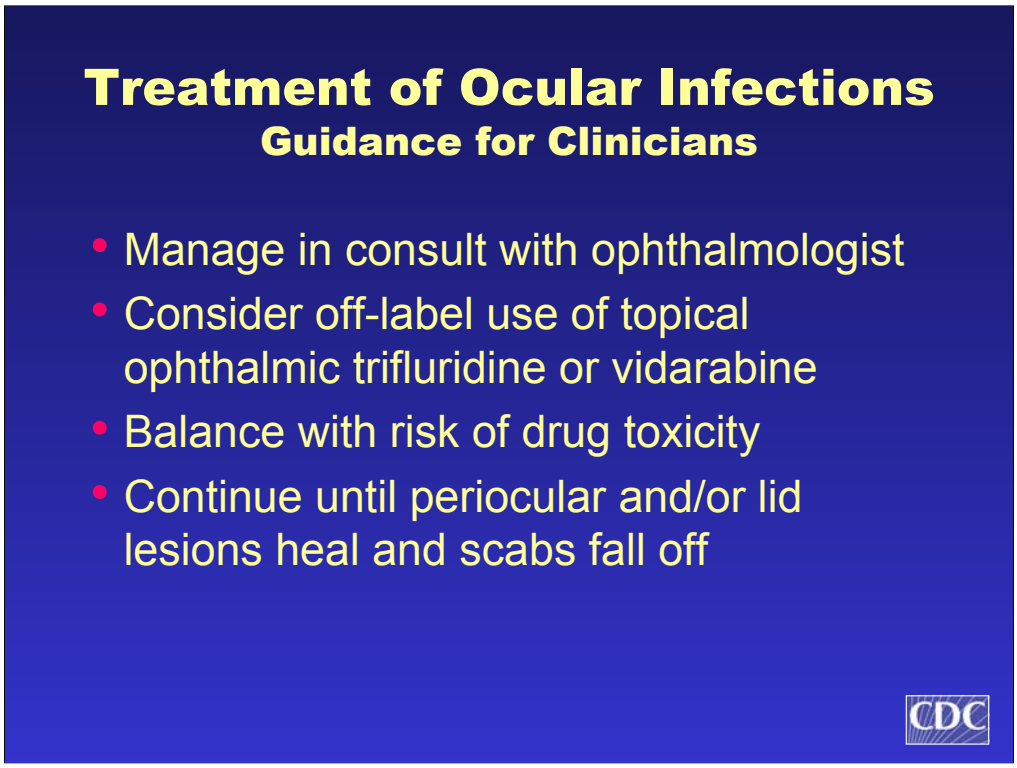
If extensive body surface area is involved, or ocular vaccinia infection, without keratitis, is present, treatment with VIG may assist recovery.

Remember that the primary prevention strategy to avoid inadvertent inoculation is to instruct vaccinees and their close contacts to avoid touching or scratching the vaccination site, and to maintain vigilant hand washing

Vaccinia Specific Adverse Events
Keratitis



The goal of therapy of ocular disease is to prevent complications, especially corneal scarring associated with keratitis.

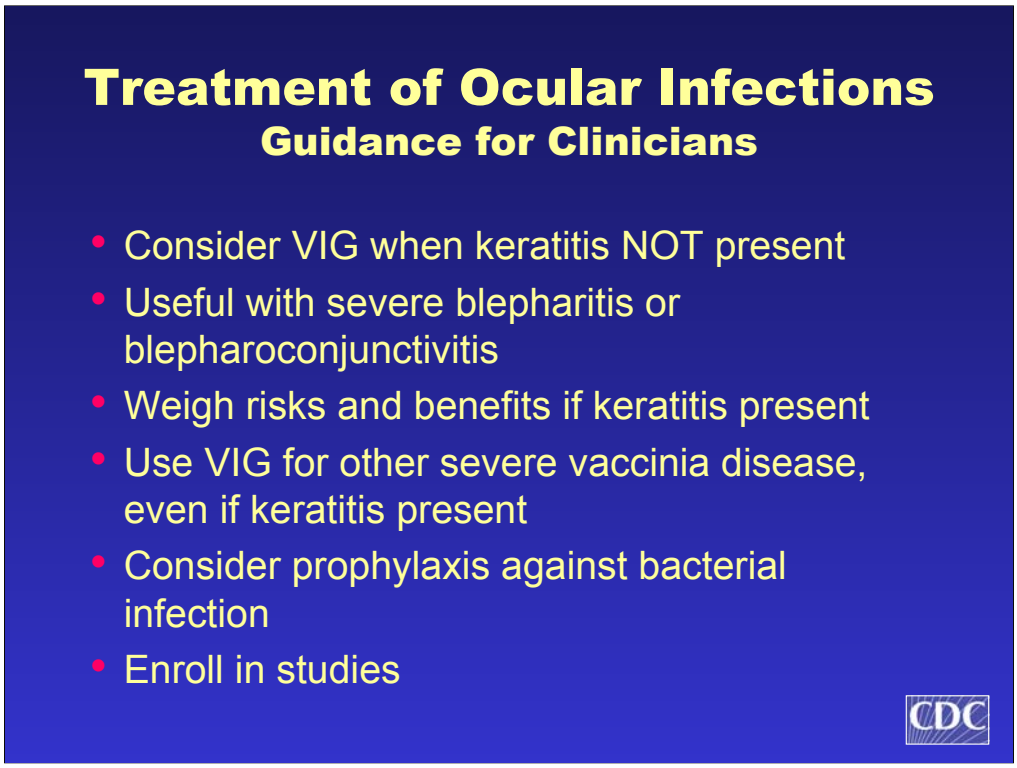


Suspected ocular vaccinia infections should be managed in consultation with an ophthalmologist whenever possible. Although this occurs rarely due to the viscosity of smallpox vaccine, vaccine splashes to the eye should be managed by immediate eye washing with water. Avoid pressure irrigation, which may cause corneal abrasion. A baseline evaluation by an ophthalmologist should be done. Further treatment may not be necessary.

