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**Abstract:**

This article is part of a collaborative effort by experts in the field of emergency preparedness to complete an overview begun by the late Michael Shannon, MD, MPH, on the current challenges and future directions in pediatric disaster readiness. This particular article, "Preparation for Terrorist Threats: Biologic and Chemical Agents," will address pertinent clinical management issues relating to biologic and chemical agents and the unique vulnerabilities and care needs of children as potential victims of such terrorism.

# Preparation for Terrorist Threats: Biologic and Chemical Agents

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**Fred M. Henretig, MD**

**I**n the aftermath of the release of the nerve agent sarin in the Tokyo subway system, the Oklahoma City federal building bombing in 1995, and the 2001 intentional spread of anthrax through the US mail, the potential for emergency care providers being confronted with children who are victims of terrorism seems greater than ever. A novel concept to most pediatric emergency medicine providers just 15 years ago, terrorist use of weapons of mass destruction, including biologic, chemical, and radiologic agents, as well as more conventional but highly lethal explosives, are recognized today as posing the threat of unique pediatric emergency management challenges, and has the capacity to overwhelm regional emergency medical services (EMS) and hospital emergency departments.

Several physiologic, psychologic, and developmental considerations are unique to the pediatric population in the context of planning for biologic and chemical terrorism. In addition, there are recognized vulnerabilities within our EMS system as it responds to critically ill children who might well be exacerbated by such an incident. Such challenges and some potential remedies are highlighted in this article.

## **BIOLOGIC AGENTS**

The Centers for Disease Control and Prevention (CDC) has identified anthrax, smallpox, plague, botulin toxin, tularemia, and the viral hemorrhagic fevers as the biologic diseases that would constitute the gravest threats to public health and security. The potential use of these agents, the clinical diseases they cause, and their management principles have been reviewed in depth elsewhere.<sup>1-9</sup> In addition, the potent phytotoxin ricin has raised

Section of Clinical Toxicology, Children's Hospital of Philadelphia; Pediatrics and Emergency Medicine University of Pennsylvania School of Medicine.

Reprint requests and correspondence:  
Fred M. Henretig, MD, Director, Section of Clinical Toxicology Children's Hospital of Philadelphia, Professor of Pediatrics and Emergency Medicine University of Pennsylvania School of Medicine.  
[HENRETIG@email.chop.edu](mailto:HENRETIG@email.chop.edu)

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concern because of its ready availability and ease of production.<sup>10</sup> Treatment protocols for these rare conditions are likely to evolve continuously, particularly if future incidents occur, as was the case when the mail-borne anthrax outbreak unfolded. The CDC offers a telephone hotline (800-232-4636) and a Web site for up-to-date management advice (<http://emergency.cdc.gov/bioterrorism/>).

The anthrax attack of 2001 provided recent clinical experience with this potentially devastating disease.<sup>11</sup> Inhalational anthrax causes a fulminant mediastinitis and pneumonia, often complicated by sepsis, meningitis, and death. Cutaneous anthrax causes a vesiculating lesion that progresses to a black, necrotic scab, and patients may develop nonspecific systemic symptoms, though sepsis is uncommon and mortality is low. The 2001 outbreak was characterized by 22 confirmed or suspect cases (11 inhalational, 11 cutaneous), with 5 deaths, resulting from presumed or known exposure to anthrax-contaminated mail. The one pediatric victim of the 2001 attack was a 7-month-old boy with cutaneous anthrax on his arm, presumably contracted after a brief visit to a New York City television news studio that had received contaminated mail.<sup>12</sup> Approaches to anthrax diagnosis and disease recognition under investigation include enhanced sample collection, rapid detection, and diagnostic testing and microbial forensics.<sup>13</sup> Research is also being directed currently toward the development of a second-generation vaccine (recombinant protective antigen based). Most experts consider ciprofloxacin or doxycycline, essential components of first-line antibiotic treatment for victims of intentional anthrax exposure. Nevertheless, morbidity and mortality remain high with inhalational disease, and there is a paucity of pharmacokinetic data for these antibiotics in children. Anthrax immune globulin shows promise as an adjunctive therapy and has recently been added to the Strategic National Stockpile. In addition, the use of monoclonal antibodies offers promise; however, neither therapy has yet been tested for use in children.

