Inhaled Anticoagulation Regimens for the Treatment of Smoke Inhalation–Associated Acute Lung Injury: A Systematic Review*

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Objective: Inhaled anticoagulation regimens are increasingly being used to manage smoke inhalation–associated acute lung injury. We systematically reviewed published and unpublished preclinical and clinical trial data to elucidate the effects of these regimens on lung injury severity, airway obstruction, ventilation, oxygenation, pulmonary infections, bleeding complications, and survival.

Data Sources: PubMed, Scopus, EMBASE, and Web of Science were searched to identify relevant published studies. Relevant unpublished studies were identified by searching the Australian and New Zealand Clinical Trials Registry, World Health Organization International Clinical Trials Registry Platform, Cochrane Library, ClinicalTrials.gov, MINDCULL.com, Current Controlled Trials, and Google.

Study Selection: Inclusion criteria were any preclinical or clinical study in which 1) animals or subjects experienced smoke inhalation exposure, 2) they were treated with nebulized or aerosolized anticoagulation regimens, including heparin, heparinoids, antithrombins, or fibrinolytics (e.g., tissue plasminogen activator), 3) a control and/or sham group was described for preclinical studies, and 4) a concurrent or historical control group described for clinical studies. Exclusion criteria were 1) the absence of a group treated with a nebulized or aerosolized anticoagulation regimen, 2) the absence of a control or sham group, and 3) case reports.

Data Extraction: Ninety-nine potentially relevant references were identified. Twenty-seven references met inclusion criteria including 19 preclinical references reporting 18 studies and eight clinical references reporting five clinical studies.

Data Synthesis: A systematic review of the literature is provided. Both clinical and methodological diversity precluded combining these studies in a meta-analysis.

Conclusions: The high mortality associated with smoke inhalation–associated acute lung injury results from airway damage, mucosal dysfunction, neutrophil infiltration, airway coagulopathy with cast formation, ventilation-perfusion mismatching with shunt, and barotrauma. Inhaled anticoagulation regimens in both preclinical and clinical studies improve survival and decrease morbidity without altering systemic markers of clotting and anticoagulation. In some preclinical and clinical studies, inhaled anticoagulants were associated with a favorable effect on survival. This approach appears sufficiently promising to merit a well-designed prospective study to validate its use in patients with severe smoke inhalation–associated acute lung injury requiring mechanical ventilation. (*Crit Care Med* 2014; 42:413–419)

Key Words: acute lung injury; anticoagulants; antithrombins; fibrinolytic agents; heparin; smoke inhalation injury

In the United States, more than 450,000 burn injuries occur annually (1). Smoke inhalation–associated acute lung injury (SI-ALI) constitutes a major cause of morbidity and mortality in victims of fire tragedies, affecting nearly 1.5–19.5% of burn patients worldwide (1.5% Israel, 8% China, and 19.5% United States) (2–4). The prevalence of SI-ALI is correlated with a greater percent of burn surface area (BSA) (3); however, significant SI-ALI may exist in the absence of cutaneous burns. When combined with cutaneous burns, inhalation injury increases fluid requirements for resuscitation, the prevalence of pulmonary complications, and the mortality rate (3, 5–8). In a retrospective analysis of 573 burn patients admitted

*See also p. 474.

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over a 4-year period to a regional burn center, patients with inhalation injury had a more than 70% prevalence of respiratory failure (hypoxemia, multiple pulmonary infections, or prolonged ventilatory support) and a 20% prevalence of acute respiratory distress syndrome (9). The reported mortality associated with SI-ALI ranges from 11% to 80% (3, 4, 8–11). The variability in mortality rates from different regions of the world and time periods likely reflects the heterogeneity of the patient populations due to age, comorbidities, severity of the primary and secondary injuries, and variations in therapy.

