

Management of acute smoke inhalation injury

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Pulmonary injury from acute smoke inhalation is common in burn patients. Smoke inhalation is present in about 22% of all burn presentations, and in 60% where there are central facial burns.¹ Mortality data for smoke inhalation is disconcerting: at least 30% of burn patients with smoke inhalation injury die, compared with 2% of those without this type of injury.² Of all fire-related fatalities, 80%–90% are attributed to smoke inhalation.³ Overall, burns are a leading cause of accidental death, and smoke inhalation is now the major contributor to the morbidity and mortality associated with serious burns.² Indeed, inhalation injury is a greater contributor to overall morbidity and mortality than either percentage of body surface area affected or age.^{4,5}

Unfortunately, the improvements to other aspects of burn care have not been mirrored in treatment of smoke inhalation, and pulmonary complications have become an increasingly important consideration in burn injuries.² A burn to 50% of the total body surface area (TBSA) with accompanying smoke inhalation injury carries a 10% mortality risk, the same risk as a 73% TBSA burn with no inhalation injury.⁶ Inhalation injury has a high incidence of progression to serious clinical consequences: a 73% incidence of progression to respiratory failure (defined as hypoxaemia, multiple pulmonary infections or prolonged ventilatory support), and a 20% incidence of acute respiratory distress syndrome (ARDS).⁷ Clearly, advances in treatment of pulmonary injury sustained in fire exposure hold great potential for improving patient outcomes.

Toxic smoke compounds

The components of smoke, including heat, differ with each event, influencing the spectrum of effects.⁸ Smoke is a heterogeneous compound unique to each fire in both chemical composition and toxic features, depending on the materials combusted and availability of oxygen. The components of smoke that cause damage are:

- Heat.
- Particulates. These are deposited in the airways according to their size, with substances less than 1 µm diameter able to reach the alveolar zone suspended in air. At that site, they increase airway resistance, cause irritation and interfere with pulmonary surfactant.⁸
- Systemic toxins. Toxins such as carbon monoxide and cyanide adversely effect oxygen transport, availability and utilisation.

ABSTRACT

Pulmonary injury from smoke inhalation is common in burn victims, significantly contributing to the morbidity and mortality of fire-related injuries. The impacts of improvement in other aspects of burn care have not been mirrored in treatment of smoke inhalation. Smoke is heterogeneous and unique to each fire; it comprises particulates, respiratory irritants and systemic toxins as well as heat, all contributing to the pathological insult. Thermal injury below the vocal cords is rare because of effective heat dissipation in the upper airway. Particulate matter is the chief contributor to the pathophysiology of smoke inhalation injury, which has been extensively described. Of paramount importance is the cascade of inflammatory mediators following interaction of irritant substances with lung parenchyma, leading to pulmonary oedema, cast formation, airway obstruction, loss of hypoxic pulmonary vasoconstriction and ventilation/perfusion mismatch. Current treatment is based on supportive care, with airway management, mechanical ventilation, humidification and aggressive airway toilet the mainstays. Nebulisation of β_2 -agonists, heparin and *N*-acetylcysteine have a role in management, as does more specific treatment of carbon monoxide or cyanide intoxication. Many promising treatments are currently under investigation. The therapeutic strategy of decontaminating the lungs early after smoke exposure to prevent inhalation injury has received little attention and may be of significant value. This could potentially utilise amphoteric, hypertonic chelating agents developed for topical and ocular chemical exposures.

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- Respiratory irritants. Several components of smoke are respiratory irritants and are thus substantially implicated in the high mortality rates. Water-soluble gases such as ammonia and hydrogen chloride react with water contained in mucous membranes and produce strong alkalis and acids, which elicit intense and prolonged inflammatory reactions. Lipid-soluble irritants (eg, oxides of nitrogen, phosgene and aldehydes) exert effects more slowly as they dissolve into the cellular membrane.⁸

Heat. Burns to the nasal and oropharyngeal mucosa are common in fire-exposed victims, but it is rare to encounter thermal injury below the vocal cords.⁸ This is because heat is effectively exchanged in the upper air passages, with the temperature of inhaled air decreasing precipitously before the lower airway is penetrated.⁸ In environments containing air, steam and smoke at sufficient temperatures to cause thermal injury to the lower airway, the heat also causes rapid oedema of the glottis, and the resultant obstruction to the airway is rapidly fatal before the sequelae of pulmonary burn becomes apparent.⁸

