Ammonia (NH₃, anhydrous ammonia) is one of the most abundant toxic chemicals. As such, it has the potential to be involved in a variety of toxicological mass events (e.g., industrial and transportation accidents, water poisoning, terror attacks, bombing of industrial areas). Since a toxicological mass event is usually unpredictable, adequate preparedness is of utmost importance. Part of such preparedness is conveying information and knowledge to clinicians, which is the objective of this review.

Ammonia is the third most abundantly produced chemical in the world and is considered to be a Toxic Industrial Compound. Nowadays ammonia is used as a fertilizer, a precursor for other fertilizers (i.e., urea, ammonium nitrate, etc.), explosives, as a chemical intermediate in the synthesis of other chemicals (such as acrylonitrile), and in other industrial processes, including metallurgy, pulp and paper production, and refrigeration [1]. In previous centuries its carbonate salt [(NH₄)₂CO₃·H₂O] was used as a smelling salt and even today it is occasionally used in the boxing ring when boxers are knocked down unconscious. Smelling salts are a less common source of household ammonia products. Often in capsule form, smelling salts, which contain approximately 20% ammonia, release a pungent odor upon breaking [2].

The large-scale production of ammonia requires large storage facilities, usually under pressure. The location of these tanks in an urban area is a potential strategic weak point as large amounts of ammonia could be released as the result of a natural disaster, equipment failure, or accidental or intentional release. This toxic chemical is transported throughout Israel or other industrialized countries in big containers or trains that are prone to accidents [3]. In addition, we review past events of massive ammonia releases from manufacturing facilities, highlighting the risk of chemical terrorism [6].

Irritant gases have been used as chemical weapons. The Russian military accused Chechen rebels of detonating bombs containing chlorine and ammonia in Grozny. The rebels had set off several of these bombs during the night and early morning near Russian positions, but the wind had blown the green cloud over the center of Grozny. The Russian troops had protective equipment against chemical weapons and were not affected. Although the toxic cloud could potentially have harmed civilians in the center of the city, there is no record of injury.

In this review we describe the clinical effects following exposure to ammonia and the appropriate treatment needed. In addition, we review past events of massive ammonia releases from manufacturing facilities, highlighting the risk of chemical terrorism [6].

Ammonia is widely used for industrial purposes. Its odor threshold is sufficiently low to acutely provide adequate warning of its presence.

Chemical and toxicological properties
Ammonia is a stable colorless gas at room temperature and is lighter than air. An ammonia cloud, on the other hand, has a white opaque appearance. It liquefies to a colorless fluid at -33°C, or under at least 10 bar pressure. Ammonia gas is highly soluble in water, forming ammonium hydroxide (NH₄OH). It is a strong alkaline with high corrosive properties. The unique pungent odor of ammonia usually provides adequate warning of its presence [7]. Ammonia is usually considered a non-flammable gas, but in exceptional conditions it may become flammable, exert noxious ammonia vapors and may even explode within a certain range of air concentrations (16–25%) [8].

Ammonia is toxic to humans in all exposure scenarios. Its odor threshold is sufficiently low to acutely provide adequate warning of its presence with an odor threshold of 5 ppm. However, ammonia causes olfactory fatigue or adaptation, making its presence difficult to detect when exposure is prolonged. Thus the odor threshold may extend up to 53 ppm, according to the Agency for Toxic Substances and Disease Registry [9,10].

ppm = parts per million
Mechanism of toxicity and pharmacology

Ammonia is extremely soluble in water and dissolves in the mucus fluid covering the mucous lining of the respiratory system to produce ammonium hydroxide, a strong base. The reaction is exothermic in nature and may inflict significant thermal injury [2].

\[
\text{NH}_3 + \text{H}_2 \text{O} \rightarrow \text{NH}_4^+ + \text{OH}^-
\]

NH\(_4\)OH causes severe alkaline chemical burns to the skin, eyes, and especially the respiratory system. Mild exposure primarily affects the upper respiratory tract, while more severe exposure tends to affect the entire respiratory system. The gastrointestinal tract may also be affected if ammonia is ingested [2].

