

# Rational Use for Inhaled Medicines Administrated by Nebulizers (2024 Edition)

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**ABSTRACT** Nebulization therapy is a direct drug delivery method that turns liquid medications into aerosol that can be inhaled into the lungs and respiratory tract and is an important strategy for various respiratory problems and diseases. In recent years, there has been a high incidence of respiratory diseases in China, with a significant increase in the popularity of nebulization therapy in primary healthcare facilities and home settings. Therefore, the standardized application and rational administration of nebulization therapy face pressing issues that need resolution. To address this, led by the Chinese Society of Clinical Pharmacy, in collaboration with the Pharmacy Administration Professional Committee and the Clinical Rational Drug Use Professional Committee of the Chinese Medical Education Association, the Expert Consensus on the Rational Use for Inhaled Medicines Administrated by Nebulizers (2024 Edition) has been jointly developed.

This consensus elaborates on the drug delivery characteristics, safety and effectiveness, medication indications, application process and pharmaceutical care of nebulization therapy, the selection of small-volume nebulizers, new drugs for nebulized inhalation, recommended dosing regimens for respiratory diseases, etc. It aims to offer professional guidance for all healthcare providers of standardized nebulization therapy and rational administration.

**KEY WORDS** Nebulization therapy; Rational administration; Pharmaceutical care; Multidisciplinary collaboration; Expert consensus

In recent years, there has been a surge in respiratory illnesses across China, leading to a noticeable rise in the demand for healthcare services. The availability of nebulizers and inhaled medicines in primary healthcare facilities has garnered widespread attention. Collaborating with the Chinese Society of Clinical Pharmacy, the Pharmacy Administration Professional Committee and the Clinical Rational Drug Use Professional Committee of the Chinese Medical Education Association has organized experts to compile the "Expert Consensus on the Rational Use for Inhaled Medicines Administrated by Nebulizers (2024 Edition)" (hereinafter referred to as the "2024 Consensus").

This document, involving experts from pharmacy, respiratory medicine, pediatrics, surgery, and ICU fields, exemplifies a multidisciplinary approach to promoting rational drug use. Compared to the 2019 edition, the "2024 Consensus" delves into the factors influencing the safety and efficacy of nebulization therapy, , proposes management recommendations

for using non-nebulized inhalation preparations in nebulization treatment, clarifies indications for nebulization therapy, standardizes application procedures, and provides comprehensive pharmaceutical care recommendations for special populations in various treatment settings, including home, outpatient, and inpatient scenarios. The "2024 Consensus" aims to provide a reference for healthcare professionals in medical institutions at all levels to standardize nebulization therapy, further promote the rational clinical application of nebulized drugs, and safeguarding patient well-being. The "2024 Consensus" was officially registered on the Practice Guideline Registration for transPAREncy (PREPARE) platform on February 1, 2024, with registration number: PREPARE-2024 CN234.

## **1. Introduction to Nebulization Therapy**

### **1.1 Characteristics of Drug Delivery in Nebulization Therapy**

#### **1.1.1 Basic Concepts of Nebulization Therapy**

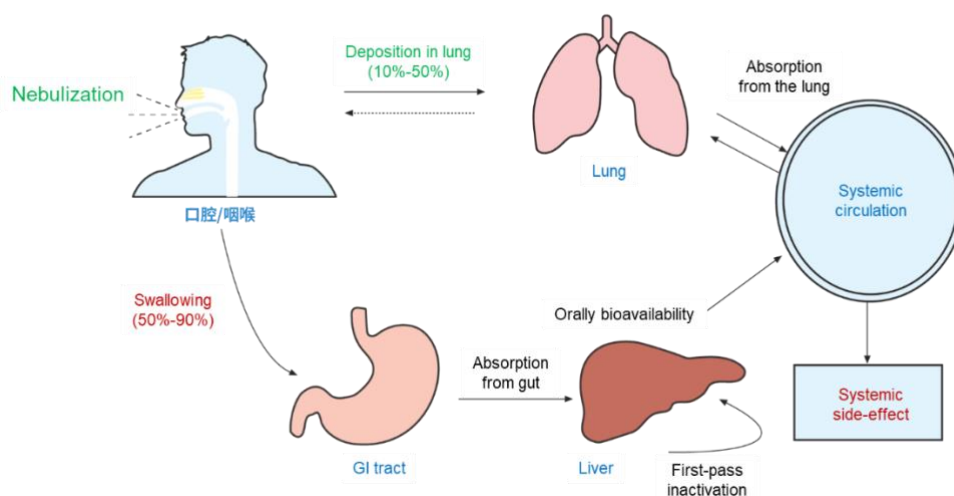
Nebulization Therapy converts liquid medications into aerosol particles (0.01 to 10  $\mu\text{m}$ ) which can be inhaled directly into the lungs. This method provides high local drug concentrations while minimizing systemic side effects. Nebulization Therapy is essential for managing respiratory diseases like asthma and bronchitis, and alleviating acute and chronic symptoms such as coughing [1-5].

#### **1.1.2 Mechanism of Action and Pharmacological Characteristics of Nebulization Therapy**

Nebulization Therapy operates based on principles of aerodynamics and particle physics, initially converting liquid medications into aerosol microparticles that are subsequently directed to the trachea, bronchi, and alveoli [3,6]. Aerosols consist of solid particles or liquid droplets suspended in gas, when inhaled into the lungs, aerosol particles interact with the respiratory mucosa through mechanisms such as inertial impaction, gravitational sedimentation, and Brownian motion, leading to deposition in the airways and lungs. The site of drug deposition correlates with the aerosol particle size and velocity. Larger particles ( $>10 \mu\text{m}$ ) primarily deposit in the nasal and/or oropharyngeal regions, particles sized 5-10  $\mu\text{m}$  deposit in the proximal conducting airways of the lower respiratory tract, while particles sized 1-5  $\mu\text{m}$  can reach and deposit in the peripheral lungs [6].

Most nebulized drugs exert local pharmacological effects upon deposition in the lungs, such as inhaled corticosteroids (ICS) and bronchodilators. Drugs deposited in the oropharynx are absorbed into bloodstream via the gastrointestinal tract following swallowing (oral bioavailability), whereas drugs deposited in the lungs are absorbed through the alveoli (pulmonary bioavailability) [7-8]. Drugs entering the systemic circulation may induce adverse reactions (Figure 1). For nebulized drugs primarily exerting local effects, the ideal pharmacological characteristics include "two shorts and one long": short

residence time on the airway mucosal surface, short plasma half-life, and long local tissue retention time.



**Fig.1 In vivo metabolic process of Nebulization Therapy**

### 1.1.3 Characteristics of Drug Delivery Routes in Nebulization Therapy

Nebulization therapy delivers drugs directly to the respiratory mucosa and alveoli, ensuring rapid localization and higher local drug concentrations while minimizing systemic side effects by bypassing gastrointestinal degradation and hepatic first-pass metabolism [3-4,9]. Unlike other inhalation methods, such as metered-dose inhalers, dry powder inhalers, or soft mist inhalers, nebulization therapy does not require hand-mouth coordination or significant patient inhalation strength, making it particularly suitable for hospitalized patients with acute exacerbations, severe respiratory distress or limited inhalation capacity [10].