Systemic toxins. These are products of incomplete combustion and include carbon monoxide and hydrogen cyanide. Carbon monoxide intoxication, together with heat incapacitation and a hypoxic environment, is the most common immediate cause of death from fire.⁸ Carbon monoxide is an odourless, colourless gas that binds with erythrocyte haemoglobin with about 250 times the affinity of oxygen. The resulting carboxyhaemoglobin molecule is inactive in oxygen transport and shifts the oxygen-dissociation curve to the left, impairing oxygen delivery at the tissue level. This results in a marked reduction in oxygen-carrying capacity of the blood.⁸ Furthermore, carbon monoxide competes with, and inhibits, oxygen binding to cytochrome oxidase, disrupting the aerobic metabolism chain and decreasing the capacity for cellular respiration.⁸ Thermal decomposition of nitrogen-containing polymers produces smoke containing hydrogen cyanide. When inhaled, cyanide combines with trivalent iron in the mitochondrial cytochrome a3 complex and thus inhibits electron transport and cellular respiration.⁸

Particulates and irritants. The chief contributor to the pathophysiology of smoke inhalation is particulate matter. Carbonaceous particles (soot) impregnated with a variety of toxins reach the alveolar level suspended in air.¹ The chemicals associated with these particles vary depending on the products combusted but commonly include aldehydes from cellulosic materials such as wood and paper; nitrogen oxides from fabric combustion; halogen acids and sulfur dioxide from rubber; ammonia from wool, silk and polyurethane; and phosgene from polyvinyl chloride.^{8,9} Water-soluble compounds are readily soluble in airway mucus and interact freely with tissue at more proximal levels of the respiratory system.⁹ Poorly water-soluble compounds (such as phosgene) penetrate the airway mucosa deeply and may cause severe delayed damage through late interaction with distal airway tissues, up to 48 hours after exposure.⁹ This is an important consideration when treating patients who present with apparently mild clinical effects after smoke inhalation.

Pathophysiology of acute smoke inhalation injury

The pathophysiology of acute smoke inhalation injury has been described in detail elsewhere.¹⁰⁻¹³ Here, I provide a brief overview as a basis for understanding the options in clinical management. As previously mentioned, above the oropharynx, thermal injury can produce significant inflammation, occluding the airway, but heat rarely causes damage below the vocal cords because it is effectively dissipated.⁸ However, the other components of smoke — particulate materials, systemic toxins and respiratory irritants⁸ — trigger a cascade of events, resulting in pulmonary oedema and ventilation/perfusion (V/Q) mismatch^{14,15} (Figure 1).

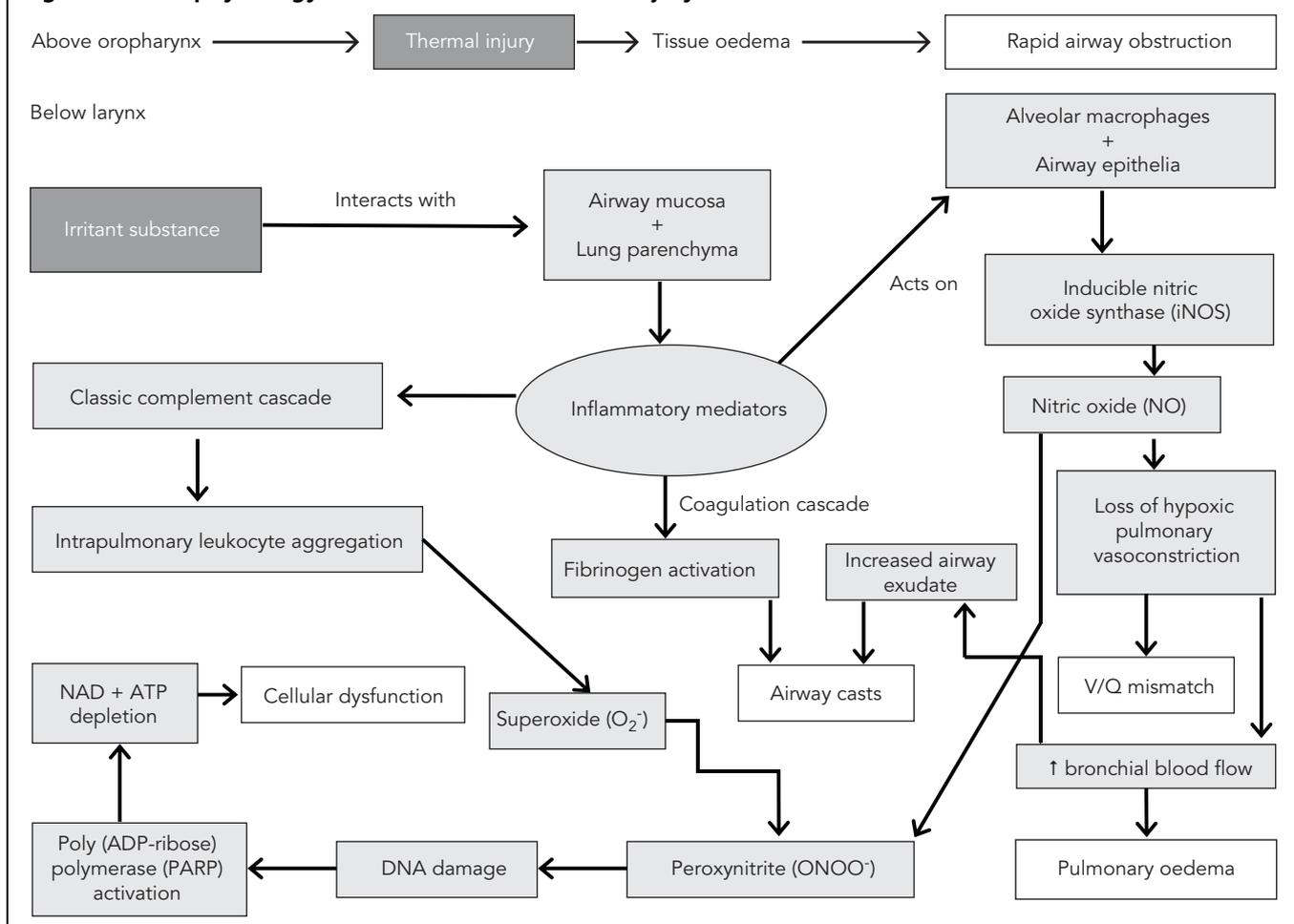
Of paramount importance is the cascade of inflammatory mediators activated by the interaction of irritant substances with the airway mucosa and lung parenchyma. Intrapulmonary leukocyte aggregation following activation of the classic complement cascade releases even more chemokines and cytokines, leading to the production of oxygen free radicals.⁷

