

Inhalation Lung Injuries

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LEARNING OBJECTIVES

1. Distinguish the differences in pathophysiology between acute and chronic inhalation lung injury (ILI).
2. Assess the differences in nebulized anticoagulant therapies for the treatment of ILI and compare with established agents to treat ILI.
3. Assess the place in therapy of corticosteroids in the treatment of ILI.
4. Evaluate the evidence for antibiotic use for acute ILI.
5. Evaluate the challenges in developing pharmacologic therapies for acute and chronic ILI.

ABBREVIATIONS IN THIS CHAPTER

aPTT	Activated partial thromboplastin time
CO	Carbon monoxide
COHb	Carboxyhemoglobin
EVALI	E-cigarette or vaping product use-associated lung injury
ILI	Inhalation lung injury
metHb	Methemoglobin
PAFR	Platelet-activating factor receptor
TBSA	Total body surface area
THC	Tetrahydrocannabinol
VEA	Vitamin E acetate

[*Table of other common abbreviations.*](#)

INTRODUCTION

Inhalation lung injury (ILI) can result in local or systemic pathophysiology. Local injury to lung tissue may occur in the setting of thermal or chemical exposure as well as secondary inflammation. In the case of smoke inhalation, direct chemical irritants may include ammonia, hydrogen chloride, and aldehydes (Mintegi 2013). Systemic effects occur secondary to exposure to toxins such as carbon monoxide (CO) and hydrogen cyanide, as well as to bacterial infection (Sheridan 2016). Morbidity and mortality can vary significantly based on concurrent injuries and risk factors.

In children of all ages, fire-related mortality is primarily the result of injuries caused by smoke inhalation rather than burns (Mintegi 2013). Inhalation injuries occur in 20%–30% of pediatric burn patients, and those who experience inhalation injuries in addition to cutaneous burns have higher resuscitation fluid requirements, increased pulmonary complications, and higher mortality rates (Miller 2014). Mortality in pediatric burn patients with concurrent ILI has been reported to be 16%, increasing to 25%–50% when patients require mechanical ventilatory support for more than 1 week. In addition, children younger than 4 years are at higher risk of mortality compared with older patients (Sen 2017). Inhalation lung injuries can be further classified into acute or chronic exposures (Megarbane 2013).

ACUTE ILI

Pathophysiology of Fire-Related ILI

Upper Airway Injury

Thermal injury is usually confined to the supraglottic airway because the glottis reflexively closes to prevent thermal injury to the lower airways (Sheridan 2016). However, thermal injuries to the lower airways are possible in the case of high humidity inhalation, most often with steam inhalation. Similar to skin burns, thermal injuries from hot

air can damage the epithelium in the oropharynx and cause erythema, ulceration, and edema (Sen 2017). Results of these injuries include increased capillary permeability at the site of injury as well as in distal airways. In the case of fire-related inhalation injuries, severe pulmonary edema can occur because of the combination of burn and smoke inhalation injuries. This pulmonary edema results in pulmonary microvascular hyperpermeability to fluids and protein by direct and indirect mechanisms of injury (Enkhbaatar 2004).

Lower Airway Injury

Inhalation lung injury caused by chemical exposure depends on the type and size of the inhaled toxicant. Larger particles (2.5–6 μm) settle into the upper bronchial tree, whereas smaller particles (less than 2.5 μm) can reach the alveoli (Megarbane 2013). The immune response associated with ILI has been studied mainly in smoke inhalation injuries, in which increased alveolar neutrophil activity has been identified and may be associated with additional epithelial and alveolar damage (Albright 2012).

Epithelial injury from smoke inhalation results in extravasated neutrophils, which, in combination with fibrin, mucus, and epithelial cell debris, form obstructive casts in the airways, resulting in local hypoventilation. As cast formation develops, healthy lung areas that are not obstructed may experience subsequent indirect alveolar damage by volutrauma because of preferential ventilation to these regions. In the setting of volutrauma, overstretched alveoli release interleukin-8, a major chemokine for neutrophils, further increasing inflammation and cast formation in areas not directly injured by smoke inhalation (Enkhbaatar 2004). A study by Albright et al. analyzed the bronchoalveolar lavage fluid of 60 adult burn survivors and found that patients

with higher degrees of ILI had a neutrophil predominance and higher interleukin-8 levels. The authors concluded that this finding may explain late effects of immune dysfunction, bacterial overgrowth, and pneumonia in smoke ILI (Albright 2012).

Ventilation is further compromised by atelectasis secondary to surfactant inactivation after smoke inhalation of combustible agents (Nieman 1980). In a small case series, intrabronchial administration of exogenous surfactant in adult patients with severe burns and acute respiratory distress syndrome resulted in temporary improvements in lung compliance and decreased fraction of inspired oxygen (FiO_2) requirements (Pallua 1998). Similarly, the effect of exogenous surfactant administration was assessed in a case series of seven pediatric burn patients, four of whom had confirmed ILI. Four of the seven patients survived to discharge, two of whom had confirmed ILI. All patients who survived had lower FiO_2 requirements the day after surfactant administration and received surfactant earlier in their course of illness (mean time to administration 4.8 ± 0.9 vs. 17.7 ± 8 days) (Sen 2012). Limited conclusions may be drawn because of the baseline characteristics of the patients who survived and the small size of the case series; however, timing of the intervention may be important. Further studies are needed to determine whether exogenous surfactant has a place in therapy for inhalation injuries.

In addition to upper and lower airway injuries, inhalation lung injuries can be associated with acute systemic toxicity. Two common inhaled toxicants associated with inhalation injuries, carbon monoxide and hydrogen cyanide, will be discussed next.

Systemic Toxicity

Carbon Monoxide

Carbon monoxide (CO) poisoning is the leading cause of poisonings in children (Sethuraman 2020). Annually, in the United States, CO poisoning accounts for 40,000–50,000 cases and 15,200 ED visits (Sethuraman 2020; Damlapinar 2016). Exposure to CO is generally accidental and associated with the use of furnaces, radiators, and indoor heating units, with most cases occurring in the winter months. Carbon monoxide toxicity due to smoke inhalation in enclosed fires is less common but is associated with higher carboxyhemoglobin (COHb) (Sethuraman 2020).

The affinity of CO to hemoglobin is 200-fold higher than that of oxygen. Thus, even at low concentrations, when CO is inhaled it rapidly diffuses through the alveolar membrane and binds to hemoglobin, resulting in COHb (Lentz 1997). The binding of CO to hemoglobin results in a conformational change in hemoglobin and drives the oxygen dissociation curve to the left, thus binding oxygen more tightly and resulting in tissue hypoxia (Damlapinar 2016). Mild CO toxicity has nonspecific symptoms and may be confused with viral illnesses. However, severe CO poisoning, commonly defined

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the lung and alveolar anatomy
- Management of community-acquired pneumonia in pediatric patients

[*Table of common laboratory reference values.*](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Infectious Diseases Society of America. [The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age](#) Clin Infect Dis 2011;53:e25-76.

as a COHb concentration exceeding 25%, is associated with signs and symptoms of anoxia and end organ dysfunction, including loss of consciousness, seizures, and cardiac abnormalities secondary to myocardial ischemia (Box 1) (Sethuraman 2020; Damlapinar 2016). The management goal for CO poisoning is to displace CO from hemoglobin with oxygen. This goal is achieved by administering 100% oxygen, which is the mainstay of therapy (Lentz 1997). Hyperbaric oxygen therapy may be considered for patients who present with symptoms of severe CO poisoning, but barriers include the limited availability of hyperbaric treatment chambers and the difficulty of transporting the patient between the hyperbaric treatment chamber and the ICU (Sethuraman 2020).

