Chapter 100

c00107

External Eye Manifestations of Biological and Chemical Warfare

Craig A. Skolnick

p0010 The spectrum of biological and chemical agents that can be used in warfare is frightening. Healthcare providers must be alert to patterns of illness and the constellation of clinical findings associated with an outbreak of biological or chemical warfare. The intentional release of an unusual infectious agent can be difficult to recognize since many of the commonly used organisms are rarely seen in their natural form. When used as weapons, there is potential for an immense number of casualties due to ease of dispersal, rapid onset of effect, and lack of preparation for containment and defense. Timely recognition of symptoms and early treatment are key to victim survival.

s0010 Background

p0015 The deliberate use of microorganisms and toxins as weapons dates back to the middle ages. During the fourteenth-century siege of Kaffa (now Feodossia, Ukraine), the attacking Tatars catapulted plague-infested cadavers into the city in order to initiate an epidemic.[1] South American aboriginals are well known for using curare and amphibian-derived toxins as arrow poisons, and British forces used smallpox against native North Americans during the French and Indian War of the mid-eighteenth century. The advent of modern microbiology and Koch's postulates during the nineteenthth century afforded the opportunity to isolate and produce stockpiles of specific pathogens. There is evidence that Germany developed an aggressive biological warfare program during World War I, including operations to infect livestock and contaminate animal feed of the Allied forces using *Bacillus anthracis* and *Burkholderia* (*Pseudomonas*) *mallei*, the etiologic agents of anthrax and glanders.

p0020 The first widespread use of chemical weapons occurred during World War I, when more than 1 million casualties resulted from the use of sulfur, mustard, and chlorine gases. These horrors led to the first international diplomatic efforts to limit weapons of mass destruction. The 1925 Geneva Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous, or Other Gases, and of Bacteriological Methods of Warfare was enacted to prohibit the use of biological weapons.[2] Unfortunately, there were no provisions for inspection, and many countries that ratified the treaty still began research programs to develop biological weapons.

p0025 During World War II, Japan conducted experiments in which prisoners were infected with various bacterial pathogens, which led to at least 10000 deaths[3] Many Chinese cities were attacked by contaminating water supplies and food items with pure cultures of *B. anthracis*, *Vibrio cholerae*, *Shigella* spp, *Salmonella* spp, and *Yersinia pestis*. International concern heightened during the late 1960s, which led to the signing of the1972 Biological and Toxin Weapons Convention. The treaty prohibited the development, possession, and stockpiling of pathogens or toxins in 'quantities that have no justification for prophylactic, protective or other peaceful purposes.'[4] Transferring technology or expertise between countries was also prohibited. In 1979, the ineffectiveness of the convention was demonstrated by an accidental airborne release of anthrax spores by a Soviet military microbiology facility in Sverdlovsk (now Ekaterinburg, Russia), which led to numerous deaths.[5] Non-state-sponsored biological terrorism began to surface in the 1980s, which culminated with the 1995 sarin gas attack of the Tokyo, Japan, subway system by the Aum Shinrikyo cult.

Mechanism of Attack

s0015

p0030 A biological weapon is more than a microorganism or toxin. It is a system composed of four major components: payload (the biological agent), munition (a container that keeps the payload intact and virulent during delivery), delivery system (missile, artillery shell, aircraft, etc.), and dispersal mechanism (an explosive force or spray device to dispense the agent to the target population).[6] Certain agents are attractive because of low visibility, small volume, high potency, and easy delivery. Aerosolization would be the predominant method of dissemination because advanced delivery systems are not required, and small quantities make transportation and concealment quite easy. In 1970, the World Health Organization predicted the effect of an aerosol release of 50 kg of biological weapon over a city of 500000 people (Table 100.1).[7,8] Highly contagious organisms with delayed onset of symptoms make ideal weapons for a covert attack. In an overt attack, chemical agents are likely to be deployed,

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t0010 **Table 100.1** Estimated casualties for a hypothetical biological warfare attack on a city of 500 000*

Agent	Downwind reach (km)	No. dead	No. incapacitated
Rift Valley fever	1	400	35 000
Tick-borne encephalitis	1	9500	35 000
Typhus	5	19 000	85 000
Brucellosis	10	500	100 000
Q fever	>20	150	125 000
Tularemia	>20	30 000	125 000
Anthrax	>20	950 000	125 000

** This model assumes that 50 kg of agent is deployed from an aircraft along a 2 km line upwind from the city.*
From reference 8, page 312, Table 2, McGovern TW, Christopher GW, Eitzen EM: Cutaneous manifestations of biological warfare and related threat agents, Arch Dermatol 135:311–322, 1999.

causing rapid onset of symptoms and an overwhelming demand for emergency medical services. Both biological and chemical weapons can incapacitate an entire city and impede the mobilization of military personnel.

s0020 ## Warning Signs

p0035 In order to recognize a bioterror attack, one must be familiar with the various clinical presentations of these agents. The American College of Physicians and the American Society of Internal Medicine have suggested that the following epidemiological clues be considered:[9]

o0010 p0040 1. Unusual temporal or geographic clustering of illness;
p0045 2. Unusual age distribution of common disease (i.e. an illness that appears to be chickenpox in adults but is really smallpox);
p0050 3. Large epidemic, with greater case loads than expected, especially in a discrete population;
p0055 4. More severe disease than expected;
p0060 5. Unusual route of exposure;
p0065 6. A disease that is outside its normal transmission season, or is impossible to transmit naturally in the absence of its normal vector;
p0070 7. Multiple simultaneous epidemics of different diseases;
p0075 8. A disease outbreak with health consequences to humans and animals;
p0080 9. Unusual strains or variants of organisms or antimicrobial resistance patterns.

p0085 The Centers for Disease Control and Prevention (CDC) of the United States has listed the high-priority biological diseases (Box 100.1)[10] that pose significant risk to national security based on the following: can be easily disseminated and/or transmitted from person to person; result in high mortality rates and have the potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness.[11] Most of these agents have significant ophthalmic manifestations that may aid in diagnosis or complicate management.

b0010 **Box 100.1** Biological diseases

Anthrax (*Bacillus anthracis*)
Botulism (*Clostridium botulinum* toxin)
Plague (*Yersinia pestis*)
Smallpox (Variola major and minor)
Tularemia (*Francisella tularensis*)
Viral hemorrhagic fevers
Filoviruses – Ebola, Marburg
Arenaviruses – Lassa, Machupo

From reference 10. Centers for Disease Control and Prevention: Biological Diseases/Agents List. Available at http http://www.bt.cdc.gov/agent/agentlist-category.asp, accessed 02/28/09.

s0025 ## Biological Diseases

s0030 ### Anthrax

p0135 *Bacillus anthracis* is the ideal biologic weapon because of its stability in spore form, its ease to grow in culture, the lack of natural immunity in many industrialized nations, and the severity of infection.

s0035 #### Microbiology/epidemiology

p0140 *Bacillus anthracis* is an encapsulated, aerobic, Gram-positive, spore-forming, rod-shaped bacterium. Spores form when environmental nutrients are depleted, such as occurs with dry soil, the natural reservoir. Spores can survive for decades in contaminated soils or workplaces and can resist temperatures of over 10°C for prolonged periods.[12,13] Inhalation (wool-sorter's disease) can occur from animal products, such as wool fibers or bone meal, leading to outbreaks in slaughterhouses, textile industries, and tanneries.[14] Herbivores such as cattle, goats, and sheep ingest spores and serve as the natural transmitters of infection. Humans become infected through direct contact with contaminated carcasses or from eating infected meat. Animal husbandmen, butchers, and veterinarians are most susceptible.[12]

s0040 #### Clinical manifestations

p0145 Three principal forms of anthrax occur in humans: cutaneous, inhalational, and gastrointestinal. The majority of naturally occurring disease is cutaneous, comprising more than 95% of cases.[12] Spores sent in mailed letters or packages can lead to either cutaneous or inhalational anthrax. The differential diagnosis of cutaneous anthrax includes cowpox, spider bite, ecthyma gangrenosum, ulceroglandular tularemia, plague, scrub typhus, rickettsial spotted fever, rat bite fever, staphylococcal or streptococcal cellulitis, and herpes simplex virus.[15,16]

