"Extracorporeal membrane oxygenation (ECMO) and beyond in near fatal asthma: a comprehensive review"

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authors name, affiliation and ORCID

Name: Lozano-Espinosa, María
Affiliation: Servicio de Medicina Intensiva, Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain
ORCID:https://orcid.org/0000-0002-9563-3016

Name: Antolín-Amérigo, Darío
Affiliation: Servicio de Alergia, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS) Madrid, Spain.
ORCID:https://orcid.org/0000-0001-5699-4022

Name: Riera del Brío, Jordi
Affiliation: Servicio de Medicina Intensiva, Hospital Universitari Vall d'Hebron; SODIR, Vall d'Hebron Institut de Recerca, Barcelona, Spain.
ORCID: 0000-0002-1738-4448

Name: Gordo Vidal, Federico
Affiliation: Servicio de Medicina Intensiva, Hospital Universitario Henares, Coslada, Madrid, Spain.
Grupo de Investigación en Patología Crítica. Universidad Francisco de Vitoria. Pozuelo de Alarcón, Madrid, Spain.
ORCID:https://orcid.org/0000-0001-9605-1918

Name: Quirce, Santiago
Affiliation: Department of Allergy, La Paz University Hospital, IdiPAZ, Madrid, Spain
ORCID: https://orcid.org/0000-0001-8086-0921

Name: Álvarez Rodríguez, Joaquín
Affiliation: Servicio de Medicina Intensiva, Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain
ORCID: https://orcid.org/0000-0002-2308-7239

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Abstract:

In severe asthma exacerbations with respiratory failure, the treatment of choice is ventilatory support, both invasive and/or non-invasive, along with different kinds of medication. When t conventional measures fail, rescue strategies, such as extracorporeal membrane oxygenation (ECMO) or extracorporeal CO2 removal (ECCO2R) may need to be implemented. Of note, the rate of mortality of patients with asthma has decreased substantially in recent years mainly due to significant advances in pharmacological treatment and other management strategies. However, the risk of death in patients with severe asthma who require invasive mechanical ventilation has been estimated between 6.5% and 10.3% ECMO does not constitute a treatment per se, but minimizes further ventilator associated lung injury (VALI) and enables diagnostic-therapeutic maneuvers in the same patient that who without ECMO could not be possible (such as bronchoscopy and transfer for diagnostic imaging). Asthma is one of the diseases that is associated with excellent outcomes for patients with refractory respiratory failure requiring ECMO support, as shown by the Extracorporeal Life Support Organization (ELSO) registry. Moreover, in such situations, the use of ECCO2R for rescue in Near-Fatal Asthma (NFA) has been described and utilized in both children and adults and is more widely spread in different hospitals than ECMO. In this article we aim to review the usefulness of these extracorporeal respiratory support measures in the management of near fatal asthma (NFA).

Manuscript

1. Background

1.1. Introduction

Patients with asthma exacerbations requiring respiratory support would benefit from being in an intensive care unit (ICU) to facilitate escalation of organ support. The vast majority of such patients can be stabilized with non-invasive respiratory support. However, in very severe cases, invasive mechanical ventilation may be needed. Approximately 2%–4% of all patients hospitalized for acute asthma require invasive mechanical ventilation.[1–3] When those severe asthma exacerbations are refractory to the traditional management strategies, further rescue strategies may have to be implemented, including extracorporeal membrane oxygenation (ECMO) or extracorporeal carbon dioxide removal (ECCO2R). Serrano-Pariente et al [4] reported that, in 2005, 225,000 people worldwide died as a result of their asthma, increasing to 428,000 deaths annually by 2030.[5] The risk of death in patients with severe asthma who require invasive mechanical ventilation has been estimated between 6.5% and 10.3%.[1,2] In this article we aim to review the usefulness of these extracorporeal respiratory support measures in the management of NFA.

2. Methods:

2.1 Review question:

The scientific question for our review was: Would adults with near fatal asthma (NFA) would benefit from the use of extracorporeal membrane oxygenation (ECMO) or extracorporeal carbon dioxide removal (ECCO2R)?

2.2 Data sources and search strategy

We searched PubMed and EMBASE without time restrictions; articles in English were considered. The first search was carried out in September 2021 but additional searches have been performed in 2022. We included all relevant references until October 2022. The search strategy was:

("status asthmaticus"[mh] AND "near fatal asthma" AND "asthma" AND "extracorporeal membrane oxygenation" OR "ECMO" AND "extracorporeal carbon dioxide removal" OR "ECCO2R" OR "ICU" OR "intensive care" OR "acute respiratory failure") **(Figure 1)**

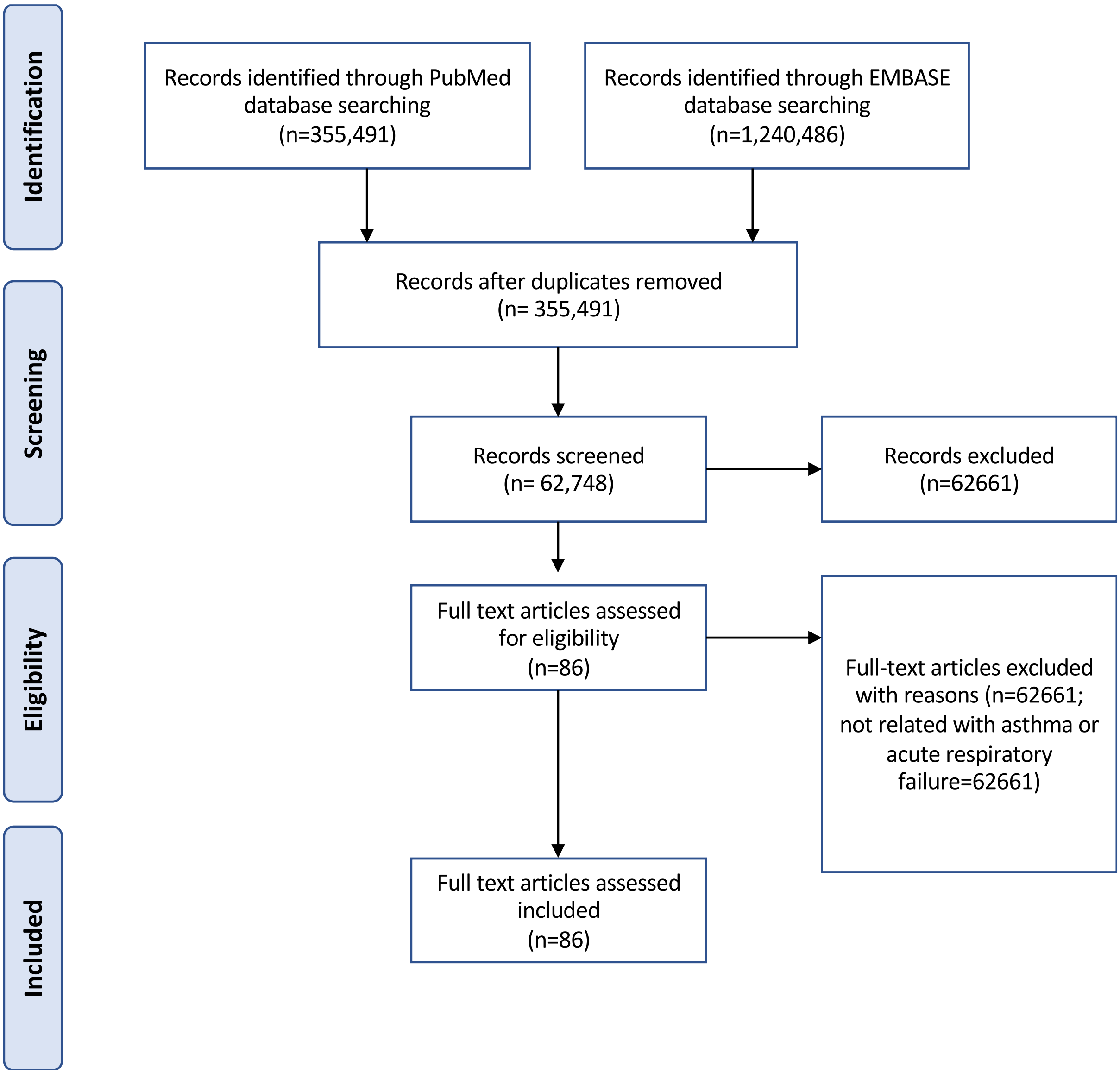
2. 3 Inclusion criteria

We included randomised controlled trials, cohort or cross-sectional studies, or reviews and meta-analyses, also including real-world data experience. We excluded articles which did not meet the inclusion criteria above or those not related with asthma or acute respiratory failure.