Tissue damage from such bases is caused by liquefaction necrosis and penetrates far deeper than that caused by an equipotent acid. In the case of ammonium hydroxide, the tissue breakdown liberates water, thus bringing about the conversion of ammonia to ammonium hydroxide. In the respiratory tract, this results in the destruction of cilia and the mucosal barrier, leading to infection. Moreover, secretions, sloughed epithelium, cellular debris, edema, and reactive smooth muscle contractions cause significant airway obstruction. Airway epithelium can regain barrier integrity within 6 hours after exposure if the basal cell layer remains intact. However, damaged epithelium is often replaced by granular tissue, which may be one of the causes of chronic lung disease following ammonia inhalation injury [2,14].

Liquid anhydrous ammonia (-33°C) freezes tissue on contact. It is known that critical skin damage begins at -4°C and becomes irreversible at -20°C. Nevertheless, the degree of tissue injury is proportional to the duration and concentration of exposure [2].

Absorbed ammonia is well distributed throughout body compartments and reacts with hydrogen ions, depending on the pH of the compartment to produce the ammonium ions. These are endogenously produced in the gut from the bacterial breakdown of nitrogenous constituents of food. Almost all of this endogenous ammonium (approximately 99% of the 4 g produced daily) is absorbed by passive diffusion from the intestinal tract before entering the hepatic portal vein [9,13]. In the liver, ammonium ions are extensively metabolized to urea and glutamine. Consequently, levels of ammonia that reach the circulation are low [9,13]. Moreover, hepatic insufficiency could affect ammonium ion metabolism.

Ammonia reaching the circulation is excreted by humans as urinary urea [9,13]. Small amounts of ammonia are excreted via the urine; the average daily excretion for humans is approximately 2–3 μg, about 0.01% of the total body burden. Small amounts of unabsorbed ammonia may also be excreted from the gastrointestinal tract in the feces [9,13].

The major clinical effects include irritation symptoms of the eyes and the respiratory tract, as well as corrosive injuries to the skin and mucous membranes. Hypoxia and respiratory failure are common and require prompt intervention.

Health effects

Ammonia is readily absorbed through mucous membranes, especially of the gastrointestinal tract [13]. Although ammonia rapidly enters the eye, systemic absorption is considered not to be quantitatively significant [13]. Nevertheless, its main route to damage is through the respiratory system. There are hardly any systemic toxicity findings following acute skin exposure [9].

Damage to the respiratory system, the skin or other organs that come in contact with ammonia is proportional to depth of inhalation or direct contact, duration of exposure, concentration and pH of the gas or liquid. Following a short-term inhalation exposure, ammonia is almost entirely retained in the upper nasal mucosa [13]. Inhalation of high concentrations of ammonia may exceed the capacity of this mechanism, leading to systemic absorption through the lungs. The main clinical effects...
of exogenous exposure to ammonia include irritation symptoms in the eyes and the respiratory tract, and corrosive injuries to the skin and mucous membranes, including the eyes, lungs, and gastrointestinal tract [14,15]. The timing of these symptoms is in direct correlation with the concentration and length of exposure. Subsequently, the higher the exposure dose the sooner the symptoms will appear. The relationship between concentration and the corresponding effects is shown in Table 2.

Following a brief ammonia exposure, damage is generally limited to the upper airway mucosa. Brief exposures at very high concentrations, however, can be overwhelming and affect the entire respiratory system. People able to escape the affected environment are usually not subjected to severe injuries; furthermore, absence of symptoms following inhalational exposure to ammonia essentially rules out significant injury.

