

## Disaster preparedness, pediatric considerations in primary blast injury, chemical, and biological terrorism

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### Abstract

Both domestic and foreign terror incidents are an unfortunate outgrowth of our modern times from the Oklahoma City bombings, Sarin gas attacks in Japan, the Madrid train bombing, anthrax spores in the mail, to the World Trade Center on September 11<sup>th</sup>, 2001. The modalities used to perpetrate these terrorist acts range from conventional weapons to high explosives, chemical weapons, and biological weapons all of which have been used in the recent past. While these weapons platforms can cause significant injury requiring critical care the mechanism of injury, pathophysiology and treatment of these injuries are unfamiliar to many critical care providers. Additionally the pediatric population is particularly vulnerable to these types of attacks. In the event of a mass casualty incident both adult and pediatric critical care practitioners will likely be called upon to care for children and adults alike. We will review the presentation, pathophysiology, and treatment of victims of blast injury, chemical weapons, and biological weapons. The focus will be on those injuries not commonly encountered in critical care practice, primary blast injuries, category A pathogens likely to be used in terrorist incidents, and chemical weapons including nerve agents, vesicants, pulmonary agents, cyanide, and riot control agents with special attention paid to

pediatric specific considerations.

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**Key words:** Terrorism; Bioterrorism; Chemical terrorism; Blast injuries; Mass casualty incidents; Disasters; Pediatrics

**Core tip:** Terrorism and mass casualty events continue to increase on a global scale. Many injuries specific to terrorist incidents including blast injury, biological, and chemical casualties are unfamiliar to the critical care provider. We review the presentation, pathophysiology and care of these casualties. We give specific consideration to the pediatric population as they are a particularly vulnerable population and both adult and pediatric critical care specialists would be called upon to care for children in the event of a massive casualty terrorist event.

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### INTRODUCTION

Terrorism is an unfortunate fact of life in current times. Children have been identified as a specific vulnerable population<sup>[1]</sup>. Additionally children have increased mortality when exposed to combat injury<sup>[2]</sup>. While these events have increased in frequency, exposure during medical training is limited. This review will cover those aspects of care of the pediatric victim of terrorist incidents that may not be familiar to the critical care provider. We will cover primary blast injury (PBI), biological weapons, and chemical weapons.

**Table 1 Pediatric specific vulnerabilities to terrorist attacks**

Vulnerability	Blast Injury	Biological agents	Chemical agents
Proximity to ground		Agents settle to the ground	Agents tend to pool in lower areas
Increased minute ventilation		Increased exposure to inhaled agents	Increased exposure to inhaled agents
Provider unfamiliarity with pediatric dosing of medications		Dosing of antibiotics different	No prepackaged store of antidotes in pediatric doses
Lack of knowledge or inability to flee danger	Either unaware or unable to flee from explosion Potentially curious about ordinance	Unlikely to recognize signs/symptoms of biologic agents	Would not know to flee from strange odor or seek medical help with symptoms
Lack of stockpile of pediatric dosed antidotes and vaccines		Prepackaged stockpiles of vaccines and antidotes not dosed for small children <sup>[32]</sup>	Lack of guidelines for dosing of antidotes in children
Less blood volume/physiologic reserve	More rapidly develop life threatening blood loss	Prone to dehydration with illness. Lower functional residual capacity	More prone to respiratory distress/failure with nerve agents, vesicants, and pulmonary agents
Thinner skin			Faster absorption of agents
Increased BSA to mass ratio	Prone to hypothermia during triage, evacuation and treatment		Prone to hypothermia with decontamination
Developmental immaturity	Unable to follow mental status exam/communicate other injuries early	Present later in the course of biologic agents	Unable to promptly communicate symptoms
Increased head size compared to body	Increased head AIS when compared to adults <sup>[2]</sup>		

AIS: Abbreviated injury score; BSA: Body surface area.

High-order explosives (HE) were first available after dynamite was developed by Alfred Nobel in 1866. Since then several other HE have been developed and are used in up to 66% of terror attacks<sup>[3]</sup>. Biological warfare dates back to the Hittites driving diseased animals into enemy territories as early as 15<sup>th</sup> century BC. In 1346, Mongols hurled bodies of those killed by plague into Crimean city of Caffa, causing an epidemic resulting in their surrender. Chemical weapons were first used on a large scale during World War I where mustard, chlorine, and phosgene were used in the trenches<sup>[4]</sup>. In more recent times, Saddam Hussein and the Iraqi military used the nerve agent sarin against Kurdish villagers and the Iranian military during the Iraq-Iran War in 1988 with 75% of casualties being women and children. Sarin has been used on at least two occasions in the mid-1990s by the Japanese terror cult Aum Shinrikyo, including an incident in 1995 at a Tokyo subway station that killed 15 and injured over 5000. Among the injured were healthcare providers who were unprepared to deal with contaminated victims. Recent events in Syria have also clearly shown that chemical weapons are a threat we still face. Finally, chemical agents may be introduced into the food supply as was seen with the placement of a nicotine-containing insecticide into ground beef in Michigan, United States in 2002 that resulted in more than 40 children becoming ill.

As mentioned, children are identified as a vulnerable population. They have several specific physiologic, anatomic, and developmental differences from adults which make the particularly vulnerable (Table 1). In 2010 the National Commission on Children and Disasters reported that while children make up 25% of the United States population only 25% of EMS agencies and 6% of hospital emergency rooms have supplies and equipment

to treat children<sup>[1]</sup>. This problem is likely more prevalent in the developing world where children make up a larger portion of the population. When planning and executing exercises and simulations of disaster events, including terrorist attacks, it is imperative that the unique aspects of treating children are taken into account<sup>[1]</sup>.

