

Recognition, Management and Surveillance of Ricin Associated Illness

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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."

Course Objectives

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.

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.

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

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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 μ 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 unabrased 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.

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 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, subtoxic 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.

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 dosedependent 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 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 whereas 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.

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 pathognomonic 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 lifethreatening 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 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.

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 tollfree hotline, 800-222-1222 which will connect the caller automatically to the closest poison center in the United States.

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.

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

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