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SMALLPOX VACCINATION REACTIONS, PROPHYLAXIS AND THERAPY OF COMPLICATIONS[a]

by

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INTRODUCTION

In October 1971, the United States Public Health Service changed its recommendations concerning smallpox vaccination from routine vaccination of preschool children to selective vaccination of persons at risk of acquiring smallpox.[1] Under the new recommendations vaccination should be given only to those individuals who are travelling to infected areas in parts of Asia and Africa, hospital employees, or personnel involved in seeing patients for public health purposes. Because of the new recommendations, the number of primary vaccinations and revaccinations should decrease markedly compared with 1970, when 3.9 million primary vaccinations and 8.0 million revaccinations were given.[2] Since the incidence of complications of vaccination is measured in terms of millions of vaccinations, the chance that a practitioner who follows the new recommendations will see a serious complication should approach zero, and the chances of seeing less serious complications will also proportionately decline.

Smallpox vaccination has several associated complications, some of which are preventable or treatable.[3,4,5] This review covers normal smallpox vaccination reactions, indications for prophylaxis, diagnostic criteria of vaccination complications, and management of complications. The problem of revaccination of a person who has had a complication is explored. The opinions presented are based on published reports and the experience of the authors.

New smallpox vaccination policy

The current United States smallpox vaccination policy recommends the vaccination of only those persons who are at great risk of contracting the disease. There are no absolute contra-indications to vaccination of an individual with a definite risk of exposure to smallpox,

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particularly persons in smallpox infected areas. The contraindications (pregnancy, age less than 12 months, history or presence of eczema or other chronic skin disease, or immune deficiency states) to vaccination are relative, because persons at greatest risk of developing serious complications from vaccination are also at greatest risk of death from smallpox.[6]

Technique - Expected reactions - Prophylaxis

Technique. The preferred site for vaccination is the skin over the insertion of the deltoid muscle or the posterior aspect of the arm over the triceps muscle. The multiple pressure technique involves cleaning the skin with water, when necessary, allowing this to dry, then placing a drop of vaccine on the cleansed area and pressing a sharp sterile needle tangentially to the skin through the vaccine. Ten pressures for primary vaccinees and 30 for revaccinees are recommended. Multiple puncture technique utilizes a bifurcated needle with a drop of vaccine which adheres between the prongs. The vaccine drop is transferred to the skin, the needle is held perpendicular to the skin and five strokes for primary vaccination or 15 for revaccination are made through the vaccine drop. Sufficient pressure to induce a trace of blood to appear will usually ensure a major reaction using either method. Excess vaccine should be wiped off and the area left uncovered.[6,7]

Expected primary and revaccination reactions. Proper inoculation of potent smallpox vaccine results in a smallpox vaccination major reaction in nearly 100% of primary vaccinees. From 70% to 100% of revaccinees should develop a major reaction, depending on the number of previous vaccinations and the time elapsed between the last major reaction and the present vaccination.[8,9,10,11,12] Two or three days after vaccination, pruritus and erythema may occur at the site of inoculation, sometimes with vesiculation. These are probably allergic phenomena and resolve after one or two days.[13] Six to eight days after vaccination, the vaccination site exhibits a Jennerian vesicle in primary and non-immune vaccinees, or an erythematous or indurated area surrounding a central lesion (either an ulcer or a scab) in individuals with residual immunity from previous smallpox infection or vaccination.[7] The Jennerian vesicle gradually resolves, and a crust forms over it by day 10 to 14. The formation of a crust often coincides with the development of sufficient immunity (both cellular and humoral) to control the reaction.[14,15] In a small percentage of patients, a Jennerian vesicle may not develop until after the eighth post-inoculation day, and crust formation will not begin until four to six days later. In some unusually severe primary reactions, the lesion may not begin to regress until 12-15 days after vaccination. Erythema with adenopathy, lymphangitis, and fever occur with many primary reactions.

An equivocal reaction is characterized by the lack of vesicle or central lesion (scab or ulcer) within six to eight days after inoculation. The presence or absence of induration and/or erythema does not affect this definition. This minimal response can be caused by impotent vaccine, poor vaccination technique, or (rarely) hyperimmunity to vaccinia. Since an equivocal response is not indicative of a boost in immunity, revaccination is indicated.