## PBI

Explosive charges can be divided into 2 types, HE, which cause a supersonic overpressure wave, or low-order explosives which are lower energy and do not cause an overpressure wave. Examples of HE include C-4, TNT, and ammonium nitrate, which was used in the bombing at the Murrah Federal Building in Oklahoma City.

Injuries caused by a blast can be divided into 4 categories; primary, secondary, tertiary, and quaternary. PBI is injury caused as a direct effect of overpressure caused by the blast wave itself passing through the tissues. Low-order explosives typically do not cause PBI due to the lack of an overpressure wave. Secondary blast injury is caused by fragments propelled by the explosion. These penetrating injuries are more easily identifiable and also more familiar to most physicians. Tertiary injuries are those injuries caused by displacement of the victim's body and are the result of impact on a surface such as fractures, traumatic brain injury (TBI), or abrasions. Quaternary injuries are burns and inhalation caused by the blast itself<sup>[5]</sup>. While we differentiate these 4 types of injury, injury in explosions is multi-mechanistic and can be difficult to determine individually<sup>[6]</sup>. We will focus on PBI as the penetrating, blunt, and thermal trauma associated with secondary, tertiary, and quaternary blast injuries are more familiar to the critical care physician. For pediatric

specific vulnerabilities in blast injury please see Table 1.

The overpressure wave that causes PBI does so through 2 mechanisms, stress and shear, which cause injuries by transmission of kinetic energy as the wave travels from tissue into air-filled organs<sup>[6,7]</sup>. Stress waves are longitudinal and cause “spalling”, which can cause significant microvascular and tissue damage. Shear waves, are transverse and cause disruption of tissue attachments<sup>[7]</sup>.

When explosions occur in closed environments, mortality is higher due to the blast wave reflecting off solid walls. In the Madrid subway bombings of 2004, 63% of patients who survived to intensive care unit admission were noted to have blast lung injury<sup>[8]</sup>. In a 1996 analysis of detonations in terrorist incidents in Israel, explosions occurring in enclosed spaces versus open air detonations had a higher rate of mortality (49.0% *vs* 7.8%) and higher incidence of primary blast injuries (77.5% *vs* 33.4%)<sup>[9]</sup>.

### **Blast lung injury**

Primary blast lung injury (PBLI) occurs in 3%-14% of blast survivors and is the most common fatal complication of initial survivors of blast injury<sup>[9,10]</sup>. Passage of the overpressure wave from tissue to the air filled alveoli causes disruption of the capillary alveolar interface resulting in pulmonary hemorrhage, pulmonary edema, pneumothorax, pulmonary fat embolus, or air embolus from arterio-venous fistulas<sup>[11]</sup>. The resultant clinical signs suggestive of PBLI are tachypnea, respiratory distress, cyanosis, and hemoptysis<sup>[7]</sup>. Chest radiographs may show bilateral central pulmonary infiltrates that are not always initially present on admission<sup>[12]</sup>. In a retrospective review from Israel all patients with PBLI had pulmonary infiltrates and hypoxia<sup>[12]</sup>. Thus PBLI should be strongly suspected in any patient with any of the above findings especially in the absence of evidence of other penetrating or blunt chest injury.

Treatment of PBLI should include maintaining patency of the airway, oxygenation, avoidance of overzealous fluid administration (which children are at increased risk of), and support of ventilation. Historically it has been taught that positive pressure ventilation should be avoided but in one series with excellent outcomes, 76% of patients required intubation and mechanical ventilation<sup>[12]</sup>. Additionally these patients are at high risk of pneumothoraces and prophylactic placement of chest tubes prior to intubation or transport should be considered<sup>[13]</sup>. Pulmonary hemorrhage should be treated with optimization of coagulation but if oxygenation cannot be maintained then positive pressure ventilation and selective ventilation of the non-involved lung is recommended. Permissive hypercapnia such as that used with acute respiratory distress syndrome has been recommended as a ventilatory strategy in PBLI patients<sup>[14]</sup>. Identification of air emboli by echocardiography, computed tomography (CT), or bronchoscopy is critical in PBLI as these are a frequently fatal. Thoracotomy on the affected side is the recommended treatment for non-traumatic air embolus but may not be effective in PBLI as there may be multiple sites of injury<sup>[15]</sup>. Therefore a more conservative approach would

be to put the patient in a modified lateral decubitus position with the injured lung down or prone position.

### **Cardiovascular blast injury**

The cardiovascular effects in victims of a blast can be complex. Secondary or tertiary injuries can cause cardiac contusion or tamponade. The stress of being in a blast can induce myocardial infarction in susceptible adults with pre-existing heart disease. Unique to blast injury is the observed phenomenon of bradycardia, apnea, and hypotension immediately following a blast<sup>[7]</sup>. Rat studies have demonstrated a similar response after a blast with a drop in systemic vascular resistance (SVR)<sup>[16]</sup>. The same authors found that when they performed a surgical vagotomy and administered atropine to rats subjected to blast that these effects were diminished suggesting a vagal response to the blast itself<sup>[17]</sup>. Some data indicate that atropine may be a useful adjunct in blast patients experiencing hemodynamic compromise<sup>[7]</sup>. Infants may be at increased risk of this vagally mediated bradycardia, apnea, and lack of compensatory increase in SVR due to immaturity of their sympathetic nervous system. Additionally, given the relative flexibility of the pediatric thoracic cage they are at increased risk for cardiac contusions.

