Acute, Generalized Vesicular or Pustular Rash Illness Testing Protocol in the United States

Introduction
This protocol has been developed to illustrate the types of laboratory testing to be undertaken in different situations involving patients with acute, generalized vesicular or pustular rash illness. The protocol is composed of four charts, each illustrating a different set of symptoms or circumstances. It has been designed to correlate with “Evaluating Patients for Smallpox: Acute, Generalized Vesicular or Pustular Rash Illness Protocol” (www.bt.cdc.gov/agent/smallpox/diagnosis/riskalgorithm).

Chart 1 lists the symptoms associated with acute, generalized vesicular or pustular rash illness and categorizes the risk of smallpox according to the patient’s signs and symptoms.

Chart 2 presents a flow chart for laboratory testing of specimens from patients presenting with acute generalized vesicular or pustular rash illness. A two-armed algorithm is presented to reduce the time to receive results and to ensure that testing of high-risk specimens is confined to laboratories with appropriate biosafety levels and expertise. The two arms of the testing algorithm are for 1) specimens from individuals with low- and moderate-risk symptoms and 2) specimens from individuals with high-risk symptoms.

Chart 3 presents a testing algorithm that should be used when a smallpox vaccine adverse event or monkeypox infection is suspected.

Chart 4 presents an orthopoxvirus testing algorithm for environmental samples.

The testing protocols are supported at Laboratory Response Network (LRN) reference laboratories. Details for performance and interpretation of each assay are specified in each LRN procedure.

Details on specimen collection can be found at the following websites:

- Smallpox vaccine: www.bt.cdc.gov/agent/smallpox/vaccination/vaccinia-specimen-collection.asp
- Monkeypox: www.cdc.gov/ncidod/monkeypox/diagspecimens.htm

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Chart 1. Acute, Generalized Vesicular or Pustular Rash Illness Protocol

From the "CDC Protocol for Evaluating Patients for Smallpox" at www.bt.cdc.gov/agent/smallpox/diagnosis/evalposter.asp

Patient with Acute, Generalized Vesicular or Pustular Rash Illness

Institute Airborne & Contact Precautions
Alert Infection Control on Admission

Low Risk of Smallpox
(see criteria below)

Moderate Risk of Smallpox
(see criteria below)

High Risk of Smallpox
(see criteria below)

Low Risk of Smallpox

Moderate Risk of Smallpox

High Risk of Smallpox

Risk of Smallpox

High Risk of Smallpox
1. Febrile prodrome AND
2. Classic smallpox lesion AND
3. Lesions in same stage of development

Moderate Risk of Smallpox
Febrile prodrome AND one other MAJOR smallpox criterion
OR
Febrile prodrome AND ≥4 MINOR smallpox criteria

Low Risk of Smallpox
No febrile prodrome
OR
Febrile prodrome AND <4 MINOR smallpox criteria

Major smallpox criteria:
• Febrile prodrome
  • >101°F, 1-4 days prior to rash onset
  • with headache, back ache, or abdominal pain
• Firm, deep seated, well circumscribed vesicles/pustules
• Lesions in the same stage of development in any one area of the body

Minor smallpox criteria:
• Centrifugal distribution
• First lesions in the pharynx, oral mucosa
• Patient appears “toxic”
• Slow evolution of rash
  ▶ 1-2 days each stage: macule, papule, vesicle
• Lesions on the palms and soles

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Chart 2. Laboratory Testing for Acute, Generalized Vesicular or Pustular Rash Illness in the United States

Consider:
• Tzanck smear (herpesviruses)
• EM, if available

Rule out variola prior to other testing. Initial case (or cases) testing will be performed by LRN Variola Surge Laboratory. CDC will also test duplicate (split) sample simultaneously, if transport is feasible.

EM at local facility
BSL-3 preparation of grids

EM (if available)

EM at local facility
BSL-3 preparation of grids

POS for non-POX
NEG

Diagnosis/ no further testing (unless clinically indicated)

Non-variola orthopoxvirus PCR: POS
Orthopox PCR: POS
Vaccine related adverse event or possible Monkeypox. Contact CDC

All orthopox tests NEG:
Perform the following:
• DFA: VZV, HSV
• PCR: VZV, HSV, Enterovirus
• Viral culture and other diagnostic tests as clinically indicated.

