Smallpox Information for Professionals

Agent: Although the disease smallpox was eradicated in 1976 and vaccination discontinued in 1980, questions remain about the presence of variola (smallpox) virus in certain countries. Because the virus is stable in the environment and can be spread by either respiratory or direct contact exposure, the virus is a prime candidate for use as a biological weapon in aerosol form or deposited onto fomites.

Reporting Requirements for Disease: Immediately report any suspect cases of smallpox to your local health authority; or, call the Texas Department of State Health Services at 1-800-252-8239.

Infection Control: Patients should be considered infectious until scabs separate, which usually takes about three weeks from the time of infection. However, separated scabs themselves may contain infectious viruses for long periods of time. Isolation with Contact and Airborne Precautions should be exercised for patients and all contacts for a minimum of 16-17 days following exposure. Since the risk for transmission is high and few hospitals will have enough negative pressure rooms for proper isolation, isolation in the home or other nonhospital facilities should be considered where possible or patients should be cared for in a hospital designated for smallpox patients.

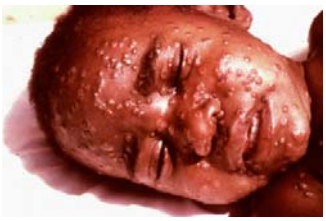
All medical personnel, family members, and other persons directly caring for a patient must be vaccinated as soon as possible but no later than four days. Outside of the hospital setting, patients and household contacts should wear a N95 or better mask. Caregivers should wear disposable gowns and gloves. Bed linens, clothing, and other exposed articles must be sterilized or incinerated. If contaminated materials cannot be readily incinerated or sterilized, it is recommended that the materials be immediately disposed of in a 10% chlorine solution. Experienced, vaccinated personnel should handle all specimens, and virus culture must be performed in BSL4 facilities.

Incubation Period: 7-17 days

Signs and Symptoms: The prodrome lasts 2-4 days and includes malaise, fever >101o F (100%), rigors (60%), severe headaches (90%), and backaches (90%). Vomiting and sore throat (50%), diarrhea, abdominal pain, confusion, or convulsions (<20%) may ensue. Coryza, conjunctivitis, and lymphadenopathy are usually absent, but cough may occur secondary to laryngeal/tracheal involvement. The prodrome is followed by defervescence and the appearance of a rash that classically progresses from maculae to papules to vesicles to pustules (that feel like hard peas beneath the skin) and scabs over a 7- to14-day period. The centrifugally distributed lesions usually appear first on the palate/pharynx, then face, proximal extremities, and finally palms/soles; within an area, lesions are in the same developmental stage. Petechiae may be seen.

Eight (WHO/Rao) types of smallpox with widely varying case fatality rates (CFRs) are recognized: early and late hemorrhagic (100% CFR) and the flat (>90% CFR) types lack typical pustular lesions; CFRs for patients with classic semiconfluent or confluent rashes range from 25 - 75% and for patients with

discrete or modified forms, from 2 -10%. Patients with “variola sine eruptione” rarely die (≤2%). Variants are distributed as 17% hemorrhagic; 20% flat; 58% ordinary; and 4% modified. All eight forms may occur during an epidemic, any one of which may be an index case. In the absence of vaccination, young adults (under the age of 30), children, and the elderly generally have more severe disease and high mortality. Vaccine provides some protection even over long periods of time. Severe disease and death is less common in the vaccinated and occurs mostly in the elderly vaccinated several years ago.