### **Gastrointestinal blast injury**

The pathophysiology of gastrointestinal (GI) tract PBI is similar to PBLI. It occurs when the overpressure wave passes from tissue into gas filled spaces causing microvascular damage and tearing across tissue planes. Incidence ranges from 3.0%-6.7% amongst initial survivors in a series of 1040 patients<sup>[18]</sup>. The regions most affected were the terminal ileum and cecum<sup>[18]</sup>. Solid organs can rupture although this occurs less frequently. Signs and symptoms include those typically seen with abdominal hemorrhage and perforation to include, abdominal pain, nausea, emesis, hematemesis, melena, hypotension, or signs of peritoneal irritation and may present several hours to days after injury<sup>[7]</sup>.

Diagnosis is primarily clinical and accomplished through serial exams, which can be more challenging in the pediatric population. Adjunctive diagnostic tests such as plain abdominal radiograph can help in diagnosis. Abdominal CT scan is very effective at demonstrating solid organ injury but may not be as sensitive with intestinal injury. Diagnostic peritoneal lavage can be used as an adjunct if other studies or clinical exam are not conclusive<sup>[18]</sup>. The treatment of GI blast injury is similar to that of blunt or penetrating abdominal injury and indications for surgical intervention are similar<sup>[18]</sup>. It should be noted that GI blast injury typically develops over several hours to days and that treatment of PBLI, cardiac injury and other life threatening injuries should be stabilized prior to treatment of the GI injuries if they are not life threatening.

### **Blast TBI**

While blast TBI (bTBI) is a common occurrence in explosions there is also a high incidence of closed TBI due to tertiary blast injury making it difficult to separate the

**Table 2 Management of chemical agents**

Agent	Pediatric dosing	Notes
Nerve agents	Atropine 0.05 mg/kg <i>iv</i> or <i>im</i> q 2-5 min (max 5 mg)	Atropine should be repeated for persistent symptoms
	Pralidoxime 25 mg/kg <i>iv</i> or <i>im</i> q 1 h (max 1 g <i>iv</i> or 2 g <i>im</i> )	
	Benzodiazepines: Midazolam <i>im</i> 0.2 mg/kg (max 10 mg) (1st choice)	
	Lorazepam <i>iv/im</i> 0.1 mg/kg (max 4 mg)	
	Diazepam <i>iv</i> 0.3 mg/kg (max 10 mg)	
Cyanide	Hydroxocobalamin 70 mg/kg (max 5 g) or	Hydroxocobalamin may be repeated × 1 if needed
	sodium nitrate; 0.33mL/kg <i>iv</i> (max 10 mL) followed by	
	sodium thiosulfate (25%) 1.65 mL/kg <i>iv</i> (max 50 mL)	

two<sup>[5]</sup>. Clinical findings in bTBI have a similar spectrum to injuries seen in the typical practice of critical care physicians and include edema, contusion, diffuse axonal injury, hematomas, and hemorrhage<sup>[5]</sup>. A study by Ling *et al*<sup>[19]</sup> based on the conflicts in Iraq in Afghanistan suggest that the pathophysiology in bTBI may be different with increased vasospasm and pseudoaneurysms as well as onset of cerebral edema much earlier in the course of bTBI than other TBI. Additionally they demonstrated early decompressive craniectomy in these patients may reduce mortality. With the exception of early craniectomy, current treatment strategies for bTBI do not differ from more common severe closed head injury<sup>[5]</sup>. Specific pediatric considerations include age appropriate equipment, assessment tools such as the pediatric Glasgow Coma Score, and recognition of the specific vulnerabilities of children to bTBI (Table 1).

### **Ophthalmologic and auditory blast injury**

Significant ophthalmologic injury may occur in up to 10% of blast victims and may include a perforated globe, foreign body, air embolism, fractures, or globe rupture from the over pressure wave<sup>[13]</sup>. Auditory injury is also common in blast injury occurring in 9%-47% of victims<sup>[7]</sup>. While both ophthalmologic and auditory injuries are common and may require follow-up (such as globe rupture within 12 h) they should be addressed after life threatening injuries.

## **CHEMICAL AGENTS**

There are estimated to be over 50 chemical agents that can be used as weapons, many of which have a high probability of injury. Children may often be the index case in the event of a chemical agent attack due to their inherent vulnerabilities (Table 1). Exposure to chemical agents is usually *via* either the respiratory system or skin with direct and systemic toxicity possible in either route.

Skin decontamination of suspected victims is imperative as it limits further absorption by the patient as well as preventing healthcare worker exposure. Decontamination ("The solution to pollution is dilution") is best done with 0.5% hypochlorite solutions or large amounts of soap and water after removal of all clothing and jewelry. Decontamination should be done by personnel in appropriate personal protective equipment<sup>[20]</sup>. Following this, the patient should be blotted dry instead of scrubbed dry as

this can lead to increased cutaneous absorption through abrasions in the skin. Isolation is not required after thorough decontamination<sup>[21]</sup>.

### **Nerve agents [Tabun (GA), Sarin (GB), Soman (GD), and VX]**

Nerve agents can be absorbed, ingested, and inhaled (if in aerosolized form). Nerve agents are colorless liquids at room temperature and generally odorless and tasteless. Although they range in severity (VX is the most potent), all are organophosphate analogs and inhibitors of the enzyme acetyl cholinesterase, resulting in excessive acetylcholine stimulation of both nicotinic and muscarinic receptors.

Signs and symptoms depend on the form of the agent, concentration, and environmental variables. Aerosolized agents produce symptoms within minutes while cutaneous exposure symptoms may not develop for hours. Initial symptoms are often best remembered by SLUDGE (salivation, lacrimation, urination, defecation, GI upset, and emesis). More severe symptoms consist of respiratory (cough, wheezing with bronchorrhea, dyspnea, respiratory depression and cyanosis), cardiovascular (bradycardia, hypotension, and atrioventricular block), and central nervous system (muscle fasciculations, seizures, ataxia, and altered mental status including coma). It is important to note that children may not exhibit miosis to the same degree as adults but do exhibit a high incidence of weakness/hypotonia. Pediatric patients are at higher risk for severe toxicity than adults (Table 1).

