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# EXTRACORPOREAL MEMBRANE OXYGENATION IN CLINICAL PRACTICE: LITERATURE REVIEW

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**Abstract.** Extracorporeal membrane oxygenation (ECMO) is a method of maintaining adequate cardiac output, oxygenation and gas exchange in patients with refractory shock and decompensated respiratory failure, when other treatments are ineffective. The publication provides historical information and an overview of modern research on the use of ECMO in adults and children in critical condition. It has been demonstrated that over the past decade, the frequency of ECMO use has increased significantly, which has significantly improved treatment outcomes, however, the main limiting factor is the timing of initiation and the duration of the operation, since when ECMO is connected in the later stages of the disease, the likelihood of failure increases significantly. It is indicated that the use of veno-arterio-venous ECMO is most effective in the treatment of critical respiratory failure associated with cardiogenic shock or end-stage lung disease. It is reflected that the main complications of ECMO include artery damage, compression syndrome, infection, stroke, acute kidney injury, bleeding and the need for blood transfusion. Marked, that the use of a central VA-ECMO connection in cardiac surgery is associated with greater in-hospital mortality. It was found that the use of levosimendan contributed to faster and smoother weaning from a respirator and improved survival of patients with cardiogenic or postcardiotomy shock. Particular attention is paid to the use of ECMO in toxicology, obstetrics and pediatric practice. Data on the high effectiveness of ECMO use in adults and children with acute poisoning with corticotropic toxicants are presented, which indicates the need for wider use of this technique in patients with a toxicological profile, especially in the early stages when there are signs of small cardiac output syndrome and cardiogenic shock. The results of studies indicating the safety and sufficient effectiveness of ECMO use during pregnancy when used in a specialized center are indicated, the maximum survival rates in pregnant women were noted when using ECMO for cardiac indications.

**Keywords:** extracorporeal membrane oxygenation, extracorporeal life support, shock, poisoning, outcome, pediatric, adult

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# ЭКСТРАКОРПОРАЛЬНАЯ МЕМБРАННАЯ ОКСИГЕНАЦИЯ В КЛИНИЧЕСКОЙ ПРАКТИКЕ: ОБЗОР ЛИТЕРАТУРЫ

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**Резюме.** Экстракорпоральная мембранная оксигенация (ЭКМО) — метод поддержания адекватного сердечного выброса, оксигенации и газообмена у пациентов с явлениями рефрактерного шока и декомпенсированной дыхательной недостаточности, когда другие методы лечения оказываются неэффективными. В публикации представлены исторические сведения и обзор современных исследований, посвященных применению ЭКМО у взрослых и детей, находящихся в критическом состоянии. Продемонстрировано, что за последнее десятилетие частота применения ЭКМО значительно возросла, что позволило существенно улучшить результаты лечения, однако основным ограничивающим фактором являются сроки инициации и длительность операции, поскольку при подключении ЭКМО на поздних стадиях заболевания вероятность неудач значительно возрастает. Указано, что использование вено-артерио-венозной ЭКМО наиболее эффективно при лечении критической дыхательной недостаточности, ассоциированной с кардиогенным шоком или терминальной стадией заболевания легких. Отражено, что основные осложнения ЭКМО включают повреждение артерии, синдром сдавления, инфицирование, инсульт, острое повреждение почек, кровотечение и необходимость переливания крови. Отмечено, что применение центрального подключения ВА-ЭКМО в кардиохирургии ассоциировано с большей внутрибольничной смертностью. Установлено, что применение левосимендана способствовало более быстрому и гладкому отлучению от респиратора и улучшению выживаемости пациентов с кардиогенным или посткардиотомным шоком. Особое внимание уделено использованию ЭКМО в токсикологии, акушерстве и педиатрической практике. Представлены данные о высокой эффективности использования ЭКМО у взрослых и детей с острыми отравлениями кортикотропными токсикантами, что свидетельствует о необходимости более широкого применения данной методики у пациентов токсикологического профиля, особенно на ранних стадиях, когда имеют место признаки синдрома малого сердечного выброса и кардиогенного шока. Указаны результаты исследований, свидетельствующие о безопасности и достаточной эффективности применения ЭКМО во время беременности при ее использовании в условиях специализированного центра, максимальные показатели выживаемости у беременных отмечены при использовании ЭКМО по «кардиальным» показаниям.