Nitric oxide (NO) synthase is induced by respiratory epithelial cells and alveolar macrophages and produces NO, a powerful vasodilator. The formation of NO increases bronchial blood flow, decreases hypoxic pulmonary vasoconstriction in poorly ventilated areas of lung, and results in V/Q mismatch. NO also combines with superoxide (O_2^-) produced in large quantities by activated neutrophils to form peroxynitrite ($ONOO^-$).¹⁵ This reactive nitrogen species leads to DNA damage and subsequent activation of poly (ADP-ribose) polymerase, an important enzyme in DNA repair. This activation and subsequent action requires a large amount of chemical energy in the form of ATP and NAD, the depletion of which causes necrotic cell death of deprived energy-dependent tissues.¹⁵

The combination of these effects contributes to tissue injury and increased pulmonary vascular permeability, leading to decreased diffusion, oedema and V/Q mismatch.¹⁵ Furthermore, neutrophil infiltration and fibrinogen activation by inflammatory mediators causes airway cast formation and widespread plugging. These casts obstruct the airway, and subsequent efforts to mechanically ventilate the lung can induce ventilator-induced barotrauma when the patent lung becomes overstretched. The further tissue injury and production of chemokines leads to a potent accumulation of damage.¹⁵

Much of the study of smoke inhalation injuries in animal models has focused on aspects of this pathophysiological sequence. Attempts to manipulate and alter the chain of effects experimentally have reinforced these theories, and also suggested exciting treatment targets. Nevertheless, few experimental treatments have proven to alter the course of smoke inhalation injury or progressed to clinical

Figure 1. Pathophysiology of acute smoke inhalation injury



trials, and the mainstay of treatment is still supportive intensive care.

Current treatment of acute smoke inhalation

The first priority at the injury scene is rescue of the victim from the source of fire to minimise exposure time. This is usually the responsibility of fire-fighters. To reduce carboxyhaemoglobin levels as soon as possible, high-flow 100% oxygen should be administered immediately via facemask. The next step is a brief but careful body check to estimate the extent of smoke inhalation and assess accompanying injuries, such as burns and trauma. In addition, it is important to determine whether the victim has been exposed to an explosion, which can cause barotrauma to the lung. If possible, information about comorbidities should be obtained. Standard cardiopulmonary monitoring (electrocardiography, pulse oximetry and non-invasive blood pressure measurement) and intravenous access should be established.¹⁶

Airway management

After these basic measures, it must be decided how best to secure the airway. The risk of rapidly developing airway oedema has to be taken into account, even if no dyspnoea is present, but endotracheal intubation (especially at the injury scene) carries risks, such as oesophageal intubation, aspiration, barotrauma and laryngeal trauma. We consider that prophylactic endotracheal intubation is not generally advised in every patient and, depending on technical skill, for every physician or paramedic. Nevertheless, it is important to realise that airway management will become more difficult over time. Heat and smoke inhalation injury combined with extensive face or neck burns mandate intubation.¹⁶ In the case of oral burns with no inhalation injury, the safest approach is to secure the airway early, but patients with smoke inhalation injury but no facial or neck burns can be carefully observed and intubated later, if it becomes necessary.¹⁷