The clinical manifestations of acute ammonia exposure are usually immediate in presentation and its toxic effects are mediated through its irritant and corrosive properties. Ammonia is an upper respiratory tract irritant and its inhalation rapidly causes irritation to the nose, throat and respiratory tract. Increased lacrimation, coughing, an increased respiratory rate as well as respiratory distress may occur [13,16]. The retention of ammonia at low concentrations in the nasal mucosa may protect against some lung effects. Substantial exposures to concentrated aerosols of ammonium hydroxide, elevated levels of ammonia gas or anhydrous ammonia fumes can cause burns of all depths in the oral cavity, nasopharynx, larynx and trachea, together with airway obstruction, respiratory distress and pulmonary edema [9,17,18]. Exposure to a massive concentration of ammonia gas may be fatal within minutes and asphyxiation may occur after exposure in poorly ventilated or enclosed spaces. Findings in fatal cases include extensive edema, full-thickness burns to the entire respiratory tract, purulent bronchitis and greatly distended lungs [19–22]. Bronchial walls may also be stripped of their epithelial lining [23,24]. Lower levels of ammonia exposure that do not result in upper airway obstruction may cause significant alkali burns throughout the tracheobronchial tree [17].

Repeated exposures to ammonia may result in a delayed onset of adverse effects. Chronic lung disease secondary to ammonia inhalation injury have been reported in the medical literature [25] but will not be discussed in this review.

Following an ocular exposure, initial symptoms include increased production of tears, a burning sensation, blepharospasm, conjunctivitis and photophobia. At higher concentrations, corneal ulcerations, iritis, anterior and posterior synechia, corneal opacification, cataracts, glaucoma and retinal atrophy may develop [22]. Permanent eye damage occurs as a result of tissue destruction and elevations in intraocular pressure [2,26].

Gaseous ammonia combines with water of the skin, eyes and airways to form ammonium hydroxide. This exothermic reaction results in both thermal and chemical burns. Liquid ammonia freezes tissue on contact and may cause full-thickness tissue damage that penetrates deeper than the more conspicuous superficial chemical burns [2]. NH₄OH saponifies the skin, causing liquefaction necrosis and converting fatty tissue into a yellow, soapy, soft substance [26]. With severe exposure, the skin may turn black and leathery [26].

Because caustic alkali burns are generally thought to occur when pH is greater than 12.5, ammonia ingestions in the home usually do not lead to significant damage. However, Klein et al. reported three cases of oropharyngeal and esophageal injury following intentional ingestion of household solutions with a pH of less than 12 [2,27]. Clinical symptoms usually consist of oropharyngeal, epigastric and retrosternal pain. Abdominal pain and other gastroenterological symptoms may occur if ingestion causes viscous perforation (may occur up to 24–72 hours post-ingestion). On the other hand, according to Dilli and co-authors [28], ingestion of diluted ammonia may not cause visible oropharyngeal symptoms. Respiratory symptoms may be present if aspiration pneumonia or pneumonitis complicates ingestion. Smelling salts are found in many first-aid kits as a treatment for syncope (at least in the United States); unfortunately, children sometimes bite into them, resulting in minor esophageal burns and mild respiratory symptoms [2].

Systemic effects following acute exposure to high concentrations of ammonia include an elevated pulse and blood pressure, bradycardia, cardiac arrest, cyanosis and hemorrhagic necrosis of the liver [9]. Major health effects are summarized in Table 3.

### Immediate and general medical care

Evacuating the victims is one of the first steps the medical team should undertake. The on-scene caregivers should be equipped with appropriate personal protection equipment. First-aid treatment should be promptly initiated and medical advice obtained as soon as possible. The immediate care includes resuscitative support and decontamination as needed. Ammonia does not have a specific antidote, therefore treatment should be supportive.
and symptomatic. Ocular decontamination should be performed by irrigation with running water or normal saline for at least 10 minutes. Dermal decontamination should be performed by removing all soaked or contaminated clothes and washing the patient with copious amounts of running water, including the hair, skin folds and nails for at least 10 minutes or until pain ceases. In case of cutaneous burns, tetanus toxoid should be given [29-31]. Since exposure to ammonia may cause severe multisystem distress, patients with various pre-existing medical conditions are generally prone to suffer worse toxic manifestations. It is important to emphasize that in case of a toxic mass casualty event, field decontamination should not be conducted except for removing all the victims’ clothing.

