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Critical Asthma Syndrome in the ICU

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Abstract Critical asthma syndrome represents the most severe subset of asthma exacerbations, and the critical asthma syndrome is an umbrella term for life-threatening asthma, status asthmaticus, and near-fatal asthma. According to the 2007 National Asthma Education and Prevention Program guidelines, a life-threatening asthma exacerbation is marked by an inability to speak, a reduced peak expiratory flow rate of <25 % of a patient's personal best, and a failed response to frequent bronchodilator administration and intravenous steroids. Almost all critical asthma syndrome cases require emergency care, and most cases require hospitalization, often in an intensive care unit. Among asthmatics, those with the critical asthma syndrome are difficult to manage and there is little room for error. Patients with the critical asthma syndrome are prone to complications, they utilize immense resources, and they incite anxiety in many care providers. Managing this syndrome is anything but routine, and it requires attention, alacrity, and accuracy. The specific management strategies of adults with the critical asthma syndrome in the hospital with a focus on intensive care are discussed. Topics include the initial assessment for critical illness, initial ventilation management, hemodynamic issues, novel diagnostic tools and interventions, and common pitfalls. We highlight the use of critical care ultrasound, and we provide practical guidelines on how to manage deteriorating patients such as those with pneumothoraces. When standard asthma management fails, we provide experience-driven recommendations coupled with available evidence to guide the care team through advanced treatment. Though we do not discuss medications in detail, we highlight recent advances.

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Introduction

Adult asthma is commonly encountered in the medical system. Most asthma that comes to clinical attention is managed either out of the hospital or in the emergency department (ED). A subset of asthma exacerbations, however, is severe and requires hospitalization. Of the 2 million cases of adult asthma seen in the ED, approximately 25,000–50,000 require intensive care unit (ICU) level care, though most of these are not intubated or mechanically ventilated [1, 2]. Another study identified that out of 33,000 cases of asthma requiring hospitalization, 10.1 % required ICU level care and 2.1 % required intubation and mechanical ventilation [3]. It is known that these severely ill patients consume higher healthcare resources, spend more days in the hospital, and have increased morbidity and mortality [3, 4]. Despite an overall decrease in asthma-related deaths in the USA, mortality is still elevated and differentially affects women and black Americans [5].

Critical asthma syndrome (CAS) is an umbrella term used to define a severe and sudden deterioration of asthma control that requires aggressive and urgent treatment, and often CAS runs the threat of respiratory failure. CAS is synonymous with life-threatening asthma, status asthmaticus, and near-fatal asthma, and most CAS requires intensive care unit admission. CAS is recognized by deteriorating vital signs and clinical appearance of an asthma patient regardless of underlying asthma severity. The National Asthma Education and Prevention Program (NAEPP) defines life-threatening asthma as an inability to speak, a reduced peak expiratory flow rate (PEFR) of <25 % of a patient's personal best, and a failed response to frequent bronchodilator administration and intravenous steroids [6].

Whether respiratory failure develops in CAS, all asthmatic patients admitted to an ICU require specialized care by pulmonologists, intensivists, respiratory therapists, and critical care nurses trained to recognize the unique features of CAS and identify the potential complications of CAS should they arise. Here we discuss the management of CAS in the hospital with a focus on ICU care. We explore the unique features of CAS including adjuncts to standard short-acting bronchodilators and systemic anti-inflammatories, the use of point-of-care testing to assist in management, and the pitfalls of ventilating the severely obstructed patient.

Initial ICU Assessment

It is incumbent for ICU providers and critical care action teams to make a thorough and accurate, yet rapid, assessment of all asthma patients. CAS patients present with a myriad of respiratory and hemodynamic derangements, and a systematic approach to the initial assessment and treatment is essential to avoid fatal asthma. We outline our bedside approach for CAS at the University of California, Davis Medical Center and highlight pitfalls that lead to unwanted complications. Rapid assessment of the airway and the likelihood of cardiopulmonary collapse using vital signs, physical examination findings, and laboratory data are all key steps.

Airway Management and Complications

The first step is to identify whether acute respiratory failure is imminent in the next 20 to 30 min in the CAS patient. Physical examination signs of impending respiratory failure include: inability to speak, upright posture, use of accessory muscles of respiration, and, paradoxically, minimal wheezing (indicating an impending loss of air movement) [7]. These patients can quickly progress to respiratory failure—lethargy, loss of wheezing, cyanosis, and reduced or paradoxical respiratory efforts—requiring emergent airway management with endotracheal intubation. Less obvious is the CAS patient who is awake but whose course is expected to decline. This includes patients with worsening hypercarbia, a failure to respond to short-acting bronchodilator therapy, and early signs of respiratory exhaustion (i.e., progressively shallow respirations, weakness, and progressive loss of alertness). In general, CAS patients who are in respiratory arrest or imminent respiratory failure should undergo emergent endotracheal intubation using rapid sequence intubation (RSI) with the largest diameter endotracheal tube available appropriate for the size of the patient [8]. A large endotracheal tube (e.g., 8.0 mm internal diameter for most average-sized adults) will facilitate airway suctioning, mucous plug removal, and fiberoptic bronchoscopy examination. The decision to intubate depends on a number of factors including available staff (i.e., intensivist, anesthesiologist, etc.), resources, and patient condition. Figure 1 provides a suggested algorithm for most practitioners, though specialized techniques such as bronchoscopy intubation will require trained operators. Though many CAS patients will be intubated in the ED, some may arrive from the floor and require intubation upon presentation to the ICU. If the CAS patient is awake but demonstrating a declining ICU course (e.g., failing bronchodilator therapy for >20 min, requiring increasing staff care, showing a worsening respiratory acidosis, or showing signs of increasing fatigue), early elective intubation is appropriate. This may be accomplished through RSI or through fiberoptic techniques such as an endotracheal tube over a bronchoscope. Intubation without the use of induction or neuromuscular blocking agents will avoid the side effects of these medications and allow the patient to provide assistive respiratory efforts. As with all non-standard intubation techniques, expertise is required.

Non-invasive positive pressure ventilation (NPPV) has been used in selected patients with asthma exacerbations. Advantages to NPPV are reduced rates of barotrauma, improved patient comfort, and reduced rates of nosocomial infections compared to invasive mechanical ventilation after endotracheal intubation [9]. A case series demonstrated that NPPV improved gas exchange and reduced rates of endotracheal intubation [10], and a retrospective review of asthma cases treated with NPPV showed an intubation rate of only 14 % [11]. Randomized trials looking at NPPV in CAS are few. Two small studies showed decreased rates of hospital admission [12] and ICU/hospital length of stay [13] for those asthmatics treated with early NPPV. Though the data is supportive, larger studies showing a benefit of NPPV in CAS are needed before this modality will become a standard recommendation. This is reflected in a recent Cochrane systematic review which only identified 206 subjects for inclusion and concluded that there is not enough rigorous data to support NPPV in acute asthma exacerbations [14] compared to NPPV use in acute exacerbations of COPD. NPPV should be discontinued promptly whenever rapid clinical deterioration or a failure to improve pH, $PaCO_2$, or oxygenation within 2 h occurs. RSI should be done and invasive mechanical ventilation begun. NPPV is contraindicated in vomiting, obtunded, or combative patients, and in those who develop imminent or overt respiratory failure.

Endotracheal Intubation and Complications

Important considerations in the CAS patient include their hemodynamic status, hypercarbia, and other concurrent conditions at the time of intubation. They often have intravascular volume depletion due to a tremendous work of breathing with accompanying tachypnea and diaphoresis resulting in significant insensible volume loss. Conditions such as sepsis may compound hemodynamic compromise.