Several mechanisms have been identified in animal models and in human pathologic studies that contribute to the development of SI-ALI. Smoke inhalation promotes airway damage and inflammation. Immediately following smoke inhalation, bronchial blood flow increases up to 20-fold (12). Increased microvascular permeability and airway edema results in plasma exudation into the airway resulting in intra-airway coagulation and fibrin deposition. Cellular debris, mucin, and fibrin deposition admix to form a fibrinocellular exudate or pseudomembranes that may develop into obstructive airway casts that promote significant mismatch in ventilation and perfusion (V/Q) (2, 13–23). The V/Q mismatch is further worsened by increased perfusion to underventilated lung regions due to impaired hypoxic vasoconstriction driven in part by increased nitric oxide production (24, 25). Furthermore, partially obstructed airways may result in air trapping and alveolar hyperinflation via a ball-valve mechanism that may promote distal airway and alveolar damage. These mechanisms may lead to impaired oxygenation and ventilation. Although on mechanical ventilation this may result in elevated peak and plateau pressures, auto-peep, and patient-ventilator dyssynchrony, this may promote regional barotrauma in some lung segments while resulting in repetitive alveolar collapse and expansion injury. Additionally, casts may also occlude endotracheal and tracheostomy tubes necessitating emergent airway revision (26).

SI-ALI is an important yet understudied clinical problem. The use of inhaled anticoagulation regimens is increasingly being used to manage SI-ALI with the goal of improving outcomes by decreasing airways fibrin deposition and obstruction (27). However, the data detailing the efficacy of this approach are limited and to our knowledge has not been compiled into a comprehensive review. We conducted this review to summarize the complex body of literature on the topic, assess the consistency of results across trials, clarify the strengths and weakness of available studies, and document the need for further prospective clinical investigation. We systematically review published and unpublished preclinical and clinical study data to elucidate the effects of such regimens on lung injury severity, airway obstruction, ventilation, oxygenation, pulmonary infections, bleeding complications, and survival.

METHODS

A systematic search was performed to capture published and unpublished preclinical and clinical studies of nebulized anticoagulation regimens as treatment for SI-ALI. PubMed, Scopus, EMBASE, and Web of Science were searched to identify relevant published studies. The search strategies were adapted to accommodate the unique searching features of each database, including database-specific MESH and EMTREE controlled vocabulary terms. Searches were not limited by date, language, or publication status. See **Appendix 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/A741) for detailed search strategies. The cited and citing references of selected studies were also searched for additional relevant material.

To minimize publication bias, relevant unpublished studies were identified by searching the Australian and New Zealand Clinical Trials Registry, World Health Organization International Clinical Trials Registry Platform, Cochrane Library, ClinicalTrials.gov, MINDCULL.com, Current Controlled Trials, and Google.

Inclusion criteria were any preclinical or clinical study in which 1) animals or subjects experienced smoke inhalation exposure, 2) they were treated with nebulized or aerosolized anticoagulation regimens, including heparin, heparinoids, antithrombins (ATs), or fibrinolytics (e.g., tissue plasminogen activator, TPA), 3) a control and/or sham group was described for preclinical studies, and 4) a concurrent or historical control group described for clinical studies. Exclusion criteria were 1) the absence of a group treated with a nebulized or aerosolized anticoagulation regimen, 2) the absence of a control or sham group, and 3) case reports.

RESULTS

The search identified 99 potentially relevant studies. Twenty-seven references met inclusion criteria (**Fig. 1**), including 19 preclinical references reporting 18 studies and eight clinical references reporting five clinical studies. One prospective clinical trial has been planned, but results are not available (28). The presence of both clinical diversity and methodological diversity precluded combining the study reports in a meta-analysis.

