Complete Summary

GUIDELINE TITLE

Smallpox vaccination and adverse reactions. Guidance for clinicians.

BIBLIOGRAPHIC SOURCE(S)

Cono J, Casey CG, Bell DM. Smallpox vaccination and adverse reactions. Guidance for clinicians. MMWR Recomm Rep 2003 Feb 21;52(RR-4):1-28. [82 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

On April 7, 2005, after concluding that the overall risk versus benefit profile is unfavorable, the FDA requested that Pfizer, Inc voluntarily withdraw Bextra (valdecoxib) from the market. The FDA also asked manufacturers of all marketed prescription nonsteroidal anti-inflammatory drugs (NSAIDs), including Celebrex (celecoxib), a COX-2 selective NSAID, to revise the labeling (package insert) for their products to include a boxed warning and a Medication Guide. Finally, FDA asked manufacturers of non-prescription (over the counter [OTC]) NSAIDs to revise their labeling to include more specific information about the potential gastrointestinal (GI) and cardiovascular (CV) risks, and information to assist consumers in the safe use of the drug. See the FDA Web site for more information.

Subsequently, on June 15, 2005, the FDA requested that sponsors of all non-steroidal anti-inflammatory drugs (NSAID) make labeling changes to their products. FDA recommended proposed labeling for both the prescription and over-the-counter (OTC) NSAIDs and a medication guide for the entire class of prescription products. All sponsors of marketed prescription NSAIDs, including Celebrex (celecoxib), a COX-2 selective NSAID, have been asked to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use. FDA regulation 21CFR 208 requires a Medication Guide to be provided with each prescription that is dispensed for products that FDA

determines pose a serious and significant public health concern. See the FDA Web site for more information.

Additional Notice

On November 10, 2005, the U.S. Food and Drug Administration (FDA) notified physicians, nurses, medical technologists, pharmacists and other healthcare professionals of the potential for life-threatening falsely elevated glucose readings in patients who have received parenteral products containing maltose or galactose, or oral xylose, and are subsequently tested using glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) based glucose monitoring systems. There have been reports of the inappropriate administration of insulin and consequent life-threatening/fatal hypoglycemia in response to erroneous test results obtained from patients receiving parenteral products containing maltose. Cases of true hypoglycemia can go untreated if the hypoglycemic state is masked by false elevation of glucose readings. A preliminary listing of U.S. products that may cause glucose test interference is provided. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Smallpox

Vaccinia-specific complications of smallpox vaccination:

- Ocular vaccinial infection
- Generalized vaccinia (GV)
- Eczema vaccinatum (EV)
- Progressive vaccinia (PV)
- Postvaccinial central nervous system disease, postvaccinial encephalopathy (PVE), postvaccinial encephalomyelitis (PVEM)
- Fetal vaccinia

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Allergy and Immunology
Dermatology
Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Ophthalmology
Pathology
Pediatrics
Pharmacology
Preventive Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To provide guidance for evaluation and treatment of patients with complications from smallpox vaccination in the preoutbreak setting
- To provide information related to reporting adverse events and seeking specialized consultation and therapies for these events

TARGET POPULATION

- Members of smallpox public health response and health care teams
- Persons who present with complications arising from smallpox vaccination

INTERVENTIONS AND PRACTICES CONSIDERED

Vaccination

1. Detailed medical history including assessment for contraindications to vaccination
2. Calf-lymph derived vaccine, Dryvax®, containing New York City Board of Health (NYCBOH) vaccinia strain
3. Use of correct vaccination technique
4. Patient education to prevent contact transmission
5. Interpretation of vaccination response (major or equivocal)
6. Treatment for robust takes (RTs) may include rest of affected limb, use of oral nonaspirin analgesic medications, as well as oral antipruritic agents.
7. Revaccination as indicated
8. Follow-up of more severe adverse reactions as indicated.

Adverse Reactions

Diagnosis

1. Medical history including route of exposure (i.e., vaccination, contact transmission), onset and duration of symptoms
2. Clinical findings (i.e., fever, pain, inflammation, rashes, lesions)
3. Laboratory tests where indicated (i.e., cerebral spinal fluid tests for postvaccinial encephalitis or encephalomyelitis)
4. Exclude differential diagnoses such as allergic reaction, bacterial infection, severe chickenpox, disseminated herpes simplex
5. Consultation with appropriate specialists as indicated

Treatment/Management

Refer to "Major Recommendations" field for appropriate indications

1. Infection-control precautions
2. Medication, such as
    - Vaccinia immune globulin (VIG) as first line therapy
    - Cidofovir as second line therapy (Vistide®)
    - Topical ophthalmic antiviral drugs

      Note: VIG and cidofovir are available under Investigational New Drug protocols

3. Symptom management
4. Hospitalization and supportive care

MAJOR OUTCOMES CONSIDERED

- Rates of adverse reactions following smallpox vaccination
- Rates of adverse reactions resulting in physician visit/hospitalization
- Rates of vaccine-related deaths
- Rates of contact transmission following smallpox vaccination
- Efficacy of medication used to treat adverse reactions (i.e., vaccinia immune globulin [VIG], cidofovir)
- Medication side effects/adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Not stated

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Contraindications to Vaccination

Refer to the "Subgroups of Patients Most Likely to be Harmed" section of this document for information on contraindications to smallpox vaccination in the preoutbreak setting. In the event of a smallpox outbreak, outbreak-specific guidance will be disseminated by Centers for Disease Control and Prevention (CDC) regarding populations to be vaccinated and specific contraindications to vaccination.

Normal Vaccination Progression

Smallpox vaccine is administered by using the multiple-puncture technique with a bifurcated needle. The vaccinia virus replicates in the dermis of the skin; 3–5 days later, a papule forms at the vaccination site of immunocompetent vaccine-naïve persons (also referred to as first-time or primary vaccinees). The papule becomes vesicular (approximately day 5–8), then pustular, and usually enlarges to reach maximum size in 8–10 days. The pustule dries from the center outward and forms a scab that separates 14–21 days after vaccination, usually leaving a pitted scar.

Formation by days 6–8 postvaccination of a papule, vesicle, ulcer, or crusted lesion, surrounded by an area of induration signifies a response to vaccination; this event is referred to as a major reaction or a take, and usually results in a scar. During the smallpox eradication era, persons with vaccination scars had much lower attack rates when exposed to smallpox cases than did nonvaccinated persons. Therefore, a take has been a surrogate correlate of immunity to smallpox. Although the level of antibody that protects against smallpox infection is unknown, >95% of first-time vaccinees (i.e., persons receiving their first dose of smallpox vaccine) have increased neutralizing or hemagglutination inhibition antibody titers.

