Guideline

Expert consensus on nebulization therapy in pre-hospital and in-hospital emergency care

Chinese College of Emergency Physicians (CCEP), Emergency Committee of PLA, Beijing Society for Emergency Medicine, Chinese Emergency Medicine

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Introduction

Emergency patients typically present with sudden onset and complex symptoms, the cause is often unclear, and many of the patients are elderly, children, or in critical conditions (1,2). Respiratory diseases and symptoms constitute a large part of the cases (1,3-6).

Nebulization therapy has a unique and vital position in the treatment of respiratory diseases. It has several advantages, such as the rapid onset of action, proved efficacy, good safety profile, and is widely used in many respiratory diseases. Nebulization therapy is suitable for most patients, including children, elderly, patients on mechanical ventilation, with a cognitive disorder or are unable to use other inhalation devices (7,8). It plays an essential role in emergency care with conditions including acute asthma attacks, acute exacerbation of the chronic obstructive pulmonary disease, acute laryngeal obstruction, acute respiratory infection, respiratory distress syndrome, severe pneumonia, acute respiratory failure, aspiration-induced lung injury, and endotracheal intubation. Nebulization therapy fulfills the needs of pre-hospital and in-hospital emergency care, which calls for rapid, effective, safe, easy to use, and widely applicable remedies, hence deserving further exploration and promotion.

However, there are no standards for the application of nebulization therapy in pre-hospital and in-hospital emergency care in China, and the utilization rate is far from clinically needs (9). In order to answer the call for national "Guidance on establishing a platform for pre-hospital and in-hospital emergency care", and to further promote nebulization therapy use and facilitate the development of an integrated platform for pre-hospital and in-hospital emergency care, the Emergency Medicine Branch of Chinese Medical Doctor Association, Emergency Medical Specialized Committee of PLA, Beijing Emergency Medicine Association and the Chinese Emergency Medicine Consortium conducted multiple rounds of consultation and discussion with experts in the field and developed this consensus statement. We hope to provide theoretical and practical guidance on nebulization use in emergency medicine, thus improving treatment and eventually benefiting more patients.

Basic principles and SOPs for nebulization therapy in pre-hospital and in-hospital emergency care

Nebulization therapy aims to deliver a therapeutic dosage of a drug by inhalation of the drug-aerosol, which is generated with a drug solution or suspension by a nebulizer, through the mouth, nose or artificial airway (including endotracheal and tracheotomy tubes) into airways and lungs. Nebulization therapy can also serve as a support and supplement to systemic therapy. It has a relatively lower requirement for patient's coordination and can be used to deliver a large dosage of drugs in combination, and in

Table 1 Comparison of characteristics of nebulizers

Nebulizer type	Advantages	Disadvantages
Jet nebulizer	Simple structure, durable, widely used in clinical applications	May generate noise, must be driven by compressed gas or power supply (mostly AC power)
Ultrasonic nebulizer	Able to generate large quantity of aerosol, no noise	Need power supply (mostly an AC power source), prone to drug degeneration; May cause inhalation of excessive water and decrease oxygen concentration when provided with too much aerosol; More water that drug in aerosol if the drug is in suspension form (the energy needed to turn water into an aerosol is lower than that needed to turn drug suspension into aerosol)
Vibrating mesh nebulizer	No noise, compact, light, battery-driven optional	Need AC power or battery, durability not fully confirmed, fewer devices available

intermittent or continuous treatment with concomitant oxygen supply, making it a flexible and convenient choice for pre-hospital and in-hospital emergency care.

Indications for nebulization therapy in pre-hospital and in-hospital emergency care

Nebulization therapy can be used to treat respiratory diseases or respiratory-related symptoms in emergency care. It can also be used as a prophylactic measure of airway management in other diseases. No absolute contraindications are noted.

The goal of nebulization therapy can be briefly summarized as "SHAPE":

- S (Relief airway Spasm): to relieve bronchospasm, coughing and wheezing;
- H (Humidify): to humidify airway;
- An (Anti-inflammation): to achieve an anti-inflammatory effect;
- P (Prevent): to prevent respiratory complications such as airway inflammation, obstruction, atelectasis, infection, and asphyxia;
- E (Expectorant): promote expectoration.

Basic principles for nebulization therapy in pre-hospital and in-hospital emergency care

Although it is an effective treatment measure, nebulization therapy can only be conducted when a patient's safety Is ensured first. If a patient is in state of, or shows the sign of unconsciousness or coma, or stupor with superficial breathing, no aortic pulsation, no breathing or abnormal breathing, cyanosis, poor or lack of pain sensation reflex, lack of vomiting reflex or cough reflex, it is essential to stabilize vital signs first and perform advanced life support measures such as cardiopulmonary resuscitation, endotracheal intubation and mechanical ventilation as needed. After the vital signs are stabilized, nebulization therapy may be considered. However, in cases when it is deemed necessary, nebulization therapy may be administered concomitantly with the stabilization of the vital signs. Also, the efficacy and adverse reactions should be evaluated and treated promptly during and after the treatment, and the treatment protocol should be adjusted accordingly.

Common nebulizers and drugs (also see *Tables S1,S2*)

Common nebulizers

The nebulizers commonly used in current clinical practice are mainly divided into three types based on the mechanism of aerosol generation: jet nebulizer, ultrasonic nebulizer, and vibrating mesh nebulizer. The characteristics are shown in *Table 1*.

Jet nebulizers are the most widely used nebulizing devices in clinical practice. It does not affect drug stability and concentration and is, therefore, suitable to be used in pre-hospital and in-hospital emergency care, such as in ambulance and emergency rescue room, infusion room, intensive care unit and emergency ward.

A jet nebulizer is mainly composed of compressed gas source and nebulizer. The compressed gas source can be either bottled compressed gas (such as high-pressure oxygen or compressed air) or power-driven compression pump. For hypoxic patients with dyspnea and wheezing, the use of oxygen-driven nebulization is recommended to improve

Table 2 Comparison of pharmacological properties of three ICSs

Pharmacological properties	Beclomethasone dipropionate/17-BMP	Budesonide	Fluticasone propionate
Glucocorticoid receptor affinity	140/1,440	850	1,540
Time for effect onset	Within 3 days	3 h	12 h
Hydrophilicity (μg/mL)	0.1/10	14	0.04
Lipophilicity (log P)	4.9/4.3	3.6	4.5
Pulmonary retention time	Short	Length	Intermediate
Plasma protein binding rate (%)	87	88	90
System clearance rate (L/h)	150/120	84	69
Elimination half-life (h)	0.5/2.7	2.8	7.8
Adrenal cortical inhibition	Low	Low	High

oxygenation and prevent the decline of the arterial partial pressure of oxygen (PaO_2) due to changes in ventilation/perfusion (V/Q) ratio after inhalation of β2 agonist. For patients prone to CO_2 retention (such as chronic obstructive pulmonary disease with respiratory failure), the use of compressed air driven nebulizer is recommended. In such patients, the respiratory excitation is mainly stimulated by hypoxia. The improvement in hypoxia leads to a decline in low oxygen stimulation, thereby resulting in an inhibition of spontaneous breathing and aggravation of CO_2 retention.

Commonly used drugs and precautions

Currently, the commonly used drugs for nebulization in China include inhaled corticosteroids (ICS), bronchodilators, and mucolytic agents. No other commercially available drugs are indicated for nebulization. It is not recommended to use drugs without indication for nebulization. The ideal drug used in emergency care should have a rapid onset of action, clear dose-effect relationship, and precise therapeutic target. The following drugs are recommended in this consensus for emergency use.

ICS

ICS remains to be the most potent topical airway anti-inflammatory drug. It exerts the effects by influencing a series of cells and molecules in inflammatory reactions. ICS has the following characteristics: (I) it is directly delivered to airways and lungs, showing more significant improvement for respiratory symptoms and lung function within the first 1 and 2 hours following administration than systemic glucocorticoids (10); (II) it can effectively control airway inflammation, inhibit mucosal hypersecretion, and reduce mortality (11); (III) **a**dministered with a low dosage, ICS has a good safety profile and lower incidence rate of adverse events than systemic glucocorticoids (12). Spontaneous remission of common adverse events such as hoarseness and sore throat is generally to be expected after drug withdrawal.

Budesonide has the most rapid onset of action among the ICS and is currently the most commonly used ICS in emergency care. Beclomethasone dipropionate (BDP) and fluticasone propionate (FP) are also used (10,13-16). A comparison of the three ICSs is shown in *Table 2*.

ICS is contraindicated in patients allergic to any glucocorticoid. In case of any misuse, intravenous injection or infusion of epinephrine should be administered immediately, with the inhalation of 100% oxygen. If necessary, tracheal intubation and cardiopulmonary resuscitation should be performed.