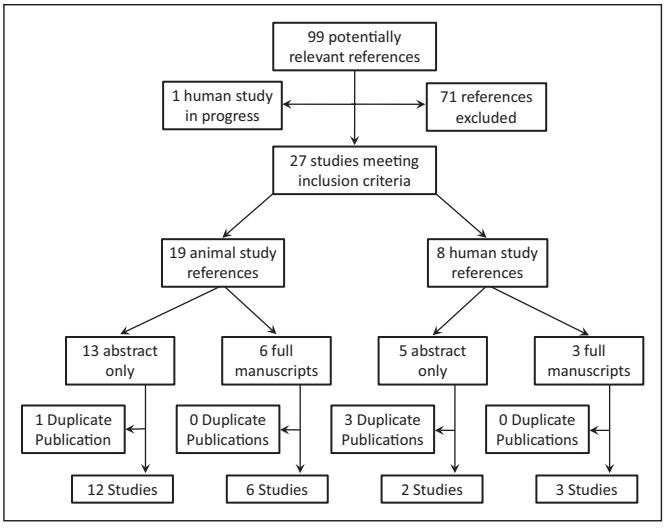

Figure 1. Schematic summary of literature review of nebulized anticoagulation regimens for the treatment of smoke inhalation–associated acute lung injury.

Preclinical Studies

The bulk of the preclinical studies were conducted using an ovine model of SI-ALI. In this model, the sheep are surgically prepared for chronic study via placement of arterial, left atrial, pulmonary artery, and lung lymphatic catheters. On postoperative days 5–7, smoke inhalation exposure is accomplished via either cooled cotton (< 40°C) (13, 29–45) or pinewood (46) smoke administered via tracheostomy or endotracheal tube. In most models, the animals undergo cutaneous thermal burn (40% BSA) at the time of smoke exposure. The animals are mechanically ventilated and volume resuscitated with IV crystalloid infusion in accordance with the Parkland formula (47). Antibiotic therapy is not administered. The most commonly investigated nebulized anticoagulation regimens include unfractionated heparin (5,000 or 10,000 IU), AT (290 U), and TPA (1 or 2 mg) either alone or in combination with anticoagulants. Depending on the study and treatment regimen, nebulized therapies are initiated at 1–4 hours postinjury and continued every 4 hours for, commonly, 24–48 hours. Endpoints are reported from 48 to 96 hours postinjury and usually include mortality, weaning from mechanical ventilation, and tracheostomy decannulation. Commonly reported markers of ventilation and oxygenation include peak and plateau airway pressures, Pa_{O_2}/F_{IO_2}, and arterial-alveolar oxygen gradient. Markers of pulmonary congestion and obstruction include the lung wet-to-dry ratio (W/D), lung lymph flow, pulmonary shunt fraction (Qs/Qt), and histological obstruction scores. Other endpoints include the results of blood coagulation and clotting cascade variables and fluid balance. **Appendix 2** (Supplemental Digital Content 1, http://links.lww.com/CCM/A741) summarizes the results of 18 preclinical studies assessing inhaled anticoagulation regimens as treatment for SI-ALI.

Characteristic findings of SI-ALI as described by findings from control groups include the following: increased mortality and impaired ventilation with elevations in peak and plateau airway pressures, decline in Pa_{O_2}/F_{IO_2} with concomitant rise in arterial-alveolar gradient, and increased evidence of airway obstruction. Increasing pulmonary congestion is often manifested as an increase in lung lymph flow, Qs/Qt, and W/D. With few exceptions, nebulized anticoagulation regimens significantly attenuated these findings (**Table 1**).

TABLE 1. Summary of the Pathophysiological Effects of Nebulized Anticoagulation Regimens in Animal Models of Smoke Inhalation–Associated Acute Lung Injury