The diagnosis of nerve agent exposure is generally made using presenting symptoms and response to antidotes. Although red blood cell or plasma acetyl cholinesterase levels can be measured, this test is not widely available on a rapid basis. In addition, nerve agent detection devices are available in certain settings (generally military and homeland defense) but not generally found in civilian healthcare settings. Decontamination (outlined above) is key to both treatment and prevention of contamination of providers.

Death, usually as a result of respiratory failure, can occur within 5-10 min of lethal dose exposure without proper treatment. Treatment consists of antidotes for both muscarinic (atropine) and nicotinic (pralidoxime chloride) with pediatric dosing provided in Table 2<sup>[22]</sup>. Atropine is indicated for all patients exhibiting signs/symptoms of nerve agent poisoning. Atropine should be



**Table 3** Guidelines for the use of Mark I kits in pediatric patients

Pediatric patients	Mark I kits
3-7 yr (approximately 13-25 kg)	One Mark I kit as maximum dose
8-14 yr (approximately 26-50 kg)	Two Mark I kits as maximum dose
> 14 yr (approximately > 51 kg)	Three Mark I kits as maximum dose

Mark I kit: 2 mg atropine and 600 mg 2-PAM; PAM: Pralidoxime.

repeated every 2-5 min if symptoms persist<sup>[22]</sup>. Both pediatric intramuscular atropine (0.25, 0.5, 1 mg dosages) and adult (2 mg) auto injectors are available although pediatric ones may be less available in some settings. Patients with severe sign/symptoms should also be given pralidoxime chloride (2-PAM) and a benzodiazepine. 2-PAM is used to treat the nicotinic receptor blockage by binding to the nerve agent, thus “re-activating” the acetylcholinesterase which can now break down the excessive acetylcholine present, provided enzyme “aging” or inactivation has not occurred. Currently there are only adult auto injectors (600 mg of 2-PAM) which together with the 2 mg atropine adult autoinjectors (Mark- I kit) can be used in pediatric patients when necessary. The Pediatric Expert Advisory Panel of Columbia University’s Program for Pediatric Preparedness at the National Center for Disaster Preparedness has published guidelines on the use of Mark I kits in pediatric patients (Table 3). There are newer types of kits that combine the two agents in to one syringe for easier administration. Benzodiazepines (with midazolam as the preferred treatment) are given concurrently with 2-PAM to both prevent as well as treat seizures.

### Vesicants

Sulfur Mustard is a vesicant that forms blisters upon skin contact and has been used on occasion since World War I including against the Kurdish population in Iraq. Although other vesicants exist such as Lewisite, they are considered to be of less risk for weaponization<sup>[4]</sup>. Vesicants are alkylating agents that cause damage to rapidly reproducing cells. Although vesicants cause less morbidity than nerve agents, they can cause significant long-term morbidity with extensive damage to skin, respiratory system, eyes, as well as bone marrow suppression. Mortality is usually from respiratory failure. Pediatric patients again exhibit a greater vulnerability to these agents due to faster skin absorption and proximity to agents settling near the ground (Table 1). If ingested, vesicants can also cause extensive intestinal mucosal injury. Although extensive clinical symptoms may not present until hours after exposure, skin damage can occur within minutes unless prompt decontamination is done. In general care is supportive (similar to traditional burn care except for not requiring high volume fluid administration as in traditional burns) except in the case of lewisite for which British Anti-Lewisite can be used (3 mg/kg *im* q 4-6 h)<sup>[20]</sup>.

### Pulmonary agents

Chlorine and phosgene are the classic pulmonary agents

but there are other pulmonary agents that can cause significant injury such as methyl isocyanate which was accidentally released in Bhopal, India in 1984 causing over 3000 deaths. Pulmonary agents have an odor of newly cut hay or grass and symptoms start with eye and skin irritation<sup>[21]</sup>. Significant respiratory symptoms can be delayed up to 24 h<sup>[23]</sup>. Symptoms include airway irritation (coughing, wheezing) with subsequent pulmonary edema and respiratory failure. Injury can occur to both Type I and II pneumocytes as well as alveolar macrophages with later release of prostaglandins and bradykinin producing vasodilatation and increased capillary permeability<sup>[23]</sup>. See Table 1 for pediatric specific vulnerabilities. Decontamination (moving to fresh air and supplying oxygen) is key to the management of these patients. Treatment for respiratory failure is similar to other causes of respiratory failure. Adjunct treatments that have been used but lack definitive recommendations include corticosteroids as well as in the case of phosgene, N-acetylcholine.

### Cyanide

Cyanide is a potent toxin that disrupts cellular metabolism by inhibiting cytochrome oxidase with interruption of oxidative phosphorylation. Cyanide intoxication can be caused by inhalation, ingestion or transdermal absorption of vapor, solid, and liquid forms. Fortunately cyanide is difficult to formulate into a chemical weapon due to it being highly volatile and chemically unstable. The classic presentation of cyanide poisoning is hypoxia without evidence of cyanosis. Mild symptoms include tachypnea, dizziness, nausea, vomiting, and headaches. Significant exposure can cause seizures, coma, respiratory arrest, and cardiac arrest within minutes.

Cyanide poisoning should be suspected in patients with a sudden change in mental status and significant metabolic acidosis. Characteristically patients have a bitter almond odor with a cherry red appearance of the skin. Laboratory testing will reveal elevated serum lactate levels, a narrow arterial-venous oxygen saturation difference, and elevated blood cyanide levels.