**Ключевые слова:** экстракорпоральная мембранная оксигенация, экстракорпоральное поддержание жизни, шок, отравления, исходы, педиатрия, взрослые

## INTRODUCTION

The history of extracorporeal membrane oxygenation (ECMO) dates back to the 17th century. In 1693, Jean-Baptiste Denis conducted the first experiments on cross-transfusion of blood from a lamb to a human to determine whether living blood could be transferred between two species.

In 1860, the famous British anesthesiologist Benjamin Ward Richardson, MD, conducted experiments on animals. He saturated blood with oxygen and injected it into the right heart to create artificial circulation. The results were promising, but due to the lack of anticoagulation, they could not be used in clinical practice.

On this subject, B.U. Richardson wrote: “I conclude that reanimation [and artificial circulation] ... is a possible process, and that it requires only time, experimentation, and patience to develop into a proven fact of modern science”.

In the 1920s, Soviet experimental scientist Professor Sergei Sergeevich Bryukhoneko and his colleagues developed a system of total body perfusion called the “autogector,” which used the lungs of animal donors to saturate the blood with oxygen. Later, they used a bubble oxygenator to conduct successful experiments on animals with the heart excluded from the circulation.

In 1931, surgeon John Gibbon eloquently described the anguish and suffering he experienced due to the loss of a young woman who died of pulmonary embolism. “During that long night, helplessly watching the patient fight for her life as her blood grew darker... it naturally occurred to me that if it were possible to continuously remove some of the blue blood... saturate that blood with oxygen... and then continuously return the now red blood to the patient’s arteries, we might be able to save her life”.

This event became the starting point for the further development of extracorporeal oxygenation. In the 1930s, J. Gibbon developed a stand-alone roller pump for extracorporeal support, and the entire artificial circulation device was the size of a small piano, which created thin films of deoxygenated blood passing through a screen, followed by their saturation with oxygen. It took 22 years before Dr. Gibbon was able to use the device in the operating room.

On the 6th of May 1953, he performed the first successful extracorporeal-assisted correction of an atrial septal defect in 18-year-old Cecilia Bavolek [1–4].

In 1975 Dr. Bartlett successfully treated the first infant using ECMO. It was a little girl whom the nurses named Esperanza, meaning “Hope”.

Five years later, the neonatal ECMO project moved with Dr. Bartlett from the University of California, Irvine, to the University of Michigan, where experience gradually increased from a few patients per year to several cases per month. He standardized the technique and exported his own ideas around the world [5].

Extracorporeal membrane oxygenation is currently used as a method of life support and restoration of bodily functions when other therapeutic strategies prove ineffective in both adults and children [6–8]. It is widely used in pediatric cardiac surgery and toxicology when severe systemic hypoxia, low cardiac output syndrome, refractory cardiogenic shock, and acute kidney injury develop [9]. Venous-arterial ECMO (VA-ECMO) has become the standard of care for true cardiogenic shock and multiple organ failure [10].

The most common indications for VA-ECMO were acute myocardial infarction (34.8%), decompensated heart failure (30.3%), and cardiac arrest (10.2%). VA-ECMO was used during cardiopulmonary resuscitation in 26.6% of cases, 48% of which were related to cardiac arrest. Complications included arterial injury (3.7%), compartment syndrome (4.1%), infection (1.2%), stroke (14.8%), acute kidney injury (52.5%), bleeding at the access site (16%), and the need for blood transfusion (83.2%). Hyperlactatemia and the presence of severe multiple organ failure were independently associated with unfavorable outcomes [11].

An analysis of the effectiveness of veno-arterio-venous ECMO, which is used as a rescue strategy in patients with critical respiratory failure combined with refractory shock, has shown that it is most effective in the treatment of critical respiratory failure associated with cardiogenic shock or end-stage lung disease, However, in septic shock, it has no significant effect on the outcome [12].

