Smallpox Vaccination
Management of Complications

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Infectious Diseases
Altru Health System
Objectives

- Describe normal and adverse events that can follow smallpox vaccination (AES).
- Identify laboratory testing useful for evaluating rash illness.
- Review pharmacology related to medical management of AES.
- Describe infection controls for patients with AES including empiric isolation for rash illness.
- List resources to assist with management of AES and rash illness.
About the photo images
www.bt.cdc.gov/training/smallpoxvaccine/reactions/default.htm

Images courtesy of:

- Vincent Fulginiti MD
- The Estate of Henry C. Kempe MD
- NIH/Smallpox Vaccination Dilution Studies
- Centers for Disease Control and Prevention
- New England Journal of Medicine
- Logical Images, Inc

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Primary Site Reaction
Smallpox Vaccine

Primary Vaccination Site Reaction

Day 4
Day 7
Day 14
Day 21
## Normal Reaction Time

<table>
<thead>
<tr>
<th>Day</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>vaccination</td>
</tr>
<tr>
<td>3-4</td>
<td>papule</td>
</tr>
<tr>
<td>5-6</td>
<td>vesicle with erythema</td>
</tr>
<tr>
<td>8-9</td>
<td>pustule</td>
</tr>
<tr>
<td>12 +</td>
<td>crusting</td>
</tr>
<tr>
<td>17 - 21</td>
<td>scar</td>
</tr>
</tbody>
</table>
Normal Systemic Symptoms

- Soreness
- Intense erythema
- Malaise
- Lymphadenopathy (local)
- Myalgia, H/A, chills, nausea
- Fever
Normal Reaction Frequency

- Lymphadenopathy: 25 – 50%
- Myalgia, H/A, chills, etc: 0.3 – 37%
- Fever > 37.7: 2.0 – 16.0%
Normal Reactions: Variants

- Local satellite reactions (2.4 - 6.6%)
- Lymphangitis
- Local edema
- Viral cellulitis
  - intense inflammation surrounding papule
- Treatment: supportive
Normal Variants of Vaccine Reaction

- Local edema at vaccination site
- Lymphangitis
- Regional lymphadenopathy (nonfluctuant)
- Satellite lesions
Local Reactions

- Allergic reactions to bandage and tape adhesives
- Large primary vaccination reactions ("robust primary takes" – RPT)
- Secondary bacterial infection
Robust Primary Takes (RPT)

- Normal variant
- >3 inches of erythema with induration, pain, warmth
- Occur in 5%-15%
- Peak at day 8-10
- Resemble bacterial infection
Satellite lesions
Lymphangitis
Viral Cellulitis
Edema
Revaccination

• Typical - pustule @ 6 - 8 days
• Major reaction - more rapid evolution
• Equivocal reaction
  – allergic reaction
  – no reaction
Revaccination
Accidental Administration

• PO, IV or IM
  – not advised

• Follow clinically
Accidental Implantation

• Autoinoculation or contact
Accidental Implantation

- Common
  - especially with primary vaccinees
Accidental Implantation

- Infants and children
- Susceptible population
  - eczema
  - skin disorders with open lesions
  - inflammatory eye lesions
Accidental Implantation

- Transfer of virus to another body part
- High viral load
Accidental Implantation - Diagnosis

• Appears like vaccination unless susceptible patients
  – eczema vaccinatum, keratitis, etc.

• Lab not required
Accidental Implantation Treatment

- One or few
  - supportive
- Multiple or large area, or toxic
  - VIG
Inadvertent Inoculation

• Uncomplicated lesions require no therapy, self-limited, resolve in ~3 weeks

• VIG may speed recovery if extensive or painful genital involvement

• Hand hygiene* after contact with vaccination site or contaminated material most effective prevention

*with soap and water or alcohol hand rub
Secondary Bacterial Infection

- More common among children than adults
- Usually *Staph aureus* or Group A beta hemolytic Streptococci
- Anaerobic and mixed infections may occur
- Evaluate with gram stain and culture
- Antibiotic therapy based on culture
Fetal Vaccinia

- Rare complication (<50 cases reported)
- Usually second or third trimester
- Fetal infection - spontaneous abortion
  Death usually occurs before birth or in perinatal period
- No known congenital malformations
- No known reliable intrauterine diagnostic test
Fetal Vaccinia

• **Clinical**
  – generalized vaccinia
  – progressive vaccinia

• **Diagnosis**
  – H/O vaccination
  – typical lesions

• **Treatment**
  – if viable - VIG
### Table 3. Rates of Complications from Vaccinia, According to Vaccination Status and Age.*