Interpreting Vaccination Results

Vaccination-site reactions are classified into two categories: major reactions and equivocal reactions. A major reaction indicates a successful vaccine take and is characterized by a pustular lesion or an area of definite induration or congestion surrounding a central lesion, which can be a scab or an ulcer. All other responses are equivocal reactions and are nontakes. Equivocal reactions can be caused by suboptimal vaccination technique, use of subpotent vaccine, or residual vaccinial immunity among previously vaccinated persons. Persons with equivocal reactions cannot be presumed to be immune to smallpox, and revaccination is recommended.

The World Health Organization (WHO) has recommended that response to vaccination be evaluated on postvaccination day 6, 7, or 8. These are the days of peak viral replication, and the period during which take should be assessed for both first-time vaccinees and revaccinees. If the response to vaccination is evaluated too early (e.g., <6 days postvaccination), certain equivocal responses will look reactive because of dermal hypersensitivity to vaccinial proteins. These reactions are sometimes referred to as immediate reactions but are not successful takes. If the response to vaccination is evaluated too late (e.g., >8 days postvaccination), the vaccination take might be missed among persons with prior immunity to vaccinia who might experience a more rapid progression of the vaccination site. Responses among revaccinees that resolve in <6 days are sometimes referred to as accelerated reactions and are not successful takes.

Expected Range of Vaccine Reactions

A range of expected reactions occurs after vaccination. These normal reactions do not require specific treatment and can include fatigue, headache, myalgia, regional lymphadenopathy, lymphangitis, pruritis, and edema at the vaccination site, as well as satellite lesions, which are benign, secondary vaccinial lesions proximal to the central vaccination lesions.

During the smallpox eradication era, fever after vaccination occurred frequently but was less common among adults than children. For adults, fever is more frequently noted among first-time vaccinees than revaccinees. In one vaccination series involving children, approximately 70% experienced >1 day of temperatures >100ÂºF during the 4–14 days after primary vaccination, and 15%–20% of children experienced temperatures >102ÂºF. After revaccination, 35% of children experienced temperatures >100ÂºF, and 5% experienced temperatures of >102ÂºF.

Satellite lesions occasionally occur at the perimeter of the vaccination site and should not be confused with the early discrete vesicles that might coalesce into a central pox-like lesion. Satellite lesions are a benign finding, do not require treatment, and should be cared for as vaccination sites.

Large Vaccination Reactions and Robust Takes (RTs)

Large vaccination reactions (i.e., >10 cm in diameter) at the site of inoculation occur in approximately 10% of first-time vaccinees and are expected variants of the typical evolution of the vaccination site. However, sometimes these large vaccination reactions have been reported as adverse events and misinterpreted as cellulitis, requiring antibiotic treatment.

Bacterial infection of the vaccination site is uncommon but affects children more often than adults, because children are more likely to touch and contaminate their vaccination sites. Specimens for bacterial cultures can be obtained by using swabs or aspiration. Gram stains can detect normal skin flora and are useful only when unusual pathogens are present. If empiric antibacterial therapy is administered, therapy should be adjusted after the bacterial pathogen and its sensitivities to various antibacterial medications are known.

Identifying RTs

Differentiating an RT from bacterial cellulitis can be difficult. RTs occur 8–10 days postvaccination, improve within 72 hours of peak of symptoms, and do not progress clinically. Fluctuant enlarged lymph nodes are not expected and warrant further evaluation and treatment. In contrast, secondary bacterial infections typically occur within 5 days of vaccination or >30 days postvaccination, and unless treated, the infection will progress. The interval of onset to peak symptoms is the key factor in diagnosing RTs. Fever is not helpful in distinguishing RTs from bacterial cellulitis because it is an expected immunologic response to vaccinia vaccination.

When an RT is suspected, management includes vigilant observation, patient education, and supportive care that includes rest of the affected limb, use of oral nonaspirin analgesic medications, as well as oral antipruritic agents. Salves, creams, or ointments, including topical steroids or antibacterial medications, should not be applied to the vaccination site.

Transmission of Vaccinia Virus

Vaccinia can be transmitted from a vaccinee´s unhealed vaccination site to other persons by close contact and can lead to the same adverse events as in the vaccinee.

No data exist to indicate that vaccinia transmission occurs by aerosolization.

Preventing Contact Transmission

Correct hand hygiene prevents the majority of inadvertent inoculations and contact transmissions after changing bandages or other contact with the vaccination site. The vaccination site can be left uncovered or covered with a porous bandage (e.g., gauze).

Preventing Contact Transmission Among Health-Care Workers

To prevent nosocomial transmission of vaccinia virus, health-care workers when involved in direct patient care should keep their vaccination sites covered with gauze or a similar material to absorb exudates that contain vaccinia. This dressing should be covered with a semipermeable dressing to provide a barrier to vaccinia virus. Using a semipermeable dressing alone is not recommended because it might cause maceration of the vaccination site and prolong irritation and itching, which subsequently leads to increased touching, scratching, and contamination of hands. 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 that includes no direct contact with patients or other persons. The vaccination site should be covered during direct patient care until the scab separates. 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.

Preventing Contact Transmission in Other Settings

Transmission of vaccinia is also possible in other settings when close personal contact with children or other persons occurs. In these situations, the vaccination site should be covered with gauze or a similar absorbent material, and long-sleeved clothing should be worn. Careful attention should be paid to handwashing, which should be done with soapy warm water or hand-rub solutions that are $\geq$60% alcohol-based. Historically, the home was the setting where the majority of contact transmission occurred, presumably because of intimate contact and relaxed infection control measures.

Recognizing Vaccinia Virus Transmission

When evaluating a skin or other condition consistent with vaccinia, a history of smallpox vaccination and exposure to a household or close contact who has been vaccinated recently will often provide a source of the virus. A history of exposure to vaccinia might be difficult to obtain. A person might have had an inadvertent exposure and be unaware of being exposed to vaccinia virus, and rarely, persons have been deliberately inoculated by others as a way to vaccinate outside the approved vaccination programs (and possibly unwilling to acknowledge this exposure to vaccinia). In either case, clinicians should obtain a thorough medical history, including possible vaccinia exposure and risk factors for smallpox vaccine-related adverse reactions. Clinicians should counsel these patients regarding appropriate infection-control measures, care of their lesions, and when appropriate, the infectious risks incurred through deliberate inoculation of others. Follow-up of the patient and administration of appropriate treatment are critical if a vaccinia-related adverse reaction develops. In addition, these patients might be at increased risk for infection from bloodborne pathogens, and they should be counseled and treated appropriately.