Hydrogen Cyanide

The most common route of exposure to hydrogen cyanide in humans is by inhalation secondary to residential fires. Hydrogen cyanide gas is released after the combustion of several household items including many plastics (polyurethane and polyacrylonitrile) and fabrics (nylon, silk, and wool) (Geller 2006). It is estimated that burning 2 lbs of polyacrylonitrile in an average-size living room may achieve a lethal concentration of cyanide gas (Baud 1991). The blood concentrations at which cyanide is toxic or fatal are not well defined because of the rapid clearance in the blood as well as variability in type of exposure, sample collection methods, and delayed sampling times, all of which may significantly impact

cyanide values (Geller 2006). In general, in adults cyanide concentrations higher than 1 mg/L (39 μmol/L) are considered toxic, whereas concentrations greater than 2.6–3 mg/L (100–115 μmol/L) have been reported to be fatal. In a study by Baud et al. of 30 pediatric patients who were injured by fire, blood samples were collected at the scene of the fire. The 13 patients who died had higher cyanide blood concentrations compared with the survivors (87.0 ± 76.1 vs. 27.4 ± 53.0 μmol/L, $p < 0.01$) (Baud 2002).

Cyanide causes elevated serum lactate concentrations by several pathways including precipitation of bradycardia, hypotension, heart failure, apnea, catecholamine release, and seizures. However, the primary toxicity from cyanide occurs in the mitochondria. Cyanide inhibits mitochondrial oxidative phosphorylation by binding to the ferric ion of cytochrome a3, resulting in noncompetitive inhibition of the cytochrome-C oxidase complex. This inhibition prevents cells from using oxygen and forces a transition to anaerobic metabolism (Baud 2002). Signs and symptoms of cyanide toxicity vary by timing and exposure, and diagnosis may be difficult, particularly in the case of smoke inhalation with burn injuries. Early signs and symptoms of low-grade toxicity may include agitation and confusion, whereas late signs of toxicity are associated neurologic impairment, cardiovascular compromise, and metabolic acidosis (Table 1) (Geller 2006; Mintegi 2013). In the context of smoke inhalation without severe burn injuries, serum lactate concentrations exceeding 10 mmol/L have a sensitivity of 87% and a specificity of 94% for cyanide toxicity with a positive predictive value of 95% (Baud 1991). For survivors of enclosed fires where severe cyanide toxicity is suspected because of clinical presentation, treatment of cyanide toxicity should be considered and should not be delayed while awaiting laboratory confirmation (Mintegi 2013).

In addition to supportive therapy including administration of 100% oxygen, several agents can be used when severe cyanide toxicity is suspected (Table 2). Of these agents, only two products are available in the United States, and only one agent is approved in children.

A combination of sodium nitrite and sodium thiosulfate is available as a kit and has FDA approval for the treatment of life-threatening cyanide toxicity in children. According to the manufacturer's package insert, the primary mechanism of sodium nitrite is the oxidation of hemoglobin to form methemoglobin (metHb). Although metHb is not capable of oxygen transport, it has a high affinity for cyanide; metHb then competes with cytochrome oxidase to bind cyanide and form non-toxic cyanomethemoglobin. Sodium nitrite also causes significant vasodilation, a possible secondary mechanism of action to treat cyanide toxicity. This secondary mechanism is supported by decreased cyanide toxicity after sodium nitrite administration, even when methylene blue was used to prevent metHb formation. In addition, compared with other oxidants that do not cause vasodilation, sodium nitrite results

Box 1. Carbon Monoxide Toxicity Signs and Symptoms

Mild (carboxyhemoglobin <25%)

- Tachycardia
- Nausea and vomiting
- Dizziness
- Headache
- Flu-like symptoms
- Weakness
- Somnolence

Severe (carboxyhemoglobin ≥25%)

- Syncope
- Loss of consciousness
- Seizure
- Focal neurologic deficits
- Myocardial ischemia (ECG changes)
- Elevated lactate
- Respiratory failure
- Coma
- Death

Information from: Sethuraman KN, Douglas TM, Bostick BB, et al. Clinical characteristics of pediatric patients with carbon monoxide poisoning. *Pediatr Emerg Care* 2020;36:178-81; Damlapinar R, Arikani FI, Sahin S, et al. Lactate level is more significant than carboxyhemoglobin level in determining prognosis of carbon monoxide intoxication of childhood. *Pediatr Emerg Care* 2016;32:377-83.

Table 1. Hydrogen Cyanide Toxicity Signs and Symptoms

Organ System	Early Signs and Symptoms	Late Signs and Symptoms
Neurologic	Headache, agitation, confusion	Seizures, mydriasis, coma, hypoxic brain injury
Cardiovascular	Tachycardia, myocardial ischemia (ECG changes), AV block	Bradycardia, hypotension, cardiovascular collapse
Respiratory and metabolic	Tachypnea, hyperglycemia	Apnea, metabolic acidosis, lactate >8 mmol/L

Information from: Baud FJ, Barriot P, Toffis V, et al. Elevated blood cyanide concentrations in victims of smoke inhalation. *N Engl J Med* 1991;325:1761-6; Baud FJ, Borron SW, Megarbane B, et al. Value of lactic acidosis in the assessment of the severity of acute cyanide poisoning. *Crit Care Med* 2002;30:2044-50; Geller RJ, Barthold C, Saiers JA, et al. Pediatric cyanide poisoning: causes, manifestations, management, and unmet needs. *Pediatrics* 2006;118:2146-58; Mintegi S, Clerigue N, Tipo V, et al. Toxicology Surveillance System of the Intoxications Working Group of the Spanish Society of Paediatric, E. Pediatric cyanide poisoning by fire smoke inhalation: a European expert consensus. *Toxicology Surveillance System of the Intoxications Working Group of the Spanish Society of Paediatric Emergencies. Pediatr Emerg Care* 2013;29:1234-40.

in better outcomes at comparable metHb levels (Mintegi 2013; Geller 2006).

It is estimated that metHb concentrations of 20%–30% are necessary to appropriately compete for cyanide; however, specific metHb concentrations should not be targeted as a therapeutic goal because of risk of fatal methemoglobinemia and because the therapeutic effects of sodium nitrite are only partially attributable to formation of metHb. Concentrations of metHb should be monitored after sodium nitrite administration, and treatment should be discontinued for metHb concentrations greater than 30%. Administration of methylene blue and/or exchange transfusion should be considered if toxic metHb concentrations are a concern (Mintegi 2013). Additional caution is warranted in patients with smoke inhalation who present with high levels of COHb because sodium nitrite administration may result in lethal concentrations of non-oxygen-carrying metHb (Mintegi 2013; Geller 2006). The risk of nitrite-induced methemoglobinemia may be higher in infants and young children because fetal hemoglobin is oxidized faster than hemoglobin and metHb reductase activity is lower compared with adults (Geller 2006). Lastly, dose adjustments for lower hemoglobin levels and renal impairment should be considered per manufacturer recommendations.

According to the manufacturer's package insert, sodium thiosulfate should be administered after administration of sodium nitrite. Cyanide can be converted to a less toxic compound, thiocyanate, by rhodanese, which is a mitochondrial thiosulfate sulfurtransferase. Sodium thiosulfate acts as a sulfur donor to increase the rate of rhodanese-catalyzed cyanide to thiocyanate transformation. In canine studies, administration of sodium thiosulfate resulted in a 30-fold increase in the rate of conversion from cyanide to thiocyanate. Sodium thiosulfate is generally well tolerated with mild adverse effects. As a result, it may be tempting to use sodium

thiosulfate as monotherapy for cyanide toxicity, but the time needed to distribute into the mitochondria and exert its therapeutic effect may not be appropriate as a single agent for the treatment of severe cyanide toxicity (Mintegi 2013).

