Pharmacy preparedness for incidents involving weapons of mass destruction

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Abstract: Recent worldwide terrorist acts and hoaxes have heightened awareness that incidents involving weapons of mass destruction (WMD) may occur in the United States. With federal funding assistance, local domestic preparedness programs have been initiated to train and equip emergency services and emergency department personnel in the management of large numbers of casualties exposed to nuclear, biological, or chemical (NBC) agents. Hospital pharmacies will be required to provide antidotes, antibiotics, antitoxins, and other pharmaceuticals in large amounts and have the capability for prompt procurement. Pharmacists should become knowledgeable in drug therapy of NBC threats with respect to nerve agents, cyanide, pulmonary irritants, radionucleotides, anthrax, botulism, and other possible WMD.

Index terms: Antidotes; Disaster planning; Biological warfare; Chemical warfare; Nuclear warfare

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Introduction

Recent events, such as the Sarin gas attack in a Tokyo subway station in March 1995 and several anthrax hoaxes in the United States, have heightened concern among public health and law enforcement agencies that a real nuclear, biological, or chemical (NBC) attack may occur in this nation. The potential for a terrorist attack using a chemical or biological agent has many individuals involved with public health and safety, equipping themselves with information, contingency plans, and procedures to cope with such threats. Information from various governmental and other agencies is available concerning preparedness for a terrorist attack involving NBC weapons.[1-5] Instruction in this area is available via journal articles, Web sites, onsite and Internet training programs, seminars, and conferences.

Most references will provide practical discussion on issues such as local and statewide planning, onsite and hospital decontamination procedures, recognition and detection of NBC agents, diagnosis and pathophysiology of disease states, protocols for first responders, and a wide range of other public health issues.[6-10]

The objective of this article is to provide the pharmacy practitioner a concise summary and description of the types of pharmaceutical products that a health care facility pharmacy may be asked to provide as part of an overall response to an incident involving a weapon of mass destruction (WMD). These products may include, but are not limited to, antidotes, antibiotics, antitoxins, and other agents used in the symptomatic and supportive care of the poisoned patient. This list has been derived from a number of sources that describe the most common potential chemicals or biologicals that may be encountered in such a situation. Pharmacy managers are urged to check inventory for these products and know where the nearest supplier (e.g., wholesaler, pharmaceutical manufacturer, etc.) is for each agent. It is important to know how these supplies can be obtained quickly in emergencies. Pharmacy managers often look to official sources (e.g., Joint Commission on the Accreditation of Healthcare Organizations, Food and Drug Administration, state health departments, etc.) for mandatory or suggested guidelines for the adequate stocking of antidotes and other pharmaceutical products needed when responding to community needs involving the use of WMD. Unfortunately, no such official "checklist" exists. Several studies have been published demonstrating inadequate

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stocking of poison antidotes used for a variety of toxicologic emergencies. These would include: digoxin immune Fab (Digibind) for cardiac glycoside poisoning, ethanol for toxic alcohol poisoning, pyridoxine hydrochloride for isoniazid overdose, etc.[11-16] The conclusions of these studies is that many health care facilities are unprepared for poisoning emergencies, let alone those involving WMD. Furthermore, small nonurban hospitals are more likely to be unprepared than larger urban, tertiary care facilities. In addition to monitoring inventory, pharmacy managers and pharmacy and therapeutics (P&T) committee members should be aware of their local or state governmental agencies that may support a depot of some of these pharmaceuticals. Often this information is classified and not readily available to individuals not serving on WMD readiness task forces or committees.

Although the likelihood of a terrorist event involving an NBC agent is greater in a large urban environment (e.g., large airport, sports stadium, shopping mall, etc.), pharmacists should avoid any complacency and support of the notion that "it can't happen here." One lesson learned from the bombing of a federal building in Oklahoma City a few years ago was that a terrorist attack could occur anywhere and at any time. Like other members of the health care delivery team, pharmacists must be prepared to share their expertise and resources when called upon in the event of an NBC incident.

The Nunn-Lugar-Domenici Domestic Preparedness Act of 1996 established a $250,000,000 program to train 120 cities in the U.S. in the principles of emergency and medical response to chemical and biological agents.[17] Headed by the Department of Defense (DOD), federal agencies involved with domestic preparedness programs include the Department of Energy (DOE), Federal Bureau of Investigation (FBI), Federal Emergency Management Agency (FEMA), and Environmental Protection Agency (EPA). Local government bodies are creating metropolitan medical response teams (MMRT) whose mission is to create a multiple level, technically diverse, professional response to any deliberate or accidental act involving an NBC agent within their jurisdiction. Antidote caches funded by federal grants to MMRTs will be intended for use by Emergency Medical Services (EMS) first responders for self-administration and to treat a number of casualties at the site of an NBC incident. The first 12 to 24 hours of any NBC emergency response will need to be managed by local resources prior to the arrival of DOD and other federal agencies. Every hospital that may receive NBC casualties should have a WMD plan as part of their disaster readiness.

Chemical agents

As defined by the U.S. Army, a chemical warfare agent is "a chemical substance intended for use in military operations to kill or seriously injure, or incapacitate humans or animals through its toxicologic effects."[18] Terrorists would find chemical agents attractive to use for several reasons. First, these poisons are extremely toxic. Second, they are readily available or easily synthesized. And third, pertinent toxicological information is easily accessible.