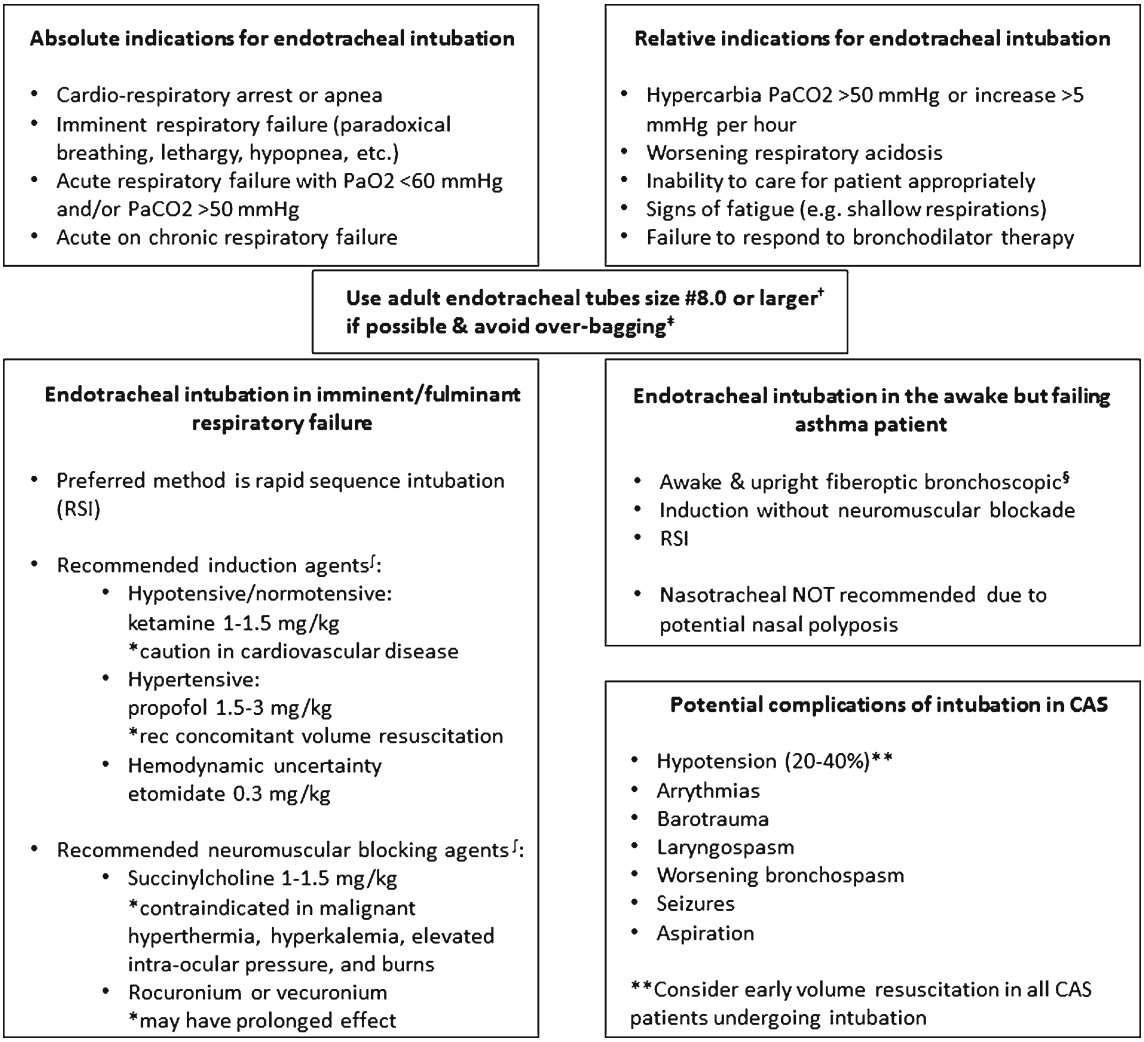

Fig. 1 Indications and recommendations for endotracheal intubation in critical asthma (CAS). Note that these are general guidelines and any decision to perform endotracheal intubation should be made on a customized basis. All intubations should be performed by skilled and qualified practitioners as a patient with CAS's respiratory and hemodynamic status is often tenuous. *dagger* Larger endotracheal tubes facilitate improved ventilation, suctioning, and bronchoscopy. Many CAS patients are at risk for mucous plugging and require frequent suctioning. *double dagger* Overly aggressive ventilation with a bag-value mask or through an endotracheal tube can lead to barotrauma; slow, even bagging is preferred. *integral symbol* A thorough understanding of induction and neuromuscular blocking agents is necessary before administering rapid sequence intubation. A full discussion of these drugs is beyond the scope of this review. *section sign* The decision to perform an awake, upright fibrotic intubation should be made on a customized basis and requires a skilled bronchoscopist or anesthesiologist. One advantage of this of intubation in the awake but failing patient with CAS is allowing spontaneous respirations and avoiding side effects of induction or neuromuscular blocking agents. *double asterisks* Early volume resuscitation may attenuate post-intubation hypotension and possibly other complications (e.g., arrhythmias). Most CAS patients have some degree of intravascular volume depletion due to overwhelming insensible loss: tachypnea, diaphoresis, etc. Dynamic hyperinflation and increased intrathoracic pressures may impair right-sided cardiac venous return, thus volume resuscitation may help

Because of the increased intra-thoracic pressure incurred through airway obstruction and dynamic hyperinflation, CAS patients may become hypotensive from impaired right-heart venous return. Endotracheal intubation may precipitate hypotension through increased intra-thoracic pressure from positive pressure ventilation and a loss of adrenergic vascular tone due to sedation and induction [15]. Preemptive restitution of intravascular volume is essential. Therefore, we recommend an initial bolus of normal saline (500 mL or 20 mL/kg) given rapidly before and during endotracheal intubation. As CAS patients may have hypercarbia due to their airflow obstruction, hypoxemia from ventilation/perfusion (V/Q) defects may soon follow. We define hypoxemia in this population as a SpO_2 <92 % or a PaO_2 <60 mmHg. It is important to remember that acute respiratory acidosis is a late finding in CAS patients who are about to develop respiratory arrest whereas acute respiratory alkalosis occurs early during a severe exacerbation. This mandates that endotracheal intubation be quick and efficient

as hypoxemia and acidemia leaves CAS patients with little room for error.

In addition to arrhythmias, laryngospasm, worsening bronchospasm, seizures, and pulmonary aspiration, one must be vigilant for post-intubation pneumothorax or pneumomediastinum. Though pneumothorax or pneumomediastinum in adult asthmatics is uncommon (only 2 % of those presenting to an ED in one study [16] and 6.1 % of intubated asthmatics over 10 years in another single center [17]), they can be rapidly fatal post-intubation. These barotraumas are thought to be due to elevated intra-thoracic pressures and hyperinflation leading to distal airway and parenchymal injury [2]. Air may track along the bronchovascular bundle into the central chest in the case of pneumomediastinum, and distal airways may rupture due to over-distention leading to pneumothorax and tension pneumothorax when mechanically ventilated. Physical examination clues include tracheal deviation away from the affected side, anterior chest or neck crepitus, a unilateral loss of lung sounds, tachycardia, hypotension, and central cyanosis. Chest computed tomography (CT) is the gold standard for diagnosing pneumothorax, though point-of-care bedside critical care ultrasound is emerging as a diagnostic tool [18]. The advantages to bedside ultrasound include rapid and real-time diagnosis, a reliable sensitivity in trained hands, and minimal harm related to ultrasound. Table 1 provides a summary of studies comparing critical care ultrasound to chest CT and chest radiography (CXR) in diagnosing pneumothorax. Figure 2 shows two ultrasound images of a normal lung and a pneumothorax. We recommend utilizing point of care ultrasound in the management of CAS in general and for rapid diagnosis of pneumothorax specifically. If ultrasound is not immediately available, the clinical situation suggests a tension pneumothorax, and the CAS patient is rapidly deteriorating, we recommend empiric placement of a chest tube for decompression *before* obtaining a CXR.

Vital Signs and Physical Examination

CAS patients almost universally have vital sign abnormalities upon admission to an ICU. Tachycardia >120 beats per minute and tachypnea >30 breaths per minute are commonly seen [19]. Some may have hypertension [20], likely owing to high adrenergic tone, though hypotension may develop as dynamic hyperinflation and increased intra-thoracic pressures attenuate right heart venous return. As described above, many CAS patients have intravascular volume depletion due to insensible fluid losses. Hypotension and tachycardia may be among the first clues to this, and expectant management with volume resuscitation is paramount. Mountain and colleagues identified that asthmatics with hypercapnia versus normocapnia during an exacerbation had wider degrees of pulsus paradoxus (23 vs. 14 mmHg), likely reflecting dynamic hyperinflation and volume status [21]. A low pulsus paradoxus should alert physicians to the presence of severe hyperinflation which can cause extracardiac tamponade. Atrial and supraventricular arrhythmias are frequently seen in stable asthmatics [22], and it is very possible to see arrhythmias during an exacerbation where patients receive high-dose beta-2-agonists and develop electrolyte abnormalities, e.g., hypokalemia [23].