Hydroxocobalamin has FDA approval for the treatment of cyanide toxicity in adults. It binds cyanide to form vitamin B12 (cyanocobalamin), which is non-toxic and renally excreted. Following administration of hydroxocobalamin, transient staining of body fluids, including, but not limited to, urine, saliva, lacrimal, and sweat gland secretions is possible because of its bright red color. In addition, hydroxocobalamin administration may be temporarily affect colorimetric assays, such as chemistry, hematology, coagulation, and urine (Geller 2006). According to the manufacturer, interference can be expected for up to 48 hours for most studies, except for bilirubin (up to 4 days) and urine (up to 28 days) studies.

A prospective, open-label clinical trial by Borron et al. assessed the outcomes of hydroxocobalamin in 69 adults treated for suspected cyanide toxicity secondary to smoke inhalation. Cyanide levels were collected before administration of hydroxocobalamin. Overall, 50 patients (72%) survived after empiric hydroxocobalamin administration. Of the 42 patients who had confirmed cyanide toxicity, 28 patients (67%) survived. Potentially lethal concentrations were identified in 19 patients, 11 of whom survived (58%). Of importance, of the 15 patients who experienced cardiac arrest at the scene, only 2 (14%) survived (Borron 2005). Pediatric data for hydroxocobalamin are limited in the United States, but this agent has been approved for pediatric use in France since 1996. In a patient case series of 41 French children (median age 5 years) with fire-related smoke injuries, overall survival after hydroxocobalamin was 56% (23 patients). Similar to results for the adult study by Borron et al., survival was highest (95%) among the 23 children who

Table 2. Antidotes for Severe Cyanide Toxicity in Children

Agent	Mechanism of Action	Dosing	Adverse Reactions	Clinical Pearls
Sulfur Donors				
Sodium thiosulfate (available as a kit) ^a	Sulfur donor for rhodanese-catalyzed transformation of cyanide to thiocyanate	250 mg/kg IV (1 mL/kg/dose or 30–40 mL/m ² of 25% solution) Maximum, 12.5 g	Hypotension, GI upset, headache	Administer immediately after sodium nitrite Chemically incompatible with hydroxocobalamin
Nitrites				
Sodium nitrite (available as a kit) ^a	Oxidizes Hb to form methHb; methHb competes with cytochrome oxidase to bind cyanide ion	6 mg/kg IV (0.2 mL/kg or 6–8 mL/m ² of 3% solution) Maximum, 300 mg	Vasodilation, hypotension, excessive methHb	Use with caution in smoke inhalation because of concurrent risk of COHb Children may be at higher risk of fatal methemoglobinemia Dose decreases may be needed in anemia or renal impairment
Cobalt Compounds				
Hydroxocobalamin	Binds cyanide to form cyanocobalamin	70 mg/kg IV Maximum, 5 g	Erythroderma, hypertension, nephrolithiasis Colorimetric assay interference (red color) Discoloration of mucus membranes and urine	Licensed for adults in United States May repeat dose, if needed Chemically incompatible with sodium thiosulfate
Dicobalt edetate ^b	Cyanide chelator	4 mg/kg IV; must be followed by 25% dextrose: < 2 yr: 25 mL > 2 yr: 50 mL	Vomiting, hypotension, anaphylaxis, ventricular arrhythmias	Dextrose may prevent free cobalt ion toxicity

COHb = carboxyhemoglobin; Hb= hemoglobin; IV= intravenously; methHb= methemoglobin.

^aCommercially available kit contains 1 vial of sodium nitrite 3% (300 mg/10 mL) and 1 vial of sodium thiosulfate 25% (12.5 g/50 mL). Note that dosing units can be expressed in mg/kg, mL/kg, and mL/m².

^bDicobalt edetate is not available in the United States and has limited international availability.

Information from: Geller RJ, Barthold C, Sainers JA, et al. Pediatric cyanide poisoning: causes, manifestations, management, and unmet needs. *Pediatrics* 2006;118:2146-58; Mintegi S, Clerigue N, Tipo V, et al. Toxicology Surveillance System of the Intoxications Working Group of the Spanish Society of Paediatric, E. Pediatric cyanide poisoning by fire smoke inhalation: a European expert consensus. *Toxicology Surveillance System of the Intoxications Working Group of the Spanish Society of Paediatric Emergencies. Pediatr Emerg Care* 2013;29:1234-40.

received hydroxocobalamin but did not experience cardiac arrest (22 patients), whereas the 18 children who received hydroxocobalamin and experienced a cardiac arrest had a survival rate of 6% (1 patient) (Borron 2007a; Geller 2006).

In patients with cyanide toxicity who have not experienced cardiac arrest, hydroxocobalamin may be an ideal agent.

Additional data are available for the use of hydroxocobalamin for cyanide toxicity caused by ingestion or inhalation.

A case series of 14 adults with non-accidental cyanide exposure describes the effects of hydroxocobalamin. Overall, 10 patients (71%) survived after hydroxocobalamin administration. Blood cyanide levels exceeding lethal concentrations were identified in 11 patients, 7 of whom survived after hydroxocobalamin administration. Adverse events included discoloration of the skin (3 patients) or urine (5 patients), tachycardia (1 patient), and hypertension (1 patient) (Borron 2007b). A small case series of 8 children with cyanide poisoning secondary to bitter cassava ingestion included 4 patients treated with hydroxocobalamin and 4 patients treated with a combination of sodium nitrite and sodium thiosulfate. All patients in the case series survived (Espinoza 1992).

Although hydroxocobalamin is generally well tolerated, infusion reactions are the most common adverse effect, particularly with rapid infusions (15 minutes). Rapid administration should be reserved for patients in extremis or other life-threatening situations, whereas more stable patients may better tolerate a 2-hour infusion. Of note, hydroxocobalamin is chemically incompatible with sodium thiosulfate. If both cyanide antidote kits available in the United States are used concurrently, hydroxocobalamin should be administered through a separate intravenous line (Mintegi 2013).

Other adverse effects of hydroxocobalamin include hypertension and acute tubular necrosis. A case report of an accidental 5-fold overdose in a pediatric patient resulted in transient bradycardia and hypertension, which resolved without intervention (Friedman 2019). Acute tubular necrosis secondary to calcium oxalate crystals was identified in post-marketing surveillance. Legrand et al. evaluated 19 adult burn patients (median age 50 years) who received hydroxocobalamin compared with 80 patients who did not. Patients in the hydroxocobalamin cohort had a higher likelihood of acute kidney injury (OR 5.8; 95% CI, 1.6–20.7) and need for renal replacement therapies (OR 4.3; 95% CI, 1.09–17). This effect persisted after adjusting for burn severity (Legrand 2016). Considering less severe toxicities compared with potentially life-threatening toxicities associated with nitrite therapy, hydroxocobalamin may be a reasonable first choice for the treatment of cyanide toxicity in children.

Dicobalt edetate is a cobalt compound that chelates cyanide to form a relatively non-toxic ion complex. This agent is not available in the United States, and no clinical trials are open as of November 2021. Where available, dicobalt edetate is generally reserved for treatment of proven cyanide toxicity because it is associated with risk of cobalt toxicity. This risk increases when the serum concentration of cyanide is too low to bind free cobalt ions, a common contaminant of dicobalt edetate. Serious adverse effects include hypotension, anaphylaxis, and ventricular arrhythmias. Dextrose may prevent free cobalt ion toxicity and should be administered concomitantly (Mintegi 2013; Geller 2006).

