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EVALUATING THE PATIENT WITH AN ACUTE, GENERALIZED VESICULAR OR PUSTULAR RASH ILLNESS AND DETERMINING THE RISK OF SMALLPOX

Editor's note: The following is reprinted from the CDC to assist clinicians in differential diagnosis of smallpox.

Many rash illnesses can present with vesicles and pustules. The purpose of this protocol is to provide a systematic approach to evaluating patients with generalized rash illnesses that will direct an appropriate clinical and public health response.

Clinicians who evaluate patients with rash illnesses need to be able to determine quickly if their patient may have smallpox. There are millions of cases of rash illness in the United States each year. Because there is no evidence that smallpox is being transmitted, the risk of smallpox is currently extremely low. For this reason, the focus is on identifying a classic case of smallpox. This means that the first case of smallpox might not be recognized in the first few days after rash onset when the presentation is nonspecific. With appropriate infection control procedures, the risk of smallpox transmission from an infected patient is low.

Clinical case definition for smallpox: an illness with acute onset of fever >101°F followed by a rash characterized by firm, deep-seated vesicles or pustules in the same stage of development without other apparent cause.

This case definition would not detect an atypical presentation of smallpox including hemorrhagic smallpox and flat-type (velvety) smallpox. In addition, given the extremely low likelihood of smallpox occurring, a case definition has been chosen that provides a high level of specificity (i.e., vesicular or pustular rash illness), rather than a high level of sensitivity (i.e., maculo or papular rash illness).

Please refer to the accompanying poster as a guide to evaluating patients with acute, generalized rash illnesses for smallpox.

The most common rash illness likely to be confused with smallpox is chickenpox (varicella). Table 1 lists characteristics that may be helpful in differentiating the two illnesses. Some other illnesses and conditions to consider in the differential diagnosis are shown in Table 2.

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Definitions:

Smallpox is infection with the variola virus
Chickenpox (varicella) is primary infection with the varicella-zoster virus (VZV), which thereafter remains dormant in the body for life
Shingles (herpes zoster) is reactivation of dormant varicella-zoster virus

ALWAYS WEAR A PROPERLY FITTED N95 (OR HIGHER QUALITY) RESPIRATOR, GLOVES AND GOWN WHEN EVALUATING A PATIENT WITH VESICULAR OR PUSTULAR RASH ILLNESS THAT COULD BE SMALLPOX.

Contact and Airborne Precautions: If a patient presents to an emergency department or clinic with an acute generalized vesicular or pustular rash illness, care should be taken to decrease the risk of disease transmission. Patients should not be left in common waiting areas but placed immediately in a private, negative airflow room with the door kept closed. If the patient is being admitted or held for observation, institute appropriate airborne and contact precautions and alert the infection control department. These precautions include:

- Patient should be placed in a private, negative airflow room (airborne infection isolation). Keep the door closed at all times, except when staff or the patient must enter or exit.
- Staff and visitors should wear respirators (N95 or higher quality), gloves and gowns.
- Patient should wear surgical mask whenever he/she must be outside of their negative pressure isolation room and must be gowned or wrapped in a sheet so that the rash is fully covered.

Table 1. Differentiating smallpox (variola) from chickenpox (varicella)

Characteristic	Smallpox	Chickenpox (varicella)
Febrile prodrome	Severe prodrome 1-4 days before rash onset with temperature > 101°F (usually 102-104°F) and systemic complaints (prostration, headache, backache, chills, vomiting, abdominal pain)	Children rarely have a prodrome; older children and adults may have a mild prodrome with low grade fever and/or malaise for 1-2 days before rash onset
Appearance of lesions	Hard/firm well circumscribed pustules; may become confluent or umbilicated	Superficial vesicles with surrounding erythema
Stage of lesions on any one part of the body	All lesions are in the same stage of development on any one part of the body	Lesions in different stages of evolution (within 24 hours of rash onset there are papules, vesicles, and crusts
Distribution of the rash on the body	Centrifugal distribution: lesions concentrated on the face and distal extremities; fewer lesions on the trunk	Centripetal distribution: lesions concentrated on the trunk with fewer lesions on the extremities; face and scalp frequently involved
Initial lesions	Oral mucosa, face or forearms	Face then trunk
Oral lesions	Yes–early on (may not be noticed by patient)	May occur
Severity of illness	Patients generally very ill; may be toxic or moribund	Most patients not severely ill; may be febrile, rarely critically ill unless complications develop
Rate of evolution of rash	Slow evolution: each stage of rash lasts 1-2 days	Rapid evolution: lesions evolve from macules to papules to crusted lesions in <24 hours
Lesions on palms or soles	Seen in the majority of cases	Occurs very rarely
Hemorrhagic lesions	Occurs in highly lethal variant of smallpox	Can occur
Exposure to varicella or herpes zoster	N/A	50-80% of cases are aware of an exposure to chickenpox or shingles 10-21 days before rash onset
History or prior chickenpox	N/A	Second cases very rare–makes varicella less likely

