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On Drugs and Therapeutics

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Many readers have asked for reprints of our articles on biologic, chemical and nuclear weapons. For more up-to-date information, visit the CDC website (www.bt.cdc.gov).

PREVENTION AND TREATMENT OF INJURY FROM CHEMICAL WARFARE AGENTS

(originally published January 7, 2002; 44:1)

The recent terrorist attacks on the US have led to many questions about the clinical effects, prevention and treatment of injury caused by chemical warfare agents.

NERVE AGENTS

Like organophosphate insecticides, nerve agents phosphorylate and inactivate acetylcholinesterase, leading to accumulation of acetylcholine at nicotinic and muscarinic receptors, and at other receptors in the central nervous system (CNS). Nerve agents that have been used in chemical weapons include tabun (GA), sarin (GB), soman (GD), cyclosarin (GF) and VX. At room temperature, all except VX are volatile. VX has the consistency of motor oil and becomes volatile only at high ambient temperatures. Nerve agent vapors are denser than air and tend to accumulate in low-lying areas. All nerve agents are lipophilic and hydrophilic, rapidly penetrating clothing, skin and mucous membranes.

CLINICAL EFFECTS – Exposure to a liquid or vapor nerve agent produces dose-dependent peripheral and CNS effects (T Suzuki et al, Lancet 1995; 345:980). Respiratory effects include rhinorrhea, bronchorrhea and bronchospasm (muscarinic), respiratory muscle paralysis (nicotinic) and depression of CNS respiratory drive. Cardiovascular effects include bradycardia and heart block (muscarinic) or tachycardia (nicotinic). CNS effects range from headache, agitation and vertigo to rapidly decreasing level of consciousness and seizures. Peripheral motor effects include initial fasciculations followed by flaccid paralysis (nicotinic). Gastrointestinal effects include nausea, vomiting and diarrhea (muscarinic). Ocular effects include miosis, eye pain, blurred vision, dim vision, conjunctival injection and tearing (muscarinic) (T Okumura et al, Ann Emerg Med 1996; 28:129).

Liquid – Dermal exposure to a large dose of liquid nerve agent may be transiently asymptomatic (10-30 minutes), followed by rapid onset of respiratory and neurologic effects. With dermal exposure to a minimal amount of nerve agent liquid, the onset of localized symptoms (sweating, fasciculations) may be delayed for up to 18 hours.

Vapor – Inhalation of a large amount of nerve agent vapor causes fulminant respiratory failure within seconds to minutes. Exposure to a small amount of vapor typically produces more limited ocular (miosis, eye pain) and airway (hypersecretion, bronchospasm) effects.

GAS MASKS – Use of military gas masks by untrained civilians is not recommended; the usual full-face mask imposes a large respiratory load and excessive dead space. The ability of military gas masks (e.g., a US military M40 mask) to provide ocular and respiratory protection depends on the fit and the integrity of the filter canister, which can be damaged by handling, water and excessive breathing pressures and must be replaced every 30 days. In Israel during the Gulf War, improper use of gas masks by civilians resulted in 13 deaths due to suffocation (failure to remove the filter cap creates a

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negative-pressure suction effect that can make the masks difficult to take off), and a total of 114 people died from cardiorespiratory causes while using masks in sealed rooms (P Barach et al, *Ann Emerg Med* 1998; 32:224).

PRETREATMENT WITH PYRIDOSTIGMINE — Pyridostigmine bromide (*Mestinon*) is an acetylcholinesterase inhibitor with a short half-life used in the treatment of myasthenia gravis; by binding to peripheral acetylcholinesterase for several hours, it temporarily blocks inactivation by nerve agents. Pyridostigmine itself does not counteract the effects of the nerve agents; it only enhances the effects of antidotes. The usual adult dose is 30 mg PO q8h (FR Sidell and J Borak, *Ann Emerg Med* 1992; 21:865). If there is a risk of imminent exposure, one dose of pyridostigmine at least 2 hours before may be helpful; 2 doses 8 hours apart are preferable. In animal studies, pretreatment with pyridostigmine has been effective against tabun or soman, ineffective against sarin or VX, and variably effective against cyclosarin, depending on the species.

DECONTAMINATION — Patients exposed to liquid nerve agent require immediate decontamination to prevent further absorption. Decontamination consists of rapid removal of clothing and jewelry, followed immediately by irrigation with tepid water and washing with soap and water. If water is limited or unavailable, 0.5% hypochlorite solution, which inactivates nerve agents, can be helpful (AG Macintyre et al, *JAMA* 2000; 283:242).

ANTIDOTES — Even in severe cases of nerve gas exposure, treatment with antidotes can be life-saving (H Nozaki et al, *Lancet* 1995; 345:980).