Reference	Inhaled Anticoagulation Regimen	Pa_{O_2}/F_{IO_2} Ratio	Alveolar to Arterial Gradient	Shunt Fraction Qs/Qt	Wet-to-Dry Ratio	Lymph Flow	Airway Pressures	Histological Obstruction	Survival
Characteristic findings in smoke inhalation–associate acute lung injury		↓	↑	↑	↑	↑	↑	↑	↓
Desai et al (29)	1, 5					↓			↑
Brown et al (30)[a]	1, 5								↑
Cindric et al (31)	4					↓			
Katahira et al (32)	1	↑				↓			
Murakami et al (34)	1	↑		↓	↓			↓	
Tasaki et al (46)	1		↓	No change	↓				
Enkhbaatar et al (13)	1, 3, 6	↑		↓	↓	↓	↓		
Enkhbaatar et al (36)	2, 6				↓	↓		↓	
Nakano et al (37)	7	↑		↓					
Enkhbaatar et al (38)	1, 3, 6	↑		↓	↓	↓	↓		
Enkhbaatar et al (39)	7	↑		↑	↓	↓	↓	↓	
Rehberg et al (40)	8			↓		↓	↓		
Asmussen et al (41)	8	↑							↑
Rehberg et al (42)	8	↑		↓		↓			
Asmussen et al (45)	8	↑							↑
Rehberg et al (44)	8	↑				↓	↓		

[a]Due to high mortality in control and DMSO-alone groups, further comparisons were only made between heparin and DMSO + heparin groups.

For studies presented, arrows indicate change from control or untreated groups, not overall change from baseline.

Inhaled anticoagulation regimens: 1, heparin inhaled; 2, tissue plasminogen activator (tPA) inhaled; 3, antithrombin (AT) inhaled; 4, GM 1892 inhaled; 5, heparin inhaled + dimethyl sulfoxide inhaled; 6, heparin inhaled + AT inhaled; 7, heparin inhaled + AT IV; 8, heparin inhaled + tPA inhaled + AT IV.

TABLE 2. Summary of Human Clinical Investigations of Inhaled Anticoagulation for Smoke Inhalation–Associated Acute Lung Injury

Reference	*n*	Protocol	Intervention	Results
Desai et al (2)	90	Retrospective analysis with historical control	Standard therapy + heparin 5,000 U inhaled alternating with 3 mL NAC inhaled every 2 hr for first 7 d following injury	↓ Mortality, ↓ reintubation rate, ↓ prevalence pneumonia and atelectasis; no significant change in duration of intubation
Rivero et al (48)[a]	16	Retrospective analysis with historical control	The nebulized heparin 10,000 IU + NAC 3 mL of 20% group consisted of nine patients with smoke inhalation acute lung injury diagnosed with bronchoscopy and necessitating mechanical ventilation and Acute Physiology and Chronic Health Evaluation III score > 35 (mean 46.66 vs 44.86 [control], $p = 0.38$); additionally, daily Lung Injury Score was calculated for 7 d and was determined by averaging the scores of chest radiograph, Pao_2/Fio_2, positive end-expiratory pressure, and respiratory system compliance	In the first two ICU days, mean lung injury scores were significantly lower in the treatment group (0.76 ± 0.53 vs 1.23 ± 0.88; $p = 0.08$); mean lung injury score during the first week was 0.91 ± 0.14 vs 1.79 ± 0.41 ($p < 0.01$) for NH-NA and non-nebulized heparin and NAC patients, respectively; mortality was 11% (1/9) in the treatment group and 43% of patients (3/7) in the control group during the first ICU week
Holt et al (50)	150	Retrospective analysis with historical control	No patient allocation; patients treated according to attending discretion; treated patients received inhaled heparin 5,000 U/1 mL, NAC 3 mL 20% solution, and albuterol 2.5 mg of 0.083% solution (3 mL) every 4 hr for the first 7 d following admission or until extubation	No significant difference in mortality, duration of mechanical ventilation, length-of-stay, or pneumonia
Miller et al (27)	30	Retrospective analysis with historical control	Standard therapy + heparin 10,000 U inhaled every 4 hr alternating with NAC 3 mL of 20% + albuterol 0.5 mL every 4 hr	↓ Mortality, ↓ lung injury score
Yip et al (49)	63	Retrospective analysis with historical control	1. Treatment group: mechanically ventilated adult patients with bronchoscopically confirmed SI-ALI admitted in a burn ICU (2006–2009); treated with heparin 5,000 IU inhaled + NAC 600 mg/3 mL of 20% aerosolized solution inhaled + salbutamol 5 mg inhaled, each every 4 hr ($n = 52$) 2. Control: mechanically ventilated SI-ALI patients (2001–2005) before protocol initiation	No significant difference in trend of activated partial thromboplastin time, prothrombin time, and platelet count over 7 d; no clinically significant increase in bleeding risk in treatment group

NAC = *N*-acetylcysteine, SI-ALI = smoke inhalation–associate acute lung injury.
[a]Published as abstract.