Other Physical Examination Findings

The remainder of the physical examination should focus on identifying triggers of CAS, complications of CAS and their management, and mimics of CAS. Examples of triggers of CAS include pulmonary infections with viral or bacterial pathogens, sepsis, pulmonary aspiration, gastroesophageal reflux, inhaled foreign body, ischemic cardiac disease, and anaphylactoid or anaphylactic reactions to drugs or foods. For example, if a CAS presents with a purulent cough, a prompt search for a pulmonary infection is mandatory as CAS without an infection does not usually present this way. Indications of

Table 1 Performance of bedside ultrasound to indentify pneumothorax

Paper	Reference	Comparison	*n*/*N*	Sensitivity	Specificity	PPV	NPV	DA
Fragou	CXR	CCUS	37/100	99.0	100.0	n/a	n/a	n/a
Galbois	CT	CCUS	44/44[a]	100.0	90.9	97.1	100.0	97.7
		CXR		60.6	100.0	100.0	64.9	70.5
Zhang	CT	CCUS	29/135	96.2	97.2	89.3	96.3	94.8
		CXR		27.6	100.0	100.0	83.5	84.4
Soldati	CT	CCUS	25/218[a]	92.0	99.5	95.8	98.9	98.6
		CXR		52.0	100.0	100.0	94.1	94.5
Rowan	CT	CCUS	11/27	100.0	93.8	91.7	100.0	96.3
		CXR		36.4	100.0	100.0	69.6	74.1
Xirouchaki	CT	CCUS	8/84[a]	75.0	93.4	54.5	97.3	91.7
		CXR		0.0	98.7	0.0	90.4	89.3
Lichtenstein	CXR/CT	CCUS	9/260	88.9	100.0	100.0	99.6	99.6

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n/*N* number affected/number in study, *PPV* positive predictive value, *NPV* negative predictive value, *DA* diagnostic accuracy

[a] *n*/*N* in terms of lung regions or hemithoraces rather than patients

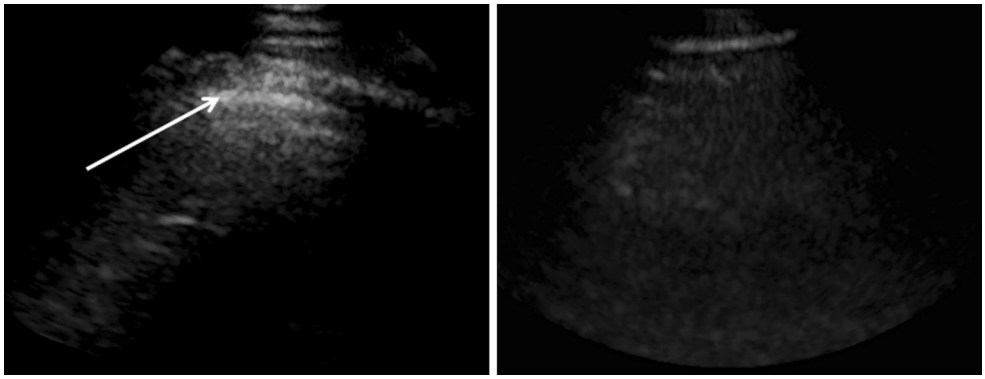

Fig. 2 Bedside critical care ultrasound images of a normal inflated lung (*left*) and a pneumothorax (*right*). In the normal lung, a shimmering horizontal line is seen (*white arrow*) indicating that the visceral and parietal pleura are together. In real-time bedside critical care ultrasound, the horizontal line would be sliding as the visceral pleura is sliding against the parietal pleura. In the image showing the pneumothorax, there is a loss of apposition between the pleural surfaces, and no sliding lung is seen

an aspirated foreign body (i.e., a tooth in a patient who fell) may include broken teeth and a radio-opaque structure seen on plain chest imaging. Complications of CAS may include pneumothorax or pneumomediastinum, which likely occur as intra-thoracic pressures increase. Findings of tracheal deviation, diminished unilateral breath sounds, crepitus on the anterior chest, and progressive hypotension may be seen. Inspissated mucous plugs are common in asthma may cause atelectasis with its associated physical examination findings. Early recognition of these complications is essential when caring for CAS patients.

Several conditions may mimic asthma and a brief survey to help identify these is useful. In fact, up to 10 % of ICU admissions for asthma may be misdiagnosed [24]. Identification of the site of wheezing (i.e., upper airway, lower airway, or focal) may provide clues to alternate or concomitant diagnoses (see Table 2). Vocal cord dysfunction is commonly mistaken for asthma and can present as CAS [25, 26]. Patients may demonstrate stridor over the trachea without associated lower airway wheezing. Flow–volume loop assessment, if a patient is able to perform this, will typically demonstrate a truncated (flattened) inspiratory limb. The gold standard diagnostic evaluation is laryngoscopy which can be performed via a flexible fiberoptic laryngoscope at bedside with minimal risk. This would reveal abnormally adducted vocal cords with a posterior "chink" evident upon inspiration. Other mimics of CAS, which are also triggers, include myocardial ischemia and an aspirated foreign body.

Initial Laboratory, Spirometry, and Imaging Tests

Arterial blood gas (ABG) measurement is essential in the management of CAS patients. ABGs provide important information of gas exchange including a CAS patient's ability to ventilate ($PaCO_2$) and oxygenate (PaO_2). They also help to determine if concomitant acid–base disturbances are present including a metabolic acidosis (lactic acidosis, or other metabolic acidosis), metabolic alkalosis (resulting from intravascular volume depletion), or respiratory alkalosis (pulmonary embolism). ABGs should be checked immediately after a CAS patient presents to the ICU and routinely thereafter. We suggest placing intra-arterial catheters to facilitate frequent ABG draws, particularly during the first few hours and days. The most common ABG abnormality seen in CAS patients is an acute respiratory alkalosis [27], though after the PEFR falls below 30 % predicted, hypercarbia and a respiratory acidosis develop [28]. A "normal" ABG seen in a CAS patient who demonstrates an increased work of breathing is an ominous

Table 2 Non-asthma causes of wheezing which may complicate or mask critical asthma syndrome

Upper airway/extra-thoracic	Central airways	Lower airways
Anaphylaxis	Tracheal stenosis	Bronchiectasis/COPD
Vocal cord dysfunction	Tracheo-bronchial tumors	Bronchiolitis
Other vocal cord (e.g., edema)	Tracheo-bronchiomalacia	Bronchiolitis obliterans
Laryngeal stenosis	Relapsing polychondritis	Cardiac
Laryngocoele	Tracheobronchial amyloid	Carcinoid
Tonsillar hypertrophy	Mucous plugging	Parasitic infections
Epiglottic swelling	Vascular rings	Vasculitis[a]
Goiter	Mediastinal masses	Anatomic airway distortion[b]
		Focal wheezing[c]

[a] Churg-Strauss syndrome or endobronchial Wegener's

[b] As may result from sarcoid, pulmonary fibrosis, etc.

[c] Aspirated foreign body, bronchial tumors, congenital cysts, etc.

signal that respiratory arrest is imminent, as illustrated in Table 3.

PEFR and bedside spirometry may help identify degrees of airflow obstruction in acute asthma exacerbations in non-intubated patients. These studies are often not obtained in CAS patients with impending respiratory failure as they generally cannot perform the required maneuvers. However, CAS patients will often have values similar to patients with NAEPP-defined life-threatening values, namely an FEV1 or PEFR <25 % predicted [6]. Serial measurements can aid in assessing therapeutic response. In addition, the flow–volume loops may reveal extra-, intra-thoracic, or fixed obstructions that provide clues to alternate or additional diagnoses (see Table 2).

Chest imaging, most commonly portable plain chest radiography, may provide important clues in CAS and should be performed upon ICU admission if not already done in the ED. Mostly, CXRs in acute asthma exacerbations are normal or show hyperinflation or minor subsegmental atelectasis [29]. In <5 % of cases, CXRs show other abnormalities including infiltrates and pnenumothoraces. Given the high morbidity associated with severe asthma, especially CAS which presents to the ICU, CXR is a potentially high-yield study with minimal downside. If a CAS patient develops respiratory failure requiring intubation and mechanical ventilation, CXR will be helpful for identifying endotracheal tube position and developing infiltrates. However, if a CAS patient is rapidly deteriorating and the clinical situation suggests a tension pneumothorax, empiric chest tube placement should *precede* CXR.

As discussed previously, bedside critical care ultrasound is becoming a routine procedure in the ICU, and its use in CAS is no exception. In CAS the most obvious use of critical care ultrasound is to assist in determining if a pneumothorax is present, especially in the decompensating CAS patient (see Fig. 2). In fact, point-of-care ultrasound is more sensitive for pneumothorax in the supine patient than CXR (see Table 1), likely owing to the fact that portable CXRs may miss anterior or loculated pneumothoraces [30]. Critical care ultrasound is generally available rapidly and can be used by non-technicians (i.e., trained intensivists and house staff). Bedside critical care ultrasound has many other uses including identification of pleural effusions, atelectasis, and consolidations which may complicate CAS [31]. Additionally, bedside ultrasound can assist in determining intravascular volume status both in spontaneously breathing and mechanically ventilated patients [32]. This is of particular interest in the CAS patient as volume status is often compromised and augmented by high intra-thoracic pressures.

Other laboratory and bedside testing should be utilized as suspected by the patient's presentation. For example, ECGs are useful in middle-age to older adults, especially since CAS promotes a tremendous catecholamine surge and may potentiate cardiac ischemia or arrhythmias. Blood count testing may indicate an infection, and particular attention should be given to the absolute eosinophil count greater than 1,500 cells/mm^3, which may alert the intensivist to allergic bronchopulmonary aspergillosis, helminthic infection (Loeffler's syndrome), or eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Chemistries may reveal electrolyte disorders and an elevated creatine kinase and give clues to concomitant disorders including hyperglycemia, renal dysfunction, and metabolic acidosis.