## EXTRACORPOREAL MEMBRANE OXYGENATION IN CARDIAC SURGERY

The most common indications for central and peripheral VA-ECMO connection in cardiac surgery are failure to wean from the heart-lung machine (38%) and development of decompensated heart failure after weaning from the heart-lung machine (48%). The 30-day in-hospital mortality rate in the general population was 66.6%. In patients who underwent peripheral VA-ECMO, it was lower compared to central connection. The use of central VA-ECMO connection was associated with higher in-hospital mortality [13].

An analysis of the use of VA-ECMO as a rescue therapy for refractory cardiogenic shock found that the average duration of support was 4 days, and treatment in the intensive care unit (ICU) was 15 days. The overall 30-day survival rate for patients included in the study was 69.6%, and the

one-year survival rate was 59.8%. For patients who were weaned off VA-ECMO, the 30-day survival rate was 100%, and the one-year survival rate was 92.9%. The results obtained demonstrate the advantages of using VA-ECMO in patients with refractory cardiogenic shock [14].

VA-ECMO provides a temporary support system for patients with cardiogenic shock who are refractory to conventional medical therapy. Levosimendan has been reported to facilitate weaning from VA-ECMO and improve survival. The primary aim of this review was to examine the effect of levosimendan use on VA-ECMO weaning and mortality in critically ill patients on VA-ECMO.

A group of authors attempted to evaluate the effectiveness of levosimendan use in the context of ECMO. Seven observational studies were selected, involving 630 patients, more than half of whom had undergone heart surgery. The duration of VA-ECMO ranged from four to twelve days. It was found that the use of levosimendan was significantly associated with successful weaning from ALV compared to the control group. To study survival, six studies (n=617) were included in the meta-analysis, involving 326 patients in the levosimendan group and 291 in the comparison group. The results showed significantly higher survival in the levosimendan group — 95%. The authors concluded that the use of levosimendan contributed to faster and smoother weaning from the ventilator and improved survival in patients with cardiogenic or post-cardiotomy shock [15].

A relatively recent case has been described involving the use of ECMO to treat cardiogenic shock caused by nodal ectopic tachycardia (JET tachycardia) in a three-month-old girl who had previously been healthy. Drug and electrical cardioversion, as well as transesophageal pacing, were unsuccessful. Echocardiography revealed atrial dilation and severe left ventricular systolic dysfunction. Approximately 8 hours after admission, VA-ECMO was initiated, which allowed successful treatment with amiodarone. ECMO lasted six days, with complete restoration of cardiac contractility without any complications or negative consequences [16].

## EXTRACORPOREAL MEMBRANE OXYGENATION IN TOXICOLOGY

A retrospective analysis of the frequency of ECMO use in poisoning cases in the United States has shown that over the past decade, this treatment method has become more widely used in both adults and children, with an increase of almost 100% since 2008 and an overall survival rate of 70%. The risk of death when using ECMO is highest in cases of poisoning with hematotoxic compounds that affect metabolism [17, 18].

Patients who have undergone VA-ECMO for refractory shock or cardiac arrest due to poisoning have a lower mortality rate than those who receive VA-ECMO for indications unrelated to poisoning. Poisoned patients treated with ECMO have lower mortality rates compared to those treated without ECMO with similar disease severity and after adjusted analyses, regardless of the type of food intake [18].

One publication demonstrates the successful use of VA-ECMO in 104 young patients with severe poisoning and cardiogenic shock. In 47.1% of cases, cardiovascular dysfunction developed after the use of cardiotoxic drugs, and 8.7% of patients had used opiates. All patients had multiple cardiac arrests before being connected to the ECMO machine, but 24 hours after ECMO initiation, there was a clear positive trend — regression of hemodynamic disturbances and normalization of blood acid-base status indicators. In 52.9% of cases, a favorable outcome was established, of which 47% of patients had episodes of cardiac arrest before being connected to VA-ECMO [19].