Off-label use of topical ophthalmic trifluridine or vidarabine should be considered for the treatment of vaccinia infection of the conjunctiva or cornea. Prophylactic therapy with these drugs should also be considered to prevent spread, if vaccinia lesions are present on the eyelid, or adjacent to the eye.

The use of these drugs for prophylaxis should be balanced against the minimal but potential risk of drug toxicity and of introducing virus into the eye by frequent manipulation. Topical antivirals should be continued until all periocular or lid lesions have healed and the scabs have fallen off. Topical trifluridine generally should not be used for more than 14 days to avoid toxicity.

When used for more than 14 days, trifluridine may lead to superficial punctate keratopathy, which resolves on discontinuation of the medication. Topical vidarabine may be preferable for use in children because it can be compounded into an ointment. This allows for less frequent dosing and is associated with less initial stinging than trifluridine.



VIG can be considered for use in severe ocular disease when keratitis is not present, such as with severe blepharitis or blepharoconjunctivitis. If keratitis accompanies these conditions, consideration of possible VIG use must be weighed against the increased risk of corneal scar formation from large doses given over several days. VIG need not be withheld if the ocular disease is severe enough to pose a substantial risk of impaired vision. If VIG is given specifically to treat ocular disease in the presence of keratitis, treatment should generally be limited to one dose. The patient or guardian should be informed of the possible risks and benefits prior to its use.

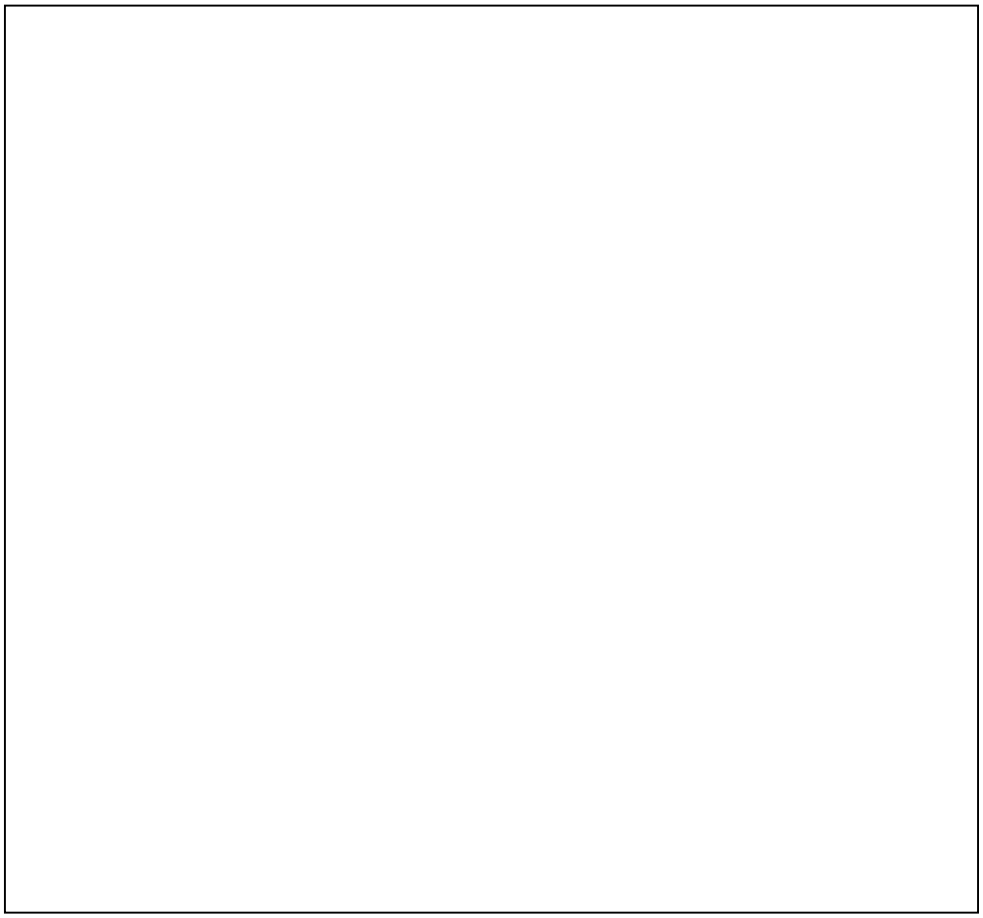
The use of VIG as recommended to treat other severe vaccinia disease, such as eczema vaccinatum, is indicated even in the presence of keratitis. For treatment of isolated keratitis, VIG has not been clearly shown to offer added benefit when topical antivirals are used. Therefore, its use is not recommended.

Topical ophthalmic antibacterials should be considered for the prophylaxis of bacterial infection in the presence of keratitis, particularly if a corneal ulcer is present or steroids are used. In severe cases of keratitis and in iritis, topical steroids should be considered after the corneal epithelium is healed to decrease immune reaction. Mydriatics are also indicated. Topical steroids should not be used without ophthalmologic consultation and should not be used acutely without topical antiviral therapy. Patients with ocular vaccinia infection should receive careful follow-up evaluation by an ophthalmologist to detect and treat possible late onset complications.

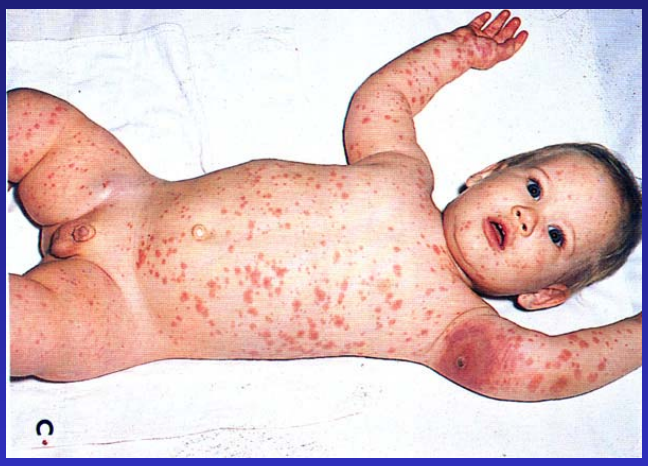
Additional studies are needed to improve the evidence base and refine recommendations for ocular vaccinia disease. Physicians treating patients with ocular vaccinia infection are encouraged to enroll in studies to help improve this evidence base.