<table>
<thead>
<tr>
<th>Complication</th>
<th>Primary Vaccination (N = 650,000)</th>
<th>Revaccination (N = 998,000)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0–4 yr</td>
<td>5–19 yr</td>
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<tr>
<td>Accidental infection</td>
<td>564</td>
<td>371</td>
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<tr>
<td>Generalized vaccinia</td>
<td>263</td>
<td>140</td>
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<tr>
<td>Erythema multiforme</td>
<td>209</td>
<td>87</td>
</tr>
<tr>
<td>Eczema vaccinatum</td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td>Postvaccinal encephalitis</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Progressive vaccinia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>222</td>
<td>214</td>
</tr>
</tbody>
</table>

*Data are from a 1968 survey of 10 states.44 No deaths occurred.
†No children under the age of one year were revaccinated.
Eczema Vaccinatum

- Generalized spread in patient with eczema or true atopic dermatitis, or a history of eczema or atopic dermatitis
- Severity independent of the activity
- Severe cases among contacts
Eczema Vaccinatum
clinical

- Skin lesions may be papular, vesicular, or pustular
- May occur anywhere on the body
- Predilection for areas of previous atopic dermatitis
- Patients often severely ill

Sibling contact
Eczema Vaccinatum

**Clinical**

- May resemble septic shock
- Can be lethal
- Bacterial superinfections
- Abscess
- Resolve with extensive scarring
Eczema vaccinatum in contact to recently vaccinated child.

- Recovered without sequelae or permanent ocular damage.
Eczema Vaccinatum diagnosis

- **Characteristic lesions**
  - H/O vaccine or contact with a vaccinee

- **Lab may be required to differentiate**
  - HSV PCR

- **Septic work up**
Eczema Vaccinatum treatment

- **Management**
  - Hemodynamic support
  - Meticulous skin care
  - *Early treatment with VIG*
  - Treatment of secondary bacterial or fungal infections as needed

- Lesions contain *vaccinia virus*
Post-Vaccinial Encephalitis

- Usually affects primary vaccinees
- Meningoencephalitis
- Cause unknown - autoimmune theory
- Variety of CNS signs (e.g., ataxia, confusion, paralysis, seizures, or coma)
- 15%-25% die, 25% develop neurological sequelae
- Occurred 3-12 cases per million primary vaccinations
Post-Vaccinial Encephalitis

- Diagnosis of exclusion
  - HSV, EBV, VZV, enterovirus, arbovirus
- CSF may have increased opening pressure, lymphocytosis, elevated protein
- Treatment is supportive
- VIG not effective
- Anticonvulsive therapy and intensive care may be required
Erythema Multiforme

- May present as macules, papules, urticaria, or bulls-eye lesions
- Usually appears within 10 days
- Does not progress
- Does not contain vaccinia virus
Erythema Multiforme

- Increasing frequency @ younger age
  - < 4  - 164 cases/million
  - .20  - 30.3 cases/million

- Most erythematous, pruritic, and benign
Erythema Multiforme

- **Mild** - few patches and blotches
  - urticaria, vesicles, and/or pustules
- **Extensive** - most of body
- **Severe** - Stevens-Johnson Syndrome
Erythema Multiforme diagnosis

- **Rash**
  - H/O vaccination

- **Vesicles and pustules**
  - Difficult to differentiate
    - generalized vaccinia
    - accidental implantation
    - occurs later
    - devoid of massive erythema
    - may require viral studies
Erythema Multiforme treatment

- **Pruritis** - antihistamine
- **Skin**
  - no special care except
    - Stevens-Johnson
      - hospitalize
- **VIG** ineffective

2/3/2003
Erythema Multiforme
Ankle, Day 8
Erythema Induration from Pustule to Elbow
Rashes Following Smallpox Vaccine

- Flat, erythematous, macular, or urticarial lesions
- Usually do not become vesicular
- Do not appear to involve viral multiplication or systemic dissemination
- Occur approximately 10 days after vaccination
- Resolve spontaneously within 2 to 4 days
Generalized Vesicular Rash, Day 11
Generalized, Flat, Erythematous Rash, Leg, Day 13
Localized Vesicular Rash on Hands
Generalized Vaccinia

- Vesicles or pustules appearing on normal skin distant from the vaccination site
- Often accompanied by fever, headache, and myalgias
- Usually occur 6-9 days after vaccination
Generalized Vaccinia

- Generally benign
- Confused with eczema vaccinatum
- Pathogenesis
  - viremia
  - skin only target
  - ? Humoral defect
Generalized Vaccinia
clinical