Atropine — Atropine is a competitive inhibitor of acetylcholine at muscarinic receptors that reverses the hypersecretory, bronchoconstrictive and gastrointestinal effects of nerve agents. The usual adult dose of atropine is 2mg IM for mild dyspnea and 6 mg for severe dyspnea. Appropriate therapeutic end points are drying of secretions and ease of ventilation. Heart rate and pupil size are poor clinical indicators of adequate atropinization, since tachycardia may reflect hypoxemia, stress or severe nicotinic effects, and miosis may persist for weeks. Repeat 2-mg doses can be given every 5-10 minutes; patients with nerve agent exposure rarely require more than 20mg of atropine in the first 24 hours.

Pralidoxime Chloride — Pralidoxime chloride (*Protopam Chloride*) is an oxime acetylcholinesterase reactivator that binds to the nerve agent, removing it from its binding site and reversing muscle weakness. It should be given at the same time as atropine. Early administration is critical, since pralidoxime is only effective when administered before the nerve agent-acetylcholinesterase bond becomes permanent ("ages"); the time it takes for half of the nerve agent to "age" is about 2 minutes for soman, 5 hours for sarin, 13 hours for tabun, and 48 hours for VX. The usual dose of pralidoxime is 1-2 g IV or IM. IV doses should be given over 20-30 minutes to prevent hypertension. Pralidoxime can be repeated at hourly intervals, if necessary, or continuously at 500 mg/hour by IV infusion.

Diazepam — Early administration of the anticonvulsant diazepam (*Valium*, and others) 10 mg IM may prevent permanent CNS damage in patients with severe nerve agent toxicity.

Tropicamide — Tropicamide (*Mydracil*), a topical cycloplegic-mydratic agent, blocks cholinergic stimulation of the iris sphincter muscle and ciliary body, relieving nerve-agent-induced eye pain (T Kato and T Hamanaka, *Am J Ophthalmol* 1996; 121:209). The adult dose is 1-2 drops of 0.5% solution in each eye, repeated as needed.

Auto-Injectors — Spring-loaded auto-injectors for intermuscular use containing (separately) atropine 2 mg, pralidoxime 600 mg, diazepam 10 mg and morphine 10 mg are available, currently to government agencies only, from Meridian Medical Technologies, Columbia, MD (www.meridianmeds.com/civdef.html).

CONCLUSION — Nerve agents inactivate acetylcholinesterase, causing cholinergic excess that leads to life-threatening respiratory and neurologic compromise. Treatment with atropine and pralidoxime can be life-saving.

VESICANTS

Sulfur mustard, an oily liquid that vaporizes at high ambient temperatures, is the most common vesicant used in chemical weapons. Mustard is lipophilic and readily penetrates skin, most textiles and rubber. It irreversibly alkylates DNA, RNA and protein, causing cell death. Moist, warm tissues (mucosa, perineum, axillae) are most vulnerable, because the chemical reaction is water- and temperature-dependent.

CLINICAL EFFECTS – Dermal exposure to liquid mustards causes burns that progress from superficial (erythema, pain) to partial thickness (bullae) and, uncommonly, to full thickness (deep bullae, ulcers). Skin contact with sulfur mustards may produce pain after a delay of minutes to hours. Inhalation exposure to mustard vapor can cause mucosal sloughing and airway obstruction. Ocular effects from exposure to liquid or vapor mustard range from ocular irritation and conjunctivitis to corneal burns and blindness. After exposure to high doses, bone marrow suppression can begin in 3-5 days, resulting in leukopenia that reaches its nadir around day 10, followed by thrombocytopenia and sometimes anemia. Nausea and vomiting are common 4-5 days post-exposure; diarrhea and bleeding can occur (J Borak and FR Sidell, *Ann Emerg Med* 1992; 21:303).

TREATMENT – Patients exposed to sulfur mustard require rapid removal of clothing, followed immediately by flushing with soap and water (KG Davis, *Ann Emerg Med* 2001; 37:653). Sloughing of the airway epithelium requires endotracheal intubation. Overhydration should be avoided; chemical burns produce less fluid loss than thermal burns. Mustard burns are especially painful and require liberal opioid analgesia. Severe burns usually require irrigation, debridement and topical antibiotics such as silver sulfadiazine 1% (KJ Smith, *Dermatol Clin* 1999; 17:41). Eye care includes irrigation, topical antibiotics and cycloplegic-mydratics; application of petroleum jelly can prevent burned lids from sticking (MR Safarinejad et al, *Milit Med* 2001; 166:67). Granulocyte colony-stimulating factor or filgrastim (*Neupogen* – Medical Letter 1991; 33:61) can be used for treatment of mustard-induced neutropenia (JJ Costa, *J Allergy Clin Immunol* 1998; 101:1).

CONCLUSION – Mustard reacts with the skin, eyes and respiratory tract to cause chemical burns and with the bone marrow to cause pancytopenia. Rapid decontamination and treatment with appropriate drugs can be helpful.