Adverse Reactions

Adverse reactions caused by smallpox vaccination range from mild and self-limited to severe and life-threatening. Certain smallpox vaccine reactions are similar to those caused by other vaccines (e.g., high fever, anaphylaxis, and erythema multiforme [EM]). Other adverse reactions specific to smallpox vaccination include inadvertent inoculation, ocular vaccinia, generalized vaccinia (GV), eczema vaccinatum (EV), progressive vaccinia (PV), postvaccinial encephalopathy (PVE) and encephalomyelitis (PVEM), and fetal vaccinia. Vaccinia-specific complications can occur among vaccinees or their contacts who have been inadvertently inoculated with vaccinia.

This guidance is for evaluation and treatment of patients with complications from smallpox vaccination administration during preoutbreak situations. In the event of a smallpox outbreak, considering smallpox disease will be necessary in the differential diagnosis of any recently vaccinated person who has an acute, generalized, vesicular, pustular rash illness. Until a determination is made regarding whether the rash is early smallpox disease or an adverse reaction to smallpox vaccine, these patients should be presumed to be highly infectious and placed in contact and respiratory isolation immediately. Appropriate local, state, and federal health and security officials should be contacted.

Common Adverse Reactions

- **Local skin reactions** can occur after smallpox vaccination. These include allergic reactions to bandage and tape adhesives, robust takes (RTs), and less commonly, bacterial infections of the vaccination site. Reactions to adhesives usually result in sharply demarcated lines of erythema that correspond to the placement of adhesive tape. Patients have local pruritis but no systemic symptoms and are otherwise well. Frequent bandage changes, periodically leaving the vaccination site open to air, or a change to paper tape might alleviate symptoms. Care should be used to vary the positioning of tape or bandages. This condition is self-limited and resolves when bandages are no longer needed. Topical and oral steroid treatment for this reaction should be avoided because the site contains live vaccinia virus. Salves, creams, or

ointments, including topical antibacterial medications, should not be applied to the vaccination site.

- Common **nonspecific rashes** associated with smallpox vaccination include fine reticular maculopapular rashes, lymphangitic streaking, generalized urticaria, and broad, flat, roseola-like erythematous macules and patches. These rashes are believed to be caused by immune response to vaccination and do not contain vaccinia. Erythematous or urticarial rashes can occur approximately 10 days (range: 4–17 days) after first-time vaccination. The vaccinee is usually afebrile, and the rash resolves spontaneously within 2–4 days. Nonspecific rashes are usually self-limited. These persons appear well and benefit from simple supportive care measures (e.g., oral anti-antihistamine agents).

Dermatologic Manifestations of Hypersensitivity Reactions

Erythema multiforme (EM), sometimes referred to as roseola vaccinia or toxic urticaria, might appear as different types of lesions, including macules, papules, urticaria, and typical bull´s-eye (targetoid or iris) lesions. Because the number of clinical descriptions of vaccinia-associated EM rashes is limited, the following details are extrapolated from common descriptions of EM occurring after herpes simplex or mycoplasma infections. The hallmark target lesion of EM associated with other infections usually appears with a central, dark papule or vesicle, surrounded by a pale zone and a halo of erythema, usually within 10 days after viral infection. The limited clinical descriptions of EM after smallpox vaccination indicate that it follows a similar course. The rash of EM might be extremely pruritic, lasting $\leq$4 weeks, and patients benefit from administration of oral antipruritics.

Less commonly, hypersensitivity reactions can appear as a more serious condition, Stevens-Johnson syndrome (SJS). SJS can also arise from EM and typically includes systemic symptoms with involvement of $\geq$ 2 mucosal surfaces or 10% of body surface area. This condition requires hospitalization and supportive care.

The role of systemic steroids for treatment of SJS is controversial; therefore, the decision to administer systemic steroids to patients with postvaccinial SJS should be made after consultation with specialists in this area (e.g., dermatologists, immunologists, or infectious disease specialists), according to the prevailing standard of care. Vaccinia immune globulin (VIG) is not used to treat nonspecific rashes, EM, or SJS, because these lesions are probably a manifestation of a hypersensitivity reaction and are not believed to contain vaccinia virus.

Vaccinia-Specific Adverse Reactions

- **Inadvertent inoculation** is a common but avoidable complication of smallpox vaccination. Inadvertent inoculation occurs when vaccinia virus is transferred from a vaccination site to a second location on the vaccinee or to a close contact. The most common sites involved are the face, eyelid, nose, mouth, lips, genitalia, and anus. Among immunocompetent persons, lesions follow the same course as the vaccination site.

A primary prevention strategy to avoid inadvertent inoculation is to instruct vaccinees and their close contacts to avoid touching or scratching the vaccination site from the time of vaccination until the scab separates. In addition, vigilant handwashing with soap and warm water or hand rubs containing ≥60% alcohol, after touching an unhealed vaccination site or changing a vaccination dressing is critical. Lesions from an inadvertent inoculation contain live vaccinia virus, and the same contact precautions necessary for a vaccination site are necessary for these secondary lesions. Persons at highest risk for inadvertent inoculation are younger persons (e.g., children aged 1–4 years) and those with disruption of the epidermis.

Periocular and ocular implantation (hereafter referred to as ocular vaccinial disease) accounted for the majority of reported inadvertent inoculations and were often noted within 7–10 days of vaccination among first-time vaccinees. Ocular vaccinial disease can occur in different forms, including blepharitis (inflammation of the eyelid), conjunctivitis, keratitis (inflammation of the cornea, including epithelial and stromal forms), iritis, or combinations thereof. When evaluating a patient with the new onset of a red eye or periocular vesicles, vaccinia infection should be considered and history of recent vaccinia exposure (e.g., smallpox vaccination or close contact with a vaccine recipient) should be sought. The goal of therapy of ocular disease is to prevent complications, including corneal scarring associated with keratitis, and the patient should be comanaged with an ophthalmologist.

Note: The 2001 Advisory Committee on Immunization Practices (ACIP) recommendation states that VIG is contraindicated in a patient with vaccinial keratitis. However, in November 2002, this recommendation was reevaluated and modified by the Public Health Service. VIG should not be withheld if a comorbid condition exists that requires administration of VIG (e.g., eczema vaccinatum [EV] or progressive vaccinia [PV]) and should be considered for severe ocular disease, except isolated keratitis. In these situations, VIG should be administered if the risk of the comorbid condition is greater than the potential risk of VIG-associated complications of keratitis.