Clinical Studies

Eight references accounting for five human clinical studies were identified (**Table 2**). Additionally, a prospective human study is planned but not yet recruiting patients (ClinicalTrials.gov #NCT014548690) (28). All human studies conducted to date have been retrospective studies with historical controls. Four of the five studies were conducted around a change in institutional protocol (2, 27, 48, 49). Three studies assessed a low-dose heparin protocol (5,000 IU) (2, 49, 50) of which one treated according to physician discretion (50), and two studies assessed a high-dose heparin regimen (10,000 IU) (27, 48). The impact of the nebulized heparin protocols on common primary endpoints is summarized in **Table 3**. Both studies assessing a standardized high-dose heparin dosing regimen (10,000 IU nebulized every 4 hr) reported statistically significant mortality improvement (27, 48). Conversely, the one study that did not report a mortality benefit used a low-dose regimen, and unlike the aforementioned studies, suffered from significant selection bias in that patients were not allocated into treatment groups but instead were treated according to physician discretion (50). Each of

TABLE 3. Summary of the Pathophysiological and Clinical Effects of Nebulized Heparin Regimens in Human Clinical Studies of Smoke Inhalation–Associated Acute Lung Injury

Reference	Lung Injury Score	Pneumonia Prevalence	Mechanical Ventilation Duration	Unplanned Reintubation	Hospital Length of Stay	Bleeding Risk	Mortality
Desai et al (2)	↓	↓	No change	↓			
Rivero et al (48)	↓						↓
Holt et al (50)[a]		No change			No change		No change
Miller et al (27)	↓						↓
Yip et al (49)						No change	

[a]No randomization or allocation into treatment groups. Patients treated at attending physician discretion with a dosing regimen half the strength of the studies by Rivero et al (48) and Miller et al (27).

three studies assessing lung injury score reported a statistically significant improvement (2, 27, 48). Only one standardized regimen (low dose) has assessed the prevalence of pneumonia, and this study reported a significant decrease in the prevalence of pneumonia (2). These results were not reproduced by the study without a standardized dosing regimen (50). Although no change in the duration of mechanical ventilation has been reported with nebulized heparin regimens, one study did report a decrease in the prevalence of unplanned reintubation (2). Similar to animal studies, nebulized heparin regimens of 5,000 IU or 10,000 IU every 4 hours in humans have not been shown to alter serum markers of anticoagulation (49).