Inhalational exposure
The patient should be moved into fresh air, while securing his or her airways. Humidified oxygen, 100%, should be administered as soon as possible, preferably by means of a face mask. A thorough respiratory assessment to determine both the type and extent of injuries should be performed. Cardiopulmonary resuscitation and mechanical ventilation should be initiated if necessary. Immediate referral to a pulmonologist may be required if the patient’s airway is compromised or complications such as pulmonary edema, pneumonia, hemoptysis, or respiratory failure arise [26]. Aerosolized bronchodilators, such as salbutamol (Ventolin®), may be administered as indicated to treat bronchospasm, together with corticosteroids [2,15,29]. Antibiotics and corticosteroids after ammonia inhalation and ingestion exposure are controversial therapies. Nevertheless, corticosteroids are recommended to treat bronchospasm, as mentioned above, in patients with underlying reactive airways disease and acute inhalation injury, or for chronic respiratory complications that follow an acute inhalation injury. Should the medical team choose to administer them, the recommended dose is 1–2 mg/kg/day of methylprednisolone for 3 weeks followed by gradual tapering. If antibiotics are administered, a broad-spectrum antibiotic is appropriate [2,26,29]. The patient should be kept under medical supervision for at least 48 hours and symptomatic treatment should be given as needed. Caregivers should be alert for possible secondary respiratory infection [32].

Ocular exposure
A complete ophthalmologic examination is required, including vision acuity, ocular pressure, extra-ocular eye movements, fundoscopic and slit-lamp examinations, and fluorescein testing [26]. Corneal damage is probable. Local anesthetics and cycloplegics should be used to enable thorough irrigation and examination. If the cornea is damaged, topical antibiotics may be administered. A follow-up ophthalmologic examination 24 hours after initial exposure is recommended. Treatment should be ultimately determined by an ophthalmologist [29,32].

Skin exposure
Liquid ammonia may cause deep burns (first, second or third-degree burns) that may require skin grafting. Several case reports recommend treating partial-thickness burns with daily debridement and sterile dressings [18,26,33]. Victims with frostbite should be kept warm and the affected organ should be kept at body temperature. For further treatment or in cases of extensive burns, patients should be referred to a burn treatment center [29-31].

Gastrointestinal exposure
Gastrointestinal injuries are usually the result of accidental ingestion of aqueous ammonia due to an accident or intentional water poisoning [28]. In case of ingestion, the patient should drink large amounts of water to dilute the chemical in the stomach. This should be guided not only by the level of consciousness but also by the presence of airway obstruction or imminent obstruction, and the time that has elapsed since the ingestion. No attempt should be made to induce vomiting, perform gastric lavage or use activated charcoal [29,32]. Most authorities recommend both intravenous corticosteroid and antibiotic administration to symptomatic patients following ammonia ingestion. Corticosteroids are administered to decrease the incidence and severity of esophageal strictures that occur during healing of significant alkaline injuries. Antibiotics are given because of increased risk of mediastinitis associated with full-thickness esophageal alkaline corrosive burns. Although controlled animal studies do support the use of these therapies, no well-controlled human trials have