Prophylaxis for persons with contraindications. When a person with a contraindication to smallpox vaccination (history or presence of eczema in either the vaccinee or a household contact; acquired or inherited immune deficiency state; pregnancy; age less than 12 months) must be vaccinated, vaccinia hyperimmune globulin (VIG)[a] given in appropriate amounts (see below) should prevent adverse reactions.[3,16] VIG does not interfere with the normal evolution of a properly administered vaccination with high potency vaccine.

Agents used for prophylaxis or therapy. VIG is the most commonly used medication for prophylaxis or treatment of smallpox vaccination complications. The recommended prophylactic dosage is 0.3 cc per kg. The recommended therapeutic dose is 0.6 mg per kg per 24 hours, to be repeated as necessary.[6] Thiosemicarbazone (Marboran, Isatin B)[a] is a commonly requested,

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[a] Inclusion of trade names is for identification only and does not imply endorsement by the Public Health Service or the United States Department of Health, Education and Welfare.

but rarely used, drug for the treatment of vaccination complications.[17] It is still in the experimental stage, and is available only through physicians licensed to test it. Other drugs, such as idoxuridine[18] (Stoxil)[a] rifampicin[19,20] (Rifampin)[a] and Cytosine arabinoside[21] (Ara-C,[a] cytosar)[a] have in vitro activity against vaccinia and may be of use in the management of severe complications, such as vaccinia necrosum. Steroids are not recommended for treatment of most vaccination complications because of the possibility of immune suppression.[22] Steroids are occasionally used for treatment of patients with the Stevens-Johnson syndrome or cerebral edema secondary to post-vaccinial encephalitis.

Prophylaxis - by contraindication

1. History or presence of eczema or other chronic skin disease

A prophylactic dose of VIG should be given at the time of vaccination to any eczematous child or child with extensive chronic skin disease, who must be vaccinated; this is to prevent eczema vaccinatum. A prophylactic dose should also be administered to an eczematous child who is accidentally vaccinated or who comes in close contact with recently vaccinated children.

2. Acquired or inherited immune deficiency

When a person with a known immunologic defect has been accidentally vaccinated or has come in contact with a person who has been recently vaccinated, VIG should be administered in therapeutic doses. The immunologically compromised patient should be followed carefully after exposure. Apparently healing vaccinations in such patients have been known to break down as long as two months after vaccination.[23]

3. Pregnancy

The incidence of foetal infection with vaccinia following vaccination of pregnant women is so low that it cannot be measured from the data available. Sixteen cases of foetal vaccinia, all occurring since 1932, were found in an extensive search of the English and American literature.[5,22,24,25] Most such infections result from primary vaccination of the mother. There is no conclusive evidence of increased foetal wastage in women vaccinated during pregnancy.[26,27,28] The virus is non-teratogenic.[29] If a pregnant woman must be vaccinated and has not had a vaccination take (major reaction) within 10 years, a prophylactic dose of VIG at the time of vaccination may be given.

4. Age - Infants less than 12 months old

VIG in prophylactic amounts may be given to infants who are less than 12 months old and require vaccination; this is mainly to protect them against post-vaccinial encephalitis. The overall incidence of post-vaccinial encephalitis in the United States is 2.9 per million primary vaccinees, while for children under the age of one year it is 6.5 per million primary vaccinees.[3,4,5] Vaccination should not be delayed until after the first birthday if there is a reasonable chance that the child will come in contact with smallpox.

Complications of vaccination: Diagnosis, Management and Prognosis

A. Vaccinia necrosum (progressive vaccinia, vaccinia gangrenosa)

1. Diagnosis. If the initial vaccination lesion continues to progress without apparent healing 15 or more days after smallpox vaccination, then vaccinia necrosum should be considered. Erythema and lymphadenopathy may or may not be present. An acquired or

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existing underlying immunologic defect is associated with this complication, and must be sought if not previously recognized.[3,23] Bacterial and fungal infections and carcinoma of the skin should be excluded.

2. Management. Any patient suspected of having this lesion should be hospitalized and consultation should be sought immediately. Management may include specific immunologic therapy, surgical debridement, proper attention to fluid and electrolyte balance, and the treatment of any associated bacterial infections. Because of the high mortality associated with this illness, treatment should be directed by a physician who has had experience in treating viral diseases in immunologically deficient patients.