2.4 Study selection

Both abstracts and manuscripts were assessed by two authors independently. Conflicting selections were resolved by consensus.

Figure 1. Flow diagram for article identification and selection



3. Near Fatal Asthma (NFA)

3.1 NFA: definition and characteristics:

Near fatal asthma (NFA), life-threatening asthma or critical asthma syndrome [6–8] comprises a subset of patients with asthma who are at increased risk for death from their disease. [9] There are two predominant phenotypes of near-fatal exacerbations: "subacute" exacerbation and "hyperacute" exacerbation. The best way to manage acute severe asthma is 3-7 days before it occurs (i.e., at the onset of symptoms or change in respiratory function) and to optimize asthma control by decreasing the number of symptomatic days and the days and/or nights with use of rescue therapy.[4,9] It should be remembered that increasing the efficacy in the therapeutic management of NFA literally means to save lives and to avoid poor outcomes.[10]

In terms of physiopathology, eosinophils present a widespread distribution within the respiratory tract in fatal cases whereas neutrophils can participate in specific situations, such as sudden-onset fatal asthma (asphyxiating asthma), mainly affecting the small airways. Interestingly, studies have shown that both viral, and to a lesser extent bacterial agents, can play a role, and co-infection may also be present and worsen prognosis in hospitalized patients, placing a portion at risk for critical asthma syndrome.[11] Viral-mediated inflammatory pathways (acute or quiescent) are also implicated in NFA and occur in as much as 50% of patients.[12] Rhinovirus-C, respiratory syncytial virus and influenza A, appear to be the most prevalent and recurring threats. [11,13–15] The association of fungal isolates with NFA is a novel finding but consistent with the association of these organisms in acute asthma.[16,17] These observations suggest the possibility of defective antifungal and/or antiviral immune pathways in these patients.

Although episodes of NFA (and asthma-related deaths) are more common in patients with severe asthma, patients with mild and moderate asthma can also suffer from NFA. The EAGLE (Estudio del Asma Grave en Latinoamérica y España) project, a case-control study in which 2593 clinical records of patients with asthma with an exacerbation episode requiring hospitalization were analyzed, showed that up to 4.9% of patients with mild–moderate asthma required ICU admission, 2.1% intubation and mechanical ventilation, 1.3% had cardiopulmonary arrest and 0.4% died during hospital admission.[18]
From these data, the authors found that a greater percentage of patients without any formal treatment for their asthma required ECMO (17% versus 4%).[3]

3.2 Risk factors for NFA

Some characteristics of patients with asthma may be risk factors for NFA are listed in **Table 1**:

Table 1. Risk factors for NFA

- History of ICU admission because of asthma exacerbation and the need of mechanical ventilation(19)
- Previous treatment with oral steroids
- A greater blood gases impairment (hypercapnia and acidosis)
- Presence of pulmonary hyperinflation on admission
- Family history of fatal asthma
- Office visits
- Major psychiatric illness
- Refusal to take corticosteroids
- Noncompliance with prescribed medications

- Fear of asthma
- Sleep apnea
- Refusal to remove an animal from the home

Other risk factors for NFA in childhood are food allergy, poverty, residence in an urban area, race/ethnicity, longer duration of asthma, male gender and multiple emergency room visits in the year before an ICU admission. [4,20,21](see **table 1**)

According to the genealogical index of familiarity, the relative risk of dying of asthma was 1.60 in first-degree relatives of cases and 1.34 in second-degree relatives. In Western countries, asthma-related mortality is currently low. However, in young patients with asthma, uncontrolled asthma continues to be an avoidable cause of sudden death.[22–24]
A recent single center retrospective review of all asthma exacerbation admissions recorded 400 NFA episodes between 2000 and 2010, found a mortality rate of 3.1%. In this particular study[25], no signs of a decreasing trend in asthma-related mortality for the decade analyzed was found.

3.3 Near-fatal asthma phenotypes

Different profiles of patients with NFA based on demographic characteristics, triggers of asthma attacks, pathogenesis of the disease, comorbidities and clinical presentation of exacerbations have been described elsewhere **(Tables 2 and 3)**. The knowledge and identification of their particular features have been crucial to design specific strategies to prevent further exacerbations.[4,26]
[modified from [4,24]].

Table 2. Different NFA phenotypes

	Rapid-onset NFA	**Slow-onset NFA**
Characteristics of patients	Young males	Women
Triggers	Respiratory allergens Environmental pollutants Emotional stress NSAID intake	Respiratory tract infections
Clinical differences	Higher hypercapnia and acidosis Absence of lung sounds Generally a more rapid recovery	Higher number of previous emergency room visits and hospital admissions

Histological findings	Airway permeability Greater tightening of the muscular layer Neutrophils exceed eosinophils in the airways submucosa Higher proportion of mast cell degranulation	Mucous plugs Lung hyperinflation Loss of airway epithelial layer Mucous gland hyperplasia Eosinophils exceed neutrophils in the airways submucosa

NSAID: Non-steroidal anti-inflammatory drugs

Table 3. Characteristics of NFA phenotypes identified by cluster analysis

	Cluster 1	**Cluster 2**	**Cluster 3**
Patient characteristics	Older More frequent female Lowest level of education Frequent psychiatric comorbidity	Frequently current smokers Frequent psychiatric comorbidity	Younger More frequent male Frequently current smokers
Asthma characteristics	Late onset Very frequent severe persistent asthma Frequent regular medical care Very frequent past hospitalization for asthma	Intermediate position between cluster 1 and 3	Early onset Very infrequent regular medical care
Allergic and functional characteristics	At least one positive skin prick test:42% Sensitized to *Alternaria* or soybean:6 % FEV1 mean:69%	At least one positive skin prick test:71% Sensitized to *Alternaria* and soy bean:7% FEV1 mean:82%	At least one positive skin prick test:78% Sensitized to *Alternaria* and soy bean:26% FEV1 mean:81%
Therapeutic characteristics	ICS:91% Oral corticosteroids:21%	ICS:50%	ICS:30%

NFA attack characteristics	Longer hospitalization	Frequent impaired consciousness level and respiratory arrest Very frequent mechanical ventilation required Highest hypercapnia	Shorter hospitalization