CHRONIC ILI

The use of electronic cigarettes, or vaping, has dramatically increased among children and adolescents in the past decade. A monitoring survey that screens for nicotine use in children and adolescents in grades 8, 10, and 12 found virtually no vaping use in 2011; in contrast, vaping accounted for most of the nicotine use in 2017. The same survey, conducted just 1 year later, found an increase in nicotine use from 23.7% to 28.9% in adolescents in grade 12 in 2018. This increase accounts for an additional 1.3 million adolescents who vaped in 2018 compared with 2017, the highest absolute increase in nicotine use in the 44-year history of the survey (Miech 2019). The prevalence of vaping among children and adolescents differs by gender and race, with greater use among boys and Hispanic or non-Hispanic white children (Krishnasamy 2020; National Academies of Sciences, Engineering, and Medicine 2018). E-cigarettes contain liquids that are aerosolized for inhalation, usually by an atomizer heating coil. Liquids that contain nicotine are considered tobacco products and are regulated by the FDA Center for Tobacco Products. It is possible that some nicotine-free products may be within the jurisdiction of the FDA; however, liquids containing tetrahydrocannabinol (THC) remain largely unregulated because of its Schedule I status in the Controlled Substance Act (National Academies 2018).

Although vaping products may have less toxicants than combustible tobacco cigarettes, e-cigarette liquid (e-liquid) generally contains four main constituents: nicotine and/or other psychoactive drugs, flavorings, water, and carrier liquids (humectants). Some of these constituents may have negative health effects. For example, typical humectants used in e-liquids include propylene glycol and glycerol. When these carriers are heated, they form volatile carbonyls, including formaldehyde, acetaldehyde, and acrolein. In addition, propylene glycol and glycerol also have hygroscopic properties that may increase the risk of viral and bacterial infections by dehydrating the airways, resulting in thickened airway mucus, airway obstruction, and increased inflammation (Hage 2020; National Academies 2018).

In addition to the components discussed previously, e-cigarette aerosols contain heavy metals, including nickel, tin, and lead, likely because of contamination from the metal coil used to heat the e-liquid. Redox-active metals from e-cigarette aerosols promote the formation of reactive oxygen species and have been shown to induce acute endothelial cell dysfunction (Hage 2020; National Academies 2018).

Additionally, the oxidative stress in airway cells up-regulates platelet-activating factor receptor (PAFR) expression. In human respiratory tract epithelial cells exposed to cigarette smoke, *Haemophilus influenzae* and *Streptococcus pneumoniae* use PAFR as an adhesion site to anchor to the airway epithelial cells resulting in enhanced bacterial colonization. In the setting of up-regulated PAFR expression, PAFR antagonists are a promising drug class to prevent bacterial

infections (Shukla 2016). To date, there are no open clinical trials for PAFR antagonists. E-cigarette vapor has been associated with additional bacterial effects. Gilpin et al. evaluated the in vitro inflammatory potential and virulence of *H. influenzae*, *S. pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* after exposure to e-cigarette vapor compared with non-exposed bacteria. Bacteria exposed to e-cigarette vapor had higher biofilm production and cytokine secretion, including interleukin-8 and tumor necrosis factor- α (Gilpin 2019).

E-Cigarette or Vaping Product Use-Associated Lung Injury

In 2019, the FDA and local health agencies began investigating a nationwide outbreak of e-cigarette or vaping product use-associated lung injury (EVALI). Data reported to the CDC from August 2019 to January 2020 included 2668 patients who required hospitalization because of EVALI. Although the median age was 26 years, pediatric patients (age 13–17 years) accounted for 15% of all cases (Siegel 2019, Gonsalves 2021). As of February 2020, 68 EVALI-related deaths had been reported (Reddy 2021). The demographics of EVALI mirror those for vaping, with most patients being male (66%) and Hispanic or non-Hispanic white (88%). Most patients (82%) reported at least some use of THC-containing products, whereas 14% reported exclusive use of nicotine-only products (Krishnasamy 2020).

Blount et al. analyzed the bronchoalveolar lavage (BAL) fluid of 51 patients with suspected EVALI and compared these findings with BAL samples from 99 healthy controls. The BAL samples for patients with EVALI showed the presence of vitamin E acetate (VEA) in 94% of samples, whereas VEA was not detected in the control samples. With the exception of coconut oil and limonene, which were identified in 2 BAL samples from the EVALI group, no other toxicants were identified. It is theorized that VEA diminishes the ability of lung surfactant to hold surface tension by penetrating the surfactant layer and changing it from a gel to a liquid. In addition, when VEA is heated, ketene is produced, which can be a direct lung irritant at high concentrations. Vitamin E acetate is not routinely used as a carrier for nicotine-only products because propylene glycol and glycerol have a preferred viscosity profile and VEA is considered too viscous. However, unregulated and THC-containing products have been particularly linked to EVALI because VEA is often used to adulterate pure THC oil based on their similar viscosity profile (Blount 2020).

Diagnosis of EVALI is difficult because it is a diagnosis of exclusion and can present with nonspecific symptoms. In a case series of 12 patients, 58% of patients who eventually received a diagnosis of EVALI had prior contact with a health care provider, and 17% received an antibiotic before hospital admission (Kalininskiy 2019). In larger case series, 323 of 339 (95%) patients who were admitted for EVALI had respiratory symptoms, defined as shortness of breath, chest pain, and/or cough. Gastrointestinal symptoms, including abdominal

pain, nausea, vomiting, and diarrhea were reported in 77% of admitted patients, whereas constitutional symptoms, including fevers, chills, and weight loss, were reported in 85% of patients (Siegel 2019). Onset of symptoms tends to be gradual over several days to weeks (Blount 2020). Radiologic findings can be varied and are summarized in Table 3 (Hage 2020). In general, basilar consolidations and ground glass opacities caused by diffuse alveolar damage, pneumonitis, or organizing pneumonia can be visualized on imaging. If these findings are observed, vaping history should be obtained and EVALI may be considered as a diagnosis (Blount 2020; Hage 2020).

Laboratory work-up for EVALI should be tailored based on patient presentation. Infectious work-up should be pursued, including obtaining a respiratory virus panel. This viral panel should include influenza during the influenza season. Because of the high prevalence of concurrent pneumonia associated with EVALI, cultures should also be ordered for typical community acquired pathogens, atypical bacteria, and opportunistic infections, whenever possible. In areas where fungal infections are prevalent, additional work up should be pursued.

Table 3. Interstitial Radiologic Findings and Disease Patterns in EVALI

Radiologic Finding	Interstitial Pattern
Ground glass opacities	Diffuse alveolar hemorrhage Acute eosinophilic pneumonia Organizing pneumonia Giant-cell interstitial pneumonia Acute lipid pneumonia
Consolidations	Diffuse alveolar hemorrhage Organizing pneumonia Acute lipid pneumonia
Pleural effusions	Hypersensitivity pneumonitis Acute eosinophilic pneumonia
Interlobular septal thickening	Hypersensitivity pneumonitis Acute lipid pneumonia
Signs of air trapping	Bronchiolitis
Poorly defined pulmonary nodules	Respiratory bronchiolitis–associated interstitial lung disease
Traction bronchiectasis	Giant-cell interstitial pneumonia

EVALI = E-cigarette or Vaping product use-Associated Lung Injury.

Information from: Hage R, Schuurmans MM. Suggested management of e-cigarette or vaping product use associated lung injury (EVALI). *J Thorac Dis* 2020;12:3460-8.

Patients with EVALI may have elevated inflammatory markers. In a large case series, leukocytosis (white blood cell count greater than 11×10^3 cells/mm³) was observed in 93% of patients, with 50% of patients demonstrating transaminitis. In patients for whom EVALI is suspected but no history suggests use of vaping products, toxicology testing for THC should be considered to assess exposure. These laboratory tests alone are not enough to diagnose EVALI but may be helpful for establishing a baseline and monitoring therapeutic progress (Siegel 2019).