In many respects, emergency response systems and health care facilities will need to respond to a WMD chemical attack in the same fashion as a hazardous materials incident. The same principles regarding triage, decontamination, and allocation of resources that shape disaster plans related to hazardous materials will go into action during a WMD chemical attack.

Chemical agents are generally classified into several groups: blood agents, nerve agents, choking agents, and blistering agents. Each agent has been designated its own North Atlantic Treaty Organization (NATO) designation symbol (a military symbol), which is not its chemical formula. For example, the NATO designation symbol for cyanide is "AC," while its chemical formula is CN, whereas the NATO designation symbol for Mace is "CN."

An important principle to recognize concerning chemical agents is that the onset of symptoms is very rapid, typically within minutes of initial exposure. Therefore, prompt initiation of rescue, decontamination, medical attention, and antidotal therapy is critical in minimizing casualties. The Chemical and Biological Hotline 800-424-8802, based in Aberdeen, Maryland, serves as an emergency resource to all health care providers for technical assistance. Much of the following information has been adapted from a seminar presented by Dr. Howard Levitin[19] and the U.S. Army handbook, *Medical Response to Chemical Warfare and Terrorism*.[18]

Cyanide. In the form of an NBC agent, cyanide would most likely be encountered as hydrogen cyanide (AC) or cyanogen chloride (CK) gases. Ingestion of sodium or potassium cyanide salts may also have lethal consequences. An explosion of an industrial storage tank containing acetonitrile or acrylonitrile would pose a high risk of delayed cyanide toxicity. Cyanide toxicity is characterized by a rapid onset of dizziness, confusion, dyspnea, tachycardia, and hypertension, followed by coma, convulsions, bradycardia, hypotension, arrhythmias, and metabolic acidosis. Death may occur within minutes following significant exposures. Cyanide is classified as a "blood agent" by some WMD references.[18-19]

Nitrites in the cyanide antidote kit convert red blood cell (RBC) hemoglobin to methemoglobin. Methemoglobin combines with cyanide to form cyanomet-hemoglobin. In synergism with 100% oxygen, thiosul-

fate combines with cyanide via the rhodenese enzyme to form less toxic thiocyanate, which is eliminated in the urine. Two other pharmaceuticals, which serve as adjunctive therapy for cyanide poisoning, are injectable sodium bicarbonate to correct metabolic acidosis and benzodiazepines (e.g., diazepam or lorazepam) as anticonvulsants. Their availability is discussed later in this article. All of the average wholesale prices (AWP) are as listed in the *1999 Drug Topics Red Book*.[20]

1. Eli Lilly & Co. no longer manufactures the cyanide antidote package. It is now available from Taylor Pharmaceuticals, a Division of Akorn, Inc. Each package contains twelve amylnitrite pearls, two 10-mL vials of 3% Sodium Nitrite for Injection USP, and two 50-mL vials of 25% Sodium Thiosulfate for Injection USP.
   Taylor Pharmaceuticals
   Division of Akorn, Inc.
   P.O. Box 5136
   San Clemente, CA 92674
   800-223-9851
   AWP = $274.56
   Shelf life: 18 months
   Note: Lower prices are available under federal purchasing programs.
2. 3% Sodium Nitrite for Injection USP—300 mg/10-mL vials of Sodium Nitrite for Injection USP is available from:
   Hope Pharmaceuticals
   7626 East Greenway Road, Suite 101
   Scottsdale, AZ 85260
   800-755-9595
   AWP = $84.95
   Shelf life: 24 months
3. Amylnitrite pearls—Packages of twelve amylnitrite pearls are available from the following manufacturers:
   James Alexander Corp.
   845 Route 94
   Blairstown, NJ 07825
   908-362-9266
   AWP = $2.90
   —and—
   Pharma-Tek, Inc.
   P.O. Box 1920
   Huntington, NY 11743-0568
   800-645-6655
   AWP = $6.25
   Shelf life: 36 months
4. Sodium Nitrite Powder USP—Sodium Nitrite Powder USP is available from these sources. It can be used to extemporaneously prepare 3% Sodium Nitrite for Injection USP, although no referenced source could be found for compounding instructions. Suppliers will add additional charges for special packaging and shipping.
   A-A Spectrum Healthcare Products
   14422 South San Pedro Street
   Gardena, CA 90248
   800-772-8786
   500 gram AWP = $14.60
   —and—
   Ruger Chemical Co., Inc.
   P.O. Box 806
   Hillside, NJ 07205
   800-274-7843
   1 pound AWP = $8.40
   —and—
   Integra Chemical Co.
   710 Thomas Avenue SW
   Renton, WA 98055
   800-474-8993
   500 gram price per manufacturer = $34.62
   2500 gram price per manufacturer = $102.57
   Shelf life: 3–5 years
5. 25% Sodium Thiosulfate for Injection USP—50-mL vials of 25% Sodium Thiosulfate for Injection USP are available from the following suppliers:
   Hope Pharmaceuticals
   7626 East Greenway Road, Suite 101
   Scottsdale, AZ 85260
   800-755-9595
   AWP = $22.49
   —and—
   Prometic Pharma USA, Inc.
   5436 West 78th Street
   Indianapolis, IN 46268
   888-313-2520 or 317-334-5600
   AWP = $24.32
   —and—
   American Regent Laboratories, Inc.
   Subsidiary of Luitpold Pharm., Inc.
   One Luitpold Drive
   Shirley, NY 11967
   800-645-1706
   AWP = $22.50
   Shelf life: 36 months; shorter for 10% solutions