ICS: inhaled corticosteroids

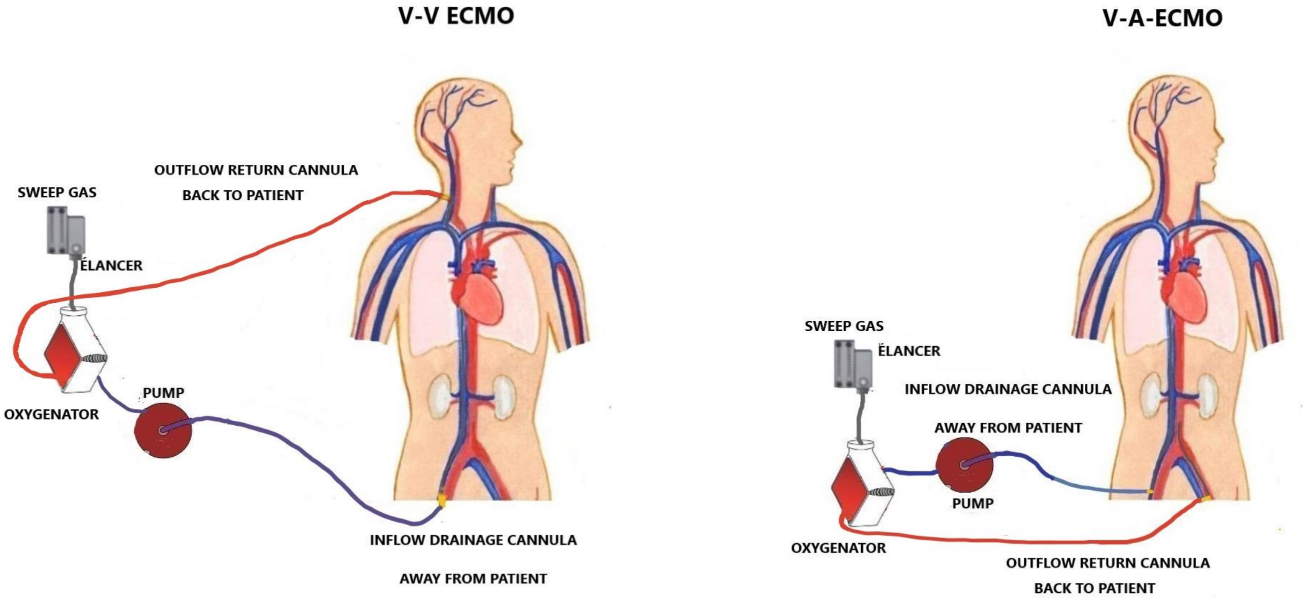
4. ECMO: definition, function and outcomes

4.1 Structure, configuration and functional definition

ECMO has different configurations. While its venovenous (V-V) configuration, is a form of extracorporeal respiratory support, allowing gas exchange to occur outside the body [27–29], the venoarterial (V-A) configuration can also provide circulatory support. Its structure is based on a centrifugal pump that generates blood movement and a gas interchanger (commonly known as oxygenator) that allows gas interchange via diffusion through a polymethylpentene membrane. Blood is drained from a central vein and returned to the same vein through a dual lumen catheter, or to another main vein (V-V) or artery (V-A) through a second cannula. The mechanism shows greater efficiency in extracting CO2 (extraction relies on sweep gas flow entering the oxygenator) than adding O2 (the increase of O2 relies on ECMO blood flow).[2] ECMO, with its V-V configuration **(figure 2**), is increasingly used to manage adults with severe respiratory failure refractory to conventional measures [26,27]. Currently, it is used for viral pneumonia (including COVID-19), Acute Respiratory Distress Syndrome (ARDS), bacterial pneumonia, pulmonary contusion and other respiratory pathologies that lead to a clinical condition refractory to conventional measures, including as a bridge to transplant, if there are poor expectations of lung recovery [30–33]. ECMO does not constitute a treatment *per se*, but minimizes the mechanical power delivered to the lung [34,35].

With its V-A configuration **(figure 2)** ECMO may help to stabilize patients with very severe hemodynamic instability due to reversible causes (cardiogenic shock due to acute myocardial infarction, myocarditis, pulmonary thromboembolism…). Further, V-A ECMO has also been used in the context of cardiac arrest with promising results.[36]

Figure 2. Veno-Venous and Veno-Arterial ECMO circuits.


V-V ECMO
SWEEP GAS
ÉLANCER
OUTFLOW RETURN CANNULA
BACK TO PATIENT
OXYGENATOR
PUMP
INFLOW DRAINAGE CANNULA
AWAY FROM PATIENT
V-A-ECMO
SWEEP GAS
ÉLANCER
INFLOW DRAINAGE CANNULA
AWAY FROM PATIENT
PUMP
OXYGENATOR
OUTFLOW RETURN CANNULA
BACK TO PATIENT

4.2. Indications and contraindications of ECMO

A general summary of the indication would be a patient with a reversible condition that leads to a critical situation that is worsening despite maximal conventional treatment. More specific details of indication criteria are summarized in **table 4**.

Table 4. General criteria for initiating ECMO [modified from [30]]

ECMO should be considered when clinical deterioration continues in-spite of optimal medical therapy especially in the presence of the following parameters:

V-V ECMO:

- **Potentially reversible**
- **Severe:**
  - PaO_2 / F_iO_2 < 60 mmHg with F_iO_2 > 0.8 over 3 hours despite rescue measures of refractory hypoxemia
  - PaO_2 / F_iO_2 < 80 mmHg with F_iO_2 > 0.8 over 6 hours despite rescue measures of refractory hypoxemia
  - Decompensated Hypercapnia ($PaCO_2$ > 80; pH < 7.25) over 6 hours despite rescue measures
- **Refractory**
  - Hypoxemia: PaO_2 does not increase over 20% after 12 hours of prone position
  - Hypercapnia: Refractory to extracorporeal life support (ECLS)-Removal CO_2.

V-A ECMO

- **Potentially reversible**
- **Severe:**
  - Systolic pressure < 90 mm Hg over 30 minutes, with cardiac index < 2.2 L/min/m^2.
- **Refractory:**
  - Evidence of inadequate oxygen delivery in spite of conventional measures:
    - Vasoactive drugs:
      - Noradrenaline > 0.5 mcg /Kg /min.
      - Dobutamine > 20 mcg /Kg /min.
    - Intra-aortic balloon pump when indicated

There are no absolute contraindications to ECMO, as each patient is considered individually with respect to risks and benefits. [30] There are conditions listed below, however, that are associated with a poor outcome despite extracorporeal respiratory support (ERS), and can be considered relative contraindications:[37]

1. Mechanical ventilation at high settings (FiO2 >0.9, P-plat >30) for 7 days or more. Many centers do not consider time on ventilation a contraindication.
2. Major pharmacologic immunosuppression (absolute neutrophil count <400/mm3)
3. Central Nervous System (CNS) hemorrhage that is recent or expanding
4. Non-recoverable comorbidity such as major CNS damage or terminal malignancy
5. Age: no specific age contraindication but consider increasing risk with increasing age
6. Bleeding diathesis

7. Contraindication to anticoagulation
8. Obesity (relative)
9. Multi organ failure

4.3 Extracorporeal carbon dioxide removal (ECCOR)

ECCO2R is a more recent strategy and is designed to remove CO_2, but, unlike ECMO, does not provide significant oxygenation.[38,39] Essentially, ECCO2R consists of a drainage cannula placed in a large central vein, a pump, a membrane lung and a return cannula, [40] or, more frequent, a double lumen venous cannula **(figure 3)**. Blood is pumped through the membrane and CO_2 is removed by diffusion. In contrast to ECMO, where the need for oxygenation requires high blood flow rates, ECCO2R could be done with much lower blood flow rates, a result of major differences in CO_2 and O_2 kinetics. Any given amount of blood is capable of carrying more CO_2 than O_2, and hence much lower blood flow rates can be utilized for CO_2 removal, typically in the order of 1 L/min. In addition, CO_2 diffuses more readily than O_2 across the extra- corporeal membrane because of greater solubility.[38]
In a recent study, the REST Trial, which was designed to decrease both pressures and the risk of damage subsequent to mechanical ventilation, among patients with acute hypoxemic respiratory failure, the use of ECCO2R to facilitate lower tidal volume mechanical ventilation, compared with conventional low tidal volume mechanical ventilation, did not significantly reduce 90-day mortality. [41] The REST trial did not find significant mortality reduction, although it did achieve adherence to lung protective ventilation it did so at the cost of mandated IMV, neuromuscular blocking-agents and had serious adverse events such as intracranial hemorrhage.[41] Therefore, nowadays these techniques are to be considered only rescue measures. **(See Table 5)**