PULMONARY TOXICANTS

The pulmonary toxicants most likely to be used as chemical weapons include chlorine, phosgene and diphosgene, which all exist as gases under ambient conditions. Diphosgene readily degrades to phosgene and nontoxic levels of chloroform. Pulmonary toxicants are denser than air and accumulate in low-lying areas. Chlorine, phosgene, and diphosgene all react with water to produce hydrochloric acid, which damages tissue, but phosgene also acylates amino, hydroxyl and sulfhydryl groups in tissue, causing a chain of oxidative injury. The most common sites of injury are mucous membranes such as the conjunctiva and respiratory tract, including the alveolar-capillary membrane.

CLINICAL EFFECTS – Chlorine dissolves readily in the moist mucosa of the upper respiratory tract, producing rhinorrhea, hypersalivation and laryngeal edema, as well as lower respiratory tract reactions such as coughing, wheezing and rales (C Winder, *Environ Res* 2001; 85:105). Phosgene and diphosgene, which are relatively insoluble, pass further into the respiratory tract where they are more slowly absorbed, producing bronchoalveolar injury, dyspnea, bronchospasm and permeability pulmonary edema. Clinical effects of pulmonary toxicants vary with the concentration and duration of exposure. Low-dose inhalation causes minor pulmonary irritation and bronchospasm. High-dose inhalation may produce laryngospasm, pneumonitis and acute lung injury with acute respiratory distress syndrome (ARDS). The delayed onset of ARDS (up to 48 hours in initially asymptomatic patients) is characteristic of pulmonary toxicant inhalation.

TREATMENT – **Oxygen** – Supplemental oxygen may improve tissue oxygenation in patients with pulmonary signs and symptoms. Airway or ventilatory compromise requires intubation. Ventilatory support management of ARDS requires positive end-expiratory pressure.

Bronchodilators – Beta₂-adrenergic agonists relax airway smooth muscle, increasing airway diameter and reducing hyperactivity in pulmonary toxicant inhalation (JD Sexton and DJ Pronchik, *J Toxicol Clin Toxicol* 1998; 36:87). The usual adult dose of albuterol (*Proventil*, and others) is 2.5 mg in

3 ml of sterile water, nebulized and repeated as needed. Theophylline may also be helpful (AM Sciuto et al, Exp Lung Res 1997; 23:317).

Corticosteroids – Corticosteroids such as prednisolone have been used in an attempt to prevent pulmonary edema in the asymptomatic latency phase following phosgene inhalation. The dose of prednisolone has been 250 mg IV. A dose of 1 g IV has been recommended for treatment of phosgene-induced pulmonary edema (J Borak and WF Diller, J Occup Environ Med 2001; 43:110). Whether it would also be helpful for chlorine inhalation is unknown.

Others – In animals, one or two large doses of ibuprofen decreased the toxicity of exposure to phosgene (AM Sciuto et al, J Appl Toxicol 1996; 16:381). An acetylcysteine aerosol, 20 ml of a 20% solution given by nebulizer, has also been effective in animals.

CONCLUSION – Pulmonary toxicants cause inhalation injury ranging from mucosal irritation and bronchospasm to ARDS. Treatment with appropriate drugs can be life-saving.

DRUGS AND VACCINES AGAINST BIOLOGICAL WEAPONS

(originally published October 15, 2001; 43:87)

Concerns have arisen anew about possible use of biological weapons. The pathogens considered most likely to be used for this purpose are discussed below. A good source for additional information is www.usamriid.army.mil/education/bluebook.html.

ANTHRAX – Inhaled anthrax spores, after an incubation period ranging from 1-2 days to 6 weeks, cause fever, cough and weakness, which can progress in 2-3 days to acute respiratory distress, septicemia, shock and meningitis, with a mortality rate higher than 80%. The disease is not transmitted from person to person.

Vaccine – BioPort Corp., Lansing, MI, has a contract with the US Department of Defense to produce anthrax vaccine, but has not produced any since 1998. The vaccine is an inactivated cell-free filtrate of an avirulent strain that expresses the protective antigen (MMWR Morb Mortal Wkly Rep 2000; 49 RR-15:1). It is not available for civilian use. In studies in rhesus monkeys, vaccination at 0 and either 2 or 4 weeks was highly effective against a lethal aerosol challenge (AM Friedlander et al, JAMA 1999; 282:2104). Erythema and tenderness, usually mild, occur commonly at the site of injection. Malaise, fever, headache and myalgia occur less commonly. For use after exposure to an anthrax aerosol, anthrax vaccine is given at 0, 2 and 4 weeks, accompanied throughout by an appropriate antibiotic.

Antibiotics – Naturally occurring strains of anthrax bacillus are usually susceptible *in vitro* to penicillin, amoxicillin, chloramphenicol, tetracyclines, ciprofloxacin and other fluoroquinolones, among others, but resistant to third-generation cephalosporins. Engineered strains resistant to penicillin and doxycycline have been reported. For post-exposure prophylaxis, ciprofloxacin 500 mg b.i.d. orally should be given for 4 weeks if the vaccine is available, and for 60 days if it is not. For susceptible strains, doxycycline 100 mg b.i.d. or amoxicillin 500 mg q8h are alternatives (TV Inglesby et al, JAMA 1999; 281:1735). Treatment after symptoms develop is probably ineffective.