Nerve agents. Nerve agents are organophosphates, which are potent inhibitors of acetylcholinesterase enzymes. Some examples of this group are Sarin (GB), Soman (GD), Tabun (GA), and VX. Some of the symptoms noted after significant exposures include the SLUDGE syndrome (Salivation, Lacrimation, Urination, Defecation, and Emesis), flaccid paralysis, apnea, and seizures. Serious poisonings are managed with three antidotal agents, atropine sulfate, pralidoxime chloride, diazepam or lorazepam.[18,19] Atropine sulfate blocks muscarinic receptor sites reversing bradycardia, bronchospasm, broncorrhea, vomiting, cramping, diarrhea, and miosis. Pralidoxime chloride (2-PAM) regenerates cholinesterase activity and reverses nicotinic toxicity demonstrated by muscle weakness, fasciculations, and respiratory depression. Diazepam or lorazepam, as anticonvulsants, are adjunctive measures to treat nerve agent induced seizures. Topical ocular homatropine or atropine can relieve miosis, pain, dim vision, and nausea.

1. Pralidoxime chloride (2-PAM, Protopam)—Protopam is available in 1-g vials only. It is manufactured by:
   Wyeth-Ayerst Laboratories
   Division of American Home Products Corp.
   P.O. Box 8299
   Philadelphia, PA 19101-8299
   800-666-7248
   AWP/6 vials = $384.76
   Shelf life: 5 years
2. Atropine Sulfate for Injection USP is available as a generic product from a variety of manufacturers. Some common forms are:

a. 0.4 mg/mL, 20-mL multidose vials (8 mg/vial)
AWP/vial: from 84¢ to $1.33
Shelf life: 24–36 months
b. Syringe sizes (0.1 mg/mL, 5-mL or 10-mL syringes)
AWP/vial: from $4.54 to $6.95
c. 1 mg/mL, 1-mL single-dose vials
AWP/25 vials: from $9.23 to $22.50
Readers are advised to refer to the *Drug Topics Red Book*[20] or nearest pharmacy wholesaler for a complete list of companies.

3. Atropine Sulfate Powder USP is also available from several suppliers. This pharmaceutical grade powder may be used to prepare Atropine Sulfate USP for Injection extemporaneously in large amounts, although no referenced source could be found for compounding instructions. The manufacturers of this pharmaceutical grade chemical have provided no shelf-life guidelines. Additional charges are added for special packaging and shipping; prices are for 5-g quantities (unless otherwise indicated), available from:
Amend Drug & Chemical
83 Cordier Street
Irvington, NJ 07111
800-274-2636
AWP = $12.00
—and—
Integra Chemical Co.
710 Thomas Avenue, S.W.
Renton, WA 98055
800-474-8993
Price per manufacturer = $19.27
25 gram price per manufacturer = $73.96
4. Diazepam for Injection USP is available as a generic product from a variety of manufacturers. Some common forms are:
a. 5 mg/mL, 2-mL prefilled syringes (10 mg/syringe)
AWP for 10 units: from $25.06 to $38.18
Shelf life: 24 months
b. 5 mg/mL, 2-mL ampuls (10 mg/amp)
AWP for 10 units: from $19.12 to $25.88
c. 5 mg/mL, 10-mL multidose vial (50 mg/vial)
AWP/vial: from $5.95 to $18.15
5. Lorazepam for Injection USP is available as a generic product from a variety of manufacturers. Some common forms are:
a. 2 mg/mL, 1-mL single-dose vial (2 mg/vial)
AWP/vial: from $9.74 to $11.41
Shelf life: 18–24 months
b. 2 mg/mL, 10-mL multidose vial (20 mg/vial)
AWP/vial: from $26.09 to $101.65
c. 4 mg/mL, 1-mL single-dose vial (4 mg/vial)
AWP/vial: from $10.18 to $13.96
d. 4 mg/mL, 10-mL multidose vial (40 mg/vial)
AWP/vial: from $89.87 to $127.05
6. Military style auto-injectors containing atropine sulfate, pralidoxime chloride, and diazepam are available from Meridian Medical Technology, formerly Survival Technology, Inc.[21] These auto-injectors are manufactured in large quantities (25,000 units and 40,000 units). Small orders may be filled if the product is in Meridian's inventory; however, the shelf life may be shorter.
a. Mark I kit (nerve agent antidote kit)
Each kit contains one atropen and one combopen
i. Atropen (atropine sulfate) 2 mg/0.7 mL
ii. Combopen (pralidoxime chloride) 600 mg/2 mL
Price: $17.00/kit
Shelf life: 5 years
b. Diazepam auto-injector
Contents: 10 mg diazepam in 2 mL
Price: $13.35
Shelf life: 2 years

Per Meridian Medical Technologies: Please note that MMT requires the following information to accompany a purchase order (excluding the training kits which do not contain drug):
i. Physician's prescription for all items.
ii. A copy of the DEA registration certificate is also required if the purchase order (P.O.) includes the diazepam and/or morphine auto-injector(s).
iii. Purchase order must include the following wording:
"We certify that the items purchased under P.O.# ____ will be used only by _____. The material will not be sold to a third party, distributed or used for any other purpose."
Meridian Medical Technology, Inc.
10240 Old Columbia Road
Columbia, MD 21046
410-309-6830
Fax: 410-309-1475