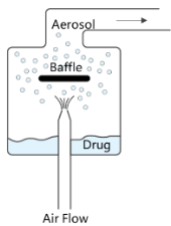
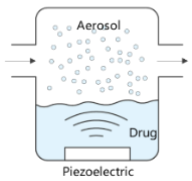
## 1.2 Selection of Commonly Used Small-Volume Nebulizers

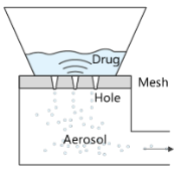
Nebulizers are devices that transform liquid medications into aerosol form for oral (or nasal) inhalation [11]. Small-volume nebulizers, with liquid storage capacities typically ranging from 5 to 20 mL, are the most commonly used nebulization devices in clinical practice [12]. When selecting a nebulizer, the key parameters to consider are related to nebulization efficiency (see Table 1). Among these, the effective particle size and the aerosol output rate are crucial selection criteria. The effective particle size refers to the diameter of aerosolized particles with therapeutic value that can deposit in the airways and lungs, with 3-5  $\mu\text{m}$  being optimal. The aerosol output rate determines the effective dose of medication delivered to the lungs. While a higher aerosol output can enhance therapeutic effects, it may also lead to increased adverse reactions due to a rapid influx of medication. Therefore, a comprehensive assessment is necessary to select an appropriate output rate that

patients can tolerate for optimal therapeutic outcomes.

Inhalers connected to nebulizers are divided into masks and mouthpieces. Masks allow for both nasal and oral inhalation, with nasal inhalation being more common. Nasal inhalation is associated with lower airflow rates, and mechanical obstruction and dead space in the nasal cavity can lead to drug retention, resulting in lower drug utilization. Mouthpieces deliver medication directly through the oral cavity, offering less drug wastage, higher lung deposition, and better therapeutic efficacy compared to masks. Generally, mouthpieces should be the first choice for nebulization therapy. However, masks are more suitable in the following scenarios: (1) children under 3 years of age; (2) patients unable to cooperate with mouthpiece inhalation due to physical, intellectual, comprehension, or coordination impairments; (3) patients with allergic rhinitis or enlarged adenoids and lower respiratory tract diseases; (4) patients with significant hypoxemia without concomitant CO<sub>2</sub> retention, as mask nebulization is more effective in improving oxygen levels than mouthpiece nebulization [13-15]. Some medications require specific nebulizers, such as the inhaled iloprost solution and tobramycin inhalation solution available in China. Therefore, the selection of an appropriate nebulizer should be based on the patient's condition, disease diagnosis, medication properties, and application scenario to enhance therapeutic efficacy, increase patient compliance, and reduce adverse events.

Tab.1 Comparison of small-volume nebulizers (SVNs)

Category	Mechanism	Effective	Output Rate (mL/min)	Residual	Drug Delivery Efficiency (%)	Noise Level (dB)	Aerosol	Portability	Advantages	Disadvantages	Application Scenarios
		Particle Size ( $\mu\text{m}$ )		Volume (mL)			Temperature Change				
 <p><b>Jet nebulizer</b></p>	Compressed air	3~8	0.2~0.6	$\leq 1$	15~30	$\leq 65$	Temperature decrease	Large volume, oxygen-driven, inconvenient to carry	Durable, high nebulization rate, easy to maintain	Not suitable for easily degradable macromolecular drugs, long nebulization time, high noise level	Widely used in various clinical and healthcare settings, as well as nursing institutions for the elderly
	shears liquid drug to produce aerosol particles		(higher pressure yields higher flow rate)			Relatively noisy					
 <p><b>Ultrasonic nebulizer</b></p>	Ultrasonic waves	1~10	0.2~0.8	0.5~1	30~40	$\leq 50$	Temperature increase, may affect drug bioactivity	Medium-sized, requires power source, portable	High nebulization rate, uniform aerosol distribution	Potential drug inactivation or concentration, risk of over-humidification	Less commonly used in medical institutions
	vibrate the gas-liquid interface to produce aerosol particles					Little to no noise					

Vibrating mesh nebulizer	High-frequency vibration forces	1~5	0.2~0.9	0.1~0.5	40~60	≤20	No	Small size, battery/power-	Portable,	Mesh prone to	Widely applicable,
							Some	temperature	minimal residual	clogging,	suitable for outpatient,
	liquid drug through						models	change	volume, high	potential	emergency, ICU
	fixed-diameter						approach	portable	nebulization	microbial growth	mechanical ventilation,
	micro-holes to generate aerosol						0dB (silent)		rate, relatively fast		home nebulization, and various other scenarios

### 1.3 Safety and Efficacy of Nebulization Therapy

#### 1.3.1 Safety of Nebulization Therapy

Key safety risks in nebulization therapy include airway irritation caused by unsuitable drug properties and infection risks associated with contaminated equipment. Mitigation strategies involve ensuring drug compatibility, maintaining appropriate pH and osmolarity of inhaled drugs, and implementing stringent hygiene practices, such as the use of single-use equipment and rigorous disinfection protocols.

(1) Drug-related factors affecting the safety of nebulization therapy: Airway exposure to aerosol particles with unsuitable physicochemical properties can easily trigger airway hyperresponsiveness and spasms. The epithelial lining fluid (ELF) in the airways is a neutral fluid. Inhaled drugs with inappropriate pH values may lead to airway irritation, damage, and inflammation. Low osmolarity of drugs could result in airway edema and congestion, while high osmolarity can cause drying of the airway mucosa. When combining drugs for nebulized inhalation, attention must be paid to drug compatibility. Incompatible drugs may precipitate or crystallize in the airways, affecting drug absorption and distribution. Airway responsiveness is heightened during inflammation, potentially leading to severe airway spasms [1,3,16].

(2) Device-related factors impacting the safety of nebulization therapy: Nebulizers with high output rates can better exert therapeutic effects. Yet, a rapid influx of aerosol into the body can cause pulmonary edema, and the dilution of airway secretions may lead to airway obstruction [7]. Furthermore, each step of nebulization therapy carries an infection risk. Residual patient secretions on nebulizers, if not thoroughly disinfected and dried, may lead to infection of subsequent users through contaminated recondensed liquid [15]. Therefore, nebulized drug storage containers, breathing circuits, masks, and related equipment should be used exclusively by designated personnel with single-use disposables. Deposition of nebulized drug particles in the oropharynx or on the face can trigger secondary infections. Immediate face washing and mouth rinsing post-nebulization are crucial. During respiratory infectious disease outbreaks, nebulization therapy may increase the risk of aerosol generation and disease transmission. In such cases, nebulization should be performed in well-ventilated environments, healthcare professionals should employ strict personal protective measures, or patients should be advised to use home

nebulization therapy to reduce the risk of cross-infection [17-18].

### 1.3.2 Efficacy of Nebulization Therapy

(1) Drug-related factors affecting the efficacy of nebulization therapy: ①Particle size: The distribution of inhaled drugs in the lungs depends on their aerodynamic diameter, which is influenced by factors such as particle size, crystal form, shape, and density [4]. ②Molecular weight, oil/water partition coefficient, esterification: Absorption of nebulized drugs in the lungs occurs through passive diffusion, and the rate and efficiency of absorption are related to the drug's molecular weight and lipophilicity. Small molecule compounds are easily absorbed through the alveolar surface, while larger molecules like sugars and enzymes are difficult to absorb. Drugs with appropriate oil/water partition coefficients facilitate absorption without increasing the risk of drug accumulation due to enlarged distribution volumes. Drugs with esterification properties can reversibly bind with lipids in airway tissues, forming long-chain fatty acid complexes stored in the cytoplasm, prolonging lung retention time and enhancing local drug efficacy [8,19-20]. ③Receptor affinity and pharmacological activity: The binding of drugs to lung receptors yields beneficial effects, while binding to extrapulmonary receptors often results in adverse effects. Varying receptor affinities manifest differing pharmacological activities [8,20].

