# Bioterrorism Introduction

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**Course Objectives**

Explore and define the role of the healthcare worker in the event of bioterrorism.

Explain the roles of the various government agencies and managing a disaster.

Define the basic signs and symptoms of the five major weapons of mass destruction.

To provide clinicians and public health officials with the following information related to ricin: Background, Clinical Presentation, Recognition and Diagnosis, Personal Protective Equipment/Decontamination, Management, and Reporting.

To provide clinicians and public health officials with information on epidemiological clues that may suggest illness associated with ricin or another chemical or biological toxin in the correct clinical context.

Upon successful completion of the program, participants should be able to:

Describe the epidemiology of nonterrorism-associated ricin poisoning.
Describe the epidemiology of terrorism-associated ricin poisoning.
Describe the clinical manifestations of oral, inhalational, and parenteral ricin poisoning.
Describe the differential diagnosis for ricin poisoning.
Explain the diagnosis of ricin poisoning.
Identify epidemiological clues suggestive of a possible covert ricin (or other chemical/biological toxin) release.
Describe the clinical management of ricin poisoning.
Describe the disposition of patients with ricin-associated illness.
And identify the proper authorities for reporting of suspected or known ricin-associated illness.

**PART 1**

**Introduction**

The events of September 11, 2001, have increased concern about the potential use of biological, chemical, and nuclear weapons by terrorists. Medical and public health professionals will be the first respondents and they must be proficient in the recognition and management of these agents. The purpose of this course is to inform and educate attendees about biological, chemical, and nuclear events, specifically to (1) identify biological pathogens of concern for use in warfare or terrorism and the characteristics that make a biological pathogen an effective weapon; (2) describe the epidemiology, clinical features, medical management, and available treatment of potential medical problems derived from the use of biological, chemical, and nuclear weapons; and (3) understand the role of organized medicine in the national response to terrorism.

**History and Overview of Weapons of Mass Destruction**

Weapons of mass destruction (WMD) have been around since the 1700s, are easy to build, easy to hide, and pose a great threat. They are classified into three categories: chemical, nuclear, and biological.

Weapons of mass destruction are attractive to potential terrorists because they create fear; are inexpensive; cause no damage to land or equipment; are difficult to detect; usually have no immediate clinical signs, ie: no burning on contact, invisible, and no taste or smell; and exhibit a delayed onset of symptoms -- nerve agents within minutes, vesicants within hours, and biological agents within days. With WMD, protection of large areas and large numbers of people is impossible.

The disadvantages to WMD are contempt, retaliation, and prohibition treaties (all of which are now being ignored); danger during deployment due to accidents and no

control over the wind; and the persistence of some agents.

**Selected Facts About Anthrax**

• Efficiency
30 kg anthrax spores = 30,000-100,000 deaths;
1,000 kg atomic bomb = 23,000-80,000 deaths.
Aircraft aerosol delivery of 100 kg anthrax spores on a clear, sunny day with a light breeze would result in 130,000-460,000 deaths; on an overcast day or night with moderate wind 420,000-1,400,000 deaths; and on a clear, calm night 1-3 million deaths.
• Risks to healthcare workers include unsuspected agents, incomplete decontamination, inadequate ventilation, and recent trend toward second bomb targeting responders.
• Diagnosis via gram stain, DFA, and culture.
• Cutaneous clinical - necrotic lesion that spontaneously heals (85%);
Inhalation clinical -- 1- to 3-day incubation with fever, dyspnea, hemorrhagic mediastinitis and hypotension leading to death.

**Selected Facts About Cyanide**

• Inhibits cellular respiration by binding to the hemoglobin iron in the final step of the electron transport chain.
• Lethal plasma concentrations can be obtained quickly via the respiratory route.
• Cyanide is detoxified via rhodanese and b-Mercaptopyruvate-cyanide-sulfur transferase.
• Therapy: sodium nitrite bolus 300 mg dose given over 3 minutes to produce methemoglobin (usually >10%); sodium thiosulfate bolus dose (12.5 gm given over 10 minutes) to detoxify.
• In a mass causality situation the use of standard therapy would be difficult at best.

Expected toxicity of WMD is as follows:

• Organophosphate nerve agents -- rapid acting, acute and chronic CNS symptoms.
• Mustard gas -- delayed toxicity >24 hours; skin, eyes, and pulmonary
• Cyanide -- rapid acting
• Botulism -- 24-72 hours, needs extensive medical support, <10% fatality
• Anthrax -- 1-7 days, >95% fatality (inhalational).

**Mitigation**

Mitigation involves limiting contamination to existing casualties, preventing new casualties, achieving early decontamination (within minutes), isolating/protecting area of contamination, ventilating transportation and treatment areas, and watching for a "second bomb." Prompt treatment provides best outcome; successful treatment requires rapid identification of agents; late treatment requires supportive care and anticipation of sequelae of agents; and time and manpower demands will be intensive. Prosecution requires collection of evidence from site and is often forgotten by healthcare providers. Reassessment includes learning from experience, identifying vulnerabilities/creating contingency plans, and including new personnel/obtaining their support.

The US policy on counterterrorism includes (1) the Presidential Decision Directive 39 (PDD-39) of 1995, which designates FBI as lead agency in crisis management response, FEMA as lead agency in consequence management response, and requires all federal agencies to support the Federal Response Plan; and (2) Defense Against Weapons of Mass Destruction Act (Nunn-Lugar-Domenici Bill) of 1996, which required the Secretary of Defense to establish a program to advise and train federal, state, and local officials until 1999 and allows the President or Attorney General to request military support for local authorities in chemical/biological incidents.

