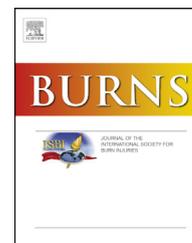


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Review

Inhalational injury and the larynx: A review

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ARTICLE INFO

Article history:

Accepted 31 October 2018

Keywords:

Airway burn

Larynx

Trachea

Inhalational injury

ABSTRACT

Objective: To review and discuss the existing research on the pathophysiology, impact and management of inhalational injury on the larynx and lower respiratory tract.**Data sources:** A literature search was conducted on the PubMed, MedLine, Embase, Web of Science and Google Scholar databases based on the keywords “airway burn”, “inhalational injury” and “larynx”.**Review methods:** Inclusion criteria included English language studies containing original and review data on airway injury. Data was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.**Conclusions:** Abnormal laryngeal and lower airway findings are common in burns patients and the incidence tends to increase with severity of the burns. Most patients with abnormal findings remain dysphonic decades after the initial injury. Larynx, the inlet to the airway, is exposed to the most intense thermal damage and highest concentration of chemical in inhalational injury. Airway injury is common and may result in long term morbidity. Healing of this tissue architecture is prolonged and different from cutaneous burn. Many patients receive prolonged intubation for medical complications that arise due to the burn injury. The degree of subglottic damage, however, is more extensive and occurs sooner compared with those without inhalational injuries.**Implications for practice:** With advances in acute medical and surgical management of burn and inhalational injury, airway injury is an important secondary outcome with lasting impact. Awareness of these potential complications and early involvement of medical and allied health team are important steps in improving patient care. A multi-disciplinary approach to management will optimise the short and long-term morbidity management and ultimately our patients' quality of life.

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1. Introduction

The incidence of reported inhalational injury amongst burns patients is wide ranging (10–47%), reflecting the lack of consensus regarding diagnostic criteria. A 6% incidence rate has gained a degree of acceptance [1]. What is agreed is that inhalational injury represents one of the most significant factors in whether a patient survives a burns injury and the potential for short and long-term morbidities [2]. In paediatric burns, lethal burn area of 10% mortality is 73% total body surface area (TBSA). If inhalational injury is involved, lethal burn area of 10% mortality falls to 50% TBSA [2,3]. Inhalational injury rises dramatically (up to 60%) in the setting of a central facial burn and places patients at risk of airway oedema and obstruction [2,4,5].

The larynx is strategically positioned for direct exposure to thermal injury and as such laryngeal burn injury is common. There is an approximately 50% chance of abnormal laryngeal findings in patients with mild to severe burns, with most of these patients remaining dysphonic decades after the initial injury [6]. An initial diagnosis of abnormal larynx following a burn injury raises patients' odds of experiencing significant morbidity in terms of airway, voice and swallow. The burn injury is often associated with other injuries and complications and as such laryngeal injury is often a secondary consideration. In contrast to advances in many aspects of burn critical care, significant gains have not been made in improving outcomes from inhalational injury [7].

The aims of this study are to review and discuss the existing research on the pathophysiology, impact and management of inhalational injury on the larynx and the lower respiratory tract.

2. Methods

A literature search was conducted on the PubMed, MedLine, and Embase databases based on the keywords “airway burn”; “inhalational injury” and “larynx”. The abstracts were scanned to assess their appropriateness to be included in our review.

3. Discussion

3.1. Pathophysiology: burn Injury

Risk of inhalational injury rises with TBSA. Burn severity depends on the duration of exposure and intensity of temperature [7]. Cuthbertson described two phases of the systemic effects: the burn shock or ebb phase, followed by a hypermetabolic or flow phase [2,5,8]. The pathophysiology is summarised in Fig. 1 [7,8].

3.2. Pathophysiology: inhalational injury

Inhalational injury occurs due to a combination of; direct thermal injury to the face and upper airway from inhalation of steam and/or hot gases, local and systemic chemical injury to the trachea, bronchi, alveolar and endothelial lining from toxic gaseous inhalation; impaired oxygen transportation due to carbon monoxide (CO) inhalation or impaired oxygen utilisation due to cyanide inhalation [5,7–9].

Individuals respond differently to respiratory insults such as mechanical ventilation, suggesting a genetic basis. Animal studies are underway to discover how genomics and inhalational injury intersect. Ma et al. examined ventilator

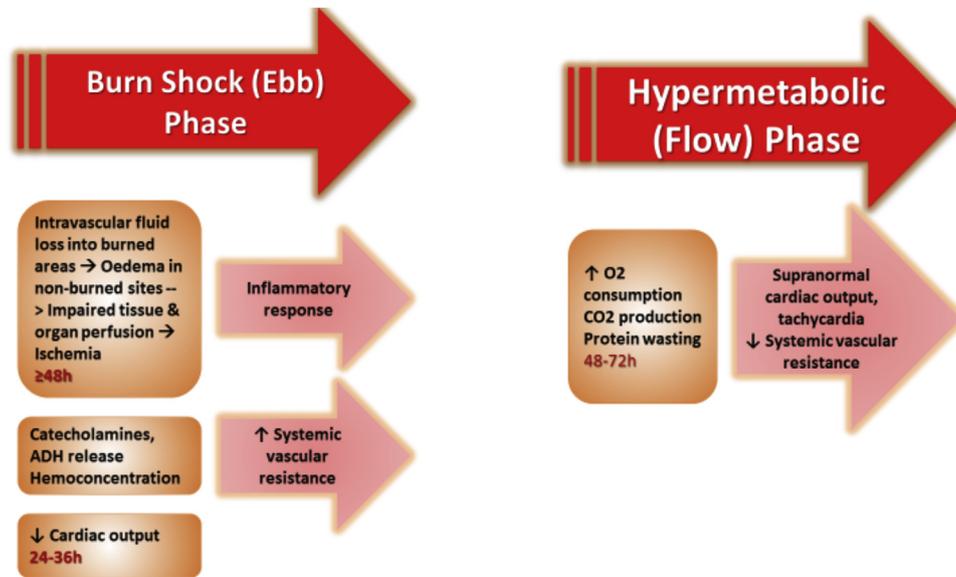


Fig. 1 – Pathophysiology of the burn injury: adapted from Source 8.