(2) Device-related factors affecting the efficacy of nebulization therapy: Commonly used nebulizers in clinical practice include jet nebulizers, ultrasonic nebulizers, and vibrating mesh nebulizers. An ideal nebulizer should produce stable, uniform aerosol particles with a high drug delivery rate. The size and distribution of aerosol particles directly affect drug deposition sites and therapeutic effects. A smaller mass median aerodynamic diameter (MMAD) allows particles to reach more distal bronchi; a smaller geometric standard deviation (GSD) indicates more uniform particle size, with a value closer to 1 indicating a narrower distribution range. Higher total delivered dose (TDD) and fine particle dose or fraction (FPD or FPF) indicate higher drug release and delivery efficiency, resulting in greater lung deposition [9,21,22].

When evaluating the clinical efficacy and safety of nebulization therapy, the nebulizer and nebulized drug should be considered as an integrated system. Extensive studies by the European Pharmaceutical Aerosol Group (EPAG) Nebulizer Sub-Team have identified critical nebulization characteristics, including delivery rate, total delivered dose, and aerodynamic particle size distribution [23]. The delivery rate assists in evaluating patient treatment duration, total delivered dose predicts the drug dose received by the patient, and aerodynamic particle size distribution reflects the dispersion of drug aerosols in the pulmonary environment, facilitating the evaluation of the safety and efficacy of inhaled medications in clinical settings [23]. The United States and Europe incorporated these standards into their pharmacopeias in 2011 and 2012 respectively, and China included them in its pharmacopoeia in 2015. China issued the "Guiding Principles for the Bioequivalence Study of Generic Orally Inhaled Dosage Forms" which also specified requirements for key nebulization characteristics (such as delivery rate, total delivered

dose, and fine particle aerodynamic characteristics) and other critical quality attributes for generic inhalation suspensions [24].

#### **1.4 Commonly Used Drugs for Nebulization Inhalation**

This section primarily introduces the domestic and international approval status of drugs for nebulization inhalation. For detailed drug information, please refer to the drug instructions and the "2019 Consensus" [21].

##### **1.4.1 Inhaled Corticosteroids (ICS)**

Currently, four ICS have been approved for nebulization inhalation internationally, including budesonide, beclomethasone dipropionate, fluticasone propionate, and flunisolide [7,19,25]. In China, there are three ICS available for nebulization inhalation: beclomethasone dipropionate inhalation suspension, budesonide inhalation suspension, and fluticasone propionate nebulization inhalation suspension. These medications have similar mechanisms of action and indications, primarily used to alleviate airway inflammation and airway hyperresponsiveness. However, there are some differences among these drugs in terms of pharmacology and pharmacokinetics.

##### **1.4.2 Bronchodilators for Nebulization Inhalation**

###### **(1) $\beta$ 2-Receptor Agonists**

Currently available  $\beta$ 2-receptor agonists for nebulization inhalation in China include: short-acting  $\beta$ 2-receptor agonists (SABAs) such as levalbuterol hydrochloride nebulization inhalation solution, salbutamol sulfate inhalation solution, and terbutaline sulfate inhalation solution, suitable for patients requiring bronchial smooth muscle relaxation and relief of spasms. Long-acting  $\beta$ 2-receptor agonists (LABAs) such as formoterol fumarate inhalation solution was approved in 2022 for maintenance treatment of airway obstruction in chronic obstructive pulmonary disease (COPD) patients, including chronic bronchitis and emphysema. Procaterol hydrochloride inhalation solution was approved in 2023 for various symptoms based on airflow limitation in diseases such as bronchial asthma, chronic bronchitis, and emphysema. Internationally, arformoterol tartrate nebulization inhalation solution is also available as a LABA, approved by the FDA for maintenance treatment of COPD patients, including chronic bronchitis and emphysema.

###### **(2) Muscarinic receptor antagonists for nebulization inhalation**

In China, available muscarinic receptor antagonists for nebulization inhalation include ipratropium bromide inhalation solution and compound ipratropium bromide inhalation solution. Ipratropium bromide inhalation solution is a short-acting muscarinic antagonist (SAMA). The compound ipratropium bromide inhalation solution is a combination of SAMA and SABA. Ipratropium bromide inhalation solution, when used in combination with SABAs,

treats reversible airway obstruction caused by acute or chronic asthma. The compound ipratropium bromide inhalation solution contains 0.500 mg of ipratropium bromide and 3.013 mg of salbutamol sulfate, suitable for patients requiring multiple bronchodilators, such as treating reversible bronchospasm caused by obstructive airway diseases.

Internationally, several long-acting muscarinic antagonists (LAMAs) have been approved, including revefenacin inhalation solution (FDA-approved in 2018) for maintenance treatment of COPD patients, and glycopyrronium bromide inhalation solution (FDA-approved in 1961) for long-term maintenance treatment of airflow obstruction in COPD patients.

### **1.4.3 Mucolytics for Nebulization Inhalation**

In China, only acetylcysteine inhalation solution and ambroxol hydrochloride inhalation solution are available for nebulization therapy.

Ambroxol hydrochloride inhalation solution acts as an active metabolite of bromhexine within the body, exhibiting mucoregulatory properties. It stimulates secretion from respiratory mucous glands while reducing mucous gland output, enhances ciliary movement in the bronchial mucosa to facilitate expectoration, promotes the production of surfactant by type II alveolar cells to reduce mucous adhesion, and additionally possesses anti-inflammatory and antioxidant effects [26]. Compared to intravenous administration, nebulized ambroxol hydrochloride significantly increases drug exposure within the epithelial lining fluid (ELF), thereby enhancing lung targeting [26].

### **1.4.4 Antimicrobials for Nebulization Inhalation**

Currently, tobramycin inhalation solution is the only approved antimicrobial for nebulization inhalation in China. Some tobramycin injection and amphotericin B for injection product labels include nebulization inhalation as a route of administration. Internationally approved antimicrobials for nebulization inhalation include amikacin liposome inhalation suspension, aztreonam inhalation solution, pentamidine inhalation solution, and ribavirin inhalation solution [27].

(1) Aminoglycosides primarily act by binding to the aminoacyl site of 16S ribosomal RNA in the 30S ribosomal subunit, leading to genetic code misreading and translocation inhibition. They are mainly used for treating Gram-negative bacterial infections. Due to their strong ototoxicity, nephrotoxicity, and limited tissue concentrations, their clinical application is somewhat limited. Combining intravenous administration with nebulization inhalation can achieve therapeutic local concentrations while reducing systemic adverse reactions.

① Tobramycin inhalation solution: approved in China in 2022 for bronchiectasis with *Pseudomonas aeruginosa* lung infection to control infection and improve symptoms. but treatment costs are high. Several domestic tobramycin intravenous formulations indicate

nebulization inhalation as adjunctive therapy for bronchial and pulmonary infections. Internationally, tobramycin inhalation solution was approved by the FDA in 1997 for use in cystic fibrosis patients with *P. aeruginosa* lung infection.

② Amikacin liposome inhalation suspension: licensed by the FDA in 2018 for treating refractory, recurrent non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* complex (MAC) in adults. Amikacin nebulization is also recommended for treating *Mycobacterium abscessus* lung infections in NTM guidelines [28].

(2) Aztreonam inhalation solution [29]: A monobactam  $\beta$ -lactam drug that acts by binding to penicillin-binding proteins on bacterial cell membranes, inhibiting cell wall synthesis and exerting bactericidal effects. Unlike most  $\beta$ -lactams, aztreonam is only effective against Gram-negative bacteria, including *P. aeruginosa*. It was approved by the FDA in 2010 for cystic fibrosis with *P. aeruginosa* lung infection.

(3) Pentamidine inhalation solution [30]: Interferes with the incorporation of nucleotides and nucleic acid into RNA and DNA in *Pneumocystis jirovecii*, and inhibits oxidative phosphorylation, thereby affecting the biosynthesis of DNA, RNA, phospholipids, and proteins. It is indicated internationally for preventing *Pneumocystis jirovecii* pneumonia (PJP) in high-risk patients who are allergic to sulfonamides.