(To read more about anthrax, see page 6.)

PLAGUE – Primary pneumonic plague in natural circumstances presents after an incubation period of 2-4 days as bronchopneumonia with high fever, chills, cough and hemoptysis, and without treatment progresses rapidly to respiratory failure and death (TV Inglesby et al, JAMA 2000; 283:2281). Pneumonic plague is readily transmitted from person to person.

Prevention – An old killed whole-cell vaccine is not protective against plague as an aerosol and is no longer available in the US. A new vaccine that has protected against pneumonic plague in animals is under development (DG Heath et al, Vaccine 1998; 16:1131).

Treatment – Streptomycin 15 mg/kg IM b.i.d. or gentamicin 5 mg/kg IM or IV once daily for 10 days is the treatment of choice. Doxycycline 200 mg IV once, then 100 mg IV or PO q12h, can be given as an alternative. Ciprofloxacin 500 mg orally b.i.d. or another fluoroquinolone should also be effective. IV chloramphenicol 25 mg/kg q.i.d. loading dose followed by 15 mg/kg q.i.d. is

recommended for treatment of meningitis. Started before or promptly after symptoms appear, any one of these antibiotics should be life-saving.

SMALLPOX — No cases of smallpox have occurred and almost no civilians have been vaccinated for more than 20 years. Respiratory exposure leads, after about 12 days, to a febrile prodrome, followed 2-3 days later by the typical rash. The mortality rate in unvaccinated patients is about 30%. Smallpox is highly transmissible.

Vaccination — No smallpox vaccine is commercially available in the US. The US Centers for Disease Control (CDC) has up to 15 million doses of the old vaccine and a supply of vaccinia immune globulin to treat complications of vaccination, which can be severe. Vaccination within 3-4 days after exposure can prevent the disease in many people and prevent death in most (MMWR Morb Mortal Wkly Rep 2001; 50 RR-10:19). More than 7 days after exposure, some experts would give vaccinia immune globulin as well. A single dose of the vaccine is generally thought to give little, if any, protection more than 20 years after vaccination. A new vaccine, also based on the vaccinia virus, is under development.

Treatment — No antiviral drugs have been shown to be effective in the treatment of smallpox. At least one drug, cidofovir (*Vistide*), has been effective *in vitro* (JW LeDuc and PB Jahrling, Emerg Infect Dis 2001; 7:155).

(To read more about smallpox, see page 7.)

TULAREMIA — Aerosolized *Francisella tularensis* can cause systemic illness or pneumonia (DT Dennis et al, JAMA 2001; 285:2763). The onset of illness occurs about 3-10 days after exposure, usually with a flu-like illness, pulmonary infiltrates and pleural effusion. Without treatment, the mortality rate is about 35%. Tularemia is not transmitted from person to person.

Prevention and Treatment — A small supply of an investigational live-attenuated vaccine given by scarification is available from the CDC, but is not recommended for post-exposure protection. Oral doxycycline 100 mg b.i.d. or ciprofloxacin 500 mg b.i.d. begun during the incubation period and continued for 14 days might prevent the disease. Once symptoms begin, gentamicin 5 mg/kg IM or IV once daily for 10-14 days is the treatment of choice. Streptomycin 15 mg/kg b.i.d., doxycycline and ciprofloxacin are alternatives.

BOTULISM — *Clostridium botulinum*, a spore-forming anaerobe, produces botulinum toxin, which could be aerosolized or used to contaminate food. The toxin causes cranial nerve palsies followed by descending skeletal muscle paralysis, beginning about 12-72 hours after exposure. Respiratory failure may develop rapidly. In foodborne botulism, initial symptoms may include abdominal cramps, nausea, vomiting and diarrhea.

Prevention — Botulinum toxin in food or drink can be inactivated by heating to 85°C for at least 5 minutes. In the US, an investigational pentavalent (ABCDE) botulinum toxoid is available from the CDC for high-risk laboratory workers and has been used by the military. It is not effective for post-exposure prophylaxis (SS Arnon et al, JAMA 2001; 285:1059).

Treatment — Botulinum equine antitoxin for types A, B and E is available from the CDC through state and local health departments. The dose is a single 10-ml vial per patient, diluted 1:10 in 0.9% saline solution and given slowly IV. Hypersensitivity reactions to the antitoxin, including anaphylaxis, can occur. A "despeciated" equine antitoxin against all 7 serotypes, considered less likely to cause allergic reactions, is being investigated by the US Army. An investigational human type-A antitoxin (California Department of Health Services), has been used in infants.

VIRAL HEMORRHAGIC FEVERS — Many viruses can cause hemorrhagic fevers. Ebola, Marburg, Lassa and Junin (which causes Argentine hemorrhagic fever) and related viruses, have been given the highest priority as possible biowarfare agents. All of these could be aerosolized and are transmissible from person to person. Signs and symptoms include conjunctivitis, fever, myalgia, petechial rash and hypotension. Diffuse bleeding can develop. The mortality rate ranges from 15% to 25% with Lassa fever to as high as 90% with Ebola.