• Skin lesion
  – similar to vaccine site except:
    • smaller
    • more rapid evolution
  – any part of the body
  – can be recurrent
    • every 4 - 6 weeks
    • as long as 1 year
Generalized Vaccinia
Differential Diagnosis

- Erythema multiforme
  - not umbilicated
  - doesn’t resemble vaccination
- Eczema vaccinatum
  - H/O eczema
  - distribution of eczema
Generalized Vaccinia

Differential Diagnosis

- Inadvertent inoculation at multiple sites
- Early progressive vaccinia
- Disseminated herpes
- Severe varicella
  - superficial vesicles
- Smallpox
Generalized Vaccinia

- Treatment
  - usually none
  - if extensive or recurrent then VIG
  - Work-up humoral defects
Generalized Vaccinia

- Generally self-limited, usually no treatment
- VIG considered for recurrent disease or severe disease
- Lesions contain vaccinia
Progressive Vaccinia

- Often life-threatening
- Other names
  - vaccinia necrosom
  - vaccinia gangrenosa
  - disseminated vaccinia
- Rare (1 / million primary vaccinees)
Progressive Vaccinia

- Primary vaccination does not heal
- Progresses to ulcerative lesion, often with central necrosis
- Little or no inflammation at the site and generally little pain
- Virus continues to spread locally and through viremia
Progressive Vaccinia
Who’s susceptible?

- Immunodeficiency
  - esp CMI
- HIV
- Cancer
- Organ transplant
- Immunomodulating drugs
Progressive Vaccinia pathogenesis

- Cell to cell spread
- Necrotic skin centrally
  - advancing edge
- Viremia
  - metastatic skin sites
  - evolve similarly
- Secondary bacteria, fungal, or parasitic (PCP)
Progressive Vaccinia
clinical

- Primary vaccine site doesn’t heal
- Ulcerative and/or pustular lesions with central necrosis
- Circumferential expansion
- Viremia cause satellite lesions
Progressive Vaccinia clinical

- No lymphadenopathy
- No splenomegaly
- Extensive tissue destruction
- Superinfections
- Sepsis, DIC
- Unmatched lymphocytes - GVHD
Progressive Vaccinia (vaccinia necrosum) in Patient with Chronic Granulocytic Leukemia
Progressive Vaccinia differential diagnosis

- Severe bacterial infection
  - severe inflammation
  - No H/O CMI
- Smallpox
- Chickenpox
  - lack vaccine site
  - superficial
  - various stages of rash
- Disseminated HSV
Progressive Vaccinia testing

- Rash and fever algorithm
- Consult Public Health & ID
- HSV PCR
- VZV PCR
- Viral cultures
- Stains
- Immunological work-up
  - HIV, flow cytometry etc
Progressive Vaccinia

- Requires aggressive therapy with VIG
  - up to 10 ml/kg
- Antiviral therapy?
  - Cidofovir
  - Ribavirin
- Surgical debridement?
  - Debulk viral load
Ocular Vaccinia

- May present as blepharitis, conjunctivitis, keratitis, iritis, or combination
- Treatment may include topical ophthalmic antiviral agents and VIG
Vaccinia keratitis

- Central grayish, disciform corneal lesion
- Progresses to deeper ring-like structure
Vaccinia keratitis

- Ophthalmologist referral
- Slit lamp
- Avoid VIG
- Vidarabine
- Trifluribine
- Acyclovir
- Combination antiviral nucleoside + IFN speeds healing
Evaluating Patients for Smallpox


current status:

acute, generalized vesicular or pustular rash illness protocol

Risk of Smallpox

1. Pastelle prodromal (defined below) AND
2. Classic oropharyngeal lesion (defined below) AND
3. Lesions in some stage of development (defined below)

Moderate Risk of Smallpox in Urgent Evaluation

1. Pastelle prodromal (defined below)
2. Other pastelle prodromal criteria (defined below)
3. 24-hour pastelle prodromal criteria (defined below)

Low Risk of Smallpox in Urgent Evaluation

1. No pastelle prodromal

If there are no naturally occurring cases of smallpoxapart in the world since 1977, a high risk of analysis is a public health and medical emergency.

