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Inhalation Injury (A Literature Review)

E.A. Zhirkova*, T.G. Spiridonova, P.A. Brygin, A.V. Makarov, A.V. Sachkov

Department of Acute Thermal Lesions
N.V. Sklifosovsky Research Institute for Emergency Medicine
3 Bolshaya Sukharevskaya Square, Moscow 129090, Russian Federation

*** Contacts:** Elena A. Zhirkova, Cand. Med. Sci., Researher of the Department of Acute Thermal Lesions, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department. Email: ZhirkovaEA@sklif.mos.ru

ABSTRACT The analysis of domestic and foreign sources of literature showed that the problem of diagnosis and treatment of inhalation injury still remains relevant as 20–30 years ago. It is known that inhalation injury causes both local and systemic disorders. Existing diagnostic methods do not allow the extent of these disorders to be accurately determined. This, in turn, leads to the absence of clear criteria for the severity of inhalation injury and treatment algorithms.

Keywords: inhalation injury, carbon monoxide, cyanide, combustion products, carboxyhemoglobin, bronchoscopy, artificial lung ventilation, bronchial obstruction syndrome

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Affiliations

Elena A. Zhirkova	Cand. Med. Sci., Researher of the Department of Acute Thermal Lesions, N.V. Sklifosovsky Research Institute for Emergency Medicine, ORCID: 0000-0002-9862-0229.
Tamara G. Spiridonova	Doctor of Medical Sciences, Scientific Consultant of the Department of Acute Thermal Lesions, N.V. Sklifosovsky Research Institute for Emergency Medicine, ORCID: 000-0001-7070-8512.
Pavel A. Brygin	Candidate of Medical Sciences, Head of the Resuscitation and Intensive Care Unit for Burn Patients, N.V. Sklifosovsky Research Institute for Emergency Medicine, ORCID: 0000-0002-8511-9646.
Aleksey V. Makarov	Endoscopist of the Department of Emergency Surgery, Endoscopy and Intensive Therapy, N.V. Sklifosovsky Research Institute for Emergency Medicine, ORCID: 0000-0001-7388-7077.
Aleksey Vladimirovich Sachkov	Candidate of Medical Sciences, Head of the Scientific Department of Acute Thermal Lesions, N.V. Sklifosovsky Research Institute for Emergency Medicine, ORCID: 0000-0003-3742-6374.

ALV – artificial lung ventilation
ARDS – acute respiratory distress syndrom
CT – computed tomography
ELT – endoscopic laser therapy
EMO – extracorporeal membrane oxygenation
FDG – fludeoxyglocose
GCS – Glasgow Coma Scale
NEP – neutral endopeptidase

BACKGROUND

The injury resulting from inhalation of combustion products is life threatening. The greatest number of deaths in a fire is associated with inhalation of smoke [1]. The mortality rate in inhalation injury without skin burns is about 10%, whereas skin burns are combined with poisoning by burning products, domestic authors recommend using the term “multifactorial lesion” [4].

Using the logistic regression method, we revealed factors aggravating the state of burn patients (age over 60, burn area over 40% of body surface), and the probability of death was calculated: 0.3% — in the absence of risk factors , 3% — with one factor, 33% — with two factors, about 90% — with all three risk factors [5].

The aim of the article was to study the current state of the issue of diagnosis and treatment of inhalation injury.

To achieve this goal, an analysis of the literature over the past 5 years (2014–2018) was carried out, and earlier sources (including experimental works) were used, which retained their relevance.

The literature sources used in this work are cited in the *PubMed* and *eLibrary databases*.

ETIOLOGY AND PATHOGENESIS

Inhalation injury has a local and systemic effect on the body. The local lesion of the airways and lung parenchyma is caused by thermal and toxic agents. Thr systemic exposure is a consequence of impaired oxygenation of tissues and organs. This occurs due to a decrease in the delivery and/or use of oxygen by inhalation of poisonous gases (carbon monoxide, cyanide and other toxic compounds [6, 7].

The composition of toxic substances depends on the stage of the fire. It is known that the burning of materials may be complete and partial. In this case, as a rule, the products of complete combustion are less dangerous than the compounds formed when there is a lack of oxygen [1, 8]. During a fire, molecules of gases or vapors may interreact and form new

chemical compounds [1].