Bronchodilators

Bronchodilators are categorized into selective β2 receptor agonist and cholinergic receptor antagonist. They can also be divided into short-acting and long-acting types depending on the onset and duration of effect. Currently, all domestic bronchodilators inhalers are short-acting. (I) Short-acting beta2 agonists (SABAs), with synergistic effects with ICS, are the main drugs for relieving bronchospasm and treating acute asthma. E.g., salbutamol and terbutaline; (II) short-acting muscarinic antagonists (SAMAs), which acts mainly on large airway rather than

Table 3 Other drugs proved by FDA for nebulization (https://www.fda.gov/)

Drug	Indication
FLUNISOLIDE	Asthma
CICLESONIDE	Asthma (NOT indicated for the relief of acute bronchospasm)
MOMETASONE FUROATE	Asthma (NOT indicated for the relief of acute bronchospasm)
FORMOTEROL FUMARATE; MOMETASONE FUROATE	For the twice-daily treatment of asthma in patients 12 years of age and older (NOT indicated for the relief of acute bronchospasm)
TOBRAMYCIN	To treat people with a certain inherited condition (cystic fibrosis) who have persistent lung infection with a certain bacteria (Pseudomonas aeruginosa).
CROMOLYN SODIUM	Adjunct in the management of patients with asthma Prevention of bronchospasm
TREPROSTINIL	Pulmonary arterial hypertension
ILOPROST	Pulmonary arterial hypertension
AZTREONAM	To improve respiratory symptoms in cystic fibrosis (CF) patients With Pseudomonas aeruginosa
PENTAMIDINE ISETHIONATE	To prevent a serious lung infection (Pneumocystis pneumonia-PCP) in people with acquired immunodeficiency syndrome (AIDS)
METHACHOLINE CHLORIDE	For the diagnosis of bronchial airway hyperreactivity in subjects who do not have clinically apparent asthma

the small airway, has a weaker bronchodilating effect, a slower onset but longer duration of effect, as compared to SABA (17). e.g., ipratropium bromide; (III) compound Ipratropium Bromide Solution for Inhalation, containing 0.5 mg of ipratropium bromide and 2.5 mg of salbutamol in each 2.5 mL dose. Caution must be exercised not to blend with other drugs in the same nebulizer. SABA is the preferred choice as bronchodilators; if necessary, use in combination with SAMA aerosol inhalation. Patients with tachycardia or concomitant cardiovascular disease should choose terbutaline based on its higher selectivity for the β2 receptor than that of salbutamol, therefore a lower risk of cardiovascular adverse events. Patients who experience palpitation during nebulization therapy should discontinue SABA and keep monitored until the symptoms disappear before continuing with nebulization therapy. If symptoms persist or deteriorated, selective β1 blockers can be administered also.

Mucolytic agent

N-acetylcysteine is a classic mucolytic agent. The unique hydrosulfuryl(-SH) group breaks the disulfide bond (-SS) between mucin molecular complexes, thereby reducing the viscosity of sputum (18). Also, it can promote ciliary movement, improve mucociliary clearance capacity (19) and increase the secretion and activity of pulmonary surfactant, thus promote mucus discharge. Furthermore, N-acetylcysteine also has a strong antioxidant effect, which can reduce oxidative stress damage in respiratory diseases (20). Recent studies have indicated that N-acetylcysteine can also impair and inhibit the formation of bacterial biological membrane. When used alone or in combination with antibiotics, it can inhibit respiratory infections (21).

Currently, N-acetylcysteine is the only mucolytic agent in China with nebulizer formulation. Upon nebulization, it can quickly reach the lung. It must be noted that although intravenous preparation of ambroxol is frequently used for nebulization therapy in clinical practice, it is not labeled for that. Further clinical studies are needed to validate the dosage, concentration, efficacy, and safety for it to be used for nebulization therapy. Case reports are suggesting that asthma attacks may be induced, which may be associated with the preservatives in the preparations. Therefore, the use of ambroxol intravenous preparation for nebulization is not recommended.

Other drugs

Some drugs (such as tobramycin, sodium cromoglycate, treprostinil, and aztreonam), are currently not commercially available with nebulizer formulation in China, but their efficacy has been clinically validated. Other FDA-approved nebulization drugs are listed in *Table 3*.

Precautions in choosing nebulization drugs

(I) Patient with a history of allergies. Avoid using the drug if there was a previous history of an allergic reaction to it (22);

(II) if the inhalation of foreign bodies caused signs and symptoms, no routine nebulization therapy is necessary;
(III) concomitant treatment contraindication: there were rare cases when concomitant administration of salbutamol and ipratropium bromide aerosol were used, patients experienced closed-angle glaucoma. Special caution must be taken when concomitantly use above-mentioned aerosolized drugs and similar agents;
(IV) patients with serious cardiovascular diseases (such as ischemic heart disease, tachyarrhythmia or severe heart failure), with a heart rate or pulse >120 beats/min or with uncontrolled thyrotoxicosis are not recommended to use SABA (refer to the package insert of Terbutaline sulfate nebulizing solution and Salbutamol sulfate inhalation solution);
(V) contraindications in patients with underlying conditions; for example, children, pregnant women, elderly, long-term bedridden patients, and patients with various complications. Special attention should be paid to the previous history of medications and contraindications; (VI) other treatment measures should also be used.

Drug and equipment requirements for nebulization therapy in pre-hospital and in-hospital emergency care

When allocating aerosol inhalation devices and drugs, the seamless connection between pre-hospital care and in-hospital care should be considered. The consistency at each link should be highlighted. Below is the list of the recommended equipment and drugs. Adjust according to actual visits and patient turnover to ensure sufficient supply.

List of aerosolized drugs:

- ICSs: recommend Budesonide suspension for inhalation 1 mg (2 mL);
- Short-acting bronchodilator (short-acting beta agonist, SABA): recommend Terbutaline sulfate solution for nebulization 5 mg (2 mL) or Salbutamol sulfate inhalation solution 5 mg (2.5 mL);
- Mucolytic agent: recommend N-acetylcysteine solution for inhalation 0.3 g (3 mL).

List of equipment and supplies:

- Compressed air nebulizer and electrical outlet, oxygen cylinder;
- Mouthpiece/facial mask;
- Nebulizing cup;
- Connecting cognitive disorder;
- The use of vibrating mesh nebulizer does not require nebulizing cup and connecting cognitive disorders. The aforementioned nebulized drugs and equipment supplies should be organized and placed for easy access.

Factors affecting nebulization efficiency

The factors affecting the nebulization efficiency can be divided into three categories, "device, drug, and patient", i.e., the inherent efficiency of the nebulizing device, the inherent characteristics of the nebulized drug, and the patient (8).

Nebulizer

The nebulizer is the device that generates aerosol. The primary factors affecting the nebulization efficiency are as follows:

(I) output efficiency of effective nebulized particles; effective nebulized particles refer to nebulized particles with therapeutic values, i.e., that can be deposited in the airway and lung, preferably with a diameter of 3.0–5.0 μm; the particles with a diameter of 5–10 μm are mainly deposited in the large airways and oropharynx. The particles with a diameter of 1–5 μm are mainly deposited in the small airways. About 40–48% of the particles with a diameter of fewer than 3 μm are deposited in the alveoli, and the particles with a diameter of fewer than 0.5 μm are excreted along with exhalation (23,24);
(II) the output volume per time unit: higher output is correlated with more inhalation and high dose and potentially stronger therapeutic efficacy. Meanwhile, higher dose within a short time can also increase adverse reaction. A comprehensive assessment should be made.

Differential nebulizing devices are based on different mechanisms:

(I) Jet nebulizer. The diameter of the generated aerosol particles and the amount of output depend on the pressure and flow rate of the compressed air, as well as on the structural parameters of internal resistance based on brand and version. The pressure and flow rate of the compressed gas

are directly proportional to the amount of output and inversely proportional to the diameter of the aerosol particles. Higher the pressure and higher the flow rate, the smaller is the diameter of the aerosol particles produced by the jet nebulizer and the larger the amount of aerosol output;

(II) Ultrasonic Nebulizer. The diameter of the released particles is negatively correlated with the ultrasonic frequency. The higher the frequency, the smaller the particle. The amount of released aerosol is positively correlated with the ultrasonic amplitude (power). The greater the intensity, the greater the amount of released mist. In general, ultrasonic nebulizer generates a higher amount of aerosol than a jet nebulizer;

(III) Vibrating mesh nebulizer. The size of produced particles depends on the diameter of the mesh. The device reduces the effect of heat generated by ultrasonic liquid vibration, exerts less effect on drug integrity. It is considered the most effective nebulizer so far.

Drug

Size and shape of the drug particle can also affect the proportion of effective drug aerosol generated, using ICS as an example. Budesonide suspension is shown as small round particles of a diameter of 2.0-3.0 μm under an electron microscope, while the drug particles of beclomethasone propionate suspension are needle-like particles about 10.0 μm in length. In vitro studies have shown that the output of effective aerosol was much higher for budesonide than that for beclomethasone using different brands of nebulizers (25).

