Diagnosis and Treatment of the Inhalation Injuries: Review of the Literature

İnhalasyon Yaralanmalarının Tanı ve Tedavisi: Literatürün Gözden Geçirilmesi

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ABSTRACT

Burn patients are one of the most challenging patient profiles at medical literature. At indoor enviroment, inhalation injury adds to the accompanying skin injury and increases the morbidity and mortality. The management of the smoke injury is difficult and complex issue for medical teams. It requires a multidisciplinary work from anesthesiologists to surgeons as inhalation injury affects whole body systems, from respiratory to cardiovascular and neurologic systems. Accordingly, the treatment of burn patients with inhalation injury is different from simple skin burn victims. Early diagnosis and treatment of inhalation injury is mandatory as it can be life saving. Therefore, markers of inhalation injury should be known by emergency sevice workers and the treatment should be started immediately after the admission of the patient. In this rewiev, we collected the medical literature about inhalation injury to create a guide for the diagnosis and the treatment of this pathology.

Keywords: Inhalation injury, smoke injury, burn

ÖZET

Yanık hastaları tıp literatüründe en karmaşık hasta profillerinden biri olmuştur. Kapalı ortamlarda cilt yanığına eklenen inhalasyon yaralanması morbidite ve mortaliteyi arttırmaktadır. Duman yaralanmasının denetimi medikal takım için zorlu ve kompleks bir konudur. Bu, anestezi uzmanından cerrahına kadar multidisipliner bir iştir. Çünkü, inhalasyon yaralanması solunum sisteminden kardiyovasküler ve nörolojik sisteme kadar tüm vücudu etkilemektedir. Ayrıca inhalasyon yaralanmalı yanık hastalarının tedavisi de basit deri yanıklı kurbanların tedavilerinden farklıdır. İnhalasyon yaralanmalı hastada erken teşhis ve tedavi önemlidir. Bu nedenle inhalasyon hasarının belirteçleri acil servis çalışanları tarafından bilinmeli ve hastanın başvurusu anında tedavi başlatılmalıdır. Bu derlemede, patolojinin denetimi ve tedavisi için bir kılavuz oluşturmak için inhalasyon yaralanmasıyla ilgili literatürü topladık.

Anahtar kelimeler: İnhalasyon hasarı, duman hasarı, yanık

INTRODUCTION

Burn injuries represent one of the most common causes of accidental death. In both the developed and developing world, smoke inhalation is a major contributor to the morbidity and mortality associated with serious burns. Inhalational injury is a greater contributor to overall morbidity or mortality than either percentage of body surface area affected or age (1-3).

Incidence and Prevalence:

Burns in children are 2,5 times more likely to occur by scalding rather than flame exposure at USA. Hence, the percentage of children who experience respiratory symptoms after burns is less than that of adults who are more often exposed to smoke-producing flames. About 50% of all burn deaths are related to inhalation injuries. Early hypoxemia is a contributor to over 50% of smoke inhalation deaths, with CO intoxication accounting for as much as 80% of the fatalities (4).

Pathophysiology:

Inhalation injury occurs in 3 ways: 1) by cell injury and pulmonary parenchymal damage by irritants, 2) hypoxemia by interruption of oxygen delivery by asphyxiants, and 3) end organ damage by systemic absorption through the respiratory tract (5).

The Pathophysiology of smoke inhalation

True airway burns are generally confined to the mouth, tongue and palatal areas. Thus, the heat from the combusting material is absorbed by the tongue and oropharynx; this diminishes the heat transferred to the lower airway and pulmonary parenchymal tissue.

Although this may protect the lungs (assuming an intact sensorium and ability of the larynx to close), the thermal injury absorbed by the upper airway results in rapid tissue swelling as increased blood and lymph flow together with transvascular migration of fluid (6). As tissue damage continues, denatured protein results in the release of histamine and other vasoactive cytokines (7). A combination of these proteins and free radical moieties exacerbates the tissue injury and local inflammatory response. Injury to the oropharynx is similar to cutaneous thermal injury, but it is more problematic due to its narrowness. If possible, patients should be transferred to the hospital in a sitting position to minimize the swelling and hence reduce the risk of

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airway obstruction. Ongoing resuscitation of the burn, make the clinician consider early intubation, as the swelling that occurs after fluid resuscitation may make intubation difficult later. The risks of under-resuscitation, and subsequent tissue ischemia and renal dysfunction, must be weighed against the potential exacerbation of oropharyngeal tissue edema and subsequent compromise of the already injured airway (1,8,9). Moreover, the aggressive pulmonary toilet seemed to be effective in removing foreign particles and accumulated secretions which also cause the inflammatory response and the obstruction in inhalation injury (10).

Damage to Airways Distal to the Oropharynx

The lower airway is protected from thermal injury by virtue of the oropharynx acting as a heat sink and the fact that air has a low heat capacity. An exception is the inhalation of heated vapors with a higher heat capacity (eg. steam), which can cause severe thermal injury to the lower airway (11). Damage is initiated by toxins that result in a rapid and profound release of inflammatory mediators and bronchoconstrictors (12). The bronchoconstriction may exacerbate pre-existing reactive airway disease, making spontaneous or mechanical ventilation exceedingly difficult. As more protein-rich fluid leaks through the denuded mucosa, it combines with the necrotic slough of dead cellular components and acute and chronic inflammatory cells to form fibrinous bronchial casts (13). This causes complete airway occlusion in medium and small-caliber airways.

Vascular Changes Associated With Smoke Inhalation

The hyperemia seen in the oropharynx is reflected in the tracheobronchial tree, where the rise in blood flow is even more marked, sometimes up to 20 times the normal bronchial blood flow (14,15). In an ovine model, in which smoke injury to one lung was induced via a double lumen tube. The injured lung showed rapid increase in lymph and blood flow; interestingly, the protected lung showed a similar increase in both lymph and blood flow despite being ventilated on oxygen with no smoke exposure (12,16). The contributors to the vasodilatory response include leukotrienes, histamine, neural neuropeptides, and nitric oxide created by neural nitric oxide synthase (17,18). Blockade of the majority of these mediators has induced some changes in bronchial blood flow in the laboratory setting, but use of agents such as nonsteroidal anti-inflammatory drugs in the clinical scenario has not been shown to improve outcome (19).

