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The Progress of Diagnosis and Management in Inhalation Injury

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Abstract: *Inhalation injury is one of the important causes of death in critically burned patients, and rich experiences have been accumulated in the diagnosis and treatment. However, the understanding of some new biomarkers, evidence-based evidences, and diagnosis and treatment measures is still very limited. In this review, on the basis of our team's experiences in clinical treatment, we discuss the new diagnostic principles (such as dynamic diagnosis, airway depth grading theory, biomarkers, etc.) and the new treatments (such as chest physical therapy, artificial nose and high flow respiratory humidification therapeutic apparatus in airway management, atmospheric pressure high concentration oxygen therapy, extracorporeal membrane oxygenation (ECMO) support, etc.). New comprehensive protocols and evidence-based evidences for the diagnosis and treatment of inhalation injury are summarized. The treatment of inhalation injury is a multi-faceted and multi-disciplinary comprehensive diagnosis and treatment. It is of great clinical significance to explore new measures to improve the early diagnosis and management.*

Keywords: *Inhalation injury; Burn; Artificial nose; High flow respiratory humidification therapeutic apparatus; Extracorporeal membrane oxygenation*

1. Introduction

Patients with head and face burns are often accompanied by inhalation injury, which is a compound injury caused by heat and/or chemical smoke. Inhalation injury is an independent predictor of the mortality of burn patients[1]. Inhalation injury has "concealment" and "double superposition effect". "Concealment" refers to the concealment of the injured site, and "double superposition effect" refers to the superposition caused by two injury factors, namely heat and chemical smoke, and the superposition caused by body surface burn and respiratory tract burn. The fatality rate of large area burn patients combined with inhalation injury is more than 50%, suggesting that inhalation injury is one of the important causes of death in critical burn patients, which should be paid great attention to[2]. In recent years, with the improvement of medical technology and the development of related disciplines, a variety of new diagnosis and treatment techniques and measures are gradually mature, providing new ideas for the successful treatment of inhalation injury and critical burn patients. Based on many years of clinical treatment experience of the author's team, this review summarizes and discusses new comprehensive protocols for diagnosis and treatment of inhalation injury as well as evidence-based evidences, which can more accurately assess the condition and guide treatment to a certain extent.

2. Early diagnosis of inhalation injury

2.1. Diagnostic principles - combinational, dynamic, comprehensive, and specialized

The accuracy and comprehensiveness of the early clinical diagnosis of inhalation injury is very important to provide basis for accurate treatment. Combined diagnosis is generally made based on the results of medical history, signs and symptoms, bronchoscopy, laboratory examination, and imagings. In recent years, some scholars have proposed to judge the severity of inhalation injury through CT scan results, and developed the radiologist's scores (RADS) system, which is, 0 points are scored for normal CT appearance, 1 point is scored for vacuolar and gap appearance, 2 points are scored for ground-glass changes, and 3 points are scored for actual changes[3]. The severity of lung injury was evaluated by

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calculating the RADS score of CT (per 1 cm axial section). Another study reported that the lung tissue damage can be dynamically observed by measuring the bronchial wall thickness 2 cm at the distal end of the patient's trachea bifurcation, which is closely related to the occurrence of pneumonia, mechanical ventilation time and length of hospital stay, and can provide reference for treatment[4].

With the progression of the disease, the severity of inhalation injury should be diagnosed in stages, and the depth of mucosal burn should be evaluated regularly (weekly). The early diagnosis should be revised, and the complications such as airway contracture and stenosis should be prevented. At the same time, with the help of medical history, evaluating whether there is smoke injury, and make a comprehensive diagnosis of the upper and lower respiratory tract with the help of various auxiliary examinations, not missing possible injuries. In addition, in the diagnosis of inhalation injury, attention should be paid to the consultation of respiratory specialists, who are more sensitive to the control of changes in respiratory diseases and more professional in the diagnosis and treatment of diseases. As a good supplement to burn specialists, they can better formulate a series of targeted and individualized programs based on the actual situation of patients.

2.2. Early biomarkers

It is important to study molecular, biochemical and pathological markers to evaluate the severity of inhalation injury. Low white blood cell (WBC) counts, low platelet counts, and high urea and creatinine levels were associated with an increased risk of death from inhalation injury[5].