(4) Ribavirin inhalation solution [31]: As a nucleoside analog, it inhibits various RNA and DNA viruses. Internationally approved for treating severe respiratory syncytial virus (RSV) infections or RSV infections during hospitalization in infants and children. Healthcare professionals are advised to avoid occupational exposure during pregnancy.

#### **1.4.5 Others**

Iloprost inhalation solution was approved in China in 2015 for treating adults with NYHA functional class III primary pulmonary arterial hypertension to improve exercise capacity and symptoms. Care should be taken to avoid skin and eye contact, as well as oral ingestion.

### **1.5 Non-nebulized Inhalation Formulations Are Not Recommended for Routine Nebulization Inhalation Therapy**

With ongoing advancements in nebulized drug formulation research, an increasing number of clinically effective products have been introduced into clinical use. However, given the limited availability of approved nebulized formulations in China, and the fact that some intravenous antibiotic formulations include nebulization inhalation as a route of administration in their product labels (e.g., tobramycin and amphotericin B intravenous formulations), clinicians may use intravenous formulations for nebulization inhalation under specific clinical circumstances, particularly with antimicrobials. Certain practices have been

endorsed by clinical guidelines or expert consensus, including the use of colistin methanesulfonate sodium for injection and lipid formulations of amphotericin B [32-33].

However, the safety of nebulizing intravenous formulations remains inadequately validated. Excipients present in intravenous formulations play a crucial role in determining the safety profile of nebulized inhalation therapy [29]. The following aspects should be carefully evaluated:

- ① Absence of preservatives;
- ② Appropriate osmolarity (150-550 mOsm·kg<sup>-1</sup> is associated with reduced airway irritation, but osmolarity may increase by 11%-62% during nebulization)
- ③ Suitable pH value (the Chinese Pharmacopoeia specifies pH 3-10 for inhalation solutions, but a narrower range of pH 4-8.5 may be more appropriate) ;
- ④ Presence of permeable anions, such as chloride ions, which can reduce airway irritation when included in nebulized solutions;
- ⑤ Low toxicity to respiratory epithelial cells and alveolar structures [5-6,9,16].

Furthermore, non-nebulized inhalation formulations may not meet the optimal aerosol particle size requirements for effective pulmonary delivery. These formulations may be less efficiently cleared from the respiratory tract, leading to increased lung infection rates, and potential for adverse local reactions in the airways, especially in patients with pre-existing lung disease. Even drugs with a generally favorable safety profile may cause airway-related adverse reactions in susceptible individuals.

The use of non-nebulized inhalation formulations for nebulization inhalation therapy must be regarded as off-label use. Based on the principle of expanded clinical application of drugs, such use is permissible only when the benefits to the patient clearly outweigh the potential risks. Off-label use must be supported by sufficient evidence-based data, approved by the Pharmacy and Therapeutics Committee, and explicit informed consent from the patient. Strict monitoring for adverse reactions during application and preemptive measures to address adverse events before drug administration are imperative. Given the current lack of sufficient evidence-based medical evidence supporting the nebulization of non-nebulized inhalation formulations, their routine use of non-nebulized inhalation formulations for nebulization inhalation therapy is strongly discouraged.

## **2. Clinical Practice of Nebulization Inhalation Therapy**

### **2.1 Indications for Nebulization Therapy**

Nebulization therapy plays a crucial role in the management of chronic respiratory diseases such as asthma and COPD. In recent years, its clinical utility has also been extensively implemented in perioperative airway management. The following sections outline the major clinical indications for nebulized therapy based on patient populations and clinical contexts.

### **2.1.1 Patients with Chronic Respiratory Diseases such as Asthma and COPD**

For patients with chronic respiratory diseases such as asthma or COPD who present with significant dyspnea, chest tightness, cough, or excessive and viscous airway secretions, nebulization therapy should be considered. Treatment selection should be based on the patient's pathophysiological characteristics, disease condition, and the pharmacological properties of the nebulized agents. The evaluation should then guide the administration of appropriate nebulized therapies aimed at anti-inflammatory, bronchodilatory, bronchospasmolytic, and expectorant effects. In cases with thick sputum, mucolytics may be co-administered via nebulization to facilitate expectoration—particularly in COPD. Caution is advised in asthma patients, as nebulized mucolytics may induce coughing or bronchospasm.

① In the acute phases, the decision to proceed with nebulization therapy should be based on the severity of the condition. Commonly used drugs at this stage include corticosteroids and bronchodilators.

② In the stable phases, nebulization is more suitable for children aged 0 – 6 years due to poor coordination and inspiratory ability. For older children and adults, portable inhalers are generally preferred, but nebulization inhalation remains an option when inhaler use is not feasible.

③ In cases with thick sputum, mucolytic drugs may be combined with nebulization inhalation. For COPD patients with abundant or viscous sputum that is difficult to expectorate, combining mucolytic drugs with nebulization inhalation on top of regular treatment can help promote sputum expectoration. For asthma patients, caution is advised when using nebulized mucolytic drugs. If necessary, close monitoring for symptoms such as coughing and worsening wheezing due to induced bronchospasm is required [18,34-36].

### **2.1.2 Non-Chronic Respiratory Disease Patients with Respiratory Symptoms such as Wheezing and Coughing**

Patients presenting with respiratory symptoms such as wheezing and coughing but without chronic respiratory diseases are not universally suitable for nebulized therapy. Conditions such as foreign body airway obstruction, airway compression by tumors, or interstitial pneumonia necessitate treatment of the underlying etiology rather than symptomatic nebulization. However, in cases where symptoms are due to lower respiratory tract infections or bronchiectasis resulting in excessive, viscous secretions, nebulized mucolytic

drugs can be used to enhance secretion clearance, reduce infection risks and improve anti-infection treatment efficacy[37-39].

### **2.1.3 Perioperative Airway Management (e.g., Thoracic Surgery)**

Perioperative airway management encompasses various strategies, particularly crucial for high-risk patients prone to postoperative airway complications, where nebulized inhalation therapy can help mitigate such risks. However, individual considerations must be made based on distinct surgical requirements and underlying conditions. Patients with COPD, asthma, or airway hyperresponsiveness should receive ICS alongside bronchodilators during the perioperative phase. The choice between portable inhalers and nebulization therapy should be individualized based on clinical circumstances. Nebulization therapy is particularly advantageous in elderly or frail patients, infants and young children, those with extremely low inspiratory flow rates, severe disease conditions, and especially in the early postoperative period when patients experiencing postoperative pain or airway edema that impairs inhaler use. [40-42].

### **2.1.4 Patients with Pulmonary Infections**

In patients with pulmonary infections characterized by increased airway secretions, thick purulent yellow sputum, or prominent respiratory symptoms such as cough and wheezing, nebulization therapy can be considered. Suitable agents include mucolytic agents, ICS, and bronchodilators tailored to the specific circumstances. However, caution is warranted regarding the potential risk of exacerbating infections with ICS.