The most frequently occurring toxic compounds in residential fires include carbon monoxide, hydrogen chloride, hydrogen cyanide, nitrogen and sulfur dioxide, acrolein and benzene. Smoke is a heterogeneous mixture of solid particles (carbon particles coated with acids, aldehydes and acroleins), vapors and heated gases. Gases are classified as irritants (such as vapors of hydrochloric acid, sulfur dioxide, nitrogen oxides and ammonia), suffocating toxins (carbon dioxide) and cellular toxins (carbon monoxide, hydrogen sulfide and hydrogen cyanide). The composition of smoke at each particular fire depends on the combustible materials, the pyrolysis rate, the absolute temperature and the availability of oxygen. Significant amounts of carbon monoxide are formed in almost all cases of burning of carbon-containing materials, especially under conditions of oxygen deficiency. Sources of cyanide are various nitrogen-containing polymers, as well as paper, wool, silk, etc. Smoke samples obtained during a fire just a few meters from each other may differ significantly [1, 9].

The features of the clinical course of poisoning by combustion products mainly determine the composition of the gas mixture [1, 6]. In some cases, this is a short-term irritation of the mucous membranes of the eyes and upper respiratory tract (the so-called transient reactions), and in others this is acute poisoning, which may lead to the death of the victim. Thus, the final toxic effect is determined by the action of a heterogeneous mixture of toxic products formed during the thermal decomposition of various materials. The timing of the manifestation of the toxic effect also depends on the active substance. In case of poisoning with some toxicants, manifestations are already registered in the fire zone, while the latent period of poisoning with delayed substances may reach 24 hours [1, 10, 11]. It was experimentally confirmed that the degree of damage to the respiratory tract depends not only on the composition of the smoke, but also on the duration of its exposure [12].

The damage to the upper respiratory tract is mainly associated with the direct temperature effects and chemical irritation and may cause the development of life-threatening edema in the laryngeal area. Due to the effective cooling function of the oropharynx and nasopharynx, direct thermal injury of the lower respiratory tract is rare, their damage is mainly associated with the irritant effect of gases [13, 14]. While hydrophilic gases quickly dissolve and cause damage to the airway epithelium, lipophilic gases penetrate deeper into the lungs and cause damage to the alveoli [6]. The particles size (toxic components of the smoke) also matters. Large particles of combustion products are deposited in the upper respiratory tract and have local mechanical and chemical irritation of the mucous membrane, small particles penetrate deeply and have not only local, but also resorptive effect [1].

The lung has a network of sensory C-fibers with a vagus nerve, which contain pro-inflammatory peptides, such as substance *P*, neurokinins, peptide, calcitonin-gene-related peptide (stimulates an early inflammatory response, contributing to the elimination of the stimulus), etc. [15-17]. The toxic components of smoke stimulate the release of neuropeptides from the peripheral ends of sensory neurons in the airways and induce cough, mucus secretion, smooth muscle contraction, plasma extravasation and neutrophil adhesion. This complex of effects is called “neurogenic inflammation” [18]. The activation of the inflammatory cascade with the formation of oxygen free radicals and activation of nitric oxide synthetase leads to pulmonary vasodilation with impaired perfusion, as well as increased vascular permeability and, in extreme cases, the development of acute respiratory distress syndrome (ARDS) [1, 6]. In addition, there is a danger of inactivation of its own surfactant, which leads to severe atelectasis as a result of alveolar collapse [11, 19, 20].

The trauma along with neurogenic inflammation leads to major pathological changes, which in turn lead to a narrowing of the lumen of the respiratory tract and, ultimately, limit the normal air flow to the alveoli. The narrowing of the lumen of the respiratory tract is explained by: 1) swelling of the mucous membrane of the respiratory tract; 2) airway obstruction (exfoliated epithelial cells, inflammatory cells, mucus and plasma-rich exudates); 3) bronchospasm [21].

The main pathophysiological change occurring due to inhalation damage is an increase in bronchial blood flow [22]. Anastomoses between the pulmonary and bronchial vessels that are poorly functioning under normal conditions, actively open after inhalation injury. In the experiment 3 hours after inhalation of smoke, a 20–30-fold pathological increase in blood flow in the airways was observed, which led to the mucous membrane edema and formation of transudate and exudate containing a large number of neutrophils and mediators. Desquamated epithelium, inflammatory cells, fibrin, and protein-rich exudate caused airway obstruction at different levels [23-24].