Table 3 Example arterial blood gas (ABG) measurements seen in the initial evaluation of CAS

ABG values[a]	Comment
pH 7.50, $PaCO_2$ 28, PaO_2 98	Acute respiratory alkalosis with normal oxygenation
	Appropriate response to CAS
pH 7.42, $PaCO_2$ 38, PaO_2 98[b]	Mild respiratory alkalosis with normal oxygenation
	Respiratory fatigue
pH 7.36, $PaCO_2$ 45, PaO_2 95	Mild respiratory acidosis with normal oxygenation
	Impending respiratory failure
pH 7.30, $PaCO_2$ 52, PaO_2 88	Acute respiratory acidosis with widening A-a gradient
	Respiratory failure

[a] Assume all measurements are on room air

[b] This ABG appears "normal", though in CAS this signifies respiratory fatigue and/or severe bronchospasm leading to inadequate ventilation

Ongoing ICU Care

After the initial assessment is complete and acute issues are addressed, CAS must be monitored closely in the ICU. Therapy with bronchodilators and systemic anti-inflammatory agents ideally starts in the ED or the hospital ward, and these should be continued and reassessed for effectiveness. Volume status should be monitored frequently either by clinical examination, central venous catheter if needed, bedside ultrasound of the inferior vena cava, or a combination of these modalities. Resuscitation should aim to maintain adequate perfusion and cardiac output, though indiscriminant and aggressive hydration is not recommended [6]. Serial ABGs should be checked to determine if the CAS patient is deteriorating with respect to gas exchange. This is important for both intubated and non-intubated CAS patients. For CAS patients on mechanical ventilation, optimization based on flow–volume loop assessment and ABG analysis is critical. If the CAS patient's response to treatment is poor, the pulmonologist and intensivist

should consider advanced treatment strategies including anesthetic medications and potentially extra-corporeal CO_2 removal ($ECCO_2R$). It is important to remember that managing CAS, especially CAS patients who are poorly responsive to therapy, requires frequent reassessment and revision to the treatment strategy. We discuss several of these treatment paradigms next.

Oxygen

Many CAS patients will have some degree of hypoxemia, largely due to hypercapnia and V/Q mismatching. A PaO_2 level below 55 mmHg is uncommon and should prompt a search for additional processes (e.g., intrapulmonary shunt from a pneumonia or atelectasis) [33]. Supplemental oxygen should be administered to correct underlying V/Q mismatch, but providing of excessive levels of oxygen may be harmful [34]. In general, using a fractional percent of inspired oxygen between 30 and 50 % should correct hypoxemia associated with CAS. If not, a search for additional causes of hypoxemia is mandated (e.g., pneumothorax, pulmonary aspiration, or acute pneumonia).

Short-Acting Bronchodilators

Short-acting bronchodilators are the initial therapeutic mainstay for acute asthma treatment, including CAS [2]. Multiple delivery routes exist including nebulization, metered-dose inhaler (MDI) of dry powder, subcutaneous, and intravenous. Most *non-intubated* CAS cases will require nebulized beta-2-agonists as this mode does not require a coordinated breathing effort for effective drug delivery. This is the delivery route of choice in CAS during the first several hours to days until the patient can tolerate using an MDI. In the non-intubated CAS patient, continuous instead of intermittent beta-2-agonist may be a superior choice. Continuous delivery may confer a more rapid clinical improvement and reduced personnel utilization compared to intermittent dosing, even for similar amount of drug used [35]. The question of high- versus lower-dose albuterol in acute asthma was addressed by Emerman et al. in 160 ED cases of acute asthma of varying severity [36]. No benefit in lung function change or hospital admission rate was seen between groups receiving 2.5 vs. 7.5 mg of albuterol, though CAS patients were underrepresented. In acute asthma exacerbations, adding a continuous short-acting antimuscarinic to a beta-2-agonist may not improve outcomes in ED patients [37], though in other patients dual therapy may improve hospitalization rates [38]. Similarly, limited data suggest that adding intravenous to inhaled beta-2-agonist does not confer benefit in adults [39]. Intravenous or subcutaneous (SQ) beta-2-agonists, such as epinephrine or terbutaline, are not routinely used for bronchospasm in adult ICUs in the USA [6]. However, they may be appropriate in the patient failing inhaled therapy or whose bronchospasm is so severe that inhaled bronchodilators cannot deposit into the airways. See Table 4 for drug dosages. In this group, there is some data that using a helium–oxygen (Heliox) gas mixture to deliver bronchodilators may improve drug deposition [40].

Intubated CAS patients should receive short-acting bronchodilators through the ventilator circuit, either in nebulized or MDI forms [41]. In our experience, MDIs inserted into the ventilator circuit is an effective and quick way to deliver bronchodilators, though MDIs cannot provide continuous medications. We recommend four to six puffs of MDIs every 1–2 h initially with a taper as the CAS patient improves.

Systemic Corticosteroids

Systemic corticosteroids are the other therapeutic mainstay in CAS treatment that should be given as soon as possible during CAS. Their use improves several outcomes including lung function, rates of hospitalization, death, and relapse after discharge [42, 43]. As corticosteroids exert their effects slowly, between 6 to 24 h, they should be given up front. Most guidelines suggest that lower doses of corticosteroids are appropriate for mild and moderate asthma exacerbations, though in the CAS population, we recommend very early use. This recommendation is supported by a small randomized blinded study where patients with status asthmaticus were given low-, medium-, and high-dose methylprednisolone upon admission to the hospital [44]. The groups receiving the high- and medium-dose steroids had significantly improved lung function after 24 and 48 h, respectively. There were minimal medication side effects. Our practice is to give 60 mg intravenous methylprednisolone every 6 h for at least 24 h [2]. If there is clinical improvement, this dose is reduced to 60 mg every 12 h for the next 2 days until the patient is switched to oral prednisone at 1 mg/kg/day with a maximum of 60 mg. Following this, the patients are placed on a 10–14-day steroid taper.

Leukotriene Receptor Antagonists

Montelukast, a leukotriene receptor antagonist, is currently used for long-term control of asthma but its use in CAS in

Table 4 Adult dosing of subcutaneous terbutaline and epinephrine for the refractory CAS patient

Drug	Dose	Comment
Terbutaline (1 mg/mL)	0.25 mg every 20 min up to 3 doses	No proven advantage of systemic over aerosolized therapy
Epinephrine 1:1,000 (1 mg/mL)	0.3–0.5 mg every 30 min up to 3 doses	No proven advantage of systemic over aerosolized therapy

particular is less well described. Montelukast has been used via the intravenous [45, 46] and oral routes [47, 48] in acute asthma. Intravenous montelukast appears to improve lung function when added to standard therapy compared to placebo in moderate to severe asthma exacerbations [46]. Though this study did not assess the ICU use of IV montelukast, the benefit contributed by the addition of montelukast alone and the large sample size ($N=583$ adults) provide compelling evidence that montelukast will confer additional benefits. Further study in a critically ill CAS group is needed. Oral montelukast preparations improved PEFR in hospitalized acute asthmatics when given daily [48], though other studies found no difference [47].

Magnesium

Magnesium acts as a smooth muscle bronchodilator by inhibiting calcium channels and blocking parasympathetic tone, and it may have anti-inflammatory properties. Intravenous magnesium is currently recommended by the NAEPP EPR-3 as adjunct therapy to those patients failing standard bronchodilator and corticosteroid therapy [6]. A recent meta-analysis assessed the roles of both intravenous and inhaled magnesium on lung function and hospitalization in acute asthma [49]. Sixteen trials using intravenous magnesium and nine using nebulized magnesium were assessed, comprising a total of 1,754 adults and children. Though there was significant heterogeneity between studies, the authors identified a small but significant improvement in lung function in adults with intravenous magnesium. They also identified significant improvements in lung function and hospital admissions in adults with nebulized magnesium. An older meta-analysis supports the use of intravenous magnesium in severe exacerbations due to a reduction in hospitalization [50]. Powell et al. assessed nebulized magnesium for the treatment of acute asthma in a recent Cochrane systematic review and meta-analysis [51]. They identified ten of 16 trials that included inhaled magnesium for the treatment of adult acute asthma, and there was considerable heterogeneity between study design and outcome measures. Lung function changes and hospital admission rates did not appear to change when nebulized magnesium was added to or compared to inhaled short-acting beta-2-agonists. The authors concluded that the evidence was insufficient to recommend inhaled magnesium. Overall, intravenous magnesium sulfate is a reasonable adjunct therapy in CAS when other standard therapies are failing, and we suggest 1–2 g given over 20 min.

Therapies Not Currently Recommended: Methylxanthines, Heparin, and Furosemide

Methylxanthines, including aminophylline and theophylline, are not recommended as front-line therapy in CAS [52]. Their toxicity profile makes them unsuitable, though there is data suggesting anti-inflammatory and bolstered corticosteroid response with methylxanthines [53]. Future use in CAS, particularly in corticosteroid-resistant CAS, may become important. Inhaled heparin [54, 55] and furosemide [56] have been proposed as adjunct agents in asthma due to their anti-inflammatory effects [57]. To date, no convincing clinical data has emerged regarding these treatments in CAS, and at present we do not recommend them outside of an experimental setting.