If the patient undergoes endotracheal intubation, the tube should be carefully secured. It should be left uncut, as

facial swelling in the next 24–48 hours can cause the end of the endotracheal tube to retreat into the oropharynx, necessitating re-intubation at the worst possible time. Accidental removal of the endotracheal tube occurs easily and may be fatal. In cases of vocal cord damage, tracheostomy may be necessary to prevent further damage.¹¹ The patient's head should be elevated to minimise facial and airway oedema. As a matter of course, haemodynamic stability is a prerequisite. Aerosolised adrenaline or corticosteroids may be beneficial to reduce upper airway oedema, but there is no conclusive evidence of their efficacy.

In the case of bronchospasm, nebulised administration of bronchodilators, such as β_2 -agonists, improves respiratory mechanics by decreasing airflow resistance and peak airway pressures. This improves dynamic compliance. In addition, β_2 -agonists have anti-inflammatory properties, decreasing inflammatory mediators such as histamine, leukotrienes and tumour necrosis factor- α . Finally, β_2 -agonists improve airspace fluid clearance and stimulate mucosal repair.^{18–21}

Treatment of specific intoxications

After initial stabilisation of the patient, information about the fire source, combustion products and estimated duration of exposure¹⁰ should be sought. In cases of a specific intoxication, appropriate therapies should be started. Carbon monoxide and cyanide toxicities have specific treatment strategies aimed at reducing serum levels of these substances, which impair tissue oxygenation.

Carbon monoxide: In the presence of elevated carboxyhaemoglobin, high-flow 100% oxygen should be delivered via facemask. Depending on the severity of injury and symptoms, the patient may need to be intubated and ventilated with an F_{iO_2} of 1.0. Rapid transportation to a facility that can provide hyperbaric oxygenation may be considered, as oxygen delivered at 3 atmospheres is able to reduce the half-life of carbon monoxide from 320 to 20 minutes.¹⁵ However, data are lacking on the efficacy of this technique.

Cyanide: Cyanide intoxication can be treated either supportively or with antidotes, the choice of which remains controversial. Amyl nitrate and sodium thiosulfate are used to oxidise haemoglobin to methaemoglobin, which preferentially binds cyanide. This is then able to dissociate freely and undergo metabolism by liver enzymes.¹⁵ However, as these substances are methaemoglobin-generators and can also impair oxygen transport, they should be used only in cases of proven diagnosis (increased plasma levels of cyanide) and under continuous monitoring in an intensive care unit. Methaemoglobin chelates cyanide to form cyanomethaemoglobin, which, as it dissociates, allows free cyanide to be converted to thiocyanate by a liver mitochondrial enzyme (rhodanase), using thiosulfate as a substrate. Thiocyanate is then excreted into the urine.¹¹

In contrast to these antidotes, hydroxocobalamin (vitamin B_{12a}), actively binds cyanide by forming cyanocobalamin, which is directly excreted via the kidney. In case of intoxication with 1 mg cyanide, hydroxocobalamin (50 mg/kg) is recommended. Because it averts methaemoglobin production, hydroxocobalamin can be used even in the preclinical setting. Accordingly, it represents the active compound of the "cyanokit" used in prehospital management of smoke inhalation injury in Europe, with a reported decrease in mortality.²²

Aggressive restoration of cardiopulmonary function augments the hepatic clearance of cyanide via rhodanase, and has been reported to be successful in severe cyanide poisoning (blood levels, 5.6–9 mg/L), as well as after ingestion, or smoke inhalation, even without the use of antidotes. The standard care of cyanide poisoning should therefore combine aggressive supportive therapy with primary pharmaceutical treatment using hydroxocobalamin.²³

Monitoring and investigations

Inhalation injury often develops with a latency of several hours. Airway management and oxygenation status of the patient, regardless of intubation status, need to be frequently re-evaluated to allow clinicians to react to the dynamic development of smoke inhalation injury.¹¹

After stabilisation of cardiopulmonary haemodynamics and pulmonary gas exchange, the assumed diagnosis of smoke inhalation injury needs to be verified. However, as there are currently no uniform criteria, diagnosis is usually a subjective decision based on the combination of history and physical examination, which is confirmed by diagnostic investigations. Symptoms of smoke inhalation injury that raise the index of clinical suspicion are listed in Table 1. Bronchoscopic examination of the airway represents the gold standard to detect a pathognomonic mucosal hyperaemia. Chest radiographs may show signs of diffuse atelectases, pulmonary oedema or bronchopneumonia.²³

The initial degree of injury is usually underestimated from the chest x-ray, as the injury is confined mainly to the airways.²⁴ Neither a uniform algorithm for assessing inhalation injury nor a reliable indicator of progressive respiratory failure in patients with smoke inhalation injury has yet been