associated injury responses in rodents to help identify the role played by gene expression in patients' responses to airway injury [11]. It is thought that one's inflammatory response, for example the level of cytokine release, can help predict response to injury and potentially tailor treatment [12]. Advances in technology are making gene analysis accessible with the aim of tailoring future treatments to patients' genetics [13]. Translational research is underway to identify diagnostic biomarkers to enable prognostication of outcome following burns injury. Using proteomic techniques to identify proteins, there may be an understanding of how an individual will respond to burns and therefore enabling the provision of a tailored treatment plan. An understanding of the genomic signature may identify individuals at increased risk of sequelae of inhalational injury (for example respiratory infection or acute respiratory distress syndrome (ARDS)) and assist treating teams to anticipate complications [14].

3.2.1. Direct thermal injury

Larynx, the inlet to the airway is exposed to intense thermal damage and the highest concentration of chemical in inhalational injury. Laryngeal injury can occur as a direct result of inhalational injury.

Thermal injury is immediate, resulting in hyperaemia, erythema and oedema, followed by haemorrhage and ulceration [3,5,10]. There is substantial variability to the injury response and airway changes (oedema secondary to hyperaemia) demonstrated in animal models. The mucosa of the aryepiglottic folds, false cords (FC) and lingual surface of the epiglottis swell significantly unlike the arytenoids, vocal fold (VF) and subglottis [15]. The latter, surprisingly, are most prone to long term scarring and stenosis [15].

Thermal injury that extends beyond the laryngeal inlet results in direct thermal injury that is generally confined to structures above the carina, with the upper airway mucosa absorbing much of the heat before it reaches trachea due to the

low heat capacity, efficient heat dissipation and cooling of air of the upper airway, as well as reflex closure of larynx [3,4,13,16,20,21]. Animal studies have shown that heat triggers a protective reflex closure of glottis, so strong it can cause asphyxiation and death [3,6].

Mild inhalational injury is characterised by simple erythema, oedema and absence of soot deposits on the initial bronchoscopy; while severe injuries are manifested by ulceration, necrosis and soot deposit [3]. Progressive tissue damage is a function of increased temperature in the acute setting. With increasing severity, the damage can extend to the superficial lamina propria, resulting in decreased or absent mucosal wave [3]. In animal models little to no VF tissue changes are observed at 80°C but beyond this there is significant oedema and laryngeal tissue damage [3,7,16]. Typically, temperatures >200°C are commonly reported in house fires, resulting in vascular congestion, neutrophil infiltration, separation of VF layers related to significant oedema, and liquefactive necrosis [3,7]. At 310°C there is complete distortion of identifiable normal laryngeal landmarks [7]. The depth of tissue damage was incremental with each increased temperature condition: heat effects extended deep into the muscle at 150-160°C [7]. Clark et al. reported severe inflammation and softening of the tracheal cartilage observed at the time of tracheostomy [16] in patients exposed to direct thermal injury. This can be delayed by 2 and 5 days after exposure with many of the most significant changes apparent ≥24h later [10].

3.2.2. Local chemical injury

Respiratory compromise is usually caused by chemical irritation, with the nature and severity dependent on the materials burnt, temperature of combustion and duration of exposure [2,5]. Rubber and plastics produce sulphur dioxide, nitrogen dioxide, ammonia and chlorine which form corrosive acids and alkalis when combined with water in alveoli [19]. The precise irritants in soot depend on the materials combusted

[20]. Nitrogen containing substances (wool for example) form hydrocarbons, aldehydes, ketones and acids; cotton and wool produces toxic aldehydes; incomplete combustion of any carbon containing matter (eg wood) produces CO and combustion of acrylic, rubber and plastics produces cyanide [4,10]. The chemicals in smoke promote neutrophil-generated superoxides and reactive oxygen species. The resulting inflammatory response impairs airway ciliary transport function, resulting in bronchoconstriction, bronchial exudate and airway casts formation [5]. The mucosal necrosis and sloughing, interstitial neutrophilic infiltrates and exudation of protein-rich viscous secretions may cause further distal airway obstruction, oedema, atelectasis, and impair bacterial clearance, increasing the risk of rapidly developing tracheo-bronchiolitis and bronchopneumonia [5,17,21]. The alveolar macrophages produce cytotoxic mediators which augment and/or regulate inflammatory responses of the lungs. If these circumstances arise the exaggerated release of cytotoxic agents can cause indiscriminate injury to neighbouring parenchymal cells [19]. The impaired chemotactic and phagocytic functions increase the risk of infection [4,14]. This can result in progressive respiratory failure over the course of 48h due to decreased lung compliance, ventilation/perfusion (V/Q) mismatch and increased dead space ventilation [5].

3.2.3. Impaired oxygen transport/utilisation

CO has a 200-fold higher affinity than oxygen to the same binding sites on haemoglobin, decreasing its oxygen carrying capacity and leading to hypoxia [5,8]. CO shifts the oxyhaemoglobin dissociation curve to the left, altering its shape and reducing oxygen release to tissues [5,8]. Exposure to CO resulting in carboxyhaemoglobin becomes toxic at a concentration of >15% and lethal at >50%, though susceptibility depends on patient factors such as pregnancy, the presence of ischaemic heart disease and extremities of age [8,22].

Cyanide poisoning should be suspected in patients with an anion gap metabolic acidosis despite apparent adequate oxygen delivery [8]. It binds to the mitochondrial cytochrome oxidase, blocking the final step in oxidative phosphorylation, forcing cells to generate adenosine triphosphate via anaerobic metabolism, resulting in lactic acidosis [5,8]. Concentration >20ppm is toxic whilst >100ppm can lead to seizures, coma, respiratory failure and death [8].