*Smallpox* is a viral infection with prominent skin lesions and systemic toxicity, and a historical mortality rate of 30%. Although the global eradication of smallpox represents one of the great success stories of public health, several factors raise concern for potential terrorist use of this agent. It is possible that stockpiles exist in the hands of belligerent nations. In addition, the entire viral genomic sequence is known and published, and thus, it is possible that new technology will permit reconstruction of the virus. Finally, it may be possible for someone to manipulate related orthopoxviruses

such as monkeypox to enhance their virulence in humans and create a disease similar to smallpox. Given these considerations and the high potential morbidity and mortality of an outbreak of this very contagious disease, the CDC in 2003 recommended a strategy of reintroducing vaccination in the United States after a nearly 30-year hiatus, with the initial goal of vaccinating up to 10 000 000 frontline EMS and health care providers. This program proved controversial and has been suspended; probably fewer than 50 000 civilians were vaccinated. In recent years, however, the US military very successfully vaccinated several hundred thousand personnel, and serious adverse events have been rare. Current directions in smallpox preparedness include emergency response planning for mass immunization and quarantine, as well as basic research directed toward development of improved vaccines (eg, next-generation modified vaccinia Ankara based) and antiviral countermeasures (eg, an oral prodrug of cidofovir and ST-246).<sup>14</sup>

*Botulism* is the paralytic disease caused by the toxin of *Clostridium botulinum*. Supportive care remains the mainstay of management. Patients may require ventilatory support for several months, making the management of a large-scale botulism outbreak especially problematic in terms of medical resources. Botulinum antitoxins are available through the CDC. Although administration of antitoxin is unlikely to reverse disease (it is most effective when given during the clinically asymptomatic, or latent, period after inhalation of the toxin), it may mitigate progression when administered to exposed persons. Currently, a heptavalent despeciated (Fab2) antitoxin is under investigation and is now available in the Strategic National Stockpile through the CDC, and monoclonal antibody therapy is ready for clinical trials.

## CHEMICAL AGENTS

In the wake of the Tokyo sarin attack in 1995, most of the modern medical literature on the clinical effects of traditional chemical weapons has focused on nerve agents. Considerable concern exists as well for potential terrorist use of cyanide, vesicants, and pulmonary agents, as well as potential exploitation of common industrial chemicals by attacking production, storage, or transportation venues of these compounds.

The general treatment of chemically contaminated victims begins with extrication, triage, emergent resuscitation as needed, and decontamination. In contrast to victims of biologic attack, decontamination of chemically exposed patients serves 2

critical purposes: the prevention of secondary exposure of health care workers and facilities, and prevention or minimization of continuing absorption by the patient. Optimal decontamination strategies for children have been the focus of considerable discussion and research activity and continue to evolve. The traditional technique of disrobement followed by soap and water-based decontamination as applied to children has been reviewed recently.<sup>15</sup>

Another approach that has been developed for the military battlefield is the use of a decontamination lotion, termed Reactive Skin Decontamination Lotion, packaged as a lotion-impregnated sponge. This functions both by physical removal and neutralization of chemical agents. However, civilian medical and, particularly, pediatric experience with this product are currently limited.

*Nerve agents* are organophosphorus esters and, like the less potent organophosphate insecticides, are potent and essentially irreversible inhibitors of acetylcholinesterase.<sup>16,17</sup> Poisoning results in the cholinergic syndrome with central nervous system (CNS), nicotinic (neuromuscular junction and sympathetic ganglia), and muscarinic (smooth muscle and exocrine gland) effects. Significant exposure produces profound, multiorgan system dysfunction and, particularly, life-threatening neurologic (coma, convulsions, central apnea, muscle weakness progressing to flaccid paralysis) and respiratory (rhinorrhea, bronchospasm and bronchorrhea causing cough, wheezing, dyspnea) toxicity.

The current treatment approach for nerve agent victims focuses on airway and ventilatory support; aggressive use of antidotes, particularly atropine and pralidoxime chloride; prompt control of seizures with benzodiazepines; and the provision of decontamination as necessary. Atropine is used for its central and antimuscarinic effects, and pralidoxime serves to reactivate acetylcholinesterase. Atropine treats bronchospasm and increased bronchial secretions, bradycardia, gastrointestinal effects and may lessen seizure activity. Pralidoxime is used to cleave organophosphate away from the cholinesterase and to regenerate intact enzyme, in an effort to relieve muscle weakness. Current research challenges include optimal antidote dosing and route of administration (especially in children); newer, potentially more efficacious oximes; nerve agent scavengers; optimal choice for a benzodiazepine anticonvulsant; and potential use of adjunct anticonvulsants.