History and Physical Examination: Ask detailed questions about any symptoms preceding rash onset, including prodromal symptoms and clinical features in the 1-4 days before rash onset, contact with any ill individuals (especially those with a rash illness), history of prior varicella or herpes zoster, and history of varicella vaccination (vaccine available since 1995). In persons born before 1972, those who served in the military or worked in medical laboratories, ask about smallpox vaccination and look for a vaccination scar (U.S. children were routinely vaccinated until 1971, military personnel until 1990, and persons working with orthopoxviruses continue to be vaccinated). In addition, determine if the patient is immunocompetent, which medications (prescription and over-the-counter) the patient has taken and whether and where the patient has traveled.

This information will be helpful in evaluating the patient, determining which illnesses are in the differential diagnosis, and finally, if smallpox is a consideration, will be used to classify a case patient into low, moderate or high risk categories for smallpox.

CRITERIA FOR DETERMINING RISK OF SMALLPOX

High Risk	Meets all three major smallpox criteria
Moderate Risk	Febrile prodrome and 1 other major smallpox criterion OR Febrile prodrome and >4 minor smallpox criteria
Low Risk	No febrile prodrome OR Febrile prodrome and <4 minor smallpox criteria

MAJOR DIAGNOSTIC CRITERIA

1. Febrile prodrome: occurring 1-4 days before rash onset: fever >101F *and* at least one of the following: prostration, headache, backache, chills, vomiting or severe abdominal pain
2. Classic smallpox lesions: deep-seated, firm/hard, round, well-circumscribed vesicles or pustules; as they evolve, lesions may become umbilicated or confluent

Table 2. Common conditions that might be confused with smallpox

Condition	Clinical Clues
Varicella (primary infection with varicella zoster virus)	Most common in children <10 years; children usually do not have a viral prodrome
Disseminated herpes zoster	Immunocompromised or elderly persons; rash looks like varicella, usually begins in dermatomal distribution
Impetigo (*Streptococcus pyogenes, Staphylococcus aureus)*	Honey-colored crusted plaques with bullae are classic but may begin as vesicles; regional not disseminated; patients generally not ill
Drug eruptions	Exposure to medications; rash often generalized
Contact dermatitis	Itching; contact with possible allergens; rash often localized in pattern suggesting external contact
Erythema multiforme minor	Target, "bull's eye" or iris lesions; often follows recurrent herpes simplex virus infections; may involve hands and feet (incl. palms and soles)
Erythema multiforme major (Stevens-Johnson Syndrome)	Major form involves mucous membranes and conjunctivae; there may be target lesions or vesicles
Enteroviruses incl. Hand, Foot and Mouth disease	Summer and fall; fever and mild pharyngitis 1-2 days before rash onset; lesions initially maculopapular but evolve into whitish-grey, tender, flat often oval vesicles; peripheral distribution (hand, feet, mounth) or disseminated
Disseminated herpes simplex	Lesions indistinguishable from varicella; immunocompromised host
Scabies; insect bites (incl. fleas)	Itching is a major symptom; patient is not febrile and is otherwise well
Molluscum contagiosum	May disseminate in immunosuppressed persons; rash is chronic and does not evolve

Variant presentations of smallpox: a small percentage of persons will present with hemorrhagic smallpox (can be mistaken for meningococcemia) or with flat-type smallpox. Both variants are highly infectious and carry a high mortality.