3.2.4. Systemic inflammatory response syndrome

The tissue destruction in burns injury results in activation of a cytokine-mediated inflammatory response that leads to dramatic pathophysiologic effects at both local and distant sites [8,9]. Respiratory compromise can occur in severe cutaneous burns without inhalational injury due to this, the effects of fluid resuscitation, infection and ventilator-associated lung injury [4,7,13]. The bronchoscopic features resemble airway injury [8]. When the burns injury exceeds 25–30% TBSA, edema may ensue even in non-injured tissues [10]. Pulmonary edema occurs due to increased vascular permeability, which is thought to be mediated by increased nitric oxide production, resulting in cellular injury and lipid peroxidation [5]. It may also develop from fluid shift-induced volume overload or persisting airway inflammation resulting in airway oedema and secretions [4,13]. Circulation play a significant role in

absorbing heat in the upper airway during a thermal burn, and the increase in bronchial blood flow may further precipitate pulmonary edema [4,13,18,19].

3.3. Sequelae: inhalational injury

Inhalational injury has important implications as it increases resuscitation fluid volumes by up to 50% and there is a significant increase in the need for ventilatory support with the majority of patients with confirmed inhalational injury with greater than 2 days of intubation [1,4,7,13].

Inhalational injury is a leading cause of mortality amongst burns patients with an incidence of 10–20% [25]. After age and TBSA, it is the most important predictive factor for mortality from burns [26]. Osler et al. developed a score to predict mortality after burns injury: age plus TBSA contribute equally to mortality, and inhalation injury adds an equivalent of 17% to a burn [27].

Respiratory infection is a common and a significant development in a burns patient. The prevalence is reported to be up to 44%, with the risk increased in inhalational injury [1,4,9,28]. The reason for this increase is likely multifactorial and includes: the presence of the underlying pulmonary injury contributing to the need for tracheostomy, greater burn size and prolonged mechanical ventilation in this group [29,30]. In burns patients with a tracheostomy or ETT there is a risk of ventilator-associated pneumonia, which is higher in inhalational injury with a reported risk ratio of 5.09 [31,32]. Evidence regarding the best ventilator setting in burns patients with inhalational injuries remains inconclusive [33].

3.4. Sequelae

Airway oedema is postulated to play a role in long-term voice and airway outcomes [7]. Younger children have a higher risk of airway obstruction compared to older children and adults due to the smaller diameter of their airways [13,34]. There is a paucity of data regarding the significance of this.

Longer term complications range from inter-arytenoid pachyderma or erythema, VF edema, webbing, granulation tissue formation, scarring, keyhole deformity, posterior glottis abnormalities, subglottic and tracheal stenosis, and laryngeal hyperfunction [3,35]. Subglottic stenosis tends to be more severe [24].

Scarring will stiffen the VF and interfere with their vibratory function, while in the posterior larynx it may result in a scar band, VF weakness or apparent paralysis [6]. Videostrobolar-yngoscopy may reveal abnormal laryngeal findings despite normal voice in burns patients [6].

Laryngeal injury may also occur secondary to endotracheal intubation (ETI). These injuries are attributed to the difficulty of intubation resulting in traumatic laryngoscopy or intubation performed at the scene of injury/non-burns centre emergency room [2]. These patients may require multiple attempts at intubation. A 2016 retrospective study by Romanowski et al. found that more than a third of facial burn patients underwent unnecessary intubation prior to transport to hospital with some patients experiencing ETI associated complications [36]. Many patients undergoing prolonged intubation for medical complications secondary to the burn injury. Laryngeal injury is more

likely when the endotracheal tube (ETT) is resting on an oedematous glottis [6]. The degree of subglottic damage from ETI is more extensive and occurs sooner in patients with inhalational injuries compared to those without [6].

It is difficult to distinguish between airway stenosis arising from ETI and that of the initial inhalational injury [36]. ETI may result in posterior commissure oedema with or without arytenoid swelling, arytenoid cartilage dislocation and VF paresis due to pressure on recurrent laryngeal nerve [3,5,27]. Other contributing factors include number of intubations, ease of intubation, ETT size, cuff material and pressure, co-existing gastroesophageal reflux disease, and ETT motion [6]. All these may have additive effects on temporary or permanent dysphonia. Aspiration can occur due to VF paresis secondary to laryngeal sphincter dysfunction in prolonged intubation or the presence of nasogastric feeding tube [3].

Awareness of these potential complications and early involvements of otolaryngologists and speech pathologists are important steps in improving their care and outcome.

3.5. Pathophysiology: laryngeal healing

VF healing is different from cutaneous burn. It is prolonged with full re-epithelialisation taking up to 10 weeks [7]. Re-epithelialisation is prolonged in the subglottis, but fibroplasia and fibrosis in the subglottic lamina propria are reported to be similar to dermal wound healing [37]. The presence or loss of the basal cell layer influences the speed of repair [38]. If this layer is disturbed granulations, cicatrization and stenosis may ensue [38].

VF collagen content, unlike the cutaneous site, does not stabilise at three weeks following injury, but rather at 6 months [36]. Within 24 h following an injury, fibrinous clot forms with premature neo-lamina propria immediately deep to this [36]. Massive cellular proliferation of inflammatory cells and fibroblasts is noted at the wound site by 72 h with primitive epithelial coverage, epithelial migration and hypertrophy at the edges of injury [36]. By day 5 after injury, epithelial hypertrophy has increased, with new collagen deposition which is denser than that in the normal mucosa, as well as the presence of new vascular channel formation [36]. This is replaced by a more mature collagen matrix deposition by 7 days with continued epithelial hypertrophy, and replacement of the necrotic epithelium [36]. By 10 days, the fibrosis appears more mature with dense, unorganised collagen deposition showing early lamination, and the epithelial coverage is complete [36]. By 3 weeks after injury, the neo-matrix is laminated with increased density over normal tissue but has yet to regain its normal layered structure. The collagen density decreases prior to scar maturation in VF [36].