In smoke inhalation, cytokines such as interleukin-8 as well as reactive molecular species can cause cellular damage (20). Nitric oxide is produced by inducible nitric oxide synthase causing vasodilation, but it may also bind with superoxide radical molecules produced by activated neutrophls to form the reactive peroxynitrate (21,22). This molecule is known to cause undifferentiated cellular damage. Recently, it has been also found to induce cellular dysfunction and death. This is due to its role in the activation of poly (adenosine 5´-diphosphate [ADP]-ribose) polymerase (PARP), a molecule also known as poly (ADPribose) synthase (PARS). The PARS molecule is an energyconsuming enzyme that is required to restructure damaged single strands of DNA. Peroxynitrate molecules cause DNA cellular damage by inducing up-regulation of PARP, thus requiring excessive consumption of energy and depletion of ATP and intracellular nicotinamide dinucleotide(NAD+). As nitric oxide and peroxynitrate are both recognized as inflammatory mediators inducing cytotoxicity, it seems reasonable that PARP inhibitors may inhibit the inflammatory excess seen in smoke inhalation injury. In a recent study several markers of lung injury, including PaO2/FiO2 ratio, wet/dry ratio, and histology scores were improved by addition of a PARP inhibitor. The volume of cellular debris due to necrosis also was diminished by PARP inhibitor. All studies using PARP inhibitors to date have been in animal models (1,23).

The Alveolus

The alveolus can be affected directly by smoke or indirectly due to obstruction by casts or systemic release of cytokines. The release of the macrophage's arsenal is deleterious to the host and results in autolysis of the macrophage. The activated dying macrophage then releases its residual cytokines and inflammatory signals into the alveolus and subsequently the pulmonary circulation (24). This is then thought to attract more macrophages from the interstitium and attract neutrophils, creating a cycle of activation followed by repetitive reactivation, thus fueling the systemic inflammatory response (1). There are increased volumes of lymph flow within the lung, and their effect can be quantified by the measurement of wet/dry weight ratio of lung tissue in experimental models of smoke inhalation (25). Consistent with the inflammatory milieu of the alveolus, there is a rapid increase in the number of neutrophils in the capillaries. These neutrophils express leucocyte-selectins and begin the process of rolling, adherence, and eventual diapedesis from capillary to the interstitium or alveolus. These neutrophils and their products, such as anti-proteases, free radical scavengers, and superoxide dismutase all diminish lymphatic flow after smoke injury (1,26).

Coagulation Dysfunction and Smoke Inhalation Injury

Patients who experience the systemic inflammatory response syndrome (SIRS) are known to be predisposed to intravascular thrombus. Recent data indicate that patients with acute respiratory distress syndrome (ARDS) have a specific intrapulmonary procoagulant tendency (27). Bronchoalveolar lavage fluid has been shown to predict the likelihood of developing ARDS later in the course of the illness, as judged by the ratio of procoagulant/anticoagulant activity in the fluid. Initially, this procoagulant activity was thought merely to reflect an overflow from the systemic circulation. However, recent research has shown that the procoagulant tendency seen in the bronchoalveolar lavage fluid is independent of the systemic circulation (28,29). In addition to procoagulation, there is reduction of fibrinolysis. Research by Prabhakaran et al. has demonstrated reduced fibrinolytic activity as shown by increased levels of plasminogen activator inhibitor(PAI-1) (30). The imbalance between endogenous pro-coagulation and anticoagulation in patients with ARDS is further evidenced by an imbalance of plasma levels of tissue factor and tissue factor pathway inhibitör (31). Systemic anticoagulation has obvious risks in patients with smoke inhalation injury, as the majority of these patients have concomitant burns. Use of drugs such as activated protein C, which has anti-inflammatory, anticoagulant, and fibrinolytic properties is contraindicated, as the risk of excess bleeding outweighs the benefit obtained from the drug for treating the smoke inhalation injury alone. The possibility exists for further studies of nebulized activated protein C or antithrombin (1,32).

In a study Enkhbaatar et al. showed that pro-inflammatory and procoagulatory surges are associated with severely depleted levels of plasma antithrombin (AT), which has both anti-inflammatory and anticoagulant effects. Because of severe epithelial damage, intravascular rhAT leaks into airways. They hypothesized that restoration of plasma AT would improve experimental burn/smoke-induced ALI (acute lung injury). A combination of intravenous rhAT and aerosolized heparin has potential therapeutic benefit in patients suffering from combined burns and inhalation injury (33).

The only anticoagulant in clinical use for smoke inhalation is heparin. Historical studies have shown improved outcomes in patients treated with nebulized heparin versus control (34). The benefit of nebulized heparin has been shown in a study of the pediatric population, in which the use of this drug compared with controls resulted in significant decreases in the rate of intubation for progressive pulmonary failure, incidence of atelectasis, and mortality related to smoke inhalation. A truly randomized doubleblind controlled trial has not yet been conducted. The causal pathway by which heparin conveys clinical benefit is not perfectly clear but seems to be related to its cationic state, which reduces cast formation. Unfortunately, studies of high-dose systemic heparin in a controlled laboratory setting have failed to show improvement (1,35).

Carbon Monoxide (CO) Poisoning

Carbon monoxide may cause xanthine dehydrase to convert to xanthine oxidase; the latter is associated with the formation of oxygen-free radicals and tissue damage. Treatment with hyperbaric oxygen will convert the xanthine oxidase back to its less toxic dehydrogenase. If neurological impairment persists, this treatment may be repeated (36-38). A subsequent study has suggested there may be some improvement in long-term cognitive sequelae with the addition of hyperbaric therapy to patients who had a documented exposure to carbon monoxide and were symptomatic of COHb toxicity (39). A recent meta-analysis does not support the use of hyperbaric oxygen therapy in this setting (40). Consequently, although the evidence is unclear at this time, it is the authors' practice not to transfer patients to the hyperbaric chamber, as the data do not support any clear outcome benefit, but to provide 100% oxygen via endotracheal tube in the safety of an ICU(Intensive Care Unit) (1).

Cyanide Toxicity

Although COHb is easily and rapidly assessed by arterial blood analysis and an appropriate analyzer, there is no rapid and readily available assay for the measurement of cyanide. A history of inhalation in the presence of an enclosed fire with reduced oxygen should alert the practitioner to the possibility of cyanide toxicity. Inexplicable lactate acidosis, despite appropriate and continued resuscitation for the concordant burn and/or inhalation injury, should raise the question of cyanide toxicity (41). The classic bitter almond smell may be difficult to detect in a patient who has simultaneous cutaneous burns.