Patient

The patient's cognition and ability to coordinate, breathing pattern, and general disease status can affect the nebulization efficiency.

(I) Cognition and ability to coordinate. The patient's cognitive status and the ability to cooperate also determines whether the nebulizer can be effectively used. Regardless of the type of the nebulizer used, as long as it is used correctly, a similar clinical effect can be achieved.

(II) Breathing pattern. The breathing parameters that affect aerosol deposition include inspiratory flow, airflow pattern, breathing frequency, inspiratory volume, inspiration/expiration ratio, and maintenance of the inspiratory state. Slow and deep breathing facilitates the deposition of aerosol particles in the lower respiratory tract and alveoli. The intrapulmonary deposition is less when the breathing rate is fast, and the inspiratory volume is small. An abnormal fast inspiratory flow rate is prone to result in local turbulence, causing aerosol to deposit on the large airway due to the collision, resulting in a significant decline in an intrapulmonary deposition. When the inspiratory capacity maintains constant, with an increase in tidal volume and the extension in inspiratory time, deep and slow breathing is more beneficial for aerosol deposition.

(III) General disease status. Status of patients' respiratory system can affect the delivery of aerosols in the respiratory tract. Inflammation, swelling, and spasm of the tracheal mucosa and retention of secretions can result in increased airway resistance and uneven distribution of inhaled aerosols; Drug concentration in the stenotic site may increase, and the drug deposition at the distal end of the obstruction site may be low, compromising the clinical efficacy. Therefore, sputum and atelectasis should be eliminated as much as possible before nebulization therapy to facilitate aerosol deposition in the lower respiratory tract and lung.

General protocol and precautions for nebulization therapy

General protocol for nebulization therapy

(I) Patient assessment: evaluate whether a patient is suitable for nebulization therapy and choose the appropriate nebulizer. Patients with clear consciousness and high cooperativeness should wear a mouthpiece. Facial masks are used in patients with a cognitive disorder, severe illness, or poor coordination (22).

(II) Keep the airway open: check for any foreign body or secretions in the respiratory tract. Excessive sputum should be removed by coughing or by suction.

(III) Patient education: briefly inform about the treatment purpose and procedures before nebulization. Inform patients to take slow and deep breaths, inhale

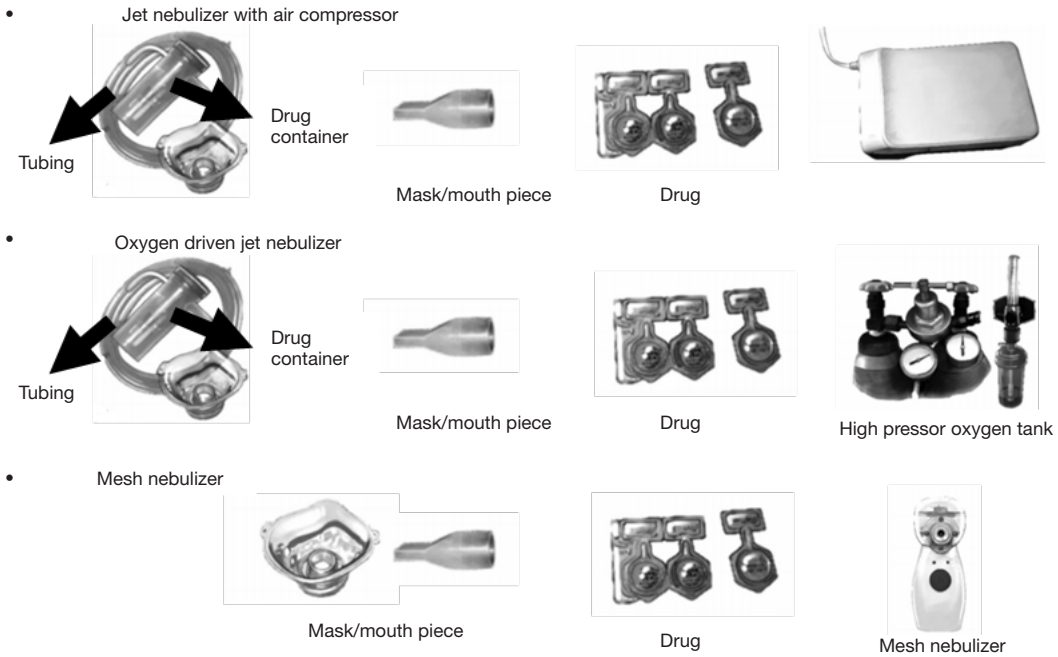

Figure 1 Item and drug preparation for nebulization therapy.

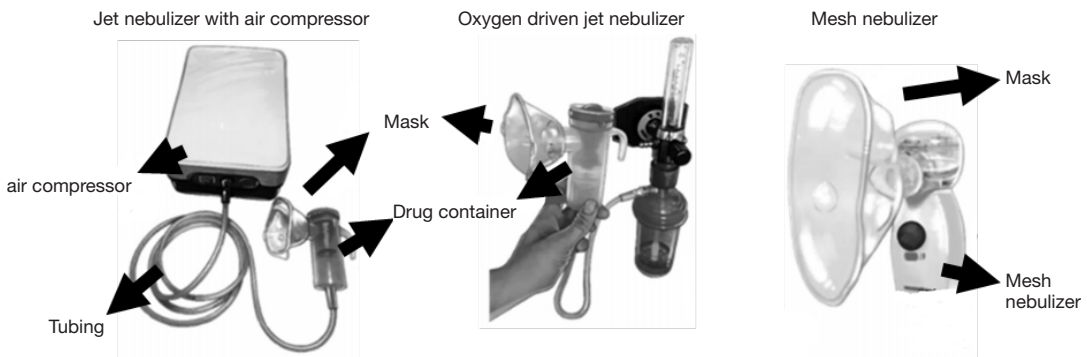

Figure 2 Connecting tubing and nebulizer.

through the mouth, and exhale the nasal cavity (22).

(IV) Appropriate body position: conscious patients are recommended to take a semi-recumbent or sitting position; patients with the cognitive disorder or weak cough are recommended to take the recumbent position, with the head of the bedstead raised by 30°, and treatment towel is placed under the patient's jaw (22).

(V) Item and drug preparation: as shown in *Figure 1*.

(VI) Tubing connection: connect the compressed air nebulizer or oxygen cylinder, and connect the tubing, nebulizer, mouthpiece, or mask; install the mask or mouthpiece on the vibrating mesh nebulizer (see *Figure 2*). Combine the mechanical ventilation with nebulization treatment, to determine whether the ventilator has the nebulization function, and adjust the parameters related to ventilator performance.

(VII) Use of mouthpiece or mask: guide and assist the patient to effectively harbor the mouthpiece in the mouth or wear a face mask. Advice patient to inhale the nebulized drug.

(VIII) Initiation of nebulization therapy: for patients using compressed air nebulizer or vibrating mesh nebulizer initiate the nebulization. For patients using an oxygen-driven nebulizer, turn on the oxygen, adjust the oxygen flow from low to high (usually 6–8 L/min), and observe the output of nebulized liquid (22). The aerosol inhalation lasts for about 15 to 20 min. Keep a close observation, monitor adverse reactions, and take timely measurements. Efficacy should be assessed meanwhile.

(IX) End of aerosol inhalation treatment: guide and assist the patient in rinsing the mouth or applying oral care. Pat on the back to force out sputum. Those who wear masks should also wash faces. Record efficacy and adverse effects. Evaluate and adjust therapeutic regimens as appropriate.

Operational precautions for nebulization treatment

(I) The nebulizing cup, breathing cognitive disorder, and nebulizing mask should be personal. The use of disposable devices is recommended.

(II) Although nebulization therapy is less demanding on inhalation technique and coordination (23,26), it is still recommended that patients be guided to practice correct breathing pattern (with mouthpiece engaged between lips, slowly inhale, hold the breath for 2–3 seconds after a deep inhalation, slowly exhale through nasal cavity), to achieve better therapeutic results.

(III) Oily facial cream should be removed before treatment if the mask is needed. Keep liquid or aerosol away from eyes to reduce irritation.

(IV) Gargling and oral care after treatment can significantly reduce the incidence of adverse reactions such as hoarseness, sore throat, and candida infection (27);

(V) The membrane at the expiratory end of the ventilator should be cleaned, tested, and replaced regularly to avoid damage to the internal precision components of the ventilator.

Efficacy evaluation of nebulization therapy

The efficacy evaluation should be carried out at 0, 5, 10, 30 minutes from the start of nebulization (27):

- Improvement: (I) elimination or improvement of original respiratory symptoms. No newly-emerging respiratory symptoms; (II) improvement of abnormal signs; for example, reduced wheezing in pulmonary auscultation, absence of newly-emerging abnormal signs; (III) respiratory rate, heart rate, or pulse return to normal as indicated by the monitoring system. SpO_2 rebounds.
- No change: (I) no change in the original respiratory symptoms. No new abnormal physical signs; (II) no change in original abnormal signs, no new abnormal physical signs; (III) no significant improvement in respiratory rate, SpO_2, heart rate, or pulse as indicated by the monitoring system. Alternatively, no consistent trend of change.
- Aggravation: (I) exacerbation of original respiratory symptoms. The occurrence of new abnormal physical signs; (II) exacerbation of original abnormal signs. The occurrence of new abnormal physical signs; (III) the appearance of abnormal respiratory rate, SpO_2, heart rate, or pulse as indicated by the monitoring system.