**Bioterrorism: Threat Potential and Readiness Strategies**

The US has dealt with WMD and biological warfare in the past but is now facing a composite continuum of issues concerning domestic biological terrorism. Terrorism acts since the early 1990s, including the Oklahoma City bombing (and a potential for more), have resulted in a new emphasis on WMD and a policy on counterterrorism. This type of event has been studied, anticipated, and practiced for five years; the new war is now a reality. A briefcase full of anthrax cannot be shot down. Medical personnel have a new role; the frontline force of protection and defense is medical in this new war. The vulnerability of the US lies in the fact that protecting large areas and large numbers of people is impossible. The US is a country of "haves" in a world of "have-

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nots"; this has made the US a prime target, and the war will not be over in the foreseeable future.

Potential bioterrorism agents include *Bacillus anthracis, Yersinia pestis, Coxiella burnetii,* Ebola virus, *Vibrio cholerae,* and *Clostridium botulinum.* Recent events involving the weaponization of anthrax have resulted in 5 fatalities and 11 confirmed inhalational cases. It is estimated that *at least* 32,000 individuals have taken ciprofloxacin HCl (CIPRO, Bayer Corporation) in response to the threat posed by the distribution of anthrax spores through the US mail.

For several years, anthrax has been recognized as a potential biological threat to military as well as civilian populations. The causative organism of anthrax, *Bacillus anthracis,* occurs naturally, is relatively easy to access, is extremely resilient (in the spore form it may live for up to 50 years in soil), and is relatively inexpensive compared to conventional weapons. Anthrax spores range in size from 2 to 5 microns, just a fraction of the diameter of a human hair. Even a small number of anthrax spores, enough to fit on the head of a pin (approximately 5,000 to 8,000 spores), is sufficient to cause the inhalational form of anthrax. The inhalational form of anthrax is difficult to diagnose in the earliest stages, difficult or impossible to treat once clinical signs become apparent, and may allow only hours for therapeutic intervention. Its efficiency and low cost make anthrax accessible to virtually any group, including non-nation/state terrorists. The anthrax organism that has been dispersed through the US mail appears to be a conventional strain of anthrax and is not known to be recombinant or genetically altered.

The protective antigen in anthrax binds with other proteins produced by the organism (edema factor and lethal factor). The resulting combination produces two highly virulent toxins, edema toxin and lethal toxin. This culminates in extensive, rapid-onset edema and hemorrhage. In the inhalational form of the disease, hemorrhagic lymphadenitis and hemorrhagic mediastinis are manifest. Up to 50% of individuals with inhalational anthax also develop hemorrhagic meningitis. The same process occurs with less severe consequences in cutaneous anthrax, emerging as an eschar on the skin associated with severe edema of surrounding tissue.

Anthrax vaccine was developed in the 1960s and is manufactured by BioPort Corp. in Lansing, Michigan. Because of FDA quality control issues, the entire amount produced has not been released. When the vaccine is administered, the antibody binds to receptor sites and precludes the ability of toxins to develop. The ability to understand the shape ofthese receptors will advance the development of antitoxins and possibly a better vaccine.In limited studies, more women than men have reported vaccine adverse reactions at the site of injection: 73% as opposed to 35%.

Current anthrax treatment recommendations have been outlined by the Centers for Disease Control and Prevention. Individuals with confirmed infections are generally treated with 2 or more antimicrobials administered intravenously. Treatment duration of 60 days is recommended unless follow-up testing rules out infection. High-dose penicillin (eg, amoxicillin or penicillin VK) when ciprofloxacin and doxycycline are contraindicated. Supplemental treatment recommendations include 7 to 10 days of corticosteroids for extensive edema involving the head/neck (cutaneous) as well as for pulmonary edema, respiratory compromise, and meningitis.

Smallpox is another potential bioterrorism agent. The US has only 15 million doses of the original vaccine. There is a current effort to dilute the vaccine 1:5 and assess its effectiveness in order to increase the number of people who can be vaccinated. Efforts to manufacture a new smallpox vaccine are currently under way. Smallpox vaccination in the US was discontinued 22 years ago; widespread immunization could resume within the next 2 years.

Bioterrorism is not always directed against people. Animal diseases can become a potential terrorist target. Foot and mouth disease has recently motivated eradication and control efforts in the UK, with more than 3.1 million animals killed; the US does not vaccinate cattle or swine against foot and mouth disease virus. There is no knowledge of how the disease was transported to the UK, but it was thought to have originated from the Pan Asian strain in China and could have been planted intentionally.

The bottom line is "What do we do about it and where do we go from here?" The US military has been concerned about bioterrorism outside its borders for years and has accumulated modular medical response data. In conventional warfare, local emergency agencies use a "hot zone," "warm zone," and "cold zone" model. The hot zone comprises a bombed facility/area, and "first responders" -- emergency medical teams of firefighters, police, EMS, and ER personnel -- are at highest risk. With bioterrorism there is no definable hot zone or first responders. Among those at greatest risk of exposure to the agents of bioterrorism are those working in the medical community.

Emergency rooms throughout the US are working at 95% capacity. Currently there is little or no ability to effectively manage a sudden, simultaneous surge in patients. From

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2005 to 2007 the number of US emergency rooms decreased more than 50% while ER visits increased 20%. Individual hospitals must be willing to address readiness issues in light of the new threats posed by bioterrorism.