Currently, evidence evaluating the efficacy and safety of nebulized antibiotics is limited and continuously evolving. Although their potential in adjunctive treatment of refractory lower respiratory tract infections (such as multidrug-resistant bacterial infections) is of significant interest, routine use is not recommended. When clinical application is necessary, strict adherence to indications is required. If non-nebulized inhalation formulations must be used for nebulization therapy, it should be managed as off-label drug use. Clinical applications typically include the following situations: ① Chronic infections related to local anatomical factors (e.g., cystic fibrosis, bronchiectasis) with positive *Pseudomonas aeruginosa* sputum culture. Nebulized tobramycin inhalation solution can effectively reduce *P. aeruginosa* burden in the airways of bronchiectasis patients and improve *P. aeruginosa* clearance rates. ② Infections caused by specific pathogens or in cases of drug resistance: When clinical assessment indicates the need for polymyxins or aminoglycosides to treat multidrug-resistant gram-negative bacilli infections, but systemic dosage cannot be increased due to dose-related toxicity, cautious selection of appropriate drugs from the same class for adjunctive nebulization therapy may be considered in addition to systemic anti-infective treatment. ③ Mycobacterial infections: FDA has approved amikacin liposome inhalation suspension as a combination anti-infective treatment for *Mycobacterium avium* complex lung infections. Active tracheobronchial tuberculosis can be treated with nebulized amikacin during the intensive phase of chemotherapy. for

cavitary or drug-resistant pulmonary tuberculosis with poor response to systemic therapy, aerosolized amikacin may be considered. ④ Invasive pulmonary fungal infections: For invasive bronchopulmonary aspergillosis with poor response to systemic antifungal treatment, treatment failure, or intolerance, combination therapy with nebulized amphotericin B may be attempted. Solid organ (lung, heart) or hematopoietic stem cell transplant recipients may benefit from nebulized amphotericin B for prophylaxis against pulmonary fungal infections. ⑤ High-risk groups for *Pneumocystis jirovecii* pneumonia (PJP) infection who are intolerant to sulfonamides may use nebulized pentamidine for PJP infection prevention[33,35,43-45].

## 2.2 Recommended Dosing Regimens for Nebulization Therapy in Common Respiratory Diseases

This consensus provides a summary of recommended dosing regimens for nebulization therapy in common chronic respiratory conditions and perioperative airway management [18,34,40-41,44,46-48] (Tables 2 and 3). For more disease-specific nebulization therapy recommendations, please refer to recently published consensus documents and clinical guidelines.

**Tab.2 Recommended nebulized drugs and dosing regimens for chronic airway diseases** [18,34,46-48]

Disease Classification	ICS	Bronchodilators
<b>Bronchial Asthma (Acute Exacerbation)</b>	<p>Commonly used drugs include budesonide, beclomethasone dipropionate, and fluticasone. High-dose nebulized corticosteroids can partially replace systemic corticosteroids, reducing systemic adverse effects.</p> <p>①Adults:</p> <p>Budesonide: 0.5-1 mg per dose, twice daily; for moderate to severe patients, 1-2 mg per dose, three times daily.</p> <p>②Children:</p> <p>Mild to moderate: In addition to inhaled SABA, use nebulized budesonide (1 mg per dose) as initial treatment, twice daily, or repeat every 4-6 hours as necessary. Adjust dosing interval based on symptom</p>	<p>Mild to moderate acute exacerbations in hospital (emergency room) management: Repeated inhalation of short-acting <math>\beta</math>2-agonists (SABA) is the most effective treatment for acute exacerbations. Alternatively, nebulized SABA and short-acting muscarinic antagonist (SAMA) solutions can be administered every 4-6 hours.</p> <p>Moderate to severe acute exacerbations in emergency room or hospital management: Inhaled SABA is the first-line treatment. In the initial treatment phase, intermittent (every 20 minutes) or continuous nebulization is recommended, followed by intermittent administration (every 4 hours) as needed.</p>

	<p>improvement, maintaining for 7-10 days.</p> <p>Moderate to severe: During the first 1-2 hours of initial treatment, concurrent use of high-dose nebulized budesonide (1 mg per dose, nebulized every 30 minutes for 3 consecutive doses) can significantly reduce hospitalization rates and oral corticosteroid use, effectively improving lung function. In non-life-threatening asthma exacerbations, it can replace or partially replace systemic corticosteroids. However, it cannot replace systemic corticosteroids in severe cases.</p>	<p>For moderate to severe asthma exacerbations or patients with poor response to inhaled SABA, combination therapy with nebulized SABA and SAMA solutions is recommended.</p>
<p><b>Chronic Obstructive Pulmonary Disease (COPD) (Acute Exacerbation)</b></p>	<p>For patients with moderate or severe COPD exacerbations, nebulized budesonide at 4 mg/day or 8 mg/day shows comparable clinical efficacy to intravenous prednisone 40 mg/day, with a treatment course of 5-7 days.</p>	<p>Initial treatment options include SABA with or without SAMA; combination therapy with SABA and SAMA is recommended for moderate to severe cases. Air-driven nebulizers are preferred over oxygen-driven nebulizers to avoid potential risk of PaCO<sub>2</sub> elevation.</p> <p>(1) Salbutamol sulfate solution for inhalation (2.5ml:5mg): 2.5-5mg/dose, up to 10mg/dose based on clinical need. Can be repeated 4 times daily. (2) Terbutaline sulfate nebulizer solution (2ml:5mg): 5mg/dose, 3 times daily. (3) Ipratropium bromide solution for inhalation (2ml:0.5mg): 0.5mg/dose, 3-4 times daily. (4) Compound ipratropium bromide solution for inhalation (2.5ml/vial, containing ipratropium bromide 0.500mg and salbutamol sulfate 3.013mg): 1 vial per dose during acute exacerbations, up to 2 vials for severe cases, 3-4 times daily for maintenance therapy.</p>

**Tab.3 Recommended nebulized drugs and dosing regimens for perioperative airway management** <sup>[40-41,44,46]</sup>

Disease Classification	ICS	Bronchodilators	Mucolytics
<b>Perioperative Airway Management</b>	<p>For surgical patients assessed as high-risk for airway complications: Recommend nebulized budesonide 3-7 days preoperatively and 3-7 days postoperatively, 2.0 mg per dose, 2 or 3 times daily.</p> <p>Perioperative pulmonary complication risk factors include:</p> <p>①Preoperative risk factors: Primarily include airway hyperresponsiveness, reduced lung function/ventilatory dysfunction, hypersecretion of mucus/sputum retention, elderly patients with underlying airway hyperreactivity or COPD, and patients with a history of airway complications.</p> <p>②Intraoperative risk factors: Mainly include general anesthesia, anesthetic intubation, mechanical ventilation and endotracheal intubation, as well as surgical approach, duration, and operative procedures. For instance, otorhinolaryngology and head and neck surgeries can lead to airway edema, airway inflammation, and even critical conditions such as laryngospasm and acute laryngeal obstruction, posing extremely high risks of airway complications.</p> <p>③Postoperative risk factors: Primarily include prolonged bed rest, extended anesthesia recovery time, pain, sputum retention, obstruction or poor drainage of tubes, which can lead to respiratory symptoms such as dyspnea, atelectasis, and pulmonary infections.</p>	<p>For patients assessed as high-risk for airway complications: Recommend ipratropium bromide, starting 3-7 days preoperatively, 0.5 mg per dose, nebulized every 6 hours; nebulize immediately before entering the operating room on the day of surgery; postoperatively, begin nebulization as early as possible within 24 hours, then every 6 hours after 24 hours, continuing for 7 days.</p>	<p>For patients with high-risk factors for postoperative pulmonary complications, prophylactic use should be initiated preoperatively and continued until discharge.</p> <p>For patients undergoing prolonged anesthesia or with severe intraoperative lung contusion, continuous use during the perioperative period is recommended (e.g., acetylcysteine solution for inhalation, 3 mL per dose, twice daily).</p>

## 2.3 Utilization of Nebulization Therapy

### 2.3.1 Pharmaceutical Supervision Process for Nebulized Inhalation Therapy Nebulization Therapy, as illustrated in Figure 2