Decontamination (soap and water) should be performed in the event of cutaneous exposure. Mild systemic symptoms generally resolve with fresh air. Severe symptoms (coma, respiratory distress, *etc.*) are an indication for administration of an antidote in addition to critical care support as indicated. Hydroxocobalamin is now recommended as first line treatment due to its improved safety profile as compared to traditional cyanide antidote kits (Table 2). Hydroxocobalamin’s mechanism of action is binding with cyanide to form cyanocobalamin which is excreted renally<sup>[24]</sup>. Traditional cyanide antidote kits consist of sodium nitrite and sodium thiosulfate. A third component, amyl nitrite is no longer recommended due to questionable efficacy. Nitrite administration is now used as a second line treatment due to concerns of overproduction of methemoglobin which may compromise oxygen-carrying capacity, especially in young children, as well as hypotension that can be seen with nitrite infusions.

### Riot control agents

Riot control agents are also known as lacrimators, “tear gas”, and pepper spray. The most commonly used riot control agents are CS and CN. Although these agents produce mostly irritant symptoms to the eye they can be fatal as seen with a terrorist attack in Russia in 2002 where over 100 were killed. These agents are also alkylating but do not produce tissue damage similar to vesicants. In general they cause pain, conjunctival injection, blepharospasm, and lacrimation. In some cases respiratory symptoms may occur (laryngospasm and bronchospasm) and is the cause of fatalities. Treatment consists of eye and skin irrigation as well as supportive respiratory care, including bronchodilators, if needed.

## BIOLOGIC AGENTS

The use of biologic weapons has been and continues to be a great threat to our population. The ability to recognize that an attack has occurred and the ability to differentiate this from a natural outbreak can be difficult as symptoms of these agents may be delayed days to weeks after the attack. It is imperative that physicians recognize patterns that could indicate the early manifestations of a bioterrorist attack. A sudden outbreak of an unusual illness or the diagnosis of a rare disease is likely to be the first indication. Epidemiologic surveillance systems have been set up for early detection with the goals of early institution of preventative measures such as vaccination, isolation, prophylaxis, and institution of other treatment modalities<sup>[25]</sup>. Children, like in previous sections, have particular vulnerabilities to biological attacks (Table 1).

The Soviet Union, United States, and Japan all developed biological weapons programs in the 20<sup>th</sup> century. It is suspected that Japanese planes dropped fleas carrying plague over China during World War II. The Convention of the Prohibition of the Development, Production, and Stockpiling of Bacteriologic and Toxin Weapons was held in 1972, with over 140 countries signing<sup>[25]</sup>. Despite the signing of this document, the threat of biological warfare continues with the rise in terrorist groups. The release of anthrax spores through the United States postal system and the release of anthrax into the population following the September 11, 2011 terrorist attacks demonstrate that this is a continued threat. The United States continues to develop aggressive measure of surveillance and protection<sup>[26]</sup>.

The Center for Disease Control (CDC) has categorized agents into three groups based on morbidity and mortality if used as a biological weapon. Category A agents pose the greatest risk due to their easy dissemination, high mortality rates, and require special action for public health preparedness. Category B agents are moderately easy to disseminate, result in high morbidity and low mortality and require enhancement of the CDC's surveillance. Category C agents include emerging pathogens that are engineered for mass dissemination in the future<sup>[27]</sup>. We will address the category A agents.

### Anthrax

Anthrax is caused by a gram-negative, spore forming bacteria, *Bacillus anthracis* (*B anthracis*). It is naturally occurring in animals as they ingest spores from the soil Anthrax occurs in humans in 3 different forms: GI, cutaneous, and inhalational anthrax. Cutaneous and GI anthrax both occur naturally and are transmitted through breaks in the skin or ingestion of infected meat respectively. Inhalational anthrax rarely occurs naturally with no cases reported in the United States since 1978. Inhalational anthrax is thought to hold the most threat as it is expected to account for the most morbidity and mortality. Anthrax secretes two exotoxins, edema toxin and lethal toxin. These result in massive edema and a cytokine storm<sup>[28]</sup>.

Papules form in cutaneous anthrax in 1-7 d following exposure. These papules then become vesicles that ulcerate and form a black eschar. Symptoms of inhalational anthrax typically occur 1-7 d after exposure but can occur as late as 60 d after exposure. Early symptoms are subtle, resembling a nonspecific upper respiratory infection. Later the child will develop a high fever, shock, and death. Autopsy studies of patients with inhalational anthrax show hemorrhagic thoracic lymphadenitis and mediastinitis with very few exhibiting signs of pneumonia. Up to 50% of patients will also develop meningitis<sup>[28,29]</sup>.

Because diagnostic tests including enzyme-linked immunosorbent assay and polymerase chain reaction are only available at the national reference laboratories diagnosis of an outbreak could be delayed. Diagnosis on routine blood culture could be missed if the laboratory is not alerted to *B anthracis* being a possible cause. Antimicrobial treatment is outlined in Table 4. No widespread vaccine distribution is currently available, and person to person transmission has not been reported<sup>[29]</sup>.

### Plague

*Yersinia pestis* is a gram-negative bacillus, sometimes coccobacillus, known to cause plague. It occurs naturally in the forms of septicemia, bubonic and pneumonic forms. Pneumonic plague is the most likely to be seen in a bioterrorism as aerosolized forms would be easily disseminated. Pneumonic plague results in a multilobar, hemorrhagic and necrotizing bronchopneumonia. Unlike naturally occurring plague, plague following a biological attack will present with respiratory symptoms without the development of the buboes. Patients would likely develop fever and cough within 6 d of exposure and rapidly progress to severe bronchopneumonia. Untreated pneumonic plague has resulted in nearly 100% mortality<sup>[29]</sup>. An additional clue of intentional dissemination would be cases presenting in areas not known to have animal infection<sup>[30]</sup>.