The official tiered response consists of these four steps: Crisis/disaster event occurs; local responders become overwhelmed and state emergency management agencies arrive; the presence of additional personnel results in confusion and chaos; and federal emergency response teams arrive. Depending on the nature of the crisis, confusion and bureaucracy may actually interfere with an effective and timely response. The goal of an effective readiness strategy is to increase awareness of the gap between the time that local/state responders arrive/become overwhelmed and the time that federal assistance arrives. Current operational strategy with the Air Force Medical Service includes supporting Air Force bases with modular medical units using real-time epidemiology technology. This technology could be used effectively in US hospitals if civilian physicians are provided an opportunity to collaborate with Air Force medical personnel in the use of this specialized equipment. The Air National Guard medical service is particularly well positioned to rapidly augment civilian medical communities in crisis situations.

Unconventional warfare, terrorist attacks, anti-government protests, and other unclear threats are not likely to disappear. The key issue is how to prepare to respond. The US has the most capable medical system in the world and the most reliable response capabilities if they are used all together.

In post-Cold War America, concern that a biological "weapon" would *eventually* be deployed by a non-nation/state terrorist against civilian populations living in the US was highlighted by the recent injection of billions (estimate $8.4 billion in the year 2000) of Federal dollars to establish a surveillance/ response infrastructure within the United States. At that time, most (although not all) authorities agreed that bioterrorism in the US was a very real and emerging threat for which the country was quite unprepared.

That was before September 11, 2001, and before anthrax spores had been sent through the US mail, killing a few, exposing hundreds . . . and scaring millions. Yet today, after continuing to pour billions more into defense against terrorism, the nation is still unprepared to meet the challenges of biological terrorism. Complacency, bureaucracy, organization, and economics are just some of the variables in a highly complex equation that underscore our vulnerability to catastrophic terrorism of the biological kind. By its very nature, *bioterrorism* is *medical* in nature and, as such, mandates that we possess an organized, swift, and effective medical response capable of meeting the health care needs of perhaps thousands of simultaneous lethal and non-lethal casualties. But, do we really understand the nature of the biologic threat(s) facing us today? Is the medical community really prepared to manage a large-scale response and do so without becoming the "canaries in the coal mine"?

Every year the Department of State, in collaboration with the intelligence community, produces a report entitled *Patterns of Global Terrorism.* The latest report describes and analyzes terrorist events through the year 2005 and attempts to identify trends in terrorism. *Patterns of Global Terrorism 2005* is an unclassified and authoritative statement by the US Government on the recent history and evolving nature of terrorist threats to the United States. Representative James Saxon, Chair of the Special Oversight Panel on Terrorism, recently highlighted a few of these:

- During the year 2000, compared to 1999, international terrorists inflicted an increased number of casualties worldwide and increased the number of attacks against the United States specifically. Globally, the number of attacks by international terrorists rose from 392 in 1999 to 423 in the year 2000. Attacks against the United States increased from 169 in 1999 to 200 in the year 2000.
- During the year 2000, the single deadliest attack against the United States by international terrorists was the bombing of the USS Cole. This terrorist attack, on October 12 in the Yemeni port of Aden, killed 17 sailors and wounded dozens of others. The attack also incapacitated a sophisticated US guided missile ship, valued at a billion dollars that is vital to the security of our aircraft carrier groups and our presence in the Persian Gulf.
- Who are the nations that sponsor international terrorism? Some states might resort to terrorism as a form of asymmetrical warfare against the United States in a future crisis or conflict. Or they might use terrorism as part of a protracted campaign to attempt to force the United States to abandon its global role and its regional interests and allies.

**Patterns of global terrorism 2000.** identifies seven governments that sponsor terrorism: Iran, Iraq, Cuba, North Korea, and Sudan. The report also identifies Pakistan and Libya as governments of concern. Ironic as it may seem, at least two of these countries have earned status (post-September 11) as political allies in America's international fight against terrorism.

**Patterns of global terrorism 2000** also notes that state-sponsored terrorism is being superceded by non-state sponsored terrorists. These non-state terrorists constitute a

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web of informally linked individuals and groups that have been involved in most of the major terrorist attacks or plots against the United States over the past 15 years. Non-state terrorists now collaborate in terrorist acts throughout the world. Their destructive influence literally spans the globe, reaching from the Philippines to the Balkans, from Central Asia to the Persian Gulf, from Western China to Somalia, and from Western Europe to South Asia.

**The Agents of Greatest Concern**

As stated in the *MMWR,* April 21, 2000/49(RR04);1-14, "The public health infrastructure must be prepared to prevent illness and injury that would result from biological and chemical terrorism, especially a covert terrorist attack. As with emerging infectious diseases, early detection and control of biological and chemical attacks depends on a strong and flexible public health system at the local, state, and federal levels. In addition, primary health-care providers throughout the United States must be vigilant because they will probably be the first to observe and report unusual illness or injuries."

**Where Do We Stand Today?**

Recent Senate hearings on whether the United States was prepared to handle a "terrorist" attack on US soil found that a maze of 46 government agencies and multiple congressional committees have jurisdiction over the issue. This, in fact, may pose one of the most significant threats to any attempt to carry out an effective response effort . . .

*Who's in charge?*
On another note, a report recently published in the *American Journal of Public Health* (Wetter et al: *Am J Public Health* 2001; 91:710-717) suggests that few US hospitals are prepared to handle victims of chemical or biological terrorism such as the 1995 nerve gas attack in a Tokyo subway. Results from a survey of nearly 200 hospital emergency departments indicated that fewer than 20% had plans for dealing with patients exposed to biological or chemical weapons (eg, anthrax or sarin -- the nerve gas used in the 1995 Tokyo subway disaster).