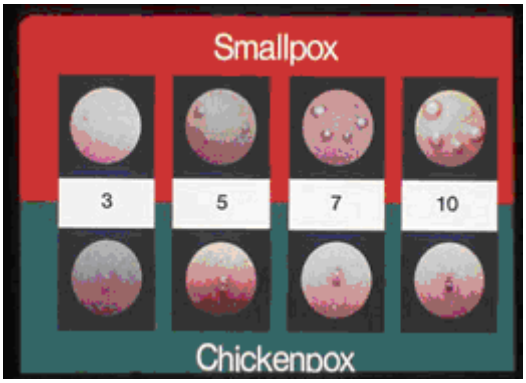


Child with Smallpox (Courtesy: Centers for Disease Control)

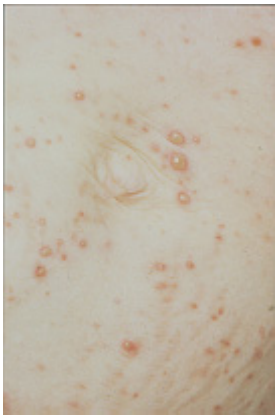
Diagnosis:
Differential Diagnosis: The most important and difficult differential diagnoses for smallpox are chickenpox and monkeypox. Chickenpox lesions generally start on the trunk in crops, which develop at different stages. Smallpox and monkeypox lesions typically start centripetally, on the face and extremities, including the palms and soles of the feet. Lesions on the soft palate are feature of measles, but are also seen in smallpox. Monkeypox is difficult to differentiate clinically from smallpox; however, monkeypox patients have enlarged lymph nodes, and their temperature is rarely as high as in smallpox. Both diseases may result in conjunctivitis, but in general smallpox is a more severe disease than either chickenpox or monkeypox.

Patients with the early and late hemorrhagic and flat types of smallpox never develop pustular lesions; their illnesses must be differentiated from other causes of acute erythroderma such as Stevens Johnson syndrome, Kawasaki syndrome, scarlet fever, toxic shock syndrome, measles, and erysipelas. Stevens Johnson syndrome, scarlet fever, toxic shock syndrome, and erysipelas lack a prodrome and Kawasaki, scarlet fever, and toxic shock syndrome patients usually have a "strawberry tongue." The petechiae, purpura, and hemorrhages that may be seen with these variants may be confused with meningococcemia; rickettsial, ehrlichial or generalized sepsis with Disseminated Intravascular Coagulopathy (DIC) and hemorrhagic fevers. Because classic smallpox evolves from a macular to pustular rash, smallpox may also be confused with measles, rubella, roseola, Rocky Mountain Spotted Fever (RMSF) and typhus, flaviviruses such as dengue and West Nile, as well as rickettsialpox.

Measles is usually accompanied by cough, coryza, and conjunctivitis; rubella and roseola, by lymphadenopathy; RMSF and typhus, by intense prodromal headache and prostration; and, chickenpox, by a centripetal (i.e., truncal) rather than centrifugal rash. Patients with syphilis and erythema multiforme have rashes that may involve the hands and feet and may have constitutional symptoms, but lack a prodrome. With Hand, Foot, and Mouth, a prodrome and enanthem precede the exanthem of the distal extremities and buttocks. A thorough history, including travel and occupations, is essential.



Smallpox vs. Chickenpox (Courtesy: WHO)



Chickenpox (Courtesy: Centers for Disease Control)

Diagnostic Tests: Since false negatives may occur using a single test, properly attired (see infection control), vaccinated personnel should obtain **three or more type of specimens from any patient** suspected of having smallpox. In general, smallpox may be rapidly distinguished from other vesicular exanthems, such as chickenpox, by negative stain electron microscopy (EM) of vesicular fluid. EM does not, however, distinguish smallpox from other poxvirus infections (vaccinia, monkeypox, and cowpox). Polymerase Chain Reaction (PCR) test using vesicle fluid or blood is rapid, sensitive, and specific. Viral isolation is possible in a BSL4 laboratory, but it takes several days. PCR, histopathology, and immunohistochemistry may be performed on autopsy specimens. Only experienced, vaccinated personnel should handle all specimens, and virus culture must be performed in BSL4 facilities. Unvaccinated personnel exposed to patients or specimens should be vaccinated as a priority.