Data for the management of EVALI are currently limited to case series with CDC guidance recommending initiation of corticosteroids and antimicrobials (Siegel 2019). In pediatric patients, methylprednisolone at doses of 1–2 mg/kg/dose (maximum dose 60 mg) every 6–12 hours have been used. Treatment duration varies but is generally 5 days of high-dose methylprednisolone followed by a 14- to 21-day taper (Reddy

2021). Initiation of corticosteroids may be withheld if a concern for primary infectious etiologies is present, particularly in cases of fungal infection (Hage 2020).

Early initiation of antimicrobials should be considered when appropriate. Antimicrobial coverage for community-acquired pneumonia should be tailored using clinical guidelines and local antibiograms. During influenza season, consider starting influenza antivirals until influenza can be ruled out (Siegel 2019). Management of EVALI should also include strategies for smoking cessation. Discontinuation of e-cigarette use may allow for a faster recovery from EVALI by eliminating a significant source of pathology, whereas resuming vaping products may cause symptom recurrence and additional lung injury (Hage 2020; Siegel 2019).

Patient Care Scenario

V.E. is a previously healthy 17-year-old male adolescent (weight 82 kg) who is evaluated by his pediatrician for emesis, diarrhea, shortness of breath, and fever. A diagnosis of community-acquired pneumonia is made, and antibiotics are prescribed. Today, 5 days after his pediatrician visit, he presents to the ED. Vital signs are axillary temperature 101°F (38.2 °C), blood pressure 110/80 mmHg, heart rate 140 beats/minute, and respiratory rate of 24 breaths/minute; oxygen saturation by pulse oximetry is 86% on room air.

Laboratory test results are negative for coronavirus disease 2019 PCR and a respiratory viral panel that

Question:

Which of the following is the most appropriate therapy for EVALI in this patient?

- A. Oseltamivir 75 mg by nasogastric tube every 12 hours
- B. Methylprednisolone 1000 mg intravenously every 24 hours for 3 days

includes influenza A/B, respiratory syncytial virus, human metapneumovirus, human rhinovirus, adenovirus, and parainfluenza 1,2,3,4. Blood, urine, and respiratory cultures show no growth to date at 48 hours. Chest radiography shows bilateral lower lobe opacities, and chest CT reveals diffuse ground glass opacities.

V.E. is admitted to the pediatric ICU for noninvasive positive-pressure ventilation. Additional history reveals that V.E. has been “vaping” by using several products and devices. He reports daily use of tetrahydrocannabinol and nicotine over the past 6 months. Over the next 12 hours, V.E.’s respiratory distress worsens, and he is intubated.

- C. Methylprednisolone 60 mg intravenously every 12 hours
- D. Immune globulin 2 g/kg intravenously for 1 day

ANSWER: C

No standard treatment exists for EVALI; however, steroids, antibiotics, and ventilatory support are appropriate empiric treatment modalities. Several case reports have shown improvement with corticosteroids, likely resulting from blunting of the inflammatory response associated with EVALI.

Because of lack of an established standard of care for EVALI, several corticosteroid regimens have been reported for the management of EVALI, with most regimens using methylprednisolone at doses of 1–2 mg/kg/

dose (maximum dose 60 mg) every 6–12 hours. Doses as high as 500 mg/day have been reported for the management of EVALI.

Interim guidance from the U.S. Department of Health and Human Services recommends that providers consider empiric use of antibiotics and antivirals based on the clinical context. For this patient, viral panel and influenza test results are negative; thus, oseltamivir is not indicated. Intravenous immune globulin has not been routinely used for management of EVALI.

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THERAPIES FOR ILI

Intra-Alveolar Anticoagulation/Fibrinolysis

Airway casts are formed when sloughed airway cells combine with mucus, inflammatory cells, and fibrin, leading to significant airway obstruction (Dries 2013). In addition to causing chemokine activation and airway obstruction, fibrin casts bind surfactant phospholipids and fatty acids because of the high affinity of fibrin for these components. The combined effect is loss of surface tension and atelectasis. The fibrin in airway casts is of particular interest because it can be targeted with pharmacologic agents (Enkhbaatar 2009; Seeger 1993). As a result, fibrin has been a target for therapies in inhalation smoke injuries.

Tissue plasminogen activator (tPA) is a fibrinolytic that has been studied in pre-clinical models of burns and smoke inhalation and showed temporary increases in pulmonary function. Other agents that have been studied in combination with tPA include antithrombin (AT), which acts as an anti-inflammatory agent by inhibiting neutrophil activation, and heparin, an anticoagulant that inhibits fibrin cast formation. In animal models, pulmonary function outcomes seem to be synergistic when all three agents (tPA, AT, and heparin) were used together. However, pediatric data are limited for the use of tPA and AT for this indication (Rehberg 2014).

Desai et al. evaluated the effect of heparin in combination with acetylcysteine, a mucolytic agent, in 47 children with confirmed burns and ILI requiring mechanical ventilation (Desai 1998). Patients received nebulization treatments with heparin 5000 units alternating with 3 mL of 20% acetylcysteine every 2 hours compared with a historical control group of 43 patients. Fewer patients in the treatment group experienced atelectasis compared with the control group (42% vs. 69%, $p < 0.05$). The effects of heparin plus acetylcysteine may go beyond atelectasis prevention. Patients who received heparin and acetylcysteine had lower reintubation rates (6% vs. 28%, $p < 0.05$) and duration of mechanical ventilation was shorter but not statistically significant (81 vs. 187 hours) compared with the control group. The treatment group also had a lower mortality compared with the control group (4% vs. 19%, $p < 0.05$) (Desai 1998). The combination of heparin and acetylcysteine has not been associated with improving clinical outcomes such as reducing the length of ventilation in the adult literature, although the combination has demonstrated a mortality benefit in some studies it is possible that different dosing regimens may have different effects (Miller 2014; Holt 2008; Elsharnouby 2014).

Anticoagulation with systemic heparin has been associated with bleeding; however, data are limited for evaluating the safety of nebulized heparin in ILI. Systemic absorption of nebulized medications by bronchial airway and alveoli is possible. Studies in healthy adults suggest that nebulized heparin does not result in clinically significant changes in coagulation variables such as activated partial thromboplastin time

(aPTT); however, it is unclear if heparin absorption is different in patients with burns or inhalation injuries (Chopra 2011; Yip 2011). A retrospective cohort study by Yip et al. evaluated the safety of nebulized heparin in 52 adult patients who required intubation after ILI compared with a historic control group (11 patients) without exposure to nebulized heparin (Yip 2011). Patients were excluded if they had any history of bleeding or pulmonary hemorrhage or if they received concomitant systemic anticoagulation. The investigators collected coagulation values, including aPTT and platelet count, and monitored for bleeding events documented in the progress notes. The median total body surface area (TBSA) burned was 20% in patients treated with heparin, compared with 51% in the control group. Increases in aPTT were observed in both groups and were not statistically different; however, bleeding events were higher in the control versus treatment group (81.8% vs. 71.2%). The authors attribute higher bleeding events in the control group to the higher percent TBSA burns (Yip 2011).