3. Prognosis. This complication was always fatal before the introduction of VIG. After the introduction of more advanced immunologic therapy, the case fatality ratio fell to about 20%,[3,4] with severity depending on the underlying cause of impairment of immune response. The absence of erythema and lymphadenopathy may indicate impairment of cell mediated immunity, and a poor prognosis.

B. Eczema vaccinatum

1. Diagnosis. This diagnosis should be considered if an individual with a history or clinical evidence of eczema develops vaccinial lesions away from the inoculation site. Clinicians should remember that vaccinia can spread by contact from a vaccinated child to an eczematous close contact. Pustular impetigo, eczema herpeticum, and smallpox should be excluded.

2. Management. VIG in therapeutic dosage should be given. New lesions should not appear more than 24 hours after initiation of treatment. Fever should lyse by 48 hours. If new lesions should occur after 24 hours, additional VIG is indicated. If new lesions continue to appear 24 hours after the second dose, the use of antiviral agents such as thiosemicarbazone (available from Burroughs Wellcome Laboratories) or idoxuridine (IDU) should be considered. Steroids are contraindicated in the management of this complication. Children less than two years of age with extensive eczematous lesions often die from dissemination of the virus, bacterial sepsis, fluid and electrolyte imbalance, or a combination of these causes.

3. Prognosis. Age, amount of skin involvement, previous vaccination status, and source of vaccinia (whether or not the child was the vaccinee or a contact of a vaccinee) are important determinants of prognosis. Case fatality ratios for untreated cases have been reported to be at least 6%.[30] Mortality of contacts, who are at greater risk, treated with VIG may be 4%.[4] Consultation is recommended for any patient who is seriously ill with this disease.

C. Post-vaccinal encephalitis

1. Diagnosis. This complication is similar to other post-infection encephalitides. It occurs in apparently normal individuals with no predisposing illness. Presenting symptoms are those usually associated with increased intracranial pressure and general encephalitis. Transverse myelitis, convulsions, muscular paralysis, polyneuritis, and brachial neuritis have also been described.[3,31,32,33] Because there are no specific diagnostic tests for this complication, other conditions that are treatable should be aggressively sought.

2. Management. VIG has not been shown to be effective in treating this syndrome once it has begun.[3] The usual therapy for cerebral edema should be undertaken, including the possible use of steroids.

3. Prognosis. Approximately 30% of those developing this complication succumb, and another 20% have permanent sequelae.[3,4]

D. Generalized vaccinia

1. Diagnosis. This is a generalized erythematous maculopapular rash occurring in primary vaccinees on otherwise normal skin. The lesions often vesiculate and then umbilicate as would any vaccinial lesion. Generalized vaccinia probably results from the rare blood-borne dissemination of virus in normal individuals. Allergic rashes are commonly confused with this rare complication. Other virus infections, including herpes simplex, enteroviruses, and smallpox, should also be ruled out.

2. Management. VIG is recommended if the patient is toxic or has a serious underlying disease. If the clinical course lasts more than 15 days, vaccinia necrosum or eczema vaccinatum should be seriously considered as alternate diagnoses.

3. Prognosis. Patients with true generalized vaccinia usually recover with little or no specific therapy.

E. Erythematous rash

1. Diagnosis. Erythematous or urticarial rashes often appear after smallpox vaccination. They generally occur about 10 days after primary vaccination (range four to 17 days), with either a roseola or an erythema multiforme appearance, accompanied occasionally by a vesicular component similar to that caused by enteroviruses. Either rash is benign, and the patient is often afebrile. Rarely, bullous erythema multiforme (Stevens-Johnson's syndrome) occurs.

2. Management. VIG is not recommended for this rash, and steroids should not be used. Since patients with Stevens-Johnson syndrome are usually quite ill, hospitalization, fluid and electrolyte therapy, and other supportive measures should be used as necessary.

3. Prognosis. These benign rashes resolve spontaneously within two to four days.

F. Accidental infection or implantation, including ocular vaccinia

1. Diagnosis. Vesicles either around the original vaccination site or the face, arms, legs, trunk, buttocks, and genitalia point to this diagnosis. They commonly occur on the eyelid or nose and are not haematogenously spread. The patient usually is not more toxic than would be expected from vaccination alone. Vaccinia virus can be cultured from these lesions.