Figure 3. ECCO2R system

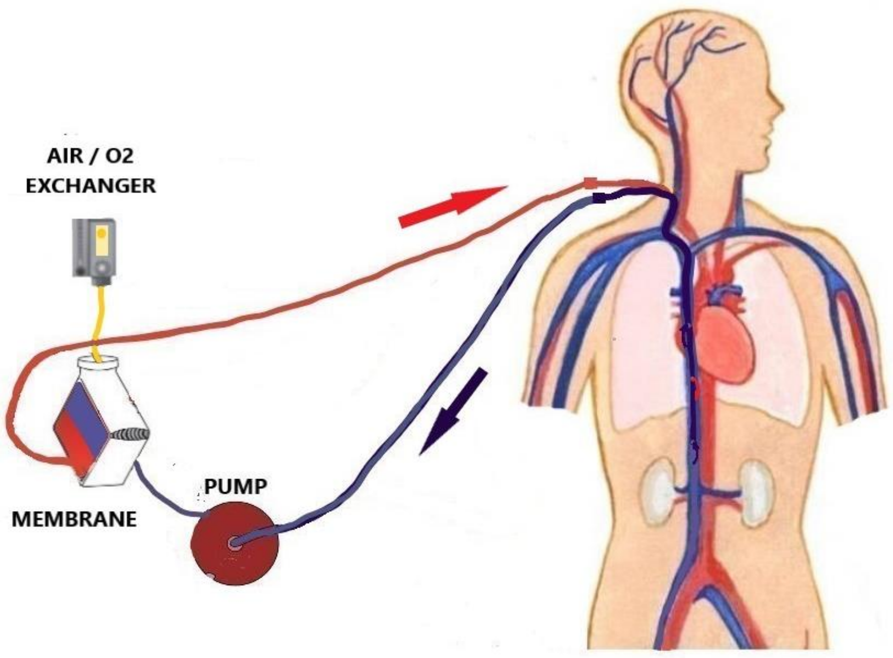


Table 5. Differences of ECMO and ECCO2R [modified from [42]]

Parameter	ECMO	ECCO2R
Oxygenation	✓	X
Ventilation (CO2 removal)	✓	✓
Hemodynamic support	✓ (minimal with V-V ECMO)	X
Blood Flow rates	High	Low
Need for anticoagulation	✓	✓
Cannula	Single or Dual	Single (dual for AVCO2R)
Complication rates	High	Usually Low

Abbreviations: AVCO2R: arteriovenous carbon dioxide removal; ECCO2R: extracorporeal carbon dioxide removal; ECMO: Extracorporeal membrane oxygenation

5. Scientific evidence

5.1 Use of ECMO in NFA:

The survival rate of patients with asthma needing ECMO support ranged from 83.5% of Yeo et al study to up to 95% of Warren study. [30,43] Yeo et al extracted data of the ELSO Registry from 272 patients with near fatal asthma refractory to mechanical ventilation who underwent ECMO between March 1992 and March 2016. [30,43] The mean time spent on ECMO was 176.4 hours. Ventilator settings, including rate, fraction of inspired oxygen (FiO2), peak inspiratory pressure (PIP), and mean airway pressure, significantly improved after ECMO initiation **(Table 6)**

Table 6. Clinical parameters to mechanical ventilation

	Pre-ECMO	Post-ECMO*
rate (breaths/min)	19.0 ±7.7	11.3 ±4.3
FiO2 (%)	81.2 ±23.0	48.8 ±19.0
PIP (cmH2O)	38.2 ±11.1	25.0 ±7.8
PEEP, cmH20	8.3 ±5.9	8.1 ±4.5
mean airway pressure (cmH2O)	21.4 ±14.2	14.2 ±10.0
driving pressure	29.5 ±12.9	16.8 ±7.8

*p<0.001

The weaning success rate was 86.7%, and the rate of survival to hospital discharge was 83.5%. The total complication rate was 65.1%, with hemorrhagic complications being the most common (28.3%). Other complications included renal (26.8%), cardiovascular (26.1%), mechanical (24.6%), metabolic (22.4%), infection (16.5%), neurologic (4.8%), and limb ischemia (2.6%). Of the hemorrhagic complications, cannulation site hemorrhage was the most common (13.6%). Using multivariate logistic regression analysis, it was found that hemorrhage was associated with increased in-hospital mortality (odds ratio, 2.97; 95% confidence interval, 1.07-8.24; p = 0.036). Hemorrhage-induced death occurred in four patients (1.5%). The most common reason for death was organ failure (37.8%).[44]

Warren et al performed an observational study in the NHS in England which included 1205 patients with severe respiratory failure refractory to conventional measures who were supported with ECMO; the majority (n=1150; 95%) had V-V ECMO alone. The survival rate at ECMO ICU discharge was 74% (n=887). Survivors had a lower median age (43 yr [32-52]), compared with non-survivors (49 yr [39-60]). Increased severity of hypoxemia at time of decision-to-cannulate was associated with a lower probability of survival: survivors had a median $Sa0_2$ of 90% (84-93%; median Pao2/Fio2, 9.4 kPa [7.7-12.6]), compared with non-survivors ($Sa0_2$ 88% [80-92%]; Pao2/Fio2 ratio: 8.5 kPa [7.1-11.5]). Patients requiring ECMO because of asthma were more likely to survive (95% survival rate (95% CI, 91-99%), compared with a survival of 71% (95% CI, 69-74%) in patients with respiratory failure attributable to other diagnoses.

An Extracorporeal Life Support Organization (ELSO) registry query for adults with asthma showed survival rates of nearly 85% with asthma being one of the best outcome subsets for patients with refractory respiratory failure requiring ECMO support.[30,63]

A more recent ELSO registry query for ECMO support for adults with asthma found successful decannulation in 86.7% and survival to discharge of 83.5%, with the most common reason for death being organ failure with some observed characteristics among non-survivors: older age, bleeding, higher pre- ECMO PEEP, higher post-ECMO FiO2, and post-ECMO driving pressure were all significantly associated with in-hospital mortality.[43] The lower survival in adults compared to children is probably due to fewer comorbidities in children and the absence of associated pulmonary comorbidities. So, it seems the ideal time to start thinking about ECMO is somewhere from failure to control hypercarbia despite all the medical and ventilatory therapies and the onset of hemodynamic compromise and cardiopulmonary arrest, but certainly before cardiac arrest.

5.2 Use of ECCO2R in NFA:

The use of ECCO2R for rescue in NFA has been described in both children and adults **(Tables 7-8)**, posing advantages to transfer patients to ECMO referral centers as ECCO2R does not need cannulation.[46,47]

The use of ECCO2R was prospectively studied in a multicenter observational study and reported its safety and efficacy in a group of 70 patients with varied etiologies of respiratory failure.[48] This study had six patients with severe asthma though the study did not report detailed outcomes by diagnostic categories. Overall survival was 50%, and only 4% mortality was reported to be ECCO2R related.

