Chapter 100

External Eye Manifestations of Biological and Chemical Warfare

Craig A. Skolnick

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.

Background

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. 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 nineteenth 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.

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. Unfortunately, there were no provisions for inspection, and many countries that ratified the treaty still began research programs to develop biological weapons.

During World War II, Japan conducted experiments in which prisoners were infected with various bacterial pathogens, which led to at least 10,000 deaths. 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 the 1972 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. 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. 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.
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.

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Downwind reach (km)</th>
<th>No. dead</th>
<th>No. incapacitated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rift Valley fever</td>
<td>1</td>
<td>400</td>
<td>35,000</td>
</tr>
<tr>
<td>Tick-borne encephalitis</td>
<td>1</td>
<td>9,500</td>
<td>35,000</td>
</tr>
<tr>
<td>Typhus</td>
<td>5</td>
<td>19,000</td>
<td>85,000</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>10</td>
<td>500</td>
<td>100,000</td>
</tr>
<tr>
<td>Q fever</td>
<td>&gt;20</td>
<td>150</td>
<td>125,000</td>
</tr>
<tr>
<td>Tularemia</td>
<td>&gt;20</td>
<td>30,000</td>
<td>125,000</td>
</tr>
<tr>
<td>Anthrax</td>
<td>&gt;20</td>
<td>95,000</td>
<td>125,000</td>
</tr>
</tbody>
</table>

* This model assumes that 50 kg of agent is deployed from an aircraft along a 2 km line upwind from the city.


### Warning Signs

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:

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

### Box 100.1 Biological diseases

<table>
<thead>
<tr>
<th>Agent</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax (Bacillus anthracis)</td>
<td></td>
</tr>
<tr>
<td>Botulism (Clostridium botulinum toxin)</td>
<td></td>
</tr>
<tr>
<td>Plague (Yersinia pestis)</td>
<td></td>
</tr>
<tr>
<td>Smallpox (Variola major and minor)</td>
<td></td>
</tr>
<tr>
<td>Tularemia (Francisella tularensis)</td>
<td></td>
</tr>
<tr>
<td>Viral hemorrhagic fevers</td>
<td></td>
</tr>
<tr>
<td>Filoviruses – Ebola, Marburg</td>
<td></td>
</tr>
<tr>
<td>Arenaviruses – Lassa, Machupo</td>
<td></td>
</tr>
</tbody>
</table>


### Biological Diseases

#### Anthrax

*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.

### Microbiology/epidemiology

*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. 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. 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.

### Clinical manifestations

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. 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, ethyema gangrenosum, ulceroglandular tularemia, plague, scrub typhus, rickettsial spotted fever, rat bite fever, staphylococcal or streptococcal cellulitis, and herpes simplex virus.
Cutaneous anthrax

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. 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.’ 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.

Ophthalmic manifestations

Ocular findings in cutaneous anthrax relate to eyelid involvement. The main complication is cicatricial ectropion due to late eyelid scarring (Fig. 100.1). 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. Temporal artery inflammation has been reported as a complication of overlying cutaneous anthrax.

Diagnosis

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. Spores have a diameter of 2–6 mm, which is ideal for entrapment in the lower respiratory tract. 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. Thus it may be hard to trace the onset of an attack, making response and containment more difficult.

Treatment

Treatment of inhalational and gastrointestinal anthrax should begin with intravenous ciprofloxacin 400 mg every 12 hours (Table 100.2). 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. Direct contact with wound or wound drainage should be avoided when caring for a patient with cutaneous anthrax.

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. 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.

Prevention

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...
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. 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.

**Microbiology**

*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). Types A, B, and E account for greater than 99% of human botulism. Type A toxin is the most potent poison known to humans, 100,000 times more toxic than sarin nerve gas. 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.

**Clinical manifestations**

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. 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.

Botulism classically presents as an acute, afebrile, symmetric, descending flaccid paralysis that always begins in the bulbar musculature (Box 100.2). Patients have a clear metric, descending flaccid paralysis that always begins in the body, followed by weakness extending to the arms and legs. As the disease progresses, weakness extends above 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. Autonomic nervous system involvement can lead to cardiovascular lability.