Monitoring and management of adverse reactions of nebulization therapy

Adverse reactions should be closely monitored during the aerosol inhalation treatment. Cause of adverse events should be immediately evaluated, and timely actions are taken. Common adverse reaction symptoms, possible causes, and recommended clinical management are listed in *Table 4*.

Application of aerosol inhalation in pre-hospital care

Indications of nebulization treatment in pre-hospital first aid

If symptoms or signs of airway hyperreactivity is indicated, the nebulization treatment is recommended:

(I) Patients with respiratory symptoms such as dyspnea, coughing, expectoration, or chest tightness.

(II) Abnormal physical signs such as cyanosis of lips, shortness of breath, and three concave sign or dry or moist rales (especially wheezing sounds) as shown in the pulmonary auscultation.

Table 4 Common adverse reactions and treatment methods in nebulization treatment

Adverse reaction symptoms	Possible causes	Recommended clinical management
Allergic reaction	Allergy to aerosolized drug or drug ingredients	Detailed Inquiry about the patient's allergic history; close monitor of the patient's reactions; intravenous administration of adrenaline and other related treatment as appropriate
Aggravation in coughing and dyspnea.	The temperature of the drug/inhalation flow is too low, may causing some irritation to the airway	Store and use the drug at room temperature; Maintain the room temperature; Maintain air-driven flow at 6–8 L/min; Nebulization treatment duration for 15 minutes
	Change of ventilation/perfusion ratio and a decline in the arterial oxygen partial pressure following nebulization treatment with the β2 receptor agonist (especially salbutamol)	Use oxygen-driven aerosol inhalation, or reduce or temporary discontinue β2 receptor agonist treatment. Apply oxygen inhalation
	In patients prone to CO_2 retention during oxygen-driven nebulization therapy, inhibition of spontaneous breathing may occur, leading to dyspnea	Use vibrating mesh nebulizer with compressed air. Avoid oxygen-driven aerosol inhalation
Severe cough, severe hypoxia	Mucus plug or massive dilution of sputum and retention in the airway	Patients with massive and thick sputum should be assisted with sputum suction and patting on the back. Oxygen inhalation can be performed if necessary
Tachycardia or arrhythmia	More common in an overdose of β2 receptor agonists inhalation (especially salbutamol)	Reduce or temporarily discontinue β2 receptor agonists
Dizziness, hand numbness	More common in young and middle-aged patients or first-time receiver for nebulization therapy. Induced by the hyperventilation resulting from nervousness or excessively frequent inhalation	Advice patients to relax and breath normally when receiving nebulization treatment

Recommendation in the nebulization treatment regimen for pre-hospital emergency care

A comprehensive assessment will be made based on the patient's conditions. The use of ICS [e.g., budesonide 2 mg (4 mL)] +/– SABA [e.g., terbutaline 5 mg (2 mL) or salbutamol 5 mg (2.5 mL)] is routinely recommended.

A compressed air-driven spray nebulizer is generally employed. In patients with obvious hypoxemia or hypoxia, an oxygen-driven jet nebulizer is recommended if possible. During the oxygen-driven nebulization, no additional oxygen inhalation is required (27).

Continued nebulization therapy from home care to pre-hospital and in-hospital emergency care

For patients who have home care nebulization system, in case of emergency, before the ambulance arrival, nebulization treatment should be performed at home based on the patient's conditions and be continued when transferred to the ambulance.

The recommended duration for nebulization treatment is 15 minutes, during which the patient's conditions are closely monitored.

If the nebulization treatment has not been completed when arriving hospital, for patients using a portable mesh nebulizer or connected with a portable oxygen cylinder on the ambulance, the nebulization treatment should be continued; For patients using a compressed air nebulizer, pause the treatment first, bring the nebulizing cup and continue the nebulization treatment when arriving hospital.

Procedures of nebulization treatment for pre-hospital first aid

Emergency medical staff should evaluate patient's vital signs and conscious state first and follow the procedure of nebulization therapy for pre-hospital first aid (*Figure 3*).

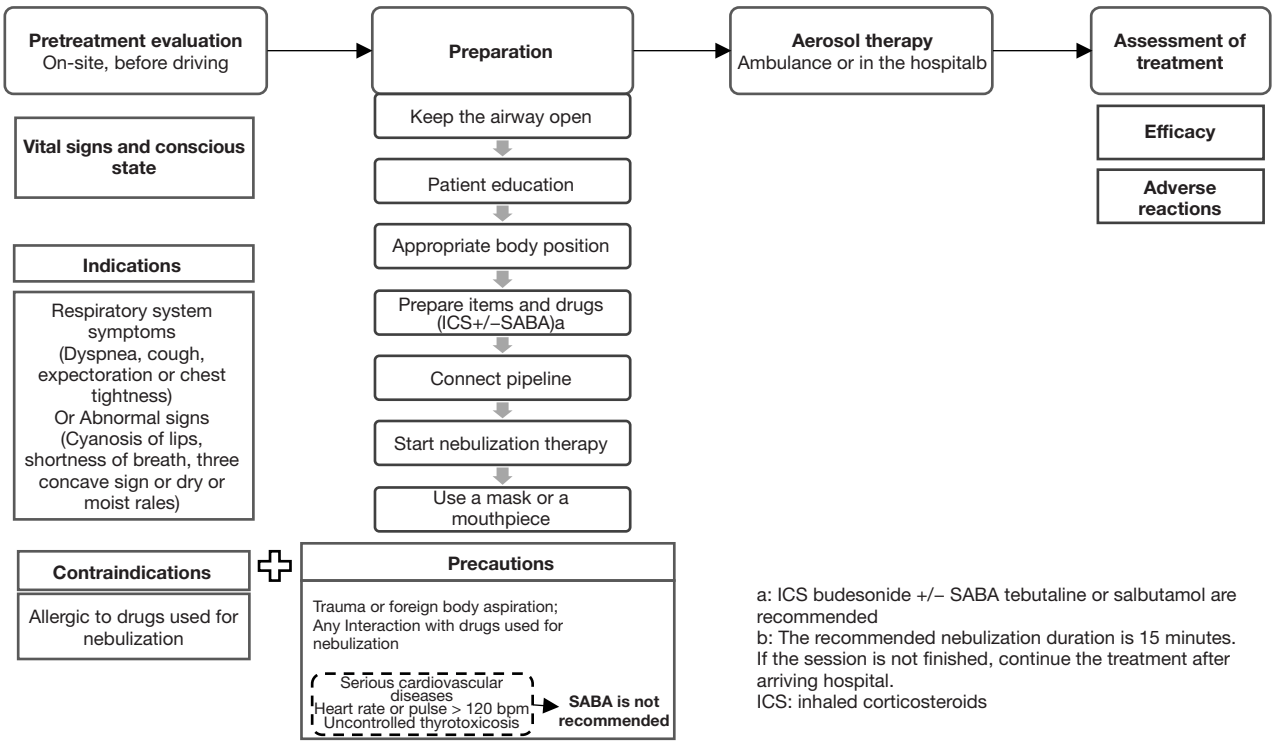

Figure 3 Procedures of nebulization therapy for pre-hospital first aid.

Table 5 Assessment criteria for the severity of an acute asthma attack (27)

Clinical characteristics	Mild	Moderate	Severe	Critical
Body position	Can lie down	Prefer sitting	Orthopnea	
speech pattern	Sentences	Phrases	Word	Unable to talk
Mental status	occasional anxiety, still quiet	Frequent anxiety or irritability	Constant anxiety and irritability	Drowsy or confused
Sweating	No	Yes	Profuse sweating	
Assisted respiratory activity and three concave signs	Usually absent	occasional present	Usually present	Paradoxical respiration of chest and abdomen
Wheezing rale	Scattered, end-stage of breathing	Loud, diffuse	Loud, diffuse	Weakened or even absent

Application of nebulization therapy in the emergency department

Acute attack of asthma

Assessment and treatment

It is essential that patients are moved away from the environment and allergens that may trigger an acute asthma attack. Patients should be assessed and graded (*Table 5*) and given corresponding treatments (*Figure 4*).