2. Management. If infants are involved and appear toxic, then VIG in therapeutic dosages may be useful. Otherwise, VIG offers little therapeutic benefit. The lesions should be cultured for bacteria, since they are occasionally secondarily infected. Antibiotic therapy should be instituted if specific bacterial pathogens are found. When lesions occur on the eyelid, an opthalmologist should examine the child for possible corneal involvement. When this occurs, topical therapy with IDU may help.[34,35] Lesions occurring after the vaccination site has begun to resolve usually do not require VIG, since cellular and humoral immunity to vaccinia has already begun to develop.

3. Prognosis. Lesions heal without scarring in most cases. Ocular infections occasionally result in loss of eyelashes or deformed eyelids. In a large retrospective study, corneal scarring occurred in only one patient out of 348 with ocular vaccinia.[35]

G. Other conditions occurring with or after smallpox vaccination

1. Chicken-pox

Management. VIG is not recommended for patients with coincidental chicken-pox and vaccinia unless the vaccinia has widely superinfected the chicken-pox lesions.

2. Trauma, burns, open wounds

Management. Autoinoculation with vaccinia resulting in possible overwhelming viral infection may occur in these patients. If the lesion is extensive but has not yet been infected with vaccinia, VIG in a prophylactic dose is recommended. If vaccinia has already involved the lesion, then VIG in therapeutic amounts is required. VIG prophylaxis is not necessary for patients with lesions which do not involve a large surface area.

3. Miscellaneous

Myocarditis,[4,36] osteomyelitis,[37] malignant meloma,[38] and a variety of other conditions have been reported in association with smallpox vaccination.[39,40,41,42] The aetiologic relationship of these conditions with vaccinia is not clear. Because of the rarity and variety of these complications, each case must be treated as a separate entity.

Revaccination after vaccination complications

Erythematous rash and accidental infection following a vaccination are not contra-indications for repeat vaccination; VIG is not recommended. People who have eczema or a history of eczema can also be revaccinated utilizing VIG as required. Some experts feel that such patients should be revaccinated at frequent intervals to take advantage of their indigenous immunity to protect them from complications.

The risk accompanying revaccination for individuals who have had post-vaccinial encephalitis is unknown. There are no reports in the literature concerning the outcome of this procedure. The pathophysiology of this complication may be consistent with allergic reaction phenomena.[43] Since the responsible agent may be an antigen in the vehicle or the virus itself, revaccination may reactivate whatever caused the original problem.

Revaccination of individuals with a history of vaccinia necrosum is contraindicated. If the immune suppression was temporary (such as drug induced), then the possibility of a recurrence of this complication should be the same as is found in the general population - less than one per million vaccinations. However, if the cause is persistent, then the risk of revaccination under the protection of thereapeutic amounts of VIG should be balanced against the risk of acquiring smallpox. Immune suppressed individuals are at greater risk than normal persons of dying of smallpox if they contract the disease, and immune suppression is a definite contraindication to vaccination in the absence of immediate risk of acquiring smallpox.

SUMMARY

Smallpox vaccination in the United States is a routine public health measure which has been under intensive review during the last decade. The most frequently occurring adverse reactions to vaccination are benign and require little or no systemic therapy. These reactions include accidental infection, erythematous and urticarial rash, and generalized vaccinia. Chicken-pox occurring concurrently with vaccination presents no problem unless vaccinia has widely superinfected the chicken-pox lesions. There is no risk to the pregnant woman who is vaccinated, but there is a slight risk that the foetus will develop foetal vaccinia. The vaccinia does not cause congenital malformations. Vaccinia hyperimmune globulin in prophylactic dosage may be given to a pregnant woman who is travelling to a smallpox infected or endemic area in order to prevent foetal vaccinia.

Vaccinia necrosum and eczema vaccinatum require vigorous systemic therapy with VIG, and often thiosemicarbazone. Post-vaccinial encephalitis, while frequently serious, has not been shown to be ameliorated by VIG therapy, although there are data which suggest VIG has some value in prophylaxis for encephalitis. Prophylaxis, prompt recognition, and proper therapy may reduce the fatality rates of these complications.

Revaccination of patients who have suffered a complication is a frequent clinical problem. Revaccination of an individual who has had post-vaccinial encephalitis or vaccinia necrosum is contraindicated unless the risk of contracting smallpox outweighs the risk of the above two diseases. Revaccination of children who have had eczema vaccinatum is not contra-indicated. Revaccination of children with a history of accidental infection or erythematous or urticarial rash presents no known or theoretically increased risk.

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