Pulmonary or choking agents. Chlorine (CI) and phosgene (CG) are poisonous gasses, which were responsible for a large number of casualties during World War I. Today, chlorine and phosgene are industrial chemicals stored in special [industrial] tanks, and they are transported around the country in railroad tanker cars. As toxins, they act primarily as pulmonary irritants causing cough, shortness of breath, and dyspnea; however, it may be several hours before serious complications become evident (e.g., pulmonary edema). No specific antidote is available for treatment of these exposures. Symptomatic and supportive care may include administration of oxygen, other ventilation support, and bronchodilators, such as albuterol sulfate. Nebulized 3.75% sodium bicarbonate has provided dramatic symptomatic improvement in chlorine exposures, as noted in several anecdotal case reports.[22-24] This may be prepared by mixing 2 mL of 7.5%

Sodium Bicarbonate for Injection USP with 2 mL of sterile 0.9% sodium chloride. Antibiotics should be reserved for those patients with an infectious process documented by sputum gram staining and culture. Intravenous steroids may be indicated in those patients demonstrating latent or overt reactive airway disease.

1. Albuterol sulfate is available as a generic product in a variety of forms:
   a. Solution for nebulization, 0.09 mg/inhalation (17 grams)
      AWP/vial: from $12.50 to $22.95
      Shelf life: 18–36 months
   b. Solution for inhalation, 0.083%, 3-mL vials
      AWP for 25 vials: from $22.40 to $35.47
   c. Solution for inhalation, 0.5%, 20 mL multi-dose vial
      AWP/vial: from $11.95 to $16.50
2. 7.5% Sodium Bicarbonate for Injection USP (50 mL) is available in prefilled syringes:
   AWP/syringe: from $2.89 to $18.58
   Shelf life: 18 months
3. Methylprednisolone Acetate for Injection USP is available as a generic product in several concentrations. Contact a pharmaceutical wholesaler or the *Drug Topics Red Book*[20] for latest prices.
   a. 20 mg/mL, 10-mL vials (200 mg/vial)
      AWP/vial: from $7.50 to $7.95
      Shelf life: 24–36 months
   b. 40 mg/mL, 5-mL vials (200 mg/vial)
      AWP/vial: from $7.20 to $12.95
   c. 80 mg/mL, 5-mL vials (400 mg/vial)
      AWP/vial: from $11.90 to $21.82

Blister agents. A number of potent alkylating agents may be used as chemical warfare agents. Examples include nitrogen mustard (HS), distilled mustard (HD), phosgene oxime (CX), and Lewisite (L). Toxicity produced by these agents includes blisters, vesiculations, eye injury, airway damage, and bone marrow stem cell suppression. Blisters may form several hours after contact with the skin. Erythema may be treated with calamine or other soothing lotion or cream. Denuded skin areas should be treated with topical antibiotics such as silver sulfadiazine or mafenide acetate.[18] Systemic analgesics should be used liberally. Lewisite is the only blistering agent for which an antidote may be useful since it is an arsenic derivative. The antidote Dimercaprol (British Anti-Lewisite; BAL) is a chelating agent for arsenicals and other heavy metals.[18,25] BAL administration may reduce systemic toxicity of Lewisite. Although not commercially available, BAL skin and eye ointments may reduce the severity of lesions when applied soon after decontamination.[18] Since BAL is formulated in peanut oil, it must be given intramuscularly. BAL is available as 300 mg/3-mL vials in quantities of 10 from:

Taylor Pharmaceuticals
942 Calle Negocio, Suite 150
San Clemente, CA 92673
800-223-9851
AWP = $747.60
Shelf life: 5 years

Dimercaptosuccinic acid (DMSA, succimer, Chemet) has been used experimentally in animals for the treatment of Lewisite exposures.[26-30] This may be preferred in the treatment of multiple exposures because it is administered orally. Chemet is supplied in 100-mg capsules and is available in quantities of 100 from:

Sanofi Pharmaceuticals, Inc.
90 Park Avenue
New York, NY 10016
800-223-1062
AWP = $417.49
Shelf life: 24 months

Incapacitating agents. BZ (3-quinuclidinyl benzilate) and Agent 15 (the Iraqi equivalent of BZ) are anticholinergic agents, which incapacitate victims by causing delirium. Patients also demonstrate anticholinergic signs and symptoms (e.g., mydriasis, tachycardia, flushed skin, urinary retention, etc.).[18] Serious symptoms may be reversed by i.v. physostigmine (Antilirium), a reversible carbamate cholinesterase inhibitor. Neostigmine (Prostigmin) and pyridostigmine (Mestinon) are quaternary amines that do not cross the blood brain barrier and therefore will not reverse CNS symptomatology caused by these agents. Antilirium is available in 2-mL vials (1 mg/mL) in quantities of 10 vials from:

Taylor Pharmaceuticals
942 Calle Negocio, Suite 150
San Clemente, CA 92673
800-223-9851
AWP = $31.90
—and—
Faulding Pharmaceutical Co.
11 Commerce Drive, 3rd Floor
Cranford, NJ 07016
877-328-5346
AWP = $111.16
Shelf life: 24 months

Riot control agents. These agents are commonly known as CN (alpha-chloroacetophenone, Mace) or CS (ortho-chlorobenzylidene malononitrile) tear gas. Usually, the exposure effects of these agents are self-limiting. They include burning, itching, and watering of the eyes, burning and tingling of the skin, and respiratory discomfort. In most cases, no specific therapy is indicated other than basic measures such as movement of patient to fresh air, eye irrigation with water, and skin washing.