Pediatric experience with organophosphate pesticide poisoning suggests that atropine and pralidoxime are optimally given intravenously. However, in a

pediatric mass casualty incident, intramuscular administration would be far more logistically feasible, and both drugs are well absorbed by this route. In fact, the Strategic National Stockpile and most US EMS systems currently stock military intramuscular autoinjector kits of 2 mg atropine and 600 mg pralidoxime (2-PAM), as well as pediatric-sized autoinjectors of atropine. Pediatric-sized 2-PAM autoinjectors are not currently available, though this prospect is currently under the Food and Drug Administration review. Some authors have suggested that in dire circumstances, even the adult autoinjectors with 0.8-in needle insertion lengths and 600 mg pralidoxime might find utility in children older than 2 to 3 years or who weigh 12 kg or more.<sup>3</sup> For infants, another study suggested feasibility of using the adult pralidoxime autoinjector as a convenient source of concentrated (300 mg/mL) pralidoxime solution suitable for intramuscular injection.<sup>17,18</sup> Alternatively, others make a case for simplified prehospital atropine dosing in children and omitting prehospital pralidoxime therapy in very young infants.<sup>19</sup> Finally, the routine administration of anticonvulsant doses of benzodiazepines is recommended in significant cases, even without observed convulsive activity, as animal studies have indicated some amelioration of subsequent seizures and morphologic brain damage with such use. Currently, intramuscular autoinjectors of diazepam are available for prehospital and/or mass casualty anticonvulsant therapy. Potential future advances in nerve agent treatment currently under investigation include the use of more effective *bis*-quaternary oximes, such as HI-6, fetal bovine serum acetylcholinesterase, scopolamine for anticholinergic effects (potentially better CNS penetration than atropine), intramuscular and/or intranasal midazolam as the pre-hospital/mass casualty anticonvulsant of choice, and the potential use of ketamine (for its *N*-methyl *D*-aspartate-receptor antagonist properties) as an adjunct to treat prolonged nerve-agent-induced seizures.

The major *vesicants*, or blistering agents, are cellular poisons and include sulfur mustard and Lewisite. Mustard forms a potent alkylating agent causing injury to rapidly reproducing cells (its systemic effects may be described as radiomimetic), and its local effects are most evident on the skin, in the eyes, and in the respiratory tract.<sup>3,20</sup> With severe exposures, the bone marrow, gastrointestinal mucosa, and the CNS may also be injured. Mustard penetrates tissue rapidly and binds to cellular components within the first 2 to 5 minutes, so the most important early intervention is decontamination as soon as possible after exposure. No specific

antidotes to mustard poisoning are currently available. Supportive care for skin lesions is analogous to that provided for burn injury, and further treatment of respiratory tract inflammation, ocular injury, and immunosuppression associated with leucopenia may be required. Therapeutic research directions include the potential salutary effect of granulocyte colony-stimulating factor in the further treatment of mustard-induced leucopenia, and the use of oral *N*-acetylcysteine both as a potential prophylactic agent and for mitigating chronic pulmonary effects.

Toxic pulmonary or *inhalant agents*, particularly chlorine and phosgene, may cause injury in several ways, including simple asphyxia by displacing oxygen, topical damage to airways or alveoli, systemic absorption through the pulmonary capillary bed, and allergic hypersensitivity reactions.<sup>3,20-22</sup> Both chlorine and phosgene were used in battle in World War I, are commonly used for industrial purposes today, and are considered significant terrorist threat agents.

Chlorine exposure results in ocular and nasal irritation, followed by cough, progressing to a choking sensation and substernal chest tightness. Bronchospasm may occur, especially in patients with a history of reactive airway disease. Pulmonary edema may follow significant exposures within 2 to 4 hours; severe exposures may cause rapid onset of pulmonary edema, within 30 to 60 minutes.

Persons with significant phosgene exposure may be initially asymptomatic, but are at risk of developing pulmonary edema after a considerable delay, typically 4 to 6 hours, but with lower exposures as late as 24 hours after exposure. Management of exposure to pulmonary agents is primarily supportive. Animal studies have suggested a modest benefit of steroid therapy in mitigating lung injury after chlorine inhalation, and thus, steroids may be considered for patients with chlorine exposure, especially as an adjunct to bronchodilators in those manifesting bronchospasm, and/or a history of asthma. In addition, some symptomatic relief has also been reported for chlorine exposure with nebulized sodium bicarbonate therapy, but the impact of this regimen on pulmonary damage is unknown.<sup>21</sup> Animal models also suggest a benefit of anti-inflammatory agents, including ibuprofen and *N*-acetylcysteine, to ameliorate phosgene-induced pulmonary edema, as well as the utilization of low tidal volume ventilation (protective ventilation), but these interventions have not yet been reported in clinical trials.

Compounds containing the *cyanide* ion (CN<sup>-</sup>) have a long history as favored agents for homicide and suicide and, if released in a crowded, closed room,

could have devastating effects as a terrorist weapon. Such compounds include the liquids hydrocyanic acid (hydrogen cyanide) and cyanogen chloride, both of which rapidly vaporize after release.

Cyanide causes toxicity by inhibiting electron transport at the cytochrome-aa<sub>3</sub> complex (cytochrome oxidase) of the mitochondrial cytochrome chain.<sup>3,20</sup> This results in cellular anoxia and a decreased arteriovenous oxygen difference (from inability of cells to use delivered oxygen), metabolic acidosis (from accumulation of hydrogen ions not incorporated with oxygen), and increased lactic acid production (from the failure to generate energy aerobically).