An experimental model of a sheep with a combined injury (smoke inhalation and skin burn) showed an increase in bronchial obstruction within 24 hours with a progressive decrease in 72 hours. At the same time, the degree of bronchiolar obstruction increased within the next 48 hours. In the early periods after injury, the bronchial casts mainly consisted of mucus, and neutrophils were the main component of bronchiolar obstructive material. With direct measurement, the average cross-sectional diameter of the airways was approximately reduced by 29% in the bronchi, 11% in the bronchioles, and 1.2% in the respiratory bronchioles. In this study, approximately 10% of the bronchi reached an obstruction rate between 90% and 100% [24].

A decrease in lung compliance (elongation) of up to 50% already in the first 2 hours after injury has been shown experimentally [19].

In an experiment, the researchers demonstrated that the increase in absorption by the lungs of fludeoxyglucose (FDG) and irregularity of ventilation and perfusion observed within 4 hours after inhalation of smoke using positron emission tomography. Although at this early stage there was no reduction in aeration of the lungs or an increase in the share of bypass of blood flow, the ventilation-perfusion coefficient decreased. The increase in FDG absorption in the lungs above the base metabolic rate was mainly associated with activated neutrophils [25].

The affinity of hemoglobin for carbon monoxide is more than 200 times greater than for oxygen. Therefore, even with a low concentration of carbon monoxide, a significant portion of hemoglobin is converted to carboxyhemoglobin and is turned off from oxygen transport. Carbon monoxide leads mainly to tissue hypoxia due to its very high affinity for the iron (Fe^{2+}) of the heme complex, as well as the allosteric change of the hemoglobin protein. More precisely, in the tetrameric hemoglobin molecule, some protomers are occupied by carbon monoxide molecules, others are occupied by oxygen. In

such hemoglobin molecules, oxygen is held stronger than in molecules that do not contain carbon monoxide, and the release of oxygen in the tissues is difficult. Thus, the occurrence of oxygen deficiency in tissues with carbon monoxide poisoning is associated with block of a portion of hemoglobin hemes and dysfunction of carbon monoxide-free hemes [11, 26].

Cyanide inhibits mitochondrial respiration as it binds with iron (Fe^{3+}) of cytochrome oxidase [6, 26]. This disruption of the electron transport chain blocks cellular aerobic respiration, which may quickly become fatal. Although the affinity of cyanide for ferric ions is strongly expressed, the process is reversible [27].

CLINICAL DIAGNOSIS

Clinically, the diagnosis of inhalation trauma is established on the basis of anamnesis (finding a patient in a smoky confined space, exposure, loss of consciousness) and physical data, including the presence of burns of the face, neck, chest, burnt nasal hairs, soot in the proximal respiratory tract, cough with sputum and soot, voice changes, signs of airway obstruction, including stridor, as well as swelling or damage to the mucous membrane of the oropharynx [4, 10].

Inhalation of gaseous products of combustion (in particular, toxic gases — carbon monoxide and cyanides) causes hypoxia as a result of systemic oxygen deficiency or impaired use, manifested mainly by central nervous system symptoms and/or cardiac symptoms (as a result of increased oxygen consumption by the brain and heart) [28]. The early clinical manifestations of cyanide intoxication are similar to the clinical manifestations of carbon monoxide intoxication and include symptoms of sympathetic activation: tachycardia, arterial hypertension, palpitation, tachypnea and anxiety, as well as nausea, headache and dizziness. As intoxication worsens, disorientation, drowsiness, convulsions, bradycardia, bradypnea, hypotension, loss of consciousness, mydriasis, cardiovascular collapse and, ultimately, death appear. The air inhaled by the patient smells classically bitter almonds [27].

A pulse oximeter cannot detect carbon monoxide poisoning. The oxyhemoglobin and carboxyhemoglobin spectra are very similar, and pulse oximeters cannot distinguish two forms of hemoglobin [11].

The informational value of assessment and prognostic scales *(APACHE, SOFA, SAPS)* in burn patients has not been proven. At the same time, the existing specialized scales (*Baux*, *PBI*, *ABSI*, *Ryan*, *Burd*, *BOBI*, Frank index) either do not take into account the presence of inhalation trauma at all, or do not take into account the degree of its severity [29].

