NEONATAL ECMO IN 2019: WHERE ARE WE NOW? WHERE NEXT?

EDITED BY: Giacomo Cavallaro, Dick Tibboel, Aparna Hoskote and Matteo Di Nardo

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NEONATAL ECMO IN 2019: WHERE ARE WE NOW? WHERE NEXT?

Topic Editors:
Giacomo Cavallaro, IRCCS Ca 'Granda Foundation Maggiore Policlinico Hospital, Italy
Dick Tibboel, Erasmus Medical Center, Netherlands
Aparna Hoskote, Great Ormond Street Hospital for Children NHS Foundation Trust, United Kingdom
Matteo Di Nardo, Bambino Gesù Children's Hospital (IRCCS), Italy

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EDITORIAL
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Editorial: Neonatal ECMO in 2019: Where Are We Now? Where Next?

Giacomo Cavallaro[1]*, *Matteo Di Nardo*[2], *Aparna Hoskote*[3] and *Dick Tibboel*[4]

[1] Neonatal Intensive Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [2] Pediatric Intensive Care Unit, Children's Hospital Bambino Gesù, IRCCS, Rome, Italy, [3] Cardiorespiratory and Critical Care Division, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [4] Intensive Care and Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, Netherlands

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Editorial on the Research Topic

Neonatal ECMO in 2019: Where Are We Now? Where Next?

Despite significant advances in neonatal intensive care, including neonatal ventilation in the current era, extracorporeal membrane oxygenation (ECMO) continues to play a crucial role in selected cases of severe cardio-respiratory failure, potentially reversible, but refractory to conventional ventilatory therapy and maximal pharmacological treatment (1).

Our Research Topic attempted to focus on some of continuing challenges in neonatal ECMO. In this issue of Frontiers in Pediatrics, we have collected a wide range of manuscripts related to the use of ECMO in the neonatal period (Broman; Butt and Chiletti; Cashen et al.; Di Nardo et al.; Kersten et al.; Macchini et al.; Perez Ortiz et al.; Rafat and Schaible; Raffaeli et al.; Raffaeli et al.; Roeleveld and Mendonca; Schiller and Tibboel).

Since the formation of the Extracorporeal Life Support Organization (ELSO) in 1989, 45,205 newborns have been supported on ECMO in 492 centers (www.elso.org) (2). Respiratory failure was the predominant reason for ECMO utilization in 33,400 newborns, whereas ECMO was used for cardiac failure in 9,561 newborns, and 2,244 were supported for refractory cardiac arrest—extracorporeal cardiopulmonary resuscitation (ECPR). Today, congenital diaphragmatic hernia (CDH) and meconium aspiration syndrome (MAS) are the exclusive neonatal diagnoses that alone represent about 46% of all cases of neonatal respiratory ECMO, reaching 92% of total ECMO if all "others" neonatal ECMO were added (2, 3). The classification of "others" includes all other diagnostic categories such as non-specific respiratory failure, congenital anomaly, pulmonary hypoplasia, hypoxic-ischemic encephalopathy, cardiorespiratory arrest, and inborn errors of metabolism (4). The mortality rate, however, varies significantly depending on the underlying respiratory disease. For instance, neonates with CDH and sepsis have higher mortality rates (47 and 49%, respectively) in contrast to those with MAS (9%) (2). Pulmonary hypertension and lung hypoplasia play a crucial role in determining survival in CDH (5). Neonates with prolonged ECMO run for >21 days have demonstrated higher mortality due to the increased risk of mechanical complications (6).

Veno-arterial (V-A) ECMO still represents the support of choice in neonates, with more than 80% receiving V-A support (2). The vessel size is the most critical limiting factor in using the veno-venous (V-V) ECMO in neonates as the smallest double-lumen venous cannula currently commercially available is 13 Fr (3, 7). However, it should be noted that mortality is not significantly different between the two types of support. However, neurological complications are reported to be

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Niranjan Kissoon, University of British Columbia, Canada

***Correspondence:**
Giacomo Cavallaro
giacomo.cavallaro@policlinico.mi.it

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lower in V-V support as compared to V-A support, although factors other than just the cannulation may account for this (3, 8).

With a wider spectrum of indications for ECMO utilization in the neonatal period as evidenced by the "others" diagnostic category in the ELSO Registry, we speculate that there is greater use of ECMO as compared to a few decades earlier (2).

Several unanswered questions remain on the use of ECMO in CDH [Rafat and Schaible; (9–11)]. The survival is dependent on several factors such as the side and size of the defect, pulmonary hypertension, associated abnormalities, gestational age at birth, and treatment (12–14). The prenatal and postnatal factors that are predictive of mortality, pulmonary hypertension, and the need for ECMO are the focus of many research groups (15). While there are scores developed from the ELSO Registry to predict outcome from ECMO in CDH, these are not to be factored in for patient selection which has to be individualized per patient. An alternative approach using the machine learning approach of the different variables that affect mortality may contribute to developing a reliable and safe predictive model (16).

Until recently, surgical procedures (excluding cardiac surgery and CDH repair) on ECMO remain infrequent (17). Bleeding has been the most feared major complication, although there was no associated increased incidence of mortality (17). Kersten et al. reported the neonatal and pediatric outcomes of surgery on ECMO (other than CDH repair), noting that 14% of patients in their series required surgery, of whom 50% had a poor prognosis. For neonates with congenital tracheobronchial malformations surgery, surgery on ECMO would have the advantage of lower anticoagulation and a wider operating field than CPB. In addition, postoperative ECMO would allow a period of lung rest better than conventional ventilation alone (3).

While pneumonia and neonatal sepsis remain an indication for ECMO support, the use of ECMO in this context has decreased like other neonatal indications. Furthermore, ECMO did not modify the high incidence of mortality related to neonatal septic shock (18), but there are some conflicting data, with some studies reporting 77% survival and others reporting 25% survival (18–20).

The ELSO indications for ECMO have remained unchanged for infants in whom sepsis is associated with pulmonary hypertension, right ventricular dysfunction, and hypoxemia (21). For those in whom sepsis presents with systemic inflammatory response, refractory septic shock, and multi-organ failure, the only indication for ECMO is treatment-resistant hypotension (21). However, time to initiation, mode of ECMO (V-V vs. V-A ECMO), ECMO flow rates, and run length remain controversial (20, 22). Therefore, the International Guidelines for the Management of Septic Shock in Children are weak evidence for recommendation on using V-V ECMO in children with sepsis-induced pediatric acute respiratory distress syndrome and refractory hypoxia. Similarly, the advice concerning V-A ECMO as a rescue treatment in children with septic shock refractory to all other therapies is weak (23).

Bleeding and thrombosis continue to be the most common complications during neonatal ECMO and are associated with increased morbidity and mortality (2, 24, 25). Knowledge of developmental hemostasis, and accurate titrated use of unfractionated heparin (UFH), with the integration of point-of-care monitoring systems based on whole blood [activated clot time (ACT), thromboelastography (TEG), or thromboelastometry (ROTEM)] to plasma tests [activated partial thromboplastin time (APTT) and anti-Factor Xa], may reduce hemorrhagic and thrombotic side effects during neonatal ECMO [Cashen et al.; Perez Ortiz et al.; (26, 27)].

In recent years, single-center studies with limited patient numbers have been published on the use of thrombin inhibitors (bivalirudin, argatroban, lepirudin) (28, 29). These thrombin inhibitors directly inhibit both bound and free thrombin and are antithrombin independent (30). However, their half-life is relatively long compared to UFH (28, 31). These safety and dosing concerns and lack of reversibility make direct thrombin inhibitors less attractive in the neonatal ECMO population as a first-line agent.

Although the indications and cases of neonatal respiratory ECMO decreased, number of cardiac ECMO cases has progressively increased, even though survival remained low ∼40% (2). The indications for cardiac ECMO include pre-operative hemodynamic stabilization, failure of weaning from cardiopulmonary bypass, low cardiac output syndrome after cardiac surgery, and ECPR (32, 33). The incidence of postoperative ECMO currently varies from center to center and ranges from 1.4 to 5% (34). Any residual lesions should be promptly identified, and interventions should be immediately undertaken (35–37). The implementation of technical performance score as a predictor of early postoperative morbidity and early diagnosis with echocardiography and cardiac catheterization in the first 24 h after surgery is crucial to improve outcomes and survival (35, 36, 38–41).

During ECMO, drug pharmacokinetics (PK) and pharmacodynamics (PD) are modified by several factors related to the patient, drugs, circuits, and interactions (Raffaeli et al.). In addition, in newborns, maturational and non-maturational factors play a crucial role in PK and PD variability (Raffaeli et al.). However, the extensive PK variability during ECMO does not facilitate an adequate understanding of the developmental aspects of PD. A mathematical approach with Monte Carlo simulation or physiologically based pharmacokinetics (PBPK) could help these cases (Raffaeli et al.). Physiologically based pharmacokinetics is a knowledge-driven technique acquired in other settings, like other populations (adult, pediatric, neonatal), other drugs, or other sources (as *in vitro*, *in vivo*, *in silico* experiments), applying mathematical modeling for automatic integration (Raffaeli et al.). Furthermore, the development of virtual organs allows us to add variables to the model, to study any modification in terms of absorption, volume of distribution, and clearance according to the different ages, diseases, or extracorporeal supports (42).

Although the number of neonatal ECMO is constant, the centralization of ECMO delivery—the hub and spoke model—also throughout by ECMO transport service is needed, allowing continuous updating and improvement of knowledge through structured training programs, cost reduction, optimization of human and material resources, and improvement of assistance with a decrease of mortality and morbidity [Broman; Macchini

et al.; (43–46)]. However, data in the literature are conflicting as some small programs have published excellent results with low mortality while some high-volume centers appear to have higher mortality that still seems to be linked to the patients' greater complexity (45, 47, 48). Moreover, keeping high quality in small ECMO programs presupposes an increase in training cost, ensuring a continuous training program, especially in machine troubleshooting and patient complications (43, 49, 50).

Independently to ECMO, follow-up of newborns with complex respiratory and cardiac pathologies is required to prevent and treat potential associated neurocognitive deficits. Therefore, long-term and multidisciplinary follow-up associated with neurorehabilitation strategies, as Cogmed working memory training, psychoeducation, compensatory techniques, and external aids, would appear to improve the lives of these tiny patients [Schiller and Tibboel; (51)].

Even though ECMO was introduced several decades ago, it is still required for some clinical conditions that endanger the life of newborns. Therefore, its use must also be based on scientific evidence that deserves careful ethical consideration (Di Nardo et al.). The ethical question is no less critical than the indications of neonatal ECMO. Commonly, the family perceives the difference between rejection and withdrawal differently. In fact, complications during ECMO often would not justify the withdrawal of support in parents' eyes, while refusal to ECMO appears justified by contraindications (Di Nardo et al.).

Although much has been done to date, much more can be done by focusing on the points still open and, above all, by formalizing the research agenda among a network of hub centers that can work together, sharing successes and failures to improve the quality of care and life of these complex newborns. The futuristic concept of using the extracorporeal circulation of the extra-uterine environment for newborn development (EXTEND) program seems attractive to improve morbidity and mortality of extremely premature babies (23–25 weeks). The goal is to mimic a typical uterine environment and provide physiological support to the fetus (52–54). Thus, we could imagine our NICUs no longer full of incubators and pulmonary ventilators but rather full of wombs and artificial placentas where newborns develop while maintaining the normal physiological process.

Therefore, although we traveled a long road, we still have many more miles in front of us.

AUTHOR CONTRIBUTIONS

GC, MD, AH, and DT contributed to the study's conception and design. GC wrote the first draft of the manuscript. MD, AH, and DT provided extensive critical revision. All authors contributed to the manuscript's critical revision, read and approved the submitted version.

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REVIEW
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Principlism and Personalism. Comparing Two Ethical Models Applied Clinically in Neonates Undergoing Extracorporeal Membrane Oxygenation Support

Matteo Di Nardo[1], Anna Dalle Ore[2], Giuseppina Testa[3], Gail Annich[4,5], Edoardo Piervincenzi[1], Giorgio Zampini[1], Gabriella Bottari[1], Corrado Cecchetti[1], Antonio Amodeo[6], Roberto Lorusso[7], Lorenzo Del Sorbo[5,8] and Roxanne Kirsch[4,5,9]*

[1] PICU, Children's Hospital Bambino Gesù, Rome, Italy, [2] Clinical Bioethics, Children's Hospital Bambino Gesù, Rome, Italy, [3] PCICU, Children's Hospital Bambino Gesù, Rome, Italy, [4] Department of Critical Care, The Hospital for Sick Children, Toronto, ON, Canada, [5] Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada, [6] Mechanical Assist Device and ECMO Unit, Children's Hospital Bambino Gesù, Rome, Italy, [7] Department of Adult Cardiac Surgery, Maastricht University Medical Centre, Maastricht, Netherlands, [8] MSICU, Toronto General Hospital, Toronto, ON, Canada, [9] Department of Bioethics, The Hospital for Sick Children, Toronto, ON, Canada

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Brian Christopher Bridges, Vanderbilt University, United States

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***Correspondence:**
Matteo Di Nardo
matteo.dinardo@gmail.com

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Extracorporeal membrane oxygenation (ECMO) is a technology used to temporarily assist critically ill patients with acute and reversible life-threatening cardiac and/or respiratory failure. This technology can often be lifesaving but is also associated with several complications that may contribute to reduced survival. Currently, neonates supported with ECMO are complex and bear an increased risk of mortality. This means that clinicians must be particularly prepared not only to deal with complex clinical scenarios, but also ethical issues associated with ECMO. In particular, clinicians should be trained to handle unsuccessful ECMO runs with attention to high quality end of life care. Within this manuscript we will compare and contrast the application of two ethical frameworks, used in the authors' institutions (Toronto and Rome). This is intended to enhance a broader understanding of cultural differences in applied ethics which is useful to the clinician in an increasingly multicultural and diverse patient mix.

Keywords: bioethic, ECMO—extracorporeal membrane oxygenation, neonates, principlism and code of ethics, personalism

INTRODUCTION

Extracorporeal Membrane Oxygenation can be used to electively stabilize neonates from ongoing deterioration because of respiratory and/or cardiac failure or to urgently rescue them in case of cardiac arrest (1–3). ECMO can be established: as a bridge to recovery (in case of reversible disease); as a bridge to a bridge (transition to a ventricular assist device), as a bridge to organ transplantation (rare in neonates); or as a bridge to decision (providing time to recovery, time for diagnosis or time to evaluate candidacy for transplantation, or for a longer term mechanical circulatory support) (4). This rapid expansion of clinical indications (5, 6) has outpaced empirical outcome data; challenging bedside clinical decisions as previously contraindicated disease states

(immunocompromised patients, recent surgery, or trauma) are now able to be supported with ECMO (7–10). This emphasizes the need to address important questions such as how decisions to offer ECMO are made as well as how and when to discontinue ECMO when unsuccessful (11–14). In general clinical practice, withholding ECMO (15), even contrary to the wishes of the family or of the legal guardians, is widely perceived as justified, while withdrawal in the face of unsuccessful therapy is often perceived differently by the family, as it requires the action of stopping a currently applied therapy (15, 16). Canadian and American bioethics grants no ethical distinction between withholding and withdrawing therapies. As a therapy, ECMO can therefore be withheld or withdrawn under the same ethical justifications as any pharmacological or technological therapy, such as mechanical ventilation or renal replacement therapy (16–18).

Comprehension of the ethical underpinnings guiding the use of medical technologies, and specifically how this relates to ECMO support in the neonatal period will help clinicians in managing decisions about neonatal ECMO. As medical technology continues to be utilized globally, understanding differences in ethical practices can help to inform and enhance the practical application of this complex technology and the evolution of guidelines for its use. We start by outlining the ethical framework of Principlism (19) and how it is applied in clinical decision making in neonatal ECMO. Then, we introduce the less globally known Personalist bioethics (20, 21) framework. We will outline pitfalls and limitations in both and demonstrate how each affects practical use of this complex resource.

A BRIEF REVIEW OF PRINCIPLIST BIOETHICS IN CLINICAL APPLICATION

The health care team in a Principlist bioethics system seeks to balance four principles of autonomy, beneficence, non-maleficence, and justice (19) when making treatment decisions (**Figure 1**). Additionally, an overarching additional concept of best interests is applied to patients incapable of participating in decision making, due to age, illness, or cognitive capabilities. Ideally, the therapy is desired by the patients, it provides benefit to them, avoids unjustified harms, the benefits outweigh harms, and medical resources are allocated in a fair manner and most often with maximization of benefit. Before initiating ECMO, wherever possible, a detailed and informed consent is undertaken with the parents or legal guardians, communicating risk, benefits, alternatives and including information on the potential for ECMO to be unsuccessful in achieving the intended goal.

THE PRINCIPLE OF AUTONOMY

Central to the ethical provision of any medical intervention is the principle of autonomy, which upholds respect for persons. This provides the basis for informed consent (19). In a practical sense, autonomy refers to the individual's rational capacity for self-determination (19). Each patient can express his preferences about therapies and his reasoning in accepting or refusing them. To uphold this principle, the health care team needs to respect the wishes of patient (presuming they have capacity) regarding medical interventions.

The sick neonate is considered a "vulnerable" patient because is unable to express his will. However, this limits only in part the application of this ethical principle because the guarantors of this principle are the parents supported by the best knowledge of the physicians. The physician "must" wisely inform the parents and act consequently taking into account all the other bioethical principles (beneficence/non maleficence and justice). Only a strong and sincere dialogue between the physicians and parents will allow to understand the real needs of the neonate.

In many countries, such as Canada, United States, United Kingdom, and others, it is both ethically and legally permissible to forgo or request discontinuation of life-sustaining therapy, even if the intervention is life prolonging or beneficial (4, 5). Otherwise said, they can choose not to act for their own benefit. This practice is supported by ethical concepts (e.g., Kan's moral theory, etc.) beyond and in addition to the framework of Principlism, although our discussion will focus only on Principlism within the scope of this article (5).

THE PRINCIPLE OF BENEFICENCE

This principle obligates the health care team to contribute to the person's welfare with any interventions conferring benefit directly to the patient (19). Benefit for the patient, however, may reach beyond medical outcome measures. The values, beliefs and culture of the patient may modify how benefit is perceived. For example, a patient may decide that a specific therapy is not beneficial because the resultant residual morbidity is untenable and will not allow a "good" life. This can be understood more readily in the patient with capacity who can express how these values influence their preferences about medical therapies.

Benefit for the patient without capacity, however, is generally not only regarded under a principle of beneficence but under an overarching concept of best interests. This is applied to any incapacitated patient, where others have to make choices that affect him on his behalf, including a child or neonate.

Best interests become more difficult to decipher, therefore, when encompassing both medical outcome and values or preferences expressed by the surrogate decision maker on behalf of the patient. This is particularly true for the child or neonate, who is incapable of having yet expressed any wishes or values. The child or neonate, because they exist within their family's values, beliefs and culture, is most likely to choose in accordance with their family and will leave a medical experience to exist within their family context. Therefore, family surrogates are generally the best choice to represent a view of the child's best interest. Additionally, the pediatric clinician is charged with protection of the child and may question the family's view as truly being in the child's best interest. In this instance they can bring into question the decisional authority of the family. If both parties have moral grounding for their judgment of best interest, however, the determination becomes even more complicated (4–6, 22, 23).

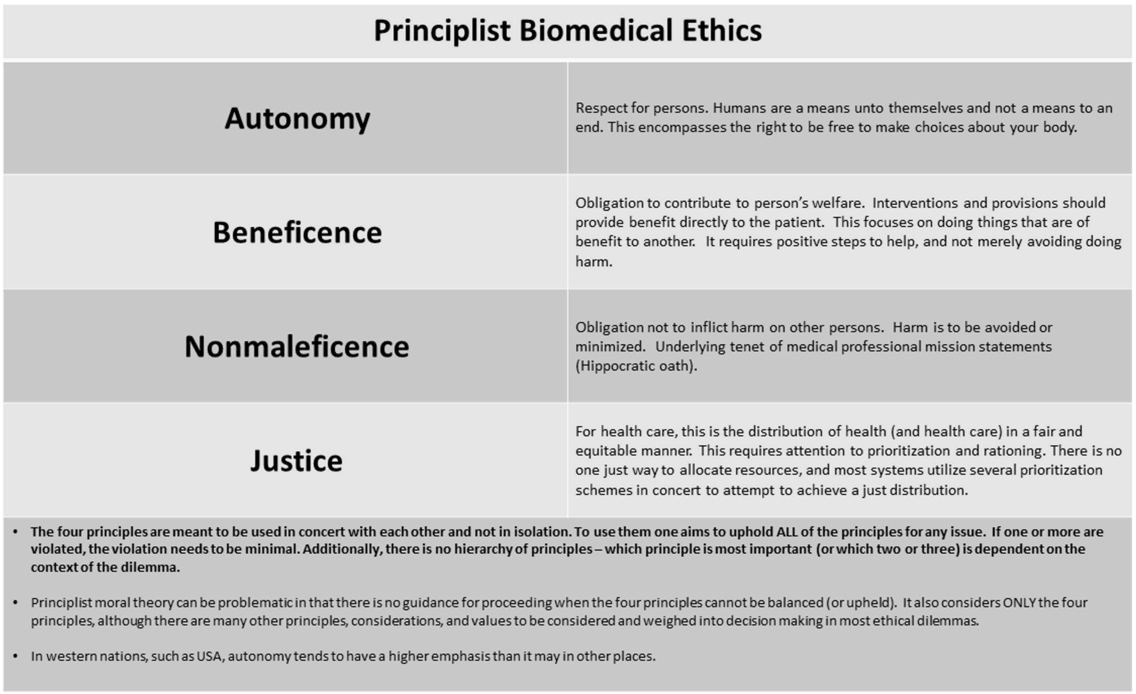

FIGURE 1 | Principlist biomedical ethics.

THE PRINCIPLE OF NON-MALEFICENCE

The principle of non-maleficence renders an obligation not to inflict harm on any person (19). Should it be impossible to avoid harm, it should be minimized, and therefore benefits of an intervention should outweigh the risks and the intendent suffering of the intervention. For example, during a neonatal ECMO run, the risks of neurological disabilities, where known are disclosed in advance before the ECMO deployment. These potential comorbidities are acknowledged by the family, especially when the neonates have other risk factors contributing to worsen their neurological outcome (prematurity, low birth weight, coagulopathy, etc.). If the probability of neurological disability is high using ECMO, or the probability of poor outcome (death or severely reduced quality of life) for the patient in general is high, the procedure may not be undertaken, as it would provide risk of harm without any benefit of longer term good outcome (4, 6).

THE PRINCIPLE OF JUSTICE

The principle of justice as it relates to health care considers the obligation to fairly and equitably distribute health and health care. This requires prioritization and rationing of competing claims (19). In health care this might be subdivided into categories of: fair distribution of scarce resources (distributive justice), respect for people's rights (rights based justice) and respect for laws (legal justice) (24). Health care providers are challenged to use resources wisely and to grant equality and equity to all sick people. The right to be treated equally and with equity can be found in many constitutions, but in the actual practice, a number of different factors may influence the access to treatment (e.g., age, place of residence, social status, ethnic background, culture, sexual preferences, disability, legal capacity, hospital budgets, insurance cover, and prognosis). The principle of justice regulates these aspects in order to avoid any form of discrimination and to provide to all the people the same respect. The sick neonate is often considered a "vulnerable person" because is still not actively part of society and is dependent on parents to survive (incapable of self-determination). However, when dealing with ECMO, this issue is solved using the dedicated "clinical criteria" which grant a fair access to this life support technique even in the less "wealthy" countries.

Good resource allocation must ensure processes that distribute or deny therapies in a fair fashion. There is no single agreed upon prioritization scheme with continued debate upon the best ways to make allocations. Generally, a combination of prioritization schema are required to attempt to achieve a just distribution. Distributing based only on quality-adjusted life years (QALY) saved, or cost-effectiveness allows for comparisons, but still requires subjective judgments about quality of life, and often fails to account for unmeasurable benefits (or harms) to the society or system (4, 25–29).