Prevention and Treatment – Ribavirin has been effective IV in treating some cases of Lassa fever and effective orally for post-exposure prophylaxis (JB McCormick et al, N Engl J Med 1986; 314:20). IV ribavirin is available from the CDC on a compassionate-use basis. An investigational vaccine developed by the US Army has been effective in preventing Argentine hemorrhagic fever, and convalescent plasma has been effective for treatment. Ribavirin also appears to be active against Argentine hemorrhagic fever (DA Enria and JI Maiztegui, Antiviral Res 1994; 23:23).

CONCLUSION – Among the agents considered likely to be used as biological weapons, those that cause anthrax, plague and tularemia could be contained effectively with commercially available antibiotics, if sufficient stocks were available and the organisms were not resistant. Smallpox can be prevented or ameliorated by vaccination even when first given after exposure. Botulism can be treated with antitoxin. There is no established treatment for the viruses that cause viral hemorrhagic fevers.

POST-EXPOSURE ANTHRAX PROPHYLAXIS

(originally published October 29, 2001; 43:91)

The Medical Letter article on Drugs and Vaccines against Biological Weapons, published in the previous issue (October 15, 2001, page 87), included a brief discussion of post-exposure prophylaxis of inhalation anthrax. Recent events call for more detail.

ANTIMICROBIAL SUSCEPTIBILITY – Naturally-occurring *Bacillus anthracis* is generally susceptible *in vitro* to many antibiotics, including penicillin G, amoxicillin, doxycycline and other tetracyclines, erythromycin, clarithromycin (*Biaxin*), azithromycin (*Zithromax*), clindamycin, chloramphenicol and the fluoroquinolones. It is not susceptible to aztreonam (*Azactam*), trimethoprim-sulfamethoxazole (*Bactrim*; *Septra*, others) or third-generation cephalosporins (TV Inglesby et al, JAMA 1999; 281:1735). Naturally occurring resistance to penicillin has been reported rarely. The only report of resistance to tetracyclines was in a strain (also resistant to penicillin) altered by genetic engineering for use in a new anthrax vaccine (AV Stepanov et al, J Biotechnol 1996; 44:155). Resistance to fluoroquinolones has not been reported. All recent clinical isolates in the US have been susceptible to ciprofloxacin, tetracyclines, including doxycycline, and penicillins, including amoxicillin. Penicillinase production may be inducible in these organisms; that could lead to development of resistance during treatment of an infection, but should not be a problem in prophylaxis.

POST-EXPOSURE PROPHYLAXIS – Ciprofloxacin was approved by the FDA last year for post-exposure prophylaxis of inhalation anthrax. Penicillin and doxycycline were previously approved for treatment of anthrax. The evidence that these drugs are effective for post-exposure prophylaxis comes mainly from a study in 60 Rhesus monkeys exposed to an inhaled dose of 4×10^5 anthrax spores (about 8 times the LD_{50}), treated for 30 days with an antibiotic, placebo and/or 2 doses of anthrax vaccine, and then observed. Death due to anthrax occurred in 9 of 10 monkeys treated with saline, 8 of 10 given only anthrax vaccine on days 1 and 15, 3 of 10 treated with procaine penicillin G, 1 of 9 treated with ciprofloxacin, 1 of 10 treated with doxycycline, and 0 of 9 given both doxycycline and vaccine. All of the deaths in antibiotic-treated monkeys occurred after discontinuation of the drugs. The last death occurred 58 days after exposure (AM Friedlander et al, J Infect Dis 1993; 167:1239).

POST-EXPOSURE ORAL ANTIBIOTIC PROPHYLAXIS AGAINST *BACILLUS ANTHRACIS*

Drug	Adults	Children
Oral fluoroquinolones		
Ciprofloxacin (<i>Cipro</i>) ¹	500 mg b.i.d.	10-15 mg/kg b.i.d. ²
Oral tetracyclines ³		
Doxycycline (<i>Vibramycin</i> , others) ⁴	100 mg b.i.d.	2.2 mg/kg b.i.d. ²
Oral penicillins ^{3,5}		
Amoxicillin (<i>Amoxil</i> , others) ⁶	500 mg t.i.d.	80 mg/kg/day divided into 3 doses

1. Other fluoroquinolones such as ofloxacin (*Floxin*) 400 mg b.i.d. or levofloxacin (*Levaquin*) 500 mg once daily may also be effective.
2. Should be changed to amoxicillin as soon as susceptibility to penicillin has been confirmed.
3. Susceptible strains.
4. Tetracycline 500 mg q.i.d. should also be effective.
5. Penicillin resistance could emerge during treatment, but should not be a problem in prophylaxis.
6. Penicillin VK 7.5 mg/kg q.i.d. in adults, or 12.5 mg/kg q.i.d. in children, should also be effective for prophylaxis.