Definitive diagnosis is by high-performance liquid chromatography; however, this is either unavailable or has limited availability in many hospitals, especially if requested after routine hours (42). Concentration of greater than 20 ppm is considered dangerous, but lower levels may be injurious in the presence of co-existing carbon monoxide poisoning. Low levels of cyanide induce symptoms of nausea and lethargy, can be associated with ST segment changes on ECG, and can induce hyperventilation by direct action on the carotid body chemoreceptor. Hyperventilation induced by cyanide may increase the dose delivered to the patient.

At higher levels of cyanide poisoning, respiratory paralysis occurs (1,43).

There are a number of specific therapies for cyanide poisoning, although they do have risks. Supportive therapy involves treatment with supplemental oxygen and protection of the airway, especially if respiratory paralysis occurs (43). Competition with cyanide for access to the cytochrome oxidase is the basis for administration of amyl nitrate, which results in the production of methemoglobin. By binding to cyanide, the methemoglobin frees the cytochrome of the toxin and allows cellular respiration. However, methemoglobin is a poor oxygen carrier and can result in inadequate oxygen delivery to the tissues (44). Administration of thiosulfate acts to oppose cyanide poisoning by a different mechanism. In this case, there is a donation of a sulfur atom to cyanide (with the assistance of the enzyme rhodanase) resulting in the formation of the less toxic thiocyanate, which in turn is slowly excreted via the kidney if kidney function is maintained or via dialysis if required. Alternatively, chelation of the cyanide molecule may be achieved by the administration of hydroxocobalamin, and the product of this chelation is then excreted in the urine. None of these additional therapies is completely without risk. They should be used for patients with symptoms of cyanide poisoning that are not relieved by supportive measures alone, and whose clinical condition is felt to merit the additional risk (1).

Mortality/Morbidity:

Inhalation injury increases the morbidity and mortality of burns significantly. Small children are especially vulnerable because they are less likely to escape a confined space and also have a higher minute ventilation. David et al. reported that the main factors increasing the mortality rate for inhalation injuries were increasing TBSA (total body surface area) and age (45).

Bacterial pneumonia often complicates inhalation injury within 4-5 days of presentation. This additional cellular damage can cause significant mortality days to weeks after the initial injury. Most of the pulmonary damage is self-limited and resolves within 2-3 days. The degree of recovery depends on the extent of the pulmonary parenchymal injury and subsequent hypoxic damage to the organs. Reports exist of residual reactive airway disease, bronchiectasis, bronchiolitis obliterans, and interstitial fibrosis. The long-term effects of inhaled toxins on pulmonary function are not yet determined. David et al. showed that the presence of pneumonia among inhalation injury patients significantly increased length of stay and doubled mortality rates. Admission carboxyhemoglobinlevels, age, and sex had no relationship to the development of pneumonia. An increase in TBSA (total body surface area > % 20)burn was associated with a higher pneumonia rate (46).

History

Underlying medical history: The presence of underlying lung disease, including asthma, makes a child more susceptible to airway irritation.

Age at exposure; children and adults are often exposed to smoke together. The extent of disease can be notably different between children and adults, despite similar exposures.

Respiratory injury

Patients with respiratory injury present with many symptoms, ranging from minor eye irritation, cough, and uncomfortable breathing to acute respiratory failure. The full extent of respiratory tract injury may not be evident at initial presentation, although symptoms are usually present within 12-24 hours. Patients presenting with dyspnea, hemoptysis, cough, tachypnea, rales, rhonchi, wheezing, facial burns, carbonaceous sputum, pulmonary infiltration on radiography, and hypoxemia with or without acidosis should be closely observed because these findings increase the risk of progressive disease (4,5,47).

Burns on the face, soot marks, and singed eyebrows or facial hair are indicative of smoke inhalation. Inhalation injury can also occur without evidence of burns. Cyanosis is an unreliable indicator of hypoxia because of the bright red color imparted to the skin when carboxyhemoglobin (CO-Hb) levels are elevated (4,5,47).

Neurologic injury

This may take longer to appear than evidence of respiratory injury. Neurologic injury may be the result of hypoxia at the time of injury or may result from hypoxia secondary to pulmonary dysfunction (4,5,47).

Patients exposed to asphyxiants, including CO and cyanide, present with hypoxic injury and subsequent central nervous system depression, lethargy, and obtundation. Hypoxia is caused by an asphyxiant and is usually evident upon presentation. Irritability, severe temporal headache, and generalized muscle weakness are also common findings (4,5,47).

The presence of coma following exposure to fire is nearly always indicative of CO poisoning and should be promptly treated with 100% oxygen. Suspect cyanide toxicity in the child whose sensorium remains clouded and who does not respond to oxygen therapy (4,5). Red retinal veins resulting from elevated venous

oxyhemoglobin saturation may be noted on funduscopic examination.

Cardiovascular injury

Complex cardiovascular changes associated with surface burns may coexist with inhalation injury. Some investigators suggested that the decreased pre-load result of vascular fluid loss is responsible for the depressed cardiovascular function in burn shock (48). On the other hand, other investigators have suggested the existence of specific myocardial depressant factors released from burned tissue (49). Recently, proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-1 have been shown as circulating myocardial depressant substances during inflammatory condition such as septic shock, ischemiareperfusion injury or burn Giroir et al. have demonstrated that TNF is a critical mediator of postburn cardiac dysfunction (49). A recent study strongly suggests that NO produced from iNOS is responsible for the myocardial contractile dysfunction that may be induced by inflammatory cytokines seen with burn and smoke combination injury in the later phase. The iNOS inhibition restored this cardiac dysfunction (50).

Causes:

Inhalants are classified as irritant, asphyxiant, or systemic toxins. Irritants cause extensive cell injury within the respiratory tract. Asphyxiants interrupt the delivery of oxygen to the tissues. Systemic toxins are absorbed through the respiratory tract and go on to damage other organ systems. Toxic gases are liberated during the combustion of a variety of substances, as listed in Table 1 (Table 1) (5,51).