Large numbers of previously healthy patients presenting with severe pneumonia, hemoptysis, and sepsis would be the first signs of a biological attack with plague. There are no rapid tests available to detect *Y pestis*. A gram stain of blood or sputum may reveal a gram-negative bacilli 24-48 h after inoculation. Table 4 outlines a variety of treatment regimens available<sup>[29]</sup>.

Table 4 Management of biologic agents

Agent	Pediatric dosing	Notes
Inhalational anthrax	Ciprofloxacin 10-15 mg/kg <i>iv</i> q 12 h (max 400 mg) or doxycycline 2.2 mg/kg <i>iv</i> q 12 h (max 100 mg) plus clindamycin 10-15 mg/kg q 8 plus penicillin G 400-600 k U/kg per day <i>iv</i> divided q 4 h prophylaxis for exposed contacts	Switch to oral therapy when patient shows signs of improvement At least one agent should have good CNS penetration Prophylaxis is for a 60 d course Amoxicillin or levofloxacin are second line
Plague	ciprofloxacin 15 mg/kg <i>po</i> q 12 h or doxycycline 2.2 mg/kg <i>po</i> q 12 h Gentamycin 2.5 mg/kg <i>iv</i> q 8 h or streptomycin 15 mg/kg <i>im</i> q 12 h (max 2 mg/d) or doxycycline 2.2 mg/kg <i>iv</i> q 12 h (max 200 mg/d) or ciprofloxacin 15 mg/kg <i>iv</i> q 12 h prophylaxis for exposed contacts trimethoprim/sulfa 4 mg/kg <i>po</i> q 12 h	Chloramphenicol or Levofloxacin can also be used Prophylaxis should be continued for 5-7 d
Tularemia	Same as therapy for plague	
Botulism	Infants < 1 yr human-derived botulinum immunoglobulin children > 1 yr equine serum botulism antitoxin	In United States call 1-800-222-1222 or 770-488-7100 Outside United States contact local health agencies

CNS: Central nervous system.

### Small pox

Any case of small pox, variola major, that is identified would be considered an act of terrorism. Small pox has been eradicated and no child has been routinely vaccinated against small pox since 1971. Small pox is highly contagious, with only a few viral molecules needed to induce disease. It is believed that the only remaining samples of this virus are kept secure at the CDC and in Russia, although there are some who believe other countries may have samples of it in their possession<sup>[29]</sup>.

The incubation period of small pox is from 7-19 d after exposure. Initially symptoms are relatively nonspecific with fever, malaise, vomiting, headache and backache. Two to three days later the patient develops an erythematous macular rash that progresses to papules and then pustules, which spread centrifugally. Death occurs in the second week of illness with multi-organ failure due to overwhelming viremia.

Diagnosis of small pox will be clinical as there are no widely available assays. Initial suspicion should be reported immediately to the health department. Patients exposed to a case will need to be monitored for a minimum of 17 d on airborne and contact precautions in the hospital or isolated in their homes. They should remain isolated until they are ruled out (PCR assays are available at national laboratories) or when the vesicles have lost their scab. Vaccines obtained in the last 3 years are thought to provide full immunity. Treatment is supportive care. There are no FDA approved anti-virals although cidofovir has been shown useful in animal models. Vaccination 72-96 h after exposure provides good protection against developing disease and also decreases severity<sup>[25]</sup>. All close contacts will require vaccination and isolation.

### Tularemia

Tularemia is caused by *Francisella tularensis*, a small, aerobic, gram-negative coccobacillus with extremely high virulence. It occurs naturally in the environment throughout North America and Europe. Humans are infected by insect bites, handling infected animal meat, or ingestion

of contaminated water or food. An act of bioterrorism with tularemia would likely be in an aerosolized form, allowing for many to become ill with a single release<sup>[31]</sup>.

In the event of an aerosolized tularemia attack, there would be an abrupt onset of patients presenting with flu-like symptoms and bronchitis 3-5 d post exposure. A large amount of those infected would present with severe cases of necrotizing hemorrhagic pneumonia, with or without bacteremia.

It is unlikely for tularemia to be identified with routine culture techniques. Rapid tests are primarily only run at research and reference laboratories. Serum antibody titers can be diagnostic but take 10 d to become positive. Standard precautions are all that is required as tularemia is not spread person to person. Patients have a significantly improved course with early initiation of the appropriate antibiotics (Table 4) and prophylaxis should be provided to others exposed to the attack<sup>[31]</sup>.

### Botulism

Botulinum toxin is produced by *Clostridium botulinum*, an anaerobic bacteria, and is the most lethal toxin known. Botulism can be spread naturally by three mechanisms: infantile botulism, wound botulism, and intestinal botulism. Botulinum toxin causes the inhibition of the release of acetylcholine at the nervous-skeletal muscle junction, thus producing a paralysis. Patients primarily die due to respiratory failure. Even with supportive care, recovery can take weeks to months as new axons must grow on each neuron<sup>[29]</sup>.