Specifically, the study looked at whether the hospitals had sufficient antibiotics to treat 50 anthrax victims or even had the equipment to manage 50 sarin victims. Hospitals were also asked whether they had overall plans of action for biological and chemical terrorism. Urban hospitals were three times as likely to have such plans as rural hospitals were. More than 60% of the hospitals surveyed were in rural areas, and all hospitals were in four states: Alaska, Idaho, Oregon, and Washington. More than one-third of all hospitals lacked sufficient antibiotic supplies to handle the anthrax scenario and just 29% had enough of the drug atropine to treat sarin patients. Far fewer had the decontamination facilities and other supplies for handling a sarin attack. Just 6% had all of the "minimum recommended physical resources" to deal with a sarin incident.

**Response Plan Facts**

- The threat of chemical and biological terrorist attacks against the United States is a national security concern. Strengthening response capabilities has been one reaction to the threat resulting in the establishment of federal stockpiles of antibiotics, antidotes, and other medical supplies. These stockpiles have been established and maintained by a number of different federal departments and agencies.
- Presidential Decision Directive 62 (PDD-62) designates the Department of Health and Human Services (HHS) as the lead federal agency to plan and prepare for a national response to medical emergencies in the event of a Weapons of Mass Destruction (WMD) attack. The Office of Emergency Preparedness (OEP) takes the lead for these activities within HHS.
- The Federal Emergency Management Agency (FEMA) has the authority to release medical resources and other supplies in the event of a disaster or emergency declared by the President. FEMA coordinates the federal response through the federal response plan (FRP) which details the roles and responsibilities of federal agencies during national emergencies.
- Local governments have much of the initial burden and responsibility for providing effective medical response to a terrorist attack with support from state and federal agencies when appropriate. Local public health systems will be called upon to provide protective and responsive medical measures for affected populations, such as patient care, immunizations or prophylactic drug treatments for exposed groups, fatalities and decontamination of the environment.
- If a terrorist event overwhelms local and state authorities and requires a presidential disaster declaration, FEMA will implement the Federal Response Plan (FRP) and coordinate not only its own response activities, including the dispatching of federal pharmaceutical stockpiles, but also those of as many as 28 other federal agencies that may provide assistance.
- The release of biological or chemical agents will require rapid access to large quantities of pharmaceutical antidotes, antibiotics and/or vaccines. These

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pharmaceuticals may not be available in the amount or locations where they would be needed unless special stockpiles are created.

- The Department of Health and Human Services has addressed the need for pharmaceuticals and medical supplies through the Centers for Disease Control and Prevention's (CDC) National Pharmaceutical Stockpile (NPS) program and through the Office of Emergency Preparedness' National Pharmaceutical Stockpile.
- The Department of Defense (DOD) Chemical and Biological Incident Response Force (CBIRF) also maintains pharmaceutical stocks that can be used in a civilian emergency under certain circumstances.

*Terrorism: Chemical and Biological Medical Supplies Are Poorly Managed,* the GAO examined the management of pharmaceutical and medical supplies set aside for use in the event of a chemical or biological terrorist incident. The report found OEP, CDC, VA, and CBIRF lacked the internal controls needed to manage the supplies effectively. Poor management of the supplies resulted in overages, shortages, discrepancies in inventory records, expired items, and a lack of security measures. In order to address these problems, GAO listed four recommendations to strengthen internal controls, including (1) conducting risk assessments, (2) arranging for periodic, independent inventories of the stockpiles, (3) implementing a tracking system that retains complete documentation for all supplies ordered, received, and destroyed, and (4) rotating stock properly.

**Public Health Surveillance and Reporting**

The following cases should be reported to local and state health agencies as well as the regional poison control center and Health Alert Network for your state:

Suspected or known cases of WMD exposure.
Any cases of WMD-associated illness.
Clinical illness consistent with WMD poisoning in conjunction with a credible threat.
Clinical illness consistent with WMD poisoning in conjunction with an applicable epidemiologic clue.

**Conclusion**

The threat of terrorism directed against civilian populations within the US has been validated. Although definitive proof that the use of "weaponized" anthrax is linked to international terrorist organizations is lacking, it could be argued that terrorism, especially involving pathogenic organisms, poses one of the most significant risks to the public health of Americans today. It could also be argued that among the greatest of risks we face today is failing to prepare to respond. The ability of our nation to rapidly mobilize an effective medical response in the face of an incident of catastrophic terrorism is a deadly serious and complex issue that confronts the entire US medical community now.

**PART 2 –**

## Recognition, Management and Surveillance of Ricin Associated Illness

On October 15, 2003, an envelope with a threatening note and a sealed container holding ricin toxin was found at a mail processing and distribution facility in Greenville, South Carolina. The note threatened to poison water supplies if demands were not met.

Ricin has long been considered a possible weapon of biological warfare or biological terrorism. In addition, rare incidents of accidental ricin poisoning have been reported. Most physicians are not familiar with the presentation or treatment of ricin intoxication and for additional resources please read the article 'Investigation of a Ricin-Containing Envelope at a Postal Facility --- South Carolina, 2003,' published in the November 21, 2003, issue of Morbidity and Mortality Weekly Report."

Ricin is a potent toxalbumin present throughout the castor bean plant (*Ricinus communis*), but it's primarily concentrated within the castor bean.

Castor bean plants are common outdoor plants that are often used as an ornamental garden plant. They are large shrubs that can grow as high as 12 feet, and have large, deep-green palmate leaves. These plants are native to Africa and common in warm climates worldwide.

Castor beans are light brown and have a mottled appearance. The beans are one-half to 2 cm long and are contained in soft spined, grayish-brown capsules.