Diagnosis of Inhalation Injury:

Lab Studies

a) Pulse oximetry:

Cutaneous pulse oximetry uses a 2-wavelength technique of light refractance to measure hemoglobin saturation that is falsely elevated by CO-bound hemoglobin. Obtain direct measures of carboxyhemoglobin and oxyhemoglobin (52). To monitor oxygen saturation, recognizing that cutaneous pulse oximetry is falsely elevated by CO is imperative (52). Cooximetry(arterial blood) uses a 4-wavelength technique of light refractance to accurately measure carboxyhemoglobin and oxyhemoglobin, in addition to deoxyhemoglobin and methemoglobin. The percent oxyhemoglobin measured by cooximetry is an accurate measure of the arterial oxygen saturation (53).

b) Arterial blood gas:

Arterial blood gas measurements are nonetheless useful to assess the adequacy of pulmonary gas exchange. While the presence of a PaO_2 that is within the reference range may not exclude significant tissue hypoxia due to the effects of CO, the presence of a low PaO_2 (< 60 mmHg in room air) or hypercarbia($PaCO_2$ >55 mmHg) are indicative of significant respiratory insufficiency (1,4,5,47).

c) Carboxyhemoglobin level:

Provide supplemental oxygen therapy to all patients with suspected CO intoxication. Smokers may have baseline levels up to 5-10% and may experience more significant CO poisoning for the same level of exposure as nonsmokers. Blood carboxyhemoglobin levels, however, may underestimate the degree of CO intoxication because of oxygen administration before arrival to the hospital. The use of nomograms to extrapolate levels to the time of rescue has been shown to have greater prognostic value. Symptoms vary with peak carboxyhemoglobin levels, but correlation between carboxyhemoglobin levels and eventual neurologic outcome is poor (Table 2) (4,5,47,54).

d) Cyanide level:

Levels correlate closely with the level of exposure and toxicity, but they may not be readily available (5). Many hospitals send out tests for cyanide levels; therefore, laboratory confirmation may take several days to a week. Persistent neurologic dysfunction unresponsive to use of supplemental oxygen, cardiac dysfunction, and severe lactic acidosis, particularly in the presence of high mixed venous oxygen saturation, are indicative of cyanide intoxication (5).

e) Electrolytes:

We must obtain tests at regular and frequent intervals to monitor for electrolyte abnormalities that result from large-volume fluid resuscitation and use results to adjust both fluid and electrolyte replacement (4,5,47).

f) Complete blood count, type, and cross:

Hemoconcentration resulting from fluid losses is common immediately following injury. Adequate restoration of intravascular volume results in a progressive fall in hematocrit. Severe anemia may require blood replacement, particularly in the presence of significant hypoxia or hemodynamic instability. A baseline white blood cell count can also be used for comparison when concerns arise about infection (4,5,47,54).

Table 1. Inhalants

Type	Inhalant	Source	Injury/Mechanism
Irritant gases	Ammonia	Fertilizer, refrigerant, manufacturing of dyes, plastics	Upper airway epithelial damage
	Chlorine	Bleaching agent, sewage and water disinfectant, cleansing products	Lower airway epithelial damage
	Sulfur dioxide	Combustion of coal, oil, cooking fuel, smelting	Upper airway epithelial damage
	Nitrogen dioxide	Combustion of diesel, welding, manufacturing of dyes, lacquers	Terminal airway epithelial damage
Asphyxiants	Carbon monoxide*	Combustion of weeds, coal, gas, heaters	Competes for oxygen sites on hemoglobin, myoglobin, heme-containing intracellular proteins
	Hydrogen cyanide†	Burning of polyurethane, nitrocellulose (silk, nylon, wool)	Tissue asphyxiation by inhibiting intracellular cytochrome oxidase activity, inhibits ATP production, leads to cellular anoxia
	Hydrogen sulfide‡	Sewage treatment facility, volcanic gases, coal mines, natural hot springs	Similar to cyanide, tissue asphyxiant by inhibition of cytochrome oxidase, leads to disruption of electron transport chain, results in anaerobic metabolism
Systemic toxins	Hydrocarbons	Inhalant abuse (toluene, benzene, Freon); aerosols; glue; gasoline; nail polish remover; typewriter correction fluid; ingestion of petroleum solvents, kerosene, liquid polishes	CNS narcosis, anesthetic stats, diffuse gastrointestinal symptoms, peripheral neuropathy with weakness, coma, sudden death, chemical pneumonitis, CNS abnormalities, gastrointestinal irritation, cardiomyopathy, renal toxicity
	Organophosphates	Insecticides, nerve gases	Blocks acetylcholinesterase, cholinergic crisis with increased acetylcholine
	Metal fumes	Metal oxides of zinc, copper, magnesium, jewelry making	Flu-like symptoms, fever, myalgia, weakness

* Major component of smoke

† Smells like almonds, component of smoke from fires

‡ Smells like rotten eggs (Adapted from Rorison, 1992; Weiss, 1994)

Table 2. Patient Symptoms in Relation to Levels of Carboxyhemoglobin in the Blood*

Carboxyhemoglobin Level (% of Total)	Patient Symptoms
0-10	Usually none
10-20	Mild headache, atypical dyspnea
20-30	Throbbing headache, impaired concentration
30-40	Severe headache, impaired thinking
40-50	Confusion, lethargy, syncope
50-60	Respiratory failure, seizures
>70	Coma, rapidly fatal

*From Rorison, 1992 (55)

Imaging Studies

a) C-spine radiography:

Test for neck injury in all unconscious patients and in those in whom a potential mechanism of injury cannot be excluded (eg, jumped from window to escape fire, fell down stairs) (4).

b) Chest radiography

Roentgenographic abnormalities are frequently delayed and may not manifest on the initial chest radiograph(4). Radiographic evidence of pulmonary injury typically appears 24-36 hours after the inhalation. Obtain a chest radiograph at the baseline examination for subsequent comparison in cases of significant injury. Radiographic studies are also useful to establish correct placement of the endotracheal tube and central venous catheters (4).

c) Electrical Impedance Tomography:

Electrical impedance tomography is a relatively new technique that generates cross-sectional images of the thoracic cavity based on the measurement of surface electrical potentials resulting from an excitation of known small electrical currents. This has been used successfully in the research laboratory to facilitate diagnosis and quantification of mechanical lung obstruction secondary to smoke inhalation (56). As yet, clinical experience of electrical impedance tomography is limited to patients with ARDS and not smoke inhalation specifically. These encouraging research reports suggest that this modality may be of use in the clinical environment in the future (1).

d) Multi-detector computed tomography:

In 2007 Koljonen et al. reported that multi-detector computed tomography is an usefull method at early diagnose of smoke inhalation (57).