LABORATORY DIAGNOSIS

A high level of carboxyhemoglobin (HbCO) in the blood, exceeding 10%, is an evidence of inhalation trauma; however, its information content is limited due to the short half-life (3-4 hours), which becomes even shorter with oxygenation [30]. The level of carboxyhemoglobin may be measured directly after trauma, but this test is rarely available at the site of the fire. Due to the inevitable delay between exposure to smoke and the control of carboxyhemoglobin, the level measured upon arrival at a medical facility does not reflect the true degree of intoxication [11, 31].

The partial pressure of oxygen in arterial blood (PaO_2) reflects the amount of oxygen dissolved in plasma, but does not characterize the saturation of hemoglobin, which is the most important determining factor for the oxygen transport of blood [11].

Indicators of cyanide in the blood during hospitalization of the patient are also not very informative. It is established that plasma lactate level correlates with the severity of cyanide toxicity due to lactate acidosis against the background of the prevailing anaerobic metabolism. Based on this, it was concluded that during the patient's hospitalization, an increased plasma lactate concentration is an indicator of cyanide intoxication of victims of a fire that do not have serious skin burns [32].

INSTRUMENTAL RESEARCH METHODS

Foreign authors at various times noted the absence of specific signs of inhalation trauma on a series of radiographs. X-ray examination was found to be ineffective in the diagnosis of inhalation injury [33-35].

In one study conducted on patients with isolated inhalation trauma, apart from the absence of specific signs of lung damage, no correlation was found between the chest X-ray and the degree of hypoxemia in the primary analysis of arterial blood gases [36].

X-ray examination may be useful for identifying complications that develop in 89% of victims. Early pulmonary changes are usually manifested by pulmonary edema caused by chemical exposure to smoke and inhaled pneumonitis. Early complications such as pulmonary microembolism, ARDS and atelectasis, as a rule, develop on the $2–5^{th}$ day after trauma. Delayed complications (more than 5 days) are severe pulmonary embolism, pneumonia, and ARDS [37].

Inhalation injury may be confirmed by diagnostic studies, including bronchoscopy, which is usually performed within the first 24 hours after arrival, and the study of respiratory function [10, 38].

Currently, bronchoscopy is a standard technique used to diagnose the presence and severity of damage to the tracheal and bronchial tree after inhalation injury. It is impossible to assess the state of the distal respiratory tract and respiratory bronchioles with bronchoscopy. Therefore, the damage to this part of the lung sometimes explains the inconsistency between the bronchoscopic and clinical picture. Despite this, the relative simplicity of the method and its accessibility make it possible to make an initial diagnosis and observe changes in dynamics [10].

Determining the severity of airway damage by bronchoscopy in most classifications is based on the presence of a cough reflex and visual assessment of the bronchial passage and bronchial secretion, the presence of soot and the degree of its fixation, and the state of the mucous membrane [4, 38]. At N.V. Sklidosovsky Research Institute, the extent of damage to the tracheobronchial tree is performed in accordance with A.Y. Skripal classification developed in 1988 under the direction of Y.V. Sinev and L.I. Gerasimova and based on the depth of damage to the mucous membrane [39].

Computed tomography (CT), 99-technetium and 133-xenon scans are also effective in diagnosing inhalation injury, but they are not used in the initial assessment of its severity due some material and technical reasons [10]. It is important that the use of xenon scanning allows the parenchymal lesian to be revealed, which can not be detected via bronchoscopy [40].

A number of studies have noted the correlation of CT data with the gas composition of the blood of victims with inhalation

trauma [34, 41, 42].

American authors who published a work in the *Burns* journal, conducted a comparative assessment between 3*D*-CT ("virtual bronchoscopy"), CT and bronchoscopy. They found that the main advantage of 3*D*-CT is that the images of CT and 3*D*-CT provide instant visibility of the entire length of the respiratory tract, including areas not passable by the bronchoscope, and can be performed earlier than bronchoscopy [34].

In some studies, the PaO_2/FiO_2 ratio is considered as a predictor of mortality [38, 43]. At the same time, *Kim Y. et al.* in their studies showed that the PaO_2/FiO_2 ratio is not a statistically significant predictor of mortality, and the need for mechanical ventilation of the lungs was determined as a prognostic factor [44]. *You K. et al.* also consider the use of artificial lung ventilation (ALV) as a predictor of mortality [30].