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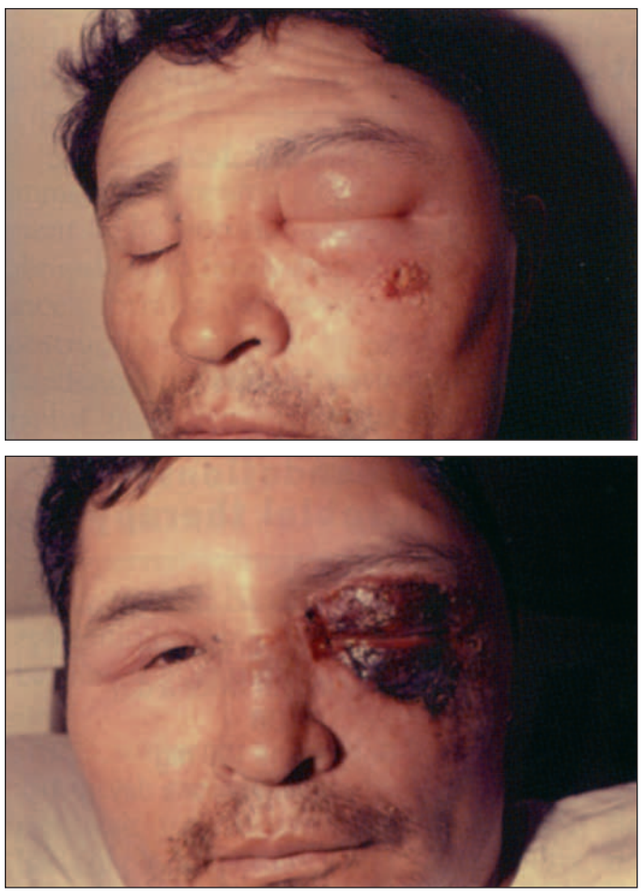
s0045 **Cutaneous anthrax**

p0150 Cutaneous disease begins as a small, painless, pruritic, red macule that progresses to a papule which vesiculates, ruptures, and ulcerates. It then forms a classic 1–5 cm brown or coal-black eschar surrounded by significant nonpitting edema.[8] The term anthrax is derived from the Greek *anthrakos* meaning 'coal.' It appears at the site of inoculation (spores or bacilli) within 3 to 10 days. The edema can spread, and translucent epidermal bullae vesicles often surround the lesion – the so-called 'pearly wreath.'[13] After 2 to 4 weeks the eschar sloughs away, leaving an exposed area of granulation tissue. Although fatalities due to cutaneous disease are rare, 10–20% of untreated patients develop malignant edema, septicemia, shock, renal failure, and death.[8]

s0050 *Ophthalmic manifestations*

p0155 Ocular findings in cutaneous anthrax relate to eyelid involvement.[13,17–20] The main complication is cicatricial ectropion due to late eyelid scarring (Fig. 100.1).[21] Lid malposition causes exposure keratopathy which can lead to epithelial breakdown and secondary infectious keratitis. Corneal scarring is more likely to occur in patients who present late without treatment during the acute stage. It appears that upper eyelid involvement is more likely to result in ectropion. Severely affected patients have undergone release of contractures and full-thickness postauricular skin grafts with satisfactory resolution of ectropion.[13] Temporal artery inflammation has been reported as a complication of overlying cutaneous anthrax.[22]



f0010 **Fig. 100.1** Cutaneous anthrax. (A) Swelling and erythema in the early phase. (B) Central ulceration with black, necrotic tissue in the latter phase. (From reference 21, page 1007, Figure 1, Noeller TP: Biological and chemical terrorism: recognition and management, Cleve Clin J Med 68(12):1001–1016, 2001.)

Diagnosis

s0055

p0160 Anthrax bacilli can be visualized by Wright or Gram stain of peripheral blood or isolated by blood culture. Diagnostic testing for cutaneous disease includes Gram stain and culture of vesicular fluid, tissue biopsy, specific enzyme-linked immunosorbent assays (ELISAs) to measure antibody titers, immunomagnetic-electrochemiluminescence (ECL) assays for antigen detection, and polymerase chain reaction (PCR) for nucleic acid detection.[14] Spores have a diameter of 2–6 mm, which is ideal for entrapment in the lower respiratory tract. The time for infection is variable because spores must germinate into bacilli after phagocytosis by tissue macrophages. The dose of anthrax in an exposure is inversely correlated with incubation time. Cases in the accidental release in Sverdlovsk developed 2 to 43 days after exposure.[14] Thus it may be hard to trace the onset of an attack, making response and containment more difficult.

Treatment

s0060

p0165 Treatment of inhalational and gastrointestinal anthrax should begin with intravenous ciprofloxacin 400 mg every 12 hours (Table 100.2).[21] Doxycycline 100 mg every 12 hours can be used, but has poorer central nervous system penetration. One or two of the following additional antibiotics should be added until susceptibility testing is performed: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Cutaneous disease can be treated with either oral ciprofloxacin or doxycycline alone. Treatment should be continued for 60 days because of the possibility of delayed germination of spores.[16] Direct contact with wound or wound drainage should be avoided when caring for a patient with cutaneous anthrax.

p0355 Despite aggressive supportive therapy and antibiotics, fatality is very high. In the twentieth-century series of 18 patients in the United States, the mortality rate of occupationally acquired inhalational anthrax was 89%, but the majority of these cases occurred before the development of critical care units and antibiotics.[23] After the September 2001 terrorist attacks on the United States, anthrax spores were sent to various locations via the postal service, resulting in 11 cases of inhalational anthrax with five deaths.[16]

Prevention

s0065

p0360 Since there are no data to support person-to-person transmission of anthrax, patient contacts do not need immunization or prophylactic treatment unless they were exposed to the aerosol or surface contamination at the time of attack. A vaccine derived from an attenuated strain of anthrax is available, and studies in rhesus monkeys indicate that it is

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t0015 **Table 100.2** CDC recommendations for antimicrobial therapy against anthrax

Indication	Adults	Children
Postexposure prophylaxis	Ciprofloxacin 500 mg by mouth twice a day OR Doxycycline 100 mg by mouth twice a day	Ciprofloxacin 10–15 mg/kg by mouth every 12 hrs* OR Doxycycline: >8 yr and >45 kg 100 mg by mouth every 12 hrs >8 yr and ≤45 kg 2.2 mg/kg by mouth every 12 hrs ≤8 yrs: 2.2 mg/kg by mouth every 12 hrs:
Cutaneous anthrax	Ciprofloxacin 500 mg by mouth twice a day OR Doxycycline 100 mg by mouth twice a day	Ciprofloxacin 10–15 mg/kg by mouth every 12 hrs* OR Doxycycline: >8 yr and >45 kg: 100 mg by mouth every 12 hrs >8 yr and ≤45 kg: 2.2 mg/kg by mouth every 12 hrs ≤8 yr: 2.2 mg/kg by mouth every 12 hrs
Inhalational anthrax	Ciprofloxacin 400 mg intravenously every 12 hrs OR Doxycycline 100 mg intravenously every 12 hrs PLUS (for either drug) One or two additional antibiotics (e.g. rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, clarithromycin)	Ciprofloxacin 10–15 mg/kg intravenously every 12 hrs* OR Doxycycline: >8 yr and >45 kg: 100 mg intravenously every 12 hrs >8 yr and ≤45 kg: 2.2 mg/kg intravenously every 12 hrs ≤8 yr: 2.2 mg/kg intravenously every 12 hrs PLUS (for either drug) One or two additional antibiotics