3.6. Management

3.6.1. Assessment

Early recognition and management of laryngeal injury in a multi-disciplinary team improves patient outcomes and limit potential morbidity.

Upper airway swelling may be delayed and not peak until 24 h after injury and therefore high index of suspicion and frequent re-evaluations with bedside fiberoptic nasendoscopy

are essential. Where the inhalational injury is due to chemicals there may be no external signs. The lack of consensus regarding the grading of inhalational injury makes it difficult to compare treatment and to reach consensus regarding best practice [7,10,39]. A uniform grading system would aid in the prediction of patients at risk for increased pulmonary dysfunction, respiratory failure and mortality. The most commonly used injury grading system is the Abbreviated Injury Score which grades damage from 0 to 5, in which a score of 0 relates to no evidence of trauma on scoping, and 5 where the patient has evidence of mucosal sloughing, necrosis and endoluminal obstruction [32,40]. With a standardised and validated scoring model, improved prognostication may be possible. A prospective multi-centre study is underway to address this using clinical, radiographic, bronchoscopic and biochemical parameters [41]. Without uniform diagnostic criteria it is not possible to build an evidence-based approach to the management of inhalational injury because outcome data between institutions becomes difficult to compare [5,42].

Bronchoscopy, generally performed under general anaesthesia is the gold standard for assessment of injury and forms the backbone of many models of injury grading [40,41]. It aids in early prediction of acute lung injury and mortality risk, as even when chest X-ray and blood gases are normal, bronchoscopy can identify early airway injury [31,34,42]. However, it is unclear whether early identification of the degree of mucosal damage correlates with improved outcomes [17]. Chest X-rays are normal until secondary complications of inflammation, infection or atelectasis develop and offer limited benefit in the acute setting [46]. To gauge the degree of pulmonary insult, chest computed tomography (CT) in combination with bronchoscopy has been shown to be better at predicting airway dysfunction than either in isolation [34,44]. There is no current consensus on optimal timing of scanning and how to interpret conflicting radiologic and scope findings.

There is no rapid diagnostic test for cyanide poisoning. Co-oximetry is used to diagnose CO poisoning, though deranged arterial blood gas and central venous saturations can be used as proxy measures of injury severity [5].

3.6.2. Treatment

The treatment of inhalational injury is generally supportive, with the aim to prevent secondary lung injury. Airway oedema generally resolves in 3–6 days and the management ranges from conservative with head of bed elevation and avoidance of excessive fluid administration in milder cases, to intubation with lung protective mechanical ventilation (empiric use of low tidal volumes ≤ 6 mL/kg ideal body weight and plateau airway pressures < 30 cm H₂O in adults) and aggressive pulmonary toilet (lavage) [5,8]. Toileting secretions and debris removes cast formation and enhances V/Q ratio. Positive pressure ventilation may increase resuscitation fluid volumes [8].

The aim of inhalational injury management is to restore airway patency, preserve a satisfactory quality of voice and progress the patient towards extubation [36]. Bronchoscopy may be used as a therapeutic tool. It plays a useful role in lavage where it reduces particulate matter load and theoretically reduces injurious inflammatory response, thereby improving airway patency. This has been shown to improve

outcomes by reducing duration of mechanical ventilation and length of Intensive Care Unit (ICU) stay [45,46].

3.6.3. Endotracheal intubation vs tracheostomy

ETI is indicated for patients with or at risk of impending airway obstruction (history of exposure to fire and smoke in enclosed space, physical findings of moderate-severe facial and/or oropharyngeal burns, circumferential neck burns or airway injury on flexible nasendoscopy), severe cognitive impairment (GCS ≤ 8), major cutaneous burn ($\geq 40\%$), treatment for respiratory insufficiency resulting in impaired oxygenation and/or ventilation due to lung injury [1,4,7,11,23,27]. These patients have an estimated 5–10% chance of difficult intubation, therefore prophylactic intubation is recommended [1,11]. Patients with inhalation injury are at significant (20–30%) risk of acute upper airway obstruction and hence prompt identification is paramount [50]. Conversely, common indications for intubation such as facial burns, singed nasal hairs or soot in the upper airway have been reported as insensitive and non-specific [1,27,34,48]. Frequent re-assessment with flexible nasendoscopy is therefore critical.

ETI is not a benign procedure with significant risks: difficulty or inability to intubate, accidental extubation, atelectasis, pneumothorax, nosocomial infection, tracheal injury and death [37]. The challenge of ETI in the acute setting is potentially compounded by location — the risks of ETI are higher when performed in the emergency department (ED) or (ICU) compared with the operating room [37]. Failed intubation is reported to occur in 1 in 50 attempts in ED/ICU compared with 1 in 2000 in the operating room [37]. Some authors have shown that the presence of tracheostomy does not contribute to the incidence of pneumonia or tracheitis but rather the ETT [2]. Romanowski et al. have highlighted the need for a guideline regarding which patients to intubate and for which it is likely to be unnecessary [36].

The use of nasotracheal intubation has been reported by some to cause less laryngeal erosion than oral intubation though this is debatable [11,52]. Patients intubated because of inhalational injury are at a significantly higher risk of post-intubation stenosis even if intubated for a little as 6 days, in contrast to the 3 weeks risk attributed to patients without inhalation injury [37,52]. Minimising ETT changes, use of low pressure cuffs, reflux prophylaxis (up to a month after extubation), use of coloured tube feedings to facilitate an early recognition of aspiration and early tracheostomy have been advocated [2,11].

Ching et al. found a lack of consensus regarding best practice around mechanical ventilation for burns patients [24,50]. Some case studies indicate success with low tidal mechanical ventilation and/or extracorporeal life support, especially in the setting of ARDS [13,54].