Facial burns
Burned lips and nasal hairs
Soot in sputum
Changed respiratory mechanics (hoarseness, coughing, stridor)
Dyspnoea
Cyanosis
Neurological deficits (current or anamnestic unconsciousness, vertigo, nausea, vomiting)

established. This is largely explained by the extreme heterogeneity of the clinical presentation. In addition, the delay in the manifestation and development of acute lung injury as a consequence of systemic inflammatory response syndrome, initiated by accompanying burns or trauma, complicate the evaluation of the isolated effects of smoke inhalation. A useful algorithm for treatment is outlined in Figure 2. Frequent blood gas and sputum analyses are useful to monitor patients with smoke inhalation injury.¹¹

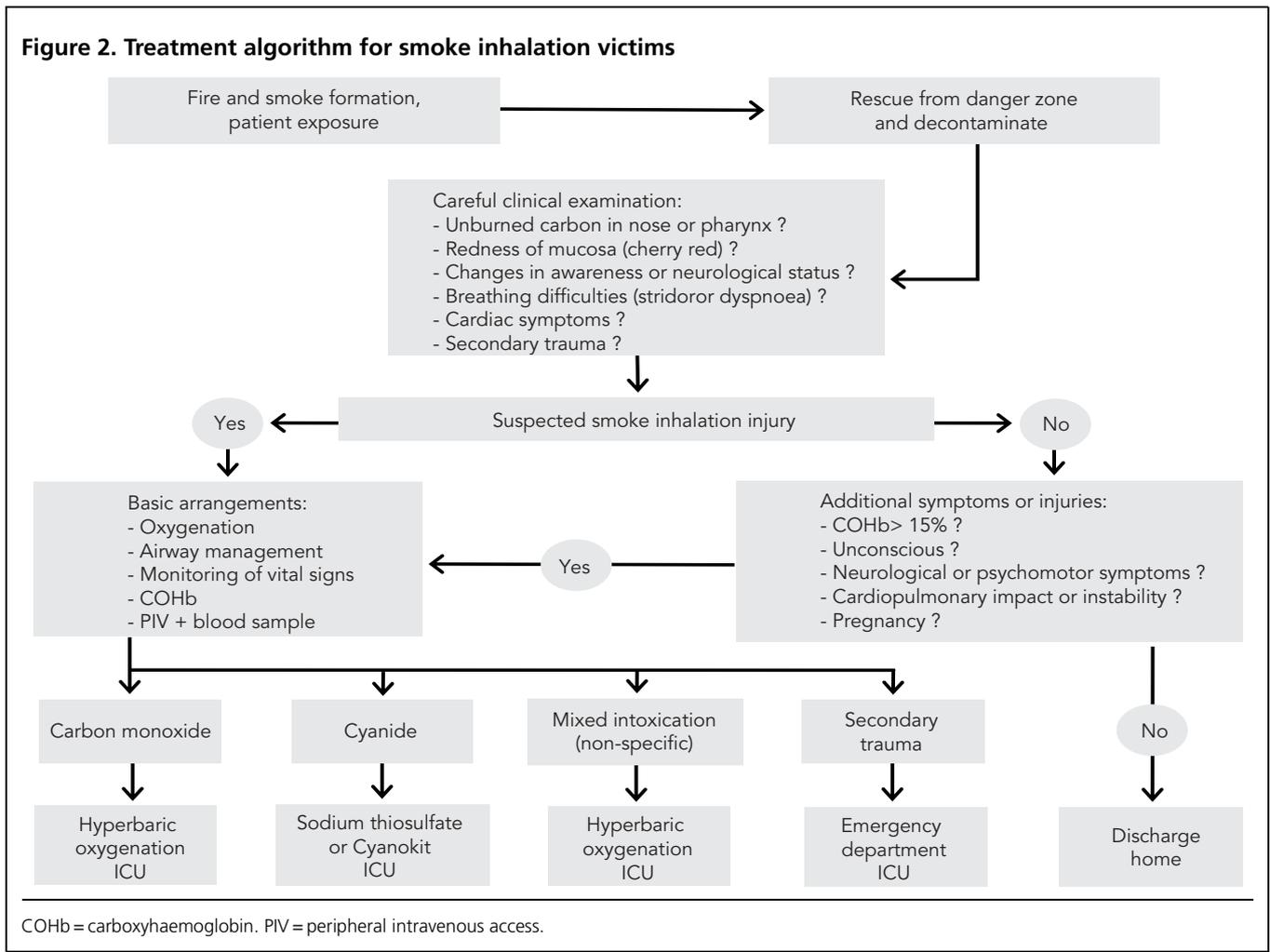
Fluid resuscitation

Appropriate fluid resuscitation for patients with smoke inhalation is still debated. It has been shown that fluid requirements are increased in smoke inhalation injury in patients with burns,²⁵ but this does not inevitably mean they are increased in isolated smoke inhalation injury. In fact, over-resuscitation may increase pulmonary microvascular pressures and oedema formation under the high-permeability conditions in early lung injury.¹³ In a retrospective study of more than 2346 trauma patients, Plurad et al found an increased incidence of late post-traumatic ARDS