An analysis of the extracorporeal life support registry from 2003 to 2019 revealed 86 cases of acute poisoning. The average age of patients was 12.0 years, and 52.9% were female. VA-ECMO was used more often than veno-venous ECMO (VV-ECMO), and its use increased significantly during the study period. A bimodal distribution of ECMO support was observed among two age groups: under three years (n=34) and 13–17 years (n=41). Hemodynamic and metabolic parameters improved in all patients during ECMO use [20].

There are reports of successful use of VA-ECMO in cases of poisoning with high doses of metformin and trazodone, amlodipine and candesartan, yew leaves, inhalation poisoning with bromine, benzene derivatives, etc. [21–24].

Russian authors in cases of severe combined methadone and alcohol poisoning obtained similar results of treatment using ECMO. The use of ECMO in these situations may become a promising therapeutic strategy that contributes to a reduction in mortality [25].

The results of VA-ECMO/ECMO-CPR (cardiopulmonary resuscitation) use in 32 patients with refractory cardiogenic shock (n=25) or cardiac arrest (n=7) caused by acute drug poisoning are presented. Twenty-six (81.2%) patients were successfully weaned from VA-ECMO, with a mean duration of surgery of 2.9±1.3 days. The overall survival rate until hospital discharge was 78.1%, and all patients were discharged with good neurological status [26].

It has been established that patient survival correlates with the timing of hospitalization and initiation of VA-ECMO,

which is much higher with the earliest possible use of VA-ECMO [27].

There is evidence that in patients with acute poisoning, the incidence of complications and mortality when using ECMO is significantly lower compared to other categories of patients who had other indications [27–29].

## EXTRACORPOREAL MEMBRANE OXYGENATION IN INFECTIONS

A retrospective analysis evaluating the effectiveness of ECMO in adults and children with meningococcal sepsis found that the overall survival rate prior to hospital discharge was 46.7%, with the highest rate observed in patients with critical respiratory failure receiving VV-ECMO, at 85.7%. Survival rates with VA-ECMO in patients with lung disease were much lower (32.4%). When VA-ECMO was used for “cardiac” indications, survival rates reached 60.9%. With extracorporeal cardiopulmonary resuscitation, survival rates were minimal (14.3%). The most common complications were hemostasis disorders, which occurred in 43.4% of patients, but they did not affect mortality rates. The presence of neurological complications was associated with increased mortality. The authors believe that ECMO can be used as a rescue therapy in children with meningococcemia and refractory cardiopulmonary failure. Optimal treatment results were obtained with VV-ECMO in hypoxemic respiratory failure. VA-ECMO was most effective when used for cardiac indications [30].

Cases of ECMO use in severe viral pneumonia caused by the influenza virus are described. The authors note that the demand for ECMO in infectious disease hospitals during periods of seasonal epidemic influenza and other acute respiratory viral infections can range from 0.01 to 1.6% of hospitalized patients [31]. In 2021, a case was published on the use of ECMO in the complex therapy of septic shock in a patient with severe lung damage caused by COVID-19 [32].

When evaluating the results of treatment of acute respiratory distress syndrome caused by the SARS-CoV-2 virus using ECMO, it was found that survivors had a shorter time interval from the onset of the disease and transfer to artificial lung ventilation (ALV) before ECMO initiation. The mortality rate was 82.4% [33].

The presence of tachycardia in patients with COVID-19 undergoing VV-ECMO does not rule out vegetative imbalance with a significant predominance of parasympathetic tone of the autonomic nervous system (ANS) over sympathetic tone, which is reliably associated with an unfavorable outcome [34].

## EXTRACORPOREAL MEMBRANE OXYGENATION DURING PREGNANCY

A systematic review has demonstrated that VV-ECMO in pregnant women, women in labor, and postpartum women can save five out of six mothers, with a survival rate of over 80%. At the same time, intrauterine fetal death rates doubled, and adverse outcomes accounted for approximately one-third (fetal survival rate was about 67.9%) [35]. A number of authors believe that the use of ECMO during pregnancy is safe and, as a rule, produces satisfactory results if performed in a specialized center [36, 37]. The most common complication of ECMO for the mother was bleeding, which occurred in 37.2% of cases [37]. The highest survival rates were observed when ECMO was used for “cardiac” indications [38].