CONSIDERATIONS ON PRINCIPLISM

The term principle has wide ranging significance. In bioethics, this term is generally used in reference to the four principles of

Beauchamp and Childress, previously addressed (19, 24, 30, 31). In any given ethical deliberation, the principles are meant to be simultaneously upheld, but if one or more principle should be violated, such violation should be minimal and mitigated where possible. However, with no hierarchical structure between the principles, they are left subject to a certain relativism that can be problematic when applied to the complex scenarios of clinical medicine and biotechnology. To overcome these limits, Jonsen et al. (32) proposed the four Box-Method to help clinicians to organize the ethical reasoning in medical indications, patient preferences, quality of life, and contextual features. These four topics provide a pattern for collecting, sorting, and ordering the facts of a clinical ethical problem. Each topic can be filled with the actual facts of the clinical case that are relevant to the identification of the ethical problems. The contents of all four topics viewed together form a comprehensive picture of the ethical dimensions of the case (**Figure 2**).

When managing complex decisions, the health care team determines which interventions might be offered to alter the course of the medical illness, considering potential survival, comorbidities, and overall quality of life outcomes so as to best inform the patient (or their surrogate decision makers) of the recommended intervention and alternate options (27, 28). Additionally, they try to understand patient or family values and preferences about what constitutes a "good life" (or an acceptable quality of life). In a deliberative process the clinician and patient (or family as surrogate decision maker) then ideally arrive together at an agreement for how to proceed with therapies (29). Disagreements may occur, and a relatively wide latitude is given to many choices of the parent or surrogate decision maker particularly when there is not a high probability of restored health or good outcome. The clinician has the additional task to question the decisional authority of the parent or guardian in instances where they do not feel the best interests of the patient are being upheld. However, disagreements may occur. Should the clinician feel the best interest of the child would be to stop ECMO for reasons of no benefit and induced suffering, while the family holds a stance on the sanctity of life even at a high degree of suffering, an impasse will appear that requires careful mediation and at times, legal determination.

Finally, most health care systems utilizing Principlist ethical justifications do not use it exclusively in any given ethical dilemma, since it considers only the four principles. For a fulsome ethical deliberation, applying the many other principles, moral theories, values and considerations of the issue at hand are required.

INTRODUCTION OF PERSONALIST BIOETHICS

Personalist bioethics was born in Italy, in a catholic context, to deal with the progression of medicine and the complex challenges it presents. The ontologically grounded Personalism was developed from an anthropological point of view by the Pope Karol Wojtyla and from a bioethical point of view by Sgreccia (20). In the personalist perspective life is considered *sacred* and is at the basis of any bioethical discussion. The person is regarded as an entity of both body and spirit (21, 31). Personhood starts from conception and remains unchanged by physical or intellectual disability. Importantly, Personalist bioethics should not be confused with theories of *individualism* (21), which considers the main constitutive feature of the person to be their capability for individual decision. Personalism is based on the principle that *all* human beings deserve respect (20, 21). Personalist bioethics therefore integrates the concept of the protection of the physical life with other bioethical principles commonly used to manage many current medical challenges (**Figure 3**).

Personalist bioethics is articulated in three ontologically-based principles: (a) the principle of freedom and responsibility, (b) the principle of proportionate therapy, and (c) the principle of sociality and subsidiarity (8). All three can be considered as corollaries of the main concept of the personalistic bioethics which regards the protection of the physical life. The body as well as the spirit is essential to the person, as it is the first embodiment in which and by means of which, the person is realized and enters into time and space, expresses and manifests himself.

The protection of the physical life embraces all people, regardless of their developmental status, illness or usefulness for the society. The sick neonate is a physical person independently if 1 day he will be able to express his autonomy, thus both the health care team and the family have the duty to protect his life (21, 33). The defense and promotion of life has its limit in death, which is part of life, and health promotion has its limitations in the disease. When disease is incurable you have to take care of the sick person.

THE PRINCIPLE OF FREEDOM AND RESPONSIBILITY

This principle requires that the protection of our own life and of the life of others are both under our responsibility (20, 21). The concept of responsibility is not detached from the concept of freedom. Freedom means the liberty to take the responsibility for one's own life first and foremost, as well as for the life of others.

In Personalist bioethics, the principle of freedom always requires informed consent (34). Informed consent means full information to the patient, patient's family or to the legal guardians before the intervention, but the responsibility for the final decision to pursue or forgo an intervention is shared between the heath care team and the family. The clinician always asks informed consent before doing an intervention on the patient, respecting the patient's freedom, while the family must always respect the freedom of the doctor to work with responsibility and consciousness. The family *cannot* choose for the child's death when there are opportunities to sustain and protect life (20). This would misuse the concept of freedom because it does not appropriately care for the child's life. In the personalist bioethics life is always sacred and must be respected. Thus, in certain cases, such as when a family refuses a treatment essential to the neonate's life and the physician has deemed

MEDICAL INDICATION (Principles of Beneficence and Nonmaleficence)	PATIENT CHOICE (Principle of Autonomy)
• Medical history, diagnosis and prognosis • Acute/chronic, reversible/irreversible pathology • Treatment goals and probabilities of success • Alternative strategies in case of failure	• Patient mentally capable and legally competent • Patient's preferences about medical treatments • Informed consent properly erogated if patient is capable • Appropriate surrogate in case of incapability • Evaluation of the patient's requests and directives
QUALITY OF LIFE (Principles of Beneficence and Nonmaleficence and Autonomy)	**CONTEXT** (Principles of loyalty and fairness)
• Possibility to return to a normal life • Possible phisical/mental/social deficits caused by the treatment • Biases that could prevent the evaluation of the patient's Quality of Life by the physician • Presence or future condition inacceptable for patient's personal evaluation • Plans to forego treatment • Plans for palliative care	• Influence of family on the treatment decision • Influence of health care providers on the treatment decision • Influence of financial/economic aspects • Problems concerning the allocation of resources • Influence of Religion/cultural aspects • Legal/legislative issues • Conflict of interest of health care providers

FIGURE 2 | Facilitating ethical and medical practice—the 4 box method.

Personalist Biomedical Ethics	
Freedom and Responsibility	The basic principle of freedom and responsibility points to the fact that the protection of our own life and the lives of others are both our responsibility.
Proportionated Therapy	The principle of totality or proportionate therapy justifies a medical intervention and poses attention to the concept that the whole body is essential for life, both on its entirety and on its details. Resources are not "equally" distributed but are proportionately allocated according to the patient's need.
Sociality and subsidiarity	The life of the child is considered important not only for its value, but also for its role in the society

- The personalist bioethics is a bioethical theory based on the person, which is considered as a whole entity of body and spirit. The concept of person starts from the moment of conception is unchanged whether any physical and intellectual disability exists.
- The protection of the physical life embraces all people, regardless of their developmental status, illness or usefulness for the society.

FIGURE 3 | Personalist biomedical ethics.

the treatment as necessary in good conscience, this principle must govern the procedure for "obligatory care." However, first and foremost the personalist bioethics seeks a "therapeutic cooperation" (35, 36) between the heath care team and the family to overcome any divergence.

THE PRINCIPLE OF PROPORTIONATE THERAPY

The principle of totality or proportionate therapy justifies a medical intervention and poses attention to the concept that

the whole body is essential for life, both on its entirety and on its details (20). The principle of inviolability of life which has been shown to be primary and fundamental is not disproved but applied when it becomes necessary to intervene in a harmful manner on part of the body in order to save the whole and the very life of the subject. This principle ultimately upholds all the legitimacy of medical and surgical treatment in the Personalist theory. Thus, any intervention on the physical life is justified only if it has a therapeutic purpose to improve the physical life of the patient.

The use of ECMO in neonates is justified, even though invasive and with associated risks, only if it is aimed to allow for cure of a disease state or as a bridge to diagnosis. When ECMO goals are no longer achieved, the intensity of care is reduced. Maintaining ECMO when there is no longer a chance of survival would represent an unjustified "gravamen" (burden) for both child, family, and often the health care team. Personalist bioethics, therefore, suggests a reduction of care. This requires utilizing the concept of proportionate care (20, 21, 31, 35, 36). Here, a treatment must be evaluated within the totality of the person in order to apply or continue it; moreover, there must be a certain proportion between the risks and damages it entails and the benefit it secures. Certain conditions are required to apply this principle: (a) the intervention on a part of the whole body can be performed only in order to save the healthy organism; (b) there is no way or means to correct that condition: (c) there is a good and proportionate chance of success; (d) the patient or the family (legal guardians) have provided consent.

THE PRINCIPLE OF SOCIALITY AND SUBSIDIARITY

The principle of sociality implies that all the citizens work toward respecting their own lives and the lives of other as good—not only a personal one but also a social one—and that they engage the social community to promote the life and the health of all, promoting the common good by promoting the good of each individual (20, 21). In terms of social justice, however, the principle obligates the community to guarantee everyone the means of accessing necessary care, even at the cost of sacrifices for the well-to-do. The principle of sociality melds with the principle of subsidiarity, whereby the community must help more where the need is greater (35, 36).

CONSIDERATIONS ON PERSONALISM

The first characteristic of Personalism is that all the principles refer to a well-defined anthropological theory, the defense of the person's physical life, the second is that all the other principles are considered corollaries of this main aspect (21, 35, 36). This anthropological theory is based on the concept of person, regardless of his functions, conscience, race, sex, and stage of development. In this case, the newborn period represents a stage of the physical life, where the individual is already a person; thus, this implies a profound attention and care. This point is very delicate, especially when a neonate is on ECMO and this support is failing to reach its goals. According to the personalist bioethics the first thing that we always have to guarantee is the protection of the physical life but, we must not maintain life at all costs. For a neonate when there is no further chance of survival and the body has not responded to therapies, continuing does not respect the physical person, but rather represents a therapeutic stubbornness, or a desperate search for "vitalism," which is not accepted in Personalist bioethics. To avoid such a search for "vitalism," Personalist bioethics considers additionally, the principles of proportionate therapy and of sociality and subsidiarity, to respect the sanctity of life. Only from the integration of these two principles can the sanctity of life be fully respected, especially in neonates who are unable to express their autonomy.

Unfortunately, many conflicts are often unresolvable using these principles (19–21), since there is not a unified moral theory from which these principles are derived (24, 30). By accepting this critique, the personalistic bioethics proposes the "personalistic norm of morality" (20) to order its principles and to work out an integral theory of the dignity of the person to manage fundamental problems in bioethics.

For proponents of Personalist bioethics, additional theories may contribute to a continuing ethical deliberation regarding complex medical scenarios, but the central point of the concept and value of the person that is key to Personalism is generally felt to be missing in other theories.

WITHHOLD AND WITHDRAWAL OF LIFE SUPPORT IN PRINCIPLIST AND PERSONALIST BIOETHICS

Neonatal ECMO when not immediately able to provide good outcome or successful discontinuation of ECMO, can lead to internal and external conflicts in determining a time to stop. This aspect introduces the considerations of futility. Futility considerations have long been argued in the medical literature, but remain ill defined (23, 27–29, 37, 38). In the recent era, futility is most often considered when the goals of a medical intervention cannot be or are not achieved (physiologic futility) (37, 38). This moment is then associated to a consideration of withhold or withdrawal of ECMO as appropriate. Most often in the Principlist bioethics, withhold or withdrawal are determined in an intersection of beneficence and non-maleficence, where autonomy dictates respect for the person so as not to continue therapies that are not of benefit to them. If no benefit for the person can be achieved and harms are being accrued, it is deemed appropriate to stop. The best interest of the patient can no more be accomplished because the purpose of ECMO support is lost or the quality of life is significantly reduced without anticipation of benefit.

This can be compared with Personalist bioethics, which would not consider the quality of life of the patient (in present or future) and would continue ECMO while any chance to cure the patient is still present (39, 40). Nonetheless, Personalist bioethics, would agree with stopping ECMO to avoid suffering when there is no longer a chance to cure.

This provides only the briefest discussion of the equivocal and controversial nature of the term futility and the extensive difficulties in understanding and applying this concept (41). Concerns for futility extend well-beyond ECMO therapy and considerations for how to deal with such concerns are multiple and require careful communication and processes for mediation. This is not unique to any institution nor is it solved in practice by any singular bioethical consideration. A more thorough consideration reaches beyond the scope of this manuscript and is well-outlined elsewhere within the literature.

DECISIONAL AUTHORITY IN ECMO

Principlism and Personalism utilize different principles to manage complex clinical scenarios and parental input (**Figure 4**). According to Principlism, the autonomy of the patients is respected in part by involving them or their surrogate (parents) in a shared decision (4, 5, 10, 28, 29, 33) to determine how to intervene for the best interest of the patient. A collaborative process that allows both the family and clinicians to reach a common health care decision has been proposed and endorsed by many international medical and nursing societies (41). In Personalist bioethics, a shared decision is also sought, but here, the main goal between the two parties (clinicians and family) is always the respect and the protection of the physical life. Both clinicians and family must protect the patient's dignity with a proportionate care to avoid suffering when there is no longer a chance for life (35).

Divergences or disagreements can come from both health care teams and patients or families (29, 42, 43). Both Personalist and Principlist bioethics concepts support mediation of disputes (2), and both look to maintain a therapeutic alliance, advocating regular communication from the very beginning of the ECMO course.

CONCLUSIONS

Applying ECMO to a patient is a medical act, invading the person and inducing a degree of suffering even though it is done in the interests of saving a life. It is therefore inherently a moral act. Like other therapies, a choice between doing "good things" (beneficence) and avoiding "bad things" (non-maleficence) is inherent to ECMO. In these complex scenarios the contribution of bioethics is fundamental to analyze the ethical underpinnings that support decisions and actions. We have attempted to briefly outline the main tenets of both Principlism and Personalism to understand differences and similarities in how these concepts are applied clinically. Overarching both is a clear support for therapeutic interventions that improve patient health. Key differences lay in the emphasis between quality of life and sanctity of life, although neither finds sanctity of life absolute and to be accomplished at all costs. Personalism considers the protection of life first and foremost qualified after by proportionality. Principlism considers the four principles in concert but without hierarchy, although in practice relies additionally on other ethical theories, frameworks, values and considerations to accomplish the best interest of the patient.

All can agree, regardless of bioethical application, that the neonate has no capability for autonomous expression. In Principlism, intervening for the patient's best interest represents a part of the principle of autonomy. In Personalism, the focus is on life first and foremost and a consideration of autonomy

A

Principlism	Heath care team	Family or legal guardians
Principle of Autonomy	The neonate is not able to express his/her will regarding the use of ECMO. The health care team proposes his therapeutic plan which minimizes costs and maximize benefits	The family or the legal guardians decides for the patient's "best interest" to: a) Start ECMO b) Withdrawal ECMO c) Withholding ECMO
Principle of beneficence and nonmaleficence	The health care team provides the "best" therapies and supports (ECMO) for the benefit of the patient avoiding excessive harm	The "best" interest for the neonate is *to reach a physical and intellectual autonomy*
Principle of Justice	The health care team allocates the resources in a fair modality in relation to the availability of means	ECMO is considered useless when it does not affect the family expectations and the psychological health of the family
In case of conflict between different principles: *balancing of duties*	*The health care team favours the neutral consult to support decisions. The solution that minimizes costs and maximize benefits always prevails*	*In case of conflicts between principles, the family chooses the minor damage for the neonate*
"Quality" of life	The quality life is evaluated with *QALYs or DALYs*	The family wants to grant to the child a good *quality of life considered as the capacity to reach his/her autonomy in the future*

B

Personalism	Heath care team	Family or legal guardians
Freedom and Responsibility	The health care team proposes the use ECMO according to their experience and knowledge. They are responsible of this procedure and of all the risks associated	The family or the legal guardians, listens to the health care team therapeutic plan including ECMO and establishes a "therapeutic alliance" to cure the child.
Proportionated Therapy	The health care team allocates resources where there is the necessity and not "equally". Proportionately to the needs of the patient	All the devices that maintain alive the child are used proportionately in order to relief the patient burden
Sociality and subsidiarity	The life of the neonate is considered important not only for its sacred value, but also for its role in the "society"	ECMO is considered as a bridge to recovery to allow the child to be part of the society
In case of conflict between different principles: *harmonization of duties*	*The heath care team evaluates the real need to use ECMO, balancing benefits and risks to protect the "physical life" and to grant to the child proportionated therapies*	*The family and the heath care team seek for a common solution finalized to the best care of the child*
"Sanctity" of life	When ECMO assistance is useless compared to the benefits for which it was started the health care team and the family often agree to withhold or withdraw choosing a treatment that involves less invasiveness and protects the *"sanctity of life"*	The therapeutic alliance established between the family and the health care team allows *to protect the physical life without maintain life at all cost (vitalism) when no chances to cure are present*

FIGURE 4 | (A) Principlist Bioethics method applied at bedside while a neonate is undergoing ECMO. **(B)** Personalist Bioethics method applied at bedside while a neonate is undergoing ECMO.

would be inappropriate for the neonate. The personalist system helps both clinicians and parents to protect life as a priority even in the face of escalating comorbidities but allows withhold or withdrawal when there is no further chance for life, in practical, when the goals for which ECMO was started are lacking. Given the complexity of medical intervention, conflict is bound to arise regardless of system. Both frameworks agree that communication, empathy, and support of the family are critical to delivering high quality care. In discussing the similarities and differences in applied ethics of both Principlism and Personalism in our cities of Toronto and Rome, it is hoped a broader understanding of cultural differences and ethical justifications can enhance the care of an increasingly multicultural and diverse patient population.

AUTHOR CONTRIBUTIONS

MD conceptualized the project and MD, AD, and GT wrote 50% of the manuscript. RK wrote the remaining 50% of the manuscript and provided oversight to form and structure. AA, EP, GZ, GB, CC, RL, GA, and LD provided revisions to the manuscript.

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Interhospital Transport on Extracorporeal Membrane Oxygenation of Neonates—Perspective for the Future

Lars Mikael Broman [1,2]*

[1] Department of Pediatric Perioperative Medicine and Intensive Care, Extracorporeal Membrane Oxygenation Centre Karolinska, Karolinska University Hospital, Stockholm, Sweden, [2] Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

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Edited by:
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Thomas Vincent Brogan,
Seattle Children's Hospital, United States

***Correspondence:**
Lars Mikael Broman
lars.broman@sll.se

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In recent years the number of extracorporeal membrane oxygenation (ECMO) cases in neonates has been relatively constant. Future expansion lays in new indications for treatment. Regionalization to high-volume ECMO centers allows for optimal utilization of resources, reduction in costs, morbidity, and mortality. Mobile ECMO services available "24-7" are needed to provide effective logistics and reliable infrastructure for patient safety. ECMO transports are usually high-risk and complex. To reduce complications during ECMO transport communication using time-out, checklists, and ECMO A-B-C are paramount in any size mobile program. Team members' education, clinical training, and experience are important. For continuing education, regular wet-lab training, and simulation practices in teams increase performance and confidence. In the future the artificial placenta for the extremely premature infant (23–28 gestational weeks) will be introduced. This will enforce the development and adaptation of ECMO devices and materials for increased biocompatibility to manage the high-risk prem-ECMO (28–34 weeks) patients. These methods will likely first be introduced at a few high-volume neonatal ECMO centers. The ECMO team brings bedside competence for assessment, cannulation, and commencement of therapy, followed by a safe transport to an experienced ECMO center. How transport algorithms for the artificial placentae will affect mobile ECMO is unclear. ECMO transport services in the newborn should firstly be an out-reach service led and provided by ELSO member centers that continuously report transport data to an expansion of the ELSO Registry to include transport quality follow-up and research. For future development and improvement follow-up and sharing of data are important.

Keywords: extracorporeal membrane oxygenation, neonatal, neonate, children, transport, inter-hospital, interhospital, prem

INTRODUCTION

At the dawn of extracorporeal membrane oxygenation (ECMO) in the 1970s the neonatal population was the first group acknowledged to benefit from this new organ support (1). The number of hospitals which offered ECMO treatment was limited and the risk of transporting neonates on conventional respiratory support was considered high (2, 3). Thus, in 1975 the alternative to transport the patient on conventional critical care support, i.e., to initiate ECMO at the referring hospital before transporting the patient was performed in a neonate (4). Subsequently, the feasibility of ECMO transports has been repeatedly confirmed (5–7).

Concerning most aspects of ECMO outcome (patient safety, resource utilization, quality, morbidity, mortality), there is concensus that ECMO is best provided at high-volume ECMO centers (8–10). However, case mix may influence survival data (11), and Bailly et al. found no association between center size and outcome (12). As recently as a decade ago, only a small number of centers worldwide provided mobile ECMO services for bedside assessment and cannulae insertion. After stabilization, the patient was transported on ECMO for continued support at an ECMO center (13, 14). A transport preceded by bedside assessment, decision, and cannulation for ECMO by direct involvement of the transport team is defined as a *primary transport* (14, 15). A *secondary transport* is a transfer of a patient already on ECMO, often for a day or more, i.e., the mobile team was not directly involved in the cannulation procedure.

In the last decades the numbers of neonatal and pediatric ECMO cases have leveled off or tended to decrease for certain diagnoses (16, 17). In adults, the volume of respiratory and cardiac ECMO treatments and number of ECMO centers are increasing (18). These "young" units gain experience over time albeit the annual treatment volume is unlikely to qualify them as high-volume centers (>20–30 respiratory runs per year) (10). In the future, however, these units may serve as support centers in larger clinical ECMO networks. One example of this, the *Hub-and-Spoke* model, has already been implemented in various health care systems (14, 19, 20). For these to be effective, a "24-7" on-call transport service is needed that provides both primary and secondary transports. Note, a network need not be restrained by national borders for certain diagnoses, i.e., congenital diaphragmatic hernia (CDH), or by a limited population too low to support a low-incidence high-cost therapy. Transports of neonates and children have been described in both national networks (14, 21, 22) and in networks transcending national borders (13, 23, 24).

During the H1N1 pandemic the need for mobile ECMO became evident. However, the medical community has lost control over the number of centers with transport capabilities and the quantity and quality of transports performed. Most importantly, we need to know more about transport related adverse events, how these should be best managed or avoided, and how they correlate to short- and long-term morbidity and mortality outcomes. ECMO transports are unregulated in most countries (14), and authorized transport programs are sparse. Only a handful of publications are based on large numbers of transports (13, 24–26). Even fewer have reported complications during transport. Despite the ELSO transport guidelines (15), an international standard concerning transport management, definitions on adverse events and follow-up are lacking (14). In mixed populations transports adverse events vary from "zero" to >30% (24, 25, 27, 28). In neonates, transport complications may reach as high as 40% as reported by Burgos et al. (23). This high number may coincide with case mix as well as a high frequency of venoarterial ECMO patients and fixed wing transport, both associated with an increased risk for transport complications (24). In a mixed group of both neonatal and pediatric patients five adverse events were reported in 20 ECMO transports (21). In an attempt to identify adverse events a four-level risk category scale was introduced by Ericsson et al. (29), and a revision recently published (24). Death during transport is reported to be rare, <0.5% (14, 24, 25). With no international registry and low published numbers, robust data on mortality is lacking. ECMO transport seems to be safe, at least in the hands of experienced teams. Besides the publications from a few high-volume mobile ECMO programs, additional data is published as cases series or case reports. In a review of 27 case series compared to all ELSO Registry patients, Bryner et al. (25) found no difference in survival for patients transported when stratified for age or ECMO indication. Similar survival results comparing ECMO retrievals and non-transported ECMO cases have been reported from single centers (13, 27).

The aim of this work is to elucidate different approaches to the future development and role for mobile ECMO in the neonatal patient population.

DISCUSSION

Where Are We Now?

The decreasing number of ECMO cases in neonates (16) may be attributed to improved technologies and experience in invasive ventilation support, e.g., inhaled nitric oxide, high frequency ventilation, percussive ventilation, etc. It may also be influenced by subtle changes in antenatal care and intervention, e.g., intrauterine procedures such as bronchial blockers used in lung hypoplasia/CDH (30, 31).

