Smallpox, Bioterrorism

SUMMARY

Signs and Symptoms: Clinical manifestations begin acutely with malaise, fever, rigors, vomiting, headache, and backache. 2-3 days later lesions appear which quickly progress from macules to papules, and eventually to pustular vesicles. They are more abundant on the extremities and face, and develop synchronously.

DIAGNOSIS

Neither electron nor light microscopy are capable of *discriminating* (telling apart) variola from vaccinia, monkeypox or cowpox. The new PCR diagnostic techniques (blood tests) may be more accurate in discriminating between variola and other *Orthopoxviruses*.

TREATMENT

At present there is no effective chemotherapy, and treatment of a clinical case remains supportive.

PROPHYLAXIS

Immediate vaccination or revaccination should be undertaken for all personnel exposed.

ISOLATION AND DECONTAMINATION

Droplet and Airborne Precautions are for a minimum of 17 days following exposure for all contacts. Patients should be considered infectious until all scabs separate and quarantined during this period. In the civilian setting strict quarantine of asymptomatic contacts may prove to be impractical and impossible to enforce. A reasonable alternative would be to require contacts to check their temperatures daily. Any fever above 38° C (101° F) during the 17-day period following exposure to a confirmed case would suggest the development of smallpox. The contact should then be isolated immediately, preferably at home, until smallpox is either confirmed or ruled out and remain in isolation until all scabs separate.

OVERVIEW

The Orthopox virus causes smallpox. Variola occurs in at least two strains, variola major and the milder disease, variola minor. Despite the global eradication of smallpox and continued availability of a vaccine, the potential weaponization of variola continues to pose a military threat. This threat can be attributed to the aerosol infectivity of the virus, the relative ease of large-scale production, and an increasingly *Orthopoxvirus*-naive populace. Although the fully developed cutaneous eruption of smallpox is unique, earlier stages of the rash could be mistaken for varicella. Secondary spread of infection constitutes a nosocomial hazard from the time of onset of a smallpox patient's exanthem until scabs have separated. Quarantine with respiratory isolation should be applied to secondary contacts for 17 days post-exposure. Vaccinia vaccination and vaccinia immune globulin each possess some efficacy in post-exposure prophylaxis.

CLINICAL FEATURES

- The incubation period of smallpox averaged 12 days, although it could range from 7-19 days following exposure. Clinical manifestations begin acutely with malaise, fever, rigors, vomiting, headache, and backache; 15% of patients developed delirium. Approximately 10% of light-skinned patients exhibited an erythematous rash during this phase. Two to three days later, an enanthem appears concomitantly with a discrete rash about the face, hands and forearms.
- Following eruptions on the lower extremities, the rash spread centrally to the trunk over the next week. Lesions quickly progressed from macules to papules, and eventually to pustular vesicles. Lesions were more abundant on the extremities and face, and this centrifugal distribution is an important diagnostic feature. In distinct contrast to varicella, lesions on various segments of the body remain generally synchronous in their stages of development. From 8 to 14 days after onset, the pustules form scabs that leave depressed depigmented scars upon healing. Although variola concentrations in the throat, conjunctiva, and urine diminish with time, virus can be readily recovered from scabs throughout convalescence. Therefore, patients

should be isolated and considered infectious until all scabs separate.

- For the past century, two distinct types of smallpox were recognized. Variola minor was distinguished by milder systemic toxicity and more diminutive pox lesions, and caused 1% mortality in unvaccinated victims. However, the prototypical disease variola major caused mortality of 3% and 30% in the vaccinated and unvaccinated, respectively. Other clinical forms associated with variola major, flat-type and hemorrhagic type smallpox were notable for severe mortality. A naturally occurring relative of variola, monkeypox, occurs in Africa, and is clinically indistinguishable from smallpox with the exception of a lower case fatality rate and notable enlargement of cervical and inguinal lymph nodes.

DIAGNOSIS

- Smallpox must be distinguished from other vesicular exanthems, such as chickenpox, erythema multiforme with bullae, or allergic contact dermatitis. Particularly problematic to infection control measures would be the failure to recognize relatively mild cases of smallpox in persons with partial immunity. An additional threat to effective quarantine is the fact that exposed persons may shed virus from the oropharynx without ever manifesting disease. Therefore, quarantine and initiation of medical countermeasures should be promptly followed by an accurate diagnosis so as to avert panic.
- The usual method of diagnosis is demonstration of characteristic virions on electron microscopy of vesicular scrapings. Under light microscopy, aggregations of variola virus particles, called Guarnieri bodies are found. Another rapid but relatively insensitive test for Guarnieri bodies in vesicular scrapings is Gispen's modified silver stain, in which cytoplasmic inclusions appear black.
- None of the above laboratory tests are capable of discriminating variola from vaccinia, monkeypox or cowpox. This differentiation classically required isolation of the virus and characterization of its growth on chorioallantoic membrane. The development of polymerase chain reaction diagnostic techniques promises a more accurate and less cumbersome method of discriminating between variola and other *Orthopoxviruses*.