Specimen Submission: Most specimens should be shipped either *on ice packs (at 4°C) if the transport time is < 24 hours or on dry ice (-80°C) if ≥ 24 hours*. The two exceptions are 1) *serum*, which should be collected into plastic tubes and carefully spun and separated *prior to being frozen if the transport times ≥ 24 hours*, and 2) *formalinized specimens*, which should **always** be shipped at *room temperature*.

All specimens must be triple contained in an approved shipping container and have biohazard labels. Before arranging hand carriage of specimens by trained, vaccinated personnel, the receiving laboratory must be alerted prior to transport by calling (800) 252-8239 ("press 1"). Newly available diagnostic tests may be discussed at that time. All specimens must be labeled and accompanied by a Specimen Submission Form (G-1A) and submitted to the Texas Department of State Health Services Laboratory, 1100 West 49th Street, Austin, TX 78756. Smallpox should be prominently mentioned on the G-1A so that appropriate biosafety precautions will be taken in the laboratory.

Specimen Collection: A wide variety of **diagnostic specimens** may be obtained from live patients, including

1) Swab or brush **posterior tonsillar** tissue with sterile cotton or Dacron swab into dry plastic screw-cap tube. Break swab into 2 ml plastic tube. Ship dry
2) Draw 5 cc **blood** into a **plastic**

purple-topped tube. Gently shake to prevent clotting
3) Draw 10 cc **blood** into a **plastic marble-topped tube or plastic yellow-topped serum separator** tube
4) After prepping a lesion, use a 20-gauge butterfly needle attached to a syringe to aspirate **papular /pustular fluid**. Drop the butterfly apparatus into a sterile screw-capped urine cup or 50 ml capped centrifuge tube.
5) After prepping a lesion, use the blunt edge of a scalpel to "decap" a papule or pustule. Swab the **decapped papule/pustule** with cotton or polyester swab, place into a sterile, screw-cap vial, break off the swab, and close the vial
6) Using sterile technique, open or remove the top of the vesicle or pustule, and place skin of vesicle top in 2-ml plastic screw-cap containers
7) Using sterile technique, obtain two **punch biopsies** using 3.5 to 4 mm punch biopsy kit. Place one biopsy into 2-ml plastic screw-cap container and ship dry; the other biopsy should be placed in formalin.

Sterile pea-sized **postmortem** specimens of **liver, spleen, lung, lymph node, kidney, or skin lesion** may be placed into a screw-cap container that is either dry or that has formalin. Shipping instructions are above.

Specimens of **possible epidemiologic interest** include early post exposure (0-24 hours) **nasal swabs or induced respiratory secretions** collected into plastic screw-cap containers. Shipping instructions are above.

Additional Tests: Leukopenia is often found in severe cases. The differential count shows granulocytopenia and a relative increase in lymphocytes. Early in the hemorrhagic form, severe thrombocytopenia, global reduction in clotting factors, circulating antithrombin, and a marked increase in immature lymphoid cells in the peripheral blood are present. Aggregations of virus particles, called Guarnieri bodies, may be seen under light microscopy in the cytoplasm of cells collected from lesions of all species of poxvirus, including variola. Usually hematoxylin and eosin are used as stains. The cytoplasmic inclusions, which are the sites of viral replication, appear black when stained with Gispen's modified silver stain.

Treatment: Antivirals for use against smallpox are under investigation. Cidofovir has proven effective *in vitro* and shown to be effective *in vivo* in experimental animals. Supportive treatment should be given.

Vaccine/Prophylaxis: Vaccine may be available in the case of a bioterrorist attack. The vaccines, Wyeth Calf Lymph Vaccine and DOD cell culture-derived vaccinia, must be given by scarification. Smallpox vaccination should be given, irrespective of prior vaccination status. Most authorities state that, with the exception of significant impairment of systemic immunity, there are no absolute contraindications to *post exposure* vaccination of a person who experiences *bona-fide* exposure to variola. However, concomitant administration simultaneously with vaccinia immune globulin (VIG) 0.6 (one source says 0.3) ml/kg IM is recommended for pregnant and eczematous persons in such circumstances.