Other Tests

a) Direct laryngoscopy and fiberoptic bronchoscopy:

Both have diagnostic and therapeutic utility. Visualization of erythema, edema, ulceration, and soot deposition make bronchoscopy useful in evaluating the extent of injury to the tracheobronchial tree, although severe vasoconstriction from hypovolemia may mask significant injury (4,5).

Fiberoptic bronchoscopy can also be used to facilitate endotracheal tube placement, even in the technically difficult airway. Bronchoscopy is more sensitive and accurate than clinical examination alone in diagnosing inhalation injury and is, therefore, particularly useful in cases where the decision to perform endotracheal intubation is unclear (4,5,47,58).

Serial bronchoscopy can help remove debris and necrotic cells in cases with aggressive pulmonary toilet or when suctioning and positive pressure ventilation are insufficient (4,5,47).

Virtual bronchoscopy is a new technique at diagnosis of inhalation injury. An early experience with virtual bronchoscopy suggests that this was a good alternative to fiberoptic bronchoscopy. It could help not only in diagnosis of inhalation injury but also in avoiding the risks inherent to fiberoptic bronchoscopy (59).

b) Radionucleotide scintigraphy:

Delayed or inhomogeneous clearance of xenon Xe 133 can be used to detect small airway parenchymal injury but adds little to the clinical management and it is not known to have any particular therapeutic advantage (60).

Likewise, increased clearance of aerosolized 99mTcDTPA (technetium Tc 99m–labeled diethylenetriaminepentaacetate) is a sensitive indicator of injury to the alveolar capillary membrane; however, its clinical utility is not yet established (60).

c) Pulmonary function tests:

With an inhalation injury, a decrease in pulmonary compliance, vital capacity, and functional residual capacity occurs. Airway obstruction causes a decrease in forced expiratory volume in one second (FEV_1) and peak flow. Although this helps determine lower airway disease and injury, similar to radionucleotide scintigraphy, it has little clinical utility in the initial stages of treatment. In patients with cutaneous burns, the reduction in vital capacity and FEV_1 correlates closely with the extent of surface burns. Full resolution

of pulmonary function test result abnormalities may take several months (1,4,5,47).

Treatment:

Management of Inhalation Injury

Prevention is the optimal treatment, and studies have shown that the presence of an inexpensive, working smoke detector reduces the risk of a serious smoke inhalation by more than 60% (61). Once an inhalational injury and/or upper airway thermal injury has been diagnosed, specific and supportive care can be instituted. However, consideration of the diagnosis is paramount, as failure to detect or assess carbon monoxide COHb levels or look for potential cyanide poisoning will delay treatment.

Management of smoke inhalation can be divided into supportive and specific measures. An airway must be obtained rapidly if the patient has a Glasgow Coma Scale score of less than 9, has a rapidly swelling oropharynx, or is at risk for aspiration. In managing the airway of the burn and smoke inhalation victim, assessment and stabilization of the cervical spine must be completed prior to placement of an artificial airway. In patients with upper airway swelling and rapidly deteriorating gas transfer, intubation may be impossible. On occasion, an awake crico-thyroidotomy or tracheostomy may be required. Respiratory management of the patient with smoke inhalation should be aimed at achieving adequate oxygenation (PaO2 60 mmHg or more) with an acceptable PaCO2 level. Hypercarbia is common in burn patients due to an increase in basal metabolic rate and the catabolic state. The majority of early deaths in burn-injured patients result from carbon monoxide poisoning. Patients with carbon monoxide poisoning should be managed with as much supplemental oxygen as possible following extrication from the conflagration (1).

Decision to admit

The patient who is at low risk for injury with no clinical symptoms can usually be observed for 4-12 hours and discharged with close follow-up and instructions to return if symptomatic. Observing the high-risk patient with only minimal symptoms for 4-12 hours and, if any symptoms or concerns arise, admit to the hospital for further observation and oximetry monitoring. The symptomatic patient with any signs of airway obstruction, bronchospasm, respiratory distress, or concurrent burns is admitted to the hospital for appropriate monitoring because edema and obstruction typically worsen over the next 24-48 hours (4).

Airways

Ensure patency and stability. Check for exposure to heat and thermal injury to the nose, mouth, face, and singed hair. Consider smoke involvement if soot is on the face and in sputum, although smoke inhalation is possible without evidence of soot. Direct laryngoscopy and fiberoptic endoscopy are useful to evaluate the extent of airway edema and burns. When upper airway injury is suspected, elective intubation should be considered because progression of edema over the next 24-48 hours may make later intubation difficult if not impossible (4,5,47,58).

There are numerous ways to safely obtain airway control and intubate the larynx, particularly in a patient with a difficult airway. Avoidance of muscle relaxants may be wise, as a diminished functional residual capacity (FRC) and swollen airway may make intubation difficult. If the airway can be intubated using local anesthesia and sedation, and perhaps fiberoptic bronchoscopy, there may be less risk of losing the airway. The largest possible endotracheal tube should be placed to facilitate pulmonary hygiene and bronchoscopy (1).

Breathing

Check for upper airway for difficulty breathing, stridor, cough, retractions, and bilateral breath sounds. Administer 100% oxygen because of the likelihood of CO inhalation in fires (4,5,47).

Circulation

Fluid Resuscitation and Management of Circulation:

The presence of a thermal injury is associated with significant fluid loss due to the damage and loss of the protective keratin layer of the skin. The multiple fluid resuscitation formulae used to guide resuscitation in the burn victim are followed in burn institutions. However, the patient with an inhalational injury generally requires a larger volume of resuscitation fluid than the patient with cutaneous injury alone. Some studies support up to a 50% increase in the initial fluid resuscitation if the burn victim has a combined smoke inhalation injury. Excessive fluid, however, can worsen oxygenation, increase lung and chest wall edema, and diminish the effectiveness of protective ventilatory strategies. Regardless of the fluid regimen chosen for the burn victim, it is appropriate to start with a standard approach such as Parkland's formula (4 mg/kg/%/body surface area of burn) and then titrate fluid resuscitation to clinical parameters including urine output, lactate, base excess, blood pressure, and circulatory end points such as mean arterial blood pressure, central venous pressure, and, if a pulmonary artery catheter is placed, pulmonary artery wedge pressure (1,62,63).

Endorf et al. reported that P/F ratio (PaO2/FiO2 ratio) can be a more accurate predictor of increased fluid requirements during the acute resuscitation. Patients with a P/F ratio less than 350 at presentation have a statisticaly significant increase in ml/kg/%TBSA(total body surface area) compared with those with P/F>350 (64).