TREATMENT

The treatment of inhalation trauma may be divided into several areas corresponding to pathogenesis. In this type of injuty, the mucous membrane of the respiratory tract, the lung parenchyma are affected, and systemic poisoning with gaseous products of combustion — carbon monoxide gas and hydrocyanic acid vapor — can also occur. Accordingly, approaches to treatment and may be systematized into three sections: sanitation of tracheobronchial tree and resolution of airway obstruction; identification, assessment of severity and treatment of respiratory failure; poisoning treatment.

For primary toilet of the mucous membrane of the tracheobronchial tree from solid products of combustion (soot), purulent-necrotic detritus and mucus, it is common to use bronchoscopy, which should be carried out as soon as possible [45]. Also, the severity of damage to the respiratory tract, as determined by bronchoscopy, may serve as a criterion for the need for mechanical ventilation [46].

In the literature we did not find any other endoscopic manipulations, except for the sanitation. Methods for the local treatment of mucosal lesions in patients with inhalation injury were developed at N.V. Sklifosovsky Reseach Institute: endoscopic laser therapy and endobronchial endoscopic applications of type 1 human collagen gel. Studies have shown that in patients who underwent endoscopic laser therapy (ELT), the healing process of the mucous membrane of the tracheobronchial tree occurred faster compared to patients in the comparison group. Under the conditions of early and systematic ELT, there was no evidence of severe purulent inflammation and acceleration of the rate of granulation tissue formation in the bottom of the ulcer and epithelialization in the marginal areas [47]. After therapeutic bronchoscopy with simultaneous application of a type 1 human collagen solution, the inflammation of the respiratory tract mucosa decreased, and the epithelialization of erosions and ulcers of the tracheobronchial tree was significantly (1.5–2 times) reduced [48].

The local treatment of the tracheobronchial tree also include quite numerous works on the nebulizer use of anticoagulants (heparin and other substances). The effectiveness of this method has not been proven [45, 49], while *Kashefi N. et al.* indicate a significant increase in the incidence of pneumonia when using the heparin/N-acetylcysteine/albuterol protocol [50]. There is evidence that the use of bronchodilators (Salbutamol) separately has a positive effect on the resolution of bronchial obstruction [51].

In experiments on sheep exposed to inhalation injury, it was found that the spraying of adrenaline significantly weakened the development of pulmonary dysfunction due to vasoconstrictive and bronchodilatory effects. Further research is needed to understand the underlying pathogenetic mechanisms and determine the optimal doses for treating patients with this injury [23].

Extracorporeal membrane oxygenation (EMO) is currently not a routine medical procedure and is used in cases resistant to standard therapy. In case of extremely severe parenchymal pulmonary insufficiency in inhalation trauma, there are separate reports on the successful application of EMO, but systematic studies have not been conducted [7, 52].

Hyperbaric oxygenation has been studied in several studies to reduce the neurological effects of exposure to carbon monoxide. Basing on one's own experience and a review of the literature, some authors argue that severe delayed neurological complications are rare, and, moreover, they are resolved with or without hyperbaric oxygenation [53]. Others, on the contrary, recommend hyperbaric oxygenation as a key treatment for carbon monoxide poisoning, which improves the outcome of some patients [28]. Currently available data on the use of hyperbaric oxygenation in this population of patients are considered only in the context of clinical studies, since the hyperbaric chamber is a complex environment for monitoring a patient and conducting infusion therapy [31, 54].

The use of exogenous human recombinant enzyme neutral endopeptidase (NEP) inhibits "neurogenic inflammation." Neutral endopeptidase exists on the surfaces of all lung cells that have receptors for neuropeptides. Also, studies have shown that corticosteroids suppress extravasation of neurogenic plasma and regulate NEP in the tissues of the human respiratory tract [18].

Overstretching of ventilated alveoli induces the synthesis and secretion of pro-inflammatory chemokines such as *IL*-8, which attracts neutrophils to the injured site, causing even greater lesion. In addition, systemic hypoxia modulates various pro-inflammatory cytokines and inflammatory mediators [56–58]. It may be advisable to use anti-inflammatory drugs along with standard smoke inhalation treatments (for example, anticoagulants, mucolytics, and bronchodilators) [22].