The outcomes and effectiveness of ECCO2R and ECMO have been assessed in moderate to severe ARDS patients.[49] While there are some physiological and technical differences between the two which have been described **(Table 8)**, in the authors experience, many patients develop consolidation of the lungs and a secondary failure in oxygenation as the underlying infection, viral or bacterial, which can often be present. It is therefore safer to use V-V ECMO which can fully support oxygenation and CO2 removal at a blood flow rate of 60 to 80 mL/kg/min in larger children and adolescents. If bronchospasm is the patient's only issue the circuit can be run at a lower blood flow rate with higher sweep with ECCO2R mode.

Table 7. Brief summary of case reports on ECCO2R and AVCO2R therapies for refractory acute severe asthma [modified from [(42)**]]**

Reference	Type of extracorporeal support	#patients	Median age (years)	Median pH	Median PaCO2 levels	Duration of ECCO2R support in hours	Survival rate

Elliot et al[50]	ECCO2R	2	74 and 52	7.08 and 7.2	106 and 120	121 and 120	100%
Aravantagi et al[44]	AVCO2R	1	9	7.09	97	120	100%
Schneider et al[51]	ECCO2R	1	67	7.24	61	34	100%
Brenner et al[52]	ECCO2R	2	48 and 59	6.94 and 7.12	147 and 78	36 and 216	100%
Pavot et al[53]	ECCO2R	2	27 and 30	7.29	49 and 90	336 and 192	100%

Table 8. Summary of studies on Extracorporeal Membrane Oxygenation and ECCO2R for refractory acute severe asthma [modified from [42]]

Reference	Pediatric/ Adult	#patients	Median age (years)	Median pH	Median PaCo2 levels (mm Hg)	Duration of ECMO/ECCO2R support (hours)	Survival rate (%)	Venovenous ECMO (%)
Hebbar et al [54]	Pediatric	64	10	6.98	120	93	95	92
Greenwald et al [55]	Pediatric	5	9	6.97	100	108	100	80
Medar et al [42]	Pediatric	3	14	7.08	100	144	100	100
Yeo et al [43]	Adults	272	36	7.1	80	176	83.4	97
Dilascio et al [56]	Adults	16	50	6.89	111	300	100	81
Vutipongsatorn et al[57]	Adults	10	38.4	Not reported	120	161	100	not reported
Mikkelsen et al [2]	Adults	24	31.3	7.17	120	112	83.4	59
Zakrajsek [58]	Adults	127	38	Not reported	Not reported	Not reported	85.4	82.7

6. Management

6.1. General management of patients with V-V ECMO support:

When ECMO is initiated, the mechanical ventilator settings should be modified, given that standard mechanical ventilation can cause lung injury by activating inflammation that worsens pulmonary damage. In one study of patients receiving ECMO, the only ventilator parameter that was independently associated with reduced mortality while on ECMO was minimizing driving pressure.[59] It has been suggested that a target tidal volume of 4 mL/kg of predicted body weight (commonly known as ultra-lung-protective ventilation) could have better outcomes than the standard 6 mL/kg.[60] Currently, the recommended ventilation strategy with ECMO is reducing tidal volume as much as possible maintaining a driving pressure ≤14 cmH2O, with PEEP level ≥ 10 cmH2O at least during the first three days.[61,62].
During ECMO, oxygenation is controlled by the ECMO circuit blood flow, membrane lung sweep gas oxygen concentration (FiO2) and oxygen carrying capacity.[38] Carbon dioxide removal is controlled by sweep gas flow.[38] In the case of severe pulmonary disease with no native lung function, the systemic arterial oxygen saturation is a result of mixing the flow of oxygenated blood from the membrane lung with the flow of venous blood which has not entered the ECMO circuit and passes directly into the right ventricle.
Recirculation is a phenomenon, exclusive to V-V ECMO, in which reinfused oxygenated blood to the patient is withdrawn again through the drainage cannula without passing to heart and the systemic circulation. Recirculation and a low ECMO-flow-to-cardiac-output ratio are two common causes of persistent hypoxemia. [62]
Recirculation is the unique complication in patients on VV-ECMO bleeding is one of the most common complications. Chatter, or rattling, of the circuit and ECLS lines and shall occur at any time after the pump is running, caused by a mismatch between circuit volume and pump circuit pressure resulting in turbulence in the system. It may be due to vasodilation as a part of systemic inflammatory response syndrome (SIRS) response upon exposure of blood to the extracorporeal circuit.[63]

6.2: ECMO Management specifics in NFA

The mechanism of hypoxemia and hypercapnia in NFA is mainly due to low ventilation perfusion, ventilation/perfusion mismatch, shunting, and hypoventilation. [64,65] The implementation of V-V ECMO may minimize these situations, or at least their consequences.

Successful management of a patient with NFA requires high levels of expertise for respiratory specialists (pulmonologists and other respiratory specialists) and intensive support in an ICU. Intensive therapy, including the careful manipulation of mechanical ventilation, and the utilization of ECMO as well as the mode change in the proper setting can be life-saving in severe asthmatic patients admitted to the ICU.[37,45]. **Table 9** summarizes the specific advantages that V-V ECMO offers in patients with NFA:

Table 9. Benefits of ECMO support in NFA patients

- Extend expiratory time, even using apnea
- Possibility to perform a bronchoscopy

- Possibility to decrease intrathoracic pressures, even normalize them
- Possibility to awaken the patient (also a benefit of IMV)
- Gradual and slow normalization of PaCO2 and pH by gentle sweep flow titration.

7. Complications:

7.1. ECMO complications:

ECMO is a complex therapy implemented in the most critically ill patient. Complications may be frequent and life-threatening. They are broadly divided in mechanical and patient-related complications. The most frequent complication process are bleeding and thrombotic events, with association with a higher risk of mortality, especially bleeding events.[66] Other feared complication is infection, also associated with a higher risk of mortality.[67] There is a peak of risk of complication during the cannulation process, especially bleeding complications but also air embolisms.

7.2. NFA specific complications:

In the process of the percutaneous insertion of the cannula in the right internal jugular vein, there would be a high risk of causing pneumothorax due to lung hyperinflation. The use of an extracorporeal circuit may boost the inflammation by cytokines release [39,68]. However, with new more biocompatible devices a significant clinical manifestation of this effect is rare. Finally excessive lung hyperinflation due to air trapping, may lead to extracorporeal flow variations.

8. Outcomes:

8.1: ECMO in NFA:

Whether ECMO confers a survival advantage in refractory acute severe asthma, compared to other treatment options, remains unknown.[2] Furthermore, while specific criteria exist for initiating ECMO in some etiologies of respiratory failure such as ARDS,[37] criteria do not exist for the initiation of ECMO for refractory severe asthma.[2] Unfortunately, a randomized controlled trial to assess the efficacy of ECMO in this population appears to be an unrealistic goal given the apparent rare use of ECMO for this disease nowadays and given the lack of recommendations in currently available asthma management guidelines worldwide.[37,69] For these reasons, it is imperative that clinicians report all ECMO cases, including interventions received an indication for initiation, and outcomes to the ECMO national registries to further our understanding of this potentially life-saving intervention.[37,45,54]

Mikkelsen´s et al [2] described the outcomes of ECMO use in adult respiratory failure due to acute severe asthma and to determine whether extracorporeal life support (ECLS) use in status asthmaticus is associated with greater survival than other indications for ECLS. This retrospective cohort study used the multi-center, International Extracorporeal Life Support

Organization (ELSO) registry. The study population included 1257 adults with respiratory failure requiring ECLS. Acute severe asthma was the primary indication for ECLS in 24 patients which is a low number of patients constituting a limitation. 83.3% of patients with asthma survived to hospital discharge, compared to 50.8% of non-asthma patients (n=1233) (OR favoring survival for asthmatics = 4.86, 95% CI 1.65–14.31, p=0.004). The survival advantage for asthmatics remained significant after adjustment for potential confounders. Complications were noted in 19 of 24 patients with asthma (79.2%). In conclusion, these authors found that status asthmaticus, as an indication for ECMO in adult respiratory failure, appeared to be associated with greater survival than other indications for ECMO.[2] Patients with asthma, compared to patients without asthma, were younger, received less mechanical ventilation pre-ECMO, were maintained on ECMO for a shorter duration, were more acidotic, and were less hypoxic with higher PaO2/FiO2 ratios **(Table 10)**. V-V ECMO was used more frequently in the patients with asthma group, while V-A ECMO was used more frequently in patients without asthma. The authors found that 93% of patients receiving ECMO for acute severe asthma survived and these favorable outcomes persisted after adjusting for potential confounders.[2] However, the authors explained as a limitation that they cannot predict how these patients would have fared had they not received ECMO.