Prevention of Contact Transmission

- Proper hand-hygiene
- Healthcare Setting
  - Cover with gauze
  - Cover gauze with semi-permeable dressing
  - Until scab separates
- Non-Healthcare Setting
  - Cover with gauze
  - Wear sleeve over site



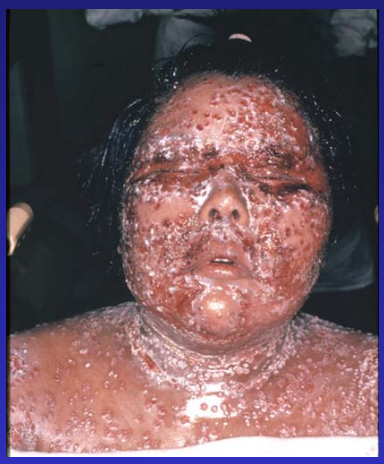
Generalized Vaccinia



Generalized vaccinia is self-limited in immunocompetent hosts. These patients appear well and do not require VIG but may benefit from simple supportive care measures such as NSAIDS and oral antipruritics. In the rare case where an immunocompetent individual appears toxic, VIG may have a role. Generalized vaccinia is often more severe in individuals with an underlying immunodeficiency. These patients may benefit from early intervention with VIG.

If maceration of the vaccination site occurs, the lesion should be left open to air to allow the vaccination site to dry during a period when there will be no direct contact with patients or other persons. Administrative leave should be considered for health care workers who are unable to adhere to the recommended infection control measures, which require that vaccination sites be covered during patient care duties.

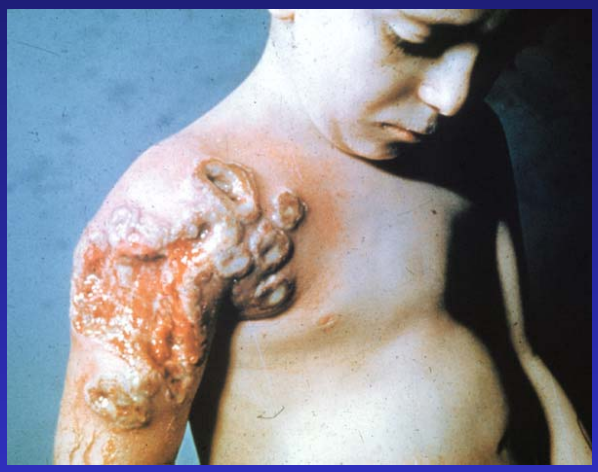
Eczema Vaccinatum



Management of Eczema Vaccinatum includes hemodynamic support and meticulous skin care, as for burn victims. Patients may require volume repletion and vigilant monitoring of electrolytes due to disruption of the dermal barrier. Patients with eczema vaccinatum are at risk of secondary bacterial and fungal infections of the lesions. Antibacterials and antifungals are indicated as necessary.

One study found that the mortality from eczema vaccinatum was reduced from 30-40% to 7% following the introduction of VIG. Therefore it is important to establish early diagnosis and not delay treatment with VIG. Patients are severely ill and often require large doses of VIG. Virus can be isolated from eczema vaccinatum lesions, making these patients highly infectious. Infection control precautions should be used to prevent secondary transmission and nosocomial infection.

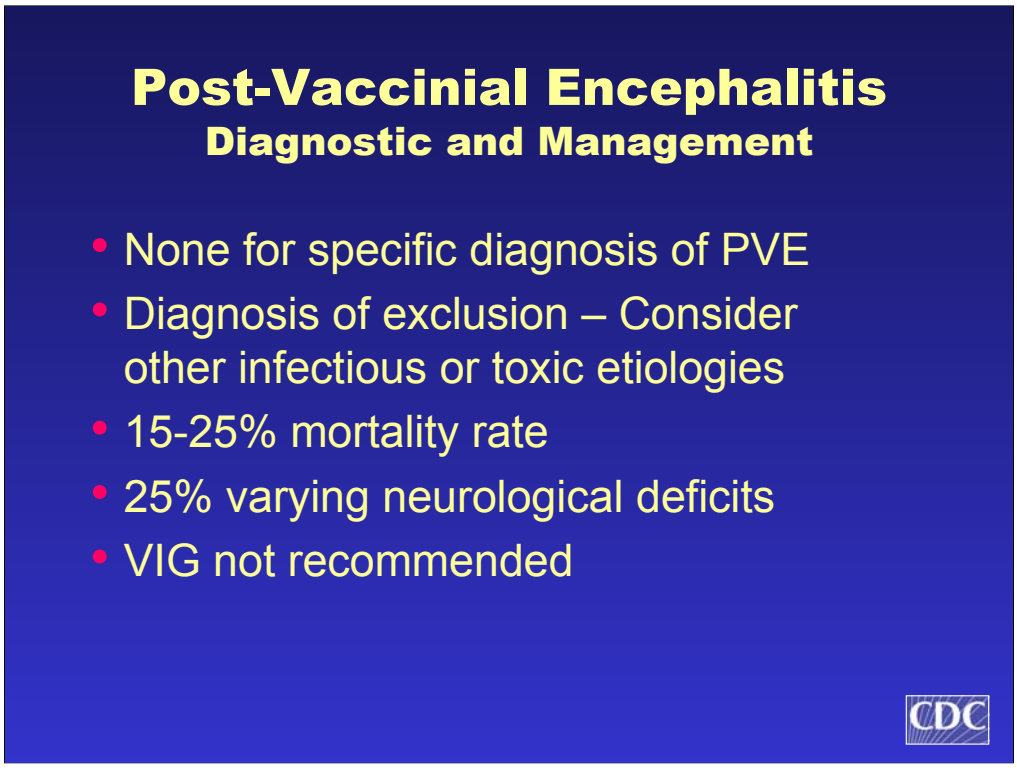
Progressive Vaccinia



Progressive vaccinia is often lethal in persons with immunodeficiency. Live vaccinia virus can be isolated from the skin lesions of Progressive Vaccinia patients. Infection control precautions, which include contact isolation is required to avoid vaccinial infection of other persons and to limit risk of secondary infections.