with rising volumes of administered crystalloids and packed red blood cells.²⁶ Unfortunately, there is currently no evidence in the specific patient population with isolated smoke inhalation injury. Thus, against the background of no proven benefit and the potential risk of detrimental effects, increased fluids should be avoided in patients with isolated smoke inhalation injury. Instead, fluid resuscitation should be guided by the urine output and haemodynamic parameters of the individual patient. Dynamic parameters (such as changes in pulse pressure) rather than static parameters (such as central venous or pulmonary artery occlusion pressure) might be helpful.¹¹

Mechanical ventilation

Management of lung injury due to smoke inhalation has, to date, been largely supportive, with mechanical ventilation providing the mainstay of care, along with humidification and aggressive airway toilet.⁹ During the past two decades, mechanical ventilation has been investigated extensively. Low tidal volume ventilation with associated permissive hypercapnia has been shown to effectively reduce ventila-



tor-induced lung injury.²⁷ The Assessment of Low Tidal Volume and Elevated End Expiratory Pressure to Obviate Acute Lung Injury (ALVEOLI) trial revealed no effects of higher positive end-expiratory pressure (PEEP) levels in ARDS patients.²⁸ In addition, prone positioning has been shown to have no beneficial effect on mortality, despite a transient improvement in oxygenation.²⁹

Nebulisation of heparin and *N*-acetylcysteine in children with massive burn injury and smoke inhalation injury resulted in a significant decrease in incidence of re-intubation for progressive pulmonary failure, decreased incidence of atelectasis, and reduced mortality.³⁰ These data underscore the present treatment strategy for smoke inhalation injury at the Shriners Burns Hospital in Galveston, USA, which includes 5000 units of heparin and 3 mL of a 20% solution of *N*-acetylcysteine aerosolised every 4 hours for the first 7 days after the injury.

Experimental treatments

Treatment options remain limited despite interventional studies targeting most levels of the pathological process, particularly via the nebulised route.³¹ More invasive techniques to support patients with severe ARDS include extracorporeal membrane oxygenation and arteriovenous carbon dioxide removal, but no single technique has made a significant impact on current management.⁹

Vigorous airway toilet can be performed to counter obstruction by casts.¹⁵ Nebulised heparin can be used to prevent formation of fibrin casts, but heparin requires antithrombin for efficacy, which is deficient after burn injury.³² Consequently, concomitant administration of nebulised heparin and antithrombin has been studied, with proven success.³² The utility of this method was demonstrated in 2008³² after initial study of nebulised anticoagulants alone.³³ The preliminary investigation appeared to follow from the use of activated protein C in sepsis, and an extension of this substance's anticoagulant properties to efficacy in combined smoke inhalation and sepsis.³⁴ High-dose intravenous heparin was studied initially (with poor effect³⁵), followed by some improvement with the use of intravenous tissue plasminogen activator,³⁶ before nebulised delivery of heparin showed encouraging results of efficacy. Miller et al in April 2009 confirmed the preliminary results by demonstrating a reduction in lung-injury scores in patients with smoke inhalation injury administered nebulised heparin and the mucolytic *N*-acetylcysteine.⁷

Many drugs have proven effective in reducing the injury to the lung parenchyma in animal models, but only a few are in clinical use.⁹ These include the anticoagulants already mentioned, as well as *N*-acetylcysteine and inhaled β_2 -agonists such as albuterol.⁹ The Galveston group showed

potential for the use of albuterol in an ovine model in 2006 and called for further randomised clinical trials before making recommendations for clinical use.^{37,38}

Other drugs studied but not used extensively in clinical practice have aimed to intervene at various levels of the pathological process. Broadly, these have included anti-inflammatory drugs, NO inhibitors and antioxidants. Methylprednisolone and the anti-epileptic drug phenytoin have also been studied for their anti-inflammatory properties, with no protective effect and modest protection, respectively.^{39,40}

Because of the significant role of NO in the pathophysiology of smoke inhalation injury, modulating the production and effects of this substance has held considerable interest for investigators. Production of NO is catalysed by NO synthase (NOS), three isoforms of which have been described — two constitutive and one induced after injury and inflammation. It was previously thought that inducible NOS (iNOS) was largely responsible for the injurious effects of NO, but the inhibition of neural NOS (nNOS) has been the subject of promising research. Inhibition of both these isoforms of NOS has been shown to restore hypoxic pulmonary vasoconstriction in lungs impaired after the activation of iNOS following tissue injury from smoke inhalation.^{31,41,42} These strategies hold great potential but have not as yet progressed past animal models.