DURATION — If exposure to *B. anthracis* is confirmed and anthrax vaccine is available, 3 doses of the vaccine should be given at 0, 2 and 4 weeks, and antibiotics should be continued throughout the 4-week period. If vaccine is not available, antibiotics should be continued for 60 days.

ADVERSE EFFECTS — Taken for 30 or 60 days, all of these drugs are likely to cause some adverse effects (*The Medical Letter Handbook of Antimicrobial Therapy* 2000; pg. 146). The most frequent adverse effects of fluoroquinolones are nausea, vomiting, abdominal pain, dizziness, headache, tremors, restlessness and confusion. Rarely they can cause psychosis and rupture of the Achilles tendon. Tetracyclines, including doxycycline, frequently cause gastrointestinal disturbances. Amoxicillin can cause diarrhea. Penicillin VK would probably be the best tolerated of these drugs for a 30- or 60-day course.

Children and Pregnancy — Doxycycline and other tetracyclines can cause staining and deformity of teeth in children up to 8 years old, and in the newborn when given to pregnant women after the fourth month of pregnancy. Ciprofloxacin and other fluoroquinolones have caused permanent cartilage damage and arthropathy in immature animals. Ciprofloxacin-associated arthropathy has been infrequent when the drug was used in children with cystic fibrosis (RW Warren, *Pediatr Infect Dis* 1997; 16:118).

PRE-EXPOSURE VACCINATION — In several studies, a total of 52 of 55 monkeys previously given 2 doses of anthrax vaccine survived a lethal aerosol challenge without antibiotics (AM Friedlander et al, *JAMA* 1999; 282:2104).

CONCLUSION — If the organism is susceptible, there is no evidence that ciprofloxacin is more effective than doxycycline or a penicillin for post-exposure prophylaxis of anthrax. Vaccination, if the vaccine were available, plus an antibiotic might be the most effective regimen.

SMALLPOX VACCINE

(originally published January 6, 2003; 45:1)

Because of concerns about the possibility of bioterrorism involving smallpox, the US government is reinstating smallpox vaccination (www.bt.cdc.gov/agent/smallpox/index.asp; www.idsociety.org/bt/toc.htm). Vaccination is currently expected to proceed in three phases: the military and hospital smallpox response teams first, other health care workers, police and firefighters second, and the general public in the third phase. Except for the military, vaccination will be voluntary.

THE DISEASE — History — Smallpox was a world-wide infectious disease, affecting only humans, until it was eradicated in 1977 by intensive case finding and vaccination. The last case in the US occurred in 1949. Smallpox vaccination in the US was discontinued in civilians in 1972 and in the military in 1990.

Epidemiology — Smallpox is transmitted by inhalation of the causative variola virus (an orthopox-virus) in droplets or aerosols from the respiratory tract, or by contact with skin lesions of infected patients or their bedding or clothing. The incubation period is 7 to 17 days, with an average of 12 days. The disease begins with fever and prostration for 2 to 4 days, followed by the rash, which lasts for weeks with slow evolution from papules to vesicles, then pustules and finally scabs, all at the same stage in any one area. Disease transmission may occur late in the prodrome but mainly occurs during the rash, and diminishes as the lesions scab. Transmission is most common in families; about 50% of unvaccinated family members become infected. In the past the mortality rate of smallpox was 20%-30% in unvaccinated populations; many survivors were left with severe scarring, and some with blindness from ocular involvement. Natural infection confers lifelong immunity.

SMALLPOX VACCINE — Formulations — Smallpox vaccine is a suspension of live vaccinia virus, a virus that apparently evolved from serial passage of cowpox. The vaccine to be used in the first and second phases of vaccination (*Dryvax* — Wyeth) is a lyophilized preparation derived from the lymph of calves that had been inoculated with vaccinia virus. According to the CDC, *Dryvax* is already available in adequate amounts for Phases I and II. It contains small amounts of polymyxin B, dihydrostreptomycin, chlortetracycline and neomycin to prevent bacterial contamination. A similar calf-derived vaccine produced by Aventis-Pasteur years ago is also available as a reserve supply. A third vaccine produced by Acambis-Baxter using the same strain of vaccinia virus as in *Dryvax*, but grown in monkey

kidney and human fibroblast cells, is expected to be available in sufficient amounts to vaccinate the entire US population in 2004.

Vaccination — Smallpox vaccine is administered by intracutaneous inoculation using a bifurcated needle to puncture the skin with 15 perpendicular strokes within an area 5 mm in diameter. The punctures are made with just enough pressure to produce a small amount of blood on the skin surface. In the past, the vaccination site was generally left uncovered, but current plans for Phase I call for it to be covered with both gauze to absorb liquid and a semipermeable membrane such as an *Op-site dressing* to prevent spread of the virus. A successful ("primary") vaccination (called a "take", indicating that good immunity to variola infection will result) is suggested by the appearance of a well-formed pustule 6 to 11 days after vaccination followed by scabbing. A "major reaction" suggesting residual immunity in a previously vaccinated person is indicated by more rapid evolution of the lesion to a vesicle or pustule at 3 to 4 days with scabbing or ulceration at 6 to 8 days. Equivocal reactions, including rapid development of erythema without evolution to a definite vesicle or pustule, may indicate some residual immunity from past vaccination or an allergy to vaccine components.