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More than 1 million tons of castor beans are processed every year worldwide. Castor beans are a commercial source of castor oil, which is extracted from the castor bean and used as an industrial lubricant, as a medical purgative, and as a laxative. Castor oil is also used in pharmaceutical preparations and as an emollient in folk remedies. Castor oil itself contains no ricin. During the preparation of castor oil, the ricin-containing resin portion of the plant is separated from the non-ricin-containing oil portion. The resin is then further treated with heat to inactivate any remaining ricin. Castor bean cakes, the material remaining after oil is removed, are fed to animals as a protein source. Again, remaining ricin is heat inactivated before feeding.

Ricin can be prepared in three different forms: liquid, crystalline, or dry powder. Ricin is water soluble, odorless, tasteless, and stable under ambient conditions.

**Mechanism of Action and Toxicity of Ricin**

Ricin is one of several types of toxalbumins that exert their toxicity by inhibiting protein synthesis in eukaryotic cells, which may ultimately lead to cell death.

Ricin is one of the most toxic biological agents known -- a Category B bioterrorism agent and a Schedule 1 chemical warfare agent. This second highest priority biological agent category includes agents that:

are moderately easy to disseminate;
result in moderate morbidity rates and low mortality rates; and
require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance.

Here are some examples of other category B Bioterrorism Agents.

Brucellosis
Glanders Q
Fever Typhus
Fever
Psittacosis
Staphylococcal Enterotoxin B
:

Ricin toxicity and lethality can vary by dose and route of exposure. In animal studies, inhalation and intravenous injection are the most lethal routes. Lethal dose for humans, by inhalation or injection, is estimated to be 5 - 10 g/kg. Because the ricin protein is large, it is probably not well absorbed orally or through the skin.

In animal studies, most orally administered ricin is not well absorbed, and it may remain in the large intestine even 24 hours after exposure until it is finally eliminated from the gut. Although ricin is less toxic by the oral route compared with inhalation and injection, there are hundreds of reported cases of toxicity, and several fatalities, from castor bean mastication and ingestion. If enough ricin is ingested, the potential for significant morbidity and mortality exists.

Ricin is not likely to be absorbed through unabraded skin; however, there are no reported studies on the dermal toxicity of ricin. The effect of adding a carrier solvent to ricin to increase dermal absorption is unknown.

In addition to the existence of ricin within the castor bean, a potentially toxic alkaloid, ricinine, is also present; however, we won't be discussing ricinine during this presentation.

**Epidemiology of Nonterrorism and Terrorism Associated Ricin Poisoning**

At this time there is very limited knowledge about the human effects of ricin poisoning. Currently our knowledge is derived in part from one homicide, three suicides, many cases of macerated castor bean ingestion, and occupational exposure to castor bean pulp, dust, and oil. Most cases of non-terrorism ricin poisoning involve mastication and ingestion of castor beans.

Since 1900, there have been over 400 reported cases of castor bean poisoning by ingestion, resulting in 14 deaths (12 of these occurring prior to 1930). Occasionally, workers in or around castor oil processing plants experience respiratory or dermal symptoms from exposure to castor bean dust, presumably related to an allergic syndrome.

In the 1940s, accidental aerosol exposures to ricin occurred in humans. These exposures were sublethal, and symptoms resolved spontaneously. The specifics of these reports will be discussed shortly in the Clinical Presentation section.

There have been very few documented cases of parenteral ricin exposures in humans with high or toxic doses.

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Because ricin has been shown to inhibit tumor growth, clinical trials investigating intravenous low-dose ricin as a potential chemotherapeutic agent have been performed.

The chemical and physical properties of ricin make it a potential agent for use as a terrorist weapon. Ricin would need to be dispersed in particles smaller than 5 microns to be used as an effective terrorist or military weapon by the inhalational route. It is very difficult to prepare particles of this size. Ricin could also be also be used as a terrorist weapon through the contamination of food, beverages, or potentially some consumer products.

Although there have never been any mass casualty reports from ricin, there have been several instances of ricin procurement for use as a terrorist or criminal weapon. For example, Georgi Markov, a prominent Bulgarian dissident and radio personality, was assassinated in London on September 10, 1978, allegedly from a ricin injection in the thigh. An estimated 500 micrograms of ricin was injected subcutaneously in a platinum pellet fired from an umbrella gun. Death followed 72 hours later.

In April 1991, 4 members of the Minnesota Patriots' Council, an anti-tax, right wing militia, acquired enough ricin to kill 100 people. They planned to assassinate a Deputy U.S. Marshal and a local sheriff by dissolving the ricin in a carrier solvent to enhance dermal absorption. Another instance happened in 1995, when an extremist was arrested at the Canadian border with a large cache of weapons and 130 grams of ricin -- enough to kill 10,000 people. At his home in Arkansas, federal agents found castor plants, beans, and recipes for large- scale production of ricin.

In 1995, a Kansas City oncologist attempted to murder her husband by contaminating his food with ricin - this story was depicted in the book Bitter Harvest.

In December 2002, six terrorist suspects were arrested in Manchester, England, in their apartment that was serving as a "ricin laboratory." Among them was a 27-year-old chemist who was producing the toxin. Later, in January 2003, sub-toxic quantities of ricin were found in the Paris Metro, which led to an investigation of a possible Chechen separatist plan to attack the Russian embassy with the toxin.

Finally, literature and equipment for ricin production was found in Osama bin Laden's deserted home in a former al-Qa'eda base in Afghanistan.