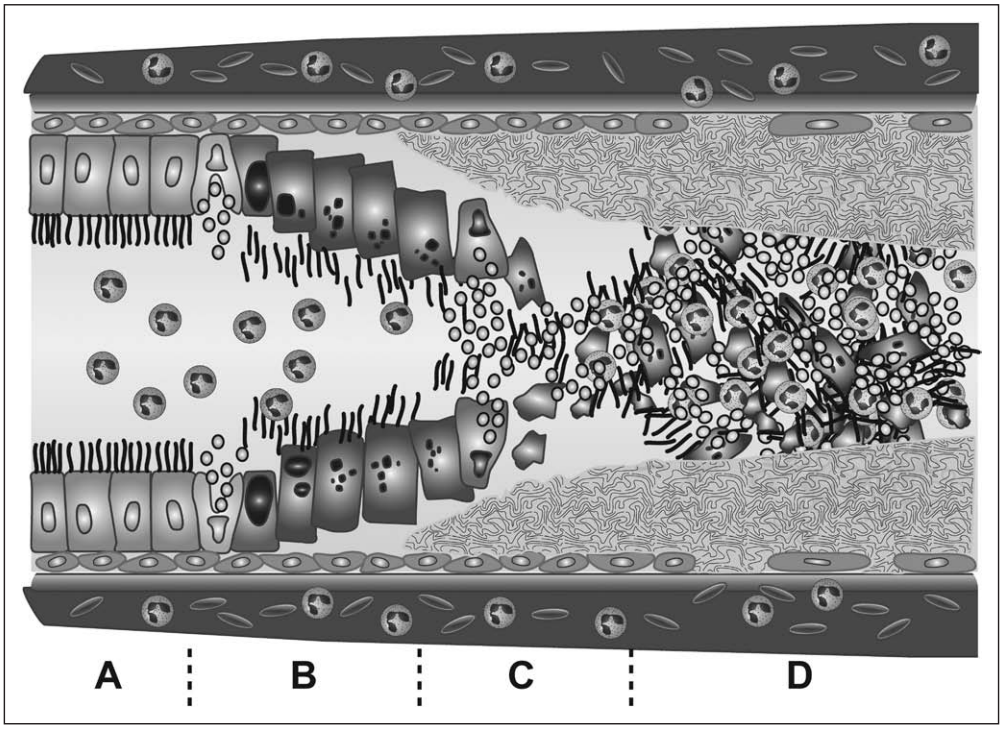

Figure 2. Depiction of airway changes in the setting of smoke inhalation–associated acute lung injury. Trachea and bronchi injury is characterized by mucosal hyperemia, increased microvascular permeability, exfoliation of the epithelial lining, mucous secretion, and an acute inflammatory cell influx (**A–C**) (57). As early as 1 hr postexposure, affected respiratory tract epithelium may display clumping, swelling, loss of cilia, blebbing, and surface erosion (B) (55). Within hours, sloughing of the respiratory mucosa progresses, a fibrinocellular pseudomembrane begins to form, and neutrophils begin to influx into the major airways (55). By 6 hr postinjury, the injured bronchi and bronchiole epithelium remains largely intact with focal areas of necrosis and sloughing (A, B) (56). Surface lining cells appear enlarged with cytoplasmic vacuolization, and neutrophils have begun to marginate and focally concentrate at points of epithelial necrosis (56). In addition, basal cells are normal in appearance, and the subepithelial connective tissue may appear slightly edematous with contained neutrophil infiltrates (56). By 24 hr, the ciliated and secretory lining cells are largely destroyed (C) (56). Cellular debris is admixed with fibroid material, mucus, and neutrophils creating a pseudomembranous fibrinocellular network that is adherent to both the cell-denuded basal lamina and the intact basal cells (C, **D**) (56). By 72 hr, injured epithelial areas are largely resurfaced by a stratified reparative epithelium with interposed areas of fibrinocellular exudate (D) (56). This epithelium is three to five cells thick, with flattened, nonciliated cells along the surface, and these cells are likely derived from proliferating and migrating basal cells (56). Subepithelial edema and inflammatory cell infiltrates begin to diminish (56). Complete repair of the respiratory tract epithelium with return of normal cilia populations may take up to 2–4 wk depending on the severity of smoke exposure.

DISCUSSION

Much of what is known of the early effects of smoke exposure on the respiratory tract has been described and validated in numerous ovine and lapine models of smoke inhalation (51–54). Although difficult to study in humans, the time course of these physiological effects is comparable to those found in burned patients with smoke inhalation injury (51).

Thermal inhalation injury only rarely affects the intrathoracic airways (55). Unless the patient is exposed to steam, which has much greater heat carrying capacity than dry air, the heat dissipating properties of the upper airway restrict direct thermal injury to the supraglottic structures (56, 57). Intrathoracic and lower airway injury is most often a chemical-associated injury related to substances that have

lower water solubility and particles less than 5 microns in diameter (58).