Nuclear agents

Although the detonation of a nuclear weapon is a concern with respect to global and international conflicts, it would be unlikely for a terrorist group to obtain, build, con-

ceal, or deliver such a weapon. Stealing and deploying radioactive material by a terrorist would most likely be designed to frighten people and create a major hazardous material clean-up crisis rather than cause many injuries.

Radiation emitted by radioactive materials can be characterized into three types: alpha particles, beta particles, and gamma rays. The health hazards of radiation are divided into acute or chronic exposure risks. Chronic exposures (i.e., a low dose over a long period of time) increase the risk of cancers and cataracts, while acute exposures produce nausea, vomiting, blood dyscrasias, and death. Since alpha and beta particles do not travel great distances, materials such as protective clothing easily block them. However, exposures due to inhalation or ingestion of alpha and beta particles pose the greatest potential for harm. Gamma rays are the most harmful because they travel great distances and require dense materials such as lead to block penetration of tissues.[19]

After exposure to a radiologic agent, patients may require treatment with either a chelator or a radionuclide blocker.[31] The following chelating agents for radionuclides are available through Radiation Emergency Assistance Center/Training Site (REAC/TS):

1. Insoluble Prussian Blue (ferric hexacyanoferrate) for cesium and thallium chelation therapy.[32]
2. Zinc-diethylenetriamine pentaacetic acid (Zn-DTPA) and calcium-DTPA (Ca-DTPA) for radioactive transuranic elements, including neptunium, plutonium, americium, curium, berkelium, and californium.[31,33-34]

REAC/TS trains, consults, and assists in the response to all types of radiation accidents or incidents. The center utilizes physicians, nurses, health physicists, radiologists, and emergency coordinators to provide 24-hour assistance at the local, national, or international level.

Other pharmaceutical chelators may be used for a variety of radionucleotide exposures and would be found in any well-stocked hospital pharmacy. These include d-penicillamine (Cuprimine), calcium disodium EDTA (Versenate), dimercaprol (BAL), succimer (Chemet), and deferoxamine (Desferal).[35] Colony stimulating factors may be considered in patients experiencing significant bone marrow suppression.

Radionuclide blocking agents saturate tissues with a nonradioactive element, which reduces the uptake of radioactive iodine. The most commonly used agents are potassium iodide tablets and Lugol's solution, both of which reduce uptake of ^{131}I into the thyroid tissue.[36] Most states with departments of nuclear safety will stock enough quantity of potassium iodide tablets to protect workers and emergency personnel involved in a nuclear reactor incident.

Lugol's solution is available from several suppliers:

AWP/480 mL: from $7.81 to $21.69
Shelf life: 2–5 years

Potassium iodide (Iosat), 130-mg tablets, are available in cases of 100 bottles (14 tablets/bottle) from:

Carter-Wallace, Inc.
P.O. Box 1001
Cranbury, NJ 08512
609-655-6147
AWP = $275.63
—and—
Anbex, Inc.
15 West 75th Street
New York, NY 10023
212-580-2810
AWP = $910.00
Shelf life: 60 months

For immediate assistance regarding a nuclear or radiological agent incident, contact the following:

1. Radiation Emergency Assistance Center/Training Site (REAC/TS)
   P.O. Box 117, MS-39
   Oak Ridge, TN 37831-0117
   Business hours: 865-576-3131
   24-hour emergency line: 865-576-1005
2. The department of nuclear safety, for the state in which the incident occurred.
3. Health physicists affiliated with hospital nuclear medicine departments can serve as expert consultants for radiation incidents.

Biological agents

As NBC terrorist weapons, biological agents may be encountered as bacteria (e.g., anthrax), viruses (e.g., smallpox), or toxins (e.g., botulinum or ricin). This fact will explain the striking difference in the manner which victims will present to health care facilities. A catastrophe caused by a chemical weapon (e.g., nerve agent or cyanide) would be characterized by immediate death, or severe disablement of individuals at the site of the attack. First responders to such an incident would be paramedics, police, and other emergency personnel.

In contrast, with respect to biologicals, there is a delayed onset of signs and symptoms since incubation may take days. Emergency department clinicians and primary care practitioners would be the first to recognize and manage exposed patients. It is beneficial to health care facility professionals, including pharmacists, to be knowledgeable of these agents and their clinical effects. Knowledge of what medical and pharmaceutical interventions may be requested in a mass casualty event is crucial. It is beyond the scope of this article to delineate all the diagnostic clues, pathophysiology, laboratory monitoring, infectious disease control, guidelines for patient isolation, epidemiologic procedures, and public health ramifications of a bioterrorism event. Pharmacists, however, would wish to take note of this exten-

sive list of pharmaceuticals (both oral and parenteral) that may be required in extraordinarily large amounts during an outbreak involving a biological weapon. Additionally, the duration of illness may be weeks to months thus creating an additional stress on the health care infrastructure. Once the cause of illness in a large number of patients has been identified as a biological agent, prompt availability and distribution of appropriate medication can greatly mitigate the destructive impact of the act of terrorism. It should be noted that special products, uncommonly used vaccines and antitoxins, would be provided via federal government storage and distribution programs. New therapies are also under development. Detailed information on diagnosis, patient management, vaccines, etc. may be obtained through COMMANDER US Army Medical Research Institute of Infectious Diseases[37] (USAMRIID) at 301-619-2833 during business hours, or at 888-USA-RIID, 24 hours/day. In the event of an emergency, contact the U.S. Army Response Center at 800-424-8802. Also, contact the Centers for Disease Control and Prevention (CDC) Bioterrorism Response Unit at 770-488-7100.