As with burn injury, use of colloid-containing solutions in the first 8 to 12 hours is not recommended. Subsequent fluid resuscitation should be of a balanced nature and may include albumen, colloid, or hypertonic saline. As the resuscitation continues, the chest and abdominal wall may be full thickness and develop a constrictive component, making ventilation more difficult in patients with already compromised direct pulmonary injury. These injuries require rapid and complete escharotomies to facilitate full respiratory excursion. The abdominal compartment may become compromised by excessive fluid resuscitation. Abdominal compartment syndrome has a negative impact on splanchnic, renal, and limb perfusion. In the burn patient, it also has a negative impact on excursion of the diaphragm (1).

Mechanical ventilation

The mainstay of management of smoke inhalation injury is mechanical ventilation. Various modalities may be used. Tidal volumes between 6 to 8 mL/kg should be titrated with inspiratory oxygen concentration titrated to patient's requirements with a positive end expiratory pressure of 5 to 10 cm/H2O. Despite humidification and aggressive airway toilet by nursing and physiotherapy staff, obstruction may stil ensue. This necessitates frequent and aggressive bronchoscopy for both diagnostic and therapeutic purposes. There are proponents and opponents of different methods of ventilation. High-frequency ventilation has a number of supporters. This modality uses minute tidal volumes at very high frequencies of 300 to 600 breaths/minute. High-frequency ventilation achieves adequate oxygenation, but it is unclear whether this translates into improved outcomes. Studies in the early 1990s suggested an improvement in lung injury scores with the use of high-frequency strategies compared with conventional ventilation. However, patients in the control arm of the study had relatively high tidal volumes (approximately 15 mL/kg). This has been shown to be associated with increased lung damage and increased mortality compared with lung-protective strategies and lower tidal volumes (65). Another variation on high-frequency ventilation is highfrequency percussive ventilation. Using similar small tidal volumes, there is high-frequency flow returning to a baseline continuous positive airway pressure. The small changes in tidal volume and small increase in airway pressure are proposed to open the alveoli slowly. There has been no large randomized controlled study analyzing the efficacy of high-frequency ventilation (or high-frequency oscillators/percussive ventilators) (HFPV). Many experienced intensivists think that this modality is useful in selected patients who are otherwise difficult to oxygenate and ventilate (1,67,68,69). Hall et al. compared HFPV with conventional mechanical ventilation between 1997 and 2005. There was a significant decrease in both morbidity and mortality in the subset of patients with treated with HFPV (70).

High frequency oscillatory ventilation (HFOV) allows the use of extremely small VTs, often less than the anatomical dead space and high frequency, often more than 180 times/min, which avoids volutraumas, barotraumas and injury of airway stretch or alveolar shearing. Studies in premature primates demonstrated that HFOV improved gas exchange, and reduced lung injury when compared with conventional ventilation. HFOV was also associated with reduced inflammatory mediators and granulocytes in lung lavaged samples and lung tissues when compared with conventional ventilation. As a result, HFOVattenuated the decrease in oxygenation and pulmonary compliance, alleviated lung tissue damage and inflammatory response. Therefore, HFOV may be a preferable option for treatment of acute lung injury induced by steam inhalation injury (71).

With declining lung function, oxygenation, and ventilation, mechanical ventilation with positive end expiratory pressure (PEEP) may be necessary. Ideally, PEEP stents alveoli open, preventing the atelectasis and alveolar flooding that can result from surfactant dysfunction, increasing interstitial fluid, and third-spacing (1,4,5,47).

Nosocomial pneumonia is a common problem in the patient with smoke inhalation injury. Burn and smoke inhalation have been identified as independent risk factors for the development of ventilatory-associated pneumonia (72). Identifying a causative organism may be difficult. The presence of systemic inflammatory response syndrome is almost universal in patients with significant smoke inhalation and/or burn injury. Chest x-ray after the first 1 to 2 days almost invariably demonstrates areas of increased opacification, which may represent interalveolar fluid that is often filled with bacteria. Routine sputum surveillance should be carried out. Changes in respiratory status, such as increased sputum and increased oxygen requirements or worsening cardiovascular instability, in association with fever or with deterioration in chest x-ray appearance, are indicative of ventilator-associated pneumonia. Routine surveillance should then be

augmented by diagnostic bronchoalveolar lavage. The antibiotics chosen for treatment of this pneumonia should be broad spectrum initially and narrowed down rapidly when the causative organism is found (1).

VapothermTM uses humidified air, which has played a role in upper airway obstruction seen in croup. When compared to neonatal CPAP devices, VapothermTM therapy is delivered by a similarly shaped but less tightly fitting nasal cannula and applied with higher flows than nasal CPAP (73). In children in whom endotracheal intubation is not possible because of severe airway edema or burns, tracheostomy can be lifesaving. In patients expected to have a long period of convalescence because of severe neurologic or pulmonary injury, tracheostomy may be desirable for patient comfort, and it is easy to maintain (74).

Risks associated with tracheostomy include subglottic stenosis, bleeding, pneumothorax, and fracture of the tracheal rings (1).

Pulmonary toilet

The use of percutaneous cupping and postural drainage seem reasonable to clear airways of cellular debris and soot, thereby preventing atelectasis and obstruction. Seung Ick Cha et al. reported that pulmoner toilet bronchoscopy would appear to be the most effective therapy for early liberation from mechanic ventilation in smoke inhalation (75).

Diet

Even with extensive burns, most patients can tolerate enteral feedings at the end of the first 24 hours. Begin enteral feedings as soon as possible. As enteral intake increases, decrease intravenous fluids accordingly.

Medication

The names of the drugs for the treatment of inhalation injury are listed at table 3 (Table 3).

Steroids:

Corticosteroids are attractive for suppressing inflammation and reducing edema. Because of the increased risk of infection and delayed wound healing, prolonged use of steroids should be discouraged. Reports show increased incidence of pulmonary infection and mortality in steroid-treated patients. However, consider a brief course of steroids in those patients with otherwise unresponsive severe lower airway obstruction (4,5,47). Corticosteroid therapy should be considered when persistent ARDS, interstitial pneumonia or bronchiolitis obliterans are suspected without evidence of active infection (76).