Mechanical Ventilation

Around 2 % of CAS patients will go on to develop respiratory failure and require mechanical ventilation. Unlike other forms of respiratory failure, CAS patients have unique considerations that must be fully understood by the ICU team to optimize management. The goals of mechanical ventilation in the CAS patient are to decrease work of breathing, reduce dynamic hyperinflation, deliver oxygen to prevent hypoxic tissue injury, improve acidemia by improving ventilation, allow optimal delivery of bronchodilators, and prevent both volutrauma and barotrauma. In this section we describe respiratory failure and its management with mechanical ventilation in the CAS patient.

Physiology of Ventilation in CAS

Figure 3 is a representation of the abnormal ventilation present in CAS. These patients have tremendously elevated airway resistance and mucous plugging which lead to airflow obstruction. Over time, this obstruction leads to dynamic hyperinflation as gas is not able to escape the lungs. As dynamic hyperinflation progresses, inspiratory capacity (IC) and inspiratory reserve volume (IRV) fall and the functional residual capacity (FRC) increases. As IC approaches total lung capacity, inspiratory efforts are thwarted by over-stretched inspiratory muscles and a flattening diaphragm, all in the face of increased ventilatory demands. This mechanical disadvantage leads to respiratory fatigue and ultimately failure. In addition, the increased intra-thoracic pressure seen in dynamic hyperinflation may lead to impaired venous return to the right heart and hemodynamic compromise. Plus, high intra-thoracic pressures may worsen dead space by reducing blood flow to alveolar units thereby worsening ventilation (known as West zone 1 lung). As ventilation is impaired, a respiratory acidosis may develop and hypercarbia ensues. This hypoxemia may lead to brain injury, myocardial injury, and death.

After intubation and the initiation of mechanical ventilation, the pathophysiologic processes are still present. In short, intubation alone does not help the CAS patient. In fact, CAS patients may worsen immediately post-intubation as described

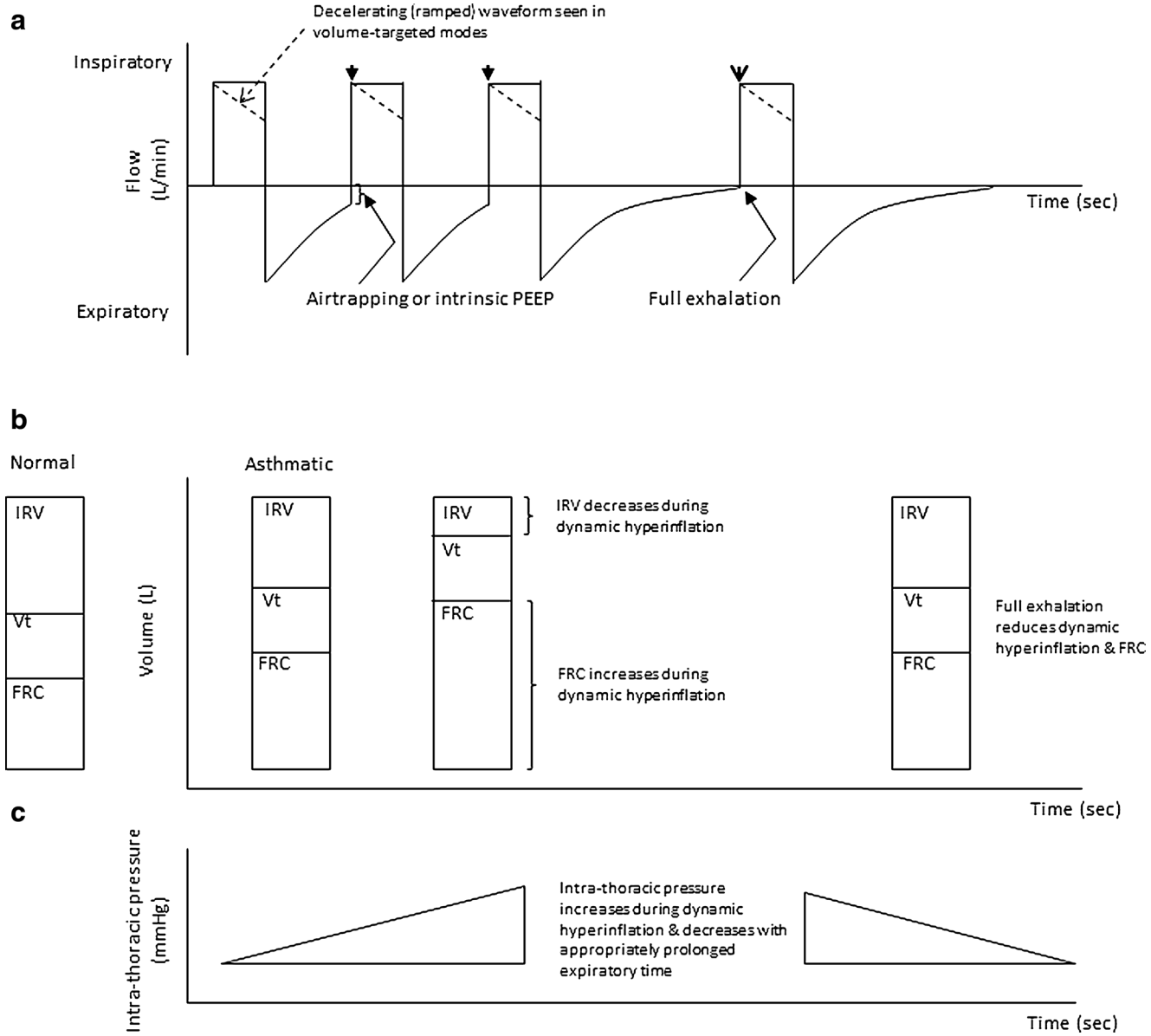

Fig. 3 **a** Flow-time graph of a mechanical ventilator in a critical asthmatic. The two breaths after the initial breath (*solid arrowheads*) are in quick succession indicating a high respiratory rate. As the patient is unable to exhale completely (i.e., persistence of expiratory flow during the subsequent inspiration), air is "trapped" causing intrinsic positive end-expiratory pressure (intrinsic PEEP). Once the respiratory rate is reduced, *open arrowheads*, the patient is allowed enough time to exhale thus diminishing the intrinsic PEEP. **b** Lung volumes of the same patient. Note as the patient has intrinsic PEEP, the FRC rises and the IRV decreases. This is called dynamic hyperinflation and can result in increases in intra-thoracic pressure, decreases in venous return, and hemodynamic compromise. Once the respiratory rate is reduced and the patient is given enough expiratory time, the FRC begins to approach normal. **c** Corresponding rise in intra-thoracic pressure seen with air trapping and increased FRC, and fall in intra-thoracic pressure seen when an appropriate expiratory time is provided. *IRV* inspiratory reserve volume, *Vt* tidal volume, *FRC* functional residual capacity

above. Simply adding positive pressure to a system with high pressures to begin with may worsen the situation. Efforts must be made to "decompress" the CAS patient by reducing dynamic hyperinflation to improve their respiratory mechanics and gas exchange. As dynamic hyperinflation is determined by minute ventilation (Ve; Ve=respiratory rate×tidal volume), inspiratory/expiratory (*I*:*E*) time, and airway resistance, a focus on these parameters becomes important.

Setting Mechanical Ventilation

In general, the initial settings on the mechanical ventilator should aim to treat the dynamic hyperinflation first and the gas exchange abnormalities second. Many physicians focus on correcting the hypercarbia and respiratory acidosis, often utilizing a high Ve strategy (respiratory rate × tidal volume). This strategy may be harmful in the CAS patient for two

reasons. First, an increased set respiratory rate in an effort to increase Ve will often lead to increasing intra-thoracic pressures in the CAS patient and actually *worsen* $PaCO_2$. This occurs because of the intrinsic positive end-expiratory pressure (PEEPi) generated when an obstructed CAS patient does not have enough time to exhale before another ventilator-delivered breath (see Fig. 3a). Second, increasing the tidal volume in order to increase the Ve may lead to unacceptably high airway pressures and potentially barotrauma.

We advocate for a low-Ve strategy to treat CAS associated with dynamic hyperinflation. Figure 3a illustrates that by *slowing* the respiratory rate, full exhalation can be achieved thereby reducing PEEPi and dynamic hyperinflation (see Fig. 3c). In general, a respiratory rate of eight to ten breaths per minute should help to achieve this, but a customized approach based on an individual CAS patient's respiratory mechanics is essential. This customized approach can be achieved for each patient by observing the flow–time curve on the ventilator and setting a rate that still allows flows to reset to zero before the next breath, if possible. Occasionally, it is necessary to *disconnect* a CAS patient from the ventilator to provide an exceptionally long expiratory time. The concomitant use of sedating medication may facilitate the goal of lowering the Ve, especially in CAS patients with a high respiratory drive. Although the NAEPP does not recommend the use of sedating medications in asthma exacerbations [6], we feel that the CAS patient on mechanical ventilation often requires it (e.g., propofol if tolerated). In addition, the application of extrinsic positive end-expiratory pressure (PEEPe; i.e., the PEEP applied by the ventilator during exhalation) may improve the CAS patient's ability to exhale by augmenting their obstruction and improving patient-ventilator dyssynchrony. In general, we recommend measuring the patient's PEEPi on the ventilator every 6 to 8 h (or more frequently up-front) and matching PEEPe to the measured PEEPi. Typically this requires 5 to 10 cm H_2O of PEEPe, though higher PEEPe early may help offload severe hyperinflation.