In the event of a bioterrorism attack, the particles would likely be released and inhaled<sup>[32]</sup>. Symptoms can present within 12-24 h after exposure, with cranial nerve palsies presenting first, followed by descending paralysis progressing to respiratory failure. Clinical symptoms are constipation, ileus, dry mouth and mydriasis. The "gold standard" for diagnosis is a bioassay but treatment should not be delayed pending these results. Supportive care and ventilator support is the most important aspect of treatment. Antitoxin is available in two forms, bivalent human



**Table 5** Viral hemorrhagic fever, virus and disease

Family	Virus	Disease
Arenaviruses	Lassa virus	Lassa fever
	Junin	Argentine hemorrhagic fever
Bunyaviruses	Machupo	Bolivian hemorrhagic fever
	CCHF	Cremiean-Congo hemorrhagic fever
	RVF	Rift Valley fever
	Hantavirus	Hemorrhagic fever with renal syndrome
Filoviruses	Ebola virus	Ebola hemorrhagic fever
	Marburg virus	Marburg hemorrhagic fever
Flavivirus	Yellow fever virus	Yellow fever
	KFD virus	KFD
	OHF virus	Omsk hemorrhagic fever
	DENV 1-4 viruses	Dengue hemorrhagic fever
Rhabdovirus	Bas-Congo virus	Bas-Congo hemorrhagic fever

CCHF: Crimean congo hemorrhagic fever; RVF: Rift valley fever; KFD: Kyasanur forest disease; OHF: Omsk hemorrhagic fever; DENV: Dengue hemorrhagic fever virus.

antiserum and equine heptavalent antitoxin, and should be administered at the first onset of symptoms. This will unlikely be available in massive quantities during a mass attack and will only shorten the course of illness. Prophylactic vaccination is reserved for at risk individuals, primarily laboratory workers<sup>[25]</sup>.

### Viral hemorrhagic fevers

The viral hemorrhagic fevers are produced by a variety of viruses originating from one of five virus families (Table 5). They are grouped by their ability to produce fever, shock, and bleeding. They are all spread by aerosolized particles, excluding dengue fever, which is blood-borne, and produce an illness with high morbidity and mortality.

All of the viral hemorrhagic fevers present with a nonspecific febrile illness including headache, myalgia and malaise. As they progress, the patient develops shock and hemorrhage. The cause of hemorrhage can vary depending on the causative agent. Most are multi-factorial in nature. Diagnosis should begin with a careful travel history to possible endemic areas as well as exposure to animals or animal feces. Patients have detectable viremia with most viruses identified through rapid enzyme immunoassays<sup>[25]</sup>.

Supportive care is the mainstay for the hemorrhagic fevers. Vigorous fluid resuscitation and control of hemorrhage with platelets, red blood cells, and clotting factors will often require intensive care. Ribavirin is indicated only in Lassa fever but has been used experimentally in a few of the other viruses<sup>[29]</sup>.

## CONCLUSION

Terrorist incidents continue to occur and it is imperative that the critical care provider be familiar with signs, symptoms, and basic treatment of the injuries and illnesses caused by potential terrorist modalities. While these events are thankfully rare, the prompt recognition of a possible chemical or biological attack is crucial to

limiting the damage caused by such an attack by instituting appropriate decontamination, treatment, and preventative measures. Familiarity with injuries specific to a blast should prepare the provider to anticipate and intervene appropriately when caring for these patients. For further information please refer to the agency for healthcare research and quality website at <http://archive.ahrq.gov/research/pedprep/index.html>.

## REFERENCES

- 1 **National Commission on Children and Disasters.** 2010 report to the President and Congress. Available from: URL: <http://archive.ahrq.gov/prep/nccdreport/index.htm>
- 2 **Matos RI, Holcomb JB, Callahan C, Spinella PC.** Increased mortality rates of young children with traumatic injuries at a US army combat support hospital in Baghdad, Iraq, 2004. *Pediatrics* 2008; **122**: e959-e966 [PMID: 18977963 DOI: 10.1542/peds.2008-1244]
- 3 **Agency for Healthcare Research and Quality.** Blast Terrorism. Available from: URL: <http://archive.ahrq.gov/research/pedprep/pedchap7.htm>
- 4 **Defense USAMRICD.** Field Management of Chemical Casualties. Chemical Casualty Care Division USAMRICD. Aberdeen Proving Ground. Frederick, MD, 2007
- 5 **Hicks RR, Fertig SJ, Desrocher RE, Koroshetz WJ, Pancrazio JJ.** Neurological effects of blast injury. *J Trauma* 2010; **68**: 1257-1263 [PMID: 20453776 DOI: 10.1097/TA.0b013e3181d8956d]
- 6 **Champion HR, Holcomb JB, Young LA.** Injuries from explosions: physics, biophysics, pathology, and required research focus. *J Trauma* 2009; **66**: 1468-1477; discussion 1477 [PMID: 19430256 DOI: 10.1097/TA.0b013e3181a27e7f]
- 7 **Ritenour AE, Baskin TW.** Primary blast injury: update on diagnosis and treatment. *Crit Care Med* 2008; **36**: S311-S317 [PMID: 18594258 DOI: 10.1097/CCM.0b013e31817e2a8c]
- 8 **Gutierrez de Ceballos JP, Turégano Fuentes F, Perez Diaz D, Sanz Sanchez M, Martin Llorente C, Guerrero Sanz JE.** Casualties treated at the closest hospital in the Madrid, March 11, terrorist bombings. *Crit Care Med* 2005; **33**: S107-S112 [PMID: 15640672 DOI: 10.1097/01.CCM.0000151072.17826.72]
- 9 **Leibovici D, Gofrit ON, Stein M, Shapira SC, Noga Y, Heruti RJ, Shemer J.** Blast injuries: bus versus open-air bombings--a comparative study of injuries in survivors of open-air versus confined-space explosions. *J Trauma* 1996; **41**: 1030-1035 [PMID: 8970558 DOI: 10.1097/00005373-199612000-00015]
- 10 **Mellor SG, Cooper GJ.** Analysis of 828 servicemen killed or injured by explosion in Northern Ireland 1970-84: the Hostile Action Casualty System. *Br J Surg* 1989; **76**: 1006-1010 [PMID: 2597940 DOI: 10.1002/bjs.1800761006]
- 11 **Tsokos M, Paulsen F, Petri S, Madea B, Puschel K, Turk EE.** Histologic, immunohistochemical, and ultrastructural findings in human blast lung injury. *Am J Respir Crit Care Med* 2003; **168**: 549-555 [PMID: 12842857 DOI: 10.1164/rccm.200304-528OC]
- 12 **Avidan V, Hersch M, Armon Y, Spira R, Aharoni D, Reisman P, Schecter WP.** Blast lung injury: clinical manifestations, treatment, and outcome. *Am J Surg* 2005; **190**: 927-931 [PMID: 16307948 DOI: 10.1016/j.amjsurg.2005.08.022]
- 13 **Centers for Disease Control and Prevention.** Explosion and blast injuries: A primer for clinicians. Last accessed 2013. Available from: URL: <http://www.cdc.gov/masstrauma/preparedness/primer.pdf>
- 14 **Sorkine P, Szold O, Kluger Y, Halpern P, Weinbroum AA, Fleishon R, Silbiger A, Rudick V.** Permissive hypercapnia ventilation in patients with severe pulmonary blast injury. *J Trauma* 1998; **45**: 35-38 [PMID: 9680008 DOI: 10.1097/00005373-199807000-00006]
- 15 **Argyros GJ.** Management of primary blast injury. *Toxicol-*