### Table 3. Major humans health effects following acute ammonia exposure*

<table>
<thead>
<tr>
<th>System</th>
<th>Acute symptoms</th>
<th>Chronic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Burning sensation, conjunctivitis, lacrimation, saponification and liquefaction of the epithelial surfaces of the eyes, edema of the eyelids, corneal edema, corneal opacities, photophobia, increased intracranial pressure, blepharospasm, uveitis, iritis, temporary or permanent blindness</td>
<td>Vision deterioration, cataract, corneal neovascularization</td>
</tr>
<tr>
<td>Skin</td>
<td>Burns, frostbite, ulcerations</td>
<td>Dermatitis, thrombosis of superficial vessels leading to ischemia and necrosis</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>Irritation of the nasal cavities, pharynx, larynx, trachea and bronchi, dyspnea, cough, laryngospasm, edema and burns of the respiratory mucosa, hemoptysis, wheezing, chemical pneumonitis, non-cardiogenic pulmonary edema, respiratory failure</td>
<td>Chronic relapsing sinusitis, chronic cough, bronchiectasis, mediastinitis, bronchiolitis obliterans</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Nausea, vomiting, abdominal pain, epigastric tenderness, gastitis, esophageal burns</td>
<td>Pentoneal signs with viscous perforation</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Loss of consciousness, increased muscle tone, cerebral edema, seizures, coma</td>
<td>Irritability, somnolence, coma leading to death</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypovolemic shock, hypertension, myocardial infarct</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

* Ref. 13,26,32,36
<table>
<thead>
<tr>
<th>Case</th>
<th>Year and Place</th>
<th>Publication</th>
<th>Intention</th>
<th>Source</th>
<th>Route</th>
<th>Time to onset</th>
<th>Clinical manifestations</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1973, Potchefstroom, South Africa</td>
<td>Michaels RA</td>
<td>Accidental</td>
<td>38 tons of anhydrous ammonia were spilled</td>
<td>Inhalational, dermal</td>
<td>Unknown</td>
<td>Cutaneous burns, ocular lesions, damage to mucous membranes, especially to the respiratory and intestinal tracts</td>
<td>Primary treatment on scene, casualties sent to nearby hospitals</td>
<td>18 deaths</td>
</tr>
<tr>
<td>2</td>
<td>1976, Houston, Texas, USA</td>
<td>A report from a transport company in Texas</td>
<td>Accidental</td>
<td>19 tons of anhydrous ammonia were released on a highway</td>
<td>Inhalational</td>
<td>Unknown</td>
<td>-</td>
<td>-</td>
<td>6 died as a result of the accident, 78 people were hospitalized, and approximately 100 others needed medical care</td>
</tr>
<tr>
<td>3</td>
<td>1989, Jonava, Lithuania</td>
<td>Kakkonen J</td>
<td>Accidental</td>
<td>7000 tons of ammonia were spilled and released into the atmosphere. The toxic cloud covered an area of about 300 km², with the plume exceeding 32 km.</td>
<td>Inhalational</td>
<td>Immediate</td>
<td>-</td>
<td>-</td>
<td>7 people died. 67 were injured, and more than 32,000 were evacuated</td>
</tr>
<tr>
<td>4</td>
<td>1992, Dakar, Senegal</td>
<td>Woto-Gaye G</td>
<td>Accidental</td>
<td>A 24 ton ammonia storage tank exploded at a peanut factory</td>
<td>Inhalational</td>
<td>Weeks</td>
<td>Burning sensation in the eyes and the respiratory tract</td>
<td>-</td>
<td>129 people died and more than 1100 were injured</td>
</tr>
<tr>
<td>5</td>
<td>2000, Bahia Blanca, Argentina</td>
<td>Brigden K et al</td>
<td>Accidental</td>
<td>200 tons of aqueous ammonia were released from a fractured storage tank at a urea production line in a local plant. Air measurements taken after the release showed levels of 40–100 ppm of ammonia in the air (less than AEGL 2 for 60 min)</td>
<td>Inhalational</td>
<td>Immediate</td>
<td>-</td>
<td>-</td>
<td>Of 11,600 people living in the area covered by the cloud, one resident was fatally injured, 11 people sustained serious injuries, 322 people sustained minor injuries, and about 60 residents living nearby had to be rescued and evacuated</td>
</tr>
<tr>
<td>6</td>
<td>2002, Minot, North Dakota, USA</td>
<td>Railroad accident report</td>
<td>Accidental</td>
<td>About 500,000 liters of ammonia were released</td>
<td>Inhalational</td>
<td>Immediate</td>
<td>Breathing difficulties</td>
<td>-</td>
<td>20 people were injured, the severely injured casualty was in an intensive care unit for 6 weeks</td>
</tr>
<tr>
<td>7</td>
<td>2006, Be’er Tuvia, Israel</td>
<td>Dadon T</td>
<td>Accidental</td>
<td>A leak at a factory. One casualty was trapped on the roof and had to get respiratory support, resuscitation and decontamination on scene</td>
<td>Inhalational mainly</td>
<td>Variant</td>
<td>Burning sensation in the eyes and shortness of breath, treated symptomatically</td>
<td>-</td>
<td>20 people were injured</td>
</tr>
</tbody>
</table>