Once Ve is acceptably low and the CAS patient's PEEPi is minimized, the next goal is to improve CO_2 gas exchange (V-dot-CO_2, abbreviated here as VCO_2). VCO_2 will improve slightly by reducing dynamic hyperinflation, but ongoing bronchospasm and remaining high intra-thoracic pressure will confound efforts to improve VCO_2. This may be disconcerting, but CAS patients can often tolerate high levels of CO_2 (e.g., $PaCO_2$ <100 mmHg) over the first few days with surprising ease [58]. More aggressive ventilation may be required if the resulting pH is <7.20. It is unclear if a lower $PaCO_2$ is required in patients with hypoxic brain injury.

Oxygen should be given judiciously after intubation while the CAS patient equilibrates, but quickly de-escalating from a FiO_2 of 1 to 0.5 over the first few hours is appropriate. If the CAS patient requires an elevated FiO_2 (i.e., FiO_2 >0.55), the pulmonologist and intensivist should search for additional causes of hypoxemia, e.g., intrapulmonary shunts (pneumonia, atelectasis, and mucous plugging), V/Q mismatching, or pulmonary embolism (PE). Avoidance of oxygen-induced lung injury is important in CAS as with all critically ill patients [34].

When choosing an initial mode of mechanical ventilation, we recommend a semi-controlled mode rather than a support or spontaneous mode. Two such modes are volume-cycled and pressure-cycled assist-control. In these modes the ventilator delivers breaths customized by the pulmonologist and intensivist with the respiratory therapist, all of whom can manipulate respiratory rate, tidal volume, inspiratory pressure, flow rate, and I:E ratio. In the recently intubated CAS patient, these manipulations are essential. Though in an assist-control mode the patient is able to trigger breaths, often heavy sedation is required initially to alleviate dynamic hyperinflation. Once the CAS patient has improved in terms of airflow obstruction, dynamic hyperinflation, and PEEPi, a trial of a spontaneous mode is appropriate.

Whether to use a volume-cycled or pressure-cycled mode of assist-control is a matter of preference, and there are advantages and limitations to both. Volume-cycled ventilation uses a set volume target with variable peak pressures and fixed flow rates. In CAS, peak pressures can be very high when the airway resistance is increased making volume-cycled ventilation problematic. However, many ventilators allow for a decelerating flow pattern which effectively reduces the flow as the volumes increase (see Fig. 2a). Pressure-cycled ventilation allows for control of the peak inspiratory pressures, but minute ventilation is harder to control as tidal volumes may vary. Regardless of the ventilation strategy, the key to successful ventilation in CAS is frequent assessment of the flow–time curves to assess for PEEPi and dynamic hyperinflation (see Fig. 3a).

With proper and vigilant ventilation in conjunction with bronchodilators and corticosteroids, most CAS patients will improve on the ventilator in 24 h. In general, CAS patients will require an average of 3 days on mechanical ventilation [2], though some will follow a refractory course [59]. The next sections discuss the refractory CAS patient and adjunct measures to aid in bronchodilation and ventilation.

The Refractory CAS Patient

In CAS patients who have persistent hypercapnea, bronchospasm, and dynamic hyperinflation with elevated PEEPi despite receiving all of the medications listed above and optimal mechanical ventilator settings, there are some potentially effective adjunct therapies.

Helium–Oxygen

NAEPP guidelines recommend considering helium–oxygen (Heliox) mixtures when patients are failing standard therapy [6]. Heliox decreases turbulent airflow in the large airways and it may have benefit in smaller obstructed airways [60]. Because helium is non-soluble in blood or human tissues, Heliox has minimal toxicity. A Cochrane systematic review identified ten trials of which seven included adults with acute asthma and three were of high quality [61]. The authors concluded that Heliox may confer benefit in lung function in severe asthma exacerbations, but numbers were small in this group. Nevertheless, Heliox is a viable choice in the failing CAS patient as it may improve airflow, ventilation, and drug delivery [40]. Practical considerations when choosing Heliox include patient oxygenation and gas delivery set up. Heliox comes in 80:20 and 70:30 mixtures of helium–oxygen. As such, the overall FiO_2 does not exceed 20–30 % and patients with higher FiO_2 requirements will not benefit from the lower FiO_2 found in Heliox. In the non-intubated patient, Heliox may be delivered by facemask, non-rebreather mask, or through a nebulizer.

Anesthetics

Several anesthetic agents may be considered in the failing CAS patient. Both intravenous and inhaled anesthetics offer bronchodilatory properties, and they may further reduce work of breathing, metabolic demand, and patient–ventilator dyssynchrony by relaxing the CAS patient [62]. Anesthetic agents should work quickly and if a clinical response is not seen early in their use (i.e., 2–4 h), they are not likely to be effective. Intravenous anesthetics are attractive for ICU use in that CAS patients do not need specialized ventilators which are required for delivery of gas anesthetics. Ketamine and propofol are intravenous anesthetics with potential benefit in CAS [62]. Ketamine is a dissociative anesthetic related to phencyclidine which exerts a catecholamine effect on bronchial smooth muscle resulting in bronchodilation [63]. Side effects include hypertension, tachycardia, an increase in oral and respiratory secretions, and elevated intra-cranial hypertension, so caution is required for use in CAS patients with cardiovascular disease or elevated intra-cranial pressure. In addition, the increased respiratory secretions may promote bronchospasm and ketamine is often administered with an anti-cholinergic agent such glycopyrrolate. Clinical data with ketamine in CAS is sparse, and a recent Cochrane review identifying just one study in non-intubated children did not find a beneficial effect [64]. Nevertheless, in our experience ketamine has been effective in selected CAS patients, and it remains a reasonable choice in the refractory CAS patient. Propofol is also associated with bronchodilatory properties, though clinical data is sparse [63, 65]. Available clinical data suggests that airway resistance [66] and wheezing are reduced with propofol [67]. Adverse effects include hypotension, propofol infusion syndrome, and a potential for allergic reaction in patients with yolk allergies [62]. Inhaled anesthetics which may improve respiratory mechanics in CAS include halothane, enflurane, isoflurane, and diethyl ether. Sevoflurane may have some bronchoconstrictive effects

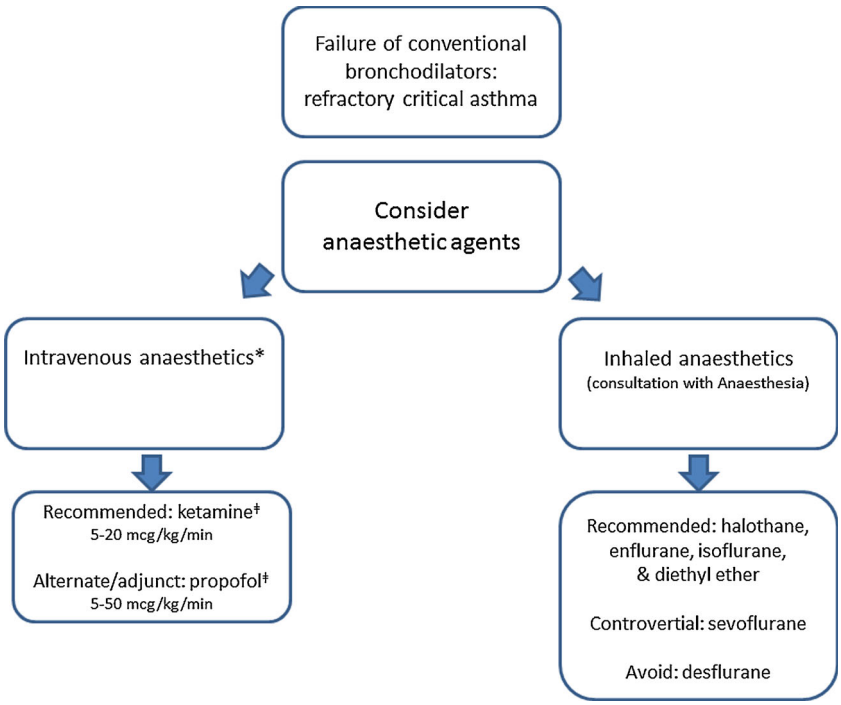

Fig. 4 Anesthetic algorithm as an adjunct to the treatment of refractory CAS. *Intravenous (*IV*) anesthetics are preferred if available and appropriate for the CAS patient. IV anesthetics are easier to administer and do not require specialized ventilators to administer. Also, IV anesthetics typically do not require consultation with an anesthesiologist if an intensivist is familiar with their use. *double dagger* Suggested ranges. In addition, familiarity with all drug toxicities, adverse effects, and contraindications to use is required

and desflurane is contraindicated [62]. If gas anesthesia is considered, consultation with an anesthesiologist and use of an appropriate ventilator are required. See Fig. 4 for an algorithm in choosing anesthetic agents for CAS.