## EXTRACORPOREAL MEMBRANE OXYGENATION IN PEDIATRIC PRACTICE

Between 1990 and 2020, there has been a steady increase in the frequency of extracorporeal cardiopulmonary resuscitation in children, which was used in more than 70% of cases of primary cardiac arrest. The overall survival rate was 46%, and survival with a favorable neurological outcome was noted in 30% of cases, which indicates the high effectiveness of this method of therapy [39].

ECMO is actively used in children with oncology and hematological diseases. The main indications are respiratory failure (46%), combined cardiorespiratory failure (28%), and heart failure (25%). VV-ECMO was used in 45% of patients, and 53% of patients were transferred to VA-ECMO. Survival before ECMO connection was 52% (62/118) in patients with cancer and 64% (20/31) in patients who underwent hematopoietic cell transplantation, and survival before hospital discharge was 36% (43/118) and 42% (13/31), respectively. The need for extracorporeal cardiopulmonary resuscitation was associated with an increased likelihood of fatal outcomes [40].

One of the indications for ECMO in children is the perioperative period during liver transplantation. It has been established that the median time from liver transplantation to ECMO initiation was 5 days (0.0–12.3), and the average duration was one day. It has been demonstrated that when ECMO was initiated within one day after liver transplantation, survival was statistically significantly higher. As the time from liver transplantation to the start of ECMO increased, the probability of death increased significantly. The overall survival rate in the entire patient population was 55.9%. These encouraging results suggest that ECMO should be considered an acceptable treatment option for potentially

reversible refractory respiratory or cardiovascular failure in children after liver transplantation [41].

A number of studies, including clinical cases, provide clear evidence of the effectiveness of ECMO in treating refractory hypoxemia and cardiogenic shock in acute poisoning in children, reducing the mortality rate to 32% of patients. Risk factors for fatal outcomes include the use of inhaled nitric oxide, lower arterial blood pH, severe hypercapnia prior to ECMO initiation, and the need for inotropic and vasopressor drugs during surgery [42]. A case of successful use of ECMO in a 12-year-old girl with severe calcium channel blocker overdose has been published, with complete recovery [43].

The use of ECMO in the treatment of sepsis and septic shock in children remains controversial. Results vary significantly depending on age, clinical presentation, and identified pathogen.

Newborns and children with septic cardiomyopathy have more optimistic outcomes [44]. The overall survival rate of children with sepsis who underwent ECMO was 59%, while in newborns it reached 73% [45].

The risk of death is highest in the presence of mixed viral infections, while no difference in mortality was found in patients with polymicrobial bacterial pneumonias.Patients with respiratory syncytial virus and SARS-CoV-2 infections had a higher mortality rate [46]. At the same time, a case of successful ECMO in an eight-year-old girl with a positive test for SARS-CoV-2 and severe hypoxemic respiratory failure was published, which resulted in complete recovery. The duration of VV-ECMO was 14 days and the duration of invasive ALV was 20 days [47].

When peripheral cannulation was used in children with sepsis and septic shock, the overall survival rate was 71%; 68% of children survived to hospital discharge. In-hospital survival was 80% for VV-ECMO and 62% for VA-ECMO. 60% of children were alive at long-term follow-up. Risk factors for in-hospital mortality were high β-lactate and plasma creatinine levels on admission [48].

One of the applications of ECMO is the care of newborn infants with decompensated hypoxemic respiratory failure requiring interhospital evacuation, which can significantly improve patient outcomes [49].

## CONCLUSION

Extracorporeal membrane oxygenation is a promising method of maintaining adequate cardiac output, oxygenation and gas exchange in primary circulatory arrest, shock of various origins and refractory respiratory failure, which can be used both in adult and pediatric practice. A prerequisite for the successful application of this therapeutic strategy is its use in the early stages of the disease, when there are no signs of secondary irreversible damage to internal organs.

## ADDITIONAL INFORMATION

**Author contribution.** Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

**Competing interests.** The authors declare that they have no competing interests.

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