Efficacy — No randomized prospective controlled trials have documented the efficacy of smallpox vaccine. Retrospective analyses in families with an index case have suggested greater than 90% protection against disease in those who were vaccinated before exposure. Vaccination can decrease the rate of severe or fatal smallpox if administered during the first 4 days, and possibly as late as 10 days, after exposure.

Duration of Immunity — Viral neutralizing antibodies appear in serum 10 to 13 days after vaccination and can persist for decades. Limited *in vitro* data indicate that cell-mediated immunity to vaccinia virus also persists for decades. The duration of clinical immunity induced by primary vaccination is uncertain. A study of an epidemic in Liverpool in 1902-03 suggested protection for decades against fatal or severe smallpox following one vaccination in childhood (J Cohen, *Science* 2001; 294:985), but the endemicity of smallpox during that time may have led to multiple natural boosts in immunity. Most experts believe that immunity after primary vaccination wanes after 5 years, but residual protection against fatal disease may persist for many years. Revaccination is considered likely to provide longer-lasting immunity.

ADVERSE EFFECTS — This live vaccine has the potential to cause many adverse effects (SE Frey et al, *N Engl J Med* 2002; 346:1275; KA Sepkowitz, *N Engl J Med* 2003; 348:5). Historically, about one death occurred per million primary vaccinations. Local reactions include satellite lesions, focal inflammation and lymphadenopathy. Brief systemic reactions typical of a viral illness (fever, muscle aches, headache, nausea and fatigue) are common after primary vaccination. Accidental inoculation of the vaccine virus into other skin sites or into the eyes, where it may cause sight-threatening keratitis, can occur. Generalized vaccinia, erythema multiforme, post-vaccinial encephalitis (more common in infants) and eczema vaccinatum (occurring in areas of healed as well as active eczema/atopic dermatitis) can also occur (RJ Engler et al, *J Allergy Clin Immunol* 2002; 110:357). Among contacts of vaccinees, complications are most frequently the result of accidental inoculation. The risk of eczema vaccinatum may be greater than in the past because eczema/atopic dermatitis is more common, occurring in up to 10%-20% of the population. Progressive vaccinia (vaccinia necrosum), which occurs mainly in patients with depressed cell-mediated immunity, might also be more common now because of HIV infection and widespread use of immunosuppressive drugs. Rare cases of fetal vaccinia have been reported after vaccination during pregnancy.

EXCLUSIONS — Smallpox vaccine currently is not recommended for children less than 18 years old except in an emergency. Vaccination is contraindicated in infants, pregnant women, patients with immunodeficiencies or receiving immunosuppressive therapy, and those with household members whose immunity is compromised. It is also contraindicated in patients with a history of atopic dermatitis/eczema, regardless of current activity, and those with household contacts who have eczema. Patients with other extensive skin diseases (acne, burns, wounds, recent incisions, impetigo, contact dermatitis or psoriasis), inflammatory eye diseases or allergy to the antibiotics contained in the vaccine also should not be vaccinated. However, there is no contraindication to use of smallpox vaccine in anyone who actually has been exposed to smallpox.

MANAGEMENT OF COMPLICATIONS — Vaccinia Immune Globulin – Vaccinia immune globulin (VIG – Baxter) is currently available in limited amounts from the CDC as an investigational drug. Its efficacy has never been evaluated in adequate controlled trials. VIG is injected into the buttocks or anterior/lateral thigh in doses of 0.6 ml/kg, and can be repeated every 2 to 3 days for severe vaccination complications with continued activity. There is little evidence that VIG is effective in patients with progressive vaccinia, and it is not useful for the treatment of post-vaccinial encephalitis. In vaccinia keratitis VIG may increase damage to the cornea; trifluridine (*Viroptic*), a pyrimidine nucleoside, has been used for this complication.

Cidofovir (*Vistide*) (Medical Letter 1997; 39:14) is a nucleotide analog that has been used to treat cytomegalovirus (CMV) infections and also has activity against pox viruses. Cidofovir is active *in vitro* against variola virus and has shown good activity in animals against vaccinia infections. Cidofovir is nephrotoxic, and can also cause neutropenia, metabolic acidosis, iritis, uveitis and ocular hypotony. It has a long half-life; for treatment of CMV infection in AIDS patients, it has been given IV once a week or every other week, with oral probenecid and IV saline to decrease the risk of nephrotoxicity. Its use should be strongly considered in patients with progressive vaccinia, severe eczema vaccinatum, generalized vaccinia or extensive accidental inoculation of vaccinia not responding to VIG, or to treat severe cases of smallpox in the event of an outbreak.