Although it is estimated that 7–8% of mechanically ventilated patients with asthma will not survive their hospitalization, a precise estimate of mortality for the most severe cases is not known. Other reports estimate the mortality of NFA treated with conventional management at nearly 30%.[30,43] The number of complications for the asthmatic group appeared to be comparable to previously published data for adult ECLS [1,2]. These findings suggest that patients with asthma experienced complications in similar proportions to the broader ECMO patient population.

Table 10. Aspects related with better ECMO outcomes in patients with acute severe asthma

Better ECMO outcomes
Younger age
Higher Body mass index
Less severe hypoxaemia

A total of 1312 patients were identified on the NHS ECMO registry between December 1st, 2011 and December 31st, 2017.[30] Overall, 74% patients survive to ECMO ICU discharge, being that the primary outcome. Out of the 1312 patients, 115 patients had asthma (10%) as a primary diagnosis. Other common diagnoses were viral pneumonia (n=267;22%) and bacterial pneumonia (n=233; 20%). The median duration of ECMO support was 191 hours, with a median 16-day length of stay. The most common patient-related complications were infection (15%), arrhythmia (11%) and pneumothorax (10.4%). Survivors had a lower median age (43 vs 49; 95% CI) and were more likely to have a primary diagnosis of asthma (12% vs 2%; 95% CI). More interestingly, patients with a primary diagnosis of asthma had a survival rate to ECMO ICU discharge of 95% (95% CI), compared with 71% of those with other diagnoses. After using multiple logistic regression models, factors associated with survival included: younger age ($p<0.001$), higher weight ($p<0.001$), primary diagnosis of asthma ($p<0.001$) and higher SaO_2 at the time for decision-to-cannulate ($p=0.008$). **(Table 10)** The authors state that the survival rate is the highest reported until now, in cohorts of adult respiratory ECMO, and significantly higher than the 60% survival reported by the January 2020 ELSO international summary for adults treated for respiratory failure, probably due to patient selection criteria, and a small number of specialist centers.[30]

ECMO has also been used in refractory cases of acute severe asthma and refractory bronchospasm.[70] In cases of intractable respiratory acidosis, where it is impossible to adequately ventilate the patient, ECMO can be an invaluable resource, as it can be much more efficient at carbon dioxide removal.[71] The major determinants of how quickly a drop in the $PaCO_2$ can be achieved are the sweep gas flow and the partial pressure of carbon dioxide in arterial blood entering the membrane lung, i.e., the higher the pCO_2, the higher the efficiency with which the carbon dioxide will be removed. A 5-year retrospective study of the outcomes of ECMO for the treatment of severe asthma among 16 patients at a tertiary center revealed rapid resolution of both hypoxemia and hypercapnia, with significant improvement noted in the first hour.[56] The use of ECMO in respiratory failure allows for the lungs to rest (using ventilator settings that would minimize ventilator-induced lung injury—the so-called “ultra-low” and low tidal volume ventilation—usually tidal volumes in the order of 4-6 mL/kg of ideal body weight). ECMO also allows for aggressive airway clearance, such as repeated therapeutic bronchoscopies for mucus plugging and then bronchoscopy-guided electro- cautery to relieve subsequent tracheal stenosis.

Patel et al suggested that the requirement for ECMO was associated, in Patel´s et al review with younger age, female sex and the presence of either fungal or rhinoviral infection in the lower airway **(Table 10)**.[3] In addition, a higher white cell count, a more profound degree of hypercapnia and acidemia, as well as an increased length of stay in the ICU and hospital overall, were observed in those requiring ECMO support.

Interestingly, a lower percentage of patients receiving moderate and high-dose inhaled corticosteroids (ICS) and/or long-acting β-agonists required ECMO compared to those requiring mechanical ventilation only (moderate: 17% versus 27%; high: 6% versus 12%). Furthermore, no patient in either treatment group had required long-term oral corticosteroids or biologic agents. In those requiring ECMO, the authors report that in the year preceding acute admission, only 31% (seven out of 22) received regular ICS, 36% had documentation of regular short-acting β-agonist use and 31% had received at least one 7-day course of oral corticosteroids (data not shown).[3]

This case series highlights rhinovirus infection as well as positive fungal isolates as being particularly associated with the need for ECMO in patients with acute severe asthma.[3,14,55] It is noteworthy that despite the severity of illness and inability to mechanically ventilate these patients, ECMO was associated with 100% survival and widespread access to this life-saving therapy should be made a priority.**(Table 9)** [3]

7. Conclusion and Unmet needs:

In cases of severe acute asthma with intractable respiratory acidosis, where it is impossible to adequately ventilate the patient, ECMO can be an invaluable resource, as it can be much more efficient at carbon dioxide removal.[49] In the future, circuits should be optimized in terms of biocompatibility, be smaller in size [59] and portabile, ideally not needing anticoagulation and showing a lower proinflammatory profile.[72] The development of bioengineering research with regards ECCOR is of special relevance. Further use of ECMO in the critical patient is expected to increase in the next few years. Although we do not expect to have solid evidence base of the use of ECMO/ECCO2R in NFA, the results of the available literature and experience recommend to have these procedures as valuable options, specially ECMO, as it has a very valuable life-saving potential provided it is performed in specialized and referral centers.[29–32,35,37,73]

Bibliography

1. Maqsood U, Patel N. Extracorporeal membrane oxygenation (ECMO) for near-fatal asthma refractory to conventional ventilation. BMJ Case Rep. 2018;2018.
2. Mikkelsen ME, Woo YJ, Sager JS, Fuchs BD, Christie JD. Outcomes using extracorporeal life support for adult respiratory failure due to status asthmaticus. ASAIO J. 2009 Jan;55(1):47–52.
3. Patel S, Shah NM, Malhotra AM, Lockie C, Camporota L, Barrett N, et al. Inflammatory and microbiological associations with near-fatal asthma requiring extracorporeal membrane oxygenation. ERJ Open Res. 2020 Jan;6(1):00267–2019.
4. Serrano-Pariente J, Plaza V. Near-fatal asthma: A heterogeneous clinical entity. Curr Opin Allergy Clin Immunol. 2017;17(1):28–35.
5. Vianello A, Caminati M, Crivellaro M, El Mazloum R, Snenghi R, Schiappoli M, et al. Fatal asthma; is it still an epidemic? World Allergy Organ J [Internet]. 2016;9(1):42. Available from: https://doi.org/10.1186/s40413-016-0129-9
6. Richards GN, Kolbe J, Fenwick J, Rea HH. Demographic characteristics of patients with severe life threatening asthma: comparison with asthma deaths. Thorax. 1993 Nov;48(11):1105–9.
7. Campbell DA, McLennan G, Coates JR, Frith PA, Gluyas PA, Latimer KM, et al. A comparison of asthma deaths and near-fatal asthma attacks in South Australia. Eur Respir J. 1994 Mar;7(3):490–7.
8. Kenyon N, Zeki AA, Albertson TE, Louie S. Definition of Critical Asthma Syndromes. Clin Rev Allergy Immunol. 2015;48(1):1–6.
9. Greenberger PA. Potentially (near) fatal asthma. Allergy asthma Proc. 2019 Nov;40(6):403–5.
10. Rodríguez-Trigo G, Plaza V, Picado C, Sanchis J. [Management according to the Global Initiative for Asthma guidelines of patients with near-fatal asthma reduces morbidity and mortality]. Arch Bronconeumol. 2008 Apr;44(4):192–6.
11. Sandrock CE, Norris A. Infection in severe asthma exacerbations and critical asthma