- ogy 1997; **121**: 105-115 [PMID: 9217319 DOI: 10.1016/S0300-483X(97)03659-7]
- 16 **Irwin RJ**, Lerner MR, Bealer JF, Brackett DJ, Tuggle DW. Cardiopulmonary physiology of primary blast injury. *J Trauma* 1997; **43**: 650-655 [PMID: 9356063 DOI: 10.1097/00005373-199710000-00015]
  - 17 **Irwin RJ**, Lerner MR, Bealer JF, Mantor PC, Brackett DJ, Tuggle DW. Shock after blast wave injury is caused by a vagally mediated reflex. *J Trauma* 1999; **47**: 105-110 [PMID: 10421195 DOI: 10.1097/00005373-199907000-00023]
  - 18 **Owers C**, Morgan JL, Garner JP. Abdominal trauma in primary blast injury. *Br J Surg* 2011; **98**: 168-179 [PMID: 21104699 DOI: 10.1002/bjs.7268]
  - 19 **Ling G**, Bandak F, Armonda R, Grant G, Ecklund J. Explosive blast neurotrauma. *J Neurotrauma* 2009; **26**: 815-825 [PMID: 19397423 DOI: 10.1089/neu.2007.0484]
  - 20 **Heon D**, Foltin GL. Pediatric Emergency Preparedness for Natural Disasters, Terrorism, and Public Health Emergencies-National Consensus Conference. *Clin Pediatr Emerg Med* 2009; **10**: 186-194 [DOI: 10.1016/j.cpem.2009.06.006]
  - 21 **Defense USAMRICD**. In: Field Management of Chemical Casualties. 2nd edn. Aberdeen Proving Ground, MD: Chemical Casualty Care Division USAMRICD; 2000: 96-135.
  - 22 **Garrett AL**, Readlener IE. Pediatric Emergency Preparedness for Natural Disasters, Terrorism, and Public Health Emergencies: A National Consensus Conference: 2009 Update. Available from: URL: <http://academiccommons.columbia.edu/catalog/ac:126143>
  - 23 **Baker DJ**. Critical care requirements after mass toxic agent release. *Crit Care Med* 2005; **33**: S66-S74 [PMID: 15640682 DOI: 10.1097/01.CCM.0000151069.06678.A5]
  - 24 **Henretig FM**. Preparation for Terrorist Threats: Biologic and Chemical Agents. *Clin Pediatr Emerg Med* 2009; **10**: 130-135 [DOI: 10.1016/j.cpem.2009.07.006]
  - 25 **Diseases UAMRIID**. Medical Management of Biological Casualties Handbook. 7th edn. Fort Detrick, Frederick, MD, 2001
  - 26 **Michael W S**, Julia A M. Chemical-biological terrorism and its impact on children. *Pediatrics* 2006; **118**: 1267-1278 [PMID: 16951026 DOI: 10.1542/peds.2006-1700]
  - 27 **Centers for Disease Control and Prevention**. Bioterrorism Agents/Diseases by Category. Available from: URL: <http://www.bt.cdc.gov/agent/agentlist-category.asp>
  - 28 **Inglesby TV**, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, Hauer J, McDade J, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Tonat K. Anthrax as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA* 1999; **281**: 1735-1745 [PMID: 10328075]
  - 29 **Pilip L**, Graham III GLF, F. Meridith Sonnett. Terrorism and Mass Casualty Events. Edited by Nichols DG, Fourth edn. In: Rogers's Textbook of Pediatric Intensive Care. Philadelphia, PA: Lippincott Williams and Wilkins; 2008: 427-440
  - 30 **Inglesby TV**, Dennis DT, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, Friedlander AM, Hauer J, Koerner JF, Layton M, McDade J, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Schoch-Spana M, Tonat K. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA* 2000; **283**: 2281-2290 [PMID: 10807389 DOI: 10.1001/jama.283.17.2281]
  - 31 **Dennis DT**, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, Friedlander AM, Hauer J, Layton M, Lillibridge SR, McDade JE, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Tonat K. Tularemia as a biological weapon: medical and public health management. *JAMA* 2001; **285**: 2763-2773 [PMID: 11386933 DOI: 10.1001/jama.285.21.2763]
  - 32 **Cieslak TJ**, Henretig FM. Ring-a-ring-a-roses: bioterrorism and its peculiar relevance to pediatrics. *Curr Opin Pediatr* 2003; **15**: 107-111 [PMID: 12544281 DOI: 10.1097/00008480-200302000-00018]

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