**Clinical Manifestation**

There are several different types of exposure of ricin:

Inhalation,
Ingestion, and
Parenteral

Exposure to ricin may occur through:

Inhalation, dermal, or ocular contact: as an aerosol, powder, or dust
Ingestion: through contamination of food, water, or consumer products
Parenteral: directly injected into a target

Particles smaller than 5 microns have been used for aerosol dispersion in animal studies. Ricin is not considered persistent in the environment, but particles of this small size may stay suspended in undisturbed air for many hours and resuspension of settled ricin from disturbed surfaces may occur. Potency varies with the particle size, even in the 1-10 micron range. Generally, it is very technologically difficult to produce ricin particles of this size and purity.

Severe systemic toxicity has been described in humans only following ingestion or injection of ricin into the body. Based on limited animal studies, ricin is expected to be a much more potent toxin when inhaled or injected, compared with the other routes of exposure.

Ricin release from castor beans ingestion requires mastication, and the degree of mastication is likely to be important in determining the extent of poisoning. Swallowing of whole beans is not likely to result in poisoning. Castor beans are reported to have a bitter taste during mastication. Toxicity by the oral route in people is limited to what is known from patients who have masticated and ingested castor beans. There are no reports of people who have ingested purified ricin toxin. It is unclear what effect this would have on toxicity, though it is logical to reason that the same dose-dependent risk of illness exists. Signs and symptoms -- from oral exposure to purified ricin -- are presumed to be similar to reports of illness after castor bean mastication and ingestion.

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Ingestion and mastication of 3 - 6 beans is the estimated fatal dose in adults. The fatal dose in children is not known but is most likely even less. Toxicity can range from mild to severe, and may progress to death.

Symptoms of mild toxicity including nausea, vomiting, diarrhea, and/or abdominal cramping are invariably present in people who chew and ingest a significant amount of castor beans. Oropharyngeal irritation may occur following ingestion as well. Bloody diarrhea and systemic signs such as hypotension, hemolysis, and renal failure are not present, and symptoms typically resolve within 24 hours.

Onset of gastrointestinal symptoms typically occurs in less than 10 hours. Delayed presentation of gastrointestinal symptoms, beyond 10 hours of ingestion, is unlikely to occur.

Moderate to severe toxicity may include: gastrointestinal symptoms - that is, persistent vomiting and voluminous bloody or nonbloody diarrhea, which typically leads to significant fluid losses. This may result in dehydration and hypovolemic shock, which would manifest as tachycardia, hypotension, decreased urine output, and possibly altered mental status (e.g., confusion, disorientation).

In severe poisoning, hepatic and renal failure and death are possible within 36 - 72 hours of exposure. The most common findings on animal autopsy are multifocal ulcerations and hemorrhages of gastric and small intestine mucosa, necrosis of mesenteric lymph nodes, hepatic necrosis, splenitis and nephritis.

Animal studies suggest that inhalation is one of the most lethal forms of ricin poisoning. Data on inhalational exposure to ricin in humans is extremely limited. Severe systemic toxicity as a result of ricin inhalation has not been described in humans.

An allergic syndrome has been reported in workers exposed to castor bean dust in or around castor oil processing plants. It is characterized by nasal and throat congestion, eye irritation, hives and skin irritation, chest tightness, and in severe cases, wheezing.

Unintentional sublethal aerosol exposures to ricin which occurred in humans in the 1940s were characterized by onset of the following symptoms within 4 - 8 hours: fever, chest tightness, cough, dyspnea, nausea, and arthralgias followed by diaphoresis. However, there was no reported progression of illness in these cases.

In a nonhuman primate study, inhalational toxicity was manifested by a dose-dependent preclinical period of 8 - 24 hours, followed by anorexia and decreased activity. On autopsy, the lungs were edematous, with accompanying necrosis and hemorrhage.

Inhalational exposure to ricin in animals may include the development of pulmonary edema and hemorrhage, hypotension, respiratory failure, and death within 36 - 72 hours.

Humans can probably be expected to follow a similarly rapid course of illness progression although dose, size of the ricin particle and duration of exposure will affect degree of poisoning.

**Parenteral Exposure to Ricin**

Intravenous ricin was administered to cancer patients in very low doses in one large clinical trial. Flu-like symptoms with fatigue and myalgias were common reported side effects and lasted 1-2 days.

In the case of the Bulgarian dissident, Georgi Markov, signs and symptoms included immediate pain at the injection site, weakness within 5 hours and fever and vomiting within 24 hours. His clinical course worsened to include shock, multi-organ failure and death over the next 3 days.

A 20-year-old man was admitted to the hospital 36 hours after injecting castor bean extract subcutaneously. He complained of nausea, weakness, dizziness, and myalgias. He developed anuria and hypotension followed by hepatorenal and cardiorespiratory failure and died 18 hours following admission.

A 36-year-old chemist extracted ricin from a castor bean and self-administered intramuscular injections for the purpose of "scientific curiosity." He developed fever, nausea, anorexia, mild elevation of liver function tests, and tissue damage at the site of injection. Symptoms persisted for 8-10 days and then improved, at which point he was discharged from the hospital.

**Clinical Course of Ricin**

The current body of knowledge, based on limited human and animal data, suggests that significant poisoning through inhalation, ingestion and parenteral exposure would

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consist of a relatively rapid progressive worsening of symptoms over approximately 4 to 36 hours from exposure.

Early ricin poisoning through ingestion may resemble a typical gastroenteritis-type or a respiratory illness through inhalation.

At first it may be difficult to discern early poisoning from other common and less virulent illnesses such as an upper respiratory infection or gastroenteritis.

Thus, suspicion of cases should occur in conjunction with

A highly suspected or known exposure
A credible threat
An epidemiologic clue suggestive of a chemical release.