MEDICAL MANAGEMENT

- Medical personnel must be prepared to recognize a vesicular *exanthem* (skin rash) in possible biowarfare theaters as potentially variola, and to initiate appropriate countermeasures. Any confirmed case of smallpox should be considered an international emergency with immediate report made to public health authorities. Droplet and Airborne Precautions for a minimum of 17 days following exposure for *all* persons in direct contact with the index case, especially the unvaccinated. In the civilian setting strict quarantine of asymptomatic contacts may prove to be impractical and impossible to enforce. A reasonable alternative would be to require contacts to check their temperatures daily. Any fever above 38° C (101° F) during the 17-day period following exposure to a confirmed case would suggest the development of smallpox. The contact should then be isolated immediately, preferably at home, until smallpox is either confirmed or ruled out and remain in isolation until all scabs separate. Patients should be considered infectious until all scabs separate. Immediate vaccination or revaccination should also be undertaken for all personnel exposed to either weaponized variola virus or a clinical case of smallpox.
- The potential for airborne spread to other than close contacts is controversial. In general, close person-to-person contact is required for transmission to reliably occur. Nevertheless, variola's potential in low relative humidity for airborne dissemination was alarming in two hospital outbreaks. Smallpox patients were infectious from the time of onset of their eruptive exanthem, most commonly from days 3-6 after onset of fever. Infectivity was markedly enhanced if the patient manifested a cough. Indirect transmission via contaminated bedding or other fomites was infrequent. Some close contacts harbored virus in their throats without developing disease, and hence might have served as a means of secondary transmission.
- Vaccination with a verified clinical “take” (vesicle with scar formation) within the past 3 years is considered to render a person immune to smallpox. However, given the difficulties and uncertainties under wartime conditions of verifying the adequacy of troops' prior vaccination, routine revaccination of all potentially exposed personnel would seem prudent if there existed a significant prospect of smallpox exposure.
- Antivirals for use against smallpox are under investigation. Cidofovir has been shown to have significant *in vitro* and *in vivo* activity in experimental animals. Whether it would offer benefit superior to immediate post-exposure vaccination in humans has not been determined.

PROPHYLAXIS

- Vaccine: Smallpox vaccine (vaccinia virus) is most often administered by intradermal inoculation with a bifurcated needle, a process that became known as scarification because of the permanent scar that resulted. Vaccination after exposure to weaponized smallpox or a case of smallpox may prevent or ameliorate disease if given as soon as possible and preferably within 7 days after exposure. A vesicle typically appears at the vaccination site 5-7 days post-inoculation, with surrounding erythema and induration. The lesion forms a scab and gradually heals over the next 1-2 weeks.
- Side effects include low-grade fever and axillary lymphadenopathy. The attendant erythema and induration of the vaccination vesicle is frequently misdiagnosed as bacterial superinfection. More severe first-time vaccine reactions include secondary inoculation of the virus to other sites such as the face, eyelid, or other persons (~ 6/10,000 vaccinations), and generalized vaccinia, which is a systemic spread of the virus to produce mucocutaneous lesions away from the primary vaccination site (~3/10,000 vaccinations).
- Vaccination is *contraindicated* in the following conditions: immunosuppression, HIV infection, history or evidence of eczema, or current household, sexual, or other close physical contact with person(s) possessing one of these conditions. In addition, vaccination should not be performed during pregnancy. Despite these caveats, 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 VIG administration is recommended for pregnant and eczematous persons in such circumstances.
- Passive Immunoprophylaxis: Vaccinia Immune Globulin (VIG) is generally indicated for treatment of complications to the smallpox (vaccinia) vaccine, and should be available when administering vaccine. Limited data suggests that vaccinia immune globulin may be of value in post-exposure prophylaxis of smallpox when given within the first week following exposure, and concurrently with vaccination. Vaccination alone is recommended for those without contraindications to the vaccine. If greater than one week has elapsed after exposure, administration of both products, if available, is reasonable. The dose for prophylaxis or treatment is 0.6 ml/kg intramuscularly. Due to the large volume (42 mls in a 70 Kg person), the dose would be given in multiple sites over 24-36 hours.

Most of this information is courtesy of US Government CDC. In times of an emergency much of this material may not apply when it comes to specialized care and testing. These are guidelines to help you when that care is not available. Some of this information is very technical and difficult to understand, but hopefully someone will be available for help in treatment and understanding.

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