Soluble urokinase plasminogen activator receptor (suPAR) is a relatively new biomarker, which is the product of protein hydrolysis in many inflammatory processes and is found in a variety of body fluids. suPAR level was elevated in bronchial lavage fluid during inhalation injury[6]. Elevated suPAR blood level has been shown to be associated with mechanical ventilation time and significantly longer hospital stays in intensive care units, and can be used to diagnose aspiration injuries and predict prognosis[7].

Pancreatic stone protein (PSP) has been gathers more attention as a marker for accurately diagnosing and determining the prognosis of critically ill patients[8]. PSP is a protein secreted by pancreatic acinar cells that inhibits the growth and nucleation of calcium carbonate crystals. Recent studies have found that PSP activates neutrophils during systemic infection and early sepsis, and is more accurate in predicting burn sepsis than procalcitonin (PCT) and C-reaction protein (CRP). It's a very promising acute phase protein for inclusion in the sepsis score system[9]. At the same time, PSP showed a more dramatic increase in patients with sepsis in the presence of aspiration injury.

Immunomodulators also play a very important role in judging the prognosis of inhalation injury. The level of their expression can not only be used to predict the prognosis, but also provide a target for immunomodulatory treatment of systemic inflammatory response. Interleukin-1 receptor antagonist (IL-1RA), an anti-inflammatory immune medium, was the most associated with injury severity and mortality related prognostic indicators[10]. Insufficient IL-1β or excessive IL-1RA can lead to systemic immune dysfunction. IL-8 is a powerful chemokine that plays an important role in the initiation and progression of aspiration injury lung inflammation[11]. Low levels of IL-7 and high levels of IL-12p70 were associated with mortality from aspiration injury[12].

Levels of inflammatory cytokines (IL-4, IL-6, IL-9, IL-15, interferon-γ) in bronchoalveolar lavage fluid, granulocyte macrophage colony stimulating factor (GM-CSF), and monocyte chemoattractant protein-1 (MCP-1)) were correlated with the severity of aspiration damage determined by bronchoscopy. The transformation of a macrophage-dominated population into a neutrophil-dominated population in the lavage fluid is thought to be a major cause of later immune dysfunction, bacterial overgrowth, and pneumonia[13].

2.3. Classification of severity

At present, in China, three-degree classification is used to determine the severity of inhalation injury. In foreign countries, it is proposed that the abbreviated injury scale (AIS) rating system can be derived from the results of fiberbronchoscopy. The AIS rating system helps to evaluate patients' conditions and judge prognosis. However, a large case-control study found that the AIS rating system could not predict mechanical ventilation duration, acute respiratory distress syndrome (ARDS), and mortality, with significant differences among different evaluators[14].

Inhalation injury is a special type of burn. The author believes that the severity of airway injury can be judged by referring to the wound depth grading. Airway mucosa is divided into upper cortex and lamina propria, and cricoid cartilage is located below the mucosa. Graded diagnosis can be made according to the depth of injury, so as to guide treatment measures and prevent complications. It should be noted that when the depth of mucosal burn is unclear, the possibility of serious injury should be vigilant and dynamic observation should be required. In addition, the patient has a history of smoke inhalation and changes in lung imaging, but no obvious airway injury was observed under bronchoscopy. Therefore, it is necessary to pay close attention to the possible lung tissue injury. The author recommends a diagnosis of severe aspiration injury, which is the inhalation of chemical substances and toxic or irritating gases combined with systemic carbonic oxide poisoning, leading to pneumonia, atelectasis, lung infection and a series of complications.

3. Treatment of inhalation injury

It mainly emphasizes the treatment idea of combining the technical method of burn treatment with the idea of respiratory medicine repairing respiratory mucosa and lung tissue.

3.1. Early first aid

For head and face burn patients with inhalation injury, it is necessary to strictly grasp the indications of tracheotomy. When emergency tracheotomy is not required, maintaining airway patency and reducing airway edema are the key treatment. Endotracheal intubation was performed when respiratory secretions were excessive, gastric contents were regurgitated, bleeding was at any time at risk of incorrect aspiration, and hypoxemia could not be corrected by oxygen inhalation through nasal catheter or mask. A retrospective study by Romanowski et al. found that more than one third of facial burn patients underwent unnecessary intubation prior to hospital admission[15]. Tracheal intubation caused combined postlaryngeal edema, with or without arytenoid swelling, arytenoid dislocation, and vocal cord paralysis, due to compression of the recurrent laryngeal nerve. Some patients had to be intubated for longer because of secondary complications. In the case of deep burns on the head, face and neck, significantly increased respiratory rate, chest tightness, breathlessness, hoarseness, and indeed high risk of edema and airway obstruction, incision should be made as soon as possible.

