

# Consensus on Physician-Pharmacist Co-management of Perioperative Airway

Pharmacists are increasingly involved in pharmaceutical care of surgical patients. By joining the surgical team and utilizing their professional pharmaceutical knowledge under the authorization of doctors, pharmacists can greatly improve the clinical outcome of patients by managing their medication. Perioperative airway management is an important part of perioperative management, and is crucial for improving the clinical prognosis of surgical patients. Perioperative pulmonary complications (POPCs) may be caused by various risk factors and diagnosis and treatment measures during perioperative period, including bronchospasm, pulmonary edema, atelectasis and pulmonary infections. Severe cases can lead to respiratory failure and even threaten the patient's life. Studies have shown that the incidence of postoperative pulmonary complications (PPCs) varies depending on the type of surgery<sup>[1]</sup>, with rates ranging from 19-59% for thoracic surgery, 16-17% for upper abdominal surgery, and 0-5% for lower abdominal surgery. The application of perioperative airway management can effectively reduce pulmonary complications, accelerate postoperative recovery and shorten hospital stay, thereby reducing readmission rates and mortality risks and saving hospitalization expenses.

Medications typically used in perioperative airway management include expectorants, antitussives, bronchodilators, antibiotics, analgesics and sedatives. However, there has not been a consensus on the selection of drugs related to airway management, the timing of administration and the management of airway complications in clinical practice. In order to promote the more rational and standardized application of airway management medications in clinical practice, this consensus is intended to summarize the common clinical issues related to perioperative airway management through the joint discussion between physicians and pharmacists, so as to provide reference for the rational use of medications in perioperative period. According to the needs of clinical practice in perioperative airway management, a national expert questionnaire was developed on the basis of literature research, and 11 clinical issues were identified after classification and summary. Relevant studies were retrieved from PubMed, Web of Science, Wanfang, and China National Knowledge Infrastructure (CNKI), from the establishment of the database to January 2023. 95 articles were included ultimately.

## **1 Conducting risk assessment before surgery to reduce the risk of POPCs**

### **1.1 Factors leading to POPCs**

There are numerous factors contributing to POPCs, which include patient-related, surgery-related, and anesthesia-related factors based on the source of risk<sup>[2]</sup>; Preoperative, intraoperative, and postoperative risk factors can be identified based on their relationship with the surgical process. Preoperative risk factors include age, body weight, ASA classification and medical history of systemic diseases such as hypoalbuminemia, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, asthma, interstitial lung disease, pulmonary hypertension and obstructive sleep apnea (OSA)<sup>[3]</sup>. Intraoperative risk factors include the type of anesthesia and surgical procedures. Postoperative risk factors include inadequate pain control and sputum clearance. Specific POPC risk factor assessments for different surgical sites can be found in the corresponding guidelines, such as for pulmonary surgery<sup>[3]</sup>, otorhinolaryngology and head and neck surgery<sup>[4]</sup> and liver transplantation<sup>[5]</sup>. For special populations, such as patients with difficult airways<sup>[6]</sup> and children<sup>[7]</sup>, their respective guidelines should be consulted. High-risk factors for POPCs in thoracic surgery include age over 70 years, smoking index over 400 pack-years, comorbidities such as asthma and chronic obstructive pulmonary disease, airway hyperresponsiveness, obesity, low lung function, pathogenic airway colonization, metabolic

disorders, history of radiation and chemotherapy, and surgical trauma<sup>[3]</sup>. The risk factors for POPCs in liver transplantation and otorhinolaryngology and head and neck surgery patients are similar to those in Table 1, which are classified into preoperative, intraoperative, and postoperative categories<sup>[4-5]</sup>. For pediatric surgery, risk factors for POPCs include age  $\leq 1$  year, airway/otorhinolaryngology surgery, respiratory system diseases such as upper respiratory tract infections, passive smoking, patient position during anesthesia, intubation, incision area, surgery time, intraoperative complications, and postoperative recovery time and pain management<sup>[7]</sup>. For patients with difficult airways, it is necessary to actively assess their airway difficulties and aspiration risk through patient facial features and airway physical examinations<sup>[6]</sup>.

## 1.2 Perioperative POPC risk assessment

The risk scoring strategies can be used to evaluate these risk factors as a whole, allowing for the determination of patient's risk of developing POPCs<sup>[8]</sup>. Current approaches for evaluating POPC risk during the perioperative period include:

### 1.2.1 ARISCAT risk index<sup>[9]</sup>

A weighted scoring system that incorporates seven independent clinical variables to define patients as low, intermediate and high-risk groups for POPCs. However, the disadvantage is that mild complications are included, which may have no significant impact on the incidence of POPCs.

### 1.2.2 The scoring systems in the assessment of postoperative pneumonia

The Arozullah postoperative pneumonia risk index (including five risk levels) and Gupta postoperative pneumonia risk calculator<sup>[10]</sup>.

### 1.2.3 The scoring systems in the assessment of respiratory failure

The Arozullah respiratory failure index (variables include preoperative and intraoperative risk factors)<sup>[11]</sup>, the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) postoperative respiratory failure prediction model, and the Gupta respiratory failure calculator (variables only include preoperative risk factors).

### 1.2.4 Evaluation of cardiopulmonary reserve function

Pulmonary ventilation and diffusion testing, exercise tolerance testing and cardiopulmonary exercise testing<sup>[12]</sup>.

Following the perioperative assessment of POPC risk, corresponding preventive and therapeutic measures can be adopted for patients identified as having a moderate to high risk of developing POPC or an expected POPC incidence rate greater than 10%, based on preoperative, intraoperative and postoperative risk factors, and postoperative risk factors. See Table 1.