** Ciprofloxacin dose in children n not to exceed 1 g/day.*
From reference 21, page 1008, Table 2, Noeller TP: Biological and chemical terrorism: recognition and management, Cleve Clin J Med 68(12):1001–1016, 2001.

protective for inhalational anthrax.[24] Should an attack occur, those exposed must be vaccinated and receive chemoprophylaxis with either ciprofloxacin or doxycycline orally until at least three doses of vaccine have been administered.[25] The safety of the vaccine was studied in military personnel, and 1% of inoculations were associated with one or more systemic events (i.e. headache, malaise, blurred vision, nausea). Isolated cases of optic neuritis have been reported after anthrax booster vaccination,[26] but a matched case-controlled study among US military personnel from 1998 through 2003 showed no statistically significant association.[27] One case of unilateral optic neuropathy, bilateral anterior uveitis, bilateral posterior scleritis, bilateral sensorineural hearing loss, and focal segmental glomerulosclerosis has been reported,[28] as well as a patient who developed central serous chorioretinopathy after vaccination.[29]

s0070 ## Botulism

4 p0365 Botulism is a serious paralytic illness caused by a nerve toxin produced by the bacterium *Clostridium botulinum*. Three forms of naturally occurring botulism exist: food-borne, wound, and intestinal. The oldest and most common form observed on a worldwide basis is food-borne, which typically occurs after ingestion of improperly prepared home-canned food that contains preformed neurotoxin.[30] It poses a major bioweapons threat because of its extreme potency and lethality, its ease of production, transportation, and misuse, and the need for prolonged intensive care among affected persons.[31]

Microbiology s0075

Clostridium botulinum is a rod-shaped, spore-forming, obligate anaerobe commonly found in soil. There are seven types of toxin designated A through G, which are defined by their absence of cross-neutralization (i.e. anti-A antitoxin does not neutralize toxin types B–G).[31] Types A, B, and E account for greater than 99% of human botulism.[30] Type A toxin is the most potent poison known to humans, 100 000 times more toxic than sarin nerve gas.[25] Once absorbed, the toxin is carried via the blood to peripheral cholinergic synapses. It irreversibly binds to the presynaptic neuromuscular junction, where it is internalized and blocks acetylcholine release, causing paralysis. Interestingly, a vial of therapeutic Botox® (Allergan, Irvine, CA, USA) contains only about 0.3% of the estimated human lethal inhalational dose and 0.005% of the estimated lethal oral dose.[30] p0370

Clinical manifestations s0080

During an attack, botulinum toxin would likely be used as an inhalational agent or to deliberately contaminate food, since it does not penetrate intact skin and is not transmitted from person to person.[31] Symptoms generally begin 12 to 72 hours after ingestion. The time of onset after an inhalational exposure is not known, but experimentally is similar to food-borne exposure.[25] p0375

Botulism classically presents as an acute, afebrile, symmetric, descending flaccid paralysis that always begins in the bulbar musculature (Box 100.2).[31,30] Patients have a clear sensorium because the toxin does not penetrate the brain tissue. The prominent bulbar palsies (the 4Ds) include diplopia, dysarthria, dysphonia, and dysphagia. If the origin is food-borne, the neurologic signs may be preceded by abdominal cramps, nausea, vomiting, or diarrhea.[32] Sensory changes are not present. As the disease progresses, weakness extends below the neck with loss of deep tendon reflexes, constipation, and unsteady gait. Severe cases lead to respiratory collapse from diaphragm and intercostal muscle involvement and airway obstruction from pharyngeal muscle paralysis.[31] Autonomic nervous system involvement can lead to cardiovascular lability. p0380

Ophthalmic manifestations s0085

Visual symptoms of diplopia, photophobia, and blurred vision are present early (Table 100.3).[30] Accommodative paresis and mydriasis account for the blurred vision and photophobia, respectively. Blepharoptosis, gaze paralysis, pupillary dilation, and nystagmus are common ophthalmic signs. Dry eye and dry mouth from parasympathetic cholinergic blockade can also be prominent. p0520

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b0015 **Box 100.2** Signs and symptoms of food-borne and wound botulism

Signs
- Ventilatory (respiratory) problems
- Extraocular muscle paresis or paralysis (including eyelids)
- Muscle paresis or paralysis
- Dry mucous membranes in mouth, throat
- Dilated, fixed pupils
- Ataxia
- Somnolence
- Hypotension (including postural)
- Nystagmus
- Decreased to absent deep tendon reflexes
- Fever (more common for wound botulism)
- Sensory deficits (very rare)

Symptoms
- Visual disturbances (blurred vision, diplopia, photophobia)
- Dysphagia
- Dry mouth
- Generalized weakness (usually bilateral)
- Nausea or vomiting
- Dizziness or vertigo
- Abdominal pain, cramps, discomfort
- Diarrhea
- Urinary retention or incontinence
- Sore throat
- Constipation
- Parasthesias

Adapted from reference 30, page 28, Tables 1 and 2, Caya JG: Clostridium botulinum and the ophthalmologist: a review of botulism, including biological warfare ramifications of botulinum toxin, Surv Ophthalmol 46:25–34, 2001.

t0020 **Table 100.3** Ophthalmic signs and symptoms of botulism

Signs and symptoms	Frequency
Blurred vision	89%
Ptosis	80%
Diplopia	59%
Abnormal pupil reaction to light	59%
Impaired accommodation	59%
Nystagmus	56%
Mydriasis	52%
Extraocular muscle dysfunction on examination	36%

Adapted from reference 30, page 31, Table 8, Caya JG: Clostridium botulinum and the ophthalmologist: a review of botulism, including biological warfare ramifications of botulinum toxin, Surv Ophthalmol 46:25–34, 2001.

p0525 Uncommon neuro-ophthalmic manifestations include complete bilateral internal ophthalmoplegia[33] which can include both permanent and transient tonic pupils. A dilated and poorly reactive pupil with loss of accommodation are typical findings. Light-near dissociation, sectoral iris contractions, and supersensitivity of the iris sphincter muscle to weak miotics (pilocarpine 0.1%) are also hallmark findings of a tonic pupil.

Diagnosis s0090

p0530 Early diagnosis of botulism is made by the history and physical examination. The differential diagnosis includes Guillain-Barré and the Miller-Fisher variant, myasthenia gravis, Lambert-Eaton syndrome, tick paralysis, stroke, and various central nervous system disorders.[21,31] Botulism differs from other causes of flaccid paralyses in that there is the presence of symmetry, absence of sensory nerve damage, and disproportionate involvement of cranial nerves compared to muscles below the neck.[31] An electromyogram can be diagnostic. Demonstration of toxin by mouse bioassay is diagnostic in samples of serum, stool, gastric aspirate, and suspect food.[31] Studies suggest that aerosolized toxin is usually not identifiable in serum or stool, but may be present on nasal mucous membranes and detected by ELISA for up to 24 hours after exposure.[25] Fecal, wound, and gastric specimens can be cultured anaerobically if a food-borne or wound source of *C. botulinum* is suspected.