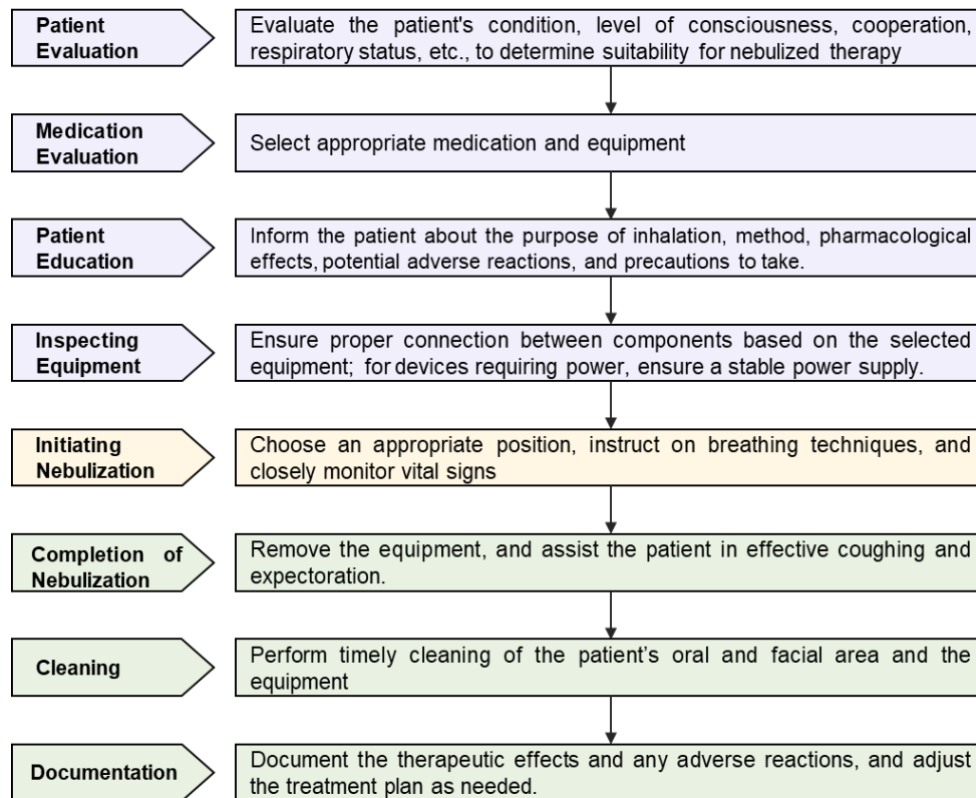


Fig.2 Schematic representation of pharmaceutical monitoring process for Nebulization Therapy [36,49]

### 2.3.2 Before Nebulization Inhalation Treatment

(1) Pre-treatment preparation: Before starting nebulization inhalation treatment, assemble the tubing, nebulizer, and mask (or mouthpiece) according to the manufacturer's instructions. Patients should not eat for 1 hour before treatment, and the oral cavity should be cleaned of secretions and food residues to prevent vomiting induced by airflow stimulation during nebulization. oil-based facial creams should not be applied to prevent drug adsorption on the skin [35,50-54].

(2) Drug preparation: Ensure that drugs are within their expiration date and show no signs of precipitation, clumping, or discoloration before use. As nebulized drugs do not contain preservatives, they should be prepared immediately before use following aseptic technique principles. Single-dose medications should be used when possible to reduce infection risk

[55].

(3) Drug compatibility: When mixing two or more drugs for nebulization, consider the compatibility between drugs and the stability of the mixture. Drugs with known incompatibilities should not be mixed. Resources like "Trissel's Stability of Compounded Formulations," Trissel's clinical pharmacology databases, and the Stabilis website offer data on the compatibility and stability of various nebulized inhalation drugs [56,57,58]. Domestically marketed iloprost inhalation solution and tobramycin inhalation solution require specific nebulizers for administration, and their instructions state "not recommended for mixing with other drugs." The instructions for compound ipratropium bromide inhalation solution state "do not mix this product with other drugs in the same nebulizer." Regarding compatibility with different concentrations of sodium chloride injection solution, most nebulized inhalation drug instructions do not mention compatibility with sodium chloride solution. When single or combined use of nebulized inhalation drugs reaches an appropriate volume (4-5 mL) and suitable nebulization time (within 20 minutes), dilution with sodium chloride injection solution is not recommended [59].

### **2.3.3 During Nebulization Inhalation Treatment**

Ensure the medication cup remains upright to avoid tilting or shaking, which ensures consistent drug delivery. Monitor aerosol output and maintain the mask within 1 cm of the face to minimize ocular exposure. Assist patients in maintaining suitable positions like sitting, semi-Fowler's position, or lateral, with the head elevated at a 30° angle to the chest. Encourage slow, deep breathing with mouth inhalation and nasal exhalation. Monitor patients for coughing, dyspnea, palpitations, difficulty breathing, pallor, rash, or adverse reactions during nebulization. Intensify monitoring for special populations and unique treatment scenarios. Refer to Section 3 for pharmaceutical care during nebulization therapy.

### **2.3.4 After Nebulization Inhalation Treatment**

Remove the mouthpiece or mask before turning off the gas and power sources. Discard any unused medication in the nebulizer cup. Encourage effective coughing for sputum clearance, recording the amount and viscosity of sputum. Perform timely facial cleansing after nebulization (if using nebulized solutions containing corticosteroids, also clean the oral cavity; for patients unable to rinse their mouths, use cotton swabs or cotton balls to wipe the oral cavity). Thoroughly clean, dry, and store the nebulizer after each use, ensuring it is for personal use only, and disinfect regularly.

### **2.3.5 Hospital Nebulization Therapy**

Adhere to hospital infection prevention and management protocols. Maintain well-lit, well-ventilated nebulization centers at 22-24°C with 50%-60% humidity,  $\geq 20$  m<sup>2</sup> area, accommodating 6-10 patients simultaneously[60-61]. The nebulization center should have a rational layout, with ventilation at least twice daily for 30 minutes each time, or use air

disinfection machines or ultraviolet lamps for air disinfection. Nebulization inhalation areas should be partitioned, and patients with respiratory infectious diseases should not be in the same room as other patients. Patients with similar respiratory diseases should be relatively concentrated in the same area. Establish medication dispensing zones, and the nebulization inhalation area should have 1-2 central oxygen inhalation positions for emergency use, equipped with necessary rescue equipment and medications.

### 2.3.6 Home Nebulization Therapy

Compared to hospital nebulization treatment, home nebulization treatment has the following advantages: ① Avoids cross-infection in hospitals; ② Simple operation of nebulization devices; ③ Compensates for limited hospital resources, saving time and transportation costs. The management process for home nebulization treatment is shown in Figure 3. After an acute exacerbation of respiratory diseases such as asthma, while waiting for further medical treatment, prompt inhalation of bronchodilators is recommended to prevent severe or life-threatening events.