3.2. Airway management

3.2.1. Atomizing inhalation

Scientific and reasonable implementation of atomization inhalation is very important for the treatment of inhalation injury. The purpose of atomization therapy is to reduce the local inflammation of respiratory tract, dilate bronchus, reduce phlegm viscosity, and promote the repair of airway mucosa.

The commonly used aerosol inhaled drugs mainly include acetylcysteine (NAC), heparin, budesonide, ipratropium bromide, salbutamol, epidermal growth factor, etc. NAC, containing active sulfhydryl compounds, has the function of scavenging reactive oxygen species (ROS) and converting into glutathione to maintain the stability of cell redox potential[16]. Nebulized heparin reduced lung injury (comprehensive evaluation measures: chest radiograph, oxygenation capacity, airway resistance, compliance, etc.) without affecting coagulation system and platelet count. Compared with the traditional treatment group, the nebulized heparin group had lower mortality, shorter mechanical ventilation duration and shorter mean length of hospital stay, but no significant differences in the incidence of pneumonia and the rate of re-intubation[17]. When heparin (10000 IU) is combined with NAC, it reduces the severity of lung injury and the duration of mechanical ventilation[18]. Scavengers such as G-tocopherol and A-tocopherol (vitamin E) block ROS production, inhibit the ROS-activated arginase pathway, and reduce collagen deposition, thereby preventing impaired lung function[19].

Inhalation nitric oxide (iNO) can also be used for the treatment of inhalation injury. iNO has the potential to dilate blood vessels and has been shown to improve arterial oxygen partial pressure, improve ventilation/blood flow imbalance, reduce pulmonary hypertension and shunt in patients with acute respiratory failure. In about two-thirds of patients, iNO improves oxygenation and survival, but has no significant effect on reducing mechanical ventilation duration and mortality, and iNO can lead to renal insufficiency and other complications[20].

Alveolar surfactants have also been reported to be used in the treatment of aspiration injury, but there is still lacking of high-quality evidence that exogenous surfactants can be routinely used to treat

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aspiration injury. Further studies are needed to determine the specific role of surfactant in the early and late treatment of aspiration injury-associated ARDS.

3.2.2. Chest physical therapy (CPT)

The essential to improve ventilation in patients with aspiration injury is timely and effective discharge of sputum in the airway and mucosal exfoliating necrotic tissue[21]. First introduced in 2007, standardized CPT measures mainly include three aspects: postural drainage, chest compression during breathing, and cough guidance[22]. Postural drainage is an important way to promote the discharge of sputum in deep lung. For patients with large area burn combined with aspiration injury, turning over the bed to button the back and using vibration expectorator to promote expectoration, especially for patients with lung infection who need adequate drainage and expectoration, the time of expectoration in prone position should be increased. If the patient cannot tolerate prolonged prone position, we should increase the frequency of turning over, and gradually prolong the prone position time. Chest compressions during breathing include two operations: 1) Pressing the patient's chest wall during exhalation to reduce end-expiratory reserve capacity; 2) Release the patient's chest at the beginning of inspiration to increase end-inspiratory reserve capacity. Cough instruction is an active breathing technique that includes deep breathing, breath control, and forced exhalation techniques (blowing). Recent studies have shown that in patients with aspiration injury, CPT can effectively shorten the duration of mechanical ventilation and hospital stay, reduce the incidence of pneumonia, and facilitate early activity in patients with aspiration injury[23].

3.2.3. Atmospheric pressure high concentration oxygen therapy

It has been reported that hyperbaric oxygen therapy can accelerate the diffusion rate of oxygen into tissues, increase the oxygen content in tissues, improve the utilization rate of oxygen, correct the hypoxia of airway tissue cells, and accelerate airway repair[24]. However, patients with large area burn combined with inhalation injury are often in critical condition, and the rescue conditions in the hyperbaric oxygen chamber are limited, which is not suitable for hyperbaric oxygen treatment.

When oxygen is administered at normal pressure and high concentration, the partial pressure of arterial blood oxygen can reach more than 300mmHg, which also has the effect of improving tissue oxygen content[25]. Therefore, the author's team proposed that intermittent use of 100% concentration pure oxygen therapy, 30 minutes each time, 1-3 times a day, can effectively promote body repair, and avoid oxygen poisoning caused by long-term high concentration oxygen inhalation, and received a good effect in clinical treatment.