Inhaled toxicants can be in the form of gases, vapors, particulate matter, and aerosols (57). Smoke from combustible material contains a variety of toxic substances that may cause direct cell injury and initiate inflammatory responses that propagate airway damage (55, 57, 58). Additionally, inhaled particulate matter (i.e., soot) may have adsorbed toxic molecules on the surfaces and sustain inflammatory responses when adherent to the airway mucosa (57).

The initial injury from smoke inhalation is limited to the trachea and bronchi and is characterized by mucosal hyperemia, increased microvascular permeability, exfoliation of the epithelial lining, mucous secretion, and an acute inflammatory cell influx (**Fig. 2 *A–C***) (53). Necrosis and sloughing of tracheal epithelium has been reported as early as 15 minutes postexposure (51). Bronchi obstruction peaks as early as 24 hours, whereas bronchiolar obstruction progressively increases to reach a maximum by 72 hours (**Fig. 2*D***) (51, 53). This may be in part due to obstructive material that migrates distally from larger airways to smaller bronchioles and disruption of mucociliary clearance (53). As highlighted in Figure 2, fundamental to the airway obstruction is the role of increased microvascular permeability and airway edema that results in plasma exudation into the airway producing intra-airway coagulation and fibrin deposits. These deposits lead to with the resultant fibrinocellular pseudomembranes composed of fibrin deposition, cellular debris, and mucin. A dose-dependent relationship between degree of smoke exposure and severity of injury has been described (55).

As intra-airway coagulation with fibrin deposition and fibrinocellular pseudomembranes begin to form within hours of smoke exposure, inhaled anticoagulation regimens may be most effective when initiated early under the premise that impairing fibrin clot deposition may decrease airway cast formation and improve oxygenation and ventilation while decreasing the risk of barotrauma. Preclinical models (Appendix 2, Supplemental Digital Content 1, http://links.lww.com/CCM/A741) most commonly initiated therapy at 1–2 hours (range, 0.5–4 hr) postinjury and continued every 4 hours for usually 48 hours (range, 24–96 hr). Human studies did not reliably report time from smoke exposure to treatment initiation. Based on preclinical studies, it may be reasonable to initiate a regimen of inhaled heparin within 4 hours postexposure (or as early as possible) and to continue it every 4 hours for 48 hours. In animal models, 72 hours injured epithelial areas are largely resurfaced by a stratified reparative epithelium with only interposed areas of fibrinocellular exudate (Fig. 2*D*) (52). Additional factors that contribute to airway cast formation are mucus secretion and the presence of a large burden of cellular debris. The addition of the mucolytic *N*-acetylcysteine to nebulized heparin regimens intervenes at an additional level to prevent or minimize formation of obstructive airway casts (2, 27, 48, 59). Future studies in SI-ALI may use combination therapy with inhaled heparin, an inhaled fibrinolytic (e.g., TPA), and mucolytic therapy (e.g., *N*-acetylcysteine). Furthermore, recombinant human deoxyribonuclease I (dornase alfa) cleaves extracellular DNA in mucous and when inhaled reduces the adhesiveness and viscoelasticity of airway mucous in patients with cystic fibrosis (60). This treatment might augment the breakdown of cellular debris and further impede the formation of fibrinocellular pseudomembranes. However, to date, no studies using this strategy in the setting of SI-ALI have been reported.

CONCLUSION

The high mortality associated with SI-ALI results from airway epithelial cell injury and inflammation, mucosal dysfunction, airway coagulopathy with cast formation resulting in ventilation-perfusion mismatch with shunt, and barotrauma. Inhaled anticoagulation regimens in both preclinical and clinical studies decrease morbidity without altering systemic markers of clotting and anticoagulation. In some preclinical and clinical studies, inhaled anticoagulants were associated with a favorable effect on survival. This approach appears sufficiently promising to merit a well-designed prospective study to validate its use in patients with severe SI-ALI requiring mechanical ventilation.

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