**Ophthalmic manifestations**

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

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postexposure prophylaxis</td>
<td>Ciprofloxacin 500 mg by mouth twice a day</td>
<td>Ciprofloxacin 10–15 mg/kg by mouth every 12 hrs*</td>
</tr>
<tr>
<td>OR</td>
<td>Doxycline 100 mg by mouth twice a day</td>
<td>Doxycline: &gt;8 yr and ≥45 kg: 100 mg by mouth every 12 hrs &gt;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</td>
</tr>
<tr>
<td>Cutaneous anthrax</td>
<td>Ciprofloxacin 500 mg by mouth twice a day</td>
<td>Ciprofloxacin 10–15 mg/kg by mouth every 12 hrs*</td>
</tr>
<tr>
<td>OR</td>
<td>Doxycline 100 mg by mouth twice a day</td>
<td>Doxycline: &gt;8 yr and ≥45 kg: 100 mg by mouth every 12 hrs &gt;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</td>
</tr>
<tr>
<td>Inhalational anthrax</td>
<td>Ciprofloxacin 400 mg intravenously every 12 hrs OR</td>
<td>Ciprofloxacin 10–15 mg/kg intravenously every 12 hrs* OR</td>
</tr>
<tr>
<td>OR</td>
<td>Doxycline 100 mg intravenously every 12 hrs PLUS (or for other drug)</td>
<td>Doxycline: &gt;8 yr and ≥45 kg: 100 mg intravenously every 12 hrs &gt;8 yr and ≤45 kg: 2.2 mg/kg intravenously every 12 hrs ≤8 yrs: 2.2 mg/kg intravenously every 12 hrs PLUS (or for other drug)</td>
</tr>
<tr>
<td>One or two additional antibiotics (e.g. rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, cildimycin, clarithromycin)</td>
<td>One or two additional antibiotics</td>
<td></td>
</tr>
</tbody>
</table>

* Ciprofloxacin dose in children n not to exceed 1 g/day.

Uncommon neuro-ophthalmic manifestations include complete bilateral internal ophthalmoplegia 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**

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. 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. An electromyogram can be diagnostic. Demonstration of toxin by mouse bioassay is diagnostic in samples of serum, stool, gastric aspirate, and suspect food. 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. Fecal, wound, and gastric specimens can be cultured anaerobically if a food-borne or wound source of *C. botulinum* is suspected.

**Treatment**

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. 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**

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.

**Microbiology**

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. Three other members of this genus (monkeypox, vaccinia, and cowpox) can infect humans but are not highly contagious.

**Epidemiology**

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%
Clinical manifestations

After an incubation period of about 12 days, patients become febrile and often develop severe constitutional symptoms. 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. 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. Chick- enpox (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.

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. Pneumonia, encephalitis, osteomyelitis, orchitis, sepsis, and overwhelming hemorrhage into the skin and mucous membranes can complicate smallpox infection. Variola minor, the less severe form of smallpox, results in milder symptoms with only a sparse rash and less than 1% mortality. Patients are most infectious during the first week of illness; however, some risk of transmission is present until all scabs have fallen off. It is thought that smallpox cannot be transmitted until the onset of the rash. So diagnosis during the prodromal stage with subsequent quarantine would be essential to limit additional exposure.

Ophthalmic manifestations

Smallpox led to blindness in 2–5% of students in blind schools of developing countries in Africa. 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. 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. 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.

Diagnosis

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. Virus culture of skin lesions, oropharynx, conjunctiva, and urine is definitive. PCR techniques can discriminate between strains and offer a more rapid result.

Treatment and vaccination

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

The interval between an aerosol release of variola and diagnosis of the first cases is as much as 2 weeks. 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

Vaccination is not without risk. Life-threatening encephalitis occurs at a rate of 1 case per 300 000. Progressive vaccinia or vaccinia gangrenosum results from necrosis of the
skin at the vaccination site, with advanced cases involving underlying bone and viscera. 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.

Vaccinia ophthalmic manifestations

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. 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.

Severe cases present with periorbital edema mimicking orbital cellulitis.

Vaccinia keratitis is the most feared ophthalmic complication. Corneal involvement develops in 20–37% of cases of ocular vaccinia. When virus infects the corneal epithelium it produces a grayish, fine granular opacity with mild epithelial edema. 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. 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. Permanent sequelae include corneal scarring, punctal stenosis, eyelid scarring, and loss of lashes.

Treatment

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, especially with orbital inflammation. Idoxuridine, an antiviral used for herpes simplex, can be used to treat early vaccinial keratitis. 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%

Tularemia

Microbiology and epidemiology

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. Humans become infected by various modes, including bites by arthropods, handling infectious animal tissues or fluids, direct contact with or ingestion of...
contaminated water, food, or soil, and inhalation of infectious aerosols.

Clinical manifestations

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. 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. Nausea, vomiting, and diarrhea can occur and nearly half of patients demonstrate a pulse-temperature dissociation.

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.

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. Person-to-person transmission is not known to occur.

Ophthalmic manifestations

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

Diagnosis

F. tularensis can be identified by examination of secretions or biopsy specimens using direct fluorescent antibody or immunohistochemical stains. Cultures are definitive, but must be performed with cysteine-enriched media. Sero logical 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. Several PCR assays have been developed that would give faster results.