Major Smallpox Criteria

1. Female prodromal: occurring 34 days before rash onset fever of 101°F and at least one of the following: vesiculaseptic, headache, backache, chills, vomiting, or severe dermatome pain
2. Classic smallpox lesions: vesicular, bullous, or pustular or vesicular and pustular; or vesicular or pustular
3. Lesions in same stage of development: on any one part of the body (i.e., the face, ears, or arms) at the lesions are in the same stage of development (i.e., all are vesicles, all are pustules)

Minor Smallpox Criteria

1. Classic lesions: occurring 1-3 days before rash onset fever of 101°F and at least one of the following: vesiculaseptic, headache, backache, chills, vomiting, or severe dermatome pain
2. Lesions in same stage of development: on any one part of the body (i.e., the face, ears, or arms) at the lesions are in the same stage of development (i.e., all are vesicles, all are pustules)

Common Conditions that Might be Confused with Smallpox

1. Hand-foot-mouth disease
2. Variola major
3. Other viral exanthems
4. Tropical smallpox
5. Chickenpox

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

Image Credits: Varicella/Zoster Image Library, National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services

For more information, please go to the CDC website: http://www.bt.cdc.gov/agent/smallpox/vsp-smallpox.asp
Evaluating Patients for Smallpox

Patient with Acute, Generalized Vesicular or Pustular Rash Illness

Institute Airborne & Contact Precautions
Alert Infection Control on Admission

Low Risk for Smallpox
(see criteria below)

- History and Exam
  Highly Suggestive of Varicella

- Varicella Testing
  Optional

Moderate Risk of Smallpox
(see criteria below)

- Diagnosis
  Uncertain

- Test for VZV and Other Conditions
  as Indicated

- Non-Smallpox Diagnosis Confirmed
  Report Results to Infx Control

- ID and/or Derm Consultation
  VZV +/- Other Lab Testing as indicated

- No Diagnosis Made
  Ensure Adequacy of Specimen
  ID or Derm Consultant Re-Evaluates Patient

- Smallpox Response Team
  Collects Specimens and Advises on Management

High Risk for Smallpox
(see criteria below)

- ID and/or Derm Consultation
  Alert Infx Control & Local and State Health Depts

- Institute Airborne & Contact Precautions

- Alert Infection Control on Admission

- Patient with Acute, Generalized Vesicular or Pustular Rash Illness

- Cannot R/O Smallpox
  Contact Local/State Health Dept

- Smallpox Testing at CDC

- NOT Smallpox
  Further Testing

- SMALLPOX

Altru Health System
Rapid Tests suitable for VSV (smallpox rule-out)

- Tzanck Smear - local cytology lab
- DFA VZV
  - done same day received at NDPHL
- Real time PCR

RULE IN VARICELLA
ND Public Health Lab (NDPHL)

- Contact: Mike Trythall or Bonna Cunningham
- Phone: 701-328-5262
- Collection kits/shipping containers -- available within 30 days to NDLRN Level A Laboratories.
  1) DFA Screen for HSV, enterovirus and varicella
     [Touch prep slides in collection kit.]
  2) RT-PCR for vaccinia – send to NDPHL
     [24 hour TAT with consultation.]
  3) Culture [M4 culture transport in collection kit.]
  4) Smallpox confirmation sent to LRN Variola Regional Labs [Contact NDPHL for assistance.]
Sample requirements for Poxvirus DNA

- Lesion “roofs” and crusts
- Vesicular fluids (touch prep)
- Biopsy, autopsy
- 10 ml clot tube; 5 ml EDTA

www.bt.cdc.gov/agent/smallpox/training/webcast/dec2002/files/laboratory-module.ppt
www.bt.cdc.gov/labissues/PackagingInfo.pdf
Lab methods for confirmation of orthopoxvirus diagnostics

- PCR DNA
- Electron microscopy
- Histopathology
- Viral Culture
Vaccinia Immune Globulin

• Immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine

• Indications:
  – eczema vaccinatum
  – progressive vaccinia
  – severe generalized vaccinia

• Limitations:
  – no role in smallpox
  – post-vaccinial encephalitis
Vaccinia Immune Globulin must weigh risk and benefits

- **Contraindications**
  - Vaccinial keratitis
    - increase scarring in rabbits
  - Serious allergy to human immunoglobulin products
  - Selective IgA deficiency
  - thimerosal allergy
- **Pregnancy - category C**
- **Lactation unknown if in breast milk**
Vaccinia Immune Globulin (IV) adverse effects

- Infusion
  - minimize with slow rate
- moderate toxicity
  - arthralgia, headaches, myalgias, fever, chills, pruritis etc.
- severe toxicity
  - anaphylaxis (IM or IV)
  - renal failure (IV)
  - aseptic meningitis (IV)
Vaccinia Immune Globulin IV formulation

- Refer to package guidelines
- Starting dose: 0.6 ml/kg = 6000U/kg = 100 mg/kg (adult and pediatrics)
- Starting infusion rate: 0.01 - 0.02 mL/kg/min, gradually increase to 0.08 mL/kg/min
- Repeat every 2 - 3 days if needed
Vaccinia Immune Globulin IM formulation