Treatment of the Infection:

Patients with pulmonary damage from inhalation injury are at increased risk for secondary bacterial infection. The most common organisms are Staphylococcus aureus and Pseudomonas aeruginosa. Direct parenteral coverage with antibiotics to cover these bacteria if infection is suspected. Antimicrobial therapy should be reserved for patients with definitive microbiologic evidence of infection that is not responding to aggressive support therapy or when clinical deterioration occurs in the first 72 hours, when infection is most likely to occur. Prophylactic antibiotics increase the risk of emergence of resistant organisms, however, and do not prevent secondary infection (1,47).

Surfactant treatment:

Although pulmonary damage includes inactivation of surfactant, the effectiveness of artificial surfactant administration has not been proven (4).

Bronchodilatators:

These agents relieve reversible bronchospasm by relaxing smooth muscles of the bronchi. Increased resistance from airway edema and reflex bronchoconstriction from irritation of airway receptors contribute to airway obstruction (4,5,47).

Beta antagonists such as salbutamol may asist with exacerbation of reactive airway disease, which is very common due to the inhalation of toxins and particulate debris. Nebulized N-acetyl cysteine has been shownto reduce cast formation and may be useful as a mucolytic (1,35).

New treatment modalities:

Percutaneous Carbon Dioxide Removal:

In 1999, Frank et al. showed that a percutaneous arteriovenous gas exchanger was effective in removing CO2 and reversing respiratory failure in an ovine model of adult respiratory distress syndrome (ARDS) produced by smoke inhalation and burn injury. In 2001, they showed that percutaneous AVCO2R produced a specific decrease in IL-8 in the smoke and burn injured animals. Furthermore, this effect was consistent with cell signaling mechanisms that increase the expression of IL-8 by cyclic stretching and the observed reduction in the number of neutrophils in the lung parenchyma (79).

Vitamin E:

Alpha tocopherol(vit. E) plays a pivotal role in clinical settings associated with oxidative stres. Oral administration of vit. E ameliorates the acute lung injury in sheep with burn and smoke inhalation injury. Aerosolized vit. E nebulization is a better treatment for patients with inhalation injury (80).

Seftazidim:

Cef abrogates the deleterious response of combined severe smoke inhalation and pneumonia to the airway and should be assessed further in studies of acute lung injury (81).

Pentoxifylline:

Pentoxifylline is a methylxanthine. It has been successfully shown in vitro and in vivo studies to inhibit cellular apoptosis and platelet activating mediators. A perliminary data of an ongoing study shows that early systemic administration of pentoxifylline in patients with severe burns and inhalation injury may decrease in-hospital mortality and days on mechanic ventilation without significant adverse effects (82).

L- Arginine:

L-Arginine (L-Arg), a nutritionally nonessential amino acid, is the critical substrate for NO production through enzymatic oxidation by NOS. It has been shown that the conversion from Arg to citrulline is significantly increased, and Arg levels are depleted in severely burned patients. With the induction of iNOS, the Arg substrate pool decreases to the extent of being the limiting reagent for the production of NO. L-Arg supplementation resulted in significant reduction in the extent of airway obstruction, with only 6,4% of bronchi and 7,0% of bronchioles obstructed (83).

Sivelestat:

Sivelestat appears to reduce neutrophil elastase concentration and neutrophil stiffness and improve pulmonary oxygenation in patients with acute lung injury at inhalation injury (84).

Outpatient Care:

After recovery from the initial injury, we must closely monitor those patients with residual airway obstruction and pulmonary damage. Patients must be refered with ongoing symptoms to a pulmonologist.

Protecting:

Primary prevention with functioning fire and smoke alarms and family education for fire hazards is critical to help avoid fire injuries. View prevention as the primary means to avoid inhalation injury and the use of smoke and CO detectors should be encouraged community-wide.

Complications:

Severe pulmonary injury, edema, and the inability to oxygenate or ventilate can result in death. Concurrent CO poisoning and inhalation of other products of combustion can cause hypoxemia, end organ injury, and morbidity.

Alexander et al. presented a patient with 80% TBSA and inhalation injury, who developed secondary spontaneous pneumothorax in the 11th post-burn week following MRSA pneumonia, which has not been previously reported (85).

The incidence of dysphonia in the population of burn patients appears to be high suggesting the need for such examination. A complete rehabilitation program for these patients should include vocal rehabilitation as well as efforts to control scar, increase range-of motion, strength and coordination, deal with posttraumatic stress disorder and facilitate social adjustment (86).

Prognose:

Most inhalation injuries are self-limited and resolve within 48-72 hours. The severity of direct pulmonary parenchymal injury depends on the extent of exposure and the type of inhaled toxins produced during combustion. In a cohort study they showed that initial CK levels appear to be a prognostic marker of the severity of injury (86).

Patient Education:

Programs aimed at educating young children about the dangers of playing with lighters and matches and programs teaching families how to safely escape from burning buildings should be used to further limit the number of children experiencing inhalation and burn injury. Anticipatory guidance during well child visits should include fire safety instructions.

Conclusion:

Smoke inhalation is associated with significant costs in human suffering, ICU and hospital length of stay, and financial expenditure. The best treatment remains prevention, and everyone should be encouraged to purchase a simple smoke detector and ensure that it is functional at all times. Early airway management, consideration for and treatment of noxious gaseous toxins, appropriate resuscitative protocols, and protective ventilatory strategies combined with aggressive management of any concomitant burn injury are the mainstays of initial treatment of the patient with smoke inhalation. The multidisciplinary team that represents modern burn management strategy is essential in the holistic approach to such a patient.

Table 3: Drugs for the treatment of inhalation injury (1, 4, 5, 47, 54, 77, 78, 99, Vademecum 2008).