The current expansion of adult respiratory and cardiac ECMO, which may see further growth if extracorporeal cardiopulmonary resuscitation becomes well established, not only brings resources but also spread knowledge and awareness concerning the utilization of extracorporeal support in all age groups. Thus, even though referrals for ECMO mainly occur in adult patients, this may also benefit neonates and pediatric patients. An adult center may, depending on local surgeons' training and skills, and hospitals' pediatric/neonatal critical care experiences, provide rescue for a rapidly deteriorating critically ill child. The child is secured, a mobile ECMO team retrieves the patient to an appropriate ECMO center. However, contemporary regional resource utilization may redirect such secondary transport to another region's neonatal or pediatric ECMO center. Adult and pediatric mobile ECMO programs may work in parallel. For example, in the United Kingdom (67 million population) one center, Glenfield Hospital, Leicester, performs

all ECMO transports of children, whereas five centers perform regionalized adult transfers (14).

Safe transport—the following applies to any size ECMO transport program.

Training and Education

The basic training and experience required to become a member of a transport team varies between centers and countries (14). Familiarity with transport equipment used and what differs from the devices used in the ward (14, 24). Guidelines for basic ECMO training and the requirements for team members are published and updated by ELSO (15, 32). Regular training for team members should be arranged with scenarios led by a senior staff. Each scenario is followed by a short discussion. "Water-drills," using a saline primed ECMO circuit are easily organized, may be performed in small groups and offer opportunities to become familiar with equipment and to train separate procedures (33, 34). Water-drills are excellent to mimic situations in narrow spaces (e.g., elevator, aircraft, etc.). Full high-fidelity simulator training is resource demanding and one complete team is taken from clinical duty for half to an entire day. If more time is allowed, such day may start with a few lectures. However, realistic scenarios are extremely valuable to all team members. Closed loop communication and clear leadership often prove to be what separates the well-performing from the less well-performing team. One to two simulation days per staff per year at centers with >10 treatments/year, and more often in centers of <5–10 treatments/year would be reasonable (33, 35, 36). Team composition, organization of transport program, funding, etc. are not the scope of this work but can be found in the literature (14, 15).

Preparing for Transport

(Given that the patient is stable enough for transport.) Infusion lines, ECMO and ventilator tubing, cables, oxygen bottles, etc. are checked, fastened, and secured accordingly. Emergency equipment, i.e., an emergency box (saline, antiseptics, sterile clamps, and scissors, connectors, syringes, 3-way stopcocks), rescue kit (dry oxygenator and centrifugal pump connected with tubing ready for priming with saline), console and drive-unit, as well as blood products are controlled according to a checklist. This checklist ensures confidence of availability of all emergency equipment at "arm's length reach" from the patient. Before unplugging from the ward a timeout is performed. In this, Situation-Background-Assessment-Recommendation (SBAR) is a suitable structured format (37, 38). Information about "red flags" is important, e.g., circuit clots, earlier bleeding site, etc. Checklist and timeout should be utilized before leaving any location, e.g., ward, CT, operating room, or vehicle (15, 39, 40).

On Transport

The timeout is extremely important for safe management when personnel unfamiliar with ECMO are asked to contribute outside their usual comfort zone. An example is when airport staff assists in a patient transfer between transport vehicles. Every step should be explained, and a clear back-up plan has to be known by all participants. The SBAR would be prolonged.

Continuous re-evaluation of the patient follows the classic A-B-C. The *ECMO A-B-C,* displayed in **Table 1**, focuses on ECMO gear and performance in a structured way and may be used:

1) In emergencies for effective and fast problem solving.
2) For the continuous re-evaluation of patient treatment.
3) In everyday practice as part of ECMO circuit and patient survey at beginning of each shift.
4) After every device or patient related intervention, i.e., if the patient has been moved from one bed to another, if equipment has been changed, etc.
5) After change from one power and/or oxygen source to another, e.g., when the patient has been "un-plugged" on the ward and now relies on batteries and gas bottles, as well as after "plug-in" in ambulance/aircraft, etc.

For all staff to use same robust algorithm, applicable to any occasion, increases confidence and safety for and around the patient.

To reduce complications in neonatal transports, data available today tell us to keep transport time short (24, 29) and to acknowledge that fixed wing (FW) aircraft transports carry a higher risk than ground ambulance. Concerning patient safety, it is important to *get to* the patient as fast as possible (15). For shorter distances <650–800 km, a rapid response concept would be to use helicopter (rotating wing, RW). The mobile ECMO team may dispatch and land at the referring hospital's roof or close nearby reaching the patient bedside much faster than in any ground ambulance and/or FW combination.

When ECMO has been commenced there is more time to consider transport options. The choice of transport vehicle has to be put in its full context as should associated complications. For transports >650–800 km the only feasible mode of transport to keep transport time down would be FW. The most likely contributors to the increased risk observed in FW are longer time on transport and two additional patient movements between transport vehicles. In these procedures, focus may be diverted from patient monitoring and thermoregulation to more practical issues. If staff is aware of which complications are to be expected in the different phases of a transport, numbers may be reduced.

Heat losses and lack of heat conservation are known problems during transports and awareness concerning these problems are important for safe transports. Experiences from transports of neonates show that these patients are at risk of accidental hypothermia (23, 24), and heaters should always be used. During movement of the patient between transport vehicles or from the ambulance to the ward the heater cannot be operated unless an uninterruptible power supply (UPS) is used. However, very few transport programs use UPS (14). In an *ex-vivo* simulation in a mock of a 3 kg newborn on body temperature presented by Ericsson and Westlund at the *35th Annual CNMS: ECMO & the Advanced Therapies for Cardiovascular and Respiratory Failure, 2019, Keystone, CO, USA*, it was not only shown that hypothermia was a risk in out-door transport but also during in-hospital transports, **Figure 1**. In future designs of transport devices heat loss due to convection and conduction should be taken seriously and prioritized. Future mobile ECMO may expand into transporting

TABLE 1 | Shows an *ECMO A-B-C* to be used for problem solving in emergencies and for routine evaluation of device performance and function in extracorporeal membrane oxygenation support.

The ECMO A-B-C includes the following items:
1.ECMO pump
i Power/electricity on
ii Revolutions per minute (rpm)—is the pump running and, at correct speed?
iii Flow—does the pump rpm create an adequate ECMO blood flow?
iv Pressures—does the pump produce a pressure adequate for flow and are the pressures obtained reasonable? Trends? Pressures are monitored before (pre-pump pressure), between pump and oxygenator (pre-oxygenator pressure), and in the return tubing back to the patient (post-oxygenator pressure)
2.Sweep gas
i Flow—sweep-gas flow correctly adjusted?
ii Pressure—is there a pressure in the gas-line to the oxygenator? (indicates integrity of line)
iii Plugged to wall or gas bottle/s? Amount of gas in bottle?
3.Heater on—Power/electricity. There is always risk of hypothermia in the smaller patients, even indoors. Tubing should be lukewarm
4.Tubing
i Look—the color is an indicator for oxygenation of the blood (darker for venous, bright red for arterial). On transport and in poor lighting conditions a flashlight may be handy for inspection
ii Feel—tubing lukewarm, otherwise check the heater. Chattering of the tubing indicates a drainage problem
iii Cannulation site/s: bleeding? Integrity of distal perfusion line?
Use your eyes and hands to assess the patient during transport. In aircraft, lighting conditions are often poor (use flashlight!), and the environment noisy. Noise reduction/hearing protection aids should be provided for the patient.

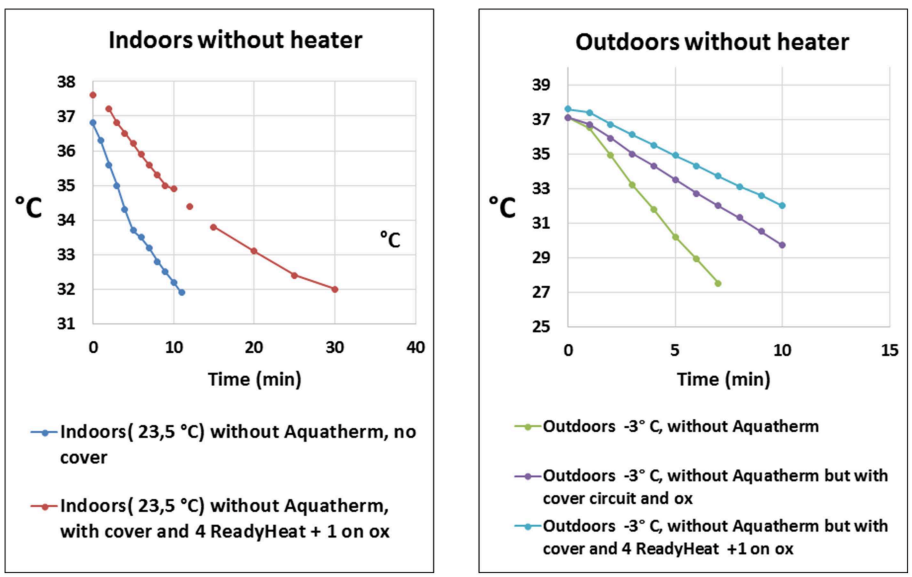

FIGURE 1 | Displays the temperature drop vs. time when simulating a transport of a 3 kg newborn on extracorporeal membrane oxygenation without activated heater (blood warmer). Different means of passive or active protection against hypothermia was used. The left panel shows patient core temperature during movement indoors at an ambient temperature of 23.5°C without activated heater. The right panel shows patient core temperature during transport outdoors at an air temperature of −3°C. With permission from A. Ericsson and C.J. Westlund, ECMO Center Karolinska, Karolinska University Hospital, Stockholm, Sweden (2019). ox, membrane oxygenator. Aquatherm: heater, HICO-AQUATHERM 660; Hirtz & Co., Cologne, Germany. ReadyHeat: Ready-Heat™, disposable self-warming blanket, TechTrade LLC, Jersey City, NJ,USA.

smaller patients, and the smaller the patient, the higher the risk for hypothermia. The importance of an ECMO A-B-C (and checklist, SBAR) cannot be emphasized enough to promote a high level of safety.

Even though ECMO in its early development centered on neonates, devices available today are in many cases developed for adults. Centrifugal pumps, for example, are with few exceptions developed for full-flow ECMO in the adult. When used in neonates these pumps may be too coarse in their flow dynamics for safe use. A centrifugal pump running at low flow speed may induce hemolysis and platelet/coagulation activation due to long residence for platelets and red blood cells inside the pump (and other circuit components) (41). Proper sizing of pump devices will reduce the risk of hemolysis and coagulation activation, thus also bleeding complications. Effective integrated heaters are important for safe transport

of the newborn. With miniaturized implantable gas-exchangers the need for heaters may decrease in the future. These products, however, are not likely to be seen in neonates initially but rather in chronic adult patients bridged for transplant, etc.

Where Will We Go?

Today the number of neonatal ECMO treatments has become rather constant in most of the developed world. Thus, the likelihood of seeing an increase in the number of neonatal ECMO transports with conventional diagnoses and established criteria for ECMO support is low. Socioeconomic and other factors slow or inhibit the extension of major ECMO programs. New methods for extracorporeal life support for the premature are in development. The artificial placenta (AP) focuses on support in the extremely premature (23–28 weeks gestational age, GA) (42–44). To predict the volume of extremely prematurely born infants to be offered AP, or the spread of this life support mode and the extent of engagement by mobile ECMO teams is impossible. First clinical trials will likely start within 5 years (45). However, this may occur sooner as single center studies in humans are planned in the near future to be followed by multicenter approaches, and the method may be commercially available in the not too distant future (*personal communication: Professor Alan W. Flake, Center for Fetal Research, Department of Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA*). A major and perhaps unforeseen impact of the AP is that it will elicit an ethical debate where public opinion and media pressure will enforce research concerning *prem-ECMO*. Prem-ECMO is support in the prematurely born GA 28–34 weeks who are "too old for the AP," but still "too young for conventional ECMO" (46, 47). Today these infants are denied ECMO due to the high risk of cerebral bleeding complications. Improvements in design are centered on coating/lining materials, pumps, gas exchangers, and cannulae. However, insights in the management of anticoagulation as well as ventilation strategies are important. The ventilated lung (and inotropes) may be part of the pathophysiology of cerebral bleedings in the preterm (48, 49). Concerning prem-ECMO transport, it could start tomorrow—the infrastructure is already available by caring for the GA 34+ weeks children.

If, or rather when, prem-ECMO transport is launched, it seems clear that these transports will include high risk patients providing new challenges. Even given that we have proper devices the risk of hypothermia remains. Smaller patient not only requires thinner cannulae, but the margin for error in placement will be small and risk of dislodgement considerable. The implementation of prem-transport has to be guided by adequate protocols and be evaluated. Today we are far beyond the time when anecdotes can mark the path to be followed.

In this article, the impact of stem cell/gene therapy in the neonate will not be discussed and what the future holds is yet to be seen (50). However, AP patients have been suggested as one group for gene therapy (44).

In ECMO transports a lowest acceptable number, or minimum of total accumulated annual transport hours required to ensure patient safety has not been published. However, it may be assumed that the larger the patient volume the better the outcome with reduced morbidity and mortality. The first step needed for us as a community would be to agree on standards, acknowledge that adverse event do occur in any mobile ECMO program and from this create a platform to improve and develop our programs. Resources should be allocated to expand the ELSO Registry with a transport module for reporting but also for extraction of own in- and processed out-put data. ELSO Centers of Excellence with recognized transport programs could be encouraged to take the lead in the development and support of interhospital mobile ECMO and act as "role-models" for safe and reliable mobile ECMO.

CONCLUSIONS

The expansion of neonatal ECMO into new geographical regions is limited. Hence, future volume increases in mobile ECMO in neonates depend on the introduction of new methods for the (extremely) premature: the artificial placenta (GA 23–28 weeks) and what comes thereafter, prem-ECMO (GA 28–34 weeks).

For safe transport of any age patient and in any size program, basic requirements for education, clinical training and experience are needed. Regular wet-lab training and high-fidelity team simulations using clinical scenarios increase performance. Time-outs, checklists and ECMO A-B-C are paramount for safety in-hospital and on transport. For future development and improvement follow-up and sharing of data is important.

ECMO transport services in the newborn should include an out-reach service provided by ELSO member centers that report transport related data to an expansion of the ELSO Registry for transport quality follow-up and research.

DATA AVAILABILITY

No datasets were generated or analyzed for this study.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of Interest Statement: LB is a Medical Advisory Board member of Eurosets (Mirandola, Modena, Italy), and of Xenios (Heilbronn, Germany).

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REVIEW
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Extracorporeal Membrane Oxygenation in Congenital Diaphragmatic Hernia

*Neysan Rafat and Thomas Schaible**

Department of Neonatology, University Children's Hospital Mannheim, University of Heidelberg, Mannheim, Germany

Congenital diaphragmatic hernia (CDH) is characterized by failure of diaphragmatic development with lung hypoplasia and persistent pulmonary hypertension of the newborn (PPHN). If conventional treatment with gentle ventilation and optimized vasoactive medication fails, extracorporeal membrane oxygenation (ECMO) may be considered. The benefits of ECMO in CDH are still controversial, since there are only few randomized trials demonstrating the advantages of this therapeutic option. At present, there is no precise prenatal and/or early postnatal prognostication parameter to predict reversibility of PPHN in CDH patients. Indications for initiating ECMO include either respiratory or circulatory parameters, which are also undergoing continuous refinement. Centers with higher case numbers and the availability of ECMO published promising survival rates, but data on long-term results, including morbidity and quality of life, are rare. Survival might be influenced by the timing of ECMO initiation and the timing of surgical repair. In this regard a trend toward early initiation of ECMO and early surgery on ECMO exists. The results concerning the cannulation modes are similar and a consensus on time limit for ECMO runs does not exist. The use of ECMO in CDH will continue to be evaluated, and prospective randomized trials and registry network are necessary to help answering the addressed questions of patient selection and management.

Keywords: congenital diaphragmatic hernia, extracorporeal membrane oxygenation, pulmonary hypertension, surgical repair, long-term outcome

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University of Tennessee Health Science Center (UTHSC), United States
Bernhard Resch,
Medical University of Graz, Austria

***Correspondence:**
Thomas Schaible
thomas.schaible@umm.de

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INTRODUCTION

Congenital diaphragmatic hernia (CDH) is currently the most common indication for extracorporeal membrane oxygenation (ECMO) in neonates (1). Survival rates reported by the extracorporeal life support organization (ELSO) have continued to drop in the modern era (2) and systematic reviews concerning a benefit of ECMO in CDH did not find an advantage for ECMO (3–5). However, some centers and networks have demonstrated an increase in survival rates in CDH with the employment of ECMO by retrospective analysis in their series (6). ECMO may perform as a true safety net when conventional treatment strategies fail or may only be a marketing strategy for a center to become a high-volume center with the positive side effect of increasing experience in the treatment of CDH. By increasing experience in the treatment of CDH, ECMO employment might be reduced, however, in some cases of CDH, pulmonary hypertension is so severe that only ECMO support can provide a chance of survival. The pathophysiology of CDH includes lung hypoplasia and abnormal development of the pulmonary vasculature with hyper-reactivity which leads to persistent pulmonary hypertension of the newborn (PPHN) (1).

Episodes of hypoxia and hypercapnia can exacerbate the PPHN, leading to severe morbidity and mortality. In patients who continue to have labile physiology and low preductal saturations despite optimal ventilation, inotropic and pulmonary vasodilatory support, the next intervention considered in the management of CDH is extracorporeal membrane oxygenation (ECMO), if available. We present a review of literature in this complex patient group and try to answer some questions about optimal time to start ECMO, recommended entry criteria, mode of ECMO, and timing of operation.

PATHOPHYSIOLOGY IN CDH AND RATIONALE FOR ECMO

In isolated CDH it seems possible to predict survival and need for ECMO and also chronic lung disease (CLD) by measuring the lung size by ultrasound or MRI. Liver herniation is also an independent risk factor for employment of ECMO (7). Data obtained by MRI seems to have lower interoperator variation and are easier to unify than data obtained by ultrasound. Categorization of severity was processed as previously described, and allows the comparison of results of different centers or ongoing studies investigating the effect of fetal tracheal occlusion (FETO) (8). As an example, we show our published data from 2006 concerning the prediction for ECMO in the group of left-sided CDH with liver up (**Figure 1**). Prognostic value in this group was only about 70%, because we could not predict how severe the pulmonary hypertension would be (9). With an optimal delivery room management, severely affected patients with liver up will present with some signs of a honeymoon (preductal saturation > 90%). That may be a reason for some optimism, since these patients with potential reversible pulmonary hypertension may benefit from ECMO. Avoiding stress, acidosis and severe hypoxemia and therefore crises of pulmonary hypertension reduces the need for ECMO. Surely some patients will be severely affected and do not have any sign of honeymoon, but an ongoing respiratory acidosis. In these cases, survival is impossible. But finding precisely the threshold for not offering ECMO is extremely difficult.

Using a multi-variate modeling to define the worst 10% of patients, Kays et al. included 172 consecutive inborn, prenatally diagnosed CDH patients in their analysis (10). Of the 19 worst patients, who were all aggressively resuscitated at birth and showed an average initial pH of 6.83 (at 1 h of life) with a PCO_2 > 100, 10 of 16 patients, eligible for ECMO, survived to discharge (63%) (10). These results are difficult to compare to our data because the underlying prenatal severity is not published. In contrast, in our experience a preductal saturation <85% and/or arterial PCO_2 > 100 after initial stabilization (at 1 h of life) is not compatible with survival despite early initiation of ECMO (within the first 4 h of life).

While evidence is missing for the necessity for employment of ECMO support, data from case series of ECMO centers offer convincing evidence of the potential for ECMO to rescue patients at the highly severe end of the CDH spectrum, a capability not well-documented for other treatment options besides ECMO so far (10). To understand the importance of ECMO support for selected cases of CDH, we will look at the pathophysiology of pulmonary hypertension in more detail.

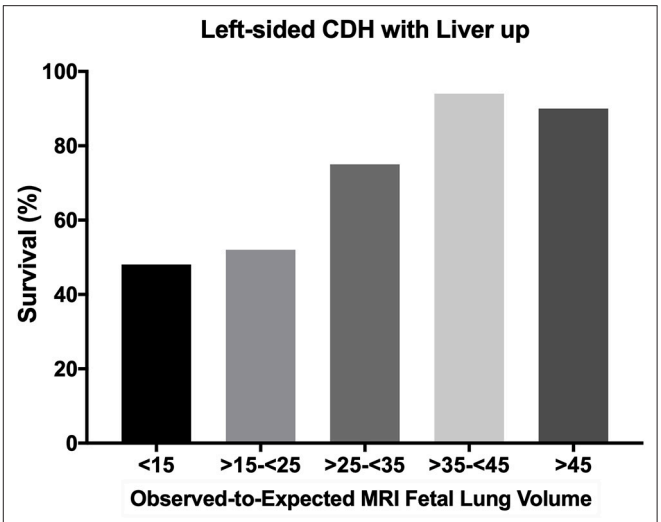

FIGURE 1 | Survival rate of left sided CDH with liver up depending on the Observed-to-Expected MRI Fetal Lung Volume. All infants with left-sided CDH with liver up, treated in the years between 2001 and 2010 ($n = 143$) at our center in Mannheim, Germany were included for this analysis. This figure was newly created from previous published data (9). CDH, congenital diaphragmatic hernia.

Reduced lung volume available for gas exchange may lead to hypoxemia and hypercarbia, and is one of the main pathological abnormalities that can determine the indication for ECMO. One difficulty is that severe lung hypoplasia is not currently reversible in the short term, and can make the possibility of weaning from ECMO difficult or impossible. PPHN can arise even in minor lung hypoplasia by causing a right-to-left shunt and persistent fetal circulation, which further exacerbates hypoxemia and hypercarbia. The vasculature of small pulmonary arteries is pathologically thickened and reaches far into distal airways. Any kind of distress as barotrauma, inflammation or cytokine release by surgical intervention may induce additional vasoconstriction of the small vessels. The presence of PPHN is a significant predictor and cause of morbidity, need for ECMO and mortality in CDH (11). Antenatal markers which accurately predict the degree of PPHN in CDH, are not really known. To best address this challenge there are some suggestions, such as measuring antenatal pulmonary artery diameter, estimation of pulmonary perfusion by doppler measurements or left ventricular volume (12, 13).

Patients with either good or bad prognostication only based on antenatal lung volumes and ratios can have a discrepant clinical course. Postnatal clinical course could be a marker of severity of PPHN, with oxygenation index (OI) or combined parameters of ventilation and oxygenation (Wilford Hall/Santa Rosa Score) on day 1 predictive of outcome (14, 15). In postnatal therapy the institution of effective gentle ventilation from the very beginning in the delivery room, either by conventional ventilation or high frequency oscillatory ventilation (HFOV),

is crucial. The VICI trial showed to some extent a benefit for conventional ventilation as the initial mode of ventilation in terms of a shorter ventilation time and a reduced need for ECMO, but not for mortality or BPD (16). The most widely used medication in PPHN management is inhaled nitric oxide (iNO). Inhaled nitric oxide (iNO) can improve oxygenation and reduce the acute need for ECMO in newborns with other causes of PPHN, but not conclusively in CDH (17). Nevertheless, the application of iNO in CDH is about 60% in reported case series (18).

Other treatment options like sildenafil or milrinone intravenously given in PPHN are applied to treat the condition in CDH with varying success (19). A European multi-center study is planned in order to investigate the effect of iNO vs. sildenafil after delivery. Systemic pressure should be maintained on normal values in order to avoid exacerbation of any right to left shunts.

Cardiac dysfunction resulting from the physiological derangements, PPHN or any associated congenital structural cardiac abnormality can complicate the clinical course (**Figure 2**). Poor cardiac output and impaired tissue oxygenation can ensue, and therefore serum lactate may be elevated and may work as an indication for employment of ECMO. In nearly all cases with suprasystemic pulmonary artery pressure and failure of reducing right-to-left shunts, a prostaglandin analog to open the ductus arteriosus and thereby unloading the right heart may help to stabilize the patient until ECMO is established.