Although the Desai study previously described did not report a higher rate of bleeding events associated with the use of heparin, there is a case report of a 2-year-old child with 87% TBSA thermal burns who received nebulized heparin and acetylcysteine per the Desai protocol (Chopra 2011; Desai 1998). While receiving this regimen, the patient had elevated aPTT values over 120 seconds and clinically significant bleeding around burn excision areas. After discontinuation of nebulized heparin, the bleeding resolved and aPTT normalized. It is possible that this patient was at higher risk of bleeding because of extensive burns, but the authors attribute the bleeding to possible increased absorption of heparin in the setting of increased epithelial permeability and systemic inflammation (Chopra 2011). Because of high risk of bleeding at baseline, burn patients with ILI who receive nebulized heparin should be monitored closely. Several nebulized agents have been used to address the possible mechanisms associated with inhalation lung injuries and are listed in Table 4.

Intra-Alveolar Inflammation: Systemic Corticosteroids

As discussed previously, severe inflammation caused by inhalation injuries can result in significant pulmonary pathophysiology. Thus, it stands to reason that steroids would be a potential option for the management of ILI. However, studies have shown that patients with thermal cutaneous injuries in addition to inhalation injuries who received corticosteroids had a 4-fold increase mortality likely due to secondary infections (Robinson 1982). Corticosteroids should be avoided in patients with ILI and cutaneous thermal injuries.

Animal models of isolated ILI evaluated the effects of hydrocortisone, methylprednisolone, and dexamethasone compared with controls. Rats who received

Table 4. Nebulized Agents for Inhalation Lung Injury

Agent	Albuterol	Epinephrine	Acetylcysteine	Heparin	tPA	ATIII
Mechanism of action	β-Agonist	β-Agonist	Antioxidant and mucolytic	Anticoagulant	Fibrinolytic	Anticoagulant, anti-inflammatory
Dose	2.5 mg in 3 mL of saline	Racemic epinephrine (2.25% solution, 0.5 mL in 3 mL of saline) administered every 4 hr	(20% solution), 3 mL nebulized every 4 hr over 7 days	5000 units every 4 hr	1–2 mg every 4 hr	290 units every 4 hr
Adverse reactions	Tachycardia	–	Bronchospasm	Coagulopathy	–	–
Formulation	Solution for inhalation (preservative-free)	–	20% solution for inhalation (preservative-free)	5000 units/0.5 mL (preservative-free injection), dilute to 3 mL with 0.9% sodium chloride	–	Recombinant human product studied in pre-clinical studies
Clinical pearls	–	–	Pre-treat with albuterol to prevent bronchospasm	10,000 units have been used in adult patients	Limited pediatric literature; do not recommend	Limited pediatric literature; do not recommend

ATIII = antithrombin III; tPA = tissue plasminogen activator.

Information from: Dries DJ, Endorf FW. Inhalation injury: epidemiology, pathology, treatment strategies. *Scand J Trauma Resusc Emerg Med* 2013;21:31; Elsharnouby NM, Eid HE, Abou Elezz NF, et al. Heparin/N-acetylcysteine: an adjuvant in the management of burn inhalation injury: a study of different doses. *J Crit Care* 2014;29:182, e181-4; Foncerrada G, Lima F, Clayton RP, et al. Safety of nebulized epinephrine in smoke inhalation injury. *J Burn Care Res* 2017;38:396-402; McGinn KA, Weigartz K, Lintner A, et al. Nebulized heparin With N-acetylcysteine and albuterol reduces duration of mechanical ventilation in patients with inhalation injury. *J Pharm Pract* 2019;32:163-6; Miller AC, Elamin EM, Suffredini AF. Inhaled anticoagulation regimens for the treatment of smoke inhalation-associated acute lung injury: a systematic review. *Crit Care Med* 2014;42:413-9; Palmieri TL. Use of beta-agonists in inhalation injury. *J Burn Care Res* 2009;30:156-9; Palmieri TL, Enkhbaatar P, Sheridan R, et al. Studies of inhaled agents in inhalation injury. *J Burn Care Res* 2009;30:169-71; Rehberg S, Yamamoto Y, Sousse LE, et al. Advantages and pitfalls of combining intravenous antithrombin with nebulized heparin and tissue plasminogen activator in acute respiratory distress syndrome. *J Trauma Acute Care Surg* 2014;76:126-33.

methylprednisolone or dexamethasone were less likely to die compared with controls; however, rats treated with hydrocortisone had higher mortality. The authors concluded that mortality benefit may stem reduced interstitial pulmonary edema from corticosteroids with glucocorticoid activity (Dressler 1976). The role of steroids in isolated ILI remains controversial, data are limited to adult studies as described in following text.

In 1978, Levine et al. conducted a prospective, randomized study of 30 patients age 16-years and older with ILI. Patients were randomized to either placebo or intravenous dexamethasone 20 mg daily for 3 days. Pulmonary complications were recorded for each group and were defined as pneumonitis, bronchitis, severe atelectasis, and lobar collapse. The 10-day mortality was 20% for both dexamethasone and placebo

groups. In the dexamethasone group, pulmonary complications were 73.2% versus 86.7% in the placebo group. Mortality attributable to pulmonary complications was lower in the dexamethasone group compared with the placebo group (26.7% vs. 46.7%); however, these differences were not statistically significant (Levine 1978). Because of the small sample size of this study, it may be difficult to draw conclusions for the effects of corticosteroids in isolated inhalation injuries.

A large retrospective observational study in 1982 of ILI patients with isolated smoke inhalation evaluated the effects of intravenous dexamethasone 10 mg every 6 hours for patients treated with corticosteroids compared with those who did not receive corticosteroids. These patients were exposed to either one of the two major hotel fires that occurred within a span of a few months in Las Vegas, were

randomly triaged to four local hospitals and received similar supportive care. Of the 225 study patients, 141 received corticosteroids as part of their management and 84 patients were included in the control group. Baseline characteristics, including duration of smoke exposure and serum COHb, were similar between the two groups with the exception of age (48 years vs. 42 years, $p < 0.01$). In the first 72 hours after hospital admission, no significant differences were observed in the rates of ventilatory insufficiency, pneumonia, or mortality between the two cohorts (Robinson 1982). Although this study monitored patients for a short period after dexamethasone administration, the effects of dexamethasone on long-term outcomes were not evaluated.

Newer data exist to evaluate the effects of systemic corticosteroids on isolated smoke inhalation up to 3 months after administration. A study by Cha et al. evaluated the effect of methylprednisolone in a patient cohort after a subway fire. The 96 patients were transported to four tertiary hospitals where they received similar supportive care—except for steroids, which were used at three of the four hospitals. Survivors of the fire were enrolled in a prospective fashion for a 3-month follow-up phase to monitor pulmonary function tests. The steroid-treated group of 22 patients received intravenous methylprednisolone 125–250 mg/day for at least 2 days (2–60 days); a control group with similar baseline characteristics consisted of 19 patients. All patients had improved FEV₁ and FVC values at 3 months, and no statistically significant differences in improvement were observed between the groups. Although it is possible that improvement of pulmonary function tests may have occurred before follow-up, this study suggests that improvement in pulmonary function tests can be accomplished without steroids after an isolated smoke injury (Cha 2007).

In general, corticosteroids should be avoided for ILI when thermal cutaneous injuries are present because of risk of infection and increased mortality. In isolated ILI in which 2- to 3-day regimens intravenous methylprednisolone or dexamethasone have been studied, but pulmonary outcomes

did not reach significance. No mortality benefit was seen with either agent. Further studies are needed to determine the role of methylprednisolone or dexamethasone in isolated pediatric ILI. Considerations for the use of systemic corticosteroids for ILI are shown in Table 5.