Patients suffering facial and cervical burns are at high risk of laryngeal burn and therefore airway obstruction. Early identification of high risk patients allows for tracheostomy planning — prophylactic as opposed to emergency tracheostomy. Prophylactic tracheostomy may be preferable as it tends to be an easier operation and holds a lower surgical risk compared to emergency tracheostomy following upper airway obstruction, though a prospective multi-center study would better elucidate which patients should have a tracheostomy

and the optimal timing for the procedure [15,18,55,56]. There is no consensus on the timing of tracheostomy, ranging from 10 to 14 days, or after the neck burn has been excised and grafted, usually within 5–7 days [46]. Saffle et al. have shown and more recent studies reiterated that early tracheostomy does not result in superior outcomes [29,30,57]. Neither extubation or decannulation were expedited, though they did show that early tracheostomy contributed to patient comfort and airway security [57]. The same study found that whether patients had early tracheostomy (performed on the next operative day) compared to conventional timing (day 14 after burn) did not affect ventilator support requirements, incidence of pneumonia or mortality [57]. The timing should be tailored to each patient's individual need as the larynx is more susceptible to ETI.

Bypassing the larynx avoids sequelae of ETI such as reflex bronchospasm instigating bronchoconstriction [37]. Difficult intubation resulting in multiple attempts risks; tracheal lacerations or esophageal perforations, pressure necrosis, ulceration, granulation, fibrosis and posterior glottic webs [37]. Tracheostomy improves ventilatory mechanism, improves secretion management with increased ease of suction, minimises laryngeal intubation and allows patients to communicate and mobilise [20,23]. Tracheostomy is not without its own complications — airway bleeding from tube friction, sub-cutaneous emphysema, sepsis, scarring, stenosis and suprastomal collapse to name a few.

3.6.4. Medical therapy

Steroids are believed to be beneficial but there is insufficient evidence of efficacy [24]. 100% and hyperbaric oxygen therapies are used to treat CO poisoning, whereas cyanide poisoning is optimally treated with hydroxycobalamin over previously favoured exogenous thiosulfate [7,53].

Preliminary studies regarding the use of chelating drugs to scavenge toxins, the role of stem cells and use of novel medications to reduce and treat airway complications are underway [10,26]. Nebulised or aerosolised heparin in combination with mucolytic agent N-acetylcysteine (NAC) can reduce airway cast formation and therefore injurious systemic responses [43,49,51,54]. Improved patient outcome measures following use of this therapy include reduced reintubation rates, atelectasis, hospital costs and mortality compared with controls [43,51]. A systematic review which encompassed treatment with heparin however urged a more circumspect approach to this treatment and caution regarding potential side effects [60]. Treatment with nebulised tissue plasminogen activator to breakdown fibrin and address cast formation has shown promise in animal trials [5]. Use of bronchodilators has been shown to improve airway compliance, cast clearance and V/Q ratio [33].

Animal studies using nebulised Epinephrine and Albuterol have shown promising results in improved partial pressure arterial oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio [52,61]. Inhaled nitric oxide (NO) has shown promise in respect to improving V/Q mismatch by acting as a potent vasodilator, reducing both pulmonary hypertension and shunting in several studies, meta-analyses however have failed to show reduction in days ventilated and overall mortality and there is a potential for NO associated complications, for example renal dysfunction [57,58,64,65].

The use of scavenger agents to mop up damaging reactive oxygen species (ROS) is preliminary but promising. Examples include the use of γ -tocopherol and α -tocopherol (vitamin E) [59,60]. These two agents block ROS which would otherwise activate the arginase pathway, causing collagen deposition which would result in impaired pulmonary function [66].

There is a growing body of evidence for the utility of stem cells (amniotic, bone marrow or fat derived for example) as potential treatments in inhalational injury. Stem cells appear to reduce airway damage by aiding repair of injured tissue. The mechanism for this is thought to relate to the ability of stem cells to induce release of growth factors, inhibit levels of both inflammatory cytokines and apoptosis [67,68]. An example of this which relates specifically to airway function: stem cells may help 'recover' lung fibroblast function, to which smoke exposure is deleterious [69].

3.6.5. Speech rehabilitation

Inhalational injury patients with voice dysfunction benefit from early voice rehabilitation with speech therapists to enhance long-term voice outcomes and to reduce the risk of webbing [38].

3.6.6. Surgical intervention

Glottic and subglottic stenoses in inhalational injury have been reported to be more severe, and multiple procedures are more common [24].

At present a consensus has not been reached regarding optimal timing of surgical intervention. Wan et al. recommend early open procedures in these patients [24]. It has been advised that the fibrosed mucous membrane be removed to the level of the perichondrium and the denuded areas grafted with local mucosal flaps, free mucosal or skin grafts [24]. T-tube stents, if used, are left in place for 8–12 weeks [24]. Early repair of subglottic stenosis may result in improved outcomes [6]. Conversely, Gaissert et al. report that delayed repair leads to fewer recurrences [38].

Airway stenosis is commonly treated with resection and prolonged tracheal stenting (mean duration of 28 months). Gaissert et al. report that this results in a high likelihood of the recovery of a functional airway and voice [38].

Optimal management of inhalational injury patients involves multi-disciplinary cooperation among emergency physicians, intensivists, anaesthetists, burns surgeons, otolaryngologists, plastic surgeons, speech and language pathologists, physiotherapists and occupational therapists [66].

4. Conclusion

With advances in acute medical and surgical management of burns and inhalational injury, laryngeal injury is an important secondary outcome with the potential for long term morbidity. Research is underway investigating the role of novel approaches and new therapies to apply to inhalational injury patients. Of note, an emerging field which holds promise in revolutionising outcomes of inhalational injury patients is gene therapy and being able to provide targeted treatments to individual patients. In addition to novel treatment, ongoing application of a multi-disciplinary approach will optimise the

short and long-term outcomes and ultimately our patients' quality of life.