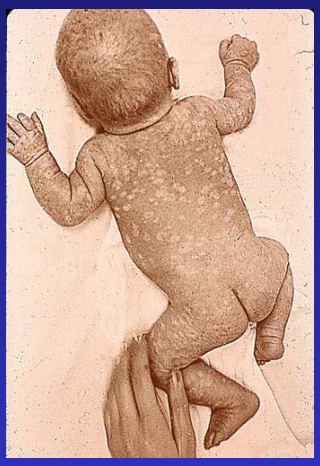
Current day management of PV should include aggressive therapy with VIG, intensive monitoring and tertiary-level supportive care. Antiviral chemotherapy has been used to treat progressive vaccinia. If elected this should be done with careful monitoring for toxicity and response, preferably in the setting of an Investigational New Drug and with reporting of data to contribute to future treatment decisions.

Despite advances in medical care, anecdotal experience suggests that, despite treatment with VIG, hosts with cell-mediated immune deficit have a poorer prognosis than those with humoral deficits. It is likely that progressive vaccinia will continue to be associated with a high mortality rate.



Post-vaccinial encephalitis, or PVE, has a fifteen to twenty-five percent mortality rate. No study has shown VIG to be an effective therapeutic for PVE and therefore VIG is not recommended. Consequently, there is no specific therapy for PVE. However, supportive care, anticonvulsants and intensive care may be required. Since the clinical symptoms of PVE are not thought to be a result of replicating vaccinia virus, the role of antivirals have not been elucidated.

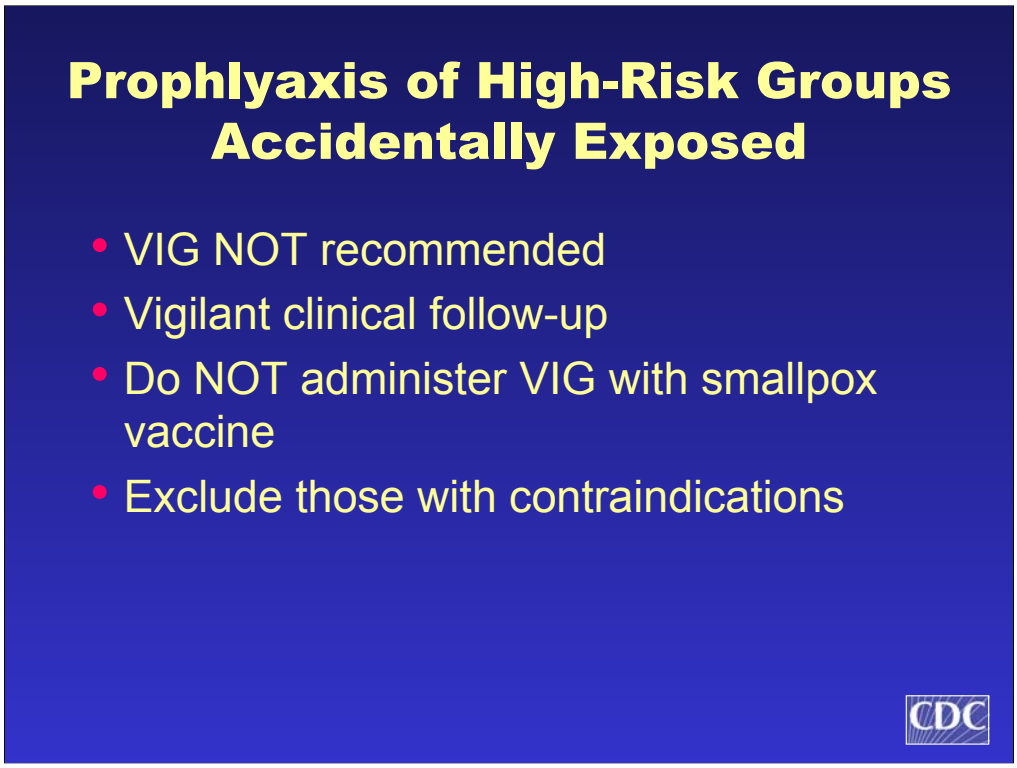
Fetal Vaccinia



Fetal vaccinia, resulting from vaccinia transfer from mother to fetus, is very rare. There is no known reliable intrauterine diagnostic test to confirm fetal infection. Apart from the characteristic pattern of FV, there is no recognizable pattern of congenital malformations associated with smallpox vaccination during pregnancy.

VIG may be considered for a viable infant born with lesions, although no data exist for dosage or efficacy. If a pregnant woman is inadvertently vaccinated or if she becomes pregnant within 4 weeks after vaccinia vaccination, she should be counseled regarding the basis of concern for the fetus. However, given the rarity of fetal vaccinia, vaccination during pregnancy should not ordinarily be a reason to terminate pregnancy. Currently there is no indication for routine, prophylactic use of VIG in an unintentionally vaccinated pregnant woman. VIG should not be withheld, however, if a pregnant woman develops a condition where VIG is needed.

To expand understanding of the risk of fetal vaccinia and to document whether adverse pregnancy outcome may be associated with vaccination, CDC will establish a smallpox vaccination pregnancy registry.



In the past, VIG has been recommended as a prophylactic treatment for individuals with contraindications who are inappropriately vaccinated, or for persons with contraindications who are exposed to the vaccinia virus through close contact with a recent vaccinee.