- Older method, IV should be used first
- **Dose**
  - 0.6 ml / kg IM
  - Buttock or anterolateral thigh
  - If dose exceeds 10 ml, divide into > 2 sites
  - **DO NOT GIVE IV**
  - May be repeated if needed
Vaccinia Immune Globulin

- Call state Public Health
- Consult with local ID doctor
Cidofovir (Vistide)

- Nucleotide analogue of cytosine
- Broad spectrum of activity against herpesviruses
- Activity against orthopoxviruses in cell-based and animal models
  - active in vitro against variola
  - active in animals against vaccinia infections
- Currently approved for treatment of CMV retinitis in persons with AIDS
- Available for treatment of vaccinia under IND
Cidofovir Adverse Events

- Renal toxicity
  - Proteinuria
  - Irreversible renal failure
- Neutropenia
- Anterior uveitis/iritis
- Metabolic acidosis
- Possible carcinogenicity and teratogenicity
- Probenecid adverse events
  - Headache, nausea, vomiting, hypersensitivity, hemolytic anemia, hepatic necrosis, gout, uric acid stones
Cidofovir Indications

- Second line treatment of complications of smallpox vaccination
- Use if patient fails to respond to VIG treatment
- Consult with CDC before use under IND
- Manufacturer recommends use with probenicid
Ribavirin

- IV ribavirin
  - Not commercially available
  - Effective in 1 case of progressive vaccinicia
Trifluridine (Viroptic)

- Pyrimidine nucleoside
- indicated HSV keratoconjunctivitis
- pregnancy risk - C
- lactation - unknown if secreted
- adverse reactions:
  - burning, stinging 1 - 10%
  - <1%: hyperemia, edema, keratopathy, keratitis, inc intraocular pressure
# Infection Controls

**for the patient with adverse event after smallpox vaccination**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less serious – normal vaccination variants, few satellite lesions, inadvertant inoculation</td>
<td>Contact Precautions</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>Standard Precautions</td>
</tr>
<tr>
<td>Vaccinia encephalitis</td>
<td>Contact and Airborne Precautions, until proven vaccina– then Standard</td>
</tr>
<tr>
<td>More Serious- generalized vaccinia, eczema vaccinatum, progressive vaccinia, fetal vaccinia</td>
<td>Contact and Airborne Precautions</td>
</tr>
<tr>
<td>Keratitis</td>
<td>Contact Precautions</td>
</tr>
<tr>
<td>Secondary Bacterial Infection</td>
<td>Contact Precautions</td>
</tr>
</tbody>
</table>
Empiric Isolation

• Screen for history of Smallpox vaccination or contact with vaccinated
  – may be unaware of an inadvertent exposure

• Meningoencephalitis
  – Droplet Isolation

• Vesicular or pustular rash illness
  – Airborne and Contact Isolation
### Infection Controls

#### Contact Isolation
- Standard precautions
- Private room
- Hand hygiene with antimicrobial soap or alcohol
- Gloves
- Gowns
- Dedicated equipment
- Good housekeeping

#### Airborne Isolation
- Standard precautions
- Negative pressure room
- N95 masks
**Infection Control- staffing**

<table>
<thead>
<tr>
<th>For routine assignment, choose HCW in this order</th>
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</thead>
<tbody>
<tr>
<td>Vaccinated HCW with “take” &lt;3 years. Wear N95 mask.</td>
</tr>
<tr>
<td>Hx of prior vaccination and no personal contraindications for smallpox vaccination. Wear N95 mask.</td>
</tr>
<tr>
<td>No prior smallpox vaccination and no personal contraindications for smallpox vaccination. Wear N95 mask.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In emergency situations when above not available</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCW with a contraindication in household member only. Scrupulous infection control precautions including N95 mask</td>
</tr>
<tr>
<td>HCW with a personal contraindication. Scrupulous infection control precautions including N95 mask</td>
</tr>
</tbody>
</table>
Resources

- www.bt.cdc.gov
- State ND
  - Health Dept 1-800-472-2180
  - Disease Control in Bismarck 701-328-2378
- CDC
  - 770-488-7100 if unable to call State PH
  - Smallpox Clinician Info Line 877-554-4625
Resources

• State Health Officers
  – Terry Dwelle, MD
  – Steve Pickard, MD

• Physicians
  – Shamoon Ahmed, MD
  – Paul Carson, MD
  – James Hargreaves, DO
  – Tze Shien Lo, MD
  – Kent Martin, MD
  – Roberto Patron, MD
  – Vinod Seith, MD
  – Raymond Smego, MD
  – Robert Tight, MD