Conflicts of interest

None.

REFERENCES

- [1] Herndon DN. Total burn care: fourth edition. , doi:<http://dx.doi.org/10.1016/C2009-0-42513-3>.
- [2] Costa Santos D, Barros F, Frazão M, Maia M. Pre-burn centre management of the airway in patients with face burns. *Ann Burns Fire Disasters* 2015;28:259–63.
- [3] Barrow RE, Spies M, Barrow LN, Herndon DN. Influence of demographics and inhalation injury on burn mortality in children. *Burns* 2004;30:72–7, doi:<http://dx.doi.org/10.1016/j.burns.2003.07.003>.
- [4] Valdez TA, Desai U, Ruhl CM, Nigri PT. Early laryngeal inhalation injury and its correlation with late sequelae. *Laryngoscope* 2006;116:283–7, doi:<http://dx.doi.org/10.1097/01.mlg.0000197932.09386.0e>.
- [5] Goh CT, Jacobe S. Ventilation strategies in paediatric inhalation injury. *Paediatr Respir Rev* 2016;20:3–9, doi:<http://dx.doi.org/10.1016/j.prrv.2015.10.005>.
- [6] Casper JK, Clark WR, Kelley RT, Colton RH. Laryngeal and phonatory status after burn/inhalation injury: a long term follow-up study. *J Burn Care Rehabil* 2002;23:235–43, doi:<http://dx.doi.org/10.1097/00004630-200207000-00003>.
- [7] Jones SW, Williams FN, Cairns BA, Cartotto R. Inhalation injury: pathophysiology, diagnosis, and treatment. *Clin Plast Surg* 2017;44:505–11, doi:<http://dx.doi.org/10.1016/j.cps.2017.02.009>.
- [8] Cuthbertson DP. Post-shock metabolic response. *Lancet* 1942;239:433–7, doi:[http://dx.doi.org/10.1016/S0140-6736\(00\)79605-X](http://dx.doi.org/10.1016/S0140-6736(00)79605-X).
- [9] Brenner M, Kreuter K, Mukai D, Burney T, Guo S, Su J, et al. Detection of acute smoke-induced airway injury in a New Zealand white rabbit model using optical coherence tomography. *J Biomed Opt* 2007;12:051701, doi:<http://dx.doi.org/10.1117/1.2798637>.
- [10] Sabri A, Dabbous H, Dowli A, Barazi A. The airway in inhalational injury: diagnosis and management. *Ann Burns Fire Disasters* 2017;30:24–9.
- [11] Ma S-F, Grigoryev DN, Taylor AD, Nonas S, Sammani S, Ye SQ, et al. Bioinformatic identification of novel early stress response genes in rodent models of lung injury. *Am J Physiol Cell Mol Physiol* 2005;289:L468–77, doi:<http://dx.doi.org/10.1152/ajplung.00109.2005>.
- [12] Cuenca AG, Gentile LF, Lopez MC, Ungaro R, Liu H, Xiao W, et al. Development of a genomic metric that can be rapidly used to predict clinical outcome in severely injured trauma patients. *Crit Care Med* 2013;41:1175–85, doi:<http://dx.doi.org/10.1097/CCM.0b013e318277131c>.
- [13] Hazeldine J, Hampson P, Lord JM. The diagnostic and prognostic value of systems biology research in major traumatic and thermal injury: a review. *Burn Trauma* 2016;4:33, doi:<http://dx.doi.org/10.1186/s41038-016-0059-3>.
- [14] Ruiz-Castilla M, Roca O, Masclans JR, Barret JP. Recent advances in biomarkers in severe burns. *Shock* 2016;45:117–25, doi:<http://dx.doi.org/10.1097/SHK.0000000000000497>.
- [15] Flexon PB, Montgomery WW, Cheney ML, Turner PA. Management of patients with glottic and subglottic stenosis resulting from thermal burns. *Ann Otol Rhinol Laryngol*