However, VIG administration is not without risk. The efficacy of VIG as a prophylactic against vaccinial infection has not been studied in a controlled setting. Until VIG is evaluated for such use, it is not recommended for prophylaxis when a person with contraindications to smallpox vaccination is inadvertently exposed. Such persons should have vigilant clinical follow-up so that prompt diagnosis and treatment of an adverse event can occur, should one develop. Furthermore, in the absence of circulating smallpox virus, VIG is not recommended to allow the vaccination of individuals with contraindications. Persons with contraindications to smallpox vaccination should not be vaccinated in the pre-outbreak setting.

Clinicians are encouraged to report these cases to the CDC so that prompt treatment can be initiated when necessary, and patients can be followed. These data will be used to assess the risk of developing an adverse event and the potential role for prophylaxis therapy in these patients.

Topical ophthalmic antiviral drugs, VIG and cidofovir are some of the therapies used to treat adverse events following smallpox vaccination.

Vaccinia Immune Globulin

- Immunoglobulin fraction of plasma
- Antibodies to vaccinia from vaccinated donors
- Previously-licensed IM product (Baxter)
  - Contains 0.01% thimerosal
- New IV products in production
- Obtain as IND product through CDC and DoD

CDC

VIG is a sterile solution of the immunoglobulin fraction of plasma, containing antibodies to vaccinia virus. This was obtained from individuals who were immunized with vaccinia virus vaccine. The currently available preparation of VIG is a previously licensed intramuscular product produced by Baxter Healthcare Corporation in 1985. It contains 0.01% thimerosal, a mercury derivative, as a preservative. Two new IV preparations are in production. All preparations of VIG are expected to be available as Investigational New Drug products through the CDC and DoD.

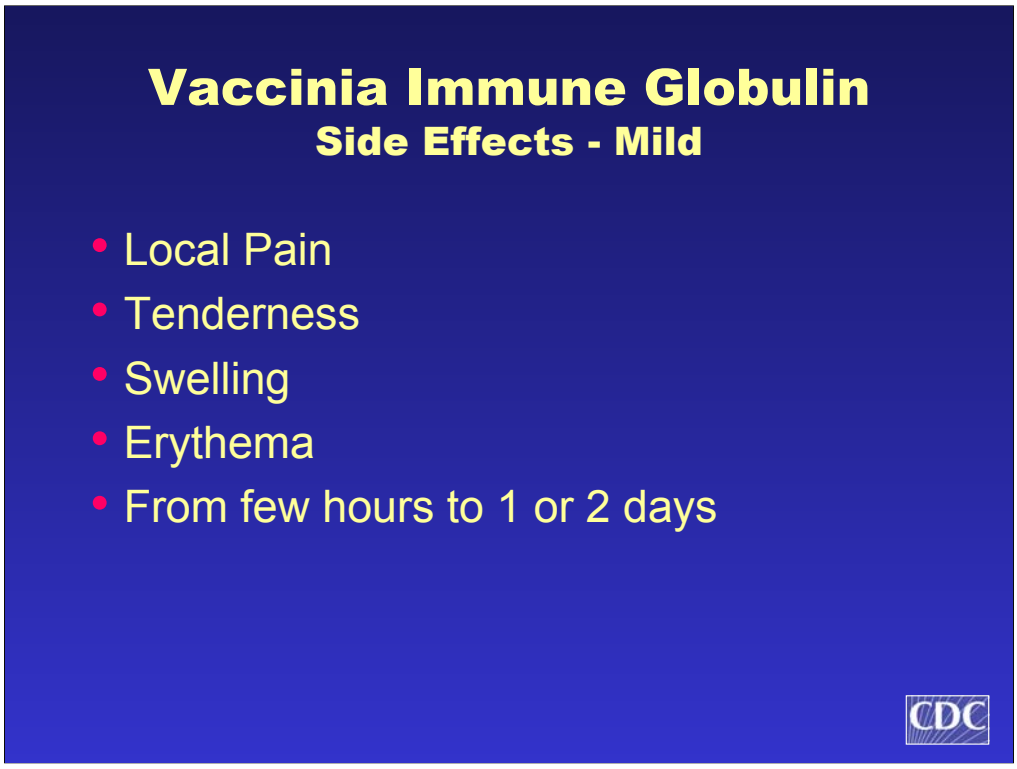
Vaccinia Immune Globulin
Indications

Recommended	Inadvertent Inoculation - severe Eczema vaccinatum Generalized vaccinia – severe or underlying illness Progressive vaccinia
Not Recommended	Inadvertent Inoculation – Not severe Generalized vaccinia – mild or limited Non-specific rashes, EM, SJS Post-vaccinial encephalitis
Consider	Ocular complications