**Differential Diagnosis**

The differential diagnosis of ricin poisoning is very complex and may include numerous medical conditions as well as many different chemical AND biological agents.

Also, the route of exposure will affect the differential, since early inhalational poisoning by ricin will have respiratory signs and symptoms where as ingested ricin will probably present with gastrointestinal symptoms first.

Examples of agents to be considered in the differential diagnosis of Inhalational ricin poisoning include:

Staphylococcal enterotoxin B
Exposure to by-products of organofluorines-pyrolysis (Teflon, Kevlar)
Nitrogen oxides
Phosgene
Influenza
Anthrax
Q-fever
Pneumonic plague

Some examples of diseases which may be considered in the differential diagnosis of ricin poisoning by ingestion includes:

Ingestion:

Enteric pathogens (e.g., salmonella, shigella)
Mushrooms
Caustics
Iron
Arsenic
Colchicine

It is important to remember that these are just SOME examples of other diagnoses to consider and not an all-inclusive list.

**Clinical Diagnosis**

An event resulting in ricin poisoning may be obvious or overt, such as a package with a letter identifying the agent, but the event may also be covert. An example of a covert event would be the intentional contamination of food in a restaurant with a harmful agent, unbeknownst to the restaurant patrons. If illness occurs in conjunction with a highly suspected or known exposure or if there is a concurrent credible threat then a clinical diagnosis can be much more easily made. However, if illness is occurring as a result of a covert event, clinical diagnosis will be much more difficult for several reasons.

These include:

Symptoms of exposure to some chemical or biological agents may be similar to common diseases such as the flu or gastroenteritis. Early symptoms of certain chemical exposures might be nonexistent or mild despite the risk for long-term problems. Exposure to contaminated food, water or consumer products might result in reports of illness to health-care providers over a long period and in various locations.

People exposed to two or more chemicals or biological agents might have symptoms not suggestive of a single agent. Healthcare providers might be less familiar with clinical presentations of chemical or biological-induced poisonings than those illnesses with which they are more familiar.

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There are certain epidemiologic clues that may suggest the covert release of a chemical agent or biological toxin such as ricin that the clinician must be aware of:

Unexplained deaths among otherwise healthy or young people.
An unusual increase in the number of patients seeking care for potential- chemical or biological toxin related illness.
Detection of unexplained odors on presenting patients.
Clusters of illness in people who have common characteristics, such as drinking water from the same source.
Rapid onset of symptoms after an exposure to a potentially contaminated source.
Unexplained death of plants, fish, or animals.
Presence of a particular syndrome known to be associated with a chemical agent or biological toxin.

These are general epidemiological clues to a potential covert release of any chemical or biological toxin.

Clinical diagnosis will also largely depend on the route of exposure.

Again, many of the clinical findings associated with early ricin poisoning may be nonspecific and may mimic signs and symptoms of less virulent diseases such as the flu or gastroenteritis.

Confirmation of ricin poisoning requires clinical manifestations of illness with laboratory detection of ricin in either biological fluids or environmental samples from the area where the patient was exposed.

There are currently no clinically validated assays for detection of ricin in biological fluids readily available. Future clinical tests for ricinine, an alkaloidal component of the castor bean plant, are being developed, but also have not been tested for clinical use. The potential uses of these tests for either ricin or ricinine in human samples would primarily be for purpose of confirming exposure or assessing the prevalence of exposure, rather than diagnostic use.

The Centers for Disease Control and Prevention and member public health laboratories in the Laboratory Response Network are able to detect ricin in environmental samples, however, testing will most likely not be immediately available to assist in clinical decision making. Environmental testing may document the potential for exposure or affirm the exposure circumstance. There are no additional laboratory tests readily available to the physician such as a cell blood count, serum electrolyte panel or radiograph that are pathnogmonic for ricin poisoning. The presence of a leukocytosis and/or abnormal liver and renal function tests may suggest ricin-associated illness in the correct clinical context but are not very specific.

Therefore, suspicion and clinical diagnosis of ricin poisoning should occur when clinically compatible illness is present in conjunction with: a highly suspected or known exposure, a credible threat or an applicable epidemiologic clue.

**Decontamination and Personal Protective Equipment**

There are only limited data or experience regarding approaches to decontamination of victims following a ricin release; therefore, what follows is based largely on inference from available information and our best judgment using a prudent public health approach.

In the event of a recognized release or exposure, patients suspected to be contaminated with ricin should receive gross decontamination to the extent possible prior to arrival in the Emergency Department. Decontamination at the scene of the release is generally preferable unless the medical condition of a victim dictates immediate transport to the hospital.

Gross decontamination consists of cutting away or otherwise removing all suspected contaminated clothing, including jewelry and watches, and washing off any obvious contamination with soap and copious amounts of water. Showering with liquid soap and warm water is widely considered the most effective and preferred method for removing remaining hazardous substances from a victim's skin. The primary goal is to make the victim "as clean as possible", after life-threatening issues have been addressed.

There is no need to perform skin decontamination for patients exposed to ricin through ingestion only.

For the comfort of the victims and to improve cooperation, the water should be at a comfortable temperature if at all possible, and attention should be given to privacy considerations and to security of personal belongings. The procedure should be explained to the victim so he/she can understand what is occurring.

Environmental surfaces or equipment, such as in the ambulance, can be cleaned with

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soap and water or a 0.1 percent sodium hypochlorite solution. Used clothing removed from the victim should be double bagged and labeled as contaminated and secured in a safe location until it can be safely disposed of.