Precautions

(I) The treatment purpose of an acute asthma attack is to relieve the patient's respiratory symptoms, mitigate bronchospasm, improve hypoxia, restore

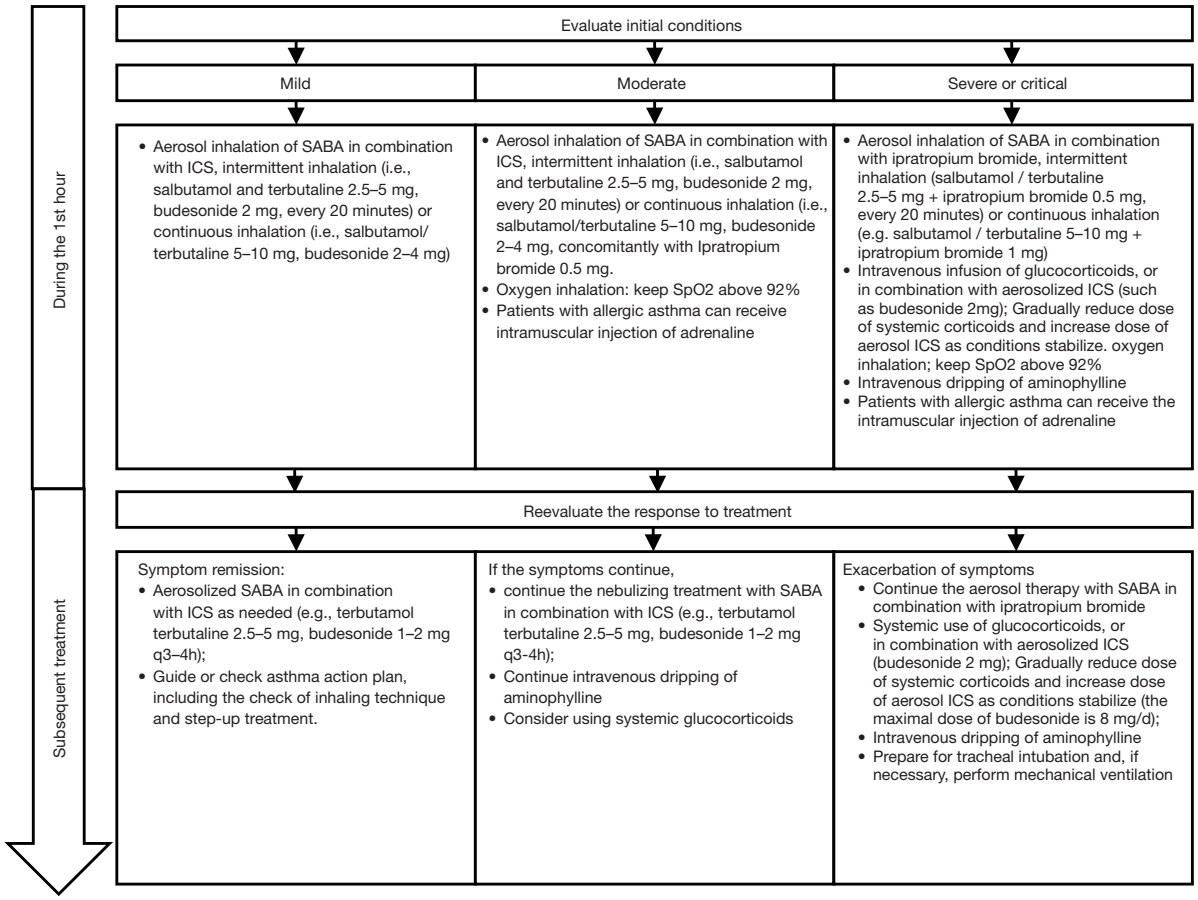

Figure 4 Procedures for the management of acute asthma attack (27).

lung function, prevent further deterioration or recurrence, and prevent complications (27).

(II) In general, if symptoms fluctuate or mild to moderate acute attacks occur during asthma control, self-management can be performed according to the "Asthma Action Plan", i.e., to repeat SABA inhalation (aerosol inhalation of salbutamol/terbutaline, initially intermittently (every 20 minutes) or continuously, followed by intermittent administration(every 4 hours), or use pMDI inhalation) , or use low-dose ICS/formoterol combination (no more than 8–12 inhalations per day in total), can use SAMA concomitantly, with ICS dose increased to 2–4 times of the usual dose, up to 1,600 μg/day for budesonide or other ICS equivalents.

(III) It must be noted that if a patient needs to frequently increase the use of bronchodilators (especially SABA) to relieve symptoms, that indicates that asthma is aggravated. More regular evaluation needs to be performed (e.g., Monitoring of daily peak flow with regular follow-up), and the asthma action plan should be updated. The maximum recommended dosage of ICS or oral glucocorticoids should be considered.

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

Assessment and treatment

Patients are graded according to severity (*Table 6*) and treatment correspondingly (*Figure 5*).

Precautions

(I) The preferred bronchodilator for AECOPD treatment is usually a single SABA inhaler or

Table 6 Evaluation and grading of AECOPD

Variables	Grade I (no respiratory failure)	Grade II (non-life-threatening acute respiratory failure)	Grade III (life-threatening acute respiratory failure)
Respiratory rate	20 to 30 bpm	>30 bpm	>30 bpm
Assisted respiratory muscle group	Not applied	Applied	Applied
Change of cognitive status	No	No	Sudden change

AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

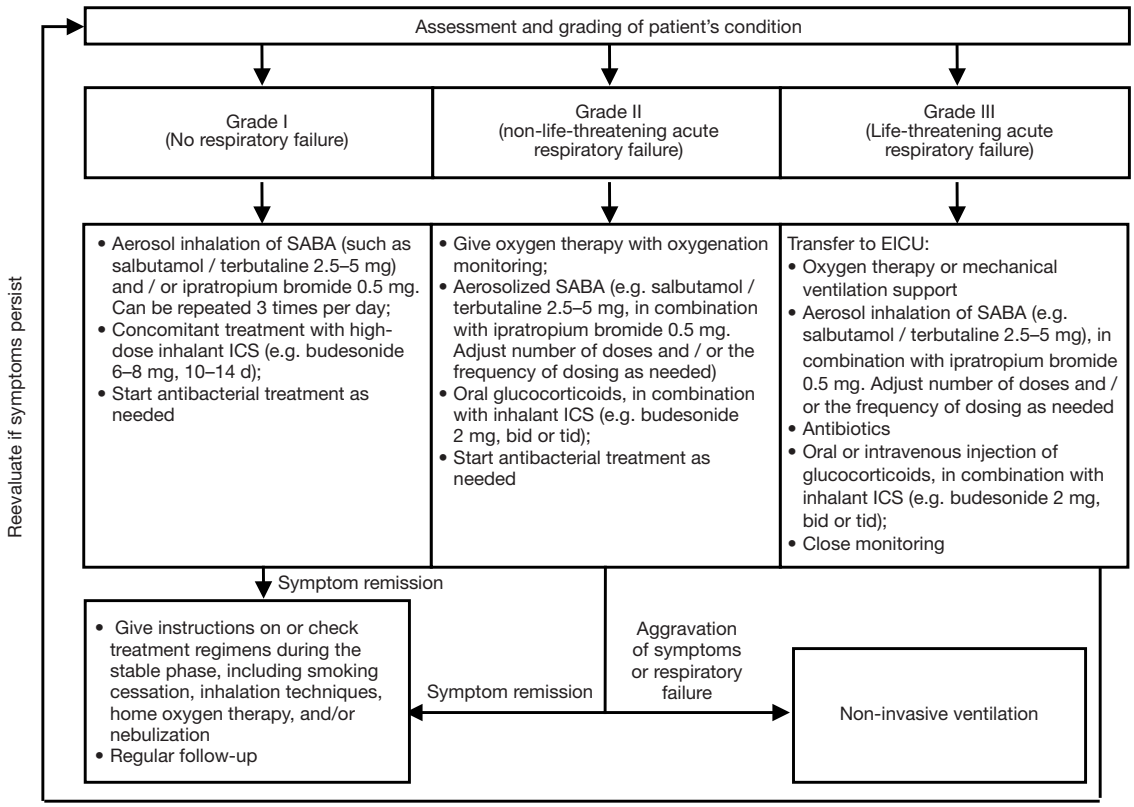

Figure 5 Procedures for the management of AECOPD. AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

concomitantly administered SAMA inhalation.

(II) The use of glucocorticoids can shorten the recovery time, improve lung function and hypoxemia, reduce the risk of early recurrence and treatment failure, and shorten hospital stay. Aerosol inhalation ICS may replace or partially replace systemic glucocorticoids (aerosol inhalation of 8 mg budesonide for AECOPD is equivalent to systemic treatment with 40 mg prednisolone in terms of efficacy).

(III) Increased sputum, thick and sticky sputum, and/or purulent sputum is one of the typical symptoms of AECOPD (28). For AECOPD patients with such symptom and/or at risk of difficulty in coughing up sputum, adding aerosol inhalation of acetylcysteine (0.3 g/time, bid) to conventional treatment is recommended to improve PaO_2 and FEV_1 as well as relieve clinical symptoms (28).