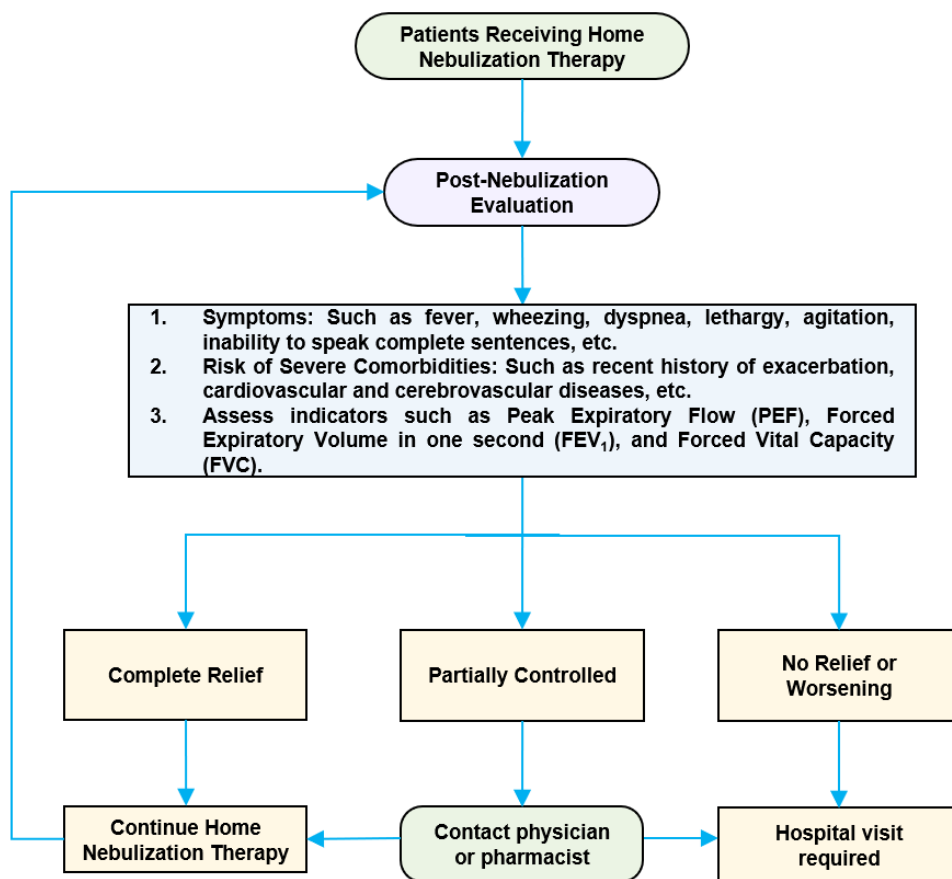


Fig.3 Management process for the home use of nebulizers

### 3. Pharmaceutical Care of Nebulization Therapy

#### 3.1 Common Adverse Drug Reactions (ADR) and Management Strategies

Nebulization therapy can lead to various oral conditions depending on the inhaled medications, including dry mouth, dental caries, oral mucosal changes, ulcers, gingivitis, periodontitis, and taste disorders. These issues are often linked to the patient's personal hygiene and inadequate oral care during treatment. After nebulization, it is crucial to maintain facial and oral hygiene. If any of the mentioned oral problems occur, prompt medical attention is advised, along with enhanced oral care, and regular oral examinations for patients undergoing long-term treatment.

During nebulization inhalation, patients may experience adverse reactions such as dry mouth, nausea, shortness of breath, palpitations, difficulty breathing, chest tightness, and decreased oxygen saturation. These reactions may be drug-related or due to factors like hyperventilation. If drug-induced, appropriate actions should be taken based on the severity. Common ADRs and pharmaceutical care for nebulization therapy are shown in Table 4.

**Tab.4 Common ADRs and pharmaceutical care of Nebulization Therapy**

<b>Drug Category</b>	<b>Common ADR</b>	<b>ADR Management/Considerations</b>
<b>ICS</b>	(1) Local oropharyngeal reactions: hoarseness, cough, throat discomfort, and candidiasis.  (2) Systemic adverse reactions with long-term high-dose inhalation: osteoporosis, hypothalamic-pituitary-adrenal axis suppression, and increased risk of pneumonia.	(1) Rinse the mouth and throat with water immediately after nebulization. If necessary, switch to dry powder inhalers (DPIs) or use a spacer to mitigate oropharyngeal adverse effects.  (2) For oropharyngeal candidiasis, local antifungal treatment can be administered without discontinuing inhaled corticosteroids.
<b>Nebulized agonists</b>	<b>β2-receptor</b> (1) Common: sinus tachycardia, muscle tremors (usually manifest as hand tremors), dizziness, headache, and elevated blood lactate.  (2) Uncommon: oropharyngeal irritation.  (3) Rare: arrhythmias, bronchospasm, and hypokalemia.	Administer as needed; avoid long-term use, monotherapy, or excessive use.
<b>Nebulized anticholinergics</b>	(1) Common: dry mouth, cough, local irritation,	Use with caution in early

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<b>(Muscarinic antagonists)</b>	<b>receptor</b>	inhalation-related bronchospasm, headache, and dizziness.	pregnancy, glaucoma, and patients with prostatic hypertrophy.
		(2) Uncommon: urticaria, angle-closure glaucoma, and increased heart rate.	
		(3) Rare: allergic reactions (angioedema of the tongue, lips, and face), eye pain, mydriasis, palpitations, tachycardia, laryngospasm, nausea, and urinary retention.	

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### **3.2 Nebulization Therapy Related Adverse Events and Management**

When using a mask for nebulization therapy, drugs may deposit in the eyes, causing irritation. If this occurs, immediately rinse with clean water and switch to a mouthpiece for nebulization. Bronchospasm may occur due to low aerosol temperature, high aerosol density, improper pH of nebulization solution, or hypo/hyperosmolar aerosols. In such cases, stop nebulization immediately and provide appropriate treatment. For severe or persistent adverse reactions, seek medical help promptly to ensure timely and effective treatment. For patients requiring long-term nebulization therapy, regular monitoring and assessment should be conducted to adjust treatment plans.

### **3.3 Pharmaceutical Care for Special Populations**

#### **3.3.1 Children**

The lower airways of children are narrower compared to adults, making them prone to spasms or obstruction, leading to increased airway resistance. Children have higher respiratory rates, lower inspiratory flow rates, and smaller lung volumes, and tend to breathe through the nose. When using a mouthpiece or crying, drugs may not be effectively delivered to the lower airways [62]. To maintain a calm breathing pattern, treatment should be administered while the child is in a calm or sleeping state, with no food intake within 30 minutes prior to therapy, with no food intake within 30 minutes prior to treatment. For infants and toddlers who cannot assume a sitting position, elevating the head at a 30° angle with the chest is advised [63]. The mask should fit snugly over the mouth and nose, and the mouthpiece should not be inserted too deeply into the throat. Children unable to use a mouthpiece can resort to mask inhalation. To prevent facial and ocular irritation from medications, the mask should be gradually brought closer to the child during treatment to allow them to acclimate to the temperature of the aerosol, thus avoiding sudden inhalation of cold mist, which can trigger a cough reflex. When using a handheld medication cup, it should be kept vertical to the ground to avoid liquid spillage. Following nebulization, for infants and young children unable to rinse their mouths, a saline-soaked cotton swab can be used to wipe their oral cavities, followed by adequate water intake.

Age restrictions should be carefully followed during nebulized inhalation, with dosing based on age groups. For long-term use of medications containing inhaled ICS, both the FDA and NMPA recommend monitoring the effects on children's growth and development and the hypothalamic-pituitary-adrenal (HPA) axis. Budesonide is the preferred ICS recommended by the World Health Organization (WHO) for treating asthma in children  $\leq 12$  years old in their List of Essential Medicines for Children [64]. The US FDA has approved its use for children  $\leq 4$  years old, with the inhalation formulation indicated for infants  $\geq 6$  months old. Fluticasone propionate inhalation suspension can be used for children and adolescents aged 4-16 years, while the age range for beclomethasone dipropionate inhalation suspension is not clearly specified for pediatric use. SABAs are the first-choice medications for treating wheezing episodes in children of any age [65-69].

### **3.3.2 Elderly Patients**

When using nebulized inhalation formulations in elderly patients, attention should be paid to improving medication adherence and accuracy, with a focus on safety. For ICS: elderly patients have a higher risk of pneumonia when using these medications [50]. For bronchodilators: elderly patients with heart conditions (such as arrhythmias, coronary heart disease, etc.) should strictly adhere to the principle of as-needed inhalation when using nebulized SABAs, as excessive frequency or dosage can easily lead to arrhythmias or exacerbation of coronary heart disease symptoms. Elderly patients with prostatic hyperplasia or bladder neck obstruction should use short-acting muscarinic antagonists (SAMAs) with caution.