Randomized controlled data on the role of ECMO in CDH is limited to two early ECMO studies and the UK ECMO trial (20–22). In the later trial, CDH patients were randomized at an oxygenation index of 40 to conventional ventilation vs. ECMO. From the 17 CDH patients randomized to conventional management all died, while in the ECMO group 4 of 18 infants survived (0 vs. 22% survival) (22). In 2006 a systematic review of ECMO in CDH was published, identifying 658 publications of which 21 (2,043 patients) met entry criteria (23). Looking at the findings of these studies, the authors concluded that employment of ECMO was associated with a reduction in CDH mortality (23). Zalla et al. (24) reviewed a single center CDH experience, dividing 16 years of treatment into four eras. In the latter two eras ECMO support was then available. *Post-hoc* analysis suggested a 73% reduction in risk of death in the ECMO eras compared to the pre-ECMO eras despite increases in CDH disease severity (24). In a recent analysis of the CDH EURO Consortium at four high volume centers in Europe, there are also higher survival rates reported from ECMO centers compared to non-ECMO centers (25).

There is only little evidence about the impact of the location of the hernia on ECMO need and postnatal prognosis. Patients with right-sided CDH have been identified as requiring increased use of ECMO [54% (26) and 71% (27)], but had better than expected ECMO survival [80% (26) and 83% (27)] (26, 27). Recently published data from the CDH study group are contrary to the before mentioned single center experiences (28). The survival without ECMO in left-sided CDH was higher compared to right-sided CDH and the use of ECMO was comparably low in right-sided CDH (36%) (28). The underlying pathophysiological mechanisms of these findings need to be investigated further. Some explanations for the different outcomes in right- vs. left-sided CDH have been suggested including the atypical dextroposition of the heart in left-sided CDH leading to adverse hemodynamic changes and an impaired cardiac function (27).

In general, improved survival without ECMO and also in ECMO centers is highly associated with the implementation of standardized treatment protocols, which mainly includes strategies to avoid ventilator associated lung injury (VALI) (29).

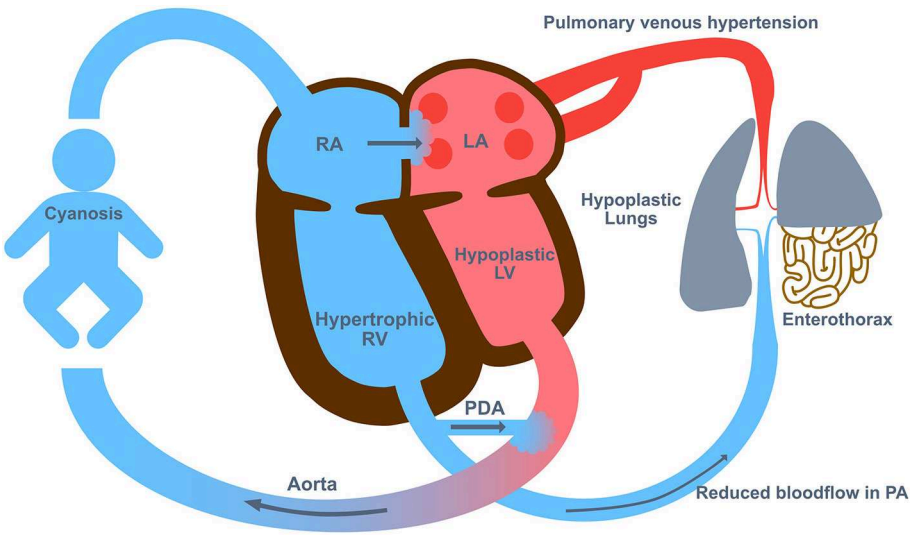

FIGURE 2 | The Pathophysiology in congenital diaphragmatic hernia (CDH). The pathophysiology of CDH includes lung hypoplasia and abnormal development of the pulmonary vasculature with hyper-reactivity which leads to persistent pulmonary hypertension of the newborn (PPHN). LA, left atrium; LV, left ventricle; PA, pulmonary artery; PDA, persistent ductus arteriosus; RA, right atrium; RV, right ventricle.

CDH ELSO INDICATIONS VS. CDH EURO CONSORTIUM INDICATIONS

Entry criteria that accurately predict high mortality prior to the initiation of ECMO in infants with CDH have not been published (1). Various parameters have been used to predict those who benefit from ECMO (30–34), however, none of these criteria has been validated in multicenter studies (1). In the past, entry criteria suggested by ELSO for CDH patients included an oxygenation index (OI)>40 for 4 h or a PaO_2 < 40 for 2 h (30), which were general entry criteria for ECMO for neonates with pulmonary hypertension of any cause. In the newest edition of their guidelines (1), ELSO has adopted their entry criteria for infants with CDH also according to the recommendations suggested by the CDH EURO Consortium Consensus −2015 Update (35). They define the following indications to initiate ECMO support in CDH patients: hypoxia, defined as preductal saturations consistently <80–85%; acidosis, defined as metabolic (lactate > 5 mmol/L or pH < 7.20) or respiratory (pH < 7.20 due to hypercarbia); hypercarbia, defined as persistent $PaCO_2$ > 70 leading to pH < 7.20; or hypotension, defined as poor tissue perfusion, urine output < 0.5 mL/kg/h or unresponsive to IV fluid and inotropic support. In addition, many centers use a specific limit on ventilator settings to avoid ventilator-associated lung injury (VALI) and transition to ECMO support when a patient does not respond appropriately (1). These include limiting the peak inspiratory pressure (PIP) (≤26 cm H_2O, HFOV to a MAP of 14–15 cm H_2O), and maintaining pH > 7.20 (usually $PaCO_2$ < 70 mmHg) (1). The only minor differences in the recommendation of the CDH EURO Consortium Consensus relate to the hypercarbia leading to a pH < 7.15 and the ventilator settings (PIP > 28 cm H_2O or MAP > 17 cm H_2O) as an entry criteria (35). There are no significant differences between the two guidelines, and the combined entry criteria for ECMO in CDH allow a center-depend individual decision.

Relative contraindications to initiating ECMO support in CDH patients are comprised of significant congenital anomalies (major cardiac anomalies), lethal chromosomal abnormalities or other lethal malformations, Grade III/IV intracranial hemorrhage, prolonged mechanical ventilation requiring prolonged high pressure, weight < 2 kg and gestational age < 34 weeks (1). The last two criteria are due to technical problems of vascular access and the complications of prematurity. In general, prematurity is more common in patients with congenital anomalies and accordingly also in CDH. Notably, preterm infants with CDH have an increased mortality compared to term infants (36).

TIMING OF ECMO DEPLOYMENT: EARLY VS. LATE

The data of the CDH Study Group highlight the trend toward employing ECMO earlier (before CDH repair) as a component of preoperative stabilization (Red Book). While the inclusion criteria for initiating ECMO have been described in detail, there is no data available on the influence of the time point, when ECMO was initiated, on the morbidity and mortality in CDH patients. Many experts have the notion that the starting point of ECMO in CDH patients might be time-sensitive, since the responsivity of the pulmonary vasculature to pulmonary arterial hypertension treatment might be higher at the beginning and potentially reversible. If treated too late and complicated by the degree of pulmonary hypoplasia and VALI, the pulmonary hypertension can progress to right heart failure.

In our retrospective review of 321 neonates treated with ECMO from January 1987 to December 2006 at our center, we have already presented, that an early referral (<24 h) of CDH patients to the ECMO center correlated with an increased survival (6).

In a small cohort of patients with less than 15% predicted lung volume on antenatal scan who underwent EXIT to ECMO, no advantage in either survival or long-term morbidity could be demonstrated (37, 38). Although there are no randomized studies on EXIT to ECMO and these patients were not randomized, results led to the suggestion of little benefit for routine use (39).

TYPE OF SUPPORT: VENO-VENOUS VS. VENO-ARTERIAL ECMO

The mode of ECMO in CDH, whether veno-venous (VV) or veno-arterial (VA), has not been demonstrated to affect survival so far, but the current available data is poorly controlled for underlying disease severity.

Veno-arterial (VA) ECMO is usually performed with an open cut-down technique where the right common carotid artery (CCA) and right internal jugular vein (IJV) are isolated and cannulated. Circuit flows are gradually increased to provide about 50 to 100 mL/kg/min. Centrifugal ECMO circuits require smaller blood volumes for priming, but may be not as exact as roller-pump systems in providing low blood flows (the minimal possible blood flow without increased risk of clotting should be 30 mL/kg KG). Also, for appropriate hemodynamic reloading of the right ventricle in VA ECMO, especially in the weaning or the idling phase at the end of the ECMO support time, the Mannheim experience suggests to apply lower blood flows. The appropriate cannula size is determined depending on the infant's weight (sizes available down to 8 Fr; hence the VA technique may be feasible for the smaller infants). VA ECMO may have some advantages in infants with cardiac dysfunction (unloading of the right ventricle and maintaining good systemic output). Due to the pathophysiology with preexisting lower blood flow through the small pulmonary vascular bed in severely affected CDH patients, we always used VA ECMO in CDH patients in Mannheim (**Figure 3**).

It is often feasible to repair the CCA at decannulation although the rates of long-term patency are unclear (the IJV is usually ligated). Our own data of repair CCAs showed patency in half of the cohort, stenosis in about one fourth and occlusion in the remaining fourth part of the cohort (40).

Cannulation to Veno-venous (VV) ECMO can be performed by open surgery or using an ultrasound-guided percutaneous technique to cannulate the IJV (thereby preserving the CCA).

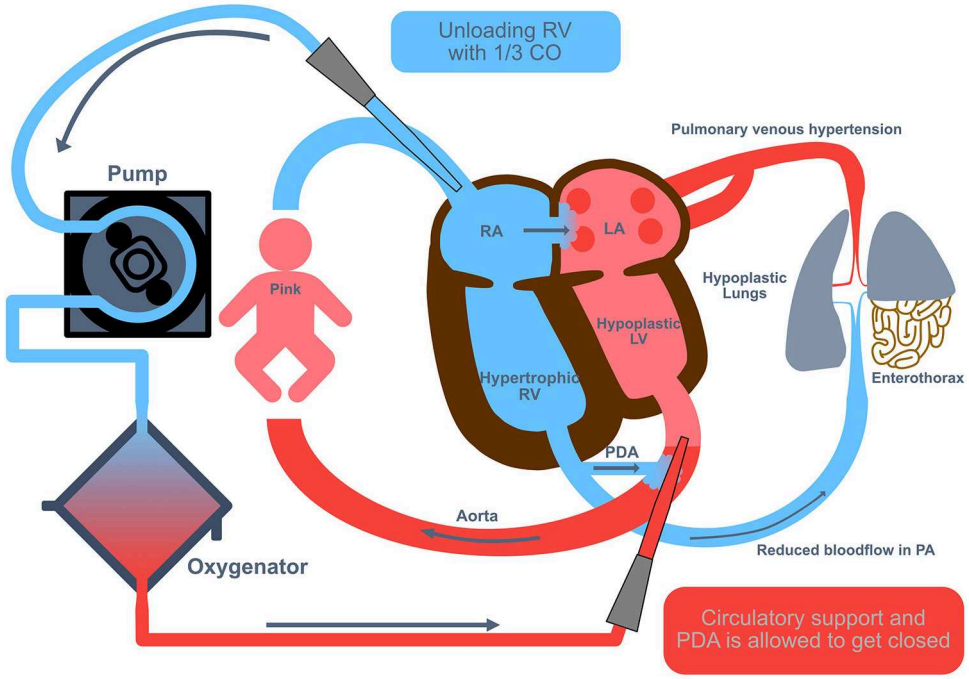

FIGURE 3 | Veno-arterial extracorporeal membrane oxygenation in congenital diaphragmatic hernia (CDH). Veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) is usually performed with an open cut-down technique where the right common carotid artery and right internal jugular vein are isolated and cannulated. Circuit flows are gradually increased to provide about 50 to 100 mL/kg/min, equivalent to an unloading of the right ventricle with 1/3 of the cardiac output. CO, cardiac output; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PDA, persistent ductus arteriosus; RA, right atrium; RV, right ventricle.

Because the cannulae are dual-lumen catheter, the smallest size used is 12 Fr, which requires the weight of the infant to be >2.5 kg. A potential advantage of this technique is that hyper-oxygenated blood is directed into the pulmonary artery and hence may reduce vascular resistance. But it is not clear whether a high amount of oxygen in the pulmonary vessels may lead to more inflammation via radical oxygen species (ROS). For unloading of the right heart, the duct should be open in the initial phase of VV- ECMO (**Figure 4**).

The VV-technique is dependent on satisfactory cardiac output and higher flows are usually required (often about 120 mL/kg/min). Recirculation of oxygenated blood up the venous lumen makes the precise catheter position more critical.

The cumulative ELSO experience on this topic was reviewed in two reports (41, 42), the latter covering 15 years from 1991 to 2006 (42). The report showed that VA ECMO was used in 82%, and VV ECMO only in 18% of the cases (42). Of the patients on VV ECMO 18% required conversion to VA ECMO, with survival dropping from 54% (VV) to 44% (switch from VV to VA), compared to 50% when ECMO was initiated as VA (42).

Although a systematic review suggested that there was no overall advantage with either the VV or VA technique, there is a difference in preferred mode of cannulation between centers (43). VA ECMO seems to be the more popular of the two modes, according to the scientific reports and ECMO registries; presumably as VA ECMO may give the additional benefit in the presence of severe cardiac dysfunction. They reported that VA was associated with slightly higher incidence of intracranial bleeding and seizure, while VV was associated with poorer renal perfusion. Size and vascular anatomy may sometimes dictate the mode used. Overall survival was similar between modes.

TIMING OF SURGICAL INTERVENTION: BEFORE, DURING OR AFTER ECMO?

Typically, the duration of ECMO support in CDH patients takes between 1 and 4 weeks. It has been demonstrated that prolonged need for ECMO is associated with both increased morbidity and mortality (44). In our experience an optimal duration of our preferred ECMO mode (VA) in Mannheim is 7–14 days with an average duration of 10 days. Two days after successful weaning from ECMO support, surgical repair of the CDH will be performed. This traditional approach is supported by some studies, which identified an increased survival rate, if repair could be delayed until ECMO support has been completed (45, 46). Weaning off ECMO includes a trial to clamp off ECMO for 10–15 min, which is performed after 2 days with a very low flow of 30 ml/kg KG. The objective is achieving adequate oxygenation and ventilation ($pCO_2 < 60$ mmHg) by a $FiO_2 \leq 0.5$ and gentle ventilation. In cases of weaning failure, we may prolong the ECMO support until a total of 21 days. If weaning fails after 21 days of ECMO support, we will offer compassionate/palliative care and a surgical repair will not be performed.

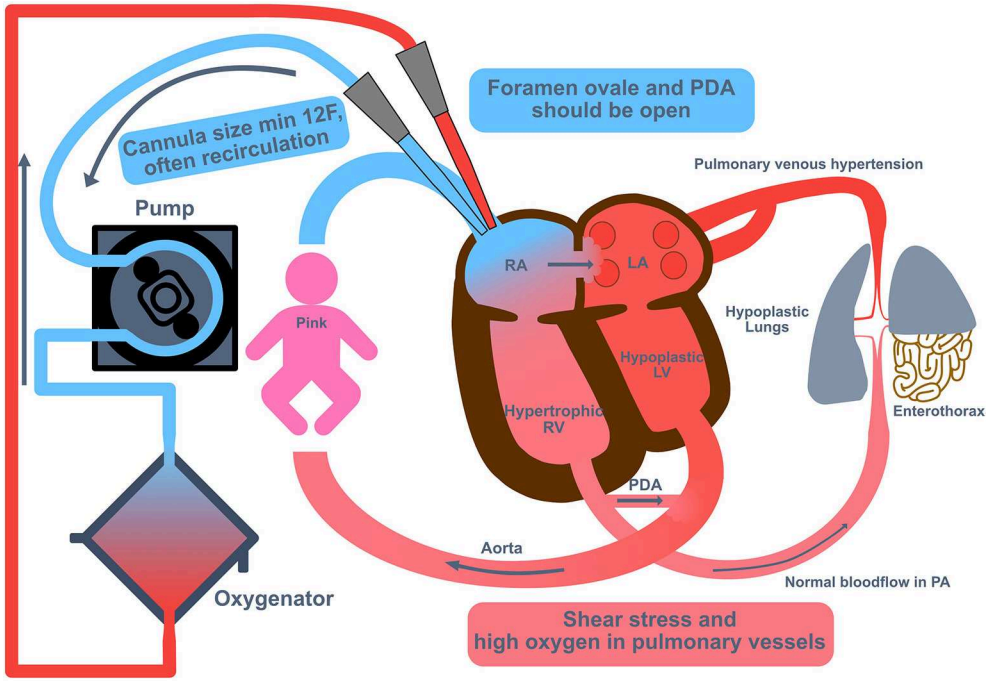

FIGURE 4 | Veno-venous extracorporeal membrane oxygenation in congenital diaphragmatic hernia (CDH). Cannulation to Veno-venous (VV) extracorporeal membrane oxygenation (ECMO) can be performed by open surgery or using an ultrasound-guided percutaneous technique to cannulate the internal jugular vein (thereby preserving the common carotid artery). Because the cannulae are dual-lumen catheter, the smallest size used is 12 Fr, which requires the weight of the infant to be >2.5 kg. For unloading of the right heart, the duct should be open in the initial phase of VV ECMO. LA, left atrium; LV, left ventricle; PA, pulmonary artery; PDA, persistent ductus arteriosus; RA, right atrium; RV, right ventricle.

A main argument against surgical repair while on ECMO support is the higher incidence of bleeding. Complications from bleeding have, however, been reduced by careful anticoagulation management and the use of tranexamic acid perioperatively (47). Whether terminating treatment on ECMO without attempting surgical repair, might be a disadvantage and has not been systematically investigated. Some centers proclaim that surgical repair may increase the chances of survival, especially in the most severe forms of CDH. Yoder et al. reported from the CDH Study Group, that patients with a preductal saturation <85% in the first 24 h of life or before ECMO support, had an increased survival rate, if surgical repair was performed (44 vs. 23%) (48). Due to this finding, surgical repair while on ECMO support was advocated. Theoretically, surgical repair while on ECMO support may improve respiratory function by restoring normal anatomy, and intestinal complications from delaying surgery (ischemia or volvulus) are possible (49).

Analyzing the studies about the timing of surgical repair in more detail, the duration of ECMO support was shorter in patients with surgical repair after ECMO (8.4 days) compared to patients with surgical correction while on ECMO (8.9 days) (45). Also, patients undergoing surgery after ECMO support seemed to have lower severity of disease (45).

Another strategy to avoid mortality due to late or non-repair on ECMO is "early" repair on ECMO. In the study of Dassinger et al. 34 CDH patients underwent surgical repair while on ECMO at an average of 55 h after ECMO initiation (50). Only 9% of the patients suffered bleeding complications requiring intervention, and a total of 22 (71%) survived (50). The same trend toward an early surgical repair while on ECMO is supported by the data of Fallon et al. (51).

A last approach of a very early surgical repair in a honeymoon-like period before decompensation was suggested by Kays et al. (52). They developed a multi-variate modeling, employing anatomic and physiologic markers of severity—including prenatal lung measurements, liver position, birth physiology, and blood gas analysis data at 1 h after birth—to assess risk for ECMO at 1 h of life. Left-sided CDH patients with liver-up, which underwent surgical repair early before ECMO (mean time to surgery was 21 h), had a survival rate of 95%, compared to 65% in an equivalent group (left-sided CDH liver-up), who underwent ECMO support without previous surgical repair (52).

The optimal timing of surgery for patients on ECMO support is difficult to ultimately establish, but it seems that there is a developing consensus that repair at an earlier stage (within 1 week) with careful management of perioperative risks, may help with either weaning off ECMO or decisions on withdrawal later, and potentially improves outcome. It seems that different patients benefit from different strategies, therefore, we have to learn to individualize some aspects of CDH treatment, e.g., the timing of surgical repair.

IMPROVING LONG-TERM OUTCOME OF CDH VIA STRUCTURED FOLLOW UP

The only outcome criteria of the ELSO-registered neonates with CDH are: transfer to another hospital or survival to discharge (53). In future, more attention should be directed to short and long-term morbidity. ECMO centers may reflect not only their survival rate, but also changes in indications for ECMO and cognitive impairment as the major long-term deficit following neonatal ECMO (54). The most important issue after ECMO in CDH is neurodevelopment outcome. During initial treatment, cerebral bleeding or infarction should be evaluated closely by cranial ultrasound. For long-term evaluation, MRI including angiography seems to be helpful for reflection of the initial decisions and may help to relate the results to the complications (40). Intelligence, memory, attention, behavior, and concentration deficits are domains of interest in school age (54–57).

Looking at the pulmonary outcome due to lung hypoplasia, the degree of CLD represents a short term complication (58); lung function testing may serve as a parameter for lung function development after severe neonatal disease (59). Furthermore, structured echocardiographic investigations may guide treatment and prognosis of pulmonary hypertension in CDH.

Surgical outcome parameters and complications after CDH repair include recurrence rates, feeding disorders and risk of ileus due to adhesions. In addition, further skeletal problems like chest wall deformations, funnel chest and scoliosis may occur. However, there is limited long-term outcome data in this regard.

Most follow-up studies in neonates and children who survived ECMO treatment have been cross-sectional, mono-center and in small study populations. With the current shift toward long-term multidisciplinary evaluations, observational follow-up-programs should be transferred toward risk stratification (60).

CONCLUSION

In conclusion, the use of ECMO in CDH remains controversial. While many centers have demonstrated very good survival, utilizing minimal to no ECMO in CDH, the highest overall survival rates are reported by centers that employ ECMO, and whose patient populations likely also include the sickest patients. Due to the exceptional potential of ECMO to rescue CDH patients with profound pulmonary hypoplasia, the role of ECMO in severe CDH seems protected. The significance of surgical repair in attaining survival of patients with CDH, especially of those on the more severe end of the spectrum, cannot be overstated. While surgical repair after ECMO works well for those that successfully wean from ECMO, an early repair strategy on or before ECMO might potentially increase survival.

Based on the presented data and significant professional experience with CDH care, we feel confident that ECMO improves survival potential in more severe CDH compared to currently available non-ECMO techniques. Improving CDH survival is still a major goal and since the majority of deaths occur in those more severely affected, improving outcomes in those CDH patients treated with ECMO is essential. However, mortality should not be the only focus and parameter when proclaiming the importance of ECMO in CDH treatment. More research is needed to assess the morbidity of CDH patients after ECMO support and their long-term outcome.

In our opinion, factors which contribute to ongoing improvement, include having updated standardized postnatal treatment guidelines and participation in networks, further referrals to high-volume center with increasing experience in the treatment of CDH and severity-specific management.

AUTHOR CONTRIBUTIONS

NR and TS contributed equally to the concept and drafting of the article. Both authors approved the final version of the article.

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REVIEW
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Neonatal Cardiac ECMO in 2019 and Beyond

Peter Paul Roeleveld[1*†] *and Malaika Mendonca*[2†]

[1] *Pediatric Intensive Care, Leiden University Medical Center, Leiden, Netherlands,* [2] *Pediatric Intensive Care Unit, Children's Hospital, Inselspital, Bern University Hospital, Bern, Switzerland*

Worldwide, the use of Extracorporeal Membrane Oxygenation (ECMO) for cardiac failure has been steadily increasing in the neonatal population and has become a widely accepted modality. Especially in centers caring for children with (congenital) heart disease, ECMO is now an essential part of care available for those with severe heart failure as a bridge to recovery, long term mechanical support, or transplantation. Short-term outcomes depend very much on indication. Hospital survival is ∼40% for all neonatal cardiac ECMO patients combined. ECMO is being used for pre- and/or post-operative stabilization in neonates with congenital heart disease and in neonates with medical heart disease such as myocarditis, cardiomyopathy or refractory arrhythmias. ECMO use during resuscitation (ECPR) or for sepsis is summarized elsewhere in this special edition of Frontiers in Pediatrics. In this review article, we will discuss the indications for neonatal cardiac ECMO, the difficult process of patients' selection and identifying the right timing to initiate ECMO, as well as outline pros and cons for peripheral vs. central cannulation. We will present predictors of mortality and, very importantly, predictors of survival: what can be done to improve the outcomes for your patients. Furthermore, an overview of current insights regarding supportive care in neonatal cardiac ECMO is given. Additionally, we will address issues specific to neonates with single ventricle physiology on ECMO, for example cannulation strategies and the influence of shunt type (Blalock-Taussig shunt vs. "right ventricle to pulmonary artery" shunt). We will not only focus on short term outcomes, such as hospital survival, but also on the importance of long-term neuro-developmental outcomes, and we will end this review with suggestions for future research.