Treatment s0095

p0535 Management is primarily supportive, with ventilatory assistance essential in advanced cases. Early administration with equine-derived trivalent (types A, B, E) antitoxin can minimize subsequent nerve damage and severity of disease, but will not reverse existing paralysis, which can last from weeks to months.[34] In a large outbreak of botulism, the need for mechanical ventilators, critical care beds, and skilled personnel might quickly exceed capacity. Research directed at recombinant vaccines and human antibody may eventually minimize the threat of botulinum toxin as a weapon of mass destruction.

Smallpox s0100

p0540 Smallpox is one of the most dreaded diseases in the history of humankind. It raged in epidemic and endemic forms for more than 3000 years, killing hundreds of millions of people. In 1966, the World Health Organization established a vaccination program with extensive educational and surveillance programs for global eradication. Smallpox was successfully eradicated in 1977, with the last case documented in Somalia.[35]

Microbiology s0105

p0545 Variola is a large, double-stranded DNA virus and member of the genus orthopoxvirus. The viruses are complex, and the virion is brick-shaped with a diameter of about 200 nm.[14] Three other members of this genus (monkeypox, vaccinia, and cowpox) can infect humans but are not highly contagious.[36]

Epidemiology s0110

p0550 There are two clinical forms of smallpox, variola major and a much milder form, variola minor. Typical variola major epidemics resulted in mortality rates of greater than 30%

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among unvaccinated persons.[36] Smallpox spreads from person to person primarily in droplet form or aerosols expelled from the oropharynx of infected persons. Contaminated bedding and clothing can also spread the virus via direct contact.[37] Smallpox would likely be used in aerosol form during a biological assault, given both its small infectious dose and significant stability.

Clinical manifestations

s0115

p0555 After an incubation period of about 12 days, patients become febrile and often develop severe constitutional symptoms.[38] Headache, backache, vomiting, abdominal pain, and malaise are common. The clinical presentation of smallpox is heralded by a diffuse maculopapular rash beginning 2 to 3 days after this prodromal phase.[39] Lesions first appear on the mucous membranes of the oropharynx. Skin lesions appear mostly on the head, torso, and extremities in a centrifugal pattern, evolving from a flat rash to a papule, a vesicle, and then a pustule which becomes crusted and scabbed. This leads to permanent scarring, usually most extensive on the face. Classically, the lesions are at one stage of development at a given point and can affect the palms and soles. Chickenpox (varicella), the disease most frequently confused with smallpox, differs in that lesions are in various stages of development at a given point. Varicella lesions are more superficial, rarely found on the palms and soles, and the distribution is centripetal, with the trunk affected more than the face and extremities.[37]

p0560 Nearly one-third of patients with smallpox will die, usually during the second week of illness. This most likely results from the toxemia and cardiovascular collapse associated with circulating immune complexes and soluble variola antigens.[36] Pneumonia, encephalitis, osteomyelitis, orchitis, sepsis, and overwhelming hemorrhage into the skin and mucous membranes can complicate smallpox infection.[40] Variola minor, the less severe form of smallpox, results in milder symptoms with only a sparse rash and less than 1% mortality.[36] Patients are most infectious during the first week of the illness; however, some risk of transmission is present until all scabs have fallen off.[37] It is thought that smallpox cannot be transmitted until the onset of the rash,[25,37] so diagnosis during the prodromal stage with subsequent quarantine would be essential to limit additional exposure.

Ophthalmic manifestations

s0120

p0565 Smallpox led to blindness in 2–5% of students in blind schools of developing countries in Africa.[41] Typically, a mild conjunctivitis appears around the fifth day of illness with subconjunctival hemorrhage in some cases. Actual pustules which resemble phlyctenules may form on the bulbar or tarsal conjunctiva and even involve the limbus.[42] These lesions are very inflamed and painful and can lead to infiltration and ulceration of the cornea. Less frequently, an interstitial or disciform keratitis evolves (Fig. 100.2). Lid alopecia and punctal stenosis may result when pustules involve the cilia and puncta, respectively. Ankyloblepharon has also been reported due to severe eyelid adhesions between the upper and lower canthi.[43] Secondary infectious keratitis can occur late and lead to significant morbidity; therefore, antibiotic prophylaxis is warranted. Dense corneal scarring can leave patients phthisical and blind.

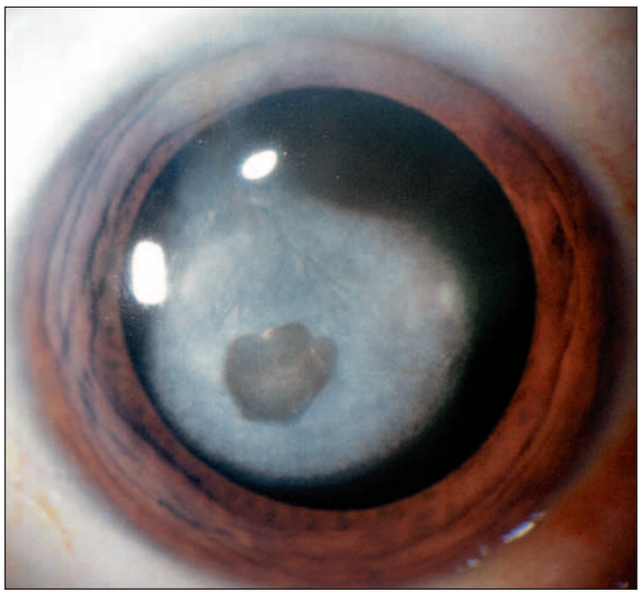

Fig. 100.2 Variola (smallpox). This patient demonstrates a central corneal scar from a smallpox or variola infection. f0015

Diagnosis

s0125

p0570 Laboratory diagnosis of smallpox can be confirmed with electron microscopy of vesicular or pustular fluid, or characteristic Guarnieri bodies can be visualized under light microscopy.[25] Virus culture of skin lesions, oropharynx, conjunctiva, and urine is definitive. PCR techniques can discriminate between strains and offer a more rapid result.[37]

Treatment and vaccination

s0130

p0575 There is no specific systemic or ocular treatment for smallpox, although cidofovir has in vitro and in vivo activity against Poxviridae.[25] In 1796, Edward Jenner demonstrated that an infection caused by cowpox protected against smallpox, which led to the worldwide practice of vaccination.[44] Currently, smallpox vaccine is prepared from live vaccinia virus using cell culture techniques.[14]

p0580 The interval between an aerosol release of variola and diagnosis of the first cases is as much as 2 weeks.[37] Fortunately, the virus is inactivated after 2 days, eliminating further exposure. Individuals in whom infection is suspected should be vaccinated within 4 days of exposure and placed under surveillance. Vaccination programs ended in 1972 in the United States, and it is presumed that few people who were vaccinated have lasting protective levels of immunity.