(IV) Patients at acute exacerbation stage with chronic bronchitis, emphysema, bronchiectasis, pulmonary fibrosis, and pulmonary heart disease often

Table 7 Evaluation and classification of laryngeal obstruction

Variables	Grade I (no respiratory failure)	Grade II	Grade III	Class IV (life-threatening)
Dyspnea	Slight difficulty at rest	Severer than grade I	Appearance of cyanosis	Severe than grade III, sitting restlessly
Four concave signs	No wheezing and four concave signs	Presence of wheezing and four concave signs at rest	Obvious wheezing and four concave signs	Severer wheezing and four concave signs
Change in cognitive status	No change	No dysphoria, no obvious change in cognitive status	Presence of dysphoria, change in cognitive status	May experience coma, gatism, suffocation, and even respiratory and cardiac arrest in severe cases

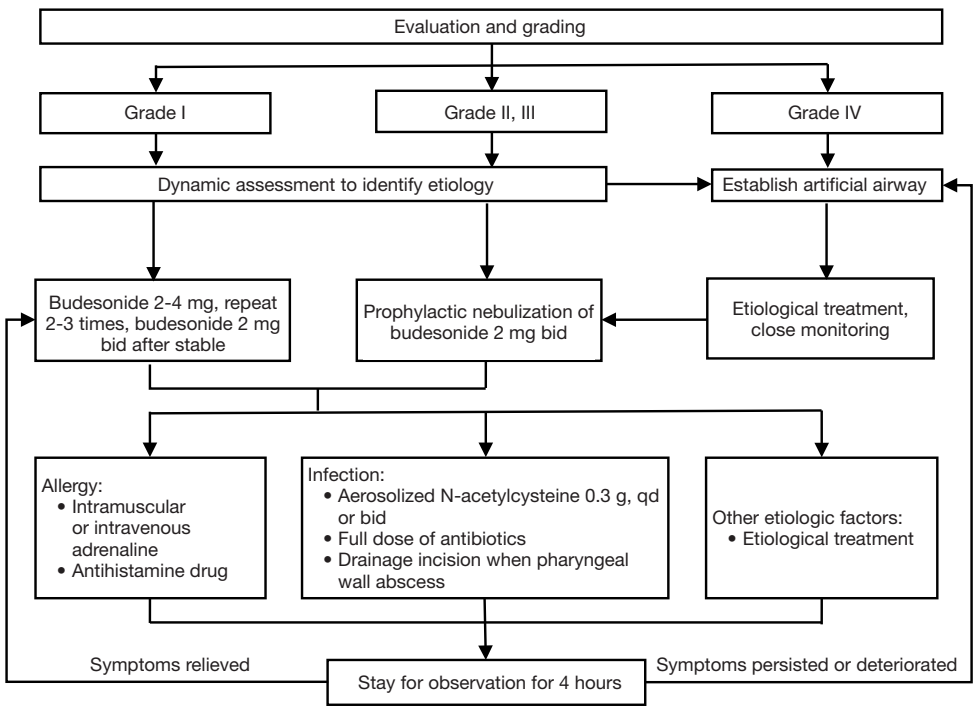

Figure 6 Procedures for the management of acute laryngeal obstruction.

have similar clinical features of AECOPD, with limited airflow, airway hyperactivity, and high secretion. Refer to AECOPD for evaluation and treatment protocol. Aerosol inhalation of ICS, bronchodilator, and N-acetylcysteine can be applied as needed.

Acute laryngeal obstruction

Assessment and treatment

Acute laryngeal obstruction (acute epiglottis, acute laryngeal edema, pharyngeal abscess, etc.) tends to aggravate progressively and may progress rapidly over a short period to a life-threatening critical stage. Instant dynamic assessment of the disease severity (*Table 7*) is required with immediate treatment (*Figure 6*).

Precautions

(I) The assessment and treatment for cute laryngeal obstruction must be decisive. For patients who may be or are at a critical stage, an artificial airway should be established as soon as possible. Causes should

be identified (such as throat inflammation, allergy, infection, trauma, foreign body, tumor, spasm, abduction paralysis of bilateral vocal cords and so on) and etiological therapy should be carried out simultaneously.

(II) Nebulization therapy is one of the emergency measures for inflammation, allergy, and convulsions. The drug can reach throat quickly, relieve the inflammation and edema at the throat, increase the ventilatory capacity, improve the hypoxic state, shorten the time for the symptoms to disappear, and improve the efficiency of rescue (29); it can also be used prophylactically to improve respiratory mucosal damage and local inflammation caused by trauma, artificial airway, as well as to increase respiratory humidity, liquefy viscous secretions, promote the subsidence of mucosal edema, and shorten the hospital stay. No nebulization therapy is required if the foreign body etiology did not cause airway damage or inflammation.

(III) The importance and necessity of adrenaline and antibiotics administration should be highlighted. Although there is no available aerosol formulation, there have been reports that the aerosol inhalation of 1 mg adrenaline leads to blood vessel contraction and improvement of laryngeal edema prognosis (including laryngeal edema following prophylactic intubation) (30).

Acute and subacute cough or chronic cough exacerbation

Coughing is a defensive nerve reflex for the body. Frequent and severe coughing can have a serious impact on work, life, and social activities. According to its duration, coughing is divided into 3 groups: acute cough (<3 weeks), subacute cough (3–8 weeks) and chronic cough (>8 weeks) (30).

The common etiology of acute cough is common cold and acute tracheal-bronchitis. The common etiology of subacute cough is post-infectious cough (PIC). The most common etiology of chronic cough is hormone-sensitive cough, including cough variant asthma (CVA), eosinophilic bronchitis (EB) and atopic cough (AC), accounting for about 2/3 of chronic cough in China (30). Other common etiologic factors include upper airway cough syndrome (UAC) and gastroesophageal reflux-related cough (GERC), which are often accompanied by postnasal drip sensation and concomitant nasal diseases, or accompanied by obvious reflux symptoms often associated with food intake (31).

In addition to other etiological treatments, for patients with severe cough or wheezing, aerosol inhalation of bronchodilators (e.g., salbutamol/terbutaline 2.5–5 mg bid) in combination with ICS (e.g., budesonide 2 mg bid) is recommended until symptom remission. Diagnostic treatment may be administered (for no less than 2 weeks) using this method for hormone-sensitive cough patients: if the symptom is relieved, the disease is judged to be hormone-sensitive cough. ICS or combined therapy with bronchodilator may be continued; If partial response is achieved, factors affecting treatment efficacy should be evaluated, and the composite etiology should be considered; In case of no response, an assessment is performed to evaluate whether the judgment is wrong, whether the dose and duration of treatment are sufficient, or whether there are factors affecting the efficacy. Other etiologic factors should also be considered. For patients with excess sputum, aerosol inhalation of mucolytic agents may be used, such as N-acetylcysteine 0.3 g (3 mL) qd or bid for 5 to 10 days. The number of doses and the frequency of dosing may be adjusted according to clinical response and therapeutic effects (32). In patients with airway hyperreactivity, the airway goblet cells are also activated, which often leads to increased mucus secretion. Therefore, for such patients, mucolytic agents may be administered via aerosol inhalation to prevent sputum from blocking the airway.

Pneumonia

Patients with pneumonia often have increased mucous secretion and sticky and thicken sputum, which leads to retention of sputum and difficulty in pathogens clearance. The aerosol inhalation of N-acetylcysteine [0.3 g (3 mL) once to twice per day] may humidify the airway, facilitate mucus discharge, keep the airway open, enhance the action of anti-infective drugs and accelerate recovery. N-acetylcysteine also impairs the formation of bacterial biofilms. In vitro studies show that N-acetylcysteine interferes with the formation of Pseudomonas aeruginosa biofilm and destroy formed biofilm in a concentration-dependent manner (33).

Pathogen stimulation can also cause airway spasm,

mucosal edema, and inflammatory exudation. If the patient shows symptoms such as shortness of breath, wheezing, dyspnea or coughing, the combined aerosol inhalation with bronchodilators (such as salbutamol/terbutaline 5 mg bid) and ICS (such as budesonide 2 mg, bid) may be considered to quickly relieve bronchospasm, reduce airway inflammation and mucosal edema, and promote airway epithelial repair and pneumonia healing (34). ICS can also be administered in combination with the mucolytic agent in nebulization therapy. Studies have shown that N-acetylcysteine in combination with budesonide inhalation is superior to budesonide alone for the treatment of bronchial pneumonia in terms of time for improvement of clinical symptoms as well as overall response rate (35).

Also, for patients with no mucus production, aerosol inhalation of hypertonic saline may be administered when collecting phlegm sample. Aerosol inhalation of non-nebulized antibacterial agents is not recommended. However, for critical patients with no response to intravenous antibiotics, which need strict control of fluid intake and have multidrug-resistant bacteria (MDR) infection, combined treatment with aerosol inhalation antibiotics may be considered.