If not disposable, personal protective equipment such as gloves, faceshields, and goggles should be decontaminated by thoroughly rinsing with soap and water, soaking in a 0.1 percent sodium hypochlorite solution for 15 minutes and then rinsing with water and allowing to air dry.

PPE for first responders, including those who are decontaminating victims at the scene, is generally determined by the Incident Commander based on a hazard assessment and site conditions including the mechanism of dispersal and whether dispersal is continuing. Preventing droplets from contacting broken skin or mucosal membranes for example, the mouth or eyes, is important when decontaminating someone or cleaning up body fluids that may contain toxin, but airborne dispersal of ricin during decontamination is an unlikely hazard.

Therefore, for those who are decontaminating victims who arrive at the hospital without having been adequately decontaminated on-scene, PPE can consist of a full chemical-resistant suit with gloves, surgical mask, and eye/face protection such as faceshield and goggles. After completing decontamination tasks, personnel should carefully remove all PPE and shower.

As previously discussed, victims should have received gross decontamination prior to arriving at the hospital or at the hospital but prior to entering the emergency department. Once this has been accomplished, the quantity of contaminant that health care workers treating these patients may encounter is expected to be dramatically less than what originally may have been deposited on them. Simply removing contaminated clothing can reduce the contaminant associated with the victim by 75 to 90 percent.

Although the risk for exposure to staff in this setting is likely to be very low, it is still prudent to follow Standard Precautions to protect yourself and other health care workers who may be coming into contact with the patient or his/her personal effects. Health care workers should follow standard precautions, wear scrubs or, preferably, a disposable gown, and a lab coat, disposable nitrile gloves, a surgical mask and safety glasses, goggles or faceshield. The surgical mask and safety glasses are suggested to prevent health care workers from inadvertently contaminating their mucous membranes. Health care workers should follow good hand hygiene practices after caring for patients.

**Clinical Management**

There is extremely limited information on the treatment of patients with ricin poisoning because there are very few reported cases.

Treatment of ricin poisoning is supportive and there is no known antidote. Ricin is not dialyzable.

Healthcare providers should continue to use standard precautions when caring for patients with suspected or known ricin-associated illness. This includes care given after skin decontamination and when dealing with patient belongings and secretions.

In cases of ricin ingestion, gastrointestinal decontamination should be performed. Gastric lavage may be considered if presentation is early, generally <1 hour after exposure, the patient is not vomiting and no general contraindications are present. If ingested ricin was in the form of a powder, liquid or similar substance, gastric lavage with a nasogastric tube, not a Ewald tube, may be considered.

A single dose of activated charcoal should be given if the patient is not already vomiting and the airway is secure.

The current medical literature suggests that poisoning by the oral route significantly contributes to gastrointestinal losses of fluid and hypotension. Hypotension will interrupt normal perfusion of tissues and cause further organ dysfunction. Therefore intravenous fluid administration and blood pressure support through the use of intravenous vasopressors should be used if needed.

Inhalational and parenteral poisoning are of much greater severity than oral poisoning based mostly on animal data. Inhalational poisoning should be treated similarly, but will most likely require greater and earlier respiratory support. This includes supplemental oxygen, pulmonary toilet and mechanical ventilation with positive end expiratory pressure to maintain oxygenation if needed. Parenteral poisoning should be treated in a similar fashion. Further care should also be supportive in nature and may consist of procedures such as hemodialysis for renal failure.

Individualized management guidelines should always be obtained by calling your regional poison control center at 800-222-1222 or consulting your local medical toxicologist.

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The disposition of patients with symptoms that are consistent with ricin poisoning will depend primarily on the presence of certain conditions mentioned previously:

Is there a highly suspected or known exposure?
Is there a credible threat?
Is there an applicable epidemiologic clue to suggest a potential chemical or biological toxin related illness?

Patients who have clinical findings consistent with ricin-associated poisoning AND have a highly suspected or known exposure to ricin or who present in the context of a credible threat should be treated appropriately and admitted to a hospital for observation of illness progression.

Although most available evidence suggests a relatively rapid progression of symptoms in significant toxicity, approximately 4 to 36 hours following exposure, experience with ricin poisoning is very limited. Subsequently the period of observation cannot be definitively specified.

Patients who have had an exposure to a highly suspected or known ricin-containing compound and who are asymptomatic should also be observed for development of ricin-associated illness. It is important to note that exposures in asymptomatic patients may vary considerably and the specific situation of each patient will help determine ultimate disposition. For instance, a patient who was on the opposite side of the room when a sealed container of ricin was discovered may not reflect a true exposure. Regardless, any patient that is sent home after a complete evaluation should be instructed to return to the hospital immediately for development of any signs or symptoms consistent with ricin-associated illness.

Some patients may have clinical findings consistent with early ricin poisoning, such as gastrointestinal symptoms for ingestion, but also consistent with a common gastroenteritis. If they present in the context of an epidemiologic clue suggestive of a possible chemical or biological toxin associated illness but with no suspected or known ricin exposure nor in conjunction with a credible threat, disposition should be determined after the proper public health authorities have been notified. This includes the regional poison control center and local and/or state health departments. If there is no highly suspected or known exposure, no credible threat, and no applicable epidemiologic clue, then disposition is left to the clinician's judgment.

The regional poison control center and the local and/or state public health agency should be contacted in all cases of illness consistent with ricin poisoning in the presence of:

A suspected or known exposure
A credible threat OR
An applicable epidemiologic clue.

The regional poison control center can be contacted by dialing the national toll-free hotline, 800-222-1222 which will connect the caller automatically to the closest poison center in the United States.

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