3. Lesions in the same stage of development: on any ONE part of the body (i.e. the face, or the arm) all the lesions are all in the same stage of development (i.e. all are vesicles or all are pustules)

MINOR SMALLPOX CRITERIA

1. Centrifugal distribution: greatest concentration of lesions on face and distal extremities
2. First lesions on the oral mucosa/palate, face, or forearms
3. Severity: Patient appears toxic or moribund
4. Slow rash evolution: lesions evolved from macules to papules to pustules over days (each stage lasts 1-2 days)
5. Lesions on the palms and/or soles

GUIDANCE FOR CLINICAL AND PUBLIC HEALTH MANAGEMENT

Moderate and high risk– obtain infectious diseases and/or dermatology consultation urgently (if available), proceed with laboratory testing for confirmation or exclusion of varicella or other diagnoses in the differential diagnosis. Initiate treatment for likely etiology as clinically indicated. Preferred tests for rapid identification of varicella-zoster virus are discussed below.

If high risk after consultation with infectious diseases or dermatology specialist:

1. Classify as a suspected smallpox case (a suspected smallpox case is a medical and public health emergency).
2. Report suspected case immediately by telephone to the Connecticut Department of Public Health (CDPH) per state requirements. CDPH's weekday number for reporting is 860-509-7994. After hours and weekends call 860-509-8000.
3. The CDPH will evaluate case; if the CDPH determines the case to be high risk for smallpox, the state will contact CDC for assistance including specimen collection and testing.
4. If possible, take digital photos for consultation with experts.
5. Treat patient as clinically indicated. Do not delay treatment for other likely conditions in the differential diagnosis while awaiting response team.

LABORATORY TESTING OF SPECIMENS FOR VARICELLA-ZOSTER VIRUS (VZV)

IMPORTANT: Collect >3 good specimens from each patient for routine and confirmatory testing. No test can

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distinguish between chickenpox (varicella) and disseminated shingles (disseminated herpes zoster) since the same virus causes both conditions. Herpes zoster is a reactivation of the virus that persists in a dormant state in the body from the time of initial infection with chickenpox. The two conditions are distinguished on the basis of prior evidence of immunity or previous disease and careful history.

Preferred tests for rapid diagnosis of varicella-zoster virus:

1. Direct fluorescence antibody (DFA)—rapid method for detecting VZV directly in cells using anti-VZV antibody conjugated to fluorescein dye; this technique is very sensitive and specific, but is critically dependent on careful specimen collection. Avoid contamination of the specimen with blood, since VZV antibodies introduced from the blood can result in false negatives. Do not draw fluid from a vesicle using a syringe since cellular material is needed for testing.

2. Indirect fluorescence antibody (IFA) –similar to DFA (above)

3. Polymerase chain reaction (PCR) of vesicular fluid or scabs is one of the most sensitive and specific methods available; it has the shortcomings of requiring 8-12 hours to perform using specialized equipment. It is not widely available, though some laboratories and tertiary care hospitals have this capability.

The CDPH Laboratory can provide rapid testing for varicella-zoster virus as needed, including on an emergency basis for smallpox suspects (860-509-8615).

Notice to Readers: Smallpox: What Every Clinician Should Know—A Self-Study Course

Smallpox disease was eradicated in 1977, but because smallpox virus could be used as an agent of bioterrorism, health-care providers should familiarize themselves with the disease and the vaccine that prevents it. On the program "Smallpox: What Every Clinician Should Know," specialists discuss methods designed to improve health-care providers' ability to recognize, diagnose, and report smallpox disease. The program may be viewed on the Internet or on videotape, and continuing education credits (CEU, CNE, CME, and CHES) are offered until the end of 2003.

Additional information and the archived webcast are available at http://www.phppo.cdc.gov/phtn/1213smallpox.asp. A videotape of the program is available from the Public Health Foundation, telephone 877-252-1200 (United States) or 301-645-7773 (International) from 9 a.m. to 5 p.m. EST, or e-mail info@phf.org. When requesting a videotape by e-mail, indicate "Smallpox: What Every Clinician Should Know" on the subject line.