Complications of vaccination

s0135

p0585 Vaccination is not without risk. Life-threatening encephalitis occurs at a rate of 1 case per 300000.[45] Progressive vaccinia or vaccinia gangrenosum results from necrosis of the

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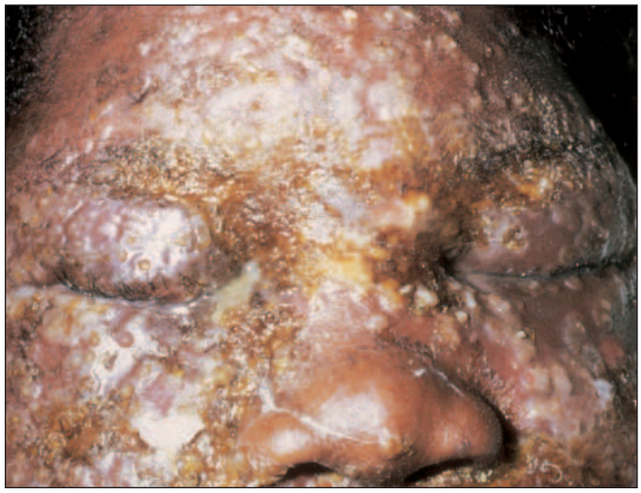

f0020 **Fig. 100.3** Eczema vaccinatum. Vaccinial skin lesions extending over the area currently afflicted with eczema. (Courtesy of Richard K. Forster, MD.)

skin at the vaccination site, with advanced cases involving underlying bone and viscera.[37] Patients with a history of eczema are at risk of developing extensive vaccinial lesions (eczema vaccinatum) over affected sites (Fig. 100.3). In some vaccine recipients, blood-borne dissemination of virus leads to a self-limiting generalized vaccinial rash. Transmission of vaccinia from the site of vaccination to close contacts, or autoinoculation to sites such as face, mouth, eyelid, and genitalia, can take place. Vaccinia immune globulin is used to treat these complications with variable success.

s0140 **Vaccinia ophthalmic manifestations**

p0590 Inadvertent autoinoculation of vaccinia from the deltoid site accounts for the ophthalmic complications of vaccination, which has an incidence of 3.6 per 100 000 inoculations.[46] The majority of patients have vaccinia of the eyelids or conjunctiva, but a smaller percentage have corneal involvement. Typically, patients present 4 to 7 days after vaccination with advanced blepharoconjunctivitis and pustules commonly affecting both lids (Fig. 100.4). The conjunctivitis is usually purulent and ulceration can occur with adherent membrane formation and preauricular lymphadenopathy.[42] Severe cases present with periorbital edema mimicking orbital cellulitis.[47]

p0595 Vaccinial keratitis is the most feared ophthalmic complication. Corneal involvement develops in 20–37% of cases of ocular vaccinia.[48] When virus infects the corneal epithelium it produces a grayish, fine granular opacity with mild epithelial edema.[47] Diseased cells stain with rose Bengal, and dendritic lesions are occasionally present. Subepithelial infiltrates may form and lead to peripheral neovascularization and ulceration. Some patients develop a disciform or necrotizing stromal keratitis with possible perforation.[42,47] The diseased epithelium is less opaque and swollen than that in herpes simplex and a conjunctival follicular reaction is usually absent. The ulceration is more rapid, extensive, and irregular than in herpes.[47] Permanent sequelae include

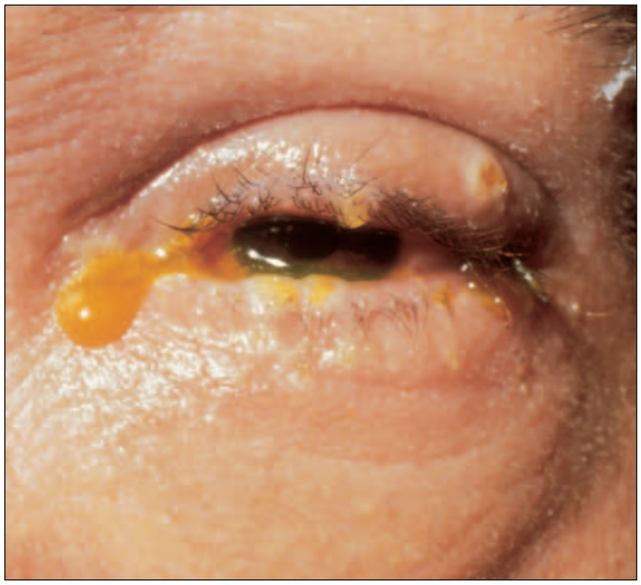

Fig. 100.4 Ocular vaccinia blepharoconjunctivitis with typical umbilicated pustules. (Courtesy of Richard K. Forster, MD.) f0025

corneal scarring, punctal stenosis, eyelid scarring, and loss of lashes.

Treatment s0145

Topical steroids are effective for stromal opacities, neovascularization, and uveitis; however, treatment of the acute infection requires viral inactivation and steroids are contraindicated. Topical and parenteral vaccinia immune globulin is effective for ocular vaccinia,[49,50] especially with orbital inflammation.[47] Idoxuridine, an antiviral used for herpes simplex, can be used to treat early vaccinial keratitis.[51] It is likely that newer antivirals (trifluridine) would be at least as effective as idoxuridine, as both inhibit viral DNA synthesis by thymidine kinase phosphorylation. Most of the cases that occurred in the Department of Defense Smallpox Vaccination Program (2002–03) were treated successfully with trifluridine 1%.[46] p0600

Tularemia s0150

Microbiology and epidemiology s0155

The causative bacterial agent of tularemia, *Francisella tularensis*, is a highly infectious, aerobic, Gram-negative coccobacillus found in widely diverse animal hosts and habitats throughout the world. Tularemia has epidemic potential, but typically occurs in isolated cases in rural areas. The natural reservoirs for infection are various small animals including rabbits, squirrels, voles, mice, and water rats that become infected through bites from ticks, flies, and mosquitoes, and through contact with contaminated soil, water, and vegetation.[52] Humans become infected by various modes, including bites by arthropods, handling infectious animal tissues or fluids, direct contact with or ingestion of p0605

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contaminated water, food, or soil, and inhalation of infective aerosols.

s0160 Clinical manifestations

p0610 The clinical forms of tularemia depend on the virulence of the bacteria as well as the site of inoculation. Disease presentations include ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, typhoidal, and septic forms.[8,52,53] After an incubation of 2 to 10 days, there is rapid onset of fever, chills, rigors, headache, myalgias, coryza, and sore throat. Frequently, there is a dry or slightly productive cough with substernal pain.[52] Nausea, vomiting, and diarrhea can occur and nearly half of patients demonstrate a pulse-temperature dissociation.[54]

p0615 Intentional aerosol release of *F. tularensis* would lead to the generalized illness with a significant number of patients developing pleuropneumonitis. Hematogenous spread may occur, with death resulting from sepsis, disseminated intravascular coagulation, adult respiratory distress syndrome, and multiple organ failure.[53,55] The largest recorded airborne outbreak of tularemia occurred in a farming community in Sweden in 1966–67. The strain was a less virulent form, but still led to 140 serologically confirmed cases. Pulmonary symptoms were present in 10%, conjunctivitis in 26%, skin ulceration in 12%, pharyngitis in 31%, oral ulcers in 9%, and 32% had various exanthemas, such as erythema multiforme and erythema nodosum.[48] Person-to-person transmission is not known to occur.[52]

s0165 Ophthalmic manifestations

p0620 Tularemia is one of the causes of Parinaud's oculoglandular syndrome.[56] Direct contamination of the eye leads to conjunctival ulceration, chemosis, and tender lymphadenopathy of the preauricular, submandibular, and cervical regions.[53] The conjunctivitis is unilateral (90%) and granulomatous, typically with multiple yellow nodules involving the tarsal or bulbar surface.[57] Rare ocular effects include corneal ulceration,[56,57] dacryocystitis,[58] acute glaucoma,[59] endogenous retinitis,[60] and optic neuritis.[58] The differential diagnosis includes bacterial conjunctivitis, adenoviral, syphilis, cat-scratch disease, herpes simplex infection, and other rare causes of Parinaud's oculoglandular syndrome.[53,58]

s0170 Diagnosis

p0625 *F. tularensis* can be identified by examination of secretions or biopsy specimens using direct fluorescent antibody or immunohistochemical stains.[52] Cultures are definitive, but must be performed with cysteine-enriched media.[52,53] Serological testing can be diagnostic; however, it can take longer than 10 days after the onset of illness for a significant change in titers, proving less useful in an outbreak.[52] Several PCR assays have been developed that would give faster results.[14]

s0175 Treatment

p0630 Treatment is with streptomycin 1 g IM b.i.d. for 10 days, with gentamicin (5 mg/kg IM or IV) as an alternative. Fluoroquinolones are probably as effective.[52,59] In a mass exposure situation or for postexposure prophylaxis, oral doxycycline 100 mg b.i.d. or ciprofloxacin 500 mg b.i.d. can be used for 14 days.[52] Treatment for ocular disease should include frequent topical gentamicin.[57,58]