Clinical manifestations relate to this cellular anoxia, and thus, those organs that are metabolically most active, particularly the brain and heart, are most severely affected. High concentrations of cyanide vapor initially produce tachypnea, hyperpnea, and hypertension within seconds; anoxic injury to the CNS and myocardium soon follow, with unconsciousness and seizures (as soon as 30 seconds after exposure), opisthotonus, decerebrate posturing, bradycardia, arrhythmias, hypotension, and eventually cardiac arrest (within 4 to 8 minutes).

Management of cyanide vapor poisoning begins with removal to fresh air, followed by attention to the basics of intensive supportive care including provision of 100% oxygen, mechanical ventilation as needed, circulatory support with crystalloid and vasopressors, correction of metabolic acidosis with parenteral sodium bicarbonate, and seizure control with benzodiazepine administration. The cyanide-induced inhibition of cellular oxygen use might suggest that supplemental oxygen would be of little value in cyanide poisoning, but in fact, administration of 100% oxygen has been found to empirically exert a beneficial effect, possibly by directly displacing cyanide from cytochrome oxidase-binding sites.

Symptomatic patients, particularly those with severe manifestations, may further benefit from specific antidotal therapy. Currently, 2 antidote regimens are available in the United States, and many EMS systems and hospitals stock one regimen or the other.

The older cyanide antidote approach used a 2-step process combining a methemoglobin-forming agent (sodium nitrite) and sodium thiosulfate, which hastens cyanide metabolism to the less toxic thiocyanate. However, nitrite administration is potentially hazardous because too rapid intravenous infusion may cause or exacerbate hypotension, and overproduction of methemoglobin may compromise oxygen-carrying capacity, especially in young children.

The newer antidote available in the United States is hydroxocobalamin, the hydroxy form of cobalamin.<sup>23,24</sup> In the presence of cyanide, it exchanges its hydroxy group for cyanide, forming cyanocobalamin (vitamin B12), which is subsequently excreted by the kidneys. Hydroxycobalamin use is not complicated by the potential for nitrite-induced hypotension or methemoglobinemia and has a low order of toxicity. Thus, hydroxocobalamin may be well suited for use in the prehospital and emergency department management of mass-casualty incidents. Although no human-controlled trials are available to compare hydroxocobalamin to nitrite/thiosulfate-based therapies, many authorities currently feel that hydroxocobalamin's efficacy and safety profile favor it as the cyanide antidote of choice, especially for children in the mass casualty context. Combined use of hydroxocobalamin and thiosulfate in severe cases might provide synergistic effects and still avoid the potential hazards of nitrite therapy. There is also research interest in newer compounds with oral availability, including cobinamide, a cobalamin precursor with high cyanide affinity, and analogs of 3-methylpyruvate, which, like thiosulfate, enhance conversion of cyanide to thiocyanate.

### Toxic Industrial Chemicals

The potential of a terrorist attack on industrial sources of dangerous chemicals such as factories, railroad and vehicular tank cars, or storage depots considerably expands the list of potential "chemical weapons." Many of the relevant industrial chemicals (eg, methyl isocyanate, ammonia, nitrogen dioxide, and sulfur oxides) might be expected to induce respiratory effects analogous to those of chlorine or phosgene discussed previously; others (eg, strong acids or alkalis, hydrogen fluoride, formaldehyde, and acrolein) could cause dermatologic injury from irritant or caustic properties, as well as more systemic effects in heavy exposures.<sup>25</sup> The importance of this diverse group of potential chemical weapons has led to recent efforts to formulate clinical protocols and guide research direction, as noted below.

### Summary of Current Challenges and Research Directions in Biologic and Chemical Terrorism

Numerous needs remain as detailed above, both in general terms of advances in diagnostics and therapeutics, and in specific pediatric applications. In addition, community planning, medication stockpiling, and preparation for mass casualty incidents involving numerous children present daunting

logistical challenges. In response to these imperatives, the US Department of Health and Human Services has taken several steps to advance our domestic preparedness for children in such disasters. Of note, a cadre of biodefense working groups has been formed recently within the National Institutes of Health, under the umbrella of the Best Pharmaceuticals for Children Act. These groups have drawn experts from academia, industry, and the federal research infrastructure and include both basic scientists and acute care clinicians. Current working groups include those devoted to infectious diseases, chemical agents, and radiation disasters. Several members of these groups are represented in the authorship of this volume of *Clinical Pediatric Emergency Medicine*. Information about the National Institutes of Health pediatric biodefense research agenda is available at the Web site: <http://bpca.nichd.nih.gov/outreach/upload/Biodefense-09-08.pdf>. 

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