Keywords: ECMO, neonate, cardiac, heart failure, post-cardiotomy, single ventricle, selection criteria

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Giacomo Cavallaro,
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Mark Danton,
Royal Manchester Children's Hospital, United Kingdom

****Correspondence:***
Peter Paul Roeleveld
p.p.roeleveld@lumc.nl

† These authors have contributed equally to this work

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INTRODUCTION

Since the inception of Extracorporeal Membrane Oxygenation (ECMO), the number of annually performed ECMO runs for neonates with cardiac disease has been steadily increasing (1) (**Figure 1**). In the last decade, ∼400–500 neonates have been supported with ECMO each year in centers reporting to the Extracorporeal Life Support Organization (ELSO). Since 1987, more than 8,000 neonates have been registered in the ELSO database (1). Hospital survival is ∼40% and hasn't really changed since 1987, despite increased experience, better equipment and enforced education and team training. This might be due to a constant widening of indications, increasing levels of complexity and acuity (2, 3).

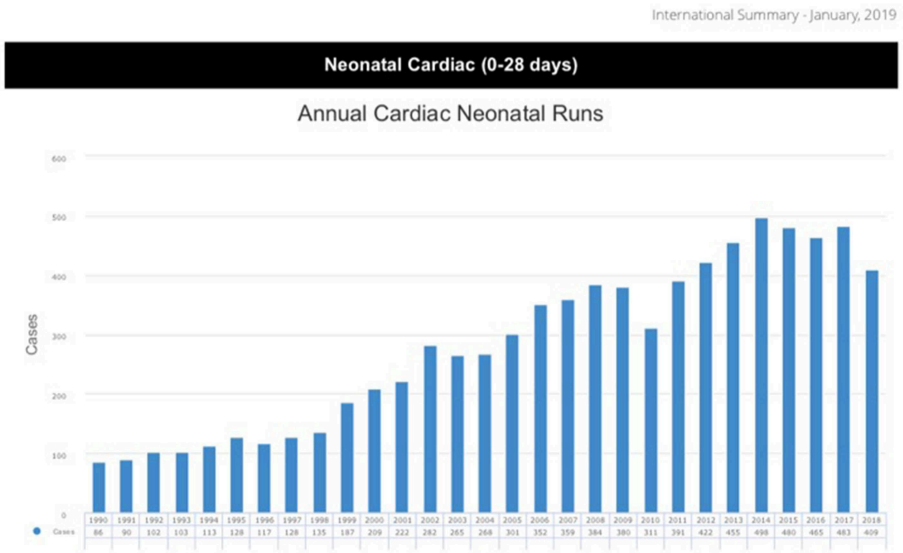

FIGURE 1 | ELSO data report 2019 (1).

In hospitals caring for children with heart disease, ECMO has become an essential part of modalities available to temporarily support these neonates when conventional therapy fails. ECMO, however is not a treatment in itself. The goal of ECMO support is to offer the failing myocardium a chance to recover while the body is provided with adequate blood supply. Most often, ECMO for neonatal cardiac disease is used as a bridge to recovery, bridge to long-term support, as a bridge to heart transplantation or bridge to decision making (e.g., diagnostic work-up, organ donor). However, ECMO is no longer a rescue treatment *per se*, as it has also found its way as elective support during diagnostic and therapeutic procedures (4).

In this review article, we will discuss the indications for neonatal cardiac ECMO, the difficult process of patients' selection, identifying the right timing to initiate ECMO, and outline pros and cons for peripheral vs. central cannulation. We will present predictors of mortality and, very importantly, predictors of survival: what can be done to improve the outcomes for your patients. It is essential that explanations are sought for the circulatory compromise leading to ECMO, so attempts can be made to correct possible reversible diseases, such as residual lesions following congenital heart surgery. It is also extremely important to decompress the heart as much as possible to decrease myocardial work and oxygen consumption aiding in recovery. Furthermore, an overview of current insights regarding supportive care in neonatal cardiac ECMO is given. Additionally, we will address issues specific to neonates with single ventricle physiology on ECMO, for example cannulation strategies and the influence of shunt type (Blalock-Taussig shunt vs. "right ventricle to pulmonary artery" shunt). We will not only focus on short-term outcomes, such as hospital survival, but also address the importance of long-term neuro-developmental outcomes and we will end this review with suggestions for future research.

INDICATIONS

Neonates receiving ECMO for cardiac disease constitute a heterogenous group and can receive ECMO for surgical or medical cardiac disease, such as cardiomyopathy, myocarditis, and/or arrhythmias (**Table 1**).

Congenital Heart Disease

In neonates with surgical cardiac disease, ECMO can be utilized for pre-operative stabilization (e.g., transposition of the great arteries with pulmonary hypertension), failure to wean from cardiopulmonary bypass (CPB), or low cardiac output syndrome (LCOS) post-operatively. Following congenital heart surgery, ECMO is utilized in 1.4–5% of operations (5–7). Cardiac arrest as an indication for ECMO is called Extracorporeal Cardiopulmonary Resuscitation (ECPR) and is discussed elsewhere in this Research Topic of *Frontiers in Pediatrics*.

According to a recent Society of Thoracic Surgeons (STS)-database study, risk factors for receiving post-operative ECMO include young age (13 vs. 195 days), low weight (3.4 vs. 6.4 kg), mechanical ventilation prior to surgery (37 vs. 15% chance of receiving ECMO), arrhythmia (4.6 vs. 2.6%), shock (7.4 vs. 1.7%), higher complexity as indicated by 'STAT' category of 4–5 (72 vs. 34%), and CPB-duration (175 vs. 94 min) (5). Also, more complex lesions have a higher chance of receiving ECMO post-operatively. For instance, in neonates following Norwood operations, incidence of ECMO is much higher with ∼13% of neonates receiving mechanical support post-operatively (8). Also,

TABLE 1 | Neonatal cardiac runs by diagnosis in the last five years (2014–2019), ELSO registry report January 2019 (1).

	Total runs	Avg run time	Longest run time	Survived	% Survived
Congenital defect	1,487	144	1,481	698	46%
Cardiac arrest	15	157	600	6	40%
Cardiogenic shock	77	153	1,746	43	55%
Cardiomyopathy	27	231	848	15	55%
Myocarditis	25	250	628	13	52%
Other	621	168	3,737	342	55%

Avg, average. Run times are given in hours.

TABLE 2 | Risk factors for receiving ECMO following neonatal heart surgery.

Risk factors for receiving post-cardiotomy ECMO	
Young age	STAT category 4–5
Lower weight	CPB duration
Mechanical ventilation pre-operative	–
Arrhythmia	Shock
Higher vasoactive-inotropic score (VIS)	–

STAT, Society of Thoracic surgeons—European Association for cardio-Thoracic surgery; CPB, cardiopulmonary bypass.

higher Vasoactive-inotropic scores have been associated with increased ECMO utilization (9) (**Table 2**).

Myocarditis/Cardiomyopathy

The incidence of myocarditis in neonates is not clearly known because the diagnosis remains challenging due to non-specific symptoms, often masquerading as respiratory or gastrointestinal infection. In 2017, a group from Finland analyzed the occurrence and features of childhood Myocarditis and found an incidence of 1.95/100,000 person-years (10). Interestingly, two peaks in occurrence were noted: in infants <1 year and in teenagers. Myocarditis in newborns is mainly caused by viral infection, such as enterovirus, parvovirus, or adenovirus (11).

Looking at the ELSO data registry, out of 2,252 neonatal cardiac runs (2014–2018), myocarditis was listed in only 25 cases as the reason for ECMO initiation (1). A recently published article from Melbourne described a series of seven neonatal myocarditis cases requiring ECMO due to Enterovirus infection (12). In this article, Cortina et al. also included 35 cases of Enterovirus Myocarditis supported with ECMO from literature review in their data analysis. The survival rate of all those cases together was 36% (15/42), which is lower than survival (to discharge or transfer) reported in the ELSO registry with 52% for this population (12).

Extracorporeal Membrane Oxygenation (ECMO) support for neonatal myocarditis is infrequent and still carries a high risk of complications and death, but in some cases can lead to complete cardiac recovery with favorable long-term outcome. But who would benefit from ECMO support and when to initiate it?

Casadonte et al. investigated risk factors for cardiac arrest or mechanical support (MCS) in children with fulminate myocarditis (13). The average age of the 28 patients in this study was 1.2 years (1 day−17 years), but no subgroup of true neonates was analyzed. They found that patients in the CPR/MCS group had higher peak b-type natriuretic peptide (BNP) and peak inotropic score. Unfortunately, there was no marker on admission identified, which could be used as a prediction tool. Other authors found associations between the need for MCS and significant arrhythmias or evidence of end organ dysfunction (14, 15).

Neonates with fulminate myocarditis are at risk for cardiovascular collapse leading to CPR and/or MCS. Unfortunately, no clinical variables predict the probability of MCS or the outcome. In children, ECMO has been shown to improve survival for circulatory collapse due to arrhythmias in myocarditis (16). Further collaboration and research in this field is needed to shed some light on the unknown elements.

A recent meta-analysis of myocarditis and ECMO described a 54–83% long-term survival with optimistic quality of life (17). The analysis included six studies, and all used slightly different criteria for initiation of ECMO, but the authors concluded that a systolic BP < 50 mmHg for neonates despite >2 inotropes or high inotrope score could be a reasonable threshold.

Arrhythmias

Neonatal arrhythmias can occur post-operatively (e.g., atrial tachycardia, junctional ectopic tachycardia, ventricular tachycardia, or complete heart block), as part of myocarditis/cardiomyopathy as discussed above, or as a primary arrhythmia (e.g., re-entry supraventricular tachycardia or Brugada syndrome). If the arrhythmia leads to refractory shock despite pharmacological treatment, ECMO can be indicated (18–20). During ECMO support, pharmacological treatment can be optimized, cardiac catheterization with possible ablation of accessory pathways can be performed, or a pacemaker can be implanted. For total AV-block, a pacemaker can be placed while supported with ECMO. The utilization of ECMO for arrhythmias is rare but carries very good survival and neurologic outcomes (21).

Pulmonary Hypertension

The indication of ECMO for persistent pulmonary hypertension of the newborn associated with diaphragmatic hernia, meconium aspiration, respiratory distress syndrome, or sepsis is beyond the scope of this review. In a large database study of neonates and children with pulmonary artery hypertension, 1.4% received ECMO with a hospital mortality of 39% and significant complications (22). ECMO for pulmonary hypertension associated with congenital heart disease has good outcomes (23, 24). Said et al. reported the example of pulmonary hypertension associated with transposition of the great arteries (25). Pulmonary hypertension following cardiac surgery is often due to temporarily increased pulmonary vascular resistance because of cardiopulmonary bypass and probably has better ECMO survival than pulmonary artery hypertension.

TABLE 3 | Hospital survival based on location of ECMO initiation in either operation room (OR) because of failure to wean from bypass or in the intensive care unit (ICU) due to low cardiac output syndrome or hypoxia (7, 26–30).

	Population	Overall survival	Hospital survival (%)		Statistical significance
			OR	ICU	
Jaggers et al. (26)	$N = 35$ (median age 19 days)	60	60	60	NS
Kolovos et al. (27)	$N = 74$ (median age 17 days)	50	64	41	$P = 0.06$
Chaturvedi et al. (28)	$N = 81$ children (median age 2.4 months)	49	64	29	$P = 0.003$
Sasaki et al. (7)	$N = 36$ (median age 64 days)	47	43	60	NS
Casadonte et al. (13)	$N = 90$ (age 6–912 days)	73	77	62	NS
Khorsandi et al. (30)	$N = 66$ Age < 16 years	44	47	38	NS

TABLE 4 | Indications to cardiac ECMO according to the ELSO guidelines (33).

Use of extracorporeal life support for cardiac failure should be considered for patients with evidence of inadequate end organ perfusion and oxygen delivery resulting from inadequate systemic cardiac output

(a) Hypotension despite maximum doses of two inotropic or vasopressor medications.

(b) Low cardiac output with evidence of end organ malperfusion despite medical support as described above: persistent oliguria, diminished peripheral pulses.

(c) Low cardiac output with mixed venous, or superior caval central venous (for single ventricle patients) oxygen saturation <50% despite maximal medical support.

(d) Low cardiac output with persistent lactate >4.0 mmol/l and persistent upward trend despite optimization of volume status and maximal medical management.

TIMING—WHEN TO INITIATE ECMO?

In neonates following congenital heart surgery, ECMO can be initiated in the operating room for failure to separate from cardiopulmonary bypass or in intensive care for either LCOS resistant to maximal medical therapy or hypoxia. Reports in the literature vary (see **Table 3**), and unfortunately offer not enough guidance as to the optimal timing of ECMO initiation. Although it might be logical to assume that earlier support may lead to better outcomes, neonates who fail to separate from bypass might be sicker and have worse myocardial depression than those that do separate from CPB and then develop worsening of LCOS although there is no data to support this hypothesis. Earlier reports suggested that failure to separate from CPB was a risk factor for increased mortality (27, 28). However, a recent ELSO database study among more than 4,000 neonates with congenital and acquired heart disease suggests that earlier initiation of ECMO may reduce mortality due to a decreased degree and duration of acidosis prior to ECMO. The authors hypothesized that acidosis probably reflected poor cardiac output and tissue hypoperfusion and that delayed use of ECMO may result in prolonged exposure of the myocardium and end-organs to reduced oxygen delivery resulting in severe or permanent myocardial or end-organ injury and reduced survival (31). But in a recent large retrospective study longer time between surgery and ECMO initiation was not associated with higher mortality although it was associated with longer ECMO duration, prolonged length of ventilation, and prolonged length of ICU and hospital stay (32).

Timing to initiate ECMO therefore remains very difficult. There are no definitive cut-off points and no evidence-based guidelines exist as to when to initiate ECMO post-operatively. The decision to proceed to ECMO cannulation is typically made on a case-to case basis based on the experience and judgment of the multidisciplinary team, which is reflected by a substantial variation in the use of mechanical support across hospitals (5, 30, 32). The ELSO advises to consider ECMO for patients with evidence of inadequate end organ perfusion and oxygen delivery resulting from inadequate systemic cardiac output (see **Table 4**) (33).

CONTRAINDICATIONS

The number of contraindications has decreased over recent years as experience and technology have advanced. The most important contraindication is lack of possible myocardial recovery and/or contraindications to heart transplantation. The ELSO guidelines list absolute and relative contraindications (**Table 5**). The absolute contraindications have an inappropriate chance of major complications and poor outcome, and therefore ECMO should not be considered in those patients. The relative contraindications also carry a high risk of poor prognosis, but careful management may lead to acceptable outcomes. But parents and the medical team involved should all be aware of the high stakes and be prepared to withdraw ECMO if irreversible damage should develop.

PERIPHERAL VS. CENTRAL CANNULATION

Due to the size of the neonatal patients, cannulation for cardiac neonatal VA-ECMO can be done two ways:

1. Peripheral cannulation: drainage via jugular vein and return via the carotid artery. The right side is the side of choice, but the left side is also possible.
2. Central cannulation: with chest opening and drainage directly out of the right atrium and return into the aortic arch.

TABLE 5 | Contraindications to cardiac ECMO according to the ELSO guidelines (33).

Use of ECLS is not recommended under certain circumstances, particularly if there is strong evidence for lack of capacity to recover or be treated
1. Cardiopulmonary extracorporeal life support is inappropriate if
(a) The condition is irreversible and/or,
(b) There is no timely, reasonable therapeutic option and/or,
(c) High likelihood of poor neurological outcome.
2. Absolute contraindications: Extracorporeal life support is not recommended in the following circumstances
(a) Extremes of prematurity or low birth weight (<30 weeks gestational age or <1 kg)
(b) Lethal chromosomal abnormalities (e.g., Trisomy 13 or 18)
(c) Uncontrollable hemorrhage
(d) Irreversible brain damage
3. Relative contraindications
(a) Intracranial hemorrhage
(b) Less extreme prematurity or low birth weight in neonates (<34 week gestational age or <2.0 kg)
(c) Irreversible organ failure in a patient ineligible for transplantation
(d) Prolonged intubation and mechanical ventilation (>2 week) prior to ECLS

TABLE 6 | Hospital survival of neonatal cardiac ECMO by congenital diagnosis.

Congenital lesion	**Number of runs**	**Survival** (%)
Left to right shunt	92	45
Left-sided obstructive lesion	87	47
Hypoplastic left heart syndrome	439	43
Right-sided obstructive lesion	52	40
Cyanotic—increased Qp	73	43
Cyanotic—pulmonary congestion	167	47
Cyanotic—decreased Qp	295	50
Other	282	51

Qp, pulmonary blood flow (1).

Regardless which way is selected, the adequate size of the cannulas (drainage and return) is crucial to be able to achieve the desired ECMO flow (100–150 ml/kg/min or 3 l/m^2/min). Every cannula has a pressure/flow chart which describes its characteristics, so the selection is easily facilitated. Most often, the largest possible cannula is inserted.

Cannulation via right carotid artery provides very good hemodynamic support, with flow to the upper body and the descending aorta, though blood flow of the right cerebral hemisphere depends on an unhindered circle of Willis. Neurological complications (such as intracranial hemorrhage, derangement of cerebral autoregulation, impairment of venous drainage and risk of embolic events) are well-described in this population (34, 35).

Other problems reported with this type of peripheral cannulation approach are dissection of the aorta or carotid artery (36). Early recognition and timely intervention to those complications are critical, and serial Echocardiograms should be provided to detect problems. For further clarification CT angiogram or catheter investigations can be helpful to identify the problem.

In some cases, the desired flow cannot be achieved via the neck cannulation, so the central route is chosen, and for inability to wean from cardiopulmonary bypass, the simple conversion to central ECMO is obvious (37). When converting CPB to ECMO, one should be aware that the arterial CPB cannula might not be large enough to support a normothermic patient for several days, especially if sepsis should develop. Complications of central cannulation include bleeding, vessel injury and embolic phenomena. A recent case report alluded to the occurrence of thrombus in the aorta (38). The cannula inserted in the aorta increases the afterload of the ventricle. Thrombosis can occur as a result of stasis within the aorta due to competing flows from the poorly ejecting native ventricle and the ECLS circuit.

Overall cannulation approaches for neonatal VA ECMO have not changed over decades, and unfortunately complications rates remain the same (1).

PREDICTORS OF SURVIVAL

Survival depends very much on the underlying reason for receiving ECMO support. Overall survival is higher in non-surgical heart disease such as myocarditis or cardiomyopathy (see **Table 1**). In neonates with congenital lesions, the risk factors of requiring ECMO post-operatively are listed in **Table 2** and are especially high following neonatal Ross-Konno repair [Odds Ratio (OR) 70], Truncus arteriosus repair (OR 42), arterial switch operation with VSD (OR 35), ALCPA-repair (OR 20), TAPVD repair (OR 18), or Norwood operation (OR 9) (5). And subsequently, mortality during ECMO is also very dependent on underlying diagnosis and type of operation. According to the STS database, mortality following Ross-Konno repair or Truncus repair is ∼70%, whereas mortality for ECMO following ALCPA repair is only 14% (5). In neonates with ECMO for congenital heart disease reported to ELSO, survival is between 40 and 51% (see **Table 6**).

Many outcome predictors have been identified in the literature and are presented in **Table 7** (7, 8, 23, 31, 39–45). Some predictors cannot be modified before or during ECMO, such as age, weight, the presence of chromosomal abnormalities, or the underlying diagnoses. Other predictors are determined by the pre-ECMO clinical course, such as inotrope score, duration of ventilation, presence of fluid overload, and CPR requirement. These predictors could possibly be influenced by early timing of ECMO initiation before these predictors occur.

Risk factors for poor outcome that may be modifiable during ECMO support include the identification of residual lesions, optimizing systemic perfusion (reflected for instance by clearance of acidosis), presence of renal failure, and fluid overload, and the duration of ECMO. As mentioned before, it is essential to determine the reason the patient requires ECMO support, and to provide optimal systemic perfusion while resting the heart as

TABLE 7 | Predictors of mortality and survival of neonatal and pediatric cardiac ECMO (7, 8, 23, 31, 39–45).

Predictors of mortality	
Higher mortality	**Lower mortality**
Younger age	
Low bodyweight (<3 kg)	Bodyweight >3.3 kg
Chromosomal abnormalities	No chromosomal abnormalities
Congenital heart disease	Myocarditis/cardiomyopathy
Single-ventricle physiology	Two-ventricles
High inotrope score	Low inotrope score
Duration of ventilation pre-ECMO >14 days	Duration of ventilation pre-ECMO <14 days
CPR pre-ECMO	No CPR pre-ECMO
Acidosis pre-ECMO (pH < 7.26)	No acidosis (pH > 7.28)
High Lactate pre-ECMO	Low lactate pre-ECMO
Failure to clear lactate <24 h	Able to clear lactate <24 h
Renal failure	No renal failure
Fluid overload on ECMO initiation	No fluid overload
Organ system complications	No organ system complications
Bleeding during ECMO	No bleeding
Cardiac catheterization on ECMO <48 h	Late or no cardiac catheterization
Duration of ECMO support >7 days	Duration of ECMO support <5 days

much as possible and limiting the duration of ECMO support and concomitant complications which can impact outcomes.

Residual Lesions

Recently, several studies have shown the importance of early catheterization aimed at identifying and treating residual lesions (43, 44, 46, 47). In a retrospective study by Agarwal et al., residual lesions were present in approximately one-quarter of post-operative cardiac surgery patients receiving ECMO support (43). They conclude that all post-operative pediatric cardiac surgery patients unable to be weaned off ECMO successfully, should be evaluated actively for residual lesions, preferably by cardiac catheterization, as echocardiography only detected 20% of all residual lesions and catheterization the remaining 80%. Furthermore, earlier detection (within 3 days of ECMO support) and reintervention are associated with improved clinical outcome. In another retrospective study of 84 neonates requiring ECMO following cardiac surgery, as many as 83% had residual lesions (44). Time to identification and/or correction of these residual lesions was significantly shorter in survivors than in non-survivors (1 vs. 2 days). Abraham et al. catheterized 35 neonates while on ECMO support, which led to direct intervention in ∼75%, significantly improving survival (46). The average interval from ECMO cannulation to catheterization was significantly shorter in survivors (1.6 days) vs. non-survivors (3.5 days). In a retrospective study by Kato et al., patients who received cardiac catheterization within 48 h after ECMO initiation demonstrated significantly better survival than those who underwent later catheterization (47).

Results of these studies clearly indicate that an early (<24 h) and proactive search for residual lesions is warranted to improve survival. Cardiac catheterization can be safely performed on patients supported by ECMO, and is a critical tool in the early recognition, diagnosis, and direct treatment of hemodynamic and/or anatomic abnormalities (48).

Clearance of Acidosis

Providing adequate systemic blood flow is an integral aspect of ECMO support. If ECMO flow is inadequate, lactate will remain high as a sign of end-organ hypoperfusion and multiple organ failure may develop impacting on outcomes (44). Therefore, aiming to normalize lactate levels as soon as possible (12–24 h post-cannulation) may improve outcomes. Lactate which has not normalized within 72 h has been associated with decreased survival (44).

Renal Failure and Fluid Overload

Renal failure and fluid overload at ECMO initiation have been identified as risk factors for poor outcomes in multiple studies (49). Acute kidney injury is probably a reflection of pre-ECMO injury but could also be due to insufficient ECMO flow. Fluid overload, with or without renal failure, may impact on respiratory mechanics and myocardial recovery (49, 50). Renal replacement therapy during ECMO is therefore advocated by ELSO, and has been shown to improve fluid balance and electrolytes (51–54). Renal replacement therapy however does not seem to shorten ECMO duration or ICU length of stay, nor to improve survival (51). It is probably best to prevent the development of renal failure and/or fluid overload prior to initiating ECMO rather than attempting fluid removal while on ECMO.