ROLE OF ANTIBIOTICS IN ILI

Patients with ILI are predisposed to secondary pneumonia at a rate of 20%–50% (Albright 2012). Despite high rates of secondary pneumonia in this patient population, routine antimicrobial prophylaxis is not currently recommended due to limited evidence. A 2015 propensity score-matched cohort study by Tagami et al. evaluated 2893 patients with severe burns, of whom 1013 received prophylactic antibiotics and 1880 who did not. In patients who required mechanical ventilation, 28-day in-hospital mortality was significantly lower for the group receiving antibiotics compared to matched controls (OR 0.65; 95% CI, 0.45–0.95). The same effect was not seen for patients who received antimicrobial prophylaxis but did not require mechanical support. In patients who did not require mechanical ventilation, mortality was 4.2% in the antibiotic group compared with 5.1% in non-intubated controls (OR 0.81; 95% CI, 0.45–1.4) (Tagami 2016). Although limited data are available, empiric antibiotics may be considered in patients with inhalation injuries who require mechanical ventilation.

Inhaled antibiotics have also been used as prophylaxis for pneumonia in severely burned patients. It is theorized that inhaled antibiotics decrease the bacterial burden in the airway and thus reduce the risk of ventilator-associated pneumonia. A study by Ackerman et al. evaluated the effects of nebulized antibiotics in adult patients with ILI. Patients were treated with tobramycin 40 mg/1 mL, amikacin 250 mg/1 mL, or colistin 125 mg/1 mL dissolved in 4 mL of 0.9% sodium chloride and nebulized. The dosing frequency was not specified. Overall, there were 29 treatment courses with amikacin, 36 with tobramycin, and 8 with colistin. A total of 69 patients were treated, with eradication of gram-negative

Table 5. Systemic Corticosteroids for Inhalation Lung Injury

Drug	Use in Isolated ILI	Intravenous Adult Dose	Use in ILI with Concurrent Thermal Cutaneous Injuries
Hydrocortisone	No	Not indicated	Risk of infection outweighs benefit
Methylprednisolone	Yes	125–250 mg/day for at least 2 days	Avoid systemic corticosteroids
Dexamethasone	Yes	20 mg daily for 3 days	

Information from: Cha SI, Kim CH, Lee JH, et al. Isolated smoke inhalation injuries: acute respiratory dysfunction, clinical outcomes, and short-term evolution of pulmonary functions with the effects of steroids. *Burns* 2007;33:200-8; Levine BA, Petroff PA, Slade CL, et al. Prospective trials of dexamethasone and aerosolized gentamicin in the treatment of inhalation injury in the burned patient. *J Trauma* 1978;18:188-93; Robinson NB, Hudson LD, Riem M, et al. Steroid therapy following isolated smoke inhalation injury. *J Trauma* 1982;22:876-9.

bacteria accomplished in 25 patients (36%). The duration of ventilation was longer in patients treated with nebulized antibiotics compared with the control group (43.8 ± 28.2 days vs. 26.9 ± 28.8 days). However, it is unclear if this difference was caused by baseline differences in the rates of ILI between treatment and control groups. After the initiation of nebulized antibiotics, antibiotic resistance was identified in 3 patients who had been treated with nebulized antibiotics for at least 7 days. Systemic absorption of nebulized medications by bronchial airway and alveoli is possible, and acute kidney injury was directly associated with nebulized colistin in 2 patients (Ackerman 2013). Nebulized antibiotics should be used with caution in this patient population because of risks of nephrotoxicity and resistance together with unclear clinical benefit.

Inhalation lung injuries are associated with higher interleukin-8 levels and neutrophil predominance, which may result in increased inflammation and altered immune response. As a result, azithromycin may be an appealing option because of its immunomodulatory effects. A 2012 cohort study using data from the Acute Respiratory Distress Syndrome Network (ARDSNet) Lisofylline and Respiratory Management of Acute Lung Injury (LARMA) trial evaluated the use of antibiotics in patients with acute lung injury. After adjusting for confounders, patients who received macrolides compared with those who received fluoroquinolones or cephalosporins had a lower 180-day mortality (HR 0.46; 95% CI, 0.23–0.92; $p=0.028$) and shorter time to successful extubation (HR 1.93; 95% CI, 1.18–3.17; $p=0.009$). The authors theorized that the benefit from macrolides may be their anti-inflammatory rather than their antimicrobial effects (Walkey 2012).

FUTURE DIRECTIONS IN PHARMACOLOGIC THERAPIES FOR ACUTE AND CHRONIC ILI

The most common ILI is fire-related smoke inhalation, and burn patients who experience ILI have an almost 20-fold increase in mortality. Despite the clinical severity of ILI, most research is limited to basic science and animal-model studies (Enkhbaatar 2016).

Clinical application of preclinical data is further hindered by a lack of consensus on the diagnosis and grading of lung injuries associated with smoke inhalation. Currently, the diagnosis of ILI includes a combination of the history for the mechanism of injury, clinical presentation, and bronchoscopy findings. Some translational studies conducted in large animals suggest that MRI may help determine the extent of airway injury (Dries 2013; Palmieri 2009b).

After addressing diagnostic barriers, finding medications that reduce the most common pathologies of acute lung injury while limiting adverse effects is warranted. Agents for the prevention of infection and inflammation are likely ideal candidates. For infection management, using medications

that target PAFR as an adhesion site and prevent bacterial colonization is an appealing approach to prevent use of antibiotics for infection prophylaxis. However, studies evaluating PAFR antagonists remain in the pre-clinical stage (Shukla 2016). Meanwhile, additional studies evaluating the use of nebulized antibiotics on clinical outcomes and toxicities are needed in this patient population.

Inflammation plays a significant role in ILI and steroids have not been shown to be helpful in isolated smoke-related lung injury (Cha 2007). Statins have shown anti-inflammatory effects in preclinical animal models for acute lung inflammation in the setting of cigarette smoke. Mice exposed to cigarette smoke received atorvastatin (10 mg/kg), pravastatin (10 mg/kg), rosuvastatin (5 mg/kg), or simvastatin (20 mg/kg), with effects on inflammatory markers varying by agent. Rosuvastatin had the most significant anti-inflammatory effect compared with other statins (Ferreira 2014).

CONCLUSION

Inhalation lung injuries can result in local or systemic pathophysiology. Local injury to lung tissue may occur in the setting of thermal or chemical exposure as well as secondary inflammation. Limited data are available for management of airway fibrin casts, but nebulized anticoagulants may provide some clinical benefit. Systemic effects may include exposure to toxins or toxic byproducts and bacterial infection. The most common systemic inhalation toxicities are caused by CO and hydrogen cyanide. Hydrogen cyanide toxicity can be managed with several agents, including hydroxocobalamin, which may have a more favorable toxicity profile compared with nitrite therapies. Inhalation lung injuries can be further divided into acute or chronic exposures. Corticosteroids may have a role in some ILIs, including EVALI. The role of the pharmacist in determining the appropriate management is paramount.

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Practice Points

Inhalation lung injuries can result in local or systemic pathophysiology. Local injury to lung tissue may occur in the setting of thermal or chemical exposure as well as secondary inflammation. Systemic effects may include exposure to toxins or toxic byproducts and bacterial infection. Inhalation lung injuries can be further divided into acute or chronic exposures. The role of the pharmacist in determining the appropriate management is paramount, with an understanding of these key points:

- Inhalation lung injuries associated with burns have a high morbidity and mortality.
- In pediatric patients with ILI, hydroxocobalamin may have a more favorable toxicity profile compared with nitrite therapies.
- In burn patients with ILI, prophylactic antibiotics are controversial; however, the risk of sepsis and pneumonia are significantly higher compared to patients with isolated cutaneous injuries.
- E-cigarette aerosols can increase the risk of viral and bacterial infection in patients via several pathogenic mechanisms.
- Depending on the clinical context, antibiotics, antivirals, and corticosteroids may be appropriate in the management of EVALI.
- Smoking cessation is an integral part of the management of EVALI.
- Steroids may help with inflammation and cytokine release in EVALI and acute ILI.
- New therapies are needed for the management of ILI; however, several mechanisms of injury and a heterogeneous patient population make this research particularly challenging.