3.2.4. Artificial nose

For patients who have undergone tracheotomy, due to the establishment of artificial airway, normal humidification, filtration, heating and other functions of the respiratory tract are lost, and the defense ability is reduced. At the same time, the respiratory tract of patients with artificial airway will lose more water (800-1000 ml/d). If directly inhaled without heating and humidification of gas, it is easy to cause thick respiratory secretions, phlegm scab, obstruction of the airway, and even serious complications such as lung infection and atelectasis.

Artificial nose, also known as warm-wet respiratory filter, is a passive humidification device. To some extent, it simulates the human nasal anatomy humidification system, with functions of humidification, heating and filtration. At the same time, it also has a vent, which can be opened in case of severe cough to timely discharge of secretions and avoid airway obstruction. It is suitable for patients with artificial airway to maintain normal physiological functions of respiratory tract[26]. In addition, the oxygen connector on the artificial nose can be adjusted freely to the most convenient and comfortable position according to the patient's position, reducing the risk of disconnection and kinks. It has been reported that sputum viscosity, sputum aspiration times and total sputum volume in patients with tracheotomy using artificial nose are all better than those in patients with conventional airway humidification, while the incidence of respiratory irritation, sputum scab formation, airway bleeding and increased respiratory resistance are all significantly reduced[27].

3.2.5. High flow respiratory humidification therapeutic apparatus

As mentioned above, artificial nose is a passive and simple humidification device, through which gas inhalation can achieve a certain degree of humidification (22-30 mg/L) and warming (29-32℃), with limited effects. For some patients with dry airway, airway humidification and sputum drainage cannot be achieved. At this time, as an upgrade of the electronic version of the artificial nose-high flow respiratory humidification therapeutic apparatus play a better role.

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The high flow respiratory humidification therapeutic apparatus is more intelligent and controllable. It is a new humidification and heating gas instrument. Through the built-in humidification and heating device, gas with 37°C and 100% (44 mgH_2O/L) relative humidity can be delivered[28]. At the same time, the built-in integrated oxygen concentration monitor can monitor various parameters (flow rate, temperature, and oxygen concentration) in real time, and has the function of flexible regulation of airway gas temperature and humidity. As a new type of oxygen therapy, the high flow respiratory humidification therapeutic apparatus can deliver gas to reach or exceed the maximum speed of the patient's active inhalation to produce a ventilation effect similar to positive end-expiratory pressure. It could counter the endogenous positive end-expiratory pressure produced in the alveolar, and produce sustained pressure to keep the respiratory tract in a dilated state. This could reduce inspiratory resistance and respiratory work, relieve respiratory fatigue, and effective relief of dyspnea in patients.

High flow respiratory humidification therapy instrument can effectively improve the humidification effect of artificial airway patients. It can also improve patients' comfort and tolerance, improve lung volume, respiratory frequency and oxygenation, conduce to the drainage of sputum in the airway, and reduce the rate of phlegm scab formation, the incidence of choking and lung infection. This can effectively improve patients' arterial partial oxygen pressure and oxygen saturation, and reduce patients' suffering and the incidence of hospital-acquired pneumonia[29].

3.3. Respiratory management

3.3.1. Mechanical ventilation

When aspiration injury patients have progressive dyspnea caused by atelectasis or lung infection, mechanical ventilation can be used. The purpose of mechanical ventilation is to improve gas exchange, increase patients' comfort, and accelerate the recovery of spontaneous respiration. For patients with different degrees of inhalation injury, mechanical ventilation can provide a variety of breathing modes. A "protective lung ventilation strategy" is generally adopted, i.e. low tidal volume (4-7 ml/kg), appropriate positive end-expiratory pressure (PEEP), and appropriate airway pressure (plateau pressure $\leq$30 cmH_20). This can open up the alveoli for gas exchange without increasing the risk of barotrauma and consequent alveolar stress and shear force, solving the lung treatment problem.

A retrospective cohort study found that high frequency oscillatory ventilation (HFOV) was not beneficial for ARDS after inhalation injury[5]. In fact, HFOV increases the incidence of severe hypercapnia and prevents standard fogging treatments (such as bronchodilators and heparin) for inhalation injuries. Although there is evidence that the use of HFOV can treat ARDS after burns[30]. However, it has not been shown to be beneficial in the treatment of ARDS with inhalation injury and can cause severe hypercapnia, so it is not the first line treatment of choice.