syndrome. Clin Rev Allergy Immunol. 2015 Feb;48(1):104–13.
12. Tan WC, Xiang X, Qiu D, Ng TP, Lam SF, Hegele RG. Epidemiology of respiratory viruses in patients hospitalized with near-fatal asthma, acute exacerbations of asthma, or chronic obstructive pulmonary disease. Am J Med. 2003 Sep;115(4):272–7.
13. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. J Allergy Clin Immunol. 2010 Jun;125(6):1178–9.
14. Jackson DJ, Makrinioti H, Rana BMJ, Shamji BWH, Trujillo-Torralbo M-B, Footitt J, et al. IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo. Am J Respir Crit Care Med. 2014 Dec;190(12):1373–82.
15. Edwards MR, Strong K, Cameron A, Walton RP, Jackson DJ, Johnston SL. Viral infections in allergy and immunology: How allergic inflammation influences viral infections and illness. J Allergy Clin Immunol. 2017 Oct;140(4):909–20.
16. O’Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O’Connell EJ, Ballard DJ, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. N Engl J Med. 1991 Feb;324(6):359–63.
17. Medrek SK, Kao CC, Yang DH, Hanania NA, Parulekar AD. Fungal Sensitization Is Associated with Increased Risk of Life-Threatening Asthma. J allergy Clin Immunol Pract. 2017;5(4):1025-1031.e2.
18. Rodrigo GJ, Plaza V, Neffen H, Levy G, Perpiñá M. Relationship between the characteristics of hospitalised acute asthma patients and the severity of their asthma. A case-control study. Allergol Immunopathol (Madr). 2009;37(5):225–9.
19. Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, Fitzgerald JM. Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. Am J Respir Crit Care Med. 1998 Jun;157(6 Pt 1):1804–9.
20. Strunk RC. Identification of the fatality-prone subject with asthma. J Allergy Clin Immunol. 1989 Feb;83(2 Pt 1):477–85.
21. McFadden ERJ, Warren EL. Observations on asthma mortality. Ann Intern Med. 1997 Jul;127(2):142–7.
22. Picado C. Barcelona’s asthma epidemics: clinical aspects and intriguing findings. Thorax. 1992 Mar;47(3):197–200.
23. Martinez-Moragón E, Plaza V, Serrano J, Picado C, Galdiz JB, López-Viña A, et al. Near-fatal asthma related to menstruation. J Allergy Clin Immunol. 2004 Feb;113(2):242–4.
24. Serrano-Pariente J, Rodrigo G, Fiz JA, Crespo A, Plaza V. Identification and characterization of near-fatal asthma phenotypes by cluster analysis. Allergy. 2015 Sep;70(9):1139–47.
25. Gonzalez-Barcala F-J, Calvo-Alvarez U, Garcia-Sanz M-T, Bourdin A, Pose-Reino A, Carreira J-M, et al. Characteristics and prognosis of near-fatal asthma exacerbations. Am J Med Sci. 2015 Aug;350(2):98–102.
26. Antó JM, Sunyer J, Reed CE, Sabrià J, Martínez F, Morell F, et al. Preventing asthma epidemics due to soybeans by dust-control measures. N Engl J Med. 1993 Dec;329(24):1760–3.
27. Camporota L, Meadows C, Ledot S, Scott I, Harvey C, Garcia M, et al. Consensus on the referral and admission of patients with severe respiratory failure to the NHS ECMO service. Vol. 9, The Lancet Respiratory Medicine. Lancet Publishing Group; 2021. p. e16–7.
28. Amado-Rodríguez L, Del Busto C, García-Prieto E, Albaiceta GM. Mechanical ventilation in acute respiratory distress syndrome: The open lung revisited. Med intensiva. 2017 Dec;41(9):550–8.
29. López Sanchez M. Mechanical ventilation in patients subjected to extracorporeal membrane oxygenation (ECMO). Med intensiva. 2017 Nov;41(8):491–6.
30. Warren A, Chiu Y-D, Villar SS, Fowles J-A, Symes N, Barker J, et al. Outcomes of the NHS England National Extracorporeal Membrane Oxygenation Service for adults with respiratory failure: a multicentre observational cohort study. Br J Anaesth. 2020

Sep;125(3):259–66.

31. Alzeer AH, Al Otair HA, Khurshid SM, El Badrawy S, Bakir BM. A case of near fatal asthma: The role of ECMO as rescue therapy. Ann Thorac Med. 2015;10(2):143–5.
32. Fernández-Mondéjar E, Fuset-Cabanes MP, Grau-Carmona T, López-Sánchez M, Peñuelas Ó, Pérez-Vela JL, et al. The use of ECMO in ICU. Recommendations of the Spanish Society of Critical Care Medicine and Coronary Units. Med intensiva. 2019 Mar;43(2):108–20.
33. Riera J, Alcántara S, Bonilla C, Fortuna P, Blandino Ortiz A, Vaz A, et al. Risk factors for mortality in patients with COVID-19 needing extracorporeal respiratory support. Vol. 59, The European respiratory journal. 2022.
34. Bartlett RH. Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: EOLIA and Beyond. Crit Care Med. 2019 Jan;47(1):114–7.
35. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. N Engl J Med. 2018 May;378(21):1965–75.
36. Ouweneel DM, Schotborgh J V, Limpens J, Sjauw KD, Engström AE, Lagrand WK, et al. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. Intensive Care Med. 2016 Dec;42(12):1922–34.
37. Extracorporeal Life Support Organization (ELSO). Guidelines for Adult Respiratory Failure. Extracorpor Life Support Organ. 2017;(August):1–32.
38. Ficial B, Vasques F, Zhang J, Whebell S, Slattery M, Lamas T, et al. Physiological basis of extracorporeal membrane oxygenation and extracorporeal carbon dioxide removal in respiratory failure. Membranes (Basel). 2021;11(3):NA.
39. Al-Fares A, Pettenuzzo T, Del Sorbo L. Extracorporeal life support and systemic inflammation. Intensive Care Med Exp. 2019;7(S1):1–14.
40. Morelli A, Del Sorbo L, Pesenti A, Ranieri VM, Fan E. Extracorporeal carbon dioxide removal (ECCO2R) in patients with acute respiratory failure. Intensive Care Med [Internet]. 2017;43(4):519–30. Available from: https://doi.org/10.1007/s00134-016-4673-0
41. McNamee JJ, Gillies MA, Barrett NA, Perkins GD, Tunnicliffe W, Young D, et al. Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure: The REST Randomized Clinical Trial. JAMA. 2021 Sep;326(11):1013–23.
42. Medar SS, Peek GJ, Rastogi D. Extracorporeal and advanced therapies for progressive refractory near-fatal acute severe asthma in children. Vol. 55, Pediatric Pulmonology. John Wiley and Sons Inc.; 2020. p. 1311–9.
43. Yeo HJ, Kim D, Jeon D, Kim YS, Rycus P, Cho WH. Extracorporeal membrane oxygenation for life-threatening asthma refractory to mechanical ventilation: Analysis of the Extracorporeal Life Support Organization registry. Crit Care. 2017;21(1).
44. Aravantagi A, Patra KP, Shekar S, Scott LK. Pumpless arteriovenous carbon dioxide removal: A novel simplified strategy for severe asthma in children. Vol. 15, Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2011. p. 224–6.
45. Tonna JE, Abrams D, Brodie D, Greenwood JC, RUBIO Mateo-Sidron JA, Usman A, et al. Management of Adult Patients Supported with Venovenous Extracorporeal Membrane Oxygenation (VV ECMO): Guideline from the Extracorporeal Life Support Organization (ELSO). ASAIO J [Internet]. 2021;67(6). Available from: https://journals.lww.com/asaiojournal/Fulltext/2021/06000/Management_of_Adult_Patients_Supported_with.1.aspx
46. Molina Lobo R, Lobo-Valbuena B, Gordo F. Management of severe ARDS due to SARS-CoV-2 pneumonia using low-flow extracorporeal CO2 extraction. Crit Care [Internet]. 2021;25(1):1–3. Available from: https://doi.org/10.1186/s13054-021-03777-1
47. Martínez-Solano J, Sousa-Casasnovas I, Espinosa MÁ. Ghost cannula after ECMO