The following information is a very brief synopsis of 13 possible threats as biological agents. Much of this information has been adapted from an article in *JAMA*[1] entitled "Clinical Recognition and Management of Patients Exposed to Biological Warfare Agents," and teleconference materials provided by the CDC and Food and Drug Administration (FDA) entitled *Biological Warfare and Terrorism*.[37]

Bacteria. *Anthrax.* The etiologic agent causing anthrax is *Bacillus anthracis*, a gram-positive spore-forming bacillus. As a biological weapon, the spores of these bacteria would be aerosolized, with inhalation being the primary route of exposure. The clinical course is characterized by a necrotizing hemorrhagic mediastinitis. Initially symptoms may resemble a flu-like illness with fever, fatigue, and malaise, also vague chest pain and non-productive cough. Initial symptoms are followed by abrupt progression to dyspnea, stridor, diaphoresis, and cyanosis. Systemic complications of sepsis, shock, and meningitis may occur in up to half of the cases. Unfortunately, once symptoms occur, treatment is usually ineffective. Intravenous ciprofloxacin should be initiated at the earliest sign of anthrax. Other fluoroquinolones may be substituted; however, no animal studies exist for quinolones other than ciprofloxacin.[38] All natural strains of anthrax have been found to be sensitive to erythromycin, chloramphenicol, and gentamicin. Historically, penicillin G has been the drug of choice for anthrax. Chemoprophylaxis with oral ciprofloxacin or doxycycline in exposed individuals should be initiated and continued for four weeks or until three doses of anthrax vaccine are administered.[38] A licensed attenuated vaccine is available for prophylaxis. This vaccine stock is owned by the Department of Defense; in order to obtain it, contact USAMRIID at 301-619-2833. It is manufactured by:

Bioport Manufacturing
3500 North Dr. Martin Luther King Jr. Blvd.
Lansing, MI 48906
517-327-1500

Brucellosis. Human infection may be caused by four species of Brucella, which is a nonspore-forming gram-negative aerobic cocco-bacillus. Clinical manifestations include fever, chills, and malaise which may lead to cough and pleuritic chest pain. Other complications may include osteomyelitis, genitourinary infection, hepatitis, endocarditis, and central nervous system (CNS) infections. Drug therapy consists of antibiotic combinations. The treatment of choice is doxycycline and rifampin; sulfamethoxazole/trimethoprim (SMZ/TMP) can be used as a substitute for rifampin. Severe systemic infectious complications may require the addition of streptomycin or other aminoglycoside agents. There are no approved vaccines or chemoprophylaxis treatments.

Cholera. This infection is caused by *Vibrio cholerae*, a gram-negative, nonspore-forming bacillus. Clinical manifestations include vomiting, abdominal distension, and pain, with little or no fever, followed rapidly by diarrhea. Fluid losses may be excessive with death caused by dehydration and shock. Antibiotic treatment may include tetracycline, ampicillin, and SMZ/TMP. Intravenous fluid/electrolyte solutions are necessary to treat dehydration. An FDA approved killed vaccine is available for prophylaxis. However, it provides only about 50% protection and lasts only six months.

Pneumonic plague. The gram-negative, nonspore-forming bacillus, *Yersinia pestis*, is responsible for both pneumonic and bubonic plague. Patients exposed to plague will have high fever, chills, malaise, cough with bloody sputum, headache, myalgia, and sepsis. Late in the course of illness, dyspnea, cyanosis, and respiratory failure may be noted. Effective antibiotic therapy includes streptomycin or gentamicin, chloramphenicol, and doxycycline. An FDA-approved vaccine is available for bubonic plague; however, its efficacy against aerosolized pneumonic plague is believed to be poor. Exposed individuals may be treated with doxycycline for chemoprophylaxis.

Q-Fever. Q-Fever is a rickettsial disease caused by *Coxiella burnetii*. The most common symptoms of Q-Fever are fever, chills, headache, fatigue, diaphoresis, malaise, anorexia, and myalgias. In some cases, cough with chest pain may be noted. Rare complications include hepatomegaly, splenomegaly, and jaundice. Effective therapies for Q-Fever include tetracycline, doxycycline,

erythromycin, and azithromycin. Inactivated whole cell vaccine for Q-Fever prophylaxis is available, under investigational new drug (IND) status, in the U.S. Tetracycline or doxycycline may be given as chemoprophylaxis to exposed patients.

Tularemia. Tularemia is caused by *Francisella tularensis*, a gram-negative aerobic cocco-bacillus. It is also known as "rabbit fever" or "deer fly fever." Inhalation of tularemia organisms produces a typhoidal tularemia. Patients present with fever, weight loss, substernal discomfort, and nonproductive cough. The drug of choice is streptomycin. Other treatment options include gentamicin, tetracycline, and chloramphenicol; however, high relapse rates are associated with these other treatment options. A live attenuated vaccine is available under IND status for prophylaxis. Doxycycline or tetracycline may be used for chemoprophylaxis.