Unloading the Ventricle

The goal of cardiac ECMO is to rest the myocardium as much as possible so it may recover as soon as possible. However, by increasing the afterload of the systemic ventricle by placing an arterial ECMO cannula in the aorta or carotid artery, the already failing myocardium may struggle to eject blood against this increased afterload, and a cardiac stun may occur. The aortic valve remains closed and the left ventricle dilates, because on ECMO there is always blood returning to the left atrium from Thebesian and bronchial veins. While dilated, the myocardium stretches and is under strain, therefore diminishing the coronary perfusion and further impacting on myocardial recovery. Also, intracavitary thrombus formation and pulmonary oedema will occur when left atrial pressure exceeds 25–30 mm Hg. Echocardiography is essential in assessing LV distension and presence of spontaneous contrast (55). To provide optimal myocardial recovery, attempts should be made to prevent dilatation of the left side of the heart. The right-side is decompressed by the ECMO circuit. And in lesions affecting RV dysfunction such as pulmonary hypertension or following pulmonary atresia repair, unloading the left ventricle is probably not necessary. In some neonates with LV dysfunction, it may be enough to support the systemic ventricle with a low dose inotrope to open the aortic valve and eject just enough blood to prevent or treat ventricular dilatation. However, in most neonates, this course of action will not be sufficient, and other steps will have to be made. A solution is to unload the left side of the heart by

either creating an atrial shunt via percutaneous atrial septostomy or surgical atrial septectomy, or by placing an extra ECMO cannula in the left atrium which drains blood to the inlet side of the ECMO circuit (the so called "left vent"). In neonates, it is not known which form of ventricular unloading is preferred, or what the best timing of unloading is. Currently, there are no standardized diagnostic criteria or guidelines for the type and timing of intervention for LV overload (56). Tentatively, left ventricular unloading should be performed with significant LV distension or spontaneous contrast on echocardiography, when the aortic valve does not open, or with signs of pulmonary oedema on chest x-ray (55, 57).

Elective decompression has been shown to decrease ECMO duration in pediatric cardiac ECMO patients, but not mortality (58). In a single center study from Boston, percutaneous atrial septostomy was used in 10% of all ECMO patients and in 50% of myocarditis patients (57). Residual atrial septal defects requiring closure occurred in only a few cases.

ECMO Duration

Duration of ECMO support is another important factor and has been associated with decreased survival in several studies (8). With longer ECMO duration, more complications such as renal failure, bleeding, thrombosis, or infection may occur which impact survival. Prolonged ECMO in children with cardiac disease carries much lower survival rates. An ELSO registry study showed that overall ECMO survival is 45% in children with cardiac disease, but drops down to 23–25% survival for ECMO between 14 and 28 days, and 13% for ECMO runs longer than 28 days (40).

SUPPORTIVE CARE

The Extracorporeal Life Support Organization (ELSO) regularly publishes informative and updated guidelines on pediatric and neonatal cardiac ECMO including supportive care (33). Anticoagulation during neonatal cardiac ECMO is essential and can be very challenging, although it is beyond the scope of this review. In this review, we restrict ourselves to a few important issues specific to neonatal cardiac ECMO. For more information on supportive care (e.g., infections, temperature management, analgesia, and sedation), we refer to the ELSO guidelines and ELSO "Red book" (33, 59).

Echocardiography

The role of echocardiography in cardiac ECMO is essential in assessing ECMO initiation and separation readiness, cannula positions, and the development of complications such as ventricular dilatation or cardiac tamponade, but also has important limitations as physiological changes induced by ECMO may alter echocardiographic findings (55). An echocardiography-trained physician should be part of the team caring for neonates and children on ECMO, and the use of specific and consistent echocardiographic protocols for patients on ECMO is recommended (55).

Mechanical Ventilation

Generally, neonates who receive cardiac ECMO have healthy lungs and have not received high ventilation pressures for prolonged periods of time prior to ECMO initiation. Also, relatively short ECMO duration of 5–7 days is expected for these patients. The goal of mechanical ventilation during ECMO is to minimize lung injury and to optimize lung function in order to allow separation from ECMO once myocardial recovery has occurred (33). Therefore, most often, low ventilation pressures can be used during ECMO aimed at maintaining normal tidal volumes (4–6 ml/kg) and preventing alveolar collapse by using PEEP of 8–10 cm H_2O. No single ventilation strategy is universally practiced, and the suggested target may be inappropriate in patients with an open sternum, poor lung compliance, pulmonary hemorrhage, or intrathoracic hematoma (33). Some neonates, however, may have atelectasis which may require inhalation therapy, physical therapy, and/or bronchoscopy as it is essential to keep the lung open. Therapy resistant atelectasis can be due to tracheal and/or bronchial compression by cardiac or vascular structures which might require contrast CT-scanning to identify.

In neonates with an open sternum, lower ventilator pressures will often suffice unless there is blood or fluid in the thoracic space which should be considered for removal or drainage. Cardiopulmonary bypass and its extension to ECMO have been shown to cause a decrease in lung compliance through reduction in the surfactant activity and surfactant has recently been used safely and effectively in neonatal cardiac ECMO patients with decreased lung compliance (60).

SINGLE VENTRICLE LESIONS

Extracorporeal support in neonatal patients with single-ventricle physiology is particularly challenging, but also represents a growing and substantial group of neonates who are being supported by ECMO worldwide. Following the stage-one operation for hypoplastic left heart syndrome, 13–20% of neonates will receive ECMO support (8, 61, 62).

General risk factors for requiring ECMO post-stage-one surgery are similar to other post-cardiotomy risk factors, such as low birthweight and longer CPB-time. More specific risk factors include a small ascending aorta (<2 mm), mitral stenosis with aortic atresia, intraoperative shunt revision, and a right ventricular to pulmonary artery shunt (RVPAs) when compared with a modified Blalock-Taussig shunt (mBTs) (62, 63). In the single-ventricle reconstruction (SVR) trial, most neonates who received ECMO post-stage one (70%) failed to separate from CPB and had significantly lower transplant-free survival rates compared to neonates not receiving ECMO post-Norwood (62). In single-center study by Hoskote et al., 56% of post-operative single-ventricle ECMO patients received ECMO because of cardiac arrest, and 44% because of LCOS, with 44% survival to discharge (64). The indication for initiation of ECMO also significantly impacts survival. In a single-center study in 44 neonates, patients cannulated for hypoxemia, and particularly shunt thrombosis, had markedly improved survival (72%)

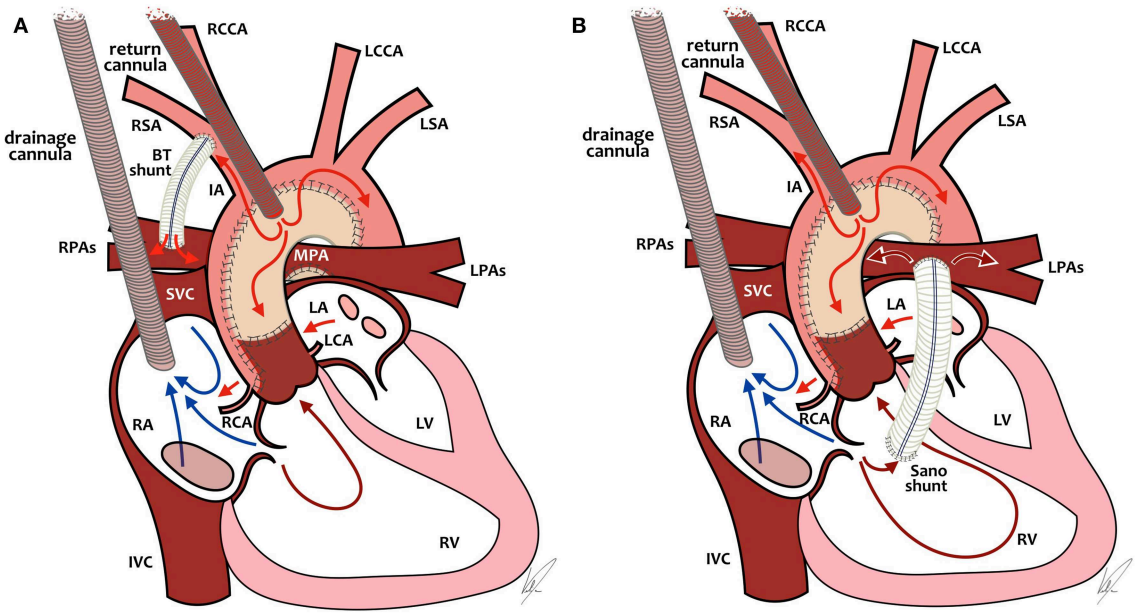

FIGURE 2 | ECMO cannulation and preferential ECMO flows in single-ventricle patients with BT-shunt (**A**, left) or Sano-shunt (**B**, right). In both diagrams **(A, B)**, the arterial cannula is placed in the neoaorta, but it can also be placed through the carotid artery or in the innominate artery. RCCA, right common carotid artery; LCCA, left common carotid artery; LSA, left subclavian artery; RSA, right subclavian artery; IA, innominate artery; RPAs, right pulmonary arteries; LPAs, left pulmonary arteries; MPA, main pulmonary artery; SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; LA, left atrium; RCA, right coronary artery; LCA, left coronary artery; RV, right ventricle; LV, left ventricle. Drawings by Marta Velia Antonini.

compared to those supported primarily for low cardiac output (21%) (65).

Without going into the complete debate about mBTs vs. RVPAs, which is out of the scope of this review, there is an important difference between the two shunts regarding ECMO management. In the SVR trial, after adjusting for surgeon and birth weight, neonates with a mBTs had smaller chances of receiving ECMO and had significantly better outcome after ECPR or ECMO compared to neonates with a RVPAs (62). Let's take a closer look at ECMO management in those two specific physiologies (**Figure 2**).

ECMO and mBTs

Because of the position of the arterial cannula relative to the mBTs and the lower vascular resistance in the pulmonary circulation relative to the systemic circulation, a large proportion of ECMO blood flow will be directed toward the pulmonary circulation, leading to underperfusion of the systemic circulation. In the past, attempts were often undertaken to partially or completely close the mBTs while on ECMO to improve systemic blood flow. That approach of "clipping the shunt," however, has been shown to increase mortality due to obstruction in the shunt or in the pulmonary vasculature after decannulation and has largely been abandoned in favor of increasing ECMO flow to desirable systemic blood flow, while accepting a significant amount of pulmonary blood flow (26, 66). We therefore recommend a higher blood flow (up to 200 ml/kg/min).

ECMO and RVPAs

In neonates with an RVPAs, the arterial ECMO cannula is positioned after the source of pulmonary blood flow. This means that if there is no pulsatility of the heart itself, there will be no pulmonary blood flow at all, which leads to the risk of clotting the shunt and/or the pulmonary vasculature. In neonates with some degree of pulsatility, there will be pulmonary blood flow which is dependent on pre-load of the right ventricle (RV) and pulmonary vascular resistance. In that scenario, increasing ECMO flows will lead to decreased pre-load as the drainage cannula will empty the RV and decrease pulmonary blood flow, with the possible risk of thrombosis of the shunt or even the RV. And absent pulmonary flow might lead to increased mortality similar to mBTs patients with clipped shunts (26). All in all, in neonates with an RVPAs, we recommend not to use high flows as in mBTS patients, but to titrate the flow as low as possible to achieve adequate systemic blood flow and also some degree of pulmonary blood flow over the RVPAs. It might be necessary to use some inotropes to promote contractility in this specific group of patients.

Survival to discharge in hypoplastic left heart patients supported by ECMO was 31% as shown in an ELSO registry study by Sherwin et al. (67). Predictors of mortality were pre-ECMO ventilation > 5 days (OR 1.9), pre-ECMO PEEP > 8 (OR 1.9), and increased ECMO duration. In a separate single-center study, survival was 62% and failure to clear lactate within 24 h was also a significant predictor of mortality (45).

A specific group are patients post-hybrid palliation of HLHS. In an ELSO registry study, survival to discharge was only 16% in neonates who received ECMO following stage 1 hybrid

palliation (68). This could be because, in many centers, hybrid palliation is reserved for high risk patients, but also could be due to cannulation challenges, and risk of stent compression or even occlusion.

Of concern is late attrition following ECMO in SV survivors. Although incidence is low, mortality is very high (69). Neonates who survive to discharge following ECMO post-Norwood have been shown to have an increased risk of death or cardiac transplant, when compared to patients who did not receive ECMO post-Norwood (45, 61, 63, 70).

For respiratory failure in SV patients, VV ECMO can also be considered as an option with good outcomes (71, 72). In an ELSO registry study of 89 patients with single-ventricle physiology and a median age of 66 days overall survival was 51% for respiratory indications which included neonates as young as 9 days (71). The most common cannulation approach for patients who were unrepaired or palliated with a central or Sano shunt was a double-lumen venous cannula in the right internal jugular vein.

Advantages could be preservation of pulsatile flow and decreased afterload on the heart, as well as avoiding cannulation of the carotid artery which precludes potential run-off through a systemic-to-pulmonary shunt. For more in-depth information on cannulation strategies, timing, circuit flow, and lung rest strategies we refer you to an excellent review by Nair and Oishi from 2016 (72).

WEANING

In adults, end-tidal CO_2 ($etCO_2$) has been shown to be a useful continuous parameter for predicting the adequate timing of weaning of ECMO for circulatory failure at the bedside (73). Many physicians dealing with neonates also use $etCO_2$ as it can indicate increasing pulmonary blood flow as a sign of increased intrinsic right ventricular output due to a healing myocardium or decreasing pulmonary vascular resistance. There is however no known cut-off $etCO_2$ when a neonate might successfully separate from ECMO, therefore it can merely be used as an indirect indication of ongoing recovery.

When weaning is not successful and additional time does not lead to adequate recovery, it is important to consider possible transplantation or withdrawal of support and shift attention to comfort of the neonate and guidance for the parents.

Survival to decannulation in neonatal cardiac ECMO is 71%, but drops down to 49% when it comes to hospital discharge or transfer (1). Often, ECMO support is removed during a still fragile state of the patient's recovery. Timing and manner of weaning support highly affect the chances of survival. Unfortunately, up to this date, very little evidence has been published to help identifying parameters which predict readiness to be separated from ECMO. Recommendations about the speed of weaning or acceptable amount of inotropic support are also lacking.

The reason of myocardial dysfunction is a relevant factor for the expected time to recovery and removal of ECMO. Recovery from cardiac dysfunction post-cardiac surgery is expected to happen between 48 and 72 h after initiation of ECMO. The absence of signs of recovery, such as increasing pulse pressure or increasing end-tidal pCO_2 after that period, should lead instantly to further assessment of remaining cardiac lesions if not already done so (44).

Recovery from a primary myocardial dysfunction, as with myocarditis, occurs over weeks or months, in some cases not at all. Transition to a VAD device as bridge to recovery or bridge to transplant need to be taken into consideration if no evidence of myocardial recovery has occurred within 2 weeks (74).

Weaning can be started with signs of myocardial recovery and adequate resolution of systemic inflammatory response or pulmonary problems (75).

Cardiac function assessment by echocardiography during full ECMO flow does not predict performance of the heart under the completely different circumstances occurring after decannulation (which will be increased preload and decreased afterload) and might only be used as a trend.

Echocardiography under low flow conditions has been shown as being predictive of successful decannulation in adult patients with cardiogenic shock (76).

However, achieving actual low flow conditions in neonates is not possible due to the required minimal flows of the ECMO devices (100–200 ml/min). Therefore, different techniques of weaning trial in which the readiness for separation from ECMO can be assessed (pulse pressure, blood pressure, inotropic needs, echocardiography) are practiced in this age group. In patients with a left-sided drainage cannula, this must be clamped and/or removed allowing restoration of LV pre-load before assessing weaning readiness.

A common approach of weaning ECMO flows in neonates includes inserting a connection ("Bridge") between the arterial and venous limb (arterio-venous bridge) of the ECMO circuit. This allows to clamp access to the patient, while there remains continuation of flow in the ECMO circuit. The patient and the circuit are isolated from each other. Now the hemodynamics such as blood pressure, CVP, lactate, as well as the demand of inotropic support to remain off circuit, can be assessed and an echocardiography should be performed. This method introduces areas of stagnant blood in stop cocks and the cannulas, with the subsequent risk of clot formation in the ECMO circuit. Most centers flush the cannulas every 10 min and limit this kind of trial off period to around 2 h (59).

Other groups promote trial off with retrograde pump flow of the ECMO circuit (77, 78). During this approach, revolutions per minute (RPM) are lowered until the patient's arterial blood pressure is slightly higher than the post-oxygenator pressure, which results in reversal of the flow. The ECMO circuit becomes an arterio-venous shunt and the patient does not receive circulatory or respiratory support. The advantage of this method is that it has no stagnant blood flow in the cannula and that it places an additional burden on the cardiac output, which therefore reassures of sufficient myocardial function. Not observed or investigated by the groups who practice this approach is the theoretical risk of flushing debris and clots absorbed in the oxygenator with the retrograde flow back into the patient. Further research must be established to further evaluate the risk.

Once readiness to be separated from ECMO is established, the process of decannulation can take place. This includes the optimization of conditions with low dose inotropic support started early enough to reach the patient, lung recruitment, correction of metabolic abnormalities, and attaching pacing wires to the pacemaker ensuring proper function of them. Furthermore, each patient should have a defined plan in place in the event of clinical deterioration after decannulation and weather reinstitution of ECMO is an option.

Decannulation for neonatal cardiac ECMO is done surgically and can be performed either in the ICU or in the operating room. Neck cannulation often leads to vessel reconstruction and the cannulation sites must be investigated carefully for any damage, which might need extended repair, such as carotid artery dissection (36). Furthermore, Di Gennaro et al. published a study showing increased risk of stroke in patients with carotid cannulation (79).

Weaning and decannulation of patients with systemic to pulmonary shunts, which are partially or completely clamped is different. In those cases, readiness to wean must be assessed without decreasing flows as this would lead to desaturations.

Separating from ECMO is a complex process and requires careful assessment and planning from the time of ECMO initiation.

NEONATAL ECMO CIRCUIT CONSIDERATIONS

Circuit technology has greatly advanced over the years, but neonates do deserve some special considerations which are nicely reviewed by Connelly and Blinman (80). Nowadays, most centers have moved from roller pumps to modern centrifugal pumps (81). Detailed discussion of the ECMO circuit is beyond the scope of this review but there are some important issues to consider. First, the relatively large priming volumes for neonates can introduce fluid shifts and can have a pharmacological impact. Second, the relatively low blood flows can make neonates more prone to (circuit) thrombosis and more difficult to wean. And third, in the small neonate accurate cannula position can be more precarious than in larger children or adults, especially in veno-venous double-lumen cannulas.

MID AND LONGTERM OUTCOMES

Neonates surviving cardiac ECMO remain at risk of ongoing health problems, unplanned cardiac interventions, unplanned rehospitalization, neurodevelopmental problems, lower mental scores, language acquisition delays, behavioral problems, and diminished quality of life compared to healthy children, children with chronic conditions, and children with congenital heart disease who did not receive ECMO (82–86).

To gain better insight in these mid and long-term outcomes, protocolized follow-up is important, with the aim of identifying neurodevelopmental delay. Hopefully, by focusing on the future development of these patients and sharing outcomes and interventions through research, the ECMO community can develop interventions aimed at minimizing ongoing health issues and optimizing quality of life for patients and their families after hospital discharge.

FUTURE (RESEARCH)

In neonatal cardiac ECMO, one must face many challenges which are common to almost all neonatal and pediatric ECMO patients, such as infection control and anticoagulation. Exciting developments are being made regarding ECMO anticoagulation, in which attempts are being made to anticoagulate the circuit (rather than the patient) by using nitric-oxide donors in the ECMO tubing (87). The balance between bleeding of the neonate and thrombosis of the circuit remains very delicate, especially in neonates with still developing hemostasis in whom the correlation of coagulation tests with the level of anticoagulant and clinical outcomes remains poor (88).

Other important steps that need to be achieved are related to identifying the right patient and the right time for ECMO. Attempts are being made to develop prediction scores, but, at the moment, these remain restricted to pulmonary ECMO and adult cardiac ECMO (89–92)[1]. No prediction scores exist as of yet for neonatal cardiac ECMO. Hopefully, by gathering more data from large databases such as ELSO or the STS-database, and by performing large multicenter trials, prediction scores can be developed in the future. However, due to the relatively small number of neonatal ECMO patients and many aggregating factors, this will be a challenging task, and identifying "the perfect ECMO candidate" will probably remain a local team decision based on experience and published results of others.

Pharmacodynamic and distribution studies are also needed in this very special group of patients. Neonates with their immature organ function, fast changes in maturation (ontogeny) and significantly increased distribution volume on ECMO, plus unknown absorption in the circuit components, are extremely challenging to manage for adequate medication levels. As mentioned before, research directed on long-term outcomes and quality of life are essential. Not only will they help at early patient intervention, but they can also teach the ECMO community the limitations of ECMO support and will help in deciding to which patients we should offer ECMO and to which patients we should not.

CONCLUSIONS

Extracorporeal Membrane Oxygenation (ECMO) is an invaluable tool for neonates with therapy resistant circulatory failure. Patient selection and timing of ECMO initiation however remain very difficult and is not yet evidence based. Mortality is very much dependent on underlying diagnosis, the ability to provide adequate systemic blood flow, duration of ECMO support and concomitant adverse events and complications. Therefore, after ECMO initiation, attempts should be made

[1]http://www.picuscientist.org/pprep

as soon as possible to identify concomitant problems whose solution would improve the outcome, such as residual lesions following cardiac surgery or arrhythmias. By adequately addressing those underlying issues and limiting the time on ECMO, preferably <7 days, while resting the heart as much as possible, mortality can be reduced. In non-surgical heart disease, restoration of adequate myocardial function can take longer, sometimes requiring ECMO support up to 2 or 3 weeks.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Drug Disposition and Pharmacotherapy in Neonatal ECMO: From Fragmented Data to Integrated Knowledge

Genny Raffaeli[1,2]*, *Pavla Pokorna*[3,4,5], *Karel Allegaert*[6,7], *Fabio Mosca*[1,2], *Giacomo Cavallaro*[1], *Enno D. Wildschut*[5] *and Dick Tibboel*[5]

[1] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NICU, Milan, Italy, [2] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy, [3] Department of Pediatrics—ICU, General University Hospital, 1st Faculty of Medicine Charles University, Prague, Czechia, [4] Department of Pharmacology, General University Hospital, 1st Faculty of Medicine Charles University, Prague, Czechia, [5] Intensive Care and Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, Netherlands, [6] Division of Neonatology, Department of Pediatrics, Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, Netherlands, [7] Department of Development and Regeneration, KU Leuven, Leuven, Belgium

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Paolo Biban, Integrated University Hospital Verona, Italy

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***Correspondence:**
Genny Raffaeli
genny.raffaeli@gmail.com

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Extracorporeal membrane oxygenation (ECMO) is a lifesaving support technology for potentially reversible neonatal cardiac and/or respiratory failure. As the survival and the overall outcome of patients rely on the treatment and reversal of the underlying disease, effective and preferentially evidence-based pharmacotherapy is crucial to target recovery. Currently limited data exist to support the clinicians in their every-day intensive care prescribing practice with the contemporary ECMO technology. Indeed, drug dosing to optimize pharmacotherapy during neonatal ECMO is a major challenge. The impact of the maturational changes of the organ function on both pharmacokinetics (PK) and pharmacodynamics (PD) has been widely established over the last decades. Next to the developmental pharmacology, additional non-maturational factors have been recognized as key-determinants of PK/PD variability. The dynamically changing state of critical illness during the ECMO course impairs the achievement of optimal drug exposure, as a result of single or multi-organ failure, capillary leak, altered protein binding, and sometimes a hyperdynamic state, with a variable effect on both the volume of distribution (Vd) and the clearance (Cl) of drugs. Extracorporeal membrane oxygenation introduces further PK/PD perturbation due to drug sequestration and hemodilution, thus increasing the Vd and clearance (sequestration). Drug disposition depends on the characteristics of the compounds (hydrophilic vs. lipophilic, protein binding), patients (age, comorbidities, surgery, co-medications, genetic variations), and circuits (roller vs. centrifugal-based systems; silicone vs. hollow-fiber oxygenators; renal replacement therapy). Based on the potential combination of the above-mentioned drug PK/PD determinants, an integrated approach in clinical drug prescription is pivotal to limit the risks of over- and under-dosing. The understanding of the dose-exposure-response relationship in critically-ill neonates on ECMO will enable the optimization of dosing strategies to ensure safety and efficacy for the individual patient. Next to *in vitro* and clinical PK data collection, physiologically-based pharmacokinetic modeling (PBPK) are emerging as alternative approaches to

provide bedside dosing guidance. This article provides an overview of the available evidence in the field of neonatal pharmacology during ECMO. We will identify the main determinants of altered PK and PD, elaborate on evidence-based recommendations on pharmacotherapy and highlight areas for further research.