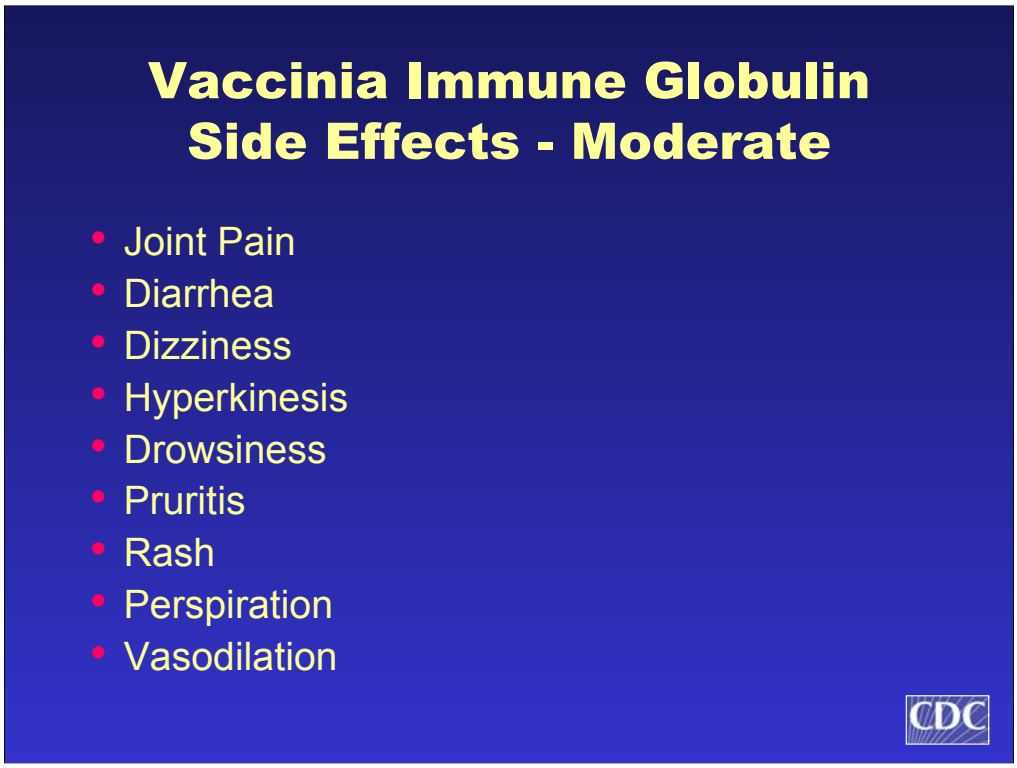
CDC

VIG has demonstrated efficacy in the treatment of smallpox vaccine adverse events that are secondary to continued vaccinia virus replication. VIG has no proven effectiveness for the treatment of post-vaccination adverse events such as PVE and has a qualified contraindication in keratitis.

VIG is recommended for the treatment of eczema vaccinatum and progressive vaccinia. Because most cases of generalized vaccinia are self-limited, VIG is recommended only if the patient is seriously ill or has serious underlying disease that is a risk factor for a complication of vaccination. VIG may also be useful in the treatment of ocular vaccinia resulting from inadvertent implantation. When ocular vaccinia with keratitis is present, the consideration of VIG should take into account the possibly increased risk of corneal scarring.



VIG administration has been associated with mild, moderate and severe adverse events. Mild adverse reactions include local pain and tenderness, swelling, and erythema at the injection site. These can persist from a few hours to 1 or 2 days following administration.



Moderate adverse reactions include:

•joint pain,

•diarrhea,

•dizziness,

•hyperkinesis,

•drowsiness,

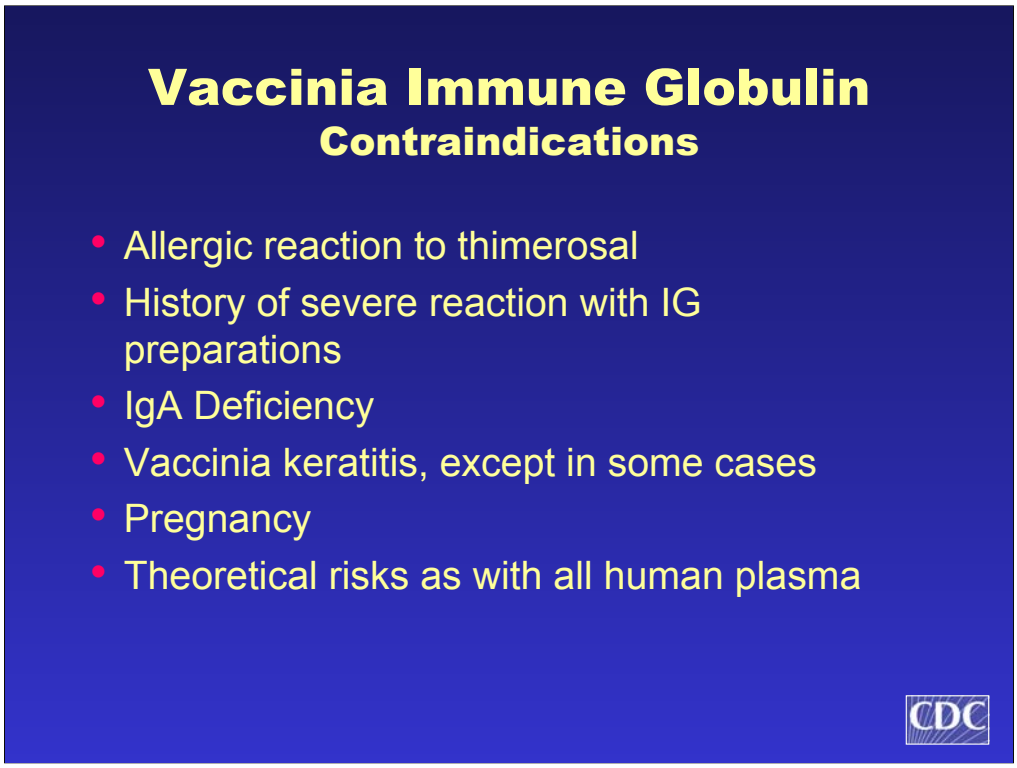
•pruritis,

•rash,

•perspiration and

•vasodilation.

Back and abdominal pain, nausea, and vomiting may occur within the first 10 minutes of injection. Chills, fever, headache, myalgia and fatigue may begin at the end of infusion and continue for several hours. More severe reactions of this type may require pretreatment with corticosteroids or acetaminophen, should another dose of VIG be required.



Contraindications to VIG administration include an acute allergic reaction to thimerosal or history of a severe reaction following administration of human immunoglobulin preparations. Persons with selective immunoglobulin A deficiency have the potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA. Vaccinia keratitis, in the absence of other conditions that require VIG treatment, is a contraindication.

It is not known whether VIG can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Clinical experience with other preparations containing immunoglobulins suggests there are no fetal adverse events from immunoglobulins. There have been no studies to date evaluating the adverse effects of VIG on the fetus. VIG should be given to a pregnant woman only if clearly needed. It is not known whether this drug is excreted in breast milk. Caution should be exercised when VIG is administered to a nursing woman.