Viral hemorrhagic fever s0180

Microbiology and epidemiology s0185

p0635 Viral hemorrhagic fever is a clinical illness associated with fever and bleeding diathesis caused by a virus belonging to one of four families: Filoviridae, Arenaviridae, Bunyaviridae, and Flaviviridae (Table 100.4).[61] All are RNA viruses that in nature reside in animal hosts or arthropod vectors. Humans are infected by the bite of an infected arthropod, via aerosol (the mechanism in a biological attack) generated from infected rodent excreta, or by direct contact with infected animal carcasses. Some viruses can lead to human-to-human transmission via direct contact with blood, secretions (oral and conjunctival), or tissues of infected patients or needlestick injuries.[61]

Clinical manifestations s0190

p0655 The vascular system is primarily targeted by these viruses. Microvascular damage with changes in vascular permeability lead to a coagulopathy and signs of bleeding which include conjunctival hemorrhage, mild hypotension, flushing, and petechiae.[61] Symptoms of fatigue, dizziness, and myalgias are present during the first week of illness. Nausea and nonbloody diarrhea may accompany the high fevers after an incubation period that ranges from 2 to 21 days.[61] Disseminated intravascular coagulation with hematuria, hematemesis, and melena occurs as a late ominous sign. In severe cases, shock and generalized mucous membrane hemorrhage results with end-organ damage and death within 1 to 2 weeks.

p0660 Some viral hemorrhagic fevers present with suggestive clinical features.[61] Ebola and Marburg (Filoviridae genus) are especially virulent and can cause necrosis of visceral organs (liver, spleen, kidneys). Adult respiratory distress syndrome is a sequela of one species of Hantavirus. Nephropathia epidemica is caused by Puumala virus, and leads to an acute hemorrhagic tubular and interstitial nephritis.

Ophthalmic manifestations s0195

Filoviridae s0200

p0665 Due to high mortality rates, Ebola and Marburg hemorrhagic fever are two of the most feared illnesses. Eye involvement presents with symptoms of pain, photophobia, tearing, and blurred vision.[62] Conjunctival injection is seen in at least one-half of patients during the acute phase, and may present with subconjunctival hemorrhage. Fifteen percent (3/20) of patients who survived the 1995 Ebola outbreak in the Democratic Republic of Congo developed acute anterior uveitis with vitreous opacities in one patient.[62] The onset of uveitis was 1 to 2 months after initial infection. Treatment with topical cycloplegics and steroids was effective in all patients. A case of recurrent anterior uveitis with elevated intraocular pressure occurred after a small outbreak of Marburg virus in Johannesburg, South Africa, in 1975. Virus was cultured from the anterior chamber aspirate at presentation, 80 days after initial infection.[63]

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Table 100.4 Hemorrhagic fever viruses* t0025

Family	Genus	Virus	Disease	Vector in nature	Geographic distribution
Filoviridae	Filovirus	**Ebola**† **Marburg**	Ebola hemorrhagic fever Marburg hemorrhagic fever	Unknown Unknown	Africa Africa
Arenaviridae	Arenavirus	**Lassa** **New World Arenaviridae**‡	Lassa fever New World hemorrhagic fever	Rodent Rodent	West Africa Americas
Bunyaviridae	Nairovirus Phlebovirus Hantavirus	Crimean-Congo hemorrhagic fever **Rift Valley fever** Agents of hemorrhagic fever with renal syndrome	Crimean-Congo hemorrhagic fever Rift Valley fever Hemorrhagic fever with renal syndrome	Tick Mosquito Rodent	Africa, central Asia, Eastern Europe, Middle East Africa, Saudi Arabia, Yemen Asia, Balkans, Europe, Eurasia§
Flaviviridae	Flavivirus	Dengue **Yellow fever** **Omsk hemorrhagic fever** **Kyasanur Forest disease**	Dengue fever, Dengue hemorrhagic fever, and Dengue shock syndrome Yellow fever Omsk hemorrhagic fever Kyasanur Forest disease	Mosquito Mosquito Tick Tick	Asia, Africa, Pacific, Americas Africa, tropical Americas Central Asia India

** Bold indicates hemorrhagic fever viruses that pose serious risk as biological weapons.*
† There are four subtypes of Ebola: Zaire, Sudan, Ivory Coast, and Reston.
‡ The New World Arenaviridae include Muchupo, the cause of Bolivian hemorrhagic fever; Junin, the cause of Argentine hemorrhagic fever; Guanarito, the cause of Venezuelan hemorrhagic fever; and Sabia, the cause of Brazilian hemorrhagic fever. An additional arenavirus has been isolated following three fatal cases of hemorrhagic fever in California, 1999–2000.
§ Additionally, the agents of Hantavirus pulmonary syndrome have been isolated in North America.
From reference 61, page 2392, Table 1, Borio L, Inglesby T, Peters CJ et al: Hemorrhagic fever virus as biological weapons: medical and public health management, JAMA 287(18):2391–2405, 2002. Copyright © (2002) American Medical Association. All rights reserved.

s0205 *Nephropathia epidemica*

p0670 Some of the other less virulent causes of viral hemorrhagic fever also have ophthalmic signs. Patients affected with nephropathia epidemica can present with eye pain, blurred vision, and photophobia. The most prominent eye finding is transient myopia due to forward movement of the anterior diaphragm and thickening of the crystalline lens.[64] Usually, the intraocular pressure is slightly lowered;[65] however, acute glaucoma has been observed.[66] Other findings include conjunctival injection and hemorrhage, iritis, and retinal edema with hemorrhage.[67] Neuro-ophthalmic findings include tonic pupils[68] and isolated abducens palsy.[69]

s0210 *Rift Valley fever*

p0675 Rift Valley fever presents predominantly with retinal findings, although conjunctival injection with photophobia and retroorbital pain is present initially. Fundus examination typically reveals cotton-wool exudates and hemorrhage in the macula and paramacular area, vascular occlusions and sheathing, macular edema, and optic pallor.[70] Vitreous hemorrhage, retinal detachment, and epiretinal membranes may also develop. Uveitis with occasional anterior chamber reaction occurs in less than one-third of patients.

s0215 ## Diagnosis

p0680 Travel history and clinical presentation can aid in the diagnosis and help determine the type of hemorrhagic fever virus. Occasionally, thrombocytopenia or leukopenia may be present. Viral cultures, rapid enzyme immunoassays (ELISA, reverse transcription-PCR), and electron microscopy can identify the specific subtype of virus.[25]

Treatment s0220

p0685 Treatment is supportive, but ribavirin may be beneficial in Arenaviruses or Bunyaviruses.[61] With the exception of yellow fever and Argentine hemorrhagic fever, there is no licensed vaccine for any of the viral hemorrhagic fevers.