Acute respiratory distress syndrome (ARDS)

ARDS is an acute and diffuse inflammatory lung injury (36), whose pathophysiological basis is the systemic inflammatory response syndrome. Glucocorticoids can inhibit inflammatory response at multiple levels, reducing pulmonary capillary permeability and alveolar membrane damage and improving tissue tolerance to hypoxia (37,38); β2 receptor agonists can activate AC and increase cAMP by acting on alveolar type II epithelial cells, thereby stabilizing the release of cellular lysosomal enzymes and reducing cellular damage (39). It is recommended in 2016 Japan ARDS Management Guide that adult patients be treated with glucocorticoids at a dose equivalent to methylprednisolone 1–2 mg/kg/d (grade 2B level of evidence) (40). Studies have shown that, during the pulmonary protective mechanical ventilation for ARDS patients, aerosolized budesonide (1 mg per time, bid) can significantly improve oxygenation index and reduce airway pressure and inflammation levels (41). Aerosolized salbutamol/terbutaline (2.5–5 mg, bid) can be concomitantly used.

Burn patients: smoke inhalation-associated acute lung injury (SI-ALI)

SI-ALI is the common cause of death in fire-burn patients. The causative factors for SI-ALI include chemical factors and thermal factors. Since the upper respiratory tract absorbs most of the heat before the smoke reaches the tracheal carina, chemical factors are the primary cause of inhalation-associated lung injury. Smoke can directly act on lung tissues and cause direct lung damages. It can also cause indirect lung damage by activating neutrophils, macrophages, and platelets. After inhalation of smoke, bronchial blood flow is significantly increased. Blood can enter the pulmonary blood vessels through the bronchial-pulmonary vascular anastomosis, resulting in pulmonary edema (42). Also, the activated neutrophils, endothelial cells, macrophages, and vascular smooth muscle cells release massive cytokines, inducing the massive production of iNOS, eventually damaging the alveolar-capillary membrane, increasing pulmonary vascular permeability, reducing pulmonary vascular diffusion ability, resulting in pulmonary edema (43,44). Particles in the smoke fill the airway and are difficult to be removed by the body. Viscous airway secretions can also cause extensive airway obstruction. Also, smoke inhalation may cause increased vascular resistance and neutrophil aggregation and activation, leading to damage to the pulmonary capillaries and alveoli (42,45). Glucocorticoids can inhibit inflammatory responses from various causes through multiple signaling pathways (46). β2 receptor agonists may dilate bronchi, reduce airflow resistance, and increase dynamic compliance of lungs (47). Anticoagulants can block the formation of fibrin clots. Tissue plasminogen activator dissolves fibrinogen and fibrin. Together they play an important role in the treatment of SI-ALI.

Other diseases or population using nebulization therapy

Other indications for nebulization therapy include: (I) non-specific inflammatory diseases such as allergic rhinitis, throat inflammation, and edema. (II) Patients with carbon monoxide poisoning, irritating gas poisoning and so on have airway mucosal damage, edema and inflammation, often accompanied by cough, expectoration, wheezing, and other symptoms. The recommended therapy is aerosolized ICS

in combination with a bronchodilator (such as budesonide 2 mg + salbutamol/terbutaline 5 mg, bid); If necessary, N-acetylcysteine may be used in combination because it can effectively reduce laryngeal edema and airway obstruction and improve related symptoms and prognosis (48). (III) Patients who are long-term bedridden or judged to be long-term bedridden and at risk of hypostatic pneumonia, including traumatic brain injury (49), chest injury (rib fracture or lung contusion, blood pneumothorax), fracture and so on, as well as tumor, stroke and other medical diseases, are prone to limited mucus-discharging ability, decreased inherent cough reflex, mistaken aspiration, obstructed discharge of phlegm, airway obstruction, mucosal edema, inflammation and infection due to limited mobility with underlying reduced respiratory function and cognitive disorder. The prophylactic use of N-acetylcysteine (0.3 g, QD to bid, for 7 days) is recommended (50). Meanwhile help the patients to turn over and pat on the back to promote sputum excretion, in order to effectively prevent the occurrence of hypostatic pneumonia. (IV) Patients with underlying respiratory conditions or airway hyperactivity at high risk of inflammation can receive the concomitant therapy with aerosolized ICS, bronchodilator, and N-acetylcysteine to help reduce mucus secretion and mucosal edema, protect epithelial barrier function, prevent infection and improve prognosis. (V) Perioperative airway management. Perioperative nebulization can improve the symptoms of bronchial obstruction, protect throat mucosa and airway epithelium, reduce post-extubation airway damage, improve postoperative airway inflammation and decrease pulmonary surfactant and the incidence of pulmonary complications (11). Preoperative prophylactic aerosol inhalation with N-acetylcysteine (0.3 g qd or bid) is recommended until the patient is recovered and discharged. Also, for patients with airway hyperactivity and high-risk factors for pulmonary function decline (such as old age, obesity, smoking history and underlying diseases), the recommended management is the aerosolized budesonide 2 mg bid or tid from one week before operation till three months after operation (11). (VI) For patients receiving laryngoscopy and bronchoscopy, aerosol inhalation can reduce airway damage and lower airway hyperactivity. (VII) Special Populations. Due to a good safety profile, nebulization therapy is advantageous in children, pregnant women, and patients with underlying diseases such as concomitant vascular disease, diabetes, and osteoporosis. The inhalation therapy of ICS can serve as a substitution for intravenous or oral corticosteroids, with the advantages of rapid onset and good safety profile.

Special application in EICU, mechanical ventilation, artificial airway establishment, and surgery

In emergency and first aid treatment, patients who are admitted into EICU and need procedures such as mechanical ventilation, artificial airway establishment, and surgery are often seriously ill with concomitant respiratory failure and physiological and metabolic disorders. Effective application of aerosol inhalation can reduce the ventilation-caused adverse reactions such as respiratory mucosa dryness and injury (51). Also, etiological treatment drug can be concomitantly administered to facilitate rapid recovery and improve the weaning efficiency from mechanical ventilator (52).

Since aerosol inhalation in mechanical ventilation is less efficient than that in autonomous inhalation, the dosage, frequency, and duration of treatment should be increased accordingly. For example, for salbutamol/terbutaline 5–10 mg, budesonide 2–4 mg, bid, the treatment should last for at least 3 days until weaning from mechanical ventilation (41). Evidence suggests that, based on the etiological therapeutic dose, during the interval of mechanical ventilation, it is more beneficial if extra doses of aerosolized ICS (budesonide 0.5 mg bid) are inhaled by spontaneous breathing (53).

In patients with established artificial airway, procedures such as tracheal intubation and extubation often cause mechanical irritation or damage to the airway, resulting in airway hyperactivity and inflammatory changes. Studies have shown that administration of ICS 12–24 hours before extubation can reduce post-extubation airway damage and incidence of airway inflammation (such as laryngeal edema and wheezing.) and pulmonary complications after extubation (54,55). Similar to patients receiving mechanical ventilation, the dose, times, and maintenance duration (days) should be appropriately increased during the establishment of the artificial airway. Based on the etiological therapeutic dose, 1 mg of budesonide is inhaled 1 hour before the recommended extubation, and 1 mg of budesonide is inhaled after extubation, bid for 2 days (56).

The application of nebulization therapy in the emergency treatment of the diseases mentioned above is summarized in (*Figure* 7).