Table 1 Common risk factors and pharmaceutical prevention and treatment interventions for POPCs

	Common risk factors	Pharmaceutical prevention and treatment interventions
Preoperative	<ul style="list-style-type: none"> <li>• Smoking history</li> <li>• ASA classification</li> <li>• Advanced age</li> <li>• History of systemic diseases</li> </ul>	<ul style="list-style-type: none"> <li>• Smoking cessation before surgery, with pharmacological smoking cessation for patients with severe nicotine dependence</li> <li>• Patients with comorbid chronic respiratory diseases should undergo disease assessment and medication intervention</li> <li>• Treatment of respiratory infections before surgery</li> <li>• Enhanced nutritional support</li> </ul>

Intraoperative	<ul style="list-style-type: none"> <li>• Type of anesthesia</li> <li>• Use of long-acting non-depolarizing muscle relaxants</li> <li>• Surgical procedures</li> </ul>	<ul style="list-style-type: none"> <li>• Optimization of anesthesia drug use, such as short-acting muscle relaxants</li> <li>• Targeted fluid therapy with restrictive fluid administration</li> <li>• Bronchospasm should be managed by addressing the underlying etiology and administering bronchodilators either locally or intravenously to alleviate spasms.</li> </ul>
Postoperative	<ul style="list-style-type: none"> <li>• Pain</li> <li>• Inadequate sputum clearance</li> </ul>	<ul style="list-style-type: none"> <li>• Effective pain control</li> <li>• Mucolytic therapy</li> <li>• Anti-asthmatic therapy</li> <li>• Treatment of lung infections</li> </ul>

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## 2 Preoperative evaluation and pharmacological intervention for patients with comorbid chronic respiratory diseases to optimize pulmonary function

Preoperative assessment of patients with comorbid chronic respiratory diseases, combined with patients' specific conditions and surgical types, can guide the selective use of bronchodilators, expectorants and other pharmacological interventions to improve patients' pulmonary function and reduce the risk of postoperative complications<sup>[13]</sup>. Appendix 1 provides a reference for commonly used nebulized medications.

### 2.1 Patients with chronic obstructive pulmonary disease (COPD)

The primary goal of preoperative management in COPD patients is to minimize symptoms<sup>[14]</sup>. The assessment of stable COPD patients is based on a comprehensive evaluation of clinical symptoms, acute exacerbation risk, severity of lung function abnormalities and comorbidities, and is managed according to the corresponding graded treatment recommended by the *Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (2021 Revised Edition)*<sup>[15]</sup>. Commonly used medications include bronchodilators, glucocorticoids and mucolytics. Inhaled bronchodilators include short-acting  $\beta_2$  receptor agonists (SABA), short-acting muscarinic antagonists (SAMA), long-acting  $\beta_2$  receptor agonists (LABA) and long-acting muscarinic antagonists (LAMA). The continuation of graded treatment plans before surgery, such as inhaled bronchodilators and inhaled corticosteroids (ICS), can effectively maintain postoperative respiratory function and quality of life in patients with moderate to severe COPD. For COPD patients with high risk of postoperative pulmonary complications, such as those with preoperative airway hyperresponsiveness or COPD, bronchodilators and ICS should be used as needed during the perioperative period. Additionally, COPD patients should be aware of the increased risk of postoperative complications associated with comorbidities such as pulmonary heart disease and other cardiovascular diseases, and receive appropriate treatment based on the patient's cardiovascular status<sup>[16]</sup>.

### 2.2 Asthma patients

The GINA guidelines recommend that elective surgery in asthmatic patients should be scheduled after achieving good asthma control<sup>[17]</sup>. For asthmatic patients undergoing elective surgery, preoperative evaluation of asthma control can be conducted through clinical symptoms, lung function, and Asthma Control Test scores, with reference to the *Guidelines for Bronchial Asthma Prevention and Management (2020 Edition)* to determine the graded treatment plan for asthmatic patients<sup>[18]</sup>. Commonly used medications include bronchodilators, glucocorticoids and leukotriene receptor antagonists. For asthma patients, it is recommended to continue using graded treatment plans such as ICS and bronchodilators (such as ICS+LABA or ICS+LABA+LAMA) during the perioperative period. For asthma patients who are evaluated to be at risk for POPCs, prophylactic inhalation of bronchodilators and glucocorticoids before anesthesia induction can reduce the incidence of intraoperative bronchospasm. For patients undergoing emergency surgery, having

poor asthma control, or requiring tracheal intubation, it is recommended to administer intravenous glucocorticoids before surgery to rapidly relieve symptoms, thereby reducing the risk of postoperative pulmonary complications in asthma patients<sup>[19]</sup>. For children with asthma, if anxiety is not well-controlled (which may lead to hyperventilation), sedatives such as midazolam can be used before surgery if necessary<sup>[20]</sup>.

### **2.3 Interstitial lung disease (ILD) patients**

A propensity score matching analysis study indicates that preoperative administration of pirfenidone may be helpful to prevent severe postoperative airway complications in patients with interstitial lung disease who are scheduled with surgery under general anesthesia<sup>[21]</sup>.

### **2.4 Lung cancer patients**

Mucolytic agents, such as N-acetylcysteine and ambroxol, have been demonstrated to reduce the incidence of postoperative pulmonary complications following lung resection. For patients with lung cancer and COPD, the use of bronchodilators can effectively improve lung function and reduce the risk of postoperative pulmonary complications after lung resection<sup>[22]</sup>. Triple therapy (ICS+LABA+LAMA) is more effective in improving lung function and reducing postoperative complications in patients with lung cancer and COPD than dual therapy (LABA+LAMA). However, ICS is not recommended for patients with a history of mycobacterial infection or recurrent pneumonia.

Patients with comorbid chronic respiratory diseases should continue their regular medication regimen until the day of surgery (including the day of surgery), except for first-generation antihistamines, promethazine and theophylline. It is recommended to temporarily discontinue first-generation antihistamines (such as chlorpheniramine maleate, diphenhydramine hydrochloride and promethazine) and promethazine on the day of surgery to avoid the potential risk of postoperative delirium or anticholinergic adverse reactions. The treatment window for theophylline is narrow, and it is recommended to temporarily discontinue theophylline on the day of surgery to avoid the potential risk of increased adverse reactions due to interactions with other concomitant medications during the perioperative period<sup>[23]</sup>. Combination therapy of glucocorticoids and bronchodilators can synergistically prevent bronchospasm and is generally recommended to be continued during the perioperative period. However, for patients who have indications for reducing oral or high-dose inhaled glucocorticoids during the perioperative period, it is necessary to avoid reducing the dose too quickly or abruptly stopping before surgery to prevent the development of adrenal insufficiency or crisis and worsening of the underlying disease<sup>[24]</sup>.

## **3 Develop a specific plan based on clinical conditions of patients with preoperative pathogenic airway bacterial colonization**

Airway pathogenic bacterial colonization refers to the continuous presence of pathogenic bacteria in the respiratory tract mucosa or mucous secretions without eliciting adverse host reactions. However, it can lead to infection during host resistance decrease, dysbiosis of the microbial community, or breakdown of natural barriers due to various factors. The distinction of infection and colonization is a dynamic process that requires monitoring of risk factors, clinical features, microbiological evidence, and patient response to treatment, diagnostic and treatment strategies should be adjusted timely in accordance. Distinguishing colonization from infection in clinical practice is often challenging, and a comprehensive evaluation based on clinical symptoms, signs, laboratory tests, imaging changes, and other patient information is necessary. When necessary, multidisciplinary discussions and decisions should be made with clinical microbiology, radiology, and clinical pharmacology.

### **3.1 Screening and decolonization of pathogenic airway bacteria before surgery**

Currently, the existence of airway microbial colonization has been confirmed in healthy smokers (29%~33%), patients with chronic obstructive pulmonary disease (40%~83%), bronchogenic carcinoma (42%), and lung cancer patients (59.1%). However, the relationship between airway colonization and postoperative pulmonary infection remains controversial. Multivariate analysis has shown a statistical correlation between preoperative pathogenic airway bacterial colonization and postoperative pulmonary infection in patients undergoing lung cancer surgery, esophagectomy, lung transplantation and hip fracture surgery. However, from a microbiological perspective, the pathogens causing postoperative pulmonary infection are not entirely identical to the airway colonization bacteria, and only 42% of infection cases demonstrate partial or complete consistency<sup>[25-31]</sup>. Evidence regarding the routine screening for pathogenic airway bacterial colonization and decolonization before surgery is inadequate. In specific situations, such as cardiac, thoracic, orthopedic and neurosurgery, where there is a high risk of adverse outcomes following surgical site infection with *Staphylococcus aureus*, preoperative screening for pathogenic airway bacterial colonization and decolonization may be necessary. In cases where carrying *Staphylococcus aureus* in the nose is confirmed, preoperative decolonization may be necessary. Currently, there is no standardized decolonization protocol, but attempts can be made to use mupirocin nasal ointment (twice a day for 5 days), chlorhexidine bathing (once a day for 5 days), or comprehensive intervention measures (including screening, nasal decolonization, chlorhexidine bathing, and perioperative prophylactic use of antibiotics)<sup>[32-38]</sup>.

### **3.2 Perioperative prophylactic administration of antibiotics**

The colonization of pathogenic airway bacteria may contribute to an increased incidence of postoperative pulmonary infection. However, prophylactic administration of antibiotics during the perioperative period can mitigate related complications. It is recommended that antibiotics for prophylaxis be selected based on the type of surgical incision, potential bacterial contamination, and evidence-based medicine on the effectiveness of antibiotic prophylaxis. In the event of postoperative pulmonary infection, a prompt microbiological examination is recommended, and antibiotic therapy should be selected based on bacterial culture and susceptibility testing.

### **3.3 Perioperative oral care**

Studies have demonstrated that pathogens causing postoperative pulmonary infection may also originate from the oropharynx. Therefore, oral care is recommended as a preventative measure for postoperative pulmonary infection<sup>[39-44]</sup>. Prior to surgery, oral care should be conducted based on the patient's oropharyngeal condition. Oral care measures should include oral health maintenance, teeth cleaning, dental calculus removal, tongue scraping with a toothbrush, and extraction of severely diseased teeth or gargling with chlorhexidine mouthwash.

## **4 Preoperative screening for pulmonary aspiration risk and medication administration to reduce the risk of aspiration in high-risk patients**

Pulmonary aspiration is defined as the entry of solid or liquid substances into the trachea and lower respiratory tract, resulting from passive reflux of gastric contents in patients with impaired swallowing or laryngeal function. Pulmonary aspiration can lead to various degrees of POPCs, including aspiration pneumonia, lung injury, and others<sup>[45]</sup>. The reported incidence of pulmonary aspiration is 26.4%, with aspiration occurring either without perception or with warning signs. However, approximately 50% to 70% of patients experience aspiration without symptoms. Screening for pulmonary aspiration can reduce the risk of pneumonia by at least one-fold, and therefore, screening and prevention of pulmonary aspiration are of significant importance for patient prognosis. Risk factors that may increase pulmonary aspiration include surgical, anesthetic and patient-related factors (see Table 2)<sup>[46]</sup>.

Table 2 Risk factors for perioperative pulmonary aspiration

Category	Risk factors
Surgical factors	Risk factors for pulmonary aspiration include peritonitis, intestinal obstruction, prolonged surgical duration, gastric cancer, pyloric stenosis, and multiple trauma
Anesthetic factors	Use of inhalational anesthetics, sedatives, opioid drugs, recurrent laryngeal nerve block, residual neuromuscular paralysis, perioperative hypotension, hypoxemia or acidemia, mask ventilation
Patient-related factors	Late-stage pregnancy, patients with gastroesophageal reflux disease, esophageal hiatus hernia, metabolic intestinal obstruction, gastric contents greater than 1.5 ml/kg

#### 4.1 Screening for pulmonary aspiration risk

Preoperative assessment and implementation of preventive measures for the risk of pulmonary aspiration can reduce the incidence of POPCs. Aspiration risk screening is recommended using standardized swallowing assessment (SSA) and water swallowing test (WST). For tracheostomy patients, WST has a high risk of aspiration during testing and is less applicable. The diagnostic efficacy of WST for aspiration risk screening depends on the volume of water swallowed. WST ( $\geq 50$  ml) and SSA are more accurate than WST ( $< 50$  ml) for aspiration risk screening<sup>[47]</sup>. Additionally, preoperative gastric ultrasonography can be utilized to evaluate the gastric contents and volume. A gastric fluid volume of less than 1.5 ml/kg is associated with a low risk of pulmonary aspiration, while a gastric fluid volume higher than 1.5 ml/kg or completely solid contents indicate a high risk of pulmonary aspiration<sup>[48]</sup>.

#### 4.2 Prevention of perioperative pulmonary aspiration

Preventive measures for perioperative pulmonary aspiration include <sup>[49]</sup>:

- (1) Reducing gastric volume: preoperative fasting can reduce the risk and severity of reflux during anesthesia.
- (2) Increasing gastric pH: the risk of aspiration pneumonitis can be reduced when the gastric pH is above 3.5. For patients with a high risk of pulmonary aspiration, preoperative administration of medications that increase gastric pH, such as H<sub>2</sub> receptor antagonists, proton pump inhibitors, and antacids (Appendix 2), should be considered.
- (3) Performing preoperative risk assessment for postoperative nausea and vomiting (PONV). For patients with a moderate to high risk of PONV, preoperative prophylaxis with antiemetics such as metoclopramide and prokinetic agents should be considered (Appendix 2)<sup>[50]</sup>.

### 5 Perioperative nicotine dependence assessment and pharmacological treatment for patients with a smoking history

Preoperative nicotine dependence assessment is recommended, and patients with severe dependence are advised to undergo pharmacological intervention prior to surgery. Smoking cessation during the perioperative period is considered an important component of Enhanced Recovery After Surgery (ERAS) protocols. Quitting smoking for more than two weeks before surgery can reduce airway secretions and improve ventilation, while smoking cessation for more than four weeks can effectively decrease the risk of postoperative pulmonary complications. The *Guidelines for Perioperative Smoking Cessation*<sup>[52]</sup> recommend providing behavioral management and nicotine replacement therapy to help smoking cessation for all elective surgeries. Smoking cessation should be started regardless the time before surgery, although the benefits of smoking cessation being dependent on the duration of abstinence. Patients exposed to secondhand smoke

are in a passive smoking state, which can also negatively impact perioperative airway management. Therefore, for example, smoking parents of pediatric patients should receive smoking cessation interventions prior to the surgery.

### **5.1 Nicotine dependence assessment**

The intensity of nicotine dependence in smokers can be evaluated using the Fagerström Test for Nicotine Dependence (FTND) and the Heaviness of Smoking Index (HSI)<sup>[53]</sup>. Individuals with mild nicotine dependence may be able to quit smoking with their own willingness, whereas those with severe dependence require professional smoking cessation treatment. Outpatient smoking cessation clinics established in hospitals offer personalized, stepwise smoking cessation interventions based on the severity of nicotine dependence.

### **5.2 Perioperative smoking cessation medications**

The first-line smoking cessation medications recommended by the World Health Organization (WHO)<sup>[54]</sup> and the *Chinese Clinical Guideline for Smoking Cessation (2015 Edition)*<sup>[55]</sup> include nicotine replacement therapy (NRT), varenicline, and bupropion. NRT products with low doses of nicotine and good safety profiles include patches, gum, inhalers, nasal sprays, lozenges/tablets and oral sprays. These products gradually substitute nicotine to achieve successful smoking cessation. Second-line medications, such as clonidine and nortriptyline, may be considered if first-line medications are ineffective. Additionally, the use of e-cigarettes should be approached with caution<sup>[56]</sup>. Most e-cigarettes contain purified nicotine, which is the primary active ingredient. The WHO has indicated that there is no sufficient evidence to support the use of e-cigarettes as smoking cessation aids.

## **6. Risk assessment and pre-treatment for perioperative bronchospasm**

Bronchospasm that occurs during the perioperative period is a functional state of bronchial smooth muscle spasm, which results in reversible expiratory obstruction and wheezing. This condition is observed as a manifestation of stress states or certain underlying diseases.

### **6.1 Perioperative risk factors**

Bronchospasm may occur due to following risk factors<sup>[57,58]</sup>: (1) airway hyperresponsiveness, such as poorly controlled asthma and COPD, smoking, and upper respiratory tract infections; (2) inappropriate depth of anesthesia: airway manipulation (tracheal intubation, extubation, suctioning, etc.) and surgical traction under light anesthesia; (3) medications, including rapid administration of volatile anesthetics (isoflurane, desflurane), medications that cause bronchial smooth muscle spasm (e.g., beta-blockers, cholinesterase inhibitors), and medications that induce histamine release (e.g., suxamethonium, atracurium, morphine); (4) allergic reactions; (5) excessive airway secretions.

### **6.2 Perioperative prevention of bronchospasm**

#### **6.2.1 Patients with airflow limitation**

For patients with airflow limitation (such as those with COPD), the use of bronchodilators before surgery can help reduce the incidence of bronchospasm<sup>[59]</sup>; For those with reversible airway obstruction, preoperative treatment with a combination of inhaled SABA and oral prednisone for five days can significantly reduce the incidence of bronchospasm after tracheal intubation<sup>[60]</sup>.

#### **6.2.2 Asthma patients**

For asthma patients: elective surgery should be postponed until bronchospasm caused by an acute asthma attack has resolved. Preoperative treatment based on the level of asthma control and the Asthma Control Test (ACT) score can reduce the risk of bronchospasm in asthma patients<sup>[61]</sup>. Furthermore, preoperative inhalation of SABA can prevent bronchospasm caused by tracheal

intubation in patients with asthma<sup>[62]</sup>.

### **6.3 Perioperative treatment of bronchospasm**

For patients who develop intraoperative bronchospasm, rapid diagnosis and removal of the triggering factor are essential. In cases where mucus obstruction of the airway is the cause, prompt suctioning of the mucus is necessary. In cases where bronchospasm is caused by an allergic reaction, the treatment methods outlined in section 9.2 on perioperative allergic reactions should be followed. Additionally, other potential causes of bronchospasm, such as foreign body obstruction (e.g. a loose tooth), malpositioned tracheal tubes, tension pneumothorax or pulmonary edema, must be ruled out. In addition, supplemental oxygen should be administered to prevent hypoxia. If the above measures fail to resolve the bronchospasm, treatment options for acute bronchospasm should be adopted<sup>[63]</sup>, as shown in Appendix 3. In refractory cases, low-dose epinephrine maintenance therapy (0.5-2 µg/min) may be necessary, with dosage adjusted based on heart rate, blood pressure and bronchodilator response.

## **7 Perioperative risk assessment and prevention of airway edema after tracheal intubation**

Airway edema is a common complication of tracheal intubation during the perioperative period. Tracheal intubation involves the insertion of a specialized endotracheal tube through the glottis into the trachea, thus creating an artificial airway.

### **7.1 Detection of airway edema**

Detection methods of airway edema following tracheal intubation include cuff leak test (CLT), ultrasound examination and laryngoscopy. Risk factors for developing airway edema after tracheal intubation include prolonged intubation time, large diameter tracheal tubes, emergency intubation, difficult airway and intraoperative fluid overload. The implementation of preventive measures targeting these risk factors can significantly reduce the incidence of airway edema following tracheal intubation<sup>[64, 65]</sup>.

### **7.2 Prevention of perioperative airway edema**

For high-risk patients with airway edema following tracheal intubation, the duration of intubation should be minimized, and intravenous administration of glucocorticoids prior to extubation is recommended for prevention: for example, intravenous methylprednisolone with a dose of 20-40 mg every 4-6 hours within 12-24 hours before extubation<sup>[66]</sup>, a single dose of intravenous methylprednisolone 40 mg at least 4 hours before extubation<sup>[67]</sup>, or intravenous dexamethasone 5 mg every 6 hours within 24 hours before extubation can be administered. For adult patients, preventive measures for airway edema should be considered before planned extubation after intubation for more than 36 hours<sup>[68]</sup>. Additionally, nebulized ICS, such as budesonide at a dose of 1 mg/4 ml every 12 hours for 48 hours<sup>[69]</sup>, has also been shown to effectively prevent postoperative airway edema.

For patients who have already developed laryngeal edema, prompt treatment should be initiated to prevent further deterioration. Treatment measures include nebulized inhalation of room temperature aerosol to ensure adequate humidification of the glottic area, nebulized ICS or intravenous administration of glucocorticoids such as methylprednisolone to alleviate laryngeal edema; For patients with severe edema, re-establishment of an artificial airway may be necessary<sup>[70]</sup>.

## **8 Evaluation and treatment of postoperative cough after pulmonary surgery**

Postoperative cough is a common complication of pulmonary surgery. Patients with cough after pulmonary surgery should be evaluated and treated according to different causes.



### **8.1 Evaluation of postoperative cough after pulmonary surgery**

The evaluation of postoperative cough includes the assessment of cough severity, monitoring of cough frequency, administration of a cough-specific quality of life questionnaire and cough sensitivity testing. Commonly used assessment tools include Cough Visual Analog Scale (VAS), Cough Evaluation Test (CET), and Leicester Cough Questionnaire (LCQ/LCQ-MC)<sup>[71]</sup>. The severity of cough is classified as mild, moderate and severe. The *Chinese National Guideline on Diagnosis and Management of Cough* recommend the use of the CET scoring system for the evaluation of cough severity<sup>[72]</sup>.

### **8.2 Treatment of postoperative cough after pulmonary surgery**

Mild postoperative cough following pulmonary surgery can be relieved through cough and sputum clearance training, respiratory training and other methods. For patients with persistent moderate to severe cough after pulmonary surgery, other possible postoperative complications such as lung infection, pleural effusion and pulmonary aspiration should be ruled out first. Subsequently, targeted treatment can be initiated based on the underlying etiology<sup>[73]</sup>:

#### **8.2.1 Treatment methods for surgical factors**

Surgical factors (such as surgical trauma, sutures and stapling instruments) can lead to postoperative coughing. The patient's proper cough is helpful to discharge airway secretions, which is beneficial to postoperative recovery. Mild cough does not require specific antitussive treatment, while moderate to severe cough requires appropriate use of peripheral antitussive medications such as codeine and benproperine, or traditional Chinese medicine antitussive agents.

#### **8.2.2 Treatment methods for anesthetic factors**

Anesthetic factors such as irritation caused by endotracheal intubation, can result in postoperative cough. The administration of ICS, such as budesonide<sup>[74]</sup>, beclomethasone<sup>[75]</sup>, or the topical application of betamethasone gel<sup>[76]</sup>, can reduce the incidence and severity of postoperative complications, including sore throat, cough and hoarseness associated with endotracheal intubation. Optimizing the selection of anesthetic drugs, such as the use of remifentanyl and intravenous lidocaine, can prevent coughing during extubation and postoperative airway complications<sup>[77, 78]</sup>. Opioids, including codeine, may be effective for acute cough during the perioperative period<sup>[79]</sup>.

#### **8.2.3 Refractory cough associated with lung cancer**

Central cough suppressants, such as dextromethorphan and methotrimeprazine, can exert an antitussive effect by inhibiting the cough center in the medulla for refractory cough associated with lung cancer<sup>[80]</sup>. Treatment strategies for lung cancer-related cough can be found in the *Chinese Expert Consensus on the Diagnosis and Treatment of Cough Related to Lung Cancer*<sup>[81]</sup>.

## **9 Evaluation and treatment of perioperative anaphylaxis**

Perioperative anaphylaxis is a severe systemic hypersensitivity reaction caused by a substance during the perioperative period. It can result in life-threatening airway, respiratory and circulatory problems, often accompanied by skin and mucosal changes.

### **9.1 Evaluation of perioperative anaphylaxis**

The modified Ring and Messmer grading system can be used to classify the severity of perioperative anaphylaxis into four grades, ranging from grade I to IV. The grading system is based on the patient's specific symptoms and can be used to select the appropriate treatment plan<sup>[82]</sup>.

### **9.2 Treatment of perioperative anaphylaxis**

For patients who experience anaphylactic reactions during perioperative anesthesia, suspected allergens, such as medications or blood products, should be discontinued immediately. High-flow oxygen should be administered, airway, respiratory and circulatory resuscitation should begin. Targeted treatment should be administered based on the severity of the anaphylactic reaction, as in Figure 1.

For patients experiencing grade II or higher anaphylactic reactions, such as bronchospasm or laryngeal edema, epinephrine is the first-line treatment. Additionally, measures such as fluid replacement and oxygen therapy should be implemented to stabilize the respiratory and circulatory systems and save the patient's life<sup>[83-85]</sup>. If grade II anaphylactic reaction occurs, a recommended dose of 300-500 µg of epinephrine can be administered by intramuscular injection in the middle of the thigh if a venous access has not yet been established. As epinephrine can cause adverse reactions such as arrhythmia, intravenous administration should be titrated based on the patient's responsiveness. For grade II anaphylactic reactions, if there is no response after the initial dose of epinephrine, the dose can be increased to 50 µg after 2 minutes. For grade III anaphylactic reactions, if there is no response after the initial dose of epinephrine, the dose can be increased to 100-200 µg after 2 minutes. Careful dilution to avoid dosing errors is necessary for children who may respond to doses as small as 1 µg/kg.

For patients with anaphylactic shock who exhibit persistent hypotension despite epinephrine treatment, other vasoactive drugs such as vasopressin and norepinephrine may be considered as adjunctive therapy<sup>[82, 84]</sup>. Inhalation of salbutamol, intravenous bronchodilators, or volatile anesthetics are recommended for persistent bronchospasm lasting more than 10 minutes or high airway pressure<sup>[86]</sup>. Glucocorticoids are not recommended as first-line treatment for anaphylactic shock but can be used as adjunctive therapy. Intravenous administration of glucocorticoids may be administered after adequate epinephrine and fluid resuscitation<sup>[87,88]</sup>. While glucocorticoids cannot relieve initial symptoms and signs, they can theoretically prevent delayed reactions associated with severe anaphylactic reactions. Antihistamines are a second-line treatment option for drug-related anaphylactic shock and should only be used when skin symptoms persist despite symptom improvement<sup>[89]</sup>. It is recommended that intramuscular or intravenous antihistamines be administered after adequate fluid resuscitation<sup>[84]</sup>.

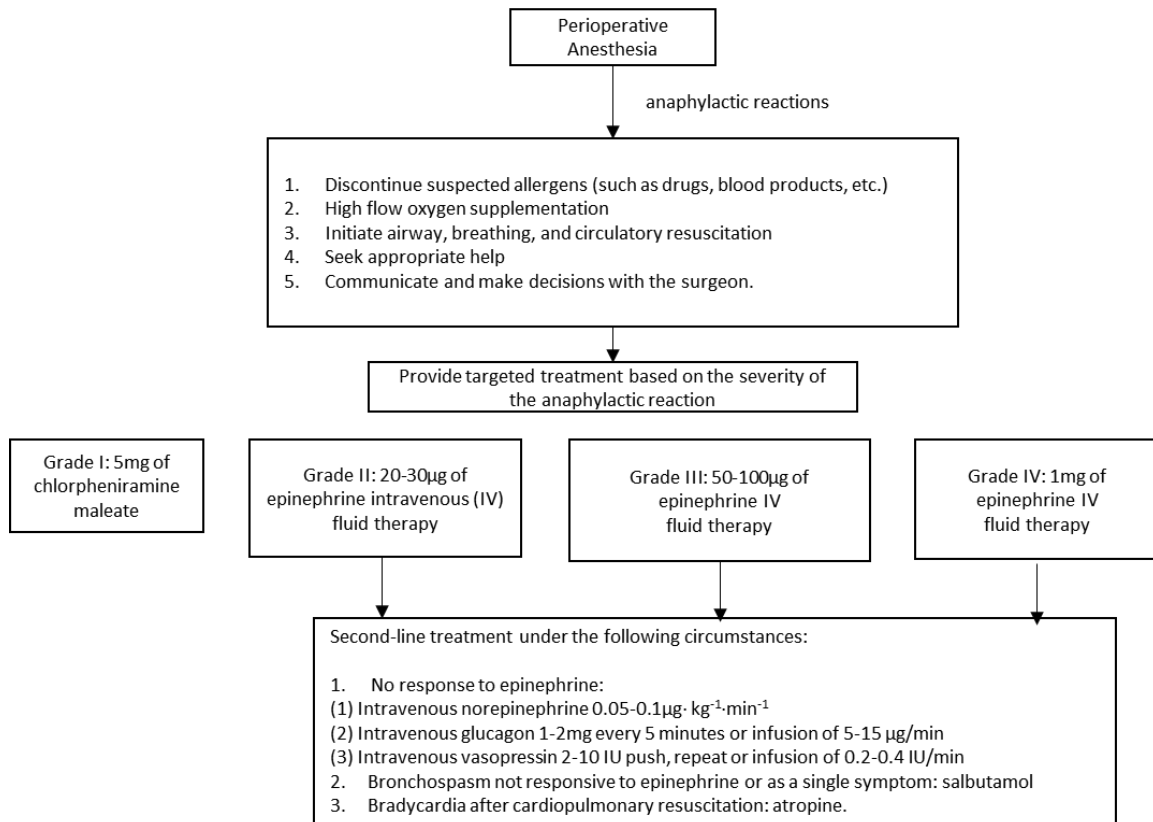


Figure 1. Management flowchart for anaphylactic reactions after anesthesia

### 10 Off-label drug use in perioperative airway management requires sufficient evidence from evidence-based medicine

Instructions in drug inserts may not always reflect current clinical practice. In order to use drugs in a rational, safe and effective manner, according to the *Physician Law*, off-label drug use must meet three criteria: there are no effective or superior treatment options, the patient has given informed consent, and there is evidence-based medicine to support the use of the drug. It is recommended that off-label drug use be approved and registered by the relevant management department of the hospital.

In the context of perioperative airway management, robust evidence for the off-label drug use only exists in certain medications, including pediatric anesthetics and ambroxol.

The commonly used pediatric anesthetic drugs in the perioperative period can be classified into four categories: inhalation anesthetics, intravenous anesthetics, muscle relaxants and local anesthetics. The evidence level refers to the five-level standard from the Oxford University Centre for Evidence-Based Medicine, as specified in the *Expert Consensus on the Off-label Drug Use of Common Pediatric Anesthetic Drugs (2017)*.

High-dose ambroxol has been shown to exert pulmonary protection through its anti-inflammatory and antioxidant effects<sup>[90]</sup>. For patients with underlying lung diseases such as COPD, asthma or diabetes, as well as those with a long history of smoking, obesity or advanced age, the administration of high-dose ambroxol has been demonstrated to significantly reduce the incidence of pulmonary complications (such as atelectasis, lung injury, hypoxemia and ARDS), and improve patient outcomes<sup>[91]</sup>. The *Catalog of Off-label Drug Use* compiled by Guangdong

Provincial Pharmaceutical Association in 2022 recommends the off-label use of ambroxol at a dose of 1 g/d (limited to the generic drug Mucosolvan) for the prevention of postoperative atelectasis in COPD patients.

## **11 Perioperative pulmonary complications of minimally invasive surgery and anesthesia techniques**

The development and progress of minimally invasive surgery have revolutionized the traditional surgical approach, providing patients with a minimally traumatic, low-risk, effective and high-quality-of-life surgical option. The adoption of minimally invasive techniques, such as thoracoscopy, has been shown to significantly reduce the incidence of postoperative complications<sup>[92]</sup>. Adverse effects of opioids during anesthesia, such as respiratory depression, nausea, allergies, and residual muscle relaxation, are known to contribute to postoperative complications. In recent years, opioid-free anesthesia (OFA)<sup>[93]</sup> and non-intubated spontaneous breathing (tubeless) strategies<sup>[94]</sup> have gained popularity in clinical practice and have been shown to offer advantages in minimally invasive surgery, including satisfactory sedation and analgesia, mild intraoperative stress reaction, and rapid postoperative recovery.

It should be noted that certain non-thoracic minimally invasive surgeries may also lead to pulmonary complications. For instance, laparoscopic procedures may cause inflation-related complications and acid-base imbalances in the peritoneum or throughout the body due to CO<sub>2</sub>. Inflation-related complications may include subcutaneous emphysema, pneumothorax, gas embolism, hypercapnia, etc. Procedures such as percutaneous cholangiolithotomy<sup>[95]</sup> and percutaneous nephrolithotomy<sup>[96]</sup> may cause pleural injury and respiratory distress as a result of puncture, and chest tube drainage may be required in the event of complications such as pneumothorax. During laparoscopic surgery, the temporary elevation of intra-abdominal pressure caused by carbon dioxide insufflation may impair pulmonary gas exchange in patients with pre-existing chronic respiratory diseases such as COPD, thereby increasing the risk of pulmonary infection.

## **12 Conclusions**

The drug related activities during the perioperative period include drug procurement, storage, distribution, preparation, quality monitoring, clinical drug management and pharmaceutical services. The co-management between physicians and pharmacists can aid healthcare professionals in recognizing potential safety risks associated with drug use, reducing medical costs, shortening hospital stays, and ensuring patient's health<sup>[97]</sup>. Drug safety concerns primarily include drug dispensing errors and adverse reactions<sup>[98]</sup>. Types of drug dispensing errors include miscalculations of dosages, concentration errors, errors in infusion frequency, drug mix-ups during administration, incorrect dosing, wrong infusion tubing, administration of known allergenic drugs to patients and failure to flush infusion tubing after administration. The co-management mode can effectively reduce the incidence of drug dispensing errors and adverse reactions.

The primary role of clinical pharmacists within the perioperative medical team is to develop patient-centered medication treatment strategies and to carry out pharmaceutical management primarily focused on rational drug use<sup>[99]</sup>. Clinical pharmacists can provide pharmaceutical services in areas such as the correct use of therapeutic drugs (such as inhalants), patient treatment compliance, drug interactions and adverse reactions, thereby assisting physicians in therapeutic drug management. The co-management between physicians and pharmacists has a significant impact on improving economic, clinical and humanistic outcomes, particularly for special populations such as elderly patients with multiple chronic underlying diseases who require simultaneous administration of multiple drugs<sup>[100]</sup>. The co-management is helpful in standardizing

the diagnosis and treatment process, improving patient treatment compliance and satisfaction, and enhancing perioperative airway management.

Optimal perioperative airway management is of great significance for preventing pulmonary complications and improving patient outcomes. Perioperative airway management can be strengthened through the co-management between physicians and pharmacists. Individualized treatment plans for airway management should be developed based on the patient's specific condition, disease severity, surgical type and surgical duration. During drug treatment, attention should be paid to indications, dosage, contraindications, drug interactions and adverse reactions. By assessing the risk of postoperative complications before surgery and optimizing drug treatment plans, the safety of surgery, good patient outcome and accelerated postoperative lung recovery can be ensured.

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## Appendix 1 Dosages and adverse reactions of commonly used nebulized medications during perioperative period

Category	Generic name	Recommended dosages (adult)	Recommended dosages (children)	Adverse reactions
ICS	Budesonide Suspension for Inhalation	Nebulized solution specifications: 0.5-1 mg per 2 ml Acute phase: 1-2 mg per dose, twice daily Stable phase: 0.5-1 mg per dose, twice daily*	Acute phase: 0.5-1 mg per dose, twice daily Stable phase: 0.25-0.5 mg per dose, twice daily*	Possible suppression of symptoms of existing infections or induction of new infections. Should be administered with caution in patients with active or latent pulmonary tuberculosis, respiratory fungal, bacterial or viral infections.
	Fluticasone Propionate Nebuliser Suspension	--	4-16 years: 1 mg per dose, twice daily	
SABA	Salbutamol Sulphate Nebules Inhalation Solution	Nebulized solution specifications: 2.5-5 mg/2.5 ml, 2.5-5.0 mg per dose, may be repeated up to 4 times daily	2.5-5 mg per dose, may be repeated up to 4 times daily	Common adverse reactions include skeletal muscle tremors and tachycardia, Should not be administered concomitantly with non-selective $\beta_2$ receptor blockers such as propranolol (Inderal).
	Terbutaline Sulphate Solution for Nebulization	Nebulized solution specifications: 5 mg/2 mL Weight>20 kg, 5.0 mg per dose; Weight<20 kg, 2.5 mg per dose; Should not be administered more than 4 times within 24 hours.	Initial treatment on-demand, not required to be administered with fixed intervals; weight>20 kg, 5.0 mg per dose; weight<20 kg, 2.5 mg per dose	
SAMA	Ipratropium Bromide Solution for Inhalation	Nebulized solution specifications: 500 $\mu$ g/2 mL, 250 $\mu$ g/2 mL; 500 $\mu$ g/2 mL per inhalation, 3-4 times daily	6-12 years: 250 $\mu$ g per dose, may be increased to 500 $\mu$ g per dose for severe cases; <6 years: 250 $\mu$ g per dose	Headache, nausea and dry mouth, should be administered with caution in patients with narrow-angle glaucoma, benign prostatic hyperplasia, or neck obstruction due to bladder cancer.

Combination preparation (ipratropium bromide and salbutamol sulfate)	Compound Ipratropium Bromide Solution for Inhalation	Nebulized solution specifications: 2.5 mL, containing 0.5 mg ipratropium bromide and 3.0 mg salbutamol sulfate 2.5-5.0 mL per dose, 3-4 times daily	--	Same as salbutamol sulfate and ipratropium bromide
Mucolytic	Acetylcysteine Solution for Inhalation	Nebulized solution specifications: 0.3 g/3 mL, 0.3 g per dose, 1-2 times daily	Nebulizer solution specifications: 0.3 g/3 mL, 0.3 g per dose, 1-2 times/day	May stimulate the nasal and gastrointestinal tract

\*adjust dose and administration interval according to the patient's condition. ICS, inhaled corticosteroids; SABA: short-acting  $\beta_2$  agonists; SAMA: short-acting muscarinic antagonist.

## Appendix 2 Medications for reducing pulmonary aspiration risk

Category	Representative medications	Recommended dosages (adult)	Recommended dosages (children)	Suggested timing of prophylactic administration	Adverse reactions
Gastrointestinal Stimulants	Metoclopramide	Intramuscular or intravenous injection: 10-20 mg per dose, daily dose not exceeding 0.5 mg/kg	Intramuscular or intravenous injection: 0.1 mg/kg for children under 6 years old, 2.5-5 mg for children aged 6-14 years	Should be given to high-risk patients 15-30 minutes before induction	Common adverse effects include sedation, agitation, and fatigue. Long-term use of high doses may lead to extrapyramidal side effects, especially in young patients.
H2 Receptor Antagonists	Cimetidine	Intramuscular injection or intravenous administration: 200 mg per dose, repeated every 4-6 hours	Not recommended	Should be given to high-risk patients 1.5-2 hours before induction	Common side effects include headache, dizziness, diarrhea, rash, muscle pain, and fatigue
	Ranitidine	Preoperative administration: 50-100 mg, slow intravenous injection or drip for 1-2 hours	Intravenous injection: 1-2 mg/kg per dose, once every 8-12 hours Intravenous infusion: 2-4 mg/kg per dose, continuously over 24 hours		Nausea/vomiting, constipation, diarrhea, abdominal discomfort, pain, reversible elevation of alanine aminotransferase
	Famotidine	Intravenous administration: 20 mg per dose, repeated every 12 hours	Not recommended		Headache, dizziness, constipation, and diarrhea
Proton Pump Inhibitors	Omeprazole	Intravenous infusion: 40 mg per dose	Not recommended	Should be given to high-risk patients 1 hour before induction	Common side effects include headache, abdominal pain, constipation, diarrhea, bloating, and nausea/vomiting

	Lansoprazole	Intravenous infusion: 30 mg per dose	Not recommended		Nausea, headache, injection site pain, abdominal pain, diarrhea, vomiting, indigestion, paresthesia, dysgeusia, vasodilation, mild elevation of liver enzymes, elevated bilirubin, and rash
	Pantoprazole	Intravenous infusion: 40 mg per dose	Not recommended		Injection site thrombophlebitis, headache, dizziness, diarrhea, nausea/vomiting, constipation, abdominal discomfort, elevated liver enzymes, rash, itching, fatigue
Antacids	Sodium bicarbonate	Oral administration: 0.5-1 g per dose, 3 times daily	Oral administration: 0.1-1 g per dose, 3 times daily, not recommended for children under 6 years	Should be given to high-risk patients 15-30 minutes before induction	Secondary gastric pain, bloating, elevated blood pressure, alkalosis, muscle weakness and spasms
	Magnesium trisilicate	Oral administration: 0.3-0.9 g per dose, 3-4 times daily	-		Mild diarrhea, occasional renal silicate stones
Antiemetics	Ondansetron	Intravenous injection: 4 mg	0.1 mg/kg, maximum dose 4 mg, slow intravenous injection	Should be given to intermediate or high-risk patients at the end of surgery	Headache, warm or flushing sensation, constipation, local reactions at the injection site

Droperidol	Intravenous administration: 2 mg per dose	Not recommended	Should be given to intermediate or high-risk patients at the end of surgery	Constipation, headache, dizziness, fatigue, abdominal pain, diarrhea
Palonosetron	Intravenous injection: 0.075 mg	-	Should be given to intermediate or high-risk patients during anesthesia induction	Prolonged QT interval, bradycardia, headache, constipation
Dexamethasone	Intravenous injection: 4-5 mg	-	Should be given to intermediate or high-risk patients during anesthesia induction	Nausea/vomiting, pancreatitis, peptic ulcer or perforation, infection, euphoria, excitement, insomnia, delirium, electrolyte imbalances, ischemic bone necrosis, osteoporosis and fractures, poor wound healing, allergies, etc.



### Appendix 3 Commonly used medications for the treatment of acute bronchospasm during perioperative period

Category	Mechanism of action	Examples of medications	Precautions
SABA	Stimulate $\beta_2$ receptors	Salbutamol, Levalbuterol, Pirbuterol	Inhalation of high doses of SABA, such as salbutamol (4-8 puffs), can achieve rapid onset of action, but overuse of salbutamol or levalbuterol has been reported to cause paradoxical bronchospasm
Intravenous glucocorticoids	Multiple anti-inflammatory effects	Methylprednisolone, Hydrocortisone, Prednisone	In cases of uncontrolled acute exacerbations, high doses of systemic corticosteroids (e.g. 125 mg methylprednisolone intravenously) are necessary
Volatile Anesthetics	Multiple pathways: including smooth muscle relaxation, vagal nerve blockade, and anti-inflammatory actions.	Isoflurane, Sevoflurane, Desflurane	Desflurane may exacerbate bronchial constriction in smokers
Intravenous Anesthetics	Inhibit vagal nerve, stimulate sympathetic nervous system and endothelin pathway	Ketamine, Propofol	Ketamine may increase oral and airway secretions
Magnesium Agents	Smooth muscle relaxation	Magnesium Sulfate	Intravenous administration of magnesium sulfate (1.2-2 g) may be effective in refractory cases, although high doses may cause weakness and central nervous system depression

SABA: short-acting  $\beta_2$  agonists.