Because VIG is made from human plasma, there is a theoretical risk of transmission of viruses Creutzfeldt-Jacob disease. The risk that these products contain infectious agents has been reduced by verbal screening of plasma donors for infection risk factors, and by testing for the presence of certain viruses in the plasma. Furthermore, manufacturing processes have been validated for their ability to inactivate and remove viruses.

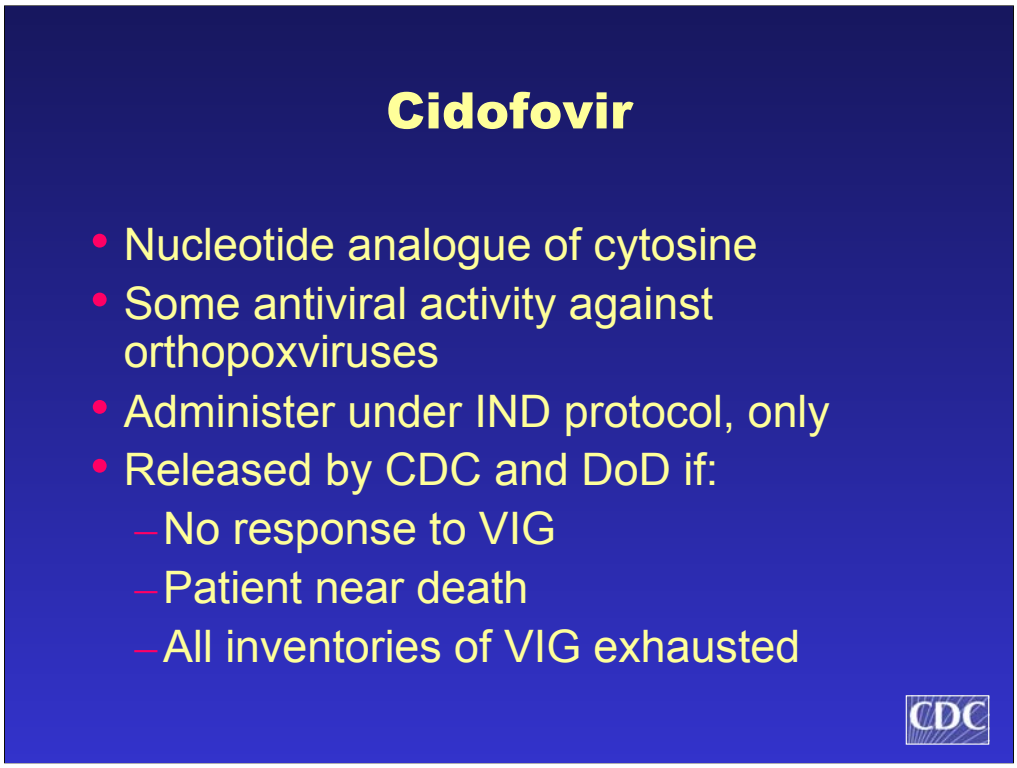
VIG Administration

- VIG-IM 0.6ml/kg
- IM, preferably in buttock or anterolateral aspect of thigh
- Divide doses > 5ml
- Refer to package insert

Detailed instructions regarding the administration of VIG are included in the Investigator's Brochure portion of the IND materials that will accompany the products.

For treatment of vaccinial complications, the recommended dose of VIGIM is 0.6 ml/kg. VIGIM is to be administered intramuscularly, preferably in the buttock or the anterolateral aspect of the thigh. Doses greater than 5 ml should be divided and injected at two or more sites to reduce local pain and discomfort.

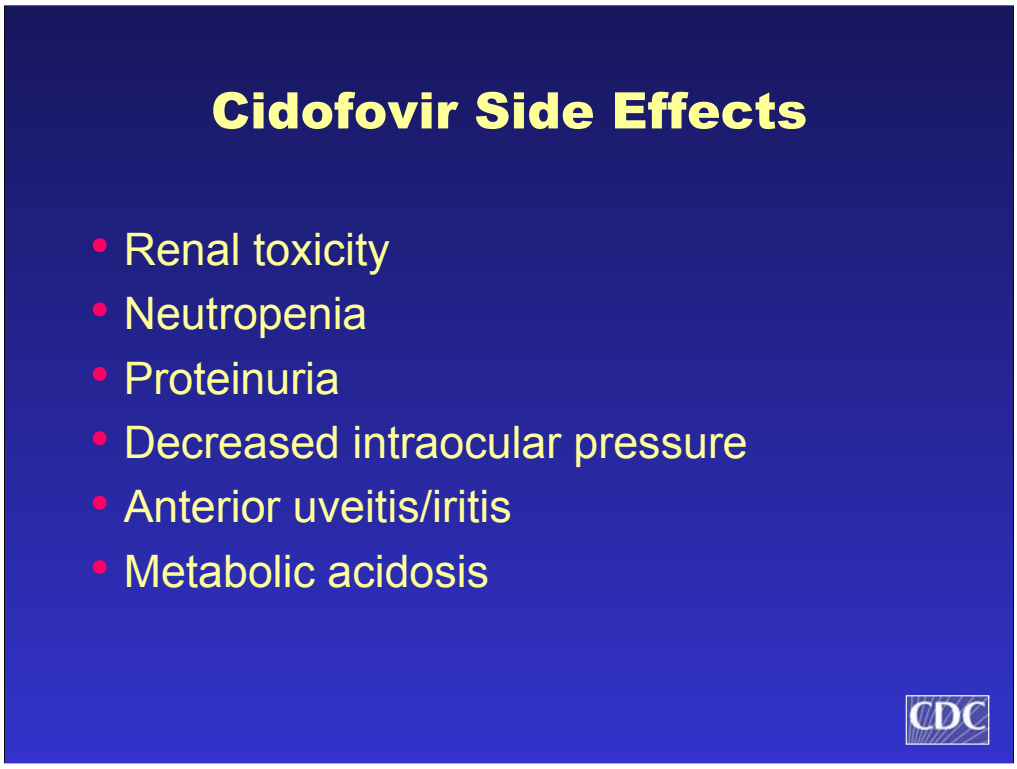
Because the concentration of the new VIGIV products differs from that of the IM preparation, clinicians should refer to the manufacturer's package insert for correct dosages.*Reference:*



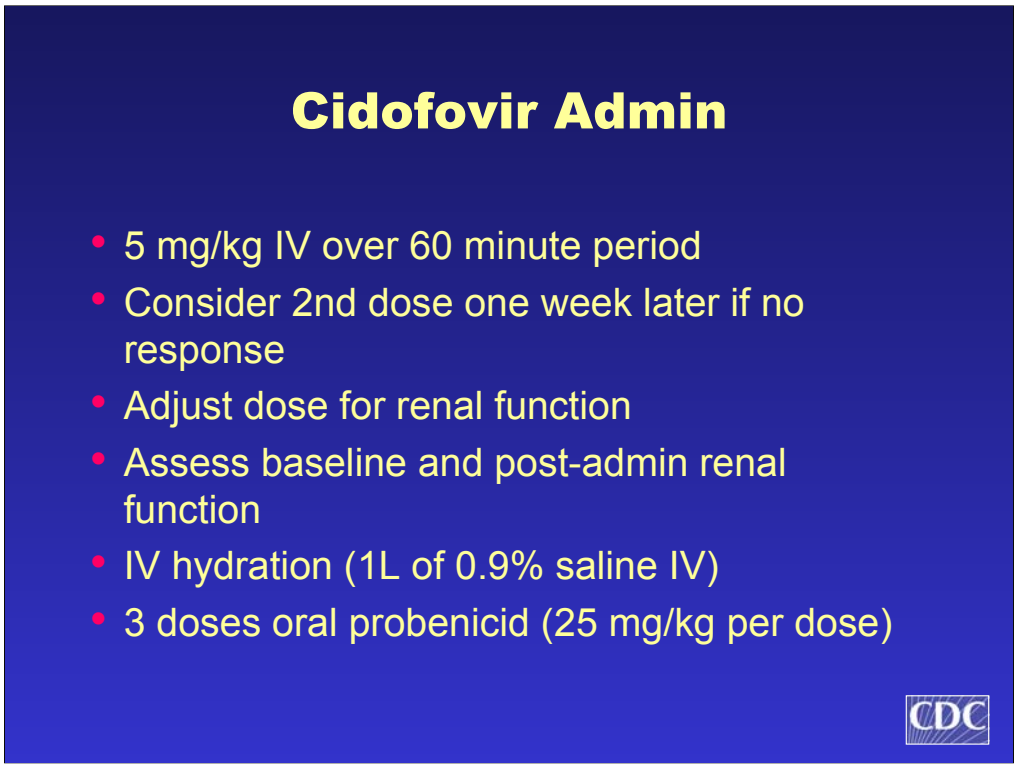
Cidofovir, a nucleotide analogue of cytosine, has shown antiviral activity against some orthopoxviruses. In addition, cidofovir exhibits antiviral activity against adenovirus and human papillomavirus. Its effectiveness in the treatment of vaccinia related complications in humans is unknown. Cidofovir has been shown to be nephrotoxic and carcinogenic even at low doses.

Its use for the treatment of smallpox vaccination complications is recommended only under an Investigational New Drug protocol sponsored by the CDC. This IND is a research protocol to evaluate the effectiveness of cidofovir as a secondary treatment of vaccinia-related complications that do not respond to VIG treatment. CDC will supply cidofovir at no cost for use under this IND.

Cidofovir will be released for civilian use by CDC and for military use by DOD, if, 1) a patient fails to respond to VIG treatment, 2) a patient is near death, or 3) all inventories of VIG have been exhausted. This proposed use of cidofovir is investigational and has not been studied in humans. Therefore the benefit of cidofovir therapy for vaccinia-related complications is uncertain. For pediatric patients, there is no information on dosing, safety, and efficacy of cidofovir to treat smallpox vaccine AEs. Dosages for these patients should be determined in consultation with experts at CDC and DoD. Additional information on dosing and administration of cidofovir is included in the Investigator's Brochure that will accompany the release of this product to the clinician when cidofovir is used under the IND protocol.



The major complication of cidofovir therapy is renal toxicity, which is sometimes irreversible. To reduce the renal toxicity of cidofovir it must be administered with careful intravenous hydration and with probenicid, a renal tubular blocking agent. Cidofovir has also been associated with the following: neutropenia, proteinuria, decreased intraocular pressure, anterior uveitis/iritis, and metabolic acidosis. Animal studies have reported carcinogenicity, teratogenicity and hypospermia.



Details for administration of cidofovir® are included with the medication and IND materials that are shipped from CDC. The proposed dose of cidofovir® for treatment of vaccinia complications is 5 mg/kg administered intravenously, one time, over a 60 minute period. A second dose one week later may be considered if there is no response to the first. Dose adjustment may be needed for renal function if a second dose is needed.

Administration procedures include assessment of baseline and post-administration renal function, intravenous hydration, and 3 doses of oral probenicid. Two doses of 25 mg/kg per dose to be administered prior to cidofovir and 1 dose after. The maximum dose is 2 grams. Patients who receive cidofovir should be followed closely both for drug toxicities and for the outcome of their serious adverse event. Monitoring for emerging viral resistance to cidofovir is required.

The protocol materials will be supplied to facilitate monitoring and information collection. Long-term follow-up is required under IND to monitor for carcinogenicity, renal insufficiency, and teratogenicity.

For More Information

- CDC Smallpox website
  www.cdc.gov/smallpox
- National Immunization Program website
  www.cdc.gov/nip

Thank you, Dr. Lane for providing that valuable overview on handling adverse events.