Others s0225

p0690 The CDC has listed additional biological agents that pose significant but lower risk to public health than the agents already described. The known ophthalmic associations of these are listed in Box 100.3.[10,71–94]

Chemical Agents s0230

p0775 Chemical attacks can easily overwhelm medical resources, especially in urban areas. Materials to manufacture chemical weapons are inexpensive and easy to obtain. The categories and types used by the CDC are listed in Box 100.4.[95] They can be found as solids, liquids, gases, vapors, and aerosols.[96] The state of an agent is chosen depending on its intended use and desired duration of exposure or persistence. Liquids and solids persist the longest, with variables that include temperature, wind conditions, agent–surface interactions, and the agent's volatility.

p1240 The efficacy of a chemical agent is determined by its degree of absorption and its toxicity. Chemicals penetrate epidermal surfaces due to their lipophilic nature and are often mixed with additional substances to enhance diffusion through protective clothing and other barriers.[96] Toxicity is determined by the dose or concentration (gas or vapor) and

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b0020 **Box 100.3** Biological agents of second highest priority and ophthalmic manifestations

Brucellosis (*Brucella* spp.) – uveitis[71,72] with iridocyclitis (acute or chronic, granulomatous or nongranulomatous) and multifocal choroiditis (nodular or geographic[73]), nummular keratitis,[74] recurrent episcleritis,[75] optic neuritis,[76] dacryoadenitis,[77] endogenous endophthalmitis[78]

Epsilon toxin of *Clostridium perfringens* – corneal ulcer,[79] endogenous endophthalmitis[80]

Salmonella spp. – Reiter's syndrome,[81] peripheral ulcerative keratitis,[82] stellate maculopathy and chorioretinitis,[83] endogenous endophthalmitis[84]

Escherichia coli O157:H7 – keratitis,[85] endogenous endophthalmitis[86]

Shigella spp. – Reiter's syndrome, keratitis[87], orbital inflammation[88]

Glanders (*Burkholderia mallei*) – none

Melioidosis (*Burholderia pseudomallei*) – anophthalmic socket infection,[89] keratitis with endophthalmitis[90]

Psittacosis (*Chlamydia psittaci*) – conjunctivitis, uveitis,[91] interstitial keratitis[92]

Q fever (*Coxiella burnetii*) – choroidal neovascularization,[93] optic neuritis[94]

Ricin toxin from *Ricinus communis* (castor beans) – none

Staphylococcal enterotoxin B – none

Trichothecene mycotoxins – none

Typhus fever (*Rickettsia prowazekii*) – none

Vibrio cholerae – none, keratitis in other Vibrio species

Viral encephalitis (alphaviruses, i.e. Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis) – none

List from reference 10, Medline search for ophthalmic involvement, Centers for Disease Control and Prevention: Biological Diseases/Agents List. Available at http http://www.bt.cdc.gov/agent/agentlist-category.asp, accessed 02/28/09.

length of exposure. Most chemical agents produce at least mild eye irritation, but nerve agents and vesicants have particular interest to ophthalmologists.

s0235 ## Nerve agents

p1245 Nerve agents are potent organophosphate compounds that inhibit acetylcholinesterase, leading to excessive acetylcholine neurotransmitter at its postsynaptic receptor sites. Both muscarinic and nicotinic receptors are affected, causing cholinergic crisis (Box 100.5).[96] Muscarinic effects involve the smooth muscles (bronchoconstriction, increased gastric motility, miosis), the glands (lacrimation, rhinorrhea, salivation, increased secretion – gastrointestinal and airway), and the heart (bradycardia). Nicotinic effects include fasciculations, twitching, fatigue, tachycardia, hypertension, and paralysis. Nerve agents cross the blood–brain barrier and can lead to confusion, altered consciousness, seizures, apnea, coma, and death. Small exposures are associated with transient effects such as poor concentration, and disturbances of vision, sleep, and emotions.

Ophthalmic manifestations s0240

p1440 On March 20, 1995, the Aum Shinrikyo cult released sarin (isopropyl methylphosphonofluoridate) gas at several points in the Tokyo, Japan, subway system.[97] A similar incident occurred on June 27, 1994, in Matsumoto, Japan.[98] Pure sarin is colorless and odorless, and when vaporized is absorbed through the respiratory tract and conjunctiva. Within minutes of exposure victims noted a sensation of darkness related to miosis. Many had conjunctival injection, with pain and impaired accommodation related to ciliary spasm. In nearly one-third of patients, there was an approximate 3-mmHG lowering of intraocular pressure. Ocular signs and symptoms resolved within several days to several weeks after treatment with topical cycloplegics.

Treatment s0245

p1445 Management includes basic life resuscitation, decontamination, drug therapy, and supportive care. Removal of clothing and jewelry, and forceful soap and water washing of the skin is recommended. Hypochlorite (0.5% solution) can be used instead of water as it inactivates nerve agents.[99] Despite decontamination, the effects may worsen with time because these agents can accumulate in fat and release slowly.[96] Atropine is a competitive inhibitor of acetylcholine at muscarinic receptors, and thus reverses the hypersecretory, bronchoconstrictive, bradycardic, and gastrointestinal effects of nerve agents.[100] Pralidoxime (Protopam, 2-PAM) can counteract nicotinic (primarily muscle weakness) effects by binding to the nerve agent and reactivating acetylcholinesterase.

Vesicants s0250

p1450 Vesicants are oily liquids that become aerosolized when dispersed by an explosive blast from a bomb or when released under high ambient temperatures. Sulfur mustard is the most common vesicant used in chemical weapons. It is lipophilic and readily penetrates skin, most textiles, and rubber.[100] Skin penetration occurs in less than 2 minutes, but there is a delay of minutes to hours in the onset of a burning sensation. In contrast, lewisite causes almost immediate burning. Once absorbed, it alkylates and denatures DNA, RNA, and proteins, leading to cell death.

Clinical manifestations s0255

p1455 Clinical effects usually appear within 4 to 8 hours after exposure to mustard. Dermal exposure produces superficial (erythema, pain) to partial-thickness (bullae) burns with uncommon full-thickness (deep bullae, ulcer) involvement.[100] Inhalation of mustard vapor can cause bronchospasm, mucosal sloughing, and hemorrhagic pulmonary edema in severe cases. Large exposure can lead to bone marrow suppression and gastrointestinal effects which may lead to secondary infection, sepsis, and death.

Ophthalmic manifestations s0260

p1460 Ocular effects range from a mild conjunctivitis to corneal burns. The eye is very susceptible to damage due to the enhanced absorption by the aqueous-mucous surface and the tendency for concentration in the oily layer of the tear

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Box 100.4

p0780 o0075 **Biotoxins**

p0790 Poisons that come from plants or animals
- o0080 p0795 Abrin
- p0800 Brevetoxin
- p0805 Colchicine
- p0810 Digitalis
- p0815 Nicotine
- p0820 Ricin
- p0825 Saxitoxin
- p0830 Strychnine
- p0835 Tetrodotoxin
- p0840 Trichothecene

p0845 **Blister agents/vesicants**

p0850 Chemicals that severely blister the eyes, respiratory tract, and skin on contact
- o0085 p0855 Mustards
  - o0090 p0860 Distilled mustard (HD)
  - p0865 Mustard gas (H) (sulfur mustard)
  - p0870 Mustard/lewisite (HL)
  - p0875 Mustard/T
  - p0880 Nitrogen mustard (HN-1, HN-2, HN-3)
  - p0885 Sesqui mustard
  - p0890 Sulfur mustard (H) (mustard gas)
- p0895 Lewisites/chloroarsine agents
  - o0095 p0900 Lewisite (L, L-1, L-2, L-3)
  - p0905 Mustard/lewisite (HL)
- p0910 Phosgene oxime (CX)

p0915 **Blood agents**

p0920 Poisons that affect the body by being absorbed into the blood
- o0100 p0925 Arsine (SA)
- p0930 Carbon Monoxide
- p0935 Cyanide
  - o0105 p0940 Cyanogen chloride (CK)
  - p0945 Hydrogen cyanide (AC)
  - p0950 Potassium cyanide (KCN)
  - p0955 Sodium cyanide (NaCN)
- p0960 Sodium monofluoroacetate (compound 1080)