Treatment

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. 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. Treatment for ocular disease should include frequent topical gentamicin.
Table 100.4 Hemorrhagic fever viruses*

<table>
<thead>
<tr>
<th>Family</th>
<th>Genus</th>
<th>Virus</th>
<th>Disease</th>
<th>Vector in nature</th>
<th>Geographic distribution</th>
</tr>
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<tr>
<td>Flaviridae</td>
<td>Flavivirus</td>
<td>Ebola†</td>
<td>Ebola hemorrhagic fever</td>
<td>Unknown</td>
<td>Africa</td>
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<td></td>
<td></td>
<td>Marburg</td>
<td>Marburg hemorrhagic fever</td>
<td>Unknown</td>
<td>Africa</td>
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<tr>
<td>Arenaviridae</td>
<td>Arenavirus</td>
<td>Lassa</td>
<td>Lassa fever</td>
<td>Rodent</td>
<td>West Africa</td>
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<tr>
<td></td>
<td></td>
<td>New World Arenavirida†</td>
<td>New World hemorrhagic fever</td>
<td>Rodent</td>
<td>Americas</td>
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<tr>
<td>Bunyaviridae</td>
<td>Nairovirus</td>
<td>Crimean-Congo hemorrhagic fever</td>
<td>Crimean-Congo hemorrhagic fever</td>
<td>Tick</td>
<td>Africa, central Asia, Eastern Europe, Middle East</td>
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<tr>
<td></td>
<td>Phlebovirus</td>
<td>Rift Valley fever</td>
<td>Rift Valley fever</td>
<td>Mosquito</td>
<td>Africa, Saudi Arabia, Yemen, Asia, Balkans, Europe, Eurasia†</td>
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<tr>
<td></td>
<td>Harantavirus</td>
<td>Agents of hemorrhagic fever with renal syndrome</td>
<td>Hemorrhagic fever with renal syndrome</td>
<td>Rodent</td>
<td></td>
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<tr>
<td>Flaviridae</td>
<td>Flavivirus</td>
<td>Dengue</td>
<td>Dengue fever, Dengue hemorrhagic fever, and Dengue shock syndrome</td>
<td>Mosquito</td>
<td>Africa, Asia, Pacific, Americas</td>
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<td></td>
<td></td>
<td>Yellow fever</td>
<td>Yellow fever</td>
<td>Mosquito</td>
<td>Africa, tropical Americas</td>
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<td></td>
<td></td>
<td>Omsk hemorrhagic fever</td>
<td>Omsk hemorrhagic fever</td>
<td>Tick</td>
<td>Central Asia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kyasanur Forest disease</td>
<td>Kyasanur Forest disease</td>
<td>Tick</td>
<td>India</td>
</tr>
</tbody>
</table>

* 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 Machupo, 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.


Nephropathia epidemica

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. Usually, the intraocular pressure is slightly lowered; however, acute glaucoma has been observed. Other findings include conjunctival injection and hemorrhage, iritis, and retinal edema with hemorrhage. Neuro-ophtalmic findings include tonic pupils and isolated abducens palsy.

Rift Valley fever

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. Vitreous hemorrhage, retinal detachment, and epiretinal membranes may also develop. Uveitis with occasional anterior chamber reaction occurs in less than one-third of patients.

Diagnosis

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.

Treatment

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

Others

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.

Chemical Agents

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. They can be found as solids, liquids, gases, vapors, and aerosols. 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.

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. Toxicity is determined by the dose or concentration (gas or vapor) and...
Sensit effects such as poor concentration, and disturbances of coma, and death. Small exposures are associated with tran-

paralysis. Nerve agents cross the blood–brain barrier and can affect the heart (bradycardia). Nicotinic effects include fascicula-
tion, increased secretion – gastrointestinal and airway), and motility, miosis), the glands (lacrimation, rhinorrhea, saliva-

the smooth muscles (bronchoconstriction, increased gastric

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

**Nerve agents**

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). Muscarinic effects involve the smooth muscles (bronchoconstriction, increased gastric motility, miosis), the glands (lacrimation, rhinorrhea, saliva-

tion, increased secretion – gastrointestinal and airway), and the heart (bradycardia). Nicotinic effects include fascicula-
tions, 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 tran-
sient effects such as poor concentration, and disturbances of vision, sleep, and emotions.

**Ophthalmic manifestations**

On March 20, 1995, the Aum Shinrikyo cult released sarin (isopropyl methylphosphonofluoridate) gas at several points in the Tokyo, Japan, subway system. A similar incident occurred on June 27, 1994, in Matsumoto, Japan. 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 approxi-

mate 3-mmHG lowering of intraocular pressure. Ocular signs and symptoms resolved within several days to several weeks after treatment with topical cycloplegics.