Drug Name	Humidified Oxygen -- Use of high oxygen flow rates and a nonrebreathing-type face mask with a tight seal facilitates delivery of high levels of supplemental oxygen, which helps reverse the oxygenation defect created by ventilation-perfusion mismatch. Inhaled oxygen also helps in the displacement of CO from hemoglobin, decreasing the half-life of carboxyhemoglobin from 4-6 h in room air to 40-60 min in 100% FiO_2.
Pediatric Dose	Oxygen therapy should be continued until acidosis is corrected, the carboxyhemoglobin levels have fallen below 15%, and neurologic symptoms have resolved, which typically takes several hours
Contraindications	None reported
Interactions	None reported
Pregnancy	A - Safe in pregnancy
Precautions	Inspired oxygen concentrations of 50-100% carry a substantial risk of lung damage (dependent on inspired pressure and treatment duration)
Drug Name	Hyperbaric oxygen therapy (HBO) -- This therapy also displaces CO from intracellular stores and may improve mitochondrial function. HBO requires special facilities that are not available at all centers, resulting in a delay in treatment while the patient is transported to facility with HBO. Hyperbaric therapy should be considered in those patients who have high carboxyhemoglobin levels, who are unconsciousness, or who have other neurologic findings.
Pediatric Dose	The half-life of carboxyhemoglobin can be further reduced to 15-30 min in 2-3 atm of HBO
Contraindications	None reported
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	The potential benefits of preventing long-term neurologic sequelae from the secondary syndrome of CO poisoning should be weighed against the lack of patient access while undergoing HBO therapy; the anticipated use of hyperbaric therapy should never preclude the use of high concentrations of supplemental O_2; complications include middle ear and sinus occlusion, air embolism and seizures
Drug Name	Nebulized albuterol (Proventil, Ventolin) -- Relaxes bronchial smooth muscle by action on beta2-receptors with little effect on cardiac muscle contractility.
Adult Dose	Nebulizer: Dilute 0,5 mL (2,5 mg) of 0,5% inhalation solution in 1-2,5 mL of NS; administer 2,5-5 mg q15-20min, then space administration according to the patient's symptoms
Pediatric Dose	<5 years (nebulizer): Dilute 0.25-0,5 mL (1.25-2,5 mg) of 0,5% inhalation solution in 1-2,5 mL of NS and administer q15-20min, then space administration according to the patient's symptoms >5 years (nebulizer): Administer as in adults
Contraindications	Documented hypersensitivity
Interactions	Beta-adrenergic blockers antagonize effects; inhaled ipratropium may increase duration of bronchodilatation by albuterol; cardiovascular effects may increase with MAOIs, inhaled anesthetics, tricyclic antidepressants, and sympathomimetic agents
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in hyperthyroidism, diabetes mellitus, and cardiovascular disorders; adverse effects include tachycardia, palpitations, tremor, insomnia, nervousness, nausea, and headache
Drug Name	Racemic epinephrine 2.25% (MicroNefrin, AsthmaNefrin, Racepinephrine) -- Alleviates airway edema and reflex bronchospasm. Although it has not been directly studied, inhaled racemic epinephrine can theoretically provide relief from both airway edema and reflex bronchospasm in this setting.
Adult Dose	Nebulizer: 0.25-0,5 mL (diluted in 3 mL of 0,9% NaCl) inhaled via nebulization q4-6h prn
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity; cardiac arrhythmias; angle-closure glaucoma
Interactions	Increases toxicity of beta- and alpha-blocking agents and that of halogenated inhalational anesthetics
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in prostatic hypertrophy, hypertension, cardiovascular disease, diabetes mellitus, hyperthyroidism, and cerebrovascular insufficiency

Drug Name	Terbutaline (Brethine) -- Used for severe bronchoconstriction, especially in patients with underlying reactive airways disease. Acts directly on beta2-receptors to relax bronchial smooth muscle, relieving bronchospasm and reducing airway resistance.
Adult Dose	Loading dose: 0.25 mg IV Maintenance dose: 0.1-0.4 mcg/kg/min IV; titrate to effect
Pediatric Dose	Loading dose: 2-10 mcg/kg IV Maintenance dose: 0.08-0.4 mcg/kg/min IV; titrate to effect
Contraindications	Documented hypersensitivity; tachycardia resulting from cardiac arrhythmias
Interactions	Concomitant use with beta-blockers may inhibit bronchodilating, cardiac, and vasodilating effects of beta agonists; concomitant administration of MAOIs with beta sympathomimetics may result in severe hypertension, headache, and hyperpyrexia, which may result in a hypertensive crisis; MAOIs may potentiate activity of beta-adrenergic agonists on the vascular system; concurrent administration of oxytocic drugs such as ergonovine with terbutaline may result in severe hypotension
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Through intracellular shunting, terbutaline may decrease serum potassium levels, which can produce adverse cardiovascular effects; decrease is usually transient and may not require supplementation; paradoxical bronchoconstriction may occur with excessive use
Drug Name	Epinephrine (Adrenaline, EpiPen) -- Used for severe bronchoconstriction, especially in patients with underlying reactive airways disease. Alpha-agonist effects that include increased peripheral vascular resistance, reversed peripheral vasodilatation, systemic hypotension, and vascular permeability. Beta-agonist effects of epinephrine include bronchodilatation, chronotropic cardiac activity, and positive inotropic effects.
Adult Dose	0.1-0,5 mg (1:1000 concentration [1 mg/mL]) IM/SC q10-15min to 4 h; alternatively, 0.1-0.25 mg IV; single dose not to exceed 1 mg
Pediatric Dose	0.01 mg/kg/dose (0.01 mL/kg of the 1:1000 concentration [1 mg/mL]); not to exceed 0.5 mg/dose
Contraindications	Documented hypersensitivity; cardiac arrhythmias or angle-closure glaucoma; local anesthesia in areas such as fingers or toes because vasoconstriction may produce sloughing of tissue; use during labor (may delay second stage of labor)
Interactions	Increases toxicity of beta- and alpha-blocking agents and that of halogenated inhalational anesthetics
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in elderly persons and patients with prostatic hypertrophy, hypertension, cardiovascular disease, diabetes mellitus, hyperthyroidism, and cerebrovascular insufficiency; rapid IV infusions may cause death from cerebrovascular hemorrhage or cardiac arrhythmias
Drug Name	Nebulized heparin
Adult Dose	Unfractionated sodium heparin in a concentration of 25,000 IUmL-1
Pediatric Dose	-
Contraindications	-
Interactions	-
Pregnancy	-
Precautions	None of these adverse reactions have been reported: spontaneous, prolonged, or excessive bleeding, or breathing difficulties after heparin inhalation.
Drug Name	n-acetylcysteine (NAC)
Adult Dose	1200 mg/day
Pediatric Dose	Age: 0-2…1x100 mg. 2-6….2-3x100 mg. 6-14…2z200 mg.
Contraindications	The person that has not got cough reflex should not use this drug.
Interactions	Tetracyclines, antitussifs(they depress the cough reflex), nitrogliserine(they make trombosite agregation together)
Pregnancy	B - Usually safe but benefits must outweigh the risks
Precautions	It can make gastric irritation at people that have gastric ulser, The person that has not got cough reflex should not use this drug.

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