Uncomplicated inadvertent inoculation lesions are self-limited, resolving in approximately 3 weeks, and require no therapy. If extensive body surface area is involved, or severe ocular vaccinia infection (without keratitis), or severe manifestation of inoculation has occurred, treatment with VIG can speed recovery and prevent spread of disease.

- **Ocular vaccinial infections** account for the majority of inadvertent inoculations. However, data upon which to base treatment recommendations are limited. To discuss treatment options for ocular vaccinia, CDC convened a meeting of ophthalmology and infectious disease consultants in November 2002. On the basis of available data and input from these consultants, the following guidance is offered:
    - Suspected ocular vaccinia infections should be managed in consultation with an ophthalmologist to ensure a thorough and accurate eye evaluation, including a slit-lamp examination, and the specialized expertise needed to manage potentially vision-threatening disease.

- Although vaccine splashes to the eye occur rarely because of the viscosity of smallpox vaccine, these occurrences should be managed by immediate eye-washing with water (avoid pressure irrigation, which can cause corneal abrasion) and a baseline evaluation by an ophthalmologist. In this situation, off-label prophylactic use of topical ophthalmic trifluridine or vidarabine has been recommended by ophthalmologists. Further treatment might not be necessary.
- Off-label use of topical ophthalmic trifluridine or vidarabine has been recommended by certain ophthalmologists and can be considered for treatment of vaccinia infection of the conjunctiva or cornea. Prophylactic therapy with these drugs might also be considered to prevent spread to the conjunctiva and cornea if vaccinia lesions are present on the eyelid, including if near the lid margin, or adjacent to the eye. The potential benefits 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, except that topical trifluridine usually is not used for >14 days to avoid possible toxicity. When used for >14 days, trifluridine can lead to superficial punctate keratopathy, which resolves on discontinuation of the medication. Topical vidarabine might be preferable for use among children because it can be compounded into an ointment that allows less frequent dosing and stings less initially than trifluridine.
- VIG should be considered for use in severe ocular disease when keratitis is not present (e.g., severe blepharitis or blepharoconjunctivitis). Severe ocular disease is defined as marked hyperemia, edema, pustules, other focal lesions, lymphadenophy, cellulitis, and fever. If keratitis is present with these conditions, consideration of possible VIG use must be weighed against evidence in an animal model for increased risk for corneal scar formation if a substantial dose is administered during multiple days.
- VIG can be considered if the ocular disease is severe enough to pose a substantial risk of impaired vision as a long-term outcome (e.g., vision-threatening lid malformation). If VIG is administered specifically to treat ocular disease in the presence of keratitis, treatment usually should be limited to 1 dose, and the patient or guardian should be informed of the possible risks and benefits before its use.
- Using VIG as recommended to treat other severe vaccinia disease (e.g., eczema vaccinatum [EV]) is indicated, even in the presence of keratitis. VIG is not recommended for treating isolated keratitis.
- Topical ophthalmic antibacterials should be considered for prophylaxis of bacterial infection in the presence of keratitis, including if a corneal ulcer is present or steroids are used. In severe cases of keratitis (e.g., with an ulcer and stromal haze or infiltrate) 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, including with keratitis or iritis, should receive careful follow-up evaluation by an ophthalmologist to detect and treat possible late onset complications (e.g., scarring and immune reactions).

- **Generalized vaccinia** (GV) is characterized by a disseminated maculopapular or vesicular rash, frequently on an erythematous base, that usually occurs 6–9 days after first-time vaccination. The rash spans the spectrum of vaccinial lesions, from maculopapules to vesicles. Maculopapules can be mistaken for erythema multiforme (EM) when they are accompanied by a substantial component of erythema. In other instances, the pearly vesicles of GV resemble the lesions of smallpox; however, GV does not follow the centrifugal distribution that is characteristic of smallpox.

  GV rash might be preceded by fever, but usually, patients do not appear ill. Lesions follow the same course as the vaccination site. Lesions can be present anywhere on the body, including the palms and soles and can be numerous or limited. GV can appear as a regional form that is characterized by extensive satellite vesiculation around the vaccination site, or as an eruption localized to a body part (e.g., arm or leg), with no evidence of inadvertent inoculation. A mild form of GV also exists, which appears with only a limited number of scattered lesions.

  The skin lesions of GV are believed to be spread by the hematogenous route and might contain vaccinia virus. Therefore, contact precautions should be used when treating these patients. Patients should be instructed to keep lesions covered and avoid physical contact with others if their lesions are too numerous to cover with bandages or clothing. The differential diagnosis of GV includes EM, EV, inadvertent inoculation at multiple sites, and uncommonly, early stages of PV or other vesicular diseases (e.g., disseminated herpes or severe chickenpox).

  GV is self-limited among immunocompetent hosts. These patients appear well and do not require VIG, but might benefit from simple supportive care measures (e.g., nonsteroidal anti-inflammatory agents [NSAIDS] and oral antipruritics). VIG might be beneficial in the rare case where an immunocompetent person appears systemically ill. GV is often more severe among persons with an underlying immunodeficiency, and these patients might benefit from early intervention with VIG.

- **Eczema vaccinatum** (EV) is a localized or generalized papular, vesicular, or pustular rash, which can occur anywhere on the body, with a predilection for areas of previous atopic dermatitis lesions. Persons with a history of atopic dermatitis are at highest risk for EV. Onset of the characteristic lesions can be noted either concurrently with or shortly after the development of the local vaccinial lesions. EV cases resulting from secondary transmission usually appeared with skin eruptions approximately 5–19 days after the suspected exposure. EV lesions follow the same dermatological course as the vaccination site in a vaccinee, and confluent lesions can occur. The rash is often accompanied by fever and lymphadenopathy, and affected persons are systemically ill. EV tends to be more severe among first-time vaccinees or unvaccinated contacts.

  Atopic dermatitis, regardless of disease severity or activity, is a risk factor for experiencing EV among either vaccinees or their close contacts, but no data exist to predict the absolute risk for these persons. The majority of primary-care providers do not distinguish between eczema and atopic dermatitis when

describing chronic exfoliative skin conditions, including among infants and young children.

EV can be associated with systemic illness that includes fever and malaise. Management includes hemodynamic support (e.g., as for sepsis) and meticulous skin care (e.g., as for burn victims). Patients might require volume repletion and vigilant monitoring of electrolytes as a result of disruption of the dermal barrier. Patients with EV are at risk for secondary bacterial and fungal infections of the lesions, and antibacterials and antifungals are indicated as necessary.

One study determined that the mortality from EV was reduced from 30%–40% to 7% after the introduction of VIG. Therefore, establishing the diagnosis early and not delaying treatment with VIG is imperative to reducing mortality. Patients are usually severely ill and can require multiple doses of VIG. Virus can be isolated from EV lesions, making these patients highly infectious. Infection-control precautions should be used to prevent secondary transmission and nosocomial infection.

- **Progressive vaccinia** (PV) (also referred to as vaccinia necrosum, vaccinia gangrenosa, prolonged vaccinia, and disseminated vaccinia), is a rare, severe, and often lethal complication that occurs among persons with immunodeficiencies. This diagnosis should be suspected if the initial vaccination lesion continues to progress without apparent healing $\geq$15 days after smallpox vaccination. Anecdotal experience suggests that, despite treatment with VIG, persons with cell-mediated immune deficits have a poorer prognosis than those with humoral deficits.

  PV is characterized by painless progressive necrosis at the vaccination site with or without metastases to distant sites (e.g., skin, bones, and other viscera). The vaccination lesion does not heal, presumably secondary to an immune derangement, and progresses to an ulcerative lesion, often with central necrosis. Initially, limited or no inflammation appears at the site, and histopathology can reveal absence of inflammatory cells in the dermis. During the weeks that follow, patients might experience bacterial infection and signs of inflammation.

  With PV, vaccinia virus continues to spread locally and can metastasize to distant sites through viremia. Live vaccinia virus can be isolated from the skin lesions of these patients. Infection-control precautions, which include contact isolation, are required to avoid vaccinial infection of other persons and to limit risk for secondary infections.

  The differential diagnosis of PV includes severe bacterial infection, severe chickenpox, other necrotic conditions (e.g., gangrene), and disseminated herpes simplex infections. Persons at highest risk for PV include those with congenital or acquired immunodeficiencies, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), cancer, and those on immunosuppressive therapies for organ transplantation or autoimmune disease. The degree and type of immunocompromise probably correlates with the risk for PV, although the protective level of cellular count or humoral immunity is unknown.

Before the introduction of VIG and early antiviral medications, PV was universally fatal; but after VIG was used for PV treatment, the survival rate improved. Surgical debridement was used infrequently with variable success to treat the primary progressive necrotic lesions of PV. Management of PV should include aggressive therapy with VIG, intensive monitoring, and tertiary-level supportive care. Despite advances in medical care, PV probably will continue to be associated with a high mortality rate.

- **Postvaccinial central nervous system disease** after smallpox vaccination is most common among infants aged <12 months and is a diagnosis of exclusion. Clinical symptoms reflect cerebral or cerebellar dysfunction with headache, fever, vomiting, altered mental status, lethargy, seizures, and coma. Central nervous system (CNS) lesions occur in the cerebrum, medulla, and spinal cord. Lumbar puncture can reveal an increased opening cerebral spinal fluid (CSF) pressure, and examination of CSF might indicate monocytosis, lymphocytosis, and elevated CSF protein.

  Both postvaccinial encephalopathy (PVE) and postvaccinial encephalomyelitis (PVEM) have been described. PVE typically affects infants aged <2 years and reflects cerebral damage as a result of vascular changes. Acute onset of symptoms occurs 6–10 days postvaccination and can include seizures, hemiplegia, aphasia, and transient amnesia. Associated histopathological changes include generalized cerebral edema, mild lymphocytic menigineal infiltration, widespread ganglion degenerative changes, and occasionally, perivascular hemorrhages. Patients can be left with cerebral impairment and hemiplegia.

  PVEM (or encephalitis) affects persons aged ≥2 years and includes abrupt onset of fever, vomiting, headache, malaise, and anorexia approximately 11–15 days after vaccination. Symptoms can progress to loss of consciousness, amnesia, confusion, disorientation, restlessness, delirium, drowsiness, seizures, and coma with incontinence or urinary retention, obstinate constipation, and sometimes menigismus. CSF, although under increased pressure, reveals normal chemistries and cell count. Histopathological features include perivenous demyelination and microglial proliferation in demyelinated areas with lymphocytic infiltration but limited cerebral edema. These pathological features are similar to what is observed in other postinfectious encephalitides.

  The strain of vaccinia virus used in smallpox vaccines might influence the frequency of PVE and PVEM. Reports based on European data indicate generally higher rates of PVE among persons vaccinated with non-NYCBOH strains. In the United States, where the principal strain used was the NYCBOH, the occurrence of PVE or PVEM was rare among first-time vaccinees.

  No clinical criteria, radiographic findings, or laboratory tests are specific for the diagnosis of PVE. PVE/PVEM are diagnoses of exclusion, and other infectious or toxic etiologies should be considered before making these diagnoses.

  No study has indicated that VIG can be an effective therapy for PVE or PVEM, and therefore, VIG is not recommended for treatment of PVE or PVEM.

The incidence of PVE after smallpox vaccination with the NYCBOH strain is low; therefore, concomitant administration of VIG at time of vaccination has never been recommended with the NYCBOH strain.

No specific therapy exists for PVE or PVEM; however, supportive care, anticonvulsants, and intensive care might be required. Because the clinical symptoms of PVE or PVEM are not believed to be a result of replicating vaccinia virus, the role of antivirals is unclear.

- **Fetal vaccinia,** resulting from vaccinial transmission from mother to fetus, is a rare, but serious, complication of smallpox vaccination during pregnancy or shortly before conception; <50 cases have been reported in the literature. Fetal vaccinia is manifested by skin lesions and organ involvement, and often results in fetal or neonatal death. The skin lesions in the newborn infant are similar to those of GV or PV and can be confluent and extensive. The number of affected pregnancies maintained until term is limited. Affected pregnancies have been reported among women vaccinated in all three trimesters, among first-time vaccinees as well as in those being revaccinated, and among nonvaccinated contacts of vaccinees. Because fetal vaccinia is so rare, the frequency of, and risks for, fetal vaccinia cannot be reliably determined. Whether virus infects the fetus through blood or by direct contact with infected amniotic fluid is unknown. No known reliable intrauterine diagnostic test is available to confirm fetal infection.

  Apart from the characteristic pattern of fetal vaccinia, smallpox vaccination of pregnant women has not been clearly associated with prematurity, low birth weight, and fetal loss. In addition, smallpox vaccine has not been demonstrated to cause congenital malformations.

  VIG might be considered for a viable infant born with lesions, although no data exist for determining the appropriate dosage or estimating 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 congenital vaccinia among live-born infants, vaccination during pregnancy should not ordinarily be a reason to consider termination of pregnancy. No indication exists for routine, prophylactic use of VIG for an unintentionally vaccinated pregnant woman; however, VIG should not be withheld if a pregnant woman experiences a condition where VIG is needed (e.g., EV).

Other Vaccine-Specific Adverse Events

Less frequently reported adverse events temporally associated with after smallpox vaccination include myocarditis, pericarditis, precipitation of erythema nodosum leprosum or neuritis among leprosy patients, and osteomyelitis (sometimes confirmed by recovery of vaccinia virus). Reported skin changes at the vaccination scar have included malignant tumors (e.g., melanoma, discoid lupus, and localized myxedema as a symptom of Graves disease). Reported neurologic complications after smallpox vaccination include transverse myelitis, seizures, paralysis, polyneuritis, and brachial neuritis.

Whether these conditions are caused by smallpox vaccination or represent coincidental occurrences after vaccination is unclear. Temporal association alone does not prove causation.

Revaccination of Persons with History of Adverse Events

Persons with a history of an adverse reaction to smallpox vaccination that leads to deferral should not knowingly be placed in a situation where they might be exposed to smallpox. No absolute contraindications exist regarding vaccination of persons with high-risk exposures to smallpox; persons at greatest risk for experiencing serious vaccination complications are also at greatest risk for death from smallpox. In this situation, the benefits of smallpox vaccination probably outweigh the risks for an adverse reaction from smallpox vaccine.

Prophylaxis for Persons at High Risk Inadvertently Exposed to Vaccinia Virus Either Through Vaccination or Contact Transmission

Historically, VIG was administered prophylactically to persons at increased risk for vaccine-related adverse events who required vaccination or who were inadvertently vaccinated. However, VIG administration is not without risk, and 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 persons with contraindications to smallpox vaccination are inadvertently exposed to vaccinia and are otherwise well. Such persons should have careful clinical follow-up to ensure prompt diagnosis and treatment of an adverse event, if one occurs. Furthermore, in the absence of circulating smallpox virus, VIG is not recommended for concomitant use with smallpox vaccination among persons with contraindications. As recommended by the Advisory Committee on Immunization Practices (ACIP), careful screening criteria should be used to exclude persons with contraindications from preoutbreak smallpox vaccination programs.

Laboratory Diagnostics

Clinical evaluation and a careful patient history of recent smallpox vaccination or contact with a recent vaccinee are the mainstays of diagnosis of smallpox vaccine-related adverse events. In situations where clinical diagnosis is not straightforward, laboratory diagnostics for vaccinia might be helpful and might prevent inappropriate use of potentially toxic therapies. However, diagnostics for conditions easily confused with vaccinia infection (i.e., varicella, herpes zoster, herpes simplex, and enteroviruses), should be considered first, in particular for a nonvaccinee or someone believed to be a noncontact of a vaccinee.

Serologic testing for vaccinia is probably uninformative because it cannot be used to distinguish vaccinia immunity from vaccinia infection unless baseline antibody titers are available. Diagnostic tests for vaccinia are available only for research purposes, but are undergoing multicenter validation studies that might enable the Federal Drug Administration (FDA) to approve the test reagents for diagnostic use.

Laboratory Specimen Collection

A suspected case of an adverse event after smallpox vaccination should be promptly reported to the appropriate local, state, or territorial health department. When appropriate, public health officials might recommend that clinical specimens be collected for further evaluation of a possible case. Specimen collection guidelines are available at www.bt.cdc.gov/agent/smallpox/vaccination/vaccinia-specimen-collection.asp.

Treatments

Vaccinia Immune Globulin (VIG)

VIG is a sterile solution of the immunoglobulin fraction of plasma, containing antibodies to vaccinia virus from persons who were vaccinated with smallpox vaccine. The available preparation of VIG is a previously licensed intramuscular (IM) product (VIGIM) (produced by Baxter Healthcare Corporation in 1994) containing 0.01% thimerosal (a mercury derivative) as a preservative. Two new intravenous (IV) preparations (VIGIV) are in production and do not contain thimerosal. All preparations of VIG will be available as Investigational New Drug (IND) products through CDC and Department of Defense (DoD).

VIG has demonstrated efficacy in the treatment of smallpox vaccine adverse reactions that are secondary to continued vaccinia virus replication after vaccination. Such adverse reactions include EV, PV, or vaccinia necrosum, and severe cases of GV. VIG has no proven effectiveness for postvaccinia central nervous system disease.

VIG is recommended for treating EV and PV. Because the majority of cases of GV are self-limited, VIG is recommended for treating GV only if the patient is seriously ill or has serious underlying disease that is a risk factor for a complication of vaccination (e.g., such immunocompromised conditions as HIV/AIDS). VIG can also be useful in treating ocular vaccinia that results from inadvertent implantation. When ocular vaccinia with keratitis is present, consideration of VIG should include the possible increased risk for corneal scarring.

VIG Side Effects

- VIG administration has been associated with mild, moderate, and severe adverse reactions. Mild adverse reactions include local pain and tenderness, swelling, and erythema at the injection site after intramuscular (IM) administration of immunoglobulins and can persist from hours to 1–2 days after administration.
- Moderate adverse reactions include joint pain, diarrhea, dizziness, hyperkinesis, drowsiness, pruritis, rash, perspiration, and vasodilation. Back and abdominal pain, nausea, and vomiting can occur within the first 10 minutes of injection. Chills, fever, headache, myalgia, and fatigue can begin at the end of infusion and continue for hours. More severe reactions of this type might require pretreatment with corticosteroids or acetaminophen, if another dose of VIG is required.

- Serious adverse events associated with administration of intravenous (IV) VIG are expected to be similar to those observed with other intravenous immune globulin (IVIG) products, and can include hypotension, anaphylaxis and anaphylactoid systemic reactions, renal dysfunction, and aseptic meningitis syndrome (AMS). When AMS occurs, it usually begins from within hours to 2 days after treatment and can occur more frequently in association with high dosage (2 g/kg body weight) therapy. It is characterized by severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Discontinuation of IVIG treatment has resulted in remission of AMS within days without sequelae.
- Anaphylaxis and anaphylactoid systemic reactions have been reported after IM or IV injection of human immunoglobulin preparations. The symptoms of classic anaphylactic reactions include flushing, facial swelling, dyspnea, cyanosis, anxiety, nausea, vomiting, malaise, hypotension, loss of consciousness, and in certain cases, death. Symptoms appear from within seconds to hours after infusion. The treatment of such reactions is immediate discontinuation of immune globulin and administration of epinephrine, oxygen, antihistamines, IV steroids, and cardiorespiratory support.
- When proteins prepared from human blood or plasma are administered, the potential for transmission of infectious agents cannot be totally excluded. This also applies to infectious agents that might not have been discovered or characterized when the current preparations of VIG were formulated. To reduce the risk of transmitting infectious agents, stringent controls are applied in the selection of blood and plasma donors, and prescribed standards are used at plasma-collection centers, testing laboratories, and fractionation facilities.

VIG Risks and Contraindications

- Contraindications to VIG administration include an acute allergic reaction to thimerosal (for VIGIM) or a history of a severe reaction after administration of human immunoglobulin preparations. Persons with selective immunoglobulin A (IgA) deficiency might have antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.
- Whether VIG can cause fetal harm when administered to a pregnant woman or if it affects reproductive capacity is unknown. Although clinical experience with other preparations containing immunoglobulins indicates that no fetal adverse events result from immunoglobulins, no studies have evaluated the adverse effects of VIG on the fetus. VIG should be administered to a pregnant woman only if clearly needed. Similarly, whether VIG is excreted in breast milk is unknown; therefore, caution should be exercised when VIG is administered to a nursing woman.
- VIG is made from human plasma; therefore, a possible risk of transmission of viruses and a theoretical risk of transmission-adventitious agents that can cause Creutzfeldt-Jacob disease exist. The risk that these products contain infectious agents has been reduced by questioning plasma donors about risk factors for infection 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

Detailed instructions regarding the administration of IM and IV VIG are included in the Investigator´s Brochure portion of the investigational new drug (IND) materials that accompany the products. Refer to the original guideline document for further details.

Cidofovir

Cidofovir, a nucleotide analogue of cytosine, has demonstrated antiviral activity against certain orthopoxviruses in cell-based in vitro and animal model studies. Its effectiveness in the treatment of vaccinia-related complications among humans is unknown. Cidofovir has been demonstrated to be nephrotoxic among humans and carcinogenic among animals, even at low doses. It is administered with probenecid and hydration.

Cidofovir is approved by the United States Food and Drug Administration (FDA) for treating cytomegalovirus (CMV) retinitis among patients with acquired immune deficiency syndrome (AIDS). Its use for treating smallpox vaccination complications is recommended only under IND protocol sponsored by CDC. (Refer to the original guideline document for more information on the IND protocol.)

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 among humans; therefore, the benefit of cidofovir therapy for vaccinia-related complications is uncertain. Insufficient information exists to determine the appropriate dosing and accompanying hydration and dosing of probenecid if antiviral therapy is needed to treat smallpox vaccine-related adverse events among the pediatric age group. Dosages for these patients should be determined in consultation with specialists at CDC and the Department of Defense (DoD). Additional information regarding dosing and administration of cidofovir is included in the Investigator´s Brochure that accompanies the release of this product to the clinician when cidofovir is used under the IND protocol.

Cidofovir Side Effects

- The major complication of cidofovir therapy is renal toxicity, which is sometimes irreversible, results in renal failure, and requires dialysis to prevent death. To reduce the renal toxicity of cidofovir, it must be administered with careful IV hydration and with probenecid, a renal tubular blocking agent. Cidofovir has also been associated with neutropenia, proteinuria, decreased intraocular pressure/ocular hypotony, anterior uveitis/iritis, and metabolic acidosis. Cidofovir-related carcinogenicity, teratogenicity, and hypospermia have been reported in animal studies.
- Probenecid has been associated with headache, anorexia, nausea, vomiting, urinary frequency, hypersensitivity reactions, anemia, hemolytic anemia, nephritic syndrome, hepatic necrosis, gout, uric acid stones, and renal colic. Probenecid should be used with caution among children, pregnant women and persons with sulfa drug allergy (see manufacturer´s package insert).

Cidofovir Administration

Details for administration of cidofovir are included with the medication and IND materials that are shipped by CDC. Refer to the original guideline document for further details.

Requests for Clinical Consultation and IND Therapies and for Registries Enrollment

In October 2002, ACIP recommended that enhanced terrorism preparedness should include vaccination of smallpox public health response and health-care teams. Implementation of this vaccination program was determined to be the responsibility of the states and territories in conjunction with local predesignated hospitals. Before participation in the vaccination program, states and territories should establish a comprehensive program to manage vaccinees and their contacts who experience an adverse event after smallpox vaccination. Hospitals that participate should assign physicians with expertise in infectious diseases, neurology, dermatology, allergy/immunology, and ophthalmology to assess and manage adverse events among vaccinees and their contacts. Vaccinees and their affected contacts should have access to evaluation and medical care for a suspected adverse event 24 hours/day and 7 days/week. CDC will provide consultation to state and territorial public health officials, their surrogate providers, and other requesting physicians regarding recognition, evaluation, diagnosis, and treatment of adverse events after smallpox vaccination through an information line for clinicians that will be staffed 24 hours/day, 7 days/week. In addition, CDC will provide consultation for evaluation and care of persons with contraindications to smallpox vaccination that have an inadvertent exposure to vaccinia virus (e.g., vaccination of a pregnant woman or a person with atopic dermatitis). These persons also will be enrolled in a vaccination registry for prospective follow-up.

Referring providers should complete a thorough vaccination history and physical examination on all patients with a suspected adverse event before accessing CDC´s Clinician Information Line. In addition, high-resolution digital photographs of dermatological manifestations of adverse events can aid in the recognition of specific dermatological manifestations of adverse events and should be obtained with the patient´s permission and forwarded whenever possible. Providers seeking assistance should first contact their state health department before accessing the CDC consultation service or requesting VIG or cidofovir (Refer to Box 3 in the original guideline document).

To aid providers in discerning the presence or severity of vaccine-related complications, CDC has developed draft clinical evaluation tools to assist with expected adverse events (refer to the original guideline document).

Smallpox Vaccine Adverse Event Reporting

Providers are strongly encouraged to report serious adverse events to Vaccine Adverse Event Reporting System (VAERS) after the administration of the smallpox vaccine (Refer to Box 4 in original guideline document). VAERS is a passive reporting system for safety monitoring of all vaccines licensed in the United States, and is jointly managed by CDC and FDA. CDC and FDA will monitor smallpox vaccine-related adverse event reports daily, and will provide enhanced surveillance of adverse events after administration of the smallpox vaccine.

However, adverse events that are judged to be serious or unexpected and which require CDC consultation or IND therapies (VIG or cidofovir) should not be solely reported to VAERS. These cases should instead be immediately reported by phone to the appropriate state health department officials and CDC, who will assist the reporting provider with completion of a VAERS form. All other smallpox vaccine adverse events that are serious, but do not require CDC consultation or administration of IND therapies, should be reported directly to VAERS within 48 hours of recognition. All other adverse events should be directly reported to VAERS within 1 week.

Additional Information

CDC, in collaboration with the U.S. Department of Health and Human Services, has developed a website, which is available at www.bt.cdc.gov/training/smallpoxvaccine/reactions. Information and photographs related to smallpox vaccination, normal vaccination reactions, adverse events after vaccination, and treatments for adverse reactions can be located at this website.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Overall

The evidence supporting the recommendations is stated throughout the body of the guideline document.

Specific

- Smallpox vaccine response and adverse reaction data are derived from:
    1. reports from the 1960s
    2. CDC Smallpox Diary Card Database, 2001-2002 (CDC, unpublished data)
    3. 2001 vaccinations of 191 federal public health smallpox response team members (CDC, unpublished data)
- Vaccinia immune globulin (VIG), cidofovir, and ophthalmic antivirals, the interventions recommended in the treatment of specific complications of smallpox vaccination have not been tested in controlled clinical trials for efficacy against vaccinial infection. The recommendation to use VIG as first-line therapy is based on worldwide historical experience.
- Data upon which to base treatment recommendations for ocular vaccinial infection are limited. Published reports are primarily case series. The recommendations are based on available data and input from ophthalmology and infectious disease consultants.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Stringent medical screening of potential vaccinees for risk factors for adverse events, coupled with improved infection control measures to prevent vaccinia transmission, will probably decrease preventable complications of vaccination
- Appropriate diagnosis, treatment, and management of adverse reactions to smallpox vaccination

POTENTIAL HARMS

Adverse Reactions to Vaccination

Refer to "Major Recommendations" Field.

Vaccinia Immune Globulin (VIG)

Side Effects

VIG administration has been associated with mild, moderate, and severe adverse reactions. Refer to "VIG Side Effects" in the "Major Recommendations" section or to the original guideline document for more information.

Potential Risks

- Whether VIG can cause fetal harm when administered to a pregnant woman or if it affects reproductive capacity is unknown.
- Similarly, whether VIG is excreted in breast milk is unknown; therefore, caution should be exercised when VIG is administered to a nursing woman.
- VIG is made from human plasma; therefore, a possible risk of transmission of viruses and a theoretical risk of transmission-adventitious agents that can cause Creutzfeldt-Jacob disease exist.

Cidofovir

Side Effects/Potential Harms:

- Use associated with renal toxicity, which is sometimes irreversible, results in renal failure and requires dialysis to prevent death.
- Cidofovir has also been associated with neutropenia, proteinuria, decreased intraocular pressure/ocular hypotony, anterior uveitis/iritis, and metabolic acidosis. Cidofovir-related carcinogenicity, teratogenicity, and hypospermia have been reported in animal studies.
- Probenecid has been associated with headache, anorexia, nausea, vomiting, urinary frequency, hypersensitivity reactions, anemia, hemolytic anemia, nephritic syndrome, hepatic necrosis, gout, uric acid stones, and renal colic.

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindications to Vaccination

Smallpox vaccination in the preoutbreak setting is contraindicated for persons who have the following conditions or have a close contact with the following conditions:

- A history of atopic dermatitis (commonly referred to as eczema), irrespective of disease severity or activity; active acute, chronic, or exfoliative skin conditions that disrupt the epidermis
- Pregnant women or women who desire to become pregnant in the 28 days after vaccination
- And persons who are immunocompromised as a result of human immunodeficiency virus or acquired immunodeficiency syndrome, autoimmune conditions, cancer, radiation treatment, immunosuppressive medications, or other immunodeficiencies

Additional contraindications that apply only to vaccination candidates but do not include their close contacts are persons with smallpox vaccine-component allergies, women who are breastfeeding, those taking topical ocular steroid medications, those with moderate-to-severe intercurrent illness, and persons aged <18 years. In addition, history of Darier disease is a contraindication in a potential vaccinee and a contraindication if a household contact has active disease.

Contraindications to Vaccinia Immune Globulin (VIG)

- Persons with an acute allergic reaction to thimerosal
- Persons with a history of a severe reaction after administration of human immunoglobulin preparations

Contraindications to Probenecid (used with Cidofovir)

Probenecid should be used with caution among children, pregnant women and persons with sulfa drug allergy

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The frequencies of smallpox vaccine-associated adverse events were identified in studies of the 1960s. Because of the unknown prevalence of risk factors among today's population, precise predictions of adverse reaction rates after smallpox vaccination are unavailable.
- Guidance for treatment of ocular vaccinial infections includes off-label uses of topical ophthalmic trifluridine or vidarabine when recommended by an ophthalmologist. Where off-label treatments are considered, they are identified by the guideline developers.

- Cidofovir is approved by the U.S. Federal Drug Administration (FDA) for treating cytomegalovirus (CMV) retinitis among patients with acquired immune deficiency syndrome (AIDS). Its use for treating smallpox vaccination complications is recommended only under investigational new drug (IND) protocol sponsored by the Centers for Disease Control and Prevention (CDC).

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Pocket Guide/Reference Cards

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Cono J, Casey CG, Bell DM. Smallpox vaccination and adverse reactions. Guidance for clinicians. MMWR Recomm Rep 2003 Feb 21;52(RR-4):1-28. [82 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Jan 24

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Prepared by: Joanne Cono, MD (Bioterrorism Preparedness and Response Program, National Center for Infectious Diseases); Christine G. Casey, MD (Epidemiology and Surveillance Division, National Immunization Program); David M. Bell, MD (Office of the Director, National Center for Infectious Diseases)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site:

- HTML Format
- Portable Document Format (PDF)

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Pocket reference guide for the smallpox vaccine adverse events. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2002. 3 p. Electronic copies: Available in Portable Document Format (PDF) from the CDC Web site.
- Notice to readers: smallpox vaccine adverse events monitoring and response system for the first stage of the smallpox vaccination program. MMWR 2003

Feb 7;52(05);88-89. Electronic copies: Available in HTML format from the CDC Web site.

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. To order copies of the pocket guide please see the Immunization Educational and Training Materials (99-7392) Brochure - Smallpox Vaccination, Method and Reactions, 2002.

Additional information regarding smallpox preparation and response activities is available from the CDC Web site.

PATIENT RESOURCES

The following are available:

- Fact sheets: smallpox basics for the general public. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2003 Jan.
- Smallpox pre-vaccination information packet. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2003 Jan. 34 p.
- Vaccine information statement. What you need to know. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2003 Jan. 3 p.

Electronic copies of these and other related materials are available from the CDC Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was prepared by ECRI on February 12, 2003. It was not verified by the guideline developer. This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on November 17, 2005, following the U.S. Food and Drug Administration advisory on parenteral maltose/parenteral galactose/oral xylose-containing products.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 11/3/2008