Promising results have also been obtained with antioxidants, again administered by the nebulised route. Gamma-tocopherol (vitamin E) has been used in aerosolised form in a sheep model to attenuate damage after smoke inhalation caused by oxygen free radicals. Pulmonary function, as measured by gas exchange, was improved in the treatment group compared with the placebo group.⁴³ Calls for further investigation into antioxidants as a treatment modality are warranted considering the positive results reported by Wang et al a decade earlier in Arizona.⁴⁴ This group nebulised 21-aminosteroid in a rabbit model, in the hope that its antioxidant effects would decrease smoke-induced oxidative damage. Pulmonary insult as measured by wet/dry lung weight and histological analysis as an indicator of pulmonary oedema were decreased, again in the treatment group. Although the rabbit model is not as widely reported, these results add further weight to antioxidant administration directly to the lungs via nebulisation as a useful treatment strategy in smoke inhalation injury.

Other strategies that have been investigated in an ovine model with no success include the endothelin-I receptor antagonist tezosentan (following the observation that the powerful vasoconstrictor endothelin-I was associated with lung injury in smoke inhalation)⁴⁵ and blockade of P-selectin, a neutrophil-adhesion promoter.⁴⁶

One of the more novel approaches with reported efficacy in attenuating severe respiratory failure after smoke inhala-

tion was reported in 1994 by LaLonde et al in Boston.⁴⁷ This group, again in an ovine model, aerosolised a complex of deferoxamine (DFO; an iron chelator) and pentastarch, and found this strategy had considerable efficacy after a standard smoke inhalation injury versus placebo and DFO alone. The authors concluded that free iron release and oxidant production in response to the injury were important in the pathophysiology of acute lung injury. Interestingly, the DFO-alone group showed no benefit versus the placebo group, suggesting that the chelating ability of DFO was less important than the antioxidant properties of the complex. DFO is specific for iron, but this study is the only one to explore the possibility of intervening early in the injury process to prevent pulmonary catastrophe, rather than reversing or minimising the injury after it has begun.

When signs of respiratory failure are present or imminent, mechanical ventilation is used supportively to ensure adequate respiratory function.¹⁵ This aims to ensure adequate ventilation to maintain alveolar patency without causing alveolar distension. Plugging from fibrin clots and cellular debris may result in barotrauma, causing further alveolar damage with mechanical ventilation.¹⁵ Several different modes are used, from conventional mechanical ventilation using a pressure-controlled rather than volume-controlled function to high-frequency percussive ventilation utilising subtidal breaths at high frequency. The latter is associated with decreased work of breathing, increased oxygenation, decreased peak pressures and decreased incidence of pneumonia.¹⁵ This method has been reported by Reper et al in Belgium, in respiratory failure following smoke inhalation in human patients, and was compared with periods of conventional ventilation in the same subjects.⁴⁸

Two randomised, controlled trials on “airway pressure release ventilation” (APRV) in mechanically ventilated patients — not patients with smoke inhalation injury — revealed beneficial effects on oxygenation and lower end-inflation pressures.^{49,50} However, there was no reduction in mortality. Further research is necessary to determine whether APRV represents a beneficial approach for ventilation of patients with smoke inhalation injury.

The volumetric diffusive ventilator (VDR; Percussionaire Corp, Sandpoint, ID, USA) is a pneumatically powered, pressure-limited ventilator that stacks oscillatory breaths to a selected peak airway pressure by means of a sliding venturi, Phasitron, resulting in low tidal volumes. In contrast to APRV, the effects of the VDR have been studied in patients with smoke inhalation injury. A prospective clinical analysis revealed improved gas exchange and a decrease in peak pressures.⁵¹ In addition, a retrospective study in 330 patients with inhalation injury reported a lower mortality rate.⁵² Although these studies compared the VDR with high-volume ventilatory strategies, data comparing it with modern low tidal volume ventilation are still lacking. Therefore VDR cannot be recommended at present.