- 1989;98:27–30, doi:<http://dx.doi.org/10.1177/000348948909800106>.
- [16] Clark WR, Bonaventura M, Myers W, Kellman R. Smoke inhalation and airway management at a regional burn unit: 1974 to 1983 II. Airway management. *J Burn Care Rehabil* 1990;11:121–34, doi:<http://dx.doi.org/10.1097/00004630-199003000-00006>.
- [17] Tasaki O, Dubick MA, Goodwin CW, Pruitt Jr. BA. Effects of burns on inhalation injury in sheep: a 5-day study. *J Trauma* 2002;52:351–8.
- [18] Fang-Gang N, Yang C, Yu-Xuan Q, Yan-Hua R, Wei-Li D, Cheng W, et al. Laryngeal morphologic changes and epidemiology in patients with inhalation injury: a retrospective study. *Burns* 2015;41:1340–6, doi:<http://dx.doi.org/10.1016/j.burns.2015.02.003>.
- [19] Vivó C, Galeiras R, del Caz MDP. Initial evaluation and management of the critical burn patient. *Med Intensiva* 2016;40:49–59, doi:<http://dx.doi.org/10.1016/j.medin.2015.11.010>.
- [20] Gill P, Martin RV. Smoke inhalation injury. *BJA Educ* 2015;15:143–8, doi:<http://dx.doi.org/10.1093/bjaceaccp/mku017>.
- [21] Bidani A, Hawkins HK, Wang CZ, Heming TA. Dose dependence and time course of smoke inhalation injury in a rabbit model. *Lung* 1999;177:111–22, doi:<http://dx.doi.org/10.1007/PL00007630>.
- [22] National Research Council (US) Committee on Acute Exposure Guideline Levels. National Research Council (US) Committee on Acute Exposure Guideline Levels. *Acute Exposure Guideline Levels for Selected Airborne Chemicals 2010vol. 8.*
- [23] Ran Z, Di LN, Wen CQ, Ning FG, Zhang GA. Circulation heat dissipation of upper airway: canine model of inhalational thermal injury. *Burns* 2013;39:1212–20, doi:<http://dx.doi.org/10.1016/j.burns.2013.01.007>.
- [24] Wan J, Zhang G, Qiu Y, Wen C, Fu T. Heat dissipation by blood circulation and airway tissue heat absorption in a canine model of inhalational thermal injury. *Burns* 2016;42:548–55, doi:<http://dx.doi.org/10.1016/j.burns.2015.11.002>.
- [25] Hogg G, Goswamy J, Khwaja S, Khwaja N. Laryngeal trauma following an inhalation injury: a review and case report. *J Voice* 2016;31(3):388.e27–31, doi:<http://dx.doi.org/10.1016/j.jvoice.2016.09.017>.
- [26] Foster K, Holmes 4th. J. Inhalation injury: state of the science 2016. *J Burn Care Res* 2017;38:137–41.
- [27] Osler T, Glance LG, Hosmer DW. Simplified estimates of the probability of death after burn injuries: extending and updating the baux score. *J Trauma* 2010;68(3):690–7, doi:<http://dx.doi.org/10.1097/TA.0b013e3181c453b3>.
- [28] Jacob S, Zhu Y, Kraft R, Cotto C, Carmical J, Wood T, et al. Physiologic and molecular changes in the tracheal epithelium of rats following burn injury. *Int J Burn Trauma* 2015; 5:36–45.
- [29] Aggarwal S, Smiles S, Dziewulski P. Tracheostomy in burns patients revisited. *Burns* 2009;35:962–6, doi:<http://dx.doi.org/10.1016/j.burns.2009.03.005>.
- [30] Hunt JL, Purdue GF, Gunning T. Is tracheostomy warranted in the burn patient? Indications and complications. *J Burn Care Rehabil* 1986;7:492–5, doi:<http://dx.doi.org/10.1097/00004630-198611000-00009>.
- [31] Cai AR, Hodgman EI, Kumar PB, Sehat AJ, Eastman AL, Wolf SE. Evaluating Pre burn center intubation practices: an update. *J Burn Care Res* 2017;38:e23–9, doi:<http://dx.doi.org/10.1097/BCR.0000000000000457>.
- [32] Ziegler B, Hirche C, Horter J, Kiefer J, Grützner PA, Kremer T, et al. In view of standardization Part 2: management of challenges in the initial treatment of burn patients in Burn Centers in Germany, Austria and Switzerland. *Burns* 2017;43:318–25, doi:<http://dx.doi.org/10.1016/j.burns.2016.08.004>.
- [33] Al Ashry HS, Mansour G, Kalil AC, Walters RW, Vivekanandan R. Incidence of ventilator associated pneumonia in burn patients with inhalation injury treated with high frequency percussive ventilation versus volume control ventilation: a systematic review. *Burns* 2016;42:1193–200, doi:<http://dx.doi.org/10.1016/j.burns.2016.02.024>.
- [34] Palmieri TL. Pediatric burn resuscitation. *Crit Care Clin* 2016;32:547–59, doi:<http://dx.doi.org/10.1016/j.ccc.2016.06.004>.
- [35] Bai C, Huang H, Yao X, Zhu S, Li B, Hang J, et al. Application of flexible bronchoscopy in inhalation lung injury. *Diagn Pathol* 2013;8, doi:<http://dx.doi.org/10.1186/1746-1596-8-174>.
- [36] Romanowski KS, Palmieri TL, Sen S, Greenhalgh DG. More than one third of intubations in patients transferred to burn centers are unnecessary: proposed guidelines for appropriate intubation of the burn patient. *J Burn Care Res* 2016;37:e409–14, doi:<http://dx.doi.org/10.1097/BCR.0000000000000288>.
- [37] Branski RC, Verdolini K, Rosen CA, Hebda PA. Acute vocal fold wound healing in a rabbit model. *Ann Otol Rhinol Laryngol* 2005;114:19–24.
- [38] Gaissert HA, Lofgren RH, Grillo HC. Upper airway compromise after inhalation injury. Complex strictures of the larynx and trachea and their management. *Ann Surg* 1993;218(2):672–8, doi:<http://dx.doi.org/10.1097/0000658-199321850-00014>.
- [39] Yeung JK, Leung LTF, Papp A. A survey of current practices in the diagnosis of and interventions for inhalational injuries in Canadian burn centres. *Can J Plast Surg* 2013;21:221–5.
- [40] Albright JM, Davis CS, Bird MD, Ramirez L, Kim H, Burnham EL, et al. The acute pulmonary inflammatory response to the graded severity of smoke inhalation injury. *Crit Care Med* 2012;40:1113–21, doi:<http://dx.doi.org/10.1097/CCM.0b013e3182374a67>.
- [41] Foster K. Scoring system for inhalation injury (NCT number: NCT01194024). Unpubl Results n.d.
- [42] Woodson LC. Diagnosis and grading of inhalation injury. *J Burn Care Res* 2009;30:143–5, doi:<http://dx.doi.org/10.1097/BCR.0b013e3181923b71>.
- [43] Walker PF, Buehner MF, Wood LA, Boyer NL, Driscoll IR, Lundy JB, et al. Diagnosis and management of inhalation injury: an updated review. *Crit Care* 2015;19:351, doi:<http://dx.doi.org/10.1186/s13054-015-1077-4>.
- [44] Hassan Z, Wong JK, Bush J, Bayat A, Dunn KW. Assessing the severity of inhalation injuries in adults. *Burns* 2010;36:212–6, doi:<http://dx.doi.org/10.1016/j.burns.2009.06.205>.
- [45] Marek K, Piotr W, Stanisław S, Stefan G, Justyna G, Mariusz N, et al. Fiberoptic bronchoscopy in routine clinical practice in confirming the diagnosis and treatment of inhalation burns. *Burns* 2007;33:554–60, doi:<http://dx.doi.org/10.1016/j.burns.2006.08.030>.
- [46] Bittner EA, Shank E, Woodson L, Martyn JAJ. Acute and perioperative care of the burn-injured patient. *Anesthesiology* 2015;122:448–64, doi:<http://dx.doi.org/10.1097/ALN.0000000000000559>.
- [48] Rue 3rd. LW, Cioffi WG, Mason AD, McManus WF, Pruitt Jr. BA. Improved survival of burned patients with inhalation injury. *Arch Surg* 1993;128:772–80.
- [49] Carr JA, Phillips BD, Bowling WM. The utility of bronchoscopy after inhalation injury complicated by pneumonia in burn patients: results from the national burn repository. *J Burn Care Res* 2009;30:967–74, doi:<http://dx.doi.org/10.1097/BCR.0b013e3181bf77b>.
- [50] Ching JA, Shah JL, Doran CJ, Chen H, Payne WG, Smith DJ. The evaluation of physical exam findings in patients assessed for suspected burn inhalation injury. *J Burn Care Res* 2015;36:197–202, doi:<http://dx.doi.org/10.1097/BCR.0000000000000175>.
- [51] Ikonomidis C, Lang F, Radu A, Berger MM. Standardizing the diagnosis of inhalation injury using a descriptive score based on mucosal injury criteria. *Burns* 2012;38:513–9, doi:<http://dx.doi.org/10.1016/j.burns.2011.11.009>.