If all tests are NEG:
• Re-evaluate patient condition and assess need for dermatologic and histologic testing, including tests for erythema multiforme; consider biopsy.
• Obtain detailed information about possible exposure to smallpox vaccines. If possible exposure, LRN lab will perform Non-variola Orthopox PCR.

If patient smallpox risk classification changes to high risk during further evaluation, follow appropriate protocol for high risk patient. Refer all specimens to CDC and/or LRN labs with Variola PCR testing capability. Sequester all viral cultures and specimens. Contact PHL for transport of specimens. Initiate chain of custody.

If VZV diagnosis is questionable, begin lab testing as clinically indicated

Take digital photos of all clinical presentations! (for downloading to CDC)

Vaccine Adverse Event or Monkeypox

Consultation with PHL and CDC

Results should not be released without CDC confirmation.
• Once reliable performance of assays in surge labs is demonstrated (post-event), CDC confirmation may be discontinued.

LRN Variola Surge Labs (C+): Enhanced BSL-3 required

• Variola real-time PCR
• Orthopox real-time PCR
• Non-variola orthopoxvirus real-time PCR
• EM (if available)

Non-variola orthopoxvirus & Orthopox PCR POS & Variola PCR NEG =
Vaccine Adverse Event or Monkeypox

Non-variola orthopox & Orthopox PCR both POSITIVE
HIGHLY suggestive of SMALLPOX
CALL CDC immediately prior to release of results

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Chart 3. Laboratory Testing for Suspected Smallpox Vaccine (Vaccinia) Adverse Events or Monkeypox in the United States

Patient with Suspected Vaccine Related Adverse Event or Monkeypox

All clinical labs and Reference LRN labs with no PCR capacity
Refer only

LRN Labs (with PCR capability)
- Non-variola orthopoxvirus real-time PCR
- Orthopox real-time PCR
- EM-(if available))

Test Results

Non-variola orthopoxvirus PCR: POS
Orthopox PCR: POS
EM(optional): POS for poxvirus

Vaccine adverse related event or Monkeypox.
Evaluate exposure history and contact CDC submit specimen for confirmatory tests.

Non-variola orthopoxvirus PCR: NEG
Orthopox PCR: NEG
EM(optional): NEG for poxvirus

- Re-evaluate patient condition and assess need for dermatologic and histologic testing, including tests for erythema multiforme; consider biopsy.
- Perform:
  - DFA: VZV, HSV
  - PCR: VZV, HSV, Enterovirus
  - Viral culture and other diagnostic tests as clinically indicated.

Non-variola orthopoxvirus PCR: NEG
Orthopox PCR: POS
EM: POS or NEG for poxvirus

Poxvirus identified - possible variola *
Refer immediately to CDC for confirmatory testing

* NOTE: Could also represent differential sensitivities of the assays

Acceptable specimens:
- Vesicular “touch prep”
- Vesicle roof
- Vesicular swab
- Ocular swab or impression slide
- Biopsy specimens

NOTE: A non-variola orthopoxvirus PCR POS and orthopox PCR NEG should not be generated. If that occurs, consult CDC.

Take digital photos of all clinical presentations!
Chart 4. Laboratory Testing for Environmental Samples in the United States

Initiate Chain-of-Custody documentation

Environmental Samples
Law Enforcement Credible Threat Assessment;
(Explosives, radiation and toxins ruled out)

Clinical Labs
Refer only

LRN Reference Labs (BSL-3)
- Orthopox real-time PCR
- Non-variola orthopoxvirus real-time PCR
- EM--(with CDC consultation only)

Test Results

Orthopox PCR: NEG
Non-variola orthopoxvirus PCR: NEG
EM: NEG for poxvirus

Orthopox PCR: POS
Non-variola orthopoxvirus PCR: POS
EM: POS or NEG for poxvirus

Orthopox PCR: POS
Non-variola orthopoxvirus PCR: NEG
EM: POS or NEG for poxvirus

Orthopoxvirus ruled out.
Assess need for further testing with law enforcement. Report negative results to other groups investigating specimens.

Orthopoxvirus identified - most likely non-variola.
Refer to CDC for confirmatory testing.

Orthopoxvirus identified - possible variola.
Refer immediately to CDC or LRN Variola Surge laboratory for confirmatory testing.

NOTE: A non-variola orthopoxvirus PCR POS and orthopox PCR NEG should not be generated. If that occurs, consult CDC.