In patients with mild burn combined with aspiration injury, high frequency percussive ventilation (HFPV) has been shown to enhance oxygenation without increasing inflammatory markers[31]. Reper et al. found that, compared with standard ventilation strategies, HFPV can improve oxygenation, but has no beneficial effect on mortality[32]. HFPV can be used to improve oxygenation in ARDS patients after inhalation injury without aggravating pre-existing lung injury, but the evidence for the use of HFPV is sparse and whether this improves survival outcomes has yet to be determined. Although HFPV cannot reverse the effects of inhalation injury, it can improve the clearance of airway secretions, provide positive pressure during mechanical ventilation, reduce airway pressure, and enhance the reserve capacity of lung function[33].

3.3.2. Extracorporeal membrane oxygenation (ECMO)

Patients with severe aspiration injury have severe complications, such as ARDS, respiratory failure, and ventilation/diffusion dysfunction. After combined with lung re-expansion, prone ventilation, high-frequency oscillatory ventilation, lung protective ventilation, intractable hypoxemia, or arterial partial oxygen pressure/inhaled oxygen concentration (PaO2/FiO2) < 100 mmHg, respiratory rate > 35 times/time, ECMO salvage therapy was considered[34]. The therapeutic effect of ECMO is closely related to wound closure, infection control and organ function maintenance. The greater the burn area, the higher the fatality rate of burn patients using ECMO. The higher the proportion of aspiration injury, the higher the fatality rate[35]. lt has been reported that the survival rate of the use of ECMO<200 hours compared with use time>200 hours was higher, suggesting that prolonged ECMO use did not improve survival. When PaO_2/FiO_2<60 mmHg, ECMO initiation did not significantly improve survival[36, 37].

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3.4. Fluid resuscitation

Generally speaking, burn patients with aspiration injury require an increased amount of fluid during shock to ensure effective perfusion of tissues and organs. A case report of isolated aspiration injuries without skin burns found that, according to the Parkland formula, the amount of fluid required for simple aspiration injuries was equivalent to that required for 27% total body surface area (TBSA) burns[38]. Dai et al. reported that the average fluid requirement increased from 3.98 ml/kg/%TBSA to 5.76 ml/kg/%TBSA when patients developed aspiration injury[39]. There is no comparison between these studies due to differences in resuscitation strategies and target urine volume.

However, for patients with post-shock or severe ARDS, restrictive fluid management is more beneficial. Restrictive fluid management strategy (RFMS) is a strategy to apply diuretics if necessary through hemodynamic monitoring and to maintain a low preload to achieve zero or negative balance of fluid on the premise of ensuring basic tissue perfusion[40]. The key to RFMS is how to correctly assess the patient's volumetric status in order to achieve zero or negative fluid balance. Some studies have shown that RFMS can improve lung function, shorten mechanical ventilation time, and reduce the occurrence of ARDS[41].

3.5. Anti-infection and wound treatment

Inhalation injury can increase the mortality of burn patients by 20% and lung infection by 60%[42]. Therefore, in the operation of patients with large area burn combined with inhalation injury, the aseptic principle should be emphasized. The changes of body temperature and respiratory rate of patients should be closely observed. Bacterial and fungal culture of sputum should be performed regularly, and the changes of various infection indicators (such as WBC, PCT, CRP, etc.) should be monitored. At the same time, sensitive antibiotics were selected for prevention and treatment according to the results of bacterial culture in sputum.

For patients with large area burn combined with aspiration injury, respiratory function and oxygenation will be affected if lung inflammation and infection are caused. Therefore, lung function should be carefully evaluated to determine whether patients can tolerate general anesthesia surgery. If there are complications such as atelectasis, pulmonary infection, ARDS, and respiratory failure, which affect the cardiopulmonary function of the patient, the operation time can be postponed appropriately.

4. Conclusions

Inhalation injury is still one of the important causes of death from critical burn. Although we have accumulated rich experiences in the diagnosis and treatment of inhalation injury in the past, the understanding of evidence-based diagnosis and treatment and some new diagnosis and treatment measures are still very limited. The diagnosis and treatment of inhalation injury is not only the diagnosis and treatment of the airway and lungs, but also a series of comprehensive diagnosis and treatment such as systemic anti-infection, fluid management, wound treatment, nutritional support, psychotherapy and respiratory specialist consultation. This article summarized the research progress of diagnosis and comprehensive treatment of inhalation injury, hoping to provide theoretical reference for clinical treatment and improve the level of clinical diagnosis and treatment.

Declaration of conflicting interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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