### **3.3.3 Pregnant and Lactating Women**

Pregnant women with asthma should use inhalers for rapid relief of asthma symptoms. Drug choices include SABAs (such as salbutamol) or combination formulations containing formoterol and low-dose ICS (such as budesonide-formoterol) [18,70-72]. Both the NAEPP expert panel and ACOG clinical guidelines state that ICS are the first-choice medications for controlling airway inflammation in pregnant and lactating women with persistent asthma [71,73-74]. Budesonide has an FDA pregnancy category B rating and is recommended as the first choice for pregnant and lactating women [75]. Beclomethasone dipropionate and fluticasone propionate are category C. Recent studies have also shown that beclomethasone dipropionate and fluticasone propionate do not increase the risk of adverse events or outcomes during pregnancy [76-77].

The American Academy of Pediatrics (AAP) states [78] that terbutaline is rarely excreted in breast milk and can be used as a preferred SABA for lactating women. Salbutamol has a lactation risk category of L1, ipratropium bromide is L2, and budesonide is L1. Human data from dry powder inhaler administration of budesonide show that infants receive approximately 0.3%-1% of the mother's inhaled dose in breast milk daily [79].

### **3.3.4 Inpatients and ICU patients**

Nebulized therapy for inpatients and ICU patients can be used to reduce airway inflammation, thin mucus secretions [35], decrease local inflammation and edema in the pharynx and larynx, and prevent laryngeal obstruction [80]. It is also an important component of airway management in Enhanced Recovery After Surgery (ERAS) protocols [41]. When administering nebulization therapy, it is important to consider various factors such as the patient's general condition, underlying diseases, and concurrent medications. For ICU patients on mechanical ventilation, the deposition of nebulized aerosols in the respiratory tract is influenced by various complex factors under positive pressure [35,44]. The inhalation efficiency during mechanical ventilation is lower than that of spontaneous breathing, necessitating adjustments such as increasing drug dosages for inhalation, shortening nebulization intervals, and increasing treatment frequency [81]. If the ventilator lacks integrated nebulization functionality, an ultrasonic nebulizer or vibrating mesh nebulizer should be used, and consider turning off or reducing the ventilator's baseline flow. If the baseline flow is turned off, the nebulizer should be placed 15 cm from the Y-piece on the inspiratory limb of the circuit. When baseline flow is present, the nebulizer should be placed at the inlet of the heated humidifier. During mechanical ventilation with nebulization therapy, assist/control ventilation modes have a higher drug deposition rate compared to pressure support modes. However, in clinical practice, the impact of mode changes on the patient's condition, especially pulmonary respiratory mechanics, should be fully considered. Adjusting the ventilation mode should not be based solely on increasing drug deposition. It is recommended that mechanically ventilated patients receiving nebulized therapy have their head elevated 30°-50° and be positioned in the lateral decubitus position on the healthy side to facilitate drug deposition on the affected side. For patients with bronchial hyperresponsiveness (BHR), the focus should be on controlling symptoms, including anti-inflammatory, anti-allergic, and bronchodilator treatments. The airway should be kept clear at all times, and patients should rinse their mouth and wash their face promptly after nebulization to prevent irritation and adverse reactions from residual medication.

Furthermore, vibrating mesh nebulizers, with the medication cup positioned above the ventilator circuit, can reduce the risk of contamination from condensation in the tubing and allow for the addition of nebulized medication through the medication cup opening without disconnecting the ventilator circuit [82]. However, the high cost of vibrating mesh nebulizer consumables currently limits their use to only selected medical institutions. Therefore, it is essential to thoroughly assess the pros and cons of nebulization and select the most appropriate nebulization equipment, medications, and regimen based on treatment needs, device characteristics, and the cost-effectiveness of medications to achieve optimal clinical outcomes.

#### **4. Conclusions:**

In recent years, China has experienced high prevalence of various respiratory diseases, primarily characterized by infectious diseases, with a trend of "one dominant disease and multiple concurrent diseases"[83-84]. Nebulization therapy has played a crucial role in treating respiratory system diseases due to its advantages of direct action on the

respiratory tract, rapid onset, and minimal side effects. However, there are still some issues in practical application, such as use without indication, inappropriate drug selection, and non-standardized usage, which to some extent affect treatment efficacy and patient safety. Hence, this consensus aims to address clinical challenges by offering standardized clinical protocols and rational medication suggestions for nebulization therapy, fostering interdisciplinary collaboration to improve treatment outcomes and ensure patient safety.

Conflict of Interest: All authors declare no conflicts of interest.

Expert Consensus on the Rational Use for Inhaled Medicines Administrated by Nebulizers  
(2024 Edition) Writing Committee

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#### Appendix: Glossary of Terms

- **Aerosol:** A dispersion system in which solid or liquid particles are stably suspended in a gaseous medium. The diameter range of pharmaceutical aerosols can be 0.01-100  $\mu\text{m}$ .
- **Small Volume Nebulizers (SVNs):** A drug delivery device that transforms medications into aerosol form for inhalation through the mouth (or nose). SVNs are currently the most commonly used nebulization devices in clinical practice, with a typical liquid capacity of 5-20 mL.
- **Effective Particle Size:** The diameter of nebulized aerosol particles that can deposit in the airways and lungs and have therapeutic value. This should be within the range of 0.5-10.0  $\mu\text{m}$ , with 3-5  $\mu\text{m}$  being optimal.
- **Output Rate:** Also known as nebulization rate, it refers to the amount of aerosol that can be inhaled from the nebulizer outlet per unit time. The output rate determines the effective amount of medication inhaled into the lungs. A higher output rate means a larger amount is inhaled in the same time period, increasing the drug dose and potentially enhancing therapeutic efficacy. However, it should be noted that an increased amount of drug entering the body in a short time may also increase adverse reactions, necessitating a comprehensive assessment.
- **Aerosol Deposition:** The process by which nebulized aerosol particles settle on absorptive surfaces. This is a crucial determinant of the effectiveness of nebulized therapy.
- **Aerodynamic Equivalent Diameter (AD):** Used to describe the size of aerosol particles. It is the diameter of a standard spherical particle with unit density (1.0 g/cm<sup>3</sup>) that has the same terminal settling velocity as the aerosol particle in question. The unit of measurement is  $\mu\text{m}$ .
- **Mass Median Aerodynamic Diameter (MMAD):** The aerodynamic diameter at which 50% of the aerosol particles by mass are larger and 50% are smaller.
- **Geometric Standard Deviation (GSD):** Used to describe the distribution state of aerosol particle sizes. It is calculated by dividing the particle size corresponding to an 84.1% cumulative percentage by the particle size corresponding to a 50% cumulative percentage on a logarithmic probability curve fitted with particle size on the X-axis and cumulative percentage on the Y-axis.
- **Total Delivered Dose (TDD):** An important parameter of nebulizers, representing the total amount of medication contained in all nebulized particles emitted when the nebulizer completes nebulization. It is a fundamental indicator of the nebulizer's drug

delivery capability.

- **Fine Particle Dose or Fraction (FPD or FPF):** The amount of drug contained in aerosol particles with an aerodynamic diameter (AD)  $\leq 5 \mu\text{m}$ , describing the dose of drug particles likely to enter the lungs. The Fine Particle Fraction (FPF) refers to the percentage of aerosol particles with AD  $\leq 5 \mu\text{m}$  that deposit in the lungs. FPD and FPF are typically used to characterize drug delivery efficiency. Higher FPD and FPF indicate higher drug delivery efficiency and greater lung deposition.