The main treatment for severe cyanide poisoning includes mechanical ventilation with pure oxygen and the introduction of an antidote. Several antidotes with different mechanisms of action and evidence of efficacy have been suggested. These antidotes include hydroxycobalamin, sodium thiosulfate, methemoglobin producing nitrites, and dicobalt edetate [27]. Although various methods have proven effective in experimental studies, the choice of antidote in clinical settings remains controversial. Only a kit containing nitrites and thiosulfate is approved for use in the United States. However, there are potential dangers of nitrite treatment in cases of combined cyanide and carbon monoxide poisoning [59]. Early empiric treatment of suspected cyanide poisoning with hydroxycobalamin is used in France [60]. In 2013, the Commission, approved by the European Society of Emergency Medical Aid, developed algorithms for both pre-hospital and inpatient treatment for cyanide poisoning. Empirical antidote treatment is recommended for persons with a history of inhalation of smoke in the prehospital stage, with a score of less than 14 on the Glasgow Coma Scale (GCS), or with unstable

hemodynamics; and in the hospital with blood lactate levels above 90 mg/dl (10 mmol/l) [61].

RESPIRATORY SUPPORT METHODS

An extremely dangerous complication that requires the start of mechanical ventilation is acute respiratory failure, which, develops in 29% of patients with inhalation trauma according to P.A. Brygin et al. [62]. The reasons for its development can be: 1) bronchial obstruction (in 60% of patients) caused by damage to the respiratory tract mucosa, 2) primary parenchymal pulmonary insufficiency caused by damage to the alveoli (in 12% of patients) and 3) preferential poisoning by burning products (in 28% patients). The simultaneous presence of airway obstruction and damage to the lung parenchyma is possible in inhalation trauma. This creates great difficulties in the selection of ventilation modes, since the approaches to ventilation in these cases are opposite and mutually exclusive. With parenchymal changes, ventilation is recommended with small respiratory volumes with a high frequency, and with obstruction, on the contrary, very rare breathing with a large respiratory volume with the maximum possible expiratory duration [63]. The use of volume controlled ventilation may result in overstretching of less damaged, open alveoli [62, 64]. Despite the fact that the incidence of bronchial obstruction in patients with acute respiratory failure reaches 60%, and the period of mechanical ventilation often exceeds 60 days [62].

There is still no consensus on the optimal modes of mechanical ventilation for patients with inhalation trauma among the leading burn centers [4, 65]. We have not found in the literature any other clinical studies on the choice of ventilation modes in patients with inhalation trauma, except for the one conducted by P.A. Brygin et al. at N.V. Sklifosovsky Research Institute [62]. All recommendations are reduced to the general principles of treatment of ARDS, while the features of bronchial obstruction typical for inhalation trauma are not discussed [2, 45].

There are studies on the use of high-frequency percussion ventilation, contributing to the purification of the respiratory tract, but its advantage over traditional methods of mechanical ventilation is questioned [66, 67].

The high risk of developing life-threatening conditions associated with impaired gas exchange requires to highlight indications for preventive tracheal intubation and mechanical ventilation in victims with multifactorial lesions, based on the data of the diagnostic bronchoscopy: third-degree skin burns of more than 40% of the body surface; location of third-degree skin burns on face and neck with the risk of progressive soft tissue edema; depression of consciousness to less than 8 score according to GCS; burns of the upper respiratory tract with damage to the larynx; damage to the respiratory tract of III degree of combustion products [4].

Onishi S. et al. consider that patients with inhalation damage should be intubated for preventive reasons if the thickness of the bronchial wall measured by CT is at least 3.5 mm and the level of blood carboxyhemoglobin is at least 4.0% [41].

Despite certain achievements, the results of respiratory support remain rather disappointing, as the mortality rate of patients with mechanical ventilation exceeds 50% [68, 69].

CONCLUSION

The analysis showed that the main problem of diagnosing inhalation injury lies in the incompatibility of the clinical and endoscopic picture, and the main challenge of treatment is the the development of mixed respiratory failure.

The severity of the patient's condition is not always respectively exists a degree of destruction of the tracheobronchial tree, revealed by bronchoscopy. In almost half of patients with respiratory failure, changes detected by bronchoscopy may be superficial or absent altogether. In this case, the patient may be in a coma and mechanical ventilation of the lungs is needed. Currently there are no clear criteria related to etiological and pathogenetic factors that could explain the severity of the patient's condition, predict the development of respiratory failure and the need for preventive intubation.

The greatest difficulties in the choice of mechanical ventilation modes are caused by the development of respiratory failure of a mixed type, which requires further research in this area.

The lack of evaluation and prognostic scales, taking into account the severity of inhalation trauma, makes difficulties in the development of treatment algorithms.

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