Viruses. *Smallpox.* The etiologic agent that causes smallpox is the *variola* major virus. Smallpox was declared eradicated by the World Health Organization in 1980. Much concern exists regarding the stockpiling of this infectious agent as a weapon of bioterrorism due to its high morbidity and mortality. Patients infected with *variola* present with fever, malaise, rigors, vomiting, headache, and backache. Dermal manifestations include appearance of a rash followed by lesions, which appear as macules, then papules, then eventually form pustular vesicles. By the second week, scabs are formed that leave depigmented scars upon healing. Patients are contagious until all the scabs are healed. All patients exposed to *variola* virus must be immediately vaccinated. Those U.S. citizens who were vaccinated against smallpox in the 1950s and 1960s are no longer protected against this virus.[39] The only smallpox vaccine in the United States is Wyeth-Ayerst's Dryvax, available by calling 800-666-7248. There is currently no chemotherapeutic agent proven effective against smallpox. The U.S. Army and CDC maintain a supply of vaccinia immune globulin (VIG) which is used for post exposure prophylaxis. Contact the CDC at 404-639-3356 or USAMRIID at 301-619-2833 to obtain VIG.

Venezuelan equine encephalitis (VEE). Members of the Alpha virus genus of the Togaviridae family produce this encephalopathic syndrome. The usual mode of transmission is mosquitoes; however, aerosolization makes those pathogens a very effective WMD. Alpha virus will produce neurologic syndromes noted by fever, headaches, confusion, drowsiness, seizures, dysphasia, ataxia, myoclonus, cranial nerve palsies, photophobia, myalgia, and vomiting. No specific chemotherapeutic agents are indicated. Treatment is symptomatic and supportive care. Antipyretics and anticonvulsants may be used in severe cases. A live attenuated vaccine for VEE TC-83 is available for prophylaxis, while inactivated vaccines are under IND status.

Viral hemorrhagic fevers (VHF). The most widely known examples of this group are the Ebola and Marburg viruses. Common features of the VHF are myalgias, fever, and prostration. Mild symptoms include conjunctival injection, mild hypotension, flushing, and petechial hemorrhaging that may progress to shock. More severe symptoms include mucous membrane hemorrhage with maculopapule rashes and disseminated intravascular coagulation (DIC). No specific antiviral agents are effective against Ebola or Marburg viruses. Other related strains may respond to ribavirin. Many different pharmaceutical agents may need to be employed in the supportive management of hypotension, shock, and DIC. No vaccines or medicinals currently exist to protect against these viral illnesses.

Toxins. *Botulinum.* Botulinum toxin is a protein exotoxin produced by *Clostridium botulinum*, an anaerobic gram-positive bacillus. There are seven types of botulism neurotoxins known as types A–G. Botulism poisonings are more commonly associated with improperly processed or canned foods. As a WMD, botulinum toxin may be inhaled from an aerosol or ingested in the form of sabotaged food. These toxins are the most toxic of all the NBC weapons. Clinical manifestations include blurred vision, mydriasis, diplopia, ptosis, photophobia, dysarthria, dysphonia, and dysphagia. Skeletal muscle paralysis follows, which presents as a symmetrical and descending progressive weakness resulting in respiratory failure. Patients are typically awake, alert, and afebrile. A trivalent equine antitoxin (types A, B, and E) for food-borne botulism is available from the CDC at eight urban quarantine sites: Atlanta, Chicago, Honolulu, Los Angeles, Miami, New York City, San Francisco, and Seattle. To obtain these antitoxins contact the CDC, 24 hours a day, at 404-639-2888 or during business hours at 404-639-2206. Connaught Laboratories, Ltd. manufactures this antitoxin for the CDC, one of only three suppliers in the world. A despeciated equine heptavalent antitoxin against all seven types was prepared and is under IND status. It should be noted that all horse serum based antitoxins pose the risk of anaphylaxis and serum sickness; therefore, skin testing is advised. A pentavalent (types A–E) toxoid is also available under IND status.

Ricin. This biological toxin is derived from the plant *Ricinus communis*, commonly known as the castor bean. After inhalation exposure, victims may experience fever, weakness, and cough, followed by hypotension and cardiovascular collapse. There is no available antitoxin. Treatment is supportive care only. Also, there is no available vaccine or other chemoprophylactic agent.

Staphylococcus enterotoxin B

(SEB). SEB is an exotoxin produced by *Staphylococcus aureus*, a gram-positive cocci. SEB is most commonly recognized as a cause of food poisoning as it is produced by bacterial growth in improperly handled foods. Inhalation of SEB in a biological warfare scenario may rapidly incapacitate its victims. Signs of exposure may include fever, chills, headache, myalgias, and non-productive cough, with severe problems including dyspnea, retrosternal chest pain, vomiting, and diarrhea. No specific antitoxin is available. Supportive therapies are directed towards adequate oxygenation and hydration. No vaccines for SEB are currently available.