*Ref. [3, 21, 36-40]*
been performed; thus, corticosteroids and antibiotics should be administered in consultation with a gastroenterologist [2].

Laboratory tests
If respiratory tract irritation or respiratory depression is evident, arterial blood gases, chest X-ray, and pulmonary function tests should be undertaken. Blood amylase levels might be elevated in case of ingestion. Blood ammonia level is not a reliable measurement of the exposure severity [14,29]. However, patients with compromised hepatic function may show increased serum ammonia levels due to inefficient metabolism [2].

Case studies
In the U.S., ammonia is the third most common chemical released accidentally from manufacturing or storage facilities [34]. Unfortunately, available data on ammonia levels during an accidental release are limited, since in most cases the air concentrations were neither measured nor estimated. In addition, since in certain cases an explosion of the storage tank or fire in the nearby facilities accompanied the discharge, it was difficult to assess the damage caused by the gas leak itself. Table 4 lists several ammonia-related accidents.

In addition to the incidents mentioned above, the United Nations Environment Program Disaster Database includes other ammonia-related events (inclusion criteria: 25 deaths or more and/or 125 injured or more and/or 10,000 evacuated or more).

Summary
Ammonia is a common household and industrial chemical. In the medical literature and the electronic press there are many descriptions of accidental spills of anhydrous ammonia, but apart from the Chechen war, there is no evidence of its intentional use by a terrorist to date. When considering its characteristics, ammonia tankers may pose an imminent threat for a civilian population nearby. This short review attempts to highlight the main health issues and basic principles of medical management after exposure to ammonia.

Ammonia can directly cause damage due to its irritating as well as alkaline properties. The management of toxic exposure to ammonia is largely supportive and there is no specific antidote. Emergency medical response on site includes rapid evacuation, life-saving procedures and decontamination if necessary and if possible. Major clinical manifestations include respiratory symptoms, such as hypoxia, bronchospasm and pulmonary edema, as well as hypovolemia and burns to the skin and eyes. The immediate medical management consists of life-saving procedures and supportive care, while broad-range antibiotics and systemic corticosteroids may have a role in preventing late onset complications.

References

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Words, like eyeglasses, obscure everything they do not make clear
Joseph Joubert (1754-1824), French moralist and essayist

Capsule
A sensitive test for HIV

Using a highly sensitive procedure for the detection of proteins, Kim and colleagues report an enhanced diagnostic test for the presence of HIV in human plasma. In their approach, the HIV p24 Gag protein was trapped between magnetic microparticles, which had been functionalized with sheep antibodies to p24, and gold nanoparticles, which had been decorated with a mix of mouse antibodies directed against p24 or a DNA bar code. The microparticles were then removed from solution magnetically, and the associated DNA was quantified. The sensitivity of this method was an order of magnitude greater than that of standard enzyme-linked immunosassays; the particle-based analysis was performed in solution, which allowed for homogeneous mixing and improved binding kinetics. Furthermore, careful design of the peptides used to raise the mouse and sheep antibodies enabled detection of the six most prevalent HIV subtypes.

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