removal. Med intensiva. 2020 Sep;

48. Augy JL, Aissaoui N, Richard C, Maury E, Fartoukh M, Mekontso-Dessap A, et al. A 2-year multicenter, observational, prospective, cohort study on extracorporeal CO(2) removal in a large metropolis area. J intensive care [Internet]. 2019 Aug 20;7:45. Available from: https://pubmed.ncbi.nlm.nih.gov/31452899
49. Aretha D, Fligou F, Kiekkas P, Karamouzos V, Voyagis G. Extracorporeal Life Support: The Next Step in Moderate to Severe ARDS-A Review and Meta-Analysis of the Literature. Biomed Res Int [Internet]. 2019 Sep 29;2019:1035730. Available from: https://pubmed.ncbi.nlm.nih.gov/31662961
50. Elliot SC, Paramasivam K, Oram J, Bodenham AR, Howell SJ, Mallick A. Pumpless extracorporeal carbon dioxide removal for life-threatening asthma. Crit Care Med. 2007 Mar;35(3):945–8.
51. Schneider T-M, Bence T, Brettner F. "Awake" ECCO(2)R superseded intubation in a near-fatal asthma attack. Vol. 5, Journal of intensive care. 2017. p. 53.
52. Brenner K, Abrams DC, Agerstrand CL, Brodie D. Extracorporeal carbon dioxide removal for refractory status asthmaticus: experience in distinct exacerbation phenotypes. Perfusion. 2014 Jan;29(1):26–8.
53. Pavot A, Mallat J, Vangrunderbeeck N, Thevenin D, Lemyze M. Rescue therapeutic strategy combining ultra-protective mechanical ventilation with extracorporeal CO2 removal membrane in near-fatal asthma with severe pulmonary barotraumas: A case report. Medicine (Baltimore). 2017 Oct;96(41):e8248.
54. Hebbar KB, Petrillo-Albarano T, Coto-Puckett W, Heard M, Rycus PT, Fortenberry JD. Experience with use of extracorporeal life support for severe refractory status asthmaticus in children. Crit Care. 2009;13(2):R29.
55. Greenawald L, Strang A, Froehlich C, Chidekel A. Status asthmaticus requiring extracorporeal membrane oxygenation associated with rhinovirus infection. J Asthma. 2020 Mar 3;57(3):343–6.
56. Di Lascio G, Prifti E, Messai E, Peris A, Harmelin G, Xhaxho R, et al. Extracorporeal membrane oxygenation support for life-threatening acute severe status asthmaticus. Perfusion. 2017 Mar;32(2):157–63.
57. Vutipongsatorn K, Fujitake E, Singh S. Extracorporeal membrane oxygenation in life-threatening asthma unresponsive to mechanical ventilation: a comparison of patient demographics and outcomes between a large London-based intensive care unit and an international registry. Vol. 19, Clinical Medicine. 2019. p. s19–s19.
58. Zakrajsek JK, Min S-J, Ho PM, Kiser TH, Kannappan A, Sottile PD, et al. Extracorporeal Membrane Oxygenation (ECMO) for Refractory Asthma Exacerbations with Respiratory Failure. Chest. 2022 Sep;
59. Serpa Neto A, Schmidt M, Azevedo LCP, Bein T, Brochard L, Beutel G, et al. Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis: Mechanical ventilation during ECMO. Intensive Care Med. 2016;42(11):1672–84.
60. Marhong JD, Munshi L, Detsky M, Telesnicki T, Fan E. Mechanical ventilation during extracorporeal life support (ECLS): a systematic review. Intensive Care Med [Internet]. 2015;41(6):994–1003. Available from: http://dx.doi.org/10.1007/s00134-015-3716-2
61. Schmidt M, Pellegrino V, Combes A, Scheinkestel C, Cooper DJ, Hodgson C. Mechanical ventilation during extracorporeal membrane oxygenation. Crit Care. 2014 Jan;18(1):203.
62. Patel B, Arcaro M, Chatterjee S. Bedside troubleshooting during venovenous extracorporeal membrane oxygenation (ECMO). J Thorac Dis. 2019;11(Suppl 14):S1698–707.
63. Krishnamurthy V, Karanth S. Rational Approach to Chatter in Venovenous Extracorporeal Membrane Oxygenation to Limit Fluid Administration: An Algorithmic Description. Indian J Crit care Med peer-reviewed, Off Publ Indian Soc Crit Care Med. 2022 Feb;26(2):244–5.

64. Sarkar M, Niranjan N, Banyal PK. Mechanisms of hypoxemia. Lung India. 2017;34(1):47–60.
65. Papiris S, Kotanidou A, Malagari K, Roussos C. art%3A10.1186%2Fcc1451. 2002;6(1).
66. Nunez JI, Gosling AF, O’Gara B, Kennedy KF, Rycus P, Abrams D, et al. Bleeding and thrombotic events in adults supported with venovenous extracorporeal membrane oxygenation: an ELSO registry analysis. Intensive Care Med. 2022 Feb;48(2):213–24.
67. Abrams D, Grasselli G, Schmidt M, Mueller T, Brodie D. ECLS-associated infections in adults: what we know and what we don’t yet know. Intensive Care Med. 2020 Feb;46(2):182–91.
68. Mcilwain B, Timpa J, Kurundkar AR, Holt DW, Kelly DR, Hartman Y, et al. Stores in the Intestine. 2010;90(1):128–39.
69. Bourdin A, Charriot J, Boissin C, Ahmed E, Suehs C, De Sevin A, et al. Will the asthma revolution fostered by biologics also benefit adult ICU patients? Allergy Eur J Allergy Clin Immunol. 2021;76(8):2395–406.
70. Mabuchi N, Takasu H, Ito S, Yamada T, Arakawa M, Hatta M, et al. Successful extracorporeal lung assist (ECLA) for a patient with severe asthma and cardiac arrest. Clin Intensive Care. 1991;2(5):292–4.
71. Kukita I, Okamoto K, Sato T, Shibata Y, Taki K, Kurose M, et al. Emergency extracorporeal life support for patients with near-fatal status asthmaticus. Am J Emerg Med. 1997 Oct;15(6):566–9.
72. Maul TM, Massicotte MP, Wearden PD. ECMO Biocompatibility: Surface Coatings, Anticoagulation, and Coagulation Monitoring. Extracorporeal Membrane Oxygenation: Advances in Therapy. 2016.
73. Lang Y, Zheng Y, Hu X, Xu L, Luo Z, Duan D, et al. Extracorporeal membrane oxygenation for near fatal asthma with sudden cardiac arrest. J Asthma. 2021;58(9):1216–20.