Concomitant pneumonia or septic complications should be treated; intravenous gentamicin and ceftazidime have been studied individually to evaluate their impact in smoke inhalation and pneumonia caused by *Pseudomonas aeruginosa*.^{53,54}

When respiratory failure is severe, extracorporeal membrane oxygenation is an option, whereby the patient’s circulation is bypassed through an extracorporeal circuit, facilitating gas exchange through a semi-permeable membrane.¹⁵ A further, similarly invasive method of treating respiratory failure is arteriovenous carbon dioxide removal, which utilises an extracorporeal circuit to remove that gas and enables lower ventilatory pressures, with subsequent reduction in barotrauma from mechanical ventilation.⁵⁵

Future treatment options

The strategies discussed focus on ameliorating or reversing the pathophysiological consequences of smoke inhalation after significant damage has occurred, and are summarised in Table 2. As a large proportion of lower airway injury after smoke inhalation is a response to toxic chemicals following

Table 2. Treatment strategies for acute smoke inhalation

Current	Under investigation
<ul style="list-style-type: none"> • Rescue victim from source • High flow 100% O₂ • Body check • Intravenous access • ± Intubation (see <i>Discussion</i>) 	<ul style="list-style-type: none"> • Activated protein C • Anti-inflammatory drugs: Methylprednisolone • Phenytoin
<p><i>If upper airway oedema:</i></p> <ul style="list-style-type: none"> • Nebulised adrenaline • Nebulised corticosteroids 	<ul style="list-style-type: none"> • Nitric oxide synthase inhibitors • Antioxidants: γ-Tocopherol • 21-Aminosteroid
<p><i>If bronchospasm:</i></p> <ul style="list-style-type: none"> • Nebulised β₂-agonists 	<ul style="list-style-type: none"> • Endothelin-I receptor antagonist (tezosentan)
<p><i>If elevated carboxyhaemoglobin:</i></p> <ul style="list-style-type: none"> • High-flow 100% O₂ • Hyperbaric oxygen 	<ul style="list-style-type: none"> • P-selectin blockade • Nebulised deferoxamine-pentastarch complex
<p><i>If cyanide Intoxication:</i></p> <ul style="list-style-type: none"> • Amyl nitrate • Sodium thiosulfate • Hydroxocobalamin (“cyanokit”) 	<ul style="list-style-type: none"> • Mechanical ventilation: High-frequency percussive ventilation • Airway pressure release ventilation • Volumetric diffusive ventilator
<ul style="list-style-type: none"> • Mechanical ventilation: Low tidal volume • Nebulised heparin • Nebulised <i>N</i>-acetylcysteine 	<ul style="list-style-type: none"> • Extracorporeal membrane oxygenation • Arteriovenous carbon dioxide removal • Pulmonary decontamination with nebulised amphoteric chelating agents

their interaction with the respiratory mucosa, efforts to reduce or abolish this process is a logical step. Such a therapeutic strategy, administered early in the course of the exposure, would essentially aim to decontaminate the lungs, analogous to the administration of activated charcoal after a toxic ingestion, and to the flushing of the cornea after an ocular burn. As burns victims often present disproportionately well, with a paucity of clinical signs considering the impending respiratory compromise, or with considerable comorbid cutaneous burns, choosing treatment targets for early intervention is difficult if a delicate risk–benefit analysis is required.

A pulmonary decontamination compound and vehicle therefore need to be minimally toxic and able to be administered to the acutely unwell and seriously compromised patient alike. Ideally, such a treatment strategy would be:

- affordable and portable for use in emergency situations by first aid personnel;
- able to decontaminate a wide variety of toxic substances sufficient for empirical use;
- non-toxic or minimally toxic, sufficient for prophylaxis in well patients and unlikely to further compromise seriously unwell burns patients; and
- able to be nebulised for rapid and uncomplicated administration to the distal airways.

Products developed to reduce the damage incurred from topical and ocular burns in industrial settings are currently on the market and have demonstrably superior efficacy to water in decontamination of such accidents. These products are amphoteric, hypertonic chelating agents. Delivered directly to the airways in the nebulised form, they have the potential to decontaminate and thus prevent the serious sequelae of smoke inhalation.⁵⁶ Their binding effect minimises penetration of chemicals through the endothelial barrier, and their hypertonic nature means they further reduce penetration of toxic substances into tissues,⁵⁶ thereby potentially having a dual mechanism of action.

Importantly, their effects are non-specific, which is beneficial in the context of empirical treatment of a variety of combustion products. As the components of smoke are highly variable and unique to each fire, it is important that early treatment options have potential efficacy across a broad spectrum of toxic substances. The dual mechanism of action is also of benefit for inhalation of substances that may not necessarily form complexes readily, or neutralise appreciably.

Smoke inhalation injury in the context of burns continues to be an important health problem. The prognosis for these patients is long overdue for improvement, considering the advances in treatment for other aspects of burn care. We are too often reminded through modern warfare, terrorist incidents such as the 2002 Bali attacks, and other disasters such as the BP oil refinery explosion in Texas, 2005, and the Black Saturday bushfires in Victoria, 2009, what a threat fire

continues to be. Continuing investigation and development of treatment strategies holds tremendous potential to improve outcomes for victims of such tragedies.

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REVIEWS

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