Keywords: ECMO, pharmacokinetics, pharmacodynamics, critical illness, developmental pharmacology, neonate

BACKGROUND

Extracorporeal membrane oxygenation (ECMO) is an established life-saving support technique for critically-ill neonates with severe cardio-respiratory failure (1, 2). Being a bridge, ECMO buys the time for cure, in part related to drugs to treat and possibly reverse the underlying disease while protecting the failing respiratory/circulatory systems from iatrogenic negative effects with long term consequences (2). Indeed, sustained and maximal mechanical ventilation may lead to hemodynamic compromise and ventilation-induced lung injury, as a result of oxygen toxicity, baro- bio-, and volutrauma (3). Generally, these critically-ill neonates are exposed to polypharmacy, as they require anticoagulants to maintain the hemostatic balance within the ECMO circuit, analgo-sedatives to ensure patient comfort, cardiovascular agents to sustain hemodynamics, anti-infectives to prevent or treat infections, and possibly other drugs to manage underlying specific conditions or complications (4, 5).

As in many of these patients the survival and overall outcome rely on medications, effective pharmacotherapy is essential to improve care and minimize side effects (5). Adequate drug dosing is based on the understanding of two concepts: (1) pharmacokinetics (PK), which explores "what the body does to the drug" and provides the drug concentration-time profile, through the evaluation of absorption, distribution, metabolism, and excretion (ADME); (2) pharmacodynamics, which represents "what the drug does to the body" and estimates action and side-effects of a given medication, based on dose and patient profile (6, 7). The main drivers of drug PK are volume of distribution (Vd), which describes the dose required to produce the desired peak concentration and clearance (Cl), which is the volume of fluid cleared of drug from the body per unit of time. Both Vd and Cl are primary determinants of drug half-life (7). Safe and efficient prescription in neonatal ECMO depends upon the knowledge of the above-mentioned concepts and the understanding of the determinants affecting drug PK and PD in the complex context of patient immaturity, critical illness, (multi)organ failure and need for supportive extracorporeal circuits (8).

Neonatal age is by itself a window of pharmacological vulnerability (9). Drug PK and PD prediction, based on time-dependent maturational changes (age, weight) is the cornerstone of developmental pharmacology (10, 11). Additionally, critical illness may contribute to impaired drug exposure, as a result of multiple organ failure and changes in physiology, such as hyperdynamic state, increased vascular permeability, catabolism, and altered protein binding (8, 12). The need for ECMO further complicates the issue, through the sequestration of drugs into the circuit and the induction of PK specific variability (4, 13, 14).

Although physicochemical properties can be used to predict the drugs' bioavailability while on ECMO (15), the pharmacotherapy in this setting remains too empirical, as a result of limited evidence due to the lack of clinical studies and ever-evolving technology.

Because of this, treating a critically-ill neonate on ECMO is challenging and requires an integrated approach, to limit the risks of under treatment or toxicity. In this review, we will discuss current knowledge of ECMO-induced PK perturbations, and subsequently discuss the relevance of these PK findings for analgo-sedatives and antimicrobial and antiviral drugs, to end with a discussion on approaches to further optimize neonatal pharmacotherapy. However, pharmacotherapy for neonates on ECMO still needs to be integrated with the physiological maturation occurring in early infancy.

THE ROLE OF DEVELOPMENTAL PHARMACOLOGY ON DRUG DISPOSITION

In neonates the evolving physiological maturation has a dynamic impact on clinical pharmacology, thus resulting in inter- and intra- individual variability in drug exposure (PK) and drug effect (PD) (9). Growth, weight, body and plasma protein composition, organ maturation, and energy requirements are the main determinants of the developmental pharmacology, which integrates the knowledge of the ontogenetic changes to deliver safe and effective pharmacological treatment across the pediatric age range (10, 16). While maturational PK considers the age-related changes of the ADME process (17, 18), the maturational PD takes into account the developmental variability of specific organ function and receptor expression (11). An extensive and contemporary description of the maturational covariates of the developmental pharmacology is beyond the scope of this review and it is available elsewhere (10, 11, 19).

THE ROLE OF NON-MATURATIONAL DETERMINANTS ON DRUG DISPOSITION: FOCUS ON PRE-ECMO DISEASE STATE

To objectivate non-maturational determinants and their impact on drug disposition in critically ill neonates is essential to integrate the concept of "precision dosing to optimize neonatal pharmacotherapy" defined as "personalized, individualized, tailored or precise pharmacotherapy" (20). Moreover, accuracy of

drug formulations, drug prescription and new drug development is needed to tune pharmacotherapy in the vulnerable neonatal population (21). Non-maturational determinants such as (perinatal) asphyxia/hypoxia, sepsis/systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS) are considered as clinically relevant variables of drug disposition (22, 23). However, they are not well understood in critically ill neonates due to dynamically changing conditions in the single patient. There is a large inter individual variability in the PK/PD of frequently used medications (antimicrobials, analgosedatives, anti-convulsives, vasopressors, and inotropes) in neonates under critical illness (24) and ECMO (25, 26). These covariates are either predictable (i.e., related to development or drug = maturational determinants), partly predictable (i.e., related to treatment modality), or almost non-predictable (i.e., related to disease = non-maturational covariates). Changes in the Vd and Cl of drugs under critically ill conditions may lead to a high intra- and inter-individual PK variability (for different drugs 30–70%) resulting in either insufficient or toxic plasma concentrations of drugs (27). This may have an impact on the drug disposition and, as a consequence, both under- and over-dosing may contribute to unfavorable outcomes.

Perinatal Asphyxia—Hypoxia

Perinatal Asphyxia (PA) is defined by the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) as a condition of severely deficient supply of oxygen to the body (oxygen deprivation) leading to coma or death (28). In 2009, based on international guidelines, therapeutic hypothermia (HT; 33–34°C) has been recommended to be used for therapy in asphyxiated (moderate to severe) neonates (29). However, the decision to place on ECMO newborns treated for perinatal asphyxia and hypoxic ischemic encephalopathy (HIE) is based on criteria of HIE severity (30). Following perinatal asphyxia, neonates may suffer from HIE (69.4%), respiratory or acute kidney failure (AKI 47–61%), cardiac and hepatic dysfunction, whose rates in the era of HT (31) are similar to the pre-cooling period (32). Multiple organ dysfunction syndrome (MODS), defined as the presence of at least one organ dysfunction in addition to HIE, occurred in 58–88% of asphyxiated neonates (33) and contributed to higher mortality rates (20.5–72.9%) (31). MODS may complicate the course of neonatal ECMO, with a negative impact on survival (34, 35). Moreover, after out of hospital pediatric cardiac arrest, AKI is very common (64% of the enrolled cases, $n = 282$), and severe (41% of the enrolled cases), without difference in incidence in severe AKI between cases that either or not underwent HT (36). As a rule of thumb, *asphyxia* may lead to changes in drug disposition such as decreased or variable drug absorption (AUC, Ka, t_{max} or F), increased (or unchanged) drug distribution (Vd) and decreased drug elimination (CL) (37). However, data on PK changes under asphyxia in neonates are sparse (ceftazidime, amikacin, gentamicin, amoxicillin, and benzylpenicillin) (37–41) and the same holds true for cardiac arrest in neonates and changes in pH (42). Moreover, PK variability in asphyxiated neonates has been reviewed in relation to the impact of HT alone (43–46) or in combination to ECMO (47). Recently, for anticonvulsive drugs such as phenobarbital, which has low hepatic Cl and low protein bound drug HT was not found to be a PK covariate (48, 49), in contrast to birth weight (BW), postnatal age (PNA) (50), and disease severity (51). The disposition of other drugs during neonatal HT has been evaluated in the recent literature (52–56) and the relevant findings are summarized in **Table 1**.

Sepsis/Systemic Inflammatory Response Syndrome

There is lack of consensus for the definition of *sepsis* in neonates (57). So far, the international consensus on pediatric sepsis and SIRS, respectively, was established to address this issue for all children (<18 years old) including term neonates (≥37 weeks completed gestation) in 2005 (58). (59) showed how mortality for MODS, in a pediatric intensive care unit, was significantly higher among term neonates compared with older children (75.4 vs. 50.9%) (59). During sepsis relevant SIRS-related physiological changes occur, which contribute to drug disposition (60). The main physiology and pharmacology considerations in sepsis/septic shock are shown in **Table 1**. *Sepsis*, and its related factors like tissue (regional) hypoperfusion, MODS (systemic) hypoperfusion, acidosis, hypoalbuminemia, SIRS, type of shock (hyperdynamic/hypodynamic), capillary leakage syndrome, or pharmacotherapy (diuretics, vasopressors, inotropic drugs) may lead to changes in PK, and therefore PD parameters (Cmax, Cmin, AUC0-24/MIC of concentration, and time dependent antibiotics, T > MIC of time-dependent antibiotics, Cmax/MIC of concentration dependent antibiotics). Moreover, sepsis and SIRS may induce a supraphysiologic renal activity, defined as augmented renal clearance (ARC) with enhanced renal pre-load and glomerular hyperfiltration (61). ARC is an established physiological response to hyperdynamic cardiovascular states in adult (61–63) and pediatric critical care patients (64, 65). However, in the neonatal period ARC has not yet been reported. In case of reduced renal functional reserve, secondary to a previously impaired kidney function or worsening organ perfusion, drug clearance may be compromised (64, 66). In children, sepsis has major impact on cytochrome P450 (CYP)3A activity (−90%), as has been illustrated with midazolam as probe drug (67). Such observations should be considered while prescribing drugs for critically ill neonates on ECMO. The interaction between the extracorporeal circuit itself with pre-ECMO disease states needs to be further characterized (68–70).

THE ROLE OF NON-MATURATIONAL DETERMINANTS ON DRUG DISPOSITION: FOCUS ON ECMO

Extracorporeal membrane oxygenation interferes with the expected attainment of a drug's therapeutic level (71). In the last decades, preclinical and clinical research have provided preliminary evidence of the causative mechanisms for reduced drugs' bioavailability. Pending specific PK studies, the loading dose (LD) is usually based on Vd, while the maintenance

TABLE 1 | Pre-ECMO non-maturational determinants of drug disposition and pharmacology considerations.

Physiology
Perfusion status: changes in tissue (regional) perfusion (↓↑), organ (systemic) perfusion (↓↑), cerebral-, splanchnic-, liver-, and renal flow (↓↑), changes in cardiac output (↓↑), SVRI (↓↑), MODS
Body water status: changes in total water volume (TV), tissue permeability, capillary leakage syndrome, intravascular volume (↓↑), extracellular water volume—ECV (↓↑)
Acid-base balance: acidosis
Protein status: hypoalbuminemia, α1-acid glycoprotein (increased plasma levels during acute phase decreases free drug plasma levels)
Pharmacology*
Absorption (AUC, F, Tmax, Ka): ↓ in asphyxia, ↓ or ↑ or = in sepsis
Distribution (Vd): ↑ or = in asphyxia, ↑ in hydrophilic drugs under sepsis, = in lipophilic drugs under sepsis
Elimination (CL): ↓ in asphyxia, ↓ or ↑ or = based on shock state (hyper/hypo-dynamic) and type of drug elimination (liver or kidney)
Metabolism*: ↓ in hypoxia and sepsis
Physicochemical properties of a drug
Route of administration: orally administered drugs F = 20–70%, intravenously administered drugs F = 100%
Drug solubility: hydrophilic/ lipophilic drugs, based on octanol/water partition coefficient—LogP - LogP <1 = water soluble - LogP 1–2 = weak water/more lipid soluble - LogP >2 = lipid soluble
Protein binding capacity (albumin, α1-acid glycoprotein): - Low binding <30% - Moderate binding 30–70% - High binding >70%
Elimination via liver: - High hepatic CL drugs= ↑extraction drugs with ↑ intrinsic hepatic metabolizing capacity, dependency on hepatic blood flow - Low hepatic CL drugs= ↓extraction drugs with ↓intrinsic hepatic metabolizing capacity, low dependence on hepatic blood flow, dependency on hepatocellular enzyme activities phase I CYP P 450 and phase II (intracellular oxygen tension, cofactors)
Elimination via kidney: - High/low renal CL drugs, dependency on renal filtration, secretion, and reabsorption
Concomitant medication*
Fluid resuscitation: Vd ↑ in hydrophilic drugs under sepsis, no changes in Vd in lipophilic drugs under sepsis
Circulatory support: CL ↓↑ in high/low hepatic lipophilic CL drugs. Renal CL↑ of active metabolites of lipophilic drugs or non-active metabolites of hydrophilic/weak hydrophilic more lipid soluble drugs
Diuretics: renal CL↑ of active metabolites of lipophilic drugs or non-active metabolites of hydrophilic/weak hydrophilic more lipid soluble drugs
Drug-drug PK interactions: Absorption variable or ↓ due to changes in gut perfusion (omeprazole, digoxin, fluconazole). Vd ↓: – competitive protein binding (phenytoin, amiodaron, non-steroidal anti-inflammatory drugs) - Biotransformation ↑↓ for inductors (barbiturates, dexamethasone) or inhibitors (midazolam, fluconazole via CYP 3A4,CYP2A6, CYP2C9, CYP2C19, CYP2D6 a CYP2E1) - Elimination due to filtration ↑↓, as changes in Vd may lead to changes in CL or changes in perfusion of vas afferent (aminoglycosides, vancomycin) - Tubular secretion ↑↓ (morphine, furosemide) - Reabsorption ↑↓ as a result of drug ionization and urinary pH (benzodiazepines)
Treatment modalities*
Therapeutic hypothermia (TH): changes in - Absorption (↓) - Distribution (↓ or ↑, no changes, or variable) - Elimination (↓ or no changes)
Extracorporeal membrane oxygenation (ECMO): changes in - Absorption (↓ or no changes)* - Distribution (↑ or no changes) - Elimination (↑or↓ or no changes)

**Limited data in neonates.*

AUC area under the concentration curve, CL clearance, F bioavailability, LogP octanol/water partition coefficient, Ka rate constant of absorption, Tmax—the time at which the Cmax (the maximum serum concentration) is observed, Vd volume of distribution, ↑, increase; ↓, decrease; = no changes.

dose (MD) is driven by the estimated Cl (72). Moreover, PK changes are strictly dependent on equipment material and circuit design (73). Most data come from *ex vivo* studies on silicone-based oxygenators. Technological advances have added further variability, through the introduction of ever-smaller circuits, new biocompatible coatings and poly-methyl-pentene(PMP) membrane oxygenators (74). Currently, we lack the knowledge of the interaction of contemporary neonatal ECMO circuits and pharmacotherapy. Hereby we summarize the available evidence, stemming from *in vitro* and *in vivo* studies.

Circuit-Drug Interaction

The modern neonatal circuitry includes cannulas (venous cannula for drainage and arterial cannula for reinfusion or a single double-lumen cannula, when allowed by patients' size), polyvinyl chloride conduit tubing, a centrifugal pump, and PMP hollow-fiber membrane oxygenator (75). Based on patients' conditions, an hemofilter or a continuous renal replacement therapy may be added to the circuit design (75).

Both size and material of each of the above-mentioned components may lead to significant PK changes as a result of three main mechanisms: (i) sequestration into the circuit; (ii) increased Vd; and (iii) altered Cl.

Drugs' Sequestration by the ECMO Circuit: Components and Materials

Significant extraction of medications occurs in off-patient ECMO systems as a result of a complex interaction among circuit components and specific physiochemical properties of drugs, notably molecular weight, ionization, hydrophilicity, and protein binding (13, 15). The octanol-water partition coefficient (LogP) is a measure of a drug's lipophilicity (76). The higher the LogP (>2), the higher the drug sequestration (13, 15, 77). Similarly, highly protein bound drugs are more prone to be adsorbed into the ECMO systems (14). These *ex vivo* findings were confirmed by *in vivo* ovine ECMO models (77).

Equipment matters, as different materials of oxygenators, tubing, coating, and pumps may have a variable impact on drug disposition (15, 78–81).

Pediatric membrane oxygenator technology underwent significant advancements over the last decades (82). Improvement of materials, surface area and priming volume may support pharmacotherapy. Indeed, the variability of drug adsorption by different membrane oxygenators has been acknowledged since the early 90's (71, 83). Lipophilic drugs were largely sequestered into silicone membranes, at variance with the polypropylene ones (15, 71, 83). Similarly, the last-generation polymethylpentene hollow fiber oxygenators have shown less drug adsorption when compared to silicone-based membranes, especially for the lipophilic drugs in the first hours after injection in off-patients experiments (84).

Polyvinylchloride (PVC) tubing was found to be the primary site for drug sequestration (85). According to *in vitro* data, fentanyl was lost to the PVC tubing by 80% after 120 min, with an additional 5% lost to the oxygenators (85). Polymethylpentene-based oxygenator had a slightly higher impact on fentanyl disposition, if compared to the microporous polypropylene-based one (85). In the same study, morphine was lost to the PVC tubing by 40% after 5 min, with almost no further adsorption by the oxygenators (85). In contrast, recombinant human albumin/heparin coating tubing showed no effect on disposition of hydrophilic drugs, such as cephalosporine and carbapenems (86). These findings were further supported in a more recent *ex vivo* study, which evaluated beta-lactams in ECMO circuits made up of polymethylpentene membrane, centrifugal pump, heat exchanger, and PVC tubing (87). Results confirmed that beta-lactams (except for ceftriaxone) were not sequestered into the circuit (87).

Although the impact of coating has been neglected for years, more recent *in vitro* studies provided evidence that surface modification may affect drug disposition to some extent (88). Coating is meant to mimic the endothelial surface to enhance biocompatibility and it is generally defined as bioactive, when it is based on heparin and nitric oxide, or biopassive, if albumin and polymers such as phosphorylcholine are used (89). *In vitro* results from a study specifically designed to investigate the influence of coating on morphine and fentanyl disposition have shown that the following four types of coating were inert to drug absorption: synthetic albumin, heparin-free biopassive polymer, recombinant human albumin ± heparin, and covalently bonded heparin coatings. In contrast, two other types of surface modifications were associated at 5 min with a significant reduction of morphine levels: poly2methoxylacrylate polymer and covalently bonded heparin (88). No significant differences were reported for fentanyl concentrations (88). These findings further illustrate how drug disposition results from a complex chemical and molecular interaction between individual drugs and ECMO components' individual characteristics. Indeed, electrochemical properties, namely the electric charge and degree of hydrophilicity of surface coatings, may contribute to modulate drugs' sequestration (90).

Although the influence of the type of pump itself has not been defined, centrifugal pump-based circuits with hollow-fiber membrane oxygenators have shown the least absorption for all drugs (13, 15), and this phenomenon is most pronounced for lipophilic drugs (15). Besides chemical drivers, mechanics could be advocated to affect drugs' PK, as blood is constantly exposed to variable pressures and flow-rates over the extracorporeal run (79). ECMO blood-flow is thought to affect drugs' PK (91), nevertheless the specific impact of blood-flow variability has not yet been characterized.

In addition, the type of priming solution and temperature are involved in the complex chemical mechanisms of drug loss and stability during ECMO (92), as explained in the next paragraph. Circuit age further affects pharmacotherapy: on one hand the saturation of binding sites may smooth the tubing impact on PK; on the other hand, it is not clear if the circuit acts as a reservoir, by releasing drugs back into the patient with a potential risk of cumulative effect and late toxicity (13, 71, 93). Thus far, the *in vitro* circuit-drug interaction has been characterized over 24 h, no data are available beyond this time frame.

ECMO-Induced Volume of Distribution Increase

The connection of a neonate to the extracorporeal circuit will affect the apparent Vd of drugs, through three main mechanisms. Firstly, as previously mentioned, the direct drug adsorption into the circuit is the driving factor (71, 93). Secondly, the haemodilution from the priming solution has been advocated for ECMO-related PK variability (92). In neonates, the priming volume of contemporary circuits approximates 250–300 ml, which equals the circulatory volume of a 3 kg neonate.

Furthermore, over the course of an ECMO run, the frequent administration of blood products and crystalloids contribute to worsen the hemodilution (94). Hydrophilic drugs are the most affected, as their Vd is limited to the extracellular compartment, with no intracellular drug reservoir available for retrograde diffusion (72). The extension of the plasma compartment during the ECMO start or in critical illness affects the LD, which is the first dose needed to guarantee the therapeutic concentration (72, 95). LD is directly proportional to the enlarged Vd and, hence, should be increased accordingly (95). The priming dilution, in conjunction with electrolytes and temperature perturbations, may affect also plasma proteins, especially albumin and alpha$_1$-acid glycoprotein, thus altering the plasmatic drug-binding (14). Hypoalbuminemia is a multifactorial process, which results from ECMO- and disease-driven physio-pathologic changes (96). The increase of unbound or free drugs may expose ECMO neonates to potential toxicity (97). Lastly, the ECMO-related physiologic changes and the underlying disease state influence Vd, as a result of the systemic inflammatory response (98–102).

ECMO-Induced Clearance Variability

Drug clearance relies on kidney and liver function, which are usually altered on ECMO, as a result of the clinical status and circuit-related factors (73, 94, 103). In the early phase of extracorporeal circulation, the SIRS releases inflammatory mediators and endogenous cytokines, thus leading to vasodilatation, increased cardiac output and renal perfusion (73, 94). In veno-arterial ECMO, non-pulsatile blood flow is associated with a reduction of the glomerular filtration rate (104). Moreover, the inflammatory state of the critically-ill is associated with the downregulation of the expression and activity of cytochrome P450 enzymes involved in the hepatic drug metabolism (67). Low clearance and consequent rise of drug levels might expose the patient to increased pharmacological effect and toxicity (67, 73).

DISPOSITION OF ANALGO-SEDATIVES ON NEONATAL ECMO

During ECMO, neonates are exposed to multiple sedatives and analgesics, mostly for prolonged periods, to provide comfort, pain relief, and safety (105). The extracorporeal circuit has a large impact on sedatives and analgesics disposition, leading to high sedative needs (106–109). Drug physicochemical properties may assist in the dose prediction, which is titrated to clinical effect (5). Indeed, lipophilic agents, like fentanyl, propofol, and midazolam are highly sequestered into the circuit (15, 93, 110), especially in the first hours of bypass (84).

In the neonatal age, prolonged and sustained analgo-sedation is associated with clinical relevant adverse effects such as tolerance, dependency, impaired brain development, and iatrogenic withdrawal syndrome (105, 111). Among opioid-sparing strategies, the daily interruption of sedation and analgesia was shown to be feasible, safe, and effective (112). However, sedation targets differ among ECMO centers, ranging from deep to conscious sedation practice (5, 113). The use of alternative non-opioid agents should be preferred (73, 84). Morphine and paracetamol have a favorable PK profile (15, 84, 114), while preliminary data on α_2-adrenergic agonists dexmedetomidine and clonidine suggest the need for increased dosing (81, 115).

In this section we will summarize current evidence of the disposition of sedatives and analgesics on contemporary neonatal ECMO circuits (**Tables 2**, **3**) (15, 83, 84, 91, 93, 108, 110, 114, 115, 117–120, 134).