- [52] Lund T, Goodwin CW, McManus WF, Shirani KZ, Stallings RJ, Mason AD, et al. Upper airway sequelae in burn patients requiring endotracheal intubation or tracheostomy. *Ann Surg* 1985;201:374-82, doi:http://dx.doi.org/10.1097/00000658-198503000-00021.
- [53] Chung KK, Rhie RY, Lundy JB, Cartotto R, Henderson E, Pressman MA, et al. A survey of mechanical ventilator practices across burn centers in North America. *J Burn Care Res* 2016;37 e:131-9, doi:http://dx.doi.org/10.1097/BCR.0000000000000270.
- [54] Nelson J, Cairns B, Charles A. Early extracorporeal life support as rescue therapy for severe acute respiratory distress syndrome after inhalation injury. *J Burn Care Res* 2009;30 (6):1035-8, doi:http://dx.doi.org/10.1097/BCR.0b013e3181bfb7fd.
- [55] Mourelo M, Galeiras R, Pértega S, Freire D, López E, Broullón J, et al. Tracheostomy in the management of patients with thermal injuries. *Indian J Crit Care Med* 2015;19:449-55.
- [56] Cancio LC. Airway management and smoke inhalation injury in the burn patient. *Clin Plast Surg* 2009;36:555-67, doi:http://dx.doi.org/10.1016/j.cps.2009.05.013.
- [57] Saffle JR, Morris SE, Edelman L. Early tracheostomy does not improve outcome in Burn patients. *J Burn Care Rehabil* 2002;23:431-8, doi:http://dx.doi.org/10.1097/00004630-200211000-00009.
- [58] MacLennan L, Moiemem N. Management of cyanide toxicity in patients with burns. *Burns* 2015;41:18-24, doi:http://dx.doi.org/10.1016/j.burns.2014.06.001.
- [59] Desai MH, Mlcak R, Richardson J, Nichols R, Herndon DN. Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcystine [correction of acetylcystine] therapy. *J Burn Care Rehabil* 1999;20:49.
- [60] Juschten J, Tuinman P, Juffermans N, Dixon B, Levi M, Schultz M. Nebulized anticoagulants in lung injury in critically ill patients-an updated systematic review of preclinical and clinical studies. *Ann Transl Med* 2017;5:444.
- [61] Lange M, Hamahata A, Traber DL, Cox RA, Kulp GA, Nakano Y, et al. Preclinical evaluation of epinephrine nebulization to reduce airway hyperemia and improve oxygenation after smoke inhalation injury. *Crit Care Med* 2011;39:718-24, doi:http://dx.doi.org/10.1097/CCM.0b013e318207ec52.
- [62] Adhikari NK, Burns KE, Friedrich JO, Granton JT, Cook DJ, Meade MO. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ* 2007;334(7597):779, doi:http://dx.doi.org/10.1136/bmj.39139.716794.55.
- [63] Taylor RW, Zimmerman JL, Dellinger RP, Straube RC, Criner GJ, Davis K, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA J Am Med Assoc* 2004;291:1603-9, doi:http://dx.doi.org/10.1001/jama.291.13.1603.
- [64] Yamamoto Y, Sousse LE, Enkhbaatar P, Kraft ER, Deyo DJ, Wright CL, et al. γ -tocopherol nebulization decreases oxidative stress, arginase activity, and collagen deposition after burn and smoke inhalation in the ovine model. *Shock* 2012;38:671-6, doi:http://dx.doi.org/10.1097/SHK.0b013e3182758759.
- [65] Kim S-Y, Lee J-H, Kim HJ, Park MK, Huh JW, Ro JY, et al. Mesenchymal stem cell-conditioned media recovers lung fibroblasts from cigarette smoke-induced damage. *Am J Physiol Lung Cell Mol Physiol* 2012;302:L891-908, doi:http://dx.doi.org/10.1152/ajplung.00288.2011.
- [66] Ihara K, Fukuda S, Enkhtaivan B, Trujillo R, Perez-Bello D, Nelson C, et al. Adipose-derived stem cells attenuate pulmonary microvascular hyperpermeability after smoke inhalation. *PLoS One* 2017;12, doi:http://dx.doi.org/10.1371/journal.pone.0185937.
- [67] Cui P, Xin H, Yao Y, Xiao S, Zhu F, Gong Z, et al. Human amnion-derived mesenchymal stem cells alleviate lung injury induced by white smoke inhalation in rats. *Stem Cell Res Ther* 2018;9, doi:http://dx.doi.org/10.1186/s13287-018-0856-7.