Ribavirin (*Virazole; Rebetol; Copegus*) is active against variola virus and vaccinia virus *in vitro* (E De Clercq, Antiviral Res 2002; 55:1). One case report suggested that IV ribavirin, which is not commercially available in the US, was effective in an immunocompromised patient with progressive vaccinia (AM Kesson et al, Clin Infect Dis 1997; 25:911).

CONCLUSION – Smallpox vaccination will begin in 2003 in the US military and health care workers. Historically, fatal complications of the vaccine occurred in about 1 per million primary vaccinees. Without vaccination, smallpox has a mortality rate of 20%-30%.

POTASSIUM IODIDE FOR THYROID PROTECTION IN A NUCLEAR ACCIDENT OR ATTACK

(originally published November 11, 2002; 44:97)

Potassium iodide (KI) taken orally before or at the time of exposure can limit or prevent uptake of radioactive iodine by the thyroid gland. Children, adolescents and young adults who as children were exposed to even small amounts of radioiodine from the Chernobyl reactor accident have had a marked increase, beginning 4 years after exposure, in the incidence of thyroid nodules and cancer (www.fda.gov/cder/guidance/4825fnl.htm).

POTENTIAL SOURCES OF EXPOSURE – Radioactive iodine is a by-product of nuclear fission. A breach-of-containment nuclear reactor accident at a functioning nuclear power plant would release radioactive iodine and other radionuclides. Radioactive iodine is unlikely to be used as the radioactive material in a "dirty bomb" because it has a short half-life. Detonation of a nuclear weapon would release radioactive iodine, as well as other radioactive isotopes. Grazing cows that feed on radioiodine-contaminated vegetation secrete radioactive iodine in their milk. Human exposure can result from inhalation of iodine particles or aerosols, or from ingestion of contaminated vegetation, dairy products or meat.

MECHANISM OF ACTION – Potassium iodide is readily absorbed within 30-60 minutes after oral administration. It is rapidly concentrated and stored in the thyroid, protecting the gland by competing with radioactive iodine for the iodine active transport system, and by preventing its organification and storage in the thyroid (P Verger et al, Thyroid 2001; 11:353). Taken within 12 hours before exposure, potassium iodide can almost completely prevent radioiodine from entering the thyroid. Taken after exposure, the degree of protection falls off to 80% after 2 hours, 40% after 8 hours, and 7% after 24 hours (PB Zanzonico and DV Becker, Health Phys 2000; 78:660).

SOURCES OF POTASSIUM IODIDE – Many potassium iodide products are available in the US, especially via the internet. Typically the drug is supplied in 65- or 130-mg tablets. Products from 3 companies have been approved by the FDA. In some states, people who live within 10 miles of a nuclear reactor are eligible to receive free potassium iodide supplied by the US Nuclear Regulatory Commission (www.nrc.gov).

FDA-APPROVED POTASSIUM IODIDE PRODUCTS

Trade-name	Availability	Tablet size	Packaging	Cost*
<i>IOSTAT</i> (Anbex)	www.nukepills.com 727-784-3483	130 mg	14 tablets	\$ 9.50
<i>Thyro-Block</i> (Medpointe)	www.nitro-pak.com 800-804-4147	130 mg	14 tablets	58.97**
<i>ThyroSafe</i> (Recip US)	www.thyrosafe.com 610-942-8972	65 mg	10 tablets	12.95

* Cost from the distributor. Also available at many pharmacies.

** Sold only in packages of 7 bottles.

DOSAGE — The risk of radioactive-iodine-induced thyroid cancer is greatest for children, adolescents and pregnant women. Adults more than 40 years old have a lower risk. The currently recommended dosage schedule for adults >18 years old is one 130-mg tablet once daily, to be taken as long as there is risk of continued exposure to radioiodine. For administration to children (4-18 years: 65 mg per day; 1 month to 3 years: 32.5 mg; <1 month 16.25 mg), an adult 130-mg tablet can be crushed and dissolved in 4 teaspoonfuls of water, then mixed with 4 additional teaspoonfuls of another liquid such as raspberry syrup, flat soda, orange juice, low-fat white or chocolate milk or water (a total of 8 teaspoons of liquid) to make it more palatable. Using this preparation, the daily dosage is 4 teaspoonfuls of the mixture for children 4-18 years old, 2 teaspoonfuls for children from 1 month to 3 years, and 1 teaspoonful for infants <1 month. The liquid mixture can be kept in the refrigerator for up to 7 days. The 65-mg tablet can also be crushed and mixed with the same volumes of liquid, and then taken in twice the amount (www.fda.gov/cder/drugprepare/kiprep.htm).

ADVERSE EFFECTS — Potassium iodide is well tolerated. Allergic reactions can occur. Iodine-induced hyper- and hypothyroidism occur rarely; a few newborns in Poland treated with potassium iodide after Chernobyl developed transient hypothyroidism. Iodine may also rarely cause parotitis.

CONCLUSION — Potassium iodide tablets, taken once daily, can decrease thyroid uptake of radioactive iodide. Treatment should be started, if possible, before or soon after exposure and continued for the duration of exposure. Children, adolescents and pregnant women are at greatest risk.

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