Benzodiazepines

Midazolam has been extensively studied in the neonatal ECMO population. Moderate sequestration into the circuit has been observed through *in vitro* experiments, based on both old (15, 93) and contemporary circuits (15, 84). Two PK studies are available in the neonatal ECMO population, with contrasting results. Although both described the increase of Vd, since the start of ECMO (108, 117), Mulla et al. found a constant Cl of midazolam in neonates on veno-venous ECMO, with a prolonged elimination half-life leading to drug accumulation after 48 h (108). In contrast, Ahsman et al. reported the increase of midazolam Cl over time in neonates on veno-arterial ECMO (117). These PK data suggest the need for an increased LD in the early phase (first 24–48 h) of extracorporeal support, following which dosage should be titrated down, given the risk of accumulation of midazolam and its metabolites (108, 117) and, consequently, prolonged sedation (135).

Opioids

Fentanyl is highly sequestered into the circuit (15, 92) and dose escalation is required in neonates and infants exposed to extracorporeal circuits (107, 136). Despite the technological improvements, the impact of contemporary hollow-fiber-based oxygenators remains high for lipophilic drugs, such as fentanyl and sufentanil (84). Most centers use morphine as analgesic and sedative during neonatal ECMO, because its PK profile is not significantly altered. Clinical PK studies have reported a two-fold increase of morphine Vd (91). The Cl decreased following ECMO cannulation (119, 134) but increased over time, in relation to creatinine clearance, reflecting age-related maturation of drug excretion (91). Moreover, when compared to fentanyl, morphine continuous infusions were associated with improved analgesia, reduced drug withdrawal and length of stay (137). Therefore, morphine remains the opioid of choice for neonatal ECMO. Dose adjustments need to be titrated to clinical sedo-analgesic targets, pending evidence on contemporary circuitry-related PK.

Non-opioid Analgesics

Based on preliminary *in vitro* studies, paracetamol has been suggested as a promising analgesic during neonatal ECMO (84, 114). However, clinical PK evaluations are needed to provide dosing recommendations.

Propofol

This highly lipophilic and protein-bound sedative-hypnotic agent is largely sequestered into the ECMO circuit (93). The drug-related toxicity and concerns for propofol infusion

TABLE 2 | *In vitro* PK datasets of contemporary neonatal ECMO circuits.

References	Drug	Pump	Timing (h)	Drug loss (%)
Wildschut et al. (15)	Cefotaxime	Centrifugal	3	2
Cies et al. (116)	Daptomycin	Centrifugal	24	0
Wagner et al. (81)	Dexmedetomidine	Roller	24	76–90
Nasr et al. (110)	Dexmedetomidine	Centrifugal	48	51
Wildschut et al. (15)	Fentanyl	Centrifugal	3	66
Raffaeli et al. (84)	Fentanyl	Centrifugal	24	84
Nasr et al. (110)	Fentanyl	Centrifugal	48	68
Wildschut et al. (15)	Meropenem	Centrifugal	3	11
Wildschut et al. (15)	Midazolam	Centrifugal	3	36
Raffaeli et al. (84)	Midazolam	Centrifugal	24	40
Nasr et al. (110)	Midazolam	Centrifugal	48	26
Wildschut et al. (15)	Morphine	Centrifugal	3	68
Raffaeli et al. (84)	Morphine	Centrifugal	24	51
Nasr et al. (110)	Morphine	Centrifugal	48	4
Wildschut et al. (15)	Paracetamol	Centrifugal	3	56
Gillogly et al. (114)	Paracetamol	Roller	6	0
Raffaeli et al. (84)	Paracetamol	Centrifugal	24	49
Raffaeli et al. (84)	Sufentanil	Centrifugal	24	83
Wildschut et al. (15)	Vancomycin	Centrifugal	3	33

All experiments were reported to be performed on new and blood-primed circuits, based on hollow-fiber membrane oxygenators. Sample site is pre-membrane.

syndrome (PRIS) (138) call for caution in the prolonged use of this drug during neonatal ECMO.

α_2-Adrenergic Agonists

Clonidine use and prescription during neonatal and pediatric ECMO is supported by a recent population PK study, which suggested higher clonidine doses, based on the increase of Vd and Cl in the specific setting of ECMO and renal replacement therapy (115). Limited *in vitro* data are available for dexmedetomidine, which is partially sequestered into the circuit: a LD may be required, although recommendations for its long-term use cannot be provided (81).

DISPOSITION OF ANTIMICROBIAL AND ANTIVIRAL DRUGS DURING NEONATAL ECMO

Infection remains a real threat for critically-ill neonates on ECMO, with an incidence rate of 5.4 and 5.7% in respiratory and cardiac runs, and reduced survival to 51 and 19%, respectively (34). A timely and adequate antimicrobial therapy is therefore pivotal to improve outcomes (139). However, the goal to provide optimal antibiotic therapy is impaired by the ECMO-induced PK changes, which can be only partially predicted, based on current knowledge on drug-circuit-patient interaction (**Figure 1**) (13, 15, 103). Moreover, antimicrobial prescribing is further complicated by the lack of clinical titratable endpoints (103). Therefore, PK and PD remain the best available predictors of antimicrobial efficacy. Pending evidence-based pharmacotherapy guidelines, neonates on ECMO are still at risk of sub-optimal antibiotic exposure, contributing to treatment failure and bacterial resistance (26). In this section we will summarize current evidence of antimicrobial bioavailability on contemporary neonatal ECMO circuits (**Tables 2–4**) (4, 15, 92, 116, 118, 121–133).

Beta-Lactams

Beta-lactams are hydrophilic time-dependent antimicrobials, with a variable degree of protein binding and renal elimination (150). Their killing activity is strictly related to the time the unbound drug is above the minimum inhibitory concentration (MIC). The knowledge of ECMO-related PK changes is limited in novel circuitry and further complicated by the well-known instability (i.e., temperature) of this class of antibiotics (151). Based on *in vitro* observations, ampicillin showed a moderate loss in older silicon-based neonatal systems (92). The impact of contemporary circuits on cefotaxime seems negligible (15).

Although the Vd of cefotaxime was increased during ECMO, Cl was comparable to the one of non-ECMO neonates (121). Based on a neonatal PK study, standard dosing regimen of cefotaxime during ECMO provided supra-MIC plasma levels (121). Therefore, given the large therapeutic window of cefotaxime, dose adjustments are usually not needed.

Broad-spectrum carbapenem agents, such as meropenem, may be required over the neonatal ECMO course (139). The impact of the ECMO circuit on drug disposition consists of a moderate drug sequestration (15), larger Vd, and higher clearance (152). The latter factor is magnified when renal replacement therapy is added to the circuit design (122).

TABLE 3 | Summary of drug physicochemical properties, ECMO-induced PK changes, and drug dosing.

Drug class	Medication	LogP	PB%	ECMO-related PK changes	Standard dosing in critically ill term neonates	Dosing recommendation for neonates on ECMO	References
Benzodiazepine	Midazolam	3.89	97	*In vitro*: moderate sequestration Clinical PK: Increased Vd	Loading dose 50–150 mcg/kg Maintenance dose 10–60 mcg/kg/h	Consider increasing the loading dose in the early phase of ECMO. Beware of drug/metabolites accumulation over time.	(15, 84, 93, 108, 109, 117, 118)
α_2-adrenergic agonist	Dexmedetomidine	3.39	94	*In vitro*: moderate sequestration No clinical PK	Loading dose 1 mcg/kg Maintenance dose 0.2–0.7 mcg/kg/h	Although sparse, data suggest the need for a loading dose.	(81, 110, 118)
	Clonidine	1.59	20–40	Clinical PK: increased Vd and clearance in a population PK study of ECMO with CVVH	Maintenance dose 0.1–1 mcg/kg/h	Although sparse, data suggest the need for higher doses.	(115, 118)
Opioid analgesics	Morphine	0.99	30–40	*In vitro*: mild to moderate drug loss in contemporary ECMO systems Clinical PK studies (older circuits): no changes	Loading dose 100 mcg/kg Maintenance dose 10–40 mcg/kg/h	Analgesic of choice during ECMO at most centers. Minimal dose adjustment may be required.	(15, 84, 91, 118, 119)
	Fentanyl	4.12	80–85	*In vitro*: high drug loss Clinical PK: need for higher doses	Loading dose 0.5–3 mcg/kg Maintenance dose 0.5–2 mcg/kg/h	Consider alternative drugs. Consider increasing the dose, when used for procedural analgesia	(15, 83, 84, 93, 118)
	Sufentanil	3.4	NA	*In vitro*: high drug loss No clinical PK available	(Pediatric dosage) Loading dose 0.25–2 mcg/kg Maintenance dose 0.5–1.5 mcg/kg/h	Limited data for dosing recommendations.	(84, 118, 120)
Anesthetic (phenolic derivative)	Propofol	3.79	95–99	*In vitro*: high drug loss No clinical PK available	Bolus 2.5 mg/kg	Drug-related toxicity, propofol-related infusion syndrome PRIS call for caution in the use of propofol during neonatal ECMO	(93, 118)
Non-opioid analgesics	Paracetamol	0.51	25	*In vitro*: conflicting data No clinical PK.	7.5 mg/kg/6h	Limited data for dosing recommendations.	(15, 84, 114, 118)
b-Lactam	Ampicillin	1.35	15–30	*In vitro*: increased Vd, low-moderate drug sequestration No clinical PK	50–70 mg/kg/8 h	Standard dosing, given the large therapeutic window.	(92, 118)
	Cefotaxime	−1.4	35	*In vitro*: low drug sequestration in contemporary systems Clinical PK: standard dosing is effective	Postnatal age < 7 days: 100–150 mg/kg/day in 2 or 3 doses Postnatal age 7–28 days: 150–200 mg/kg/day in 3 or 4 doses	Standard dosing; perform TDM to verify adequate supra-MIC levels.	(15, 118, 121)
	Meropenem	−0.69	2	*In vitro*: large increase in Vd and low-moderate drug loss Clinical PK: increased Vd and increased Cl, in ECLS + RRT	Postnatal age < 7 days: 20 mg/kg every 12 h Postnatal age 7–28 days:20 mg/kg every 8 h Meningitis: 40 mg/kg every 8 h	Standard dosing. Perform TDM to verify adequate supra-MIC levels. Consider higher dosing or continuous infusion in case of increased clearance or RRT.	(15, 118, 122)
Glycopeptide	Vancomycin	−1.4	50	*In vitro*: large increase in Vd, minimal to moderate loss Conflicting clinical PK data in contemporary circuits, in terms of impact on Cl	Postnatal age < 7 days: 10–15 mg/kg every 8/12 h >7 days: 15 mg/kg every 6/8 h	Dosing guidelines based on age and renal clearance. Suggested dose in neonates: 25 mg/kg/dose every 12–24 h. TDM for dosing monitoring and adjustement.	(3, 15, 92, 118, 123–125)

(Continued)

TABLE 3 | Continued

Drug class	Medication	LogP	PB%	ECMO-related PK changes	Standard dosing in critically ill term neonates	Dosing recommendation for neonates on ECMO	References
Aminoglycoside	Gentamicin	−3.1	0–30	*In vitro*: increased Vd, reduced Cl. Low drug sequestration	Term neonates with normal renal function: 3.5–5 mg/kg every 24 h	Dosing guidelines based on age and renal clearance. Initial dose 2.5 mg/kg/dose every 18 h, subsequent doses individualized through TDM. Once ECMO is discontinued, dosage should be readjusted according to body water shifts.	(3, 118, 126–129)
Antiviral	Oseltamivir	1.3	3	NA	3 mg/kg/dose every 12 h, orally	Standard dosing	(118, 130, 131)
Azole anti-fungal	Fluconazole	0.5	11–12	*In vitro*: minimal sequestration PK-PD study available	Prophylaxis: 3 mg/kg every 72 h	Loading dose 12 mg/kg followed by 6 mg/kg/die	(118, 132, 133)

CVVH, continuous veno-venous hemofiltration; Vd, volume of distribution; NA, not available; PK, pharmacokinetics; PRIS, propofol-related infusion syndrome; RRT, renal replacement therapy; TDM, therapeutic drug monitoring.

Glycopeptides

Vancomycin is a hydrophilic time-dependent antimicrobial, largely used in the NICUs for treatment of Gram-positive infections (118, 153). Given the narrow therapeutic window and the risk of nephrotoxicity, the PK profile of vancomycin has been extensively evaluated both *in vitro* and *in vivo* neonatal settings since the 90's (154–156). Vancomycin Cl is strictly related to renal function (155, 157) and the drug half-life was found to be prolonged in ECMO patients (156). However, these findings referred to older roller pump-based systems. Although data on contemporary circuits are limited, recent neonatal PK studies have revealed enhanced Cl, potentially leading to under-exposure (123). An empiric dosing strategy of 25–30 mg/kg/dose every 12–24 h is suggested, with a close therapeutic drug monitoring (TDM) (125).

Continuous vancomycin infusions were found to be associated with earlier and improved attainment of target concentrations compared to the intermittent modality in neonates, with no difference in terms of adverse effects (158). However, no evidence is available for the optimal infusion modality during ECMO.

Another glycopeptide antimicrobial which may be used during neonatal ECMO is teicoplanin. Although specific neonatal data of teicoplanin disposition in the extracorporeal setting are lacking, the evidence from an adult PK study suggests the need for higher doses during ECMO (159). In this prospective population PK evaluation, the predictive target attainment was reduced during ECMO for every simulated dosing, despite the Vd was lower and Cl was not affected by the extracorporeal circuit (159). Based on the hydrophilic profile of the drug, the hemodilution and protein binding could be addressed as the main drivers for teicoplanin disposition on ECMO (159).

Aminoglycosides

Gentamicin is a hydrophilic antimicrobial with a relatively low protein binding, largely used in the NICUs for the treatment of infections due to Gram-negative bacteria (118, 153). During ECMO, gentamicin has been found to have an increased Vd, as a result of the large exogenous blood volume for circuit priming and decreased Cl, leading to a prolonged elimination half-life (4, 126, 128). The renal dysfunction, which is a common multifactorial condition during ECMO, may be considered as the main determinant of the prolonged elimination half-life of gentamicin (72). Given the concentration-dependent antimicrobial activity of aminoglycosides, it is highly recommended to perform TDM to ensure adequate antimicrobial exposure.

Antivirals

Oseltamivir is a neuraminidase inhibitor of both type A and B influenza virus (160). This drug is approved by the Food and Drug Administration (FDA) for the treatment of children older than 2 weeks of age with flu (130, 161). Oseltamivir is an oral pro-drug which is rapidly converted to oseltamivir carboxylate, the active metabolite (150, 160). Based on previous pediatric PK ECMO case series, the impact of ECMO on oseltamivir disposition is negligible with no need for dosing adjustment

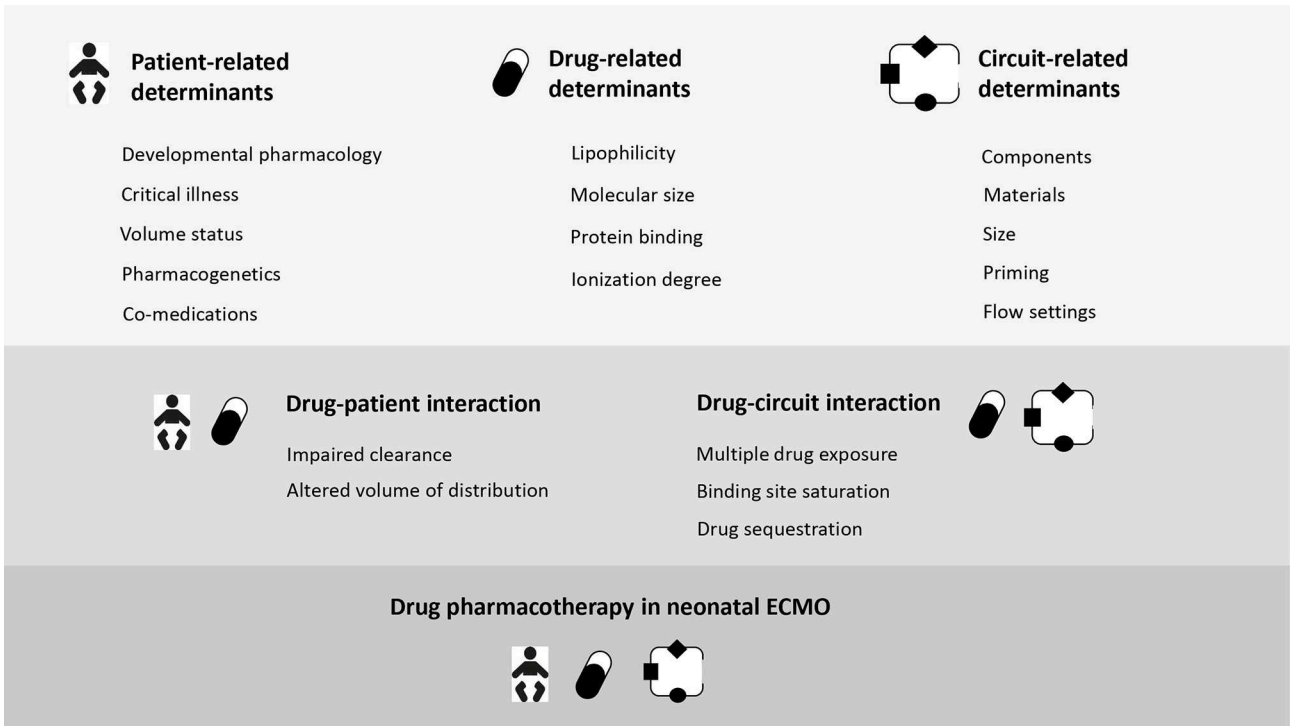

FIGURE 1 | Determinants of drug disposition during neonatal ECMO.

(131). However, oral bioavailability was reported to decrease in patients with impaired gastric motility and enteral absorption (131). Although evidence in the neonatal setting is scant, adult data support the lack of effect of ECMO on the oseltamivir's PK (162, 163).

FROM FRAGMENTED DATA TO INTEGRATED KNOWLEDGE

Obviously, also in neonates and children on ECMO, pharmacotherapy is a very important tool in the medical management. As a result of the large PK-PD variability, drug dosing is only to a very limited extent validated in the setting of neonatal ECMO (164). Methodological development within the field of clinical pharmacology and modeling should assist ECMO physicians to improve our practices. The other way around, modelers will need the data to get this job done.

A knowledge-driven improvement strategy necessitates sufficient understanding of human developmental biology to subsequently translate such knowledge into prediction differences in drug absorption, distribution, metabolism, and excretion (PK). Only once this PK is sufficiently well covered, an appreciation of the developmental aspects of drug-receptor or -target interactions (PD) can be considered. Physiologically-based PK (PBPK) modeling is such a structured approach to translate knowledge into prediction, but the development of such modeling techniques necessitates the collaboration of clinicians with researchers specifically skilled in modeling techniques (165). PBPK approaches provide a potent systematic way to make the most of already acquired knowledge (physiology, system knowledge) to adapt drug dosing to the needs of children on ECMO, as has recently been illustrated for fluconazole (166).

The aim is not to describe the workflow and technical details related to the development of pediatric or neonatal PBPK model (167, 168), but to illustrate how ECMO physicians and clinical researchers can contribute to improved ECMO-related pharmacotherapy in neonates and children by generating data on ECMO related (patho)-physiology, including aspects related to the initial indication to initiate ECMO, and by sharing PK datasets and data on neonatal and pediatric equipment.

PBPK Methodology

In essence, PBPK is a structured method for data integration, hypothesis testing and knowledge generation (167, 168). Moreover, one may check consistency of data obtained from different sources (*in vitro*, *in vivo*, *in silico*) or predict outcome (PK, PD) of future experiments, hereby enabling decision making or optimization of study design. PBPK ("so-called bottom-up") applies mathematical models for mechanistic integration of pharmacology principles, assumptions, and data along the drug development process. It hereby integrates different types of information, such as clinical data and *in silico*, *in vitro*, and *in vivo* observations. PBPK hereby explicitly discriminates between physiological properties of the population (system parameters, like cardiac output, renal function, liver size, weight, plasma protein, different between populations) and compound specific

TABLE 4 | Overview of the Pubmed (ecmo, newborn, pharmacokinetics, $n = 72$) search on pharmacokinetics of 16 different compounds.

References	Compound	Protein binding*	pKa*	Comments
Pokorna et al. (140)	Phenobarbital	20–45%	8.14 (acid)	Hepatic, mostly via CYP2C19
Cies et al. (123)	Vancomycin	50%	2.99 (acid)	Mainly by renal route, renal transporters likely involved
			9.93 (basic)	
Kleiber et al. (115)	Clonidine	20–40%	8.16 (basic)	Renal (about 50%) and hepatic (about 50%), including CYP2D6
Niimi et al. (141)	Anti-thrombin	n.a.	n.a.	Protein, no specific elimination routes described
Watt et al. (132)	Fluconazole	11–12%	12.71 (acid)	Renal (90%) and hepatic (10%)
			2.56 (basic)	
Ahsman et al. (117)	Midazolam	97%	6.57 (basic)	Intestinal and hepatic metabolism, CYP3A
Ahsman et al. (121)	Cefotaxime	n.a.	3.18 (acid)	Renal elimination (20–40%) and metabolism (desacetyl derivative is the major metabolite)
			4.15 (basic)	
Ahsman et al. (142)	Sildenafil	96%	7.29 (acid)	Hepatic metabolism, CYP3A4 > 2C9
			5.97 (basic)	
Kendrick et al. (143)	Amiodarone	>96%	8.47 (basic)	Almost exclusively hepatic, CYP2B8
Peters et al. (144)	Morphine	30–40%	10.92 (acid)	90% hepatic, glucuronidation >> demethylation
			9.12 (basic)	
Mulla et al. (145)	Theophylline	40%	7.82 (acid)	Hepatic metabolism, demethylation, hydroxylation and N-methylation (CYP1A2) to caffeine
			−0.78 (basic)	
Wells et al. (146)	Ranitidine	15%	8.08 (basic)	N-oxidation is the most relevant metabolite
Aebi et al. (147)	Ribavirin	n.a.	11.88 (acid)	(de)phosphorylation
			−1.2 (basic)	
Wells et al. (148)	Bumetanide	97%	4.69 (acid)	45% primary renal, oxidation 55%
			2.7 (basic)	
Bhatt-Metha et al. (129)	Gentamicin	Low, 0–30%	12.55 (acid)	Primary renal, by glomerular filtration
			10.18 (basic)	
Pokorna et al. (149)	Sufentanil	79–93% (alpha-acid glycoprotein)	8.86 (basic)	Hepatic, oxidative N-, and O-dealkylation

**Data on protein binding and pKa values were retrieved on www.drugbank.ca [CYP, cytochrome P450; n.a., not available/applicable].*

(chemical, pH, solubility) properties, not different between populations (**Figure 2**). Using this approach, it has applications in drug development for first-in-human, first-in-child, or first in ECMO-patients, and became an established tool for drug development and regulatory needs, like e.g., data in cases with hepatic or renal impairment, drug-drug or drug-food interactions to avoid the need to recruit an impossible number of patients with very specific issues while still have sufficient confidence in the dosing regimens. The final intention is to generate dosing recommendations, or alternatively, simulations to subsequently conduct PK studies, as highlighted in **Figure 2** for the specific ECMO setting (#).

Why ECMO Physicians and Clinical Researchers Are Needed to Develop Such Models

As illustrated in **Figure 2**, the workflow to develop and build confidence in PBPK models tailored to neonatal and pediatric ECMO pharmacotherapy necessitates availability of *in vivo* PK data (*), data on disease state (**), and on ECMO circuit parameters (***), and this is exactly why clinicians should become aware of the usefulness of such data beyond compound specific relevance (164, 165, 167, 168).

Availability of *in vivo* PK Dataset (*, Figure 2)

To illustrate that there are indeed already quite some compound specific PK observations, we conducted a structured search in PubMed on 15 January 2019 with [*ECMO*, *newborn*, and *pharmacokinetics*] as search terms. This resulted in 72 hits, and additional search with "infant" resulted in 79 hits, but no additional compounds. The results of this search are provided in **Table 4**, reporting on the compounds ($n = 16$) retrieved and supported by the most recent reference (115, 117, 121, 123, 132, 140–149). From a PBPK perspective, it is important to realize that these compounds are quite different when we consider protein binding, pKa (reflecting the chemical characteristics of the compound) and can be used to evaluate and optimize a variety of elimination routes, including renal, phase 1, and phase 2 processes: a perfect mix to validate