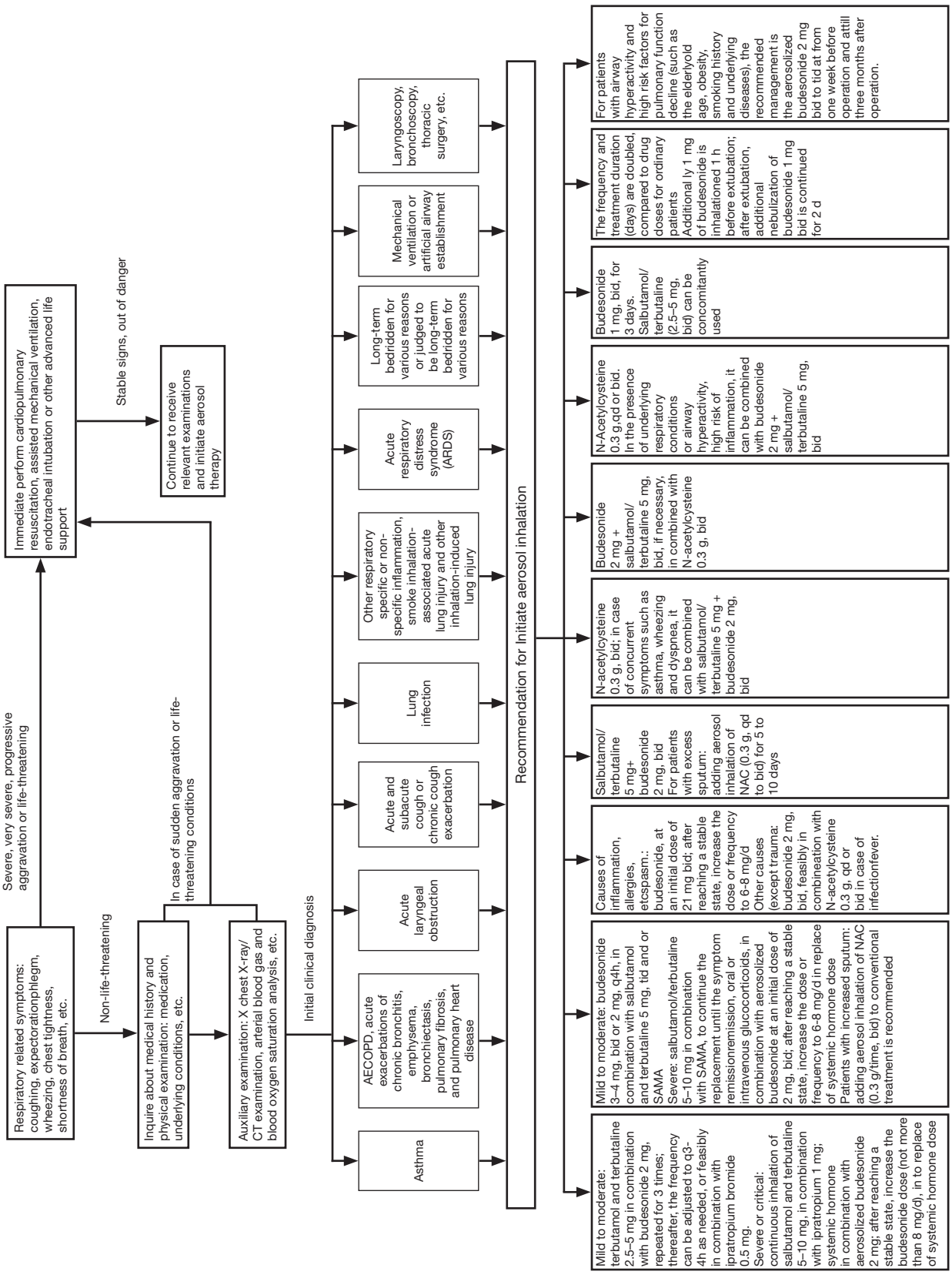

Figure 7 Flow chart of emergency treatment for respiratory diseases.

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None.

Footnotes

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Parameters for nebulization efficiency of some clinically used nebulizers

Nebulizer	Nebulizer type	Diameter of aerosol	The volume of drug solution	Output rate
Omron NE-C28	Jet nebulizer	Less than 5 μm	About 2–7 mL	About 0.4 mL/min
Omron NE-C900	Jet nebulizer	3–5 μm	About 2–7 mL	About 0.4 mL/min
Philips medical ultrasonic nebulizer	Ultrasonic nebulizer	4.07±0.6 μm	Maximum storage capacity up to 8 mL	0.55 mL/min
Homed 2311HD	Jet nebulizer	0.5–6 μm	8 mL	> 0.25 mL/min

Table S2 Drugs used for nebulization in emergency care

Drug type/name	Usage	Dosage and administration	Contraindications	Common adverse reactions
Inhaled glucocorticoids				
Budesonide	Treat bronchial asthma, rapidly reduce inflammation, relieve airway mucosal edema, and improve wheezing signs and lung function	Acute asthma attack: 1–2 mg intermittently (every 20 minutes) or continuous nebulization over the first hour, followed by nebulization as needed; it can replace or partially replace systemic hormones, at a dose of no more than 8 mg per day. AECOPD: it can replace or partially replace systemic hormones for no more than 8 mg per day. Others: the conventional dose is 1–2 mg bid, dose and dosing frequency can be adjusted according to the specific situation	It is contraindicated in patients who are allergic to budesonide or any other ingredient	Mild throat irritation, pyrexia, sinusitis, pain, pharyngitis, bronchospasm, bronchitis, and headache
Beclomethasone dipropionate	It can treat asthma and improve bronchial obstruction. With the anti-inflammatory, anti-allergic and anti-itching effects, it can inhibit bronchial exudate, eliminate bronchial mucosal swelling, and relieve bronchospasm	Adult: packaged in a single-dose vial, administered via a nebulizer, one vial per time, once to twice per day. Adult: a half dose of the single-dose vial, administered via a nebulizer, 0.5 vials per time, once to twice per day. The half dose is marked with a graduation on the single dose vial. Shake well before use	Patients with the local virus and cognitive disorder culosis infection during active or stationary phase. Patients are allergic to any component of this product. The use of pregnant women and lactating women is forbidden	Candidiasis, hoarseness, and throat irritation in the mouth and throat
Fluticasone propionate	Moderate acute asthma attack in children and adolescents aged 4–16 years	1 mg/time, bid. The maximum initial dose is recommended for an acute asthma attack. Use for no more than 7 days, followed by dose reduction. Dilute with sodium chloride injection immediately before administration to prolong the duration of drug inhalation. It is recommended to use a mouthpiece inhaler and a non-ultrasonic nebulizer	It is contraindicated in patients who are allergic to any of the ingredients in the drug product	Candidiasis of the oropharynx, contusion of cutaneous and subcutaneous tissue, and hoarseness
Bronchodilatation drug				
Salbutamol	Relief of bronchospasm from asthma or chronic obstructive lung disease, as well as the acute prevention of movement-induced asthma, or allergen-induced bronchospasm	Acute asthma attack: 2.5–5 mg intermittently (every 20 minutes) or 5–10 mg continuous nebulization until symptom improvement. AECOPD: 2.5–5 mg bid, dose, or frequency can be increased depending on the specific conditions. Others: the conventional dose is 2.5–5 mg bid, dose and dosing frequency can be adjusted according to the specific situation	Contraindicated in patients with premonitory abortion and those who are allergic to any component in this product	Tremors, headache, tachycardia, palpitation, irritation of the mouth and throat, muscle spasms. Cautions for patients taking high-dose sympathomimetic drugs concomitantly. Cautions in patients with thyrotoxicosis. Non-isotonic or non-neutral solutions or benzalkonium chloride-containing solutions can cause paradoxical bronchospasm in rare cases; The treatment using β_2— receptor agonists (mainly via parenteral and aerosolized administration) has the potential of inducing serious hypokalemia. Special attention should be paid to patients with serious acute asthma because the concomitant administration of xanthine derivatives and corticosteroids, diuretics, and hypoxia will increase the occurrence of hypokalemia. It is suggested that the blood potassium level is monitored for the conditions mentioned above. Salbutamol can cause reversible metabolic changes, such as elevated levels of blood glucose. The concomitant use of corticosteroids can aggravate these effects. A few cases of angle-closure glaucoma when concomitantly receiving aerosolized salbutamol and ipratropium bromide. Caution should be exercised when concomitantly use aerosolized anticholinergic drugs and aerosolized salbutamol. Lactic acidosis associated with high-dose short-acting β-agonists for intravenous and nebulization therapy are rare and are found primarily in asthma patients with acute aggravation undergoing treatment. On-site monitor for elevated serum lactate levels and the concomitant metabolic acidosis is recommended. Caution for Athletes
Terbutaline	With the rapid onset of action for relief of bronchospasm. Has less impact on heart rate, making it particularly suitable for patients with coronary heart disease, tachycardia, and other cardiovascular diseases	Acute asthma attack: 5 mg intermittently (every 20 minutes) or 5–10 mg continuous nebulization until symptom improvement. AECOPD: 5 mg bid, dose, or frequency can be increased depending on specific conditions; recommended three times per day	It is contraindicated in patients allergic to terbutaline sulfate or any of the ingredients in the drug product	Headache, palpitation, tachycardia, tremors, muscle spasm
Ipratropium bromide	Improve lung function and improve arterial oxygen saturation.	Regular dose 0.5 mg/time, single dose vial, 3–4 times per day; adjusted according to specific conditions. Administered under medical supervision for daily dose over 2 mg	Contraindicated in patients allergic to atropine and its derivatives and any other ingredients in this drug product	Headache, dizziness, anxiety, tachycardia, skeletal muscle fine tremor, palpitation, potential severe hypokalemia, nausea, vomiting, sweating, muscle weakness, myalgia, muscle cramp. Severe anticholinergic side effects should not occur based on the broad therapeutic range of its nebulized inhalation solution and the adopted method of topical administration. Mild systemic anticholinergic effects include dry mouth, the disorder in visual accommodation, and tachycardia
Mucolytic agent				
N-acetylcysteine	Reduce the viscosity of the sputum, making the mucus clearance easy	The conventional dose is 0.3 g per time, once to twice per day. Dose and frequency of dosing can be adjusted according to the clinical response and treatment effect	Contraindicated in patients allergic to acetylcysteine	Irritation to the nasopharynx and gastrointestinal tract. Nasal discharge, stomatitis, nausea, and vomiting