Trichothecene (T-2) mycotoxins. Fungi of the genera *Fusarium, Myrotecium, Trichoderma*, and *Stachybotrys* produce these compounds. Clinical manifestations of exposure include skin irritation, pruritis, redness, vesicles, necrosis, sloughing of the epidermis, nose and throat pain, nasal discharge, fever, cough, dyspnea, chest pain, and hemoptusis. Serious cases are associated with prostration, weakness, shock, and death. There is no antidote or antitoxin. Treatment is supportive care. No vaccine or chemoprophylactic agent exists for T-2 mycotoxins.

The following are some of the aforementioned pharmaceutical products available for the treatment of patients exposed to biological warfare agents. If a variety of sizes and formulations are available for a particular pharmaceutical product, only the largest dose forms are listed. Readers are advised to refer to the *Drug Topics Red Book*[20] or nearest pharmaceutical wholesaler for a complete list of companies for the following products.

1. Ciprofloxacin is available in several different oral and parenteral dosage forms. These are available from:

   Bayer Corporation
   Pharmaceutical Division
   400 Morgan Lane
   West Haven, CT 06516-4175
   800-288-8370
   500-mg tablets (100 tabs) AWP = $399.47
   750-mg tablets (100 tabs) AWP = $412.78
   10 mg/mL, 120-mL bulk vial (1200 mg/vial) AWP/6 vials = $466.38
   400 mg/200-mL premixed i.v. AWP/24 i.v.s = $720.29
2. Doxycycline hyclate is available from a number of generic suppliers in 100 mg tablets or capsules.
   100-mg tablets or capsules
   AWP/100 tabs: from $8.76 to $45.90
3. Erythromycin is available in a large variety of salt forms and strengths.
   500-mg tablets
   AWP/100 tabs: from $22.50 to $121.96
4. Penicillin V and G are available in a variety of formulations, both oral and intravenous.
   500-mg tablets
   10-million-unit vials
   AWP/100 tabs: from $9.05 to $23.01
   AWP/vial: from $6.40 to $40.55
5. Gentamicin sulfate is a powerful aminoglycoside antibiotic that is only used for systemic infections. It is available in a variety of formulations.
   a. 40 mg/mL, 20-mL multidose vials (800 mg/vial)
      AWP/vial: from $7.10 to $12.64
   b. 40 mg/mL, 2-mL single-use vials (80 mg/vial)
      AWP/25 vials: from $26.04 to $57.50
6. Streptomycin is a rarely used antibiotic; however, it has efficacy against several of the biological warfare agents. It is supplied in 1-g vials for injection. Streptomycin is available from:

   Pharma-Tek, Inc.
   P.O. Box 1920
   Huntington, NY 11743-0568
   800-645-6655
   AWP/vial = $5.95
7. Chloramphenicol is another rarely used antibiotic. It can be obtained in vials or large quantities may be obtained in powdered form. This may be required to treat a large number of casualties.
   a. 1000-mg vial, AWP/vial: from $6.51 to $6.65
   b. 25-g USP powder, AWP: from $29.85 to $59.04
8. SMZ/TMP is another antibiotic that has efficacy against several of the biological warfare agents. The most commonly used formulation contains 800 mg of sulfamethoxazole and 160 mg of trimethoprim (Bactrim DS).
   SMZ/TMP (800/160) tablets
   AWP/ 100 tabs: from $10.86 to $114.89
9. Rifampin is available in 300-mg capsules or in large quantities in powdered form.
   a. 300-mg capsules, AWP/100 caps: from $162.93 to $197.46
   b. 500-g USP powder, AWP: from $273.91 to $792.00
10. Tetracycline is available in 500-mg capsules or also in powdered form.
    a. 500-mg capsules, AWP/100 caps: from $5.78 to $12.78
    b. 100-g USP powder, AWP: from $56.70 to $59.40

Conclusion

With the increasing probability of an incident involving a WMD agent, many local, state, and federal agencies have initiated plans for appropriate and effective emergency medical response. Experts in the area of EMS, emergency medicine, infectious disease, and public health are becoming trained in the medical management of exposure to NBC agents.

Any large mass casualty scenario will demand the expertise and professional services of a hospital pharmacy. Therefore, pharmacists should equip themselves with knowledge of antidotes, antibiotics, antitoxins, and other supportive agents used to treat

casualties and how they may be obtained quickly in the event of an act of terrorism. Currently, there are no guidelines mandating minimum hospital inventory of the pharmaceutical products that may be needed. Pharmacy managers and P&T committee members are urged to participate in, or at least be familiar with, plans coordinated through local domestic preparedness programs.

[a] Drugs, dosages, and AWPs were current at the time of original publication. The AWPs quoted are from the year 2000.

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Addendum

Web sites with information on weapons of mass destruction

CDC Bioterrorism Preparedness and Response
www.bt.cbc.gov

Chemical and Biological Defense Information Analysis Center (CBIAC)
www.cbiac.apgea.army.mil

EmergencyNET
www.emergency.com

FEMA Rapid Response Information System (RRIS)
www.rris.fema.gov

Medical NBC Online Information Server
www.nbc-med.org

National Disaster Medical System (NDMS)
www.oep-ndms.dhhs.gov

Nuclear, Biological, and Chemical Weapons
www.biochemweapons.com

The Terrorism Research Center
www.terrorism.com/chembio/chembio.html

US Army Medical Research Institute of Infectious Diseases (USAMRIID)
www.usamriid.army.mil

Editors' note: *At the time of publication, these Web site URLS were accurate.*