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Self-Assessment Questions

1. A 2-year-old girl is found on the scene of a house fire and admitted to the pediatric ICU. She incurred minimal thermal injury but there's suspicion for significant smoke inhalation. Which of the following is the most likely short-term complication in acute smoke inhalation?
 - A. Subglottic thermal injury
 - B. Intra-alveolar inflammation
 - C. Bacterial infection
 - D. Fluid overload
 2. An 8-year-old girl is admitted to the pediatric ICU following a house fire, where she had soot on her mouth and nose. She has 27% total body surface area (TBSA) burns. Which of the following is the most common cause of fire-related mortality in pediatric patients?
 - A. Thermal injury
 - B. Smoke inhalation
 - C. Methemoglobinemia
 - D. Carbon monoxide (CO) toxicity
 3. A 4-year-old boy arrives to pediatric ICU after being found unconscious at the site of a home fire. He is unresponsive and has soot on his face but has minimal skin burns. Relevant laboratory findings include a serum lactate concentration of 12 mmol/L and carboxyhemoglobin (COHb) of 20%. In addition to 100% oxygen, which of the following is the best initial treatment option for this patient?
 - A. Sodium thiosulfate
 - B. Methylene blue
 - C. Sodium nitrite
 - D. Hydroxocobalamin
 4. A 3-year-old girl is transported to the ED for flu-like symptoms and increased somnolence. She did not have signs and symptoms before going to bed. Both parents report symptoms of headache, nausea, and vomiting. They mention that a gas oven was left on to help heat up the home for the night. Which of the following is the most likely cause of her signs and symptoms?
 - A. Severe CO toxicity
 - B. Mild CO toxicity
 - C. Early hydrogen cyanide toxicity
 - D. Late hydrogen cyanide toxicity
 5. Because of limited pediatric data, you are asked to conduct a drug use evaluation of hydroxocobalamin use for cyanide toxicity at your pediatric burn center. Which of the following is the most appropriate conclusion about the safety of hydroxocobalamin in pediatric patients for cyanide toxicity?
 - A. The risk of acute tubular necrosis is well established in pediatric patients.
 - B. Hypotension is commonly seen after hydroxocobalamin infusion.
 - C. Infusion reactions are the most common adverse reaction.
 - D. Hydroxocobalamin is not licensed in children and should not be used.
 6. Which of the following statements best expresses the effects of nebulized heparin for smoke inhalation lung injury (ILI)?
 - A. Inhibits fibrin cast formation
 - B. Increases blood flow
 - C. Provides antioxidants
 - D. Promotes nitric oxide production
- Questions 7 and 8 pertain to the following case:**
- S.L. is a 2-year-old boy is admitted to the pediatric ICU because of ILI during a house fire. He requires mechanical ventilation and vasoactive support.
7. A provider asks about the role of heparin and acetylcysteine in addition to supportive care. Which of the following is the most appropriate statement for the management of S.L.?
 - A. Heparin alone has been shown to reduce mortality in mechanically ventilated burn patients.
 - B. The combination of heparin and acetylcysteine has been shown to increase ventilation days in children.
 - C. The combination of heparin and acetylcysteine has been shown to decrease mortality in children.
 - D. The combination of heparin and acetylcysteine does not impact on mortality in children.
 8. The medical team would like to use prophylactic antibiotics for S.L. Which of the following statements best summarizes the data for the use of prophylactic antibiotics for smoke ILI?
 - A. Because of high rates of secondary pneumonia, prophylactic antibiotics should be used in all burn patients.
 - B. In patients who did not require mechanical ventilation, prophylactic antibiotics increased 28-day mortality.
 - C. Because of low rates of secondary pneumonia, prophylactic antibiotics should not be used for burn patients.
 - D. In mechanically ventilated burn patients, prophylactic antibiotics may reduce 28-day mortality.

9. A provider is trying to determine the risk versus benefit of heparin and acetylcysteine, and data are conflicting on whether its use is appropriate. Which of the following is the most likely reason for this clinical controversy?
 - A. Limited data exist in children, and these data have not been reproduced in adults.
 - B. Adult data do not support its use and have shown increased bleeding events.
 - C. Animal data are abundant, but no human data exist.
 - D. Retrospective cohorts with historical controls are well matched and powered.
10. An 8-year-old girl is receiving nebulization treatments with heparin 5000 units alternating with 3 mL of 20% acetylcysteine every 2 hours for treatment of smoke inhalation after an enclosed fire. After acetylcysteine is administered, she experiences worsening tachypnea, cough, and elevated end-tidal carbon dioxide. Which of the following nebulized agents is best to recommend for this patient?
 - A. Albuterol
 - B. Alteplase
 - C. Epinephrine
 - D. Antithrombin
11. Three days ago, a 3-year-old boy who was intubated because of smoke ILI and 88% total body surface area (TBSA) burns was started on nebulized heparin and acetylcysteine. The medical team asks you about the bleeding risk associated with nebulized heparin for this patient. Which of the following is the most appropriate response to this question?
 - A. In higher percent TBSA burns, nebulized heparin is not systemically absorbed and does not increase bleeding risk
 - B. In higher percent TBSA burns, nebulized heparin can increase activated partial thromboplastin time (aPTT) but does not increase bleeding risk
 - C. In higher percent TBSA burns, nebulized heparin alone decreased mortality but close monitoring is needed
 - D. In higher percent TBSA burns, nebulized heparin increased bleeding and close monitoring is needed
12. An 18-year-old man with history of type 1 diabetes mellitus presents with a 3-day history of diarrhea, shortness of breath, and fever is admitted to the pediatric ICU for infectious work-up and concern for impending respiratory failure. He endorses use of a vaping device and multiple e-liquids from various illicit sources. Which of the following is the best statement regarding the use of methylprednisolone for this patient with likely EVALI?
 - A. Infection should be ruled out before using methylprednisolone.
 - B. Start intravenous methylprednisolone 1000 mg/day.
 - C. Do not start steroids due to increased risk of secondary infection.
 - D. Start intravenous methylprednisolone 30 mg every 6 hours.
13. A 12-year-old girl is admitted for 27% TBSA burn injury and ILI. Inhaled antibiotics are being considered for this patient. Which of the following best describes the effect of nebulized antibiotic use in inhalation lung injury?
 - A. Reduction in ventilator support days
 - B. Prevention of acute kidney injury
 - C. Treatment of bacterial pneumonia
 - D. Eradication of airway bacteria
14. A 17-year-old female adolescent with ILI has received inhaled tobramycin for 10 days. Which of the following is the most likely adverse effect expected with prolonged nebulized antibiotic regimens?
 - A. Acute kidney injury
 - B. Bronchospasm
 - C. Pulmonary hemorrhage
 - D. Antimicrobial resistance
15. Which of the following best describes a barrier to studying ILI?
 - A. Pre-clinical ILI models are lacking.
 - B. Consensus for lung injury grading is lacking.
 - C. ILI occurs in a homogenous population.
 - D. Management innovations mirror advances in thermal burn management.

Learner Chapter Evaluation: Inhalation Lung Injuries

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
 - Agree
 - Neutral
 - Disagree
 - Strongly disagree
1. The content of the chapter met my educational needs.
 2. The content of the chapter satisfied my expectations.
 3. The author presented the chapter content effectively.
 4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
 5. The content of the chapter was objective and balanced.
 6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
 7. The content of the chapter was useful to me.

8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.
12. The activity met the stated learning objectives.
13. If any objectives were not met, please list them here.

OTHER COMMENTS

14. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
15. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter: