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Davide Chiumello
Department of Anesthesia and Intensive Care
ASST Santi Paolo e Carlo
San Paolo University Hospital
Milan, Italy
Department of Health Sciences
University of Milan
Milan, Italy
Coordinated Research Center on Respiratory Failure
University of Milan
Milan, Italy
davide.chiumello@unimi.it

Giulia Catozzi
Department of Health Sciences
University of Milan
Milan, Italy
giulia.catozzi@unimi.it

Ventilatory Support for Asthma - An Overview of Critical Asthma Management

Critical asthma is relatively uncommon, with its incidence on the decline; however, it can require intensive care, including mechanical ventilation. This article provides an overview of critical asthma management.

Introduction

Critical asthma (CA) is an umbrella term embracing different definitions, all referring to an acute asthma exacerbation that can rapidly deteriorate into respiratory failure, often necessitating intensive care treatment and possibly mechanical ventilation (MV). In this article, we summarise the current evidence on the management of critical asthma.

Definition and Incidence

Asthma is a complex and heterogeneous lung disease marked by chronic airway inflammation and variable respiratory symptoms, including wheezing, shortness of breath, cough and chest tightness due to reversible airflow obstruction and excessive bronchial reactivity. These symptoms can vary in intensity and frequency, often triggered by factors like air pollution, allergens, respiratory infections or exercise (GINA Committee 2024).

The incidence of asthma has declined over the past 30 years, along with its mortality rate (Cao et al. 2022; Ebmeier et al. 2017). However, asthma continues to be one of the most prevalent chronic respiratory conditions and remains a leading cause of hospital readmissions in the months following discharge (Cao et al. 2022; Gonzalez-Barcala et al. 2018). It is estimated that there are 300 million people with asthma worldwide (Masoli et al. 2004). In Europe, in 2009, asthma led to an average of 53 hospital admissions per 100,000 inhabitants (Bousquet et al. 2014). In a study conducted in the United States, 10% of the admissions for asthma as a primary diagnosis were referred to the intensive care unit (ICU) and 2% required intubation (Pendergraft et al. 2004). Notably, the majority of patients admitted to the ICU were female. Asthma patients who required ICU admission and/or intubation experienced higher mortality rates, longer hospital stays (+1.75 days on average) and were more likely to be readmitted to the hospital or ICU compared to those with standard admissions (Pendergraft et al. 2004).

Risk Factors and Comorbidities

The exact cause of asthma is unknown, but various risk factors and gene-environment interactions contribute to its development. Increased risk of asthma includes other factors such as early-life respiratory infections, especially severe viral infections, atopic conditions and environmental factors, such as inhalant allergens, smoke, pollution and chemical exposure; in addition, other factors like stress, diet and microbiome components (Mims 2015).

Asthma patients, particularly those with severe forms, have higher rates of both pulmonary and extrapulmonary comorbidities, with older women, former smokers, and corticosteroid-dependent patients being especially affected (Tomisa et al. 2021). Alvarez et al. (2005) investigated the risk factors associated with CA (particularly near-fatal asthma and fatal asthma). Identified risk factors included smoking, atopy, increased need for medications (nebulised beta-agonists, oral corticosteroids and oral theophylline), history of hospital and/or ICU admission and need for MV. Also, low access to healthcare, drug abuse, and a concomitant psychiatric condition are associated with a higher risk of CA (Louie et al. 2012).

Outcome

The overall hospital mortality for asthma exacerbations ranges from 0.5-5%, with older age (>65 years), female sex, and African American ethnicity associated with higher mortality rates (Krishnan et al. 2006; Louie et al. 2012). Mortality in CA ranges from 3 to 10%, with death occurring mainly for hypoxaemia, cerebral anoxia, and cardiopulmonary arrest (Gonzalez-Barcala et al. 2015). Previous history of near-fatal asthma increases the mortality by 16 times (Louie et al. 2012).

Critical Asthma Management

Typically, at clinical assessment, patients present with tachypnoea, usually higher than 30 breath/min, wheezing, use of accessory muscles and peripheral cyanosis. Paradoxical breathing may be a sign of imminent respiratory arrest. Tachycardia (>120 bpm) and haemodynamic instability are common. Intensive care admission is recommended when patients present with hypoxaemia (SpO_2 <92%) despite receiving oxygen therapy, severe hypercapnia,

neurologic alterations like decreased consciousness, dizziness, lethargy or encephalopathy, cardiac disturbances, presence of barotrauma (pneumothorax or pneumomediastinum) or require respiratory support (Adams et al. 2012; Schivo et al. 2015). A chest x-ray is recommended to detect potential complications such as atelectasis, barotrauma, pneumonia or pneumothorax. Essential monitoring includes serial gas exchange through serial blood gas analysis, tissue perfusion, adequate cardiac output and hydro-electrolyte status.

Cornerstones of CA management involve reversing bronchoconstriction and controlling the symptoms with the correction of hypoxaemia, as well as preventing exacerbation and reducing the risk of death. Initial treatment includes oxygen therapy, bronchodilators, systemic anti-inflammatory agents and respiratory support. An overview of CA management is presented in **Figure 1**.

Asthma and Acid-Base Disorders

CA is characterised by airway obstruction, hypercapnia, and respiratory acidosis, which finding is correlated with the need for intubation and higher mortality (Vasileiadis et al. 2019). Furthermore, CA can cause lactic acidosis due to hypoxaemia and tissue hypoperfusion, cardiac dysfunction, and respiratory muscle fatigue. Treatment with high-dose bronchodilators may also lead to lactic acidosis, hypokalaemia and hypophosphataemia, which can further worsen muscle fatigue and tissue oxygenation, complicating the clinical outcome (Vasileiadis et al. 2019).

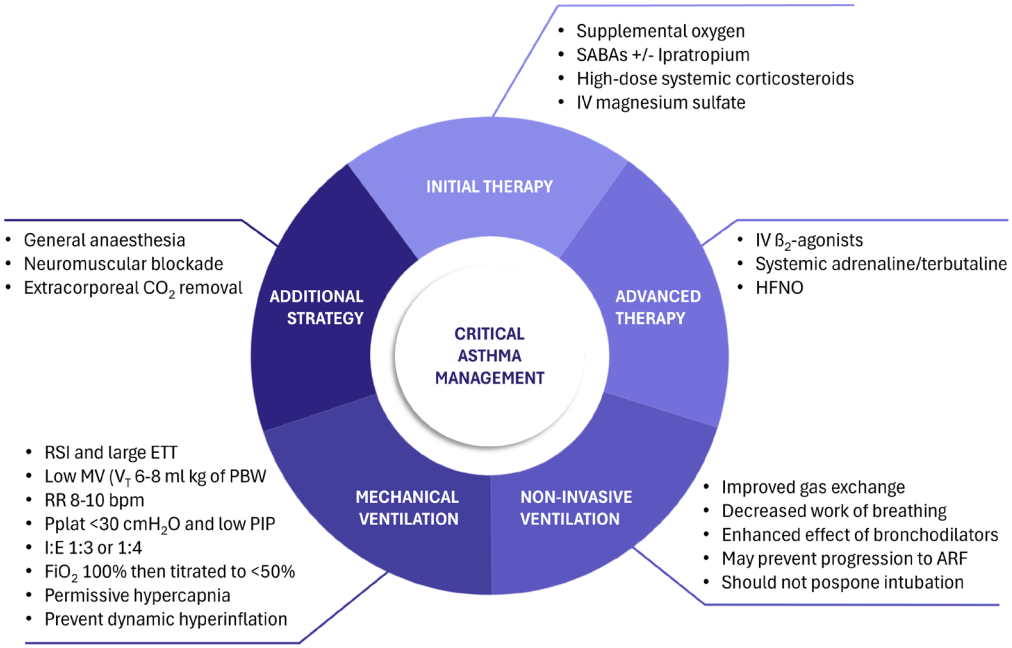

Figure 1. Overview of Critical Asthma Management
ARF: acute respiratory failure; ETT: endotracheal tube; FiO_2: inspired fraction of oxygen; HFNO: high-flow nasal oxygenation; I:E: ratio of inspiratory to expiratory time; IV: intravenous; MV: minute ventilation; PBW: predicted body weight; PIP: peak inspiratory pressure; Pplat: plateau pressure; RR: respiratory rate; RSI: rapid sequence intubation; SABAs: short-acting ß2-agonists; VT: tidal volume.

Pathophysiology and Lung Mechanics

Asthma has traditionally been considered primarily a condition of airway inflammation. Lung mechanics can be affected by excessive airway narrowing, where a decrease in airway diameter leads to a substantial increase in airway resistance. This increased resistance can result in various lung function impairments, including limited expiratory flow with augmented exhalation time, air trapping and intrinsic positive end-expiratory pressure (PEEP), dynamic hyperinflation, ventilation inhomogeneity, ventilation/perfusion mismatch, and increased work of breathing (Kaminsky and Chapman 2020; Scala 2010). The conventional understanding of airway narrowing involves two primary mechanisms: bronchoconstriction, which results from the activation of airway smooth muscle, and luminal narrowing, which is caused by airway wall thickening due to oedema, inflammatory infiltration and excessive mucus secretion. In addition to airway narrowing, which is most evident during asthma attacks, in chronic asthma, structural changes resulting from tissue remodelling can also impact respiratory compliance (Mims 2015).

In this context, CA frequently manifests with the most severe forms of the alterations described earlier. Airway narrowing, resulting from thickened walls and inflammatory infiltration, may be up to 300% greater than normal (James 2020), accompanied by significant smooth muscle hypertrophy and excessive mucus production, which can lead to airway obstruction. Lung hyperinflation and severe ventilation/perfusion mismatch are primary contributors to impaired oxygenation and hypoxaemia. This is due to poorly ventilated regions on one hand and altered perfusion from capillary leak following acute inflammation on the other (Louie et al. 2012). Incipient hypercapnia occurs when forced expiratory volume in one second (FEV1) is below

30% of the predictive value (McFadden Jr and Hejal 1995) with increased dead space (Louie et al. 2012).

Medical Therapy

Inhaled short-acting β2-agonists (SABAs) remain the primary treatment for acute asthma, with salbutamol recommended for bronchodilation, either in continuous or intermittent administration. High-dose salbutamol does not show additional benefits over lower doses. Full agonists like formoterol and isoproterenol may be useful when the response to salbutamol is inadequate, though they carry a higher risk of cardiovascular side effects. Inhaled ipratropium and tiotropium, short-acting muscarinic antagonists, enhance bronchodilation when used in association with SABAs. They act by relaxing airway smooth muscles and relieving airway narrowing. Systemic corticosteroids are essential for preventing fatal asthma by decreasing airway inflammation, reducing the recurrence of exacerbations and minimising long-term airway remodelling (Rowe et al. 2001). High doses of corticosteroids have been shown to significantly improve lung function and enhance the effectiveness of SABAs by reducing airway sensitivity. Methylprednisolone should be administered early in treatment in cases of CA, starting with 60 to 80 mg every 6 hours and then tapered as the patient improves (McFadden 2003). Magnesium sulphate inhibits calcium channels and blocks parasympathetic tone. Intravenous administration (2 g over 20 minutes infusion), when used as an adjunct to other bronchodilator treatments, has been shown to improve pulmonary function and reduce hospital readmissions (GINA committee 2024; Kew et al. 2014); however, it has not been proven to lower mortality rates (Irazuzta and Chiriboga 2017).

Advanced bronchodilator therapy for CA includes systemic β2-agonists, primarily intravenous salbutamol, especially when the use of SABAs is not feasible. Administration of parenteral adrenaline and terbutaline (subcutaneous or intravenous) can also be used when patients are unresponsive to inhaled therapy. However, they lack strong evidence and may yield potential side effects (tachycardia, tachyarrhythmias, myocardial damage and acid-base disorders) (GINA committee 2024). For this reason, current recommendations reserve their use for CA patients unable to use inhaled bronchodilators.

Oxygen Therapy

Hypoxaemia results from airway narrowing or obstruction and ventilation/perfusion mismatch. Supplemental oxygen is a standard in acute asthma management. The goal of oxygen therapy in CA is to maintain SpO_2 above 92% (GINA committee 2024). Inspired oxygen fractions ranging from 30% to 50% are typically sufficient to correct hypoxia; higher fractions should be avoided, as hyperoxia can be harmful and has been shown to increase airway responsiveness (Kallet and Matthay 2013; Rodriguez-Roisin et al. 1989). Oxygen is generally delivered via nasal cannulas or, occasionally, via face mask. If hypoxia persists despite supplemental oxygen, complications such as pneumonia or pneumothorax should be considered (Schivo et al. 2015).

Non-Invasive Respiratory Support

Non-invasive respiratory support changed the approach to respiratory failure and has been widely adopted since its introduction. While its efficacy is well-established in chronic obstructive pulmonary disease exacerbations and acute cardiogenic pulmonary oedema, the use of non-invasive support in acute asthma is still a matter of debate (Osadnik et al. 2017; Vital et al. 2013).

HFNO

High-flow nasal oxygenation (HFNO) has emerged as a promising option for CA, though evidence supporting its use in severe asthma remains limited. In a study by Geng et al. (2020), patients receiving HFNO experienced reductions in heart and respiratory rates compared to those receiving standard oxygen therapy, but no additional clinical benefits were identified.

Non-invasive ventilation

Bilevel non-invasive ventilation (NIV) is widely adopted as a non-invasive strategy in CA, although data on its efficacy are limited to few studies and benefits on mortality and prevention of intubation are not consistent (Gupta et al. 2010; Lim et al. 2012; Soroksky et al. 2003; Stefan et al. 2016).

In carefully selected patients with CA, it can be a beneficial intervention, mitigating the risks associated with invasive MV. In fact, NIV has been shown to improve lung function and gas exchange, reduce respiratory rate, decrease muscle fatigue and work of breathing connected to airway obstruction and lung hyperinflation, which can ultimately prevent the progression to respiratory failure (Brandao et al. 2009; Gupta et al. 2010; Lim et al. 2012; Soroksky et al. 2003). It has also been demonstrated to enhance the effectiveness of inhaled bronchodilators, likely by promoting a more homogeneous distribution of the medication throughout the airways (Brandao et al. 2009; Pollack et al. 1995). It has also been shown to decrease hospital length of stay, but evidence regarding its role in reducing mortality is still scarce (Manglani et al. 2021). Indeed, European Respiratory Society/American Thoracic Society guidelines on acute respiratory failure are not able to recommend the use of non-invasive support, as there is no data showing clinically relevant differences in outcomes when compared to standard care (Rochwerg et al. 2017).

Failure of non-invasive respiratory support, defined as the need for intubation, has decreased over the years, with younger patients being more likely to fail NIV and require MV (Ganesh et al. 2015). In a retrospective study by Manglani et al. (2021), failure of NIV was not associated with baseline asthma severity, body mass index and history of smoking; also, the use of NIV did not increase complications as barotrauma.

Although non-invasive respiratory support appears to be a safe option in well-selected CA patients, escalation of non-invasive devices should not delay intubation, as delay of MV initiation is associated with a worse outcome (Lim et al. 2012). Studies suggest that when respiratory rate, respiratory effort, and hypercapnia worsen in the first 1-2 hours following the start of NIV, MV should be promptly initiated. Contraindications for NIV include nausea, vomiting, altered level of consciousness, haemodynamic instability and respiratory distress or imminent respiratory arrest (Schivo et al. 2015). The intensity of respiratory support should be adjusted to the work of breathing and hypoxaemia/hypercapnia improvement.

Invasive Respiratory Support

Mechanical ventilation

Intubation and initiation of MV in asthma exacerbations is based on clinical decision, as there is no consensus on indication for intubation (Brenner et al. 2009). MV should be started when patients fail to respond to medical treatment and non-invasive respiratory support, with signs of impending muscle exhaustion, altered mental status, deteriorating hypercapnia, severe respiratory acidosis and hypoxaemia refractory to supplemental oxygenation (Gayen et al. 2024; Talbot et al. 2024). Furthermore, the decision to intubate must weigh the potential risks associated with MV. Indeed, MV requires careful management, as it can lead to complications such as barotrauma, pneumothorax and pneumomediastinum. It can worsen dynamic hyperinflation and extend the inflammatory response, as well as increase the risk of infection (Blanch et al. 1991; Zimmerman et al. 1993). Additionally, increased intrathoracic pressure may result in new or worsened haemodynamic instability and increased dead space. The goals of MV include maintaining adequate oxygenation, relieving respiratory effort, reducing dynamic hyperinflation, avoiding barotrauma and preventing severe acidaemia (Oddo et al. 2006).

Endotracheal intubation in CA patients can be challenging and should be made electively whenever possible. Asthma patients are more likely to experience laryngospasm and aggravating bronchospasm, haemodynamic instability and pulmonary aspiration following intubation (Brenner et al. 2009). Hypotension is common, especially in patients who are hypovolaemic due to insensible losses (Garner et al. 2022). Rapid sequence intubation is generally recommended, and bag ventilation should be avoided as it can lead to excessive hyperinflation and barotrauma (Brenner et al. 2009; Garner et al. 2022). Endotracheal tubes should be 0.5-1 size larger than standard to reduce airway resistance and facilitate bronchial aspiration and bronchoscopy (Adams et al. 2012; Burburan et al. 2007).

General anaesthesia with deep sedation and neuromuscular blockade might be necessary to increase patient-ventilator synchrony and lower the metabolic requests, e.g. in patients with high respiratory drive (Burburan et al. 2007; Louie et al. 2012). Indeed, CA patients are prone to dyssynchronies, as ineffective triggering when intrinsic PEEP requires a greater effort to trigger the ventilator (Demoule et al. 2020). In addition, some anaesthetic agents, such as propofol and ketamine, can reduce bronchospasm.

Ventilator settings should be targeted to optimise asthma underlying pathophysiology and lung mechanics alterations. The optimal ventilation mode is not established and should be adapted to each patient, to guarantee patient-ventilator synchrony. Both assisted and controlled ventilation modes can be utilised in the early phase of CA, and no specific mode has proven to be superior (Demoule et al. 2020). A low-minute ventilation strategy, through low tidal volume (6-8 ml per kg of predicted body weight) and low respiratory rate (8-10 breaths/min), is suggested to avoid high peak and plateau pressure (Pplat below 30 cmH2O), in combination with prolonged expiratory time (I:E of 1:3 or 1:4) to facilitate expiration and prevent air trapping (Brenner et al. 2009; Leatherman 2015). A low PEEP level should be set below 5 cmH_2O, with serial measurements of auto-PEEP. SpO_2 should be maintained above 92%, avoiding hyperoxia, initially setting the inspired fraction of oxygen (FiO_2) at 100% and then titrating it below 50% (Leatherman 2015). Complications, such as pneumonia, pulmonary oedema and embolism, should be investigated if a higher FiO_2 is required after a few hours (Kallet and Matthay 2013). Permissive hypercapnia is generally tolerated. Indeed, it is crucial to emphasise that correct gas exchange is not the priority in the early phase of MV; instead, maintaining a pH between 7.25-7.30 is sufficient (Darioli and Perret 1984), with greater attention on preventing complications from hyperinflation. Dynamic hyperinflation, in fact, occurs when the patient is not able to exhale completely between one breath and the other, due to a decreased expiratory flow and an increased expiratory effort. Hyperinflation causes overdistention and increased Pplat (airway pressure at end-inspiration), bearing the risk of barotrauma, pneumothorax, pneumomediastinum and cardiovascular collapse. Therefore, it must be assessed regularly (Demoule et al. 2020) by measuring Pplat; a cut-off of 30 cmH_2O of Pplat is considered as safe.

Additional Strategies

Patients with CA refractory to conventional treatment despite optimal MV, with declining lung function, persistent bronchospasm and dynamic hyperinflation with high intrinsic PEEP, worsening gas exchange and severe acidosis may be targeted to additional therapies, including extracorporeal CO_2 removal.

Extracorporeal CO_2 removal is considered a life-saving intervention and has shown benefits in the most severe cases of CA, particularly in patients with a pH <7.2, severe dynamic hyperinflation, and compromised haemodynamics (Patel et al. 2020; Tajimi et al. 1988). In a cohort of 24 CA patients treated with extracorporeal CO_2 removal, survival was significantly higher compared to patients with refractory CA (Mikkelsen et al. 2009). However, the use of extracorporeal circulation comes with increased risks, including sepsis, thrombosis, haemorrhage, and organ failure, and its implementation may not be feasible in all centres.

Conflict of Interest

None.

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