Extra-corporeal CO_2 Removal ($ECCO_2R$)

A rarely used but potentially effective strategy in refractory CAS is the extra-corporeal removal of CO_2 or $ECCO_2R$. In this technique, the CAS patient is placed on respiratory "bypass" where the function of the lung to exchange gas is circumvented and gas exchange takes place at an external site. Most $ECCO_2R$ employed for asthma is veno-venous, meaning that the external circuitry would run from a vein (e.g., the internal jugular) to the gas-exchanging surface and back to another vein (e.g., the femoral vein). However, in the face of concomitant cardiac pump dysfunction, the system could be veno-arterial. In a retrospective cohort study of 24 asthmatics placed on $ECCO_2R$ compared to over 1,200 refractory CAS cases, the odds ratio for survival was 4.86 (95 % CI, 1.65–14.31, $p=0.004$) favoring $ECCO_2R$ [68]. The small number of cases indicates the relative infrequency of $ECCO_2R$ use in refractory CAS, though survival may actually increase as $ECCO_2R$ techniques improve. Despite limited data, $ECCO_2R$ may be an important adjunct in refractory CAS.

Liberation from Mechanical Ventilation

Most CAS patients who undergo intubation and mechanical ventilation will be weaned in a mean of 3.5 days [2]. Once dynamic hyperinflation, gas exchange, work of breathing, and the need for sedation improve, changing the CAS patient to a spontaneous ventilation mode is appropriate. As the requirement for ventilator assistance decreases, the pulmonologist and intensivist may challenge the CAS patient with a spontaneous breathing trial such as a CPAP of 5 cm H_2O or a T-piece trial [69]. Recently extubated CAS patients will need careful observation over the next 24 h as bronchospasm can recrudesce. If the CAS patient remains stable after 24 h, transfer out of the ICU to the hospital ward is appropriate.

Conclusions

CAS requires coordinated ICU care, especially in the first few hours to days of presentation. Recognition of complications that can accompany CAS—including dynamic hyperinflation, intravascular volume depletion, and the risk of pneumothorax and pneumomediastinum—is paramount. Attention to details, alacrity, and accurate assessment and *reassessment* are vital. Keeping a broad differential diagnosis may uncover alternate or additional conditions with similar presentation to CAS such as vocal cord dysfunction. Utilizing technologies such as point-of-care bedside critical care ultrasound may enable faster delivery of care, and correlating ABG findings to the clinical condition of the CAS patient (even when the ABG appears "normal") is essential. Though most CAS does not go on to develop respiratory failure, early recognition of those CAS patients with impending respiratory failure is crucial. Also, most CAS patients improve with standard therapy such as bronchodilators and intravenous steroids. However, the pulmonologist and intensivist must be aware of adjunct medications and ventilation strategies to help the refractory CAS patient. With a high level of vigilance, awareness of possible complications and a familiarity with the armamentarium of useful treatments, patients can receive optimal ICU care to survive and recover from CAS.

References

1. Rudd RA, Moorman JE (2007) Asthma incidence: data from the national health interview survey, 1980–1996. J asthma Off J Assoc Care Asthma 44:65–70
2. Louie S, Morrissey BM, Kenyon NJ, Albertson TE, Avdalovic M (2012) The critically ill asthmatic—from ICU to discharge. Clin Rev allergy immunol 43:30–44
3. Pendergraft TB, Stanford RH, Beasley R, Stempel DA, Roberts C, McLaughlin T (2004) Rates and characteristics of intensive care unit admissions and intubations among asthma-related hospitalizations. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol 93:29–35
4. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, FitzGerald JM (2009) Economic burden of asthma: a systematic review. BMC Pulm Med 9:24
5. (ALA) ALA. Trends in asthma morbidity and mortality: http://www.Lung.Org/finding-cures/our-research/trend-reports/asthma-trend-report.Pdf. [Online database] 2012 7/12/2013]
6. National Heart L, and Blood Institute (NHLBI) (2007) National asthma education and prevention program (NAEPP): Expert panel report-3 (epr-3). In: Services DoHH, editor. National Institutes of Health, Washington, DC, p 373–417
7. Brenner BE, Abraham E, Simon RR (1983) Position and diaphoresis in acute asthma. Am J Med 74:1005–1009
8. Adams JY, Sutter ME, Albertson TE (2012) The patient with asthma in the emergency department. Clin Rev allergy Immunol 43:14–29
9. Hess DR (2013) Noninvasive ventilation for acute respiratory failure. Respir Care 58:950–972
10. Meduri GU, Cook TR, Turner RE, Cohen M, Leeper KV (1996) Noninvasive positive pressure ventilation in status asthmaticus. Chest 110:767–774
11. Fernandez MM, Villagra A, Blanch L, Fernandez R (2001) Non-invasive mechanical ventilation in status asthmaticus. Intensive Care Med 27:486–492
12. Soroksky A, Stav D, Shpirer I (2003) A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. Chest 123:1018–1025
13. Gupta D, Nath A, Agarwal R, Behera D (2010) A prospective randomized controlled trial on the efficacy of noninvasive ventilation in severe acute asthma. Respir Care 55:536–543
14. Lim WJ, Mohammed Akram R, Carson KV, Mysore S, Labiszewski NA, Wedzicha JA, Rowe BH, Smith BJ (2012) Non-invasive

positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. Cochrane Database Syst Rev 12, CD004360
15. Martin JG, Shore S, Engel LA (1982) Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. Am Rev Respir Dis 126:812–817
16. Zieverink SE, Harper AP, Holden RW, Klatte EC, Brittain H (1982) Emergency room radiography of asthma: an efficacy study. Radiology 145:27–29
17. Kao CC, Jain S, Guntupalli KK, Bandi V (2008) Mechanical ventilation for asthma: a 10-year experience. J Asthma Off J Assoc Care Asthma 45:552–556
18. Ashton-Cleary DT (2013) Is thoracic ultrasound a viable alternative to conventional imaging in the critical care setting? Br J Anaesth
19. FitzGerald JM, Hargreave FE (1989) The assessment and management of acute life-threatening asthma. Chest 95:888–894
20. Molfino NA, Nannini LJ, Martelli AN, Slutsky AS (1991) Respiratory arrest in near-fatal asthma. N Engl J Med 324:285–288
21. Mountain RD, Sahn SA (1988) Clinical features and outcome in patients with acute asthma presenting with hypercapnia. Am Rev Respir Dis 138:535–539
22. Warnier MJ, Rutten FH, Kors JA, Lammers JW, de Boer A, Hoes AW, de Bruin ML (2012) Cardiac arrhythmias in adult patients with asthma. J Asthma Off J Assoc Care Asthma 49:942–946
23. Kokot F, Hyla-Klekot L (2008) Drug-induced abnormalities of potassium metabolism. Pol Arch Med Wewn 118:431–434
24. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Doucette S, Fergusson D (2008) Overdiagnosis of asthma in obese and nonobese adults. CMAJ Can Med Assoc J = J de l'Assoc Med Can 179:1121–1131
25. Morris MJ, Christopher KL (2010) Diagnostic criteria for the classification of vocal cord dysfunction. Chest 138:1213–1223
26. Balkissoon R, Kenn K (2012) Asthma: vocal cord dysfunction (VCD) and other dysfunctional breathing disorders. Sem Respir Crit Care Med 33:595–605
27. Mountain RD, Heffner JE, Brackett NC Jr, Sahn SA (1990) Acid–base disturbances in acute asthma. Chest 98:651–655
28. Nowak RM, Tomlanovich MC, Sarkar DD, Kvale PA, Anderson JA (1983) Arterial blood gases and pulmonary function testing in acute bronchial asthma. Predicting patient outcomes. JAMA 249:2043–2046
29. White CS, Cole RP, Lubetsky HW, Austin JH (1991) Acute asthma. Admission chest radiography in hospitalized adult patients. Chest 100:14–16
30. Kirkpatrick AW, Sirois M, Laupland KB, Liu D, Rowan K, Ball CG, Hameed SM, Brown R, Simons R, Dulchavsky SA, Hamiilton DR, Nicolaou S (2004) Hand-held thoracic sonography for detecting post-traumatic pneurnothoraces: the extended focused assessment with sonography for trauma (efast). J Trauma 57:288–295
31. Gardelli G, Feletti F, Nanni A, Mughetti M, Piraccini A, Zompatori M (2012) Chest ultrasonography in the ICU. Respir Care 57:773–781
32. Arntfield RT, Millington SJ (2012) Point of care cardiac ultrasound applications in the emergency department and intensive care unit—a review. Curr Cardiol Rev 8:98–108
33. Corbridge TC, Hall JB (1995) The assessment and management of adults with status asthmaticus. Am J Respir Crit Care Med 151:1296–1316
34. Kallet RH, Matthay MA (2013) Hyperoxic acute lung injury. Respir Care 58:123–141
35. Rodrigo GJ, Rodrigo C (2002) Continuous vs intermittent beta-agonists in the treatment of acute adult asthma: a systematic review with meta-analysis. Chest 122:160–165
36. Emerman CL, Cydulka RK, McFadden ER (1999) Comparison of 2.5 vs 7.5 mg of inhaled albuterol in the treatment of acute asthma. Chest 115:92–96
37. Salo D, Tuel M, Lavery RF, Reischel U, Lebowitz J, Moore T (2006) A randomized, clinical trial comparing the efficacy of continuous nebulized albuterol (15 mg) versus continuous nebulized albuterol (15 mg) plus ipratropium bromide (2 mg) for the treatment of acute asthma. J Emerg Med 31:371–376
38. Rodrigo GJ, Castro-Rodriguez JA (2005) Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. Thorax 60:740–746
39. Travers AH, Milan SJ, Jones AP, Camargo CA Jr, Rowe BH (2012) Addition of intravenous beta(2)-agonists to inhaled beta(2)-agonists for acute asthma. Cochrane Database Syst Rev 12, CD010179
40. Kress JP, Noth I, Gehlbach BK, Barman N, Pohlman AS, Miller A, Morgan S, Hall JB (2002) The utility of albuterol nebulized with heliox during acute asthma exacerbations. Am J Respir Crit Care Med 165:1317–1321
41. Sellers WF (2013) Inhaled and intravenous treatment in acute severe and life-threatening asthma. Br J Anaesth 110:183–190
42. Rowe BH, Edmonds ML, Spooner CH, Diner B, Camargo CA Jr (2004) Corticosteroid therapy for acute asthma. Respir Med 98:275–284
43. Krishnan JA, Davis SQ, Naureckas ET, Gibson P, Rowe BH (2009) An umbrella review: corticosteroid therapy for adults with acute asthma. Am J Med 122:977–991
44. Haskell RJ, Wong BM, Hansen JE (1983) A double-blind, randomized clinical trial of methylprednisolone in status asthmaticus. Arch Intern Med 143:1324–1327
45. Adachi M, Taniguchi H, Tohda Y, Sano Y, Ishine T, Smugar SS, Hisada S (2012) The efficacy and tolerability of intravenous montelukast in acute asthma exacerbations in Japanese patients. J Asthma Off J Assoc Care Asthma 49:649–656
46. Camargo CA Jr, Gurner DM, Smithline HA, Chapela R, Fabbri LM, Green SA, Malice MP, Legrand C, Dass SB, Knorr BA, Reiss TF (2010) A randomized placebo-controlled study of intravenous montelukast for the treatment of acute asthma. J Allergy Clin Immunol 125:374–380
47. Zubairi AB, Salahuddin N, Khawaja A, Awan S, Shah AA, Haque AS, Husain SJ, Rao N, Khan JA (2013) A randomized, double-blind, placebo-controlled trial of oral montelukast in acute asthma exacerbation. BMC Pulm Med 13:20
48. Ramsay CF, Pearson D, Mildenhall S, Wilson AM (2011) Oral montelukast in acute asthma exacerbations: a randomised, double-blind, placebo-controlled trial. Thorax 66:7–11
49. Shan Z, Rong Y, Yang W, Wang D, Yao P, Xie J, Liu L (2013) Intravenous and nebulized magnesium sulfate for treating acute asthma in adults and children: a systematic review and meta-analysis. Respir Med 107:321–330
50. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA, Jr (2000) Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Cochrane Database Syst Rev: CD001490
51. Powell C, Dwan K, Milan SJ, Beasley R, Hughes R, Knopp-Sihota JA, Rowe BH (2012) Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev 12, CD003898
52. Parameswaran K, Belda J, Rowe BH (2000) Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Cochrane Database Syst Rev: CD002742
53. Barnes PJ (2013) Theophylline. Am J Respir Crit Care Med
54. Stelmach I, Jerzynska J, Stelmach W, Majak P, Brzozowska A, Gorski P, Kuna P (2003) The effect of inhaled heparin on airway responsiveness to histamine and leukotriene d4. Allergy Asthma Proc Off J Reg State Allergy Soc 24:59–65
55. Tutluoglu B, Gurbuz N, Atis S, Abanozlu S, Ibis R, Kanik A (2001) Effects of heparin on hypertonic potassium chloride-induced bronchoconstriction. Ann Pharmacother 35:1161–1165
56. Bhure UN, Bhure SU, Bhatt BM, Mistry S, Pednekar SJ, Chari VV, Desai SA, Joshi JM, Paidhungat AJ (2009) Lung epithelial

permeability and inhaled furosemide: added dimensions in asthmatics. Ann Nucl Med 23:549–557
57. Niven AS, Argyros G (2003) Alternate treatments in asthma. Chest 123:1254–1265
58. Mutlu GM, Factor P, Schwartz DE, Sznajder JI (2002) Severe status asthmaticus: management with permissive hypercapnia and inhalation anesthesia. Crit Care Med 30:477–480
59. Afessa B, Morales I, Cury JD (2001) Clinical course and outcome of patients admitted to an ICU for status asthmaticus. Chest 120:1616–1621
60. Gluck EH, Onorato DJ, Castriotta R (1990) Helium–oxygen mixtures in intubated patients with status asthmaticus and respiratory acidosis. Chest 98:693–698
61. Rodrigo G, Pollack C, Rodrigo C, Rowe BH (2006) Heliox for nonintubated acute asthma patients. Cochrane Database Syst Rev: CD002884.
62. Burburan SM, Xisto DG, Rocco PR (2007) Anaesthetic management in asthma. Minerva Anestesiol 73:357–365
63. Brown RH, Wagner EM (1999) Mechanisms of bronchoprotection by anesthetic induction agents: propofol versus ketamine. Anesthesiology 90:822–828
64. Jat KR, Chawla D (2012) Ketamine for management of acute exacerbations of asthma in children. Cochrane Database Syst Rev 11, CD009293
65. Conti G, Dell'Utri D, Vilardi V, De Blasi RA, Pelaia P, Antonelli M, Bufi M, Rosa G, Gasparetto A (1993) Propofol induces bronchodilation in mechanically ventilated chronic obstructive pulmonary disease (COPD) patients. Acta Anaesthesiol Scand 37:105–109
66. Eames WO, Rooke GA, Wu RS, Bishop MJ (1996) Comparison of the effects of etomidate, propofol, and thiopental on respiratory resistance after tracheal intubation. Anesthesiology 84:1307–1311
67. Pizov R, Brown RH, Weiss YS, Baranov D, Hennes H, Baker S, Hirshman CA (1995) Wheezing during induction of general anesthesia in patients with and without asthma. A randomized, blinded trial. Anesthesiology 82:1111–1116
68. Mikkelsen ME, Woo YJ, Sager JS, Fuchs BD, Christie JD (2009) Outcomes using extracorporeal life support for adult respiratory failure due to status asthmaticus. ASAIO J 55:47–52
69. Meade M, Guyatt G, Cook D, Griffith L, Sinuff T, Kergl C, Mancebo J, Esteban A, Epstein S (2001) Predicting success in weaning from mechanical ventilation. Chest 120:400S–424S
70. Fragou M, Zacharaki A, Zotos P, Tsikritsaki K, Damelou A, Poularas I, Katsarelis N, Koukoulitsios G, Karakitsos D, Karabinis A (2010) Identification of pneumothorax by lung echography in trauma patients. Intensive Care Med 36:S300–S300
71. Galbois A, Ait-Oufella H, Baudel JL, Kofman T, Bottero J, Viennot S, Rebate C, Jabbouri S, Bouzeman A, Guidet B, Offenstadt G, Maury E (2010) Pleural ultrasound compared with chest radiographic detection of pneumothorax resolution after drainage. Chest 138:648–655
72. Zhang M, Liu ZH, Yang JX, Gan JX, Xu SW, You XD, Jiang GY (2006) Rapid detection of pneumothorax by ultrasonography in patients with multiple trauma. Crit Care 10
73. Soldati G, Testa A, Sher S, Pignataro G, La Sala M, Silveri NG (2008) Occult traumatic pneumothorax—diagnostic accuracy of lung ultrasonography in the emergency department. Chest 133:204–211
74. Rowan KR, Kirkpatrick AW, Liu D, Forkheim KE, Mayo JR, Nicolaou S (2002) Traumatic pneumothorax detection with thoracic US: correlation with chest radiography and CT—initial experience. Radiology 225:210–214
75. Xirouchaki N, Magkanas E, Vaporidi K, Kondili E, Plataki M, Patrianakos A, Akoumianaki E, Georgopoulos D (2011) Lung ultrasound in critically ill patients: comparison with bedside chest radiography. Intensive Care Med 37:1488–1493
76. Lichtenstein DA, Meziere GA (2008) Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the blue protocol. Chest 134:117–125