**Treatment**

Management includes basic life resuscitation, decontamina-
tion, 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. Despite decontamination, the effects may worsen with time because these agents can accumulate in fat and release slowly. Atro-

pine is a competitive inhibitor of acetylcholine at muscarinic receptors, and thus reverses the hypersecretory, broncho-

onstrictive, bradycardic, and gastrointestinal effects of nerve agents. Pralidoxime (Protopam, 2-PAM) can counteract nicotinic (primarily muscle weakness) effects by binding to the nerve agent and reactivating acetylcholinesterase.

**Vesicants**

Vesicants are oily liquids that become aerosolized when dis-
persed 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. 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**

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) involve-

ment. Inhalation of mustard vapor can cause bronchos-
pasm, 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**

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
Box 100.4

**Biotoxins**

Poisons that come from plants or animals
- Abrin
- Brevetoxin
- Colchicine
- Digitalis
- Nicotine
- Ricin
- Saxitoxin
- Strychnine
- Tetradotoxin
- Trichothecene

**Blister agents/vesicants**

Chemicals that severely blister the eyes, respiratory tract, and skin on contact
- Mustards
  - Distilled mustard (HD)
  - Mustard gas (H) (sulfur mustard)
  - Mustard/lewiste (HL)
  - Mustard/T
  - Nitrogen mustard (HN-1, HN-2, HN-3)
  - Sesqui mustard
  - Sulfur mustard (H) (mustard gas)
- Lewisites/chloroarsine agents
  - Lewisite (L, L-1, L-2, L-3)
- Mustard/lewiste (HL)
  - Mustard/lewiste (HL)
  - Phosgene oxime (CX)

**Blood agents**

Poisons that affect the body by being absorbed into the blood
- Arsine (SA)
- Carbon Monoxide
- Cyanide
  - Cyanogen chloride (CK)
  - Hydrocyanic acid (HC)
  - Potassium cyanide (KCN)
  - Sodium cyanide (NaCN)
  - Sodium monofluoroacetate (compound 1080)

**Caustics (acids)**

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

**Choking/lung/pulmonary agents**

Chemicals that cause severe irritation or swelling of the respiratory tract (lining of the nose, throat, and lungs)
- Ammonia
- Bromine (CA)
- Chlorine (CL)
- Hydrogen chloride
- Methyl bromide
- Methyl isocyanate
- Osmium tetroxide

**Incapacitating agents**

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

**Long-acting anticoagulants**

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

**Metals**

Agents that consist of metallic poisons
- Arsenic
- Barium
- Mercury
- Thallium

**Nerve agents**

Highly poisonous chemicals that work by preventing the nervous system from working properly
- G agents
  - Sarin (GB)
  - Soman (GD)
  - Tabun (GA)
- V agents
  - VX

**Organic solvents**

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

**Riot control agents/tear gas**

Highly irritating agents normally used by law enforcement for crowd control or by individuals for protection (for example, mace)
- Bromobenzylcyaide (CA)
- Chloroacetophenone (CN)
- Chlorobenzylidenemalononitrile (CS)
- Chloropicrin (PS)
- Dibenzoxazepine (CR)

**Toxic alcohols**

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

**Vomiting agents**

Chemicals that cause nausea and vomiting
- 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.
Goblet and endothelial cell injury, respectively. Recovery conjunctival mucus with occlusion of blood vessels due to sloughing of the epithelium. Microscopically, there is loss of erosions. Vesication of the cornea can lead to complete erythema, and lacrimation. Moderate injury leads to periorbital edema, which exposes the free unmyelinated nerve endings.

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. Mild injury causes blepharospasm, eyelid erythema, and lacrimation. Moderate injury leads to periorbital edema, corneal epithelial edema, and punctate corneal erosions. Vescication 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. Recovery typically occurs without significant adverse sequelae; however, about 90% of mildly affected patients are visually disabled for approximately 10 days. Severe injury (about 10% of patients) can result in conjunctival chemoysis 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. Chronic angle closure glaucoma and phthisis can lead to blindness.

An unusual delayed type of keratopathy develops in 0.5% of patients up to 40 years after severe exposure to mustard gas. 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. Areas of stromal calcification with overlying epithelial breakdown are characterizedly located in the lower and central cornea. Aneurysmatic dilations and tortuosity of conjunctival and corneal vessels exists with intraocular 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.

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. 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.

References


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45. Sutcliffe J, Duin A. A history of medicine. London: Morgan Samuel Edi-