p0965 **Caustics (acids)**

p0970 Chemicals that burn or corrode people's skin, eyes, and mucus membranes (lining of the nose, mouth, throat, and lungs) on contact
- o0110 p0975 Hydrofluoric acid (hydrogen fluoride)

p0980 **Choking/lung/pulmonary agents**

p0985 Chemicals that cause severe irritation or swelling of the respiratory tract (lining of the nose, throat, and lungs)
- o0115 p0990 Ammonia
- p0995 Bromine (CA)
- p1000 Chlorine (CL)
- p1005 Hydrogen chloride
- p1010 Methyl bromide
- p1015 Methyl isocyanate
- p1020 Osmium tetroxide
- p1025 Phosgene
  - o0120 p1030 Diphosgene (DP)
  - p1035 Phosgene (CG)
- p1040 Phosphine
- p1045 Phosphorus, elemental, white or yellow
- p1050 Sulfuryl fluoride

p1055 **Incapacitating agents**

p1060 Drugs that make people unable to think clearly or that cause an altered state of consciousness (possibly unconsciousness)
- o0125 p1065 BZ
- p1070 Fentanyls & other opioids

p1075 **Long-acting anticoagulants**

p1080 Poisons that prevent blood from clotting properly, which can lead to uncontrolled bleeding
- o0130 p1085 Super warfarin

p1090 **Metals**

o0135 p1095 Agents that consist of metallic poisons
- p1100 Arsenic
- p1105 Barium
- p1110 Mercury
- p1115 Thallium

p1120 **Nerve agents**

p1125 Highly poisonous chemicals that work by preventing the nervous system from working properly
- o0140 p1130 G agents
  - o0145 p1135 Sarin (GB)
  - p1140 Soman (GD)
  - p1145 Tabun (GA)
- p1150 V agents
  - p1155 VX

p1160 **Organic solvents**

p1165 Agents that damage the tissues of living things by dissolving fats and oils
- o0150 p1170 Benzene

p1175 **Riot control agents/tear gas**

p1180 Highly irritating agents normally used by law enforcement for crowd control or by individuals for protection (for example, mace)
- o0155 p1185 Bromobenzylcyanide (CA)
- p1190 Chloroacetophenone (CN)
- p1195 Chlorobenzylidenemalononitrile (CS)
- p1200 Chloropicrin (PS)
- p1205 Dibenzoxazepine (CR)

p1210 **Toxic alcohols**

p1215 Poisonous alcohols that can damage the heart, kidneys, and nervous system
- o0160 p1220 Ethylene glycol

p1225 **Vomiting agents**

p1230 Chemicals that cause nausea and vomiting
- o0165 p1235 Adamsite (DM)

From reference 95, exact copy from website, Centers for Disease Control and Prevention: Chemical Agents List and Information. Available at http://emergency.cdc.gov/agent/agentlistchem-category.asp, last updated 04/01/2008.

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Box 100.5

p1250 o0170 Nerve agent signs

p1260 Muscarinic
o0175 p1265 Smooth muscle
p1270 Bronchoconstriction
p1275 Increased gastric motility
p1280 Miosis
p1285 Glands
p1290 Lacrimation
p1295 Rhinorrhea
p1300 Salivation
p1305 Increased gastrointestinal secretions
p1310 Bronchorrhea
p1315 Diaphoresis
p1320 Other
p1325 Bradycardia
p1330 Heart block
p1335 Hypotension
p1340 Urinary incontinence

p1345 Nicotinic
o0180 p1350 Muscle
p1355 Fasciculations
p1360 Twitching
p1365 Fatigue
p1370 Flaccid paralysis
p1375 Other
p1380 Tachycardia
p1385 Hypertension

p1390 Central nervous system
o0185 p1395 Headaches
p1400 Vertigo
p1405 Agitation
p1410 Anxiety
p1415 Slurred speech
p1420 Delirium
p1425 Coma
p1430 Seizures
p1435 Central respiratory depression

Adapted from reference 96, American College of Physicians-American Society of Internal Medicine: Bioterrorism Summaries from Annual Session 2002. Available at http://www.acponline.org/bioterro/as_sum1.htm, last accessed 11/05/02.

film due to mustard's lipophilic quality.[101] The cornea is thus exposed for a prolonged period of time leading to pain from loosening of the epithelial layer, which exposes the free unmyelinated nerve endings.

p1465 Symptoms begin with eye pain, photophobia, lacrimation, and blurred vision. A mild conjunctivitis is commonly seen within an hour of exposure and is one of the earliest clinical signs.[101] Mild injury causes blepharospasm, eyelid erythema, and lacrimation. Moderate injury leads to periorbital edema, corneal epithelial edema, and punctate corneal erosions. Vesication of the cornea can lead to complete sloughing of the epithelium. Microscopically, there is loss of conjunctival mucus with occlusion of blood vessels due to goblet and endothelial cell injury, respectively.[102] Recovery typically occurs without significant adverse sequelae; however, about 90% of mildly affected patients are visually disabled for approximately 10 days.[103]

p1470 Severe injury (about 10% of patients) can result in conjunctival chemosis and blanching due to destruction of conjunctival and limbal blood vessels. There is corneal stromal edema with diminished or absent sensation, which can lead to ulceration, secondary microbial keratitis, and perforation. Deeper penetration may result in anterior uveitis, the formation of posterior synechiae, a transient elevation of intraocular pressure, and lens opacification. Corneal pannus formation begins within a few weeks due to persistent inflammation and limbal stem cell deficiency. Corneal scarring and conjunctivalization lead to impaired vision in the months that follow the acute injury. Conjunctival scrape cytology in soldiers with chronic eye problems after exposure to mustard gas during the Iraq–Iran war has shown dysplasia in 41% (9 of 22) studied, but none with squamous cell carcinoma.[104] Chronic angle closure glaucoma and phthisis can lead to blindness.

p1475 An unusual delayed type of keratopathy develops in 0.5% of patients up to 40 years after severe exposure to mustard gas.[101] After an inactive period, the patient experiences a recurrent attack of stromal keratitis starting near the limbus and advancing centrally. There is a pathognomonic porcelain-white episcleral area adjacent to the peripheral corneal ulceration.[105] Areas of stromal calcification with overlying epithelial breakdown are characteristically located in the lower and central cornea.[106] Aneurysmatic dilatations and tortuosity of conjunctival and corneal vessels exists with intracorneal hemorrhage. Advanced cases lead to corneal opacification with crystal and cholesterol deposits. The pathogenesis is unknown, but may involve degenerative processes that accompany the deposition of cholesterol, as well as immunological reaction to corneal proteins that were structurally modified by the mustard.[101]

Treatment

s0265

p1480 Management of acute exposure should include removal of contaminated clothes and flushing of the skin with soap and water. Absorbent powders, such as calcium chloride and magnesium oxide, are also effective if available.[107] The eyes of both symptomatic and asymptomatic patients should be irrigated with tap water as soon as possible. Topical antibiotics and cycloplegics should be prescribed, but the use of topical steroids is controversial. Steroid use within 7 to 10 days can limit polymorphonuclear cell migration, inhibit collagenolysis and quell chemical anterior uveitis. The disadvantage is impaired epithelial wound healing with the possibility of subsequent corneal ulceration and perforation. Vitamin C (ascorbate), citrate, and N-acetylcysteine (Mucomyst) may be beneficial adjunctive therapies. Frequent lubrication, bandage contact lenses, and tarsorrhaphy aid in management. Ocular surface reconstruction with amniotic membrane and/or limbal stem cell transplantation along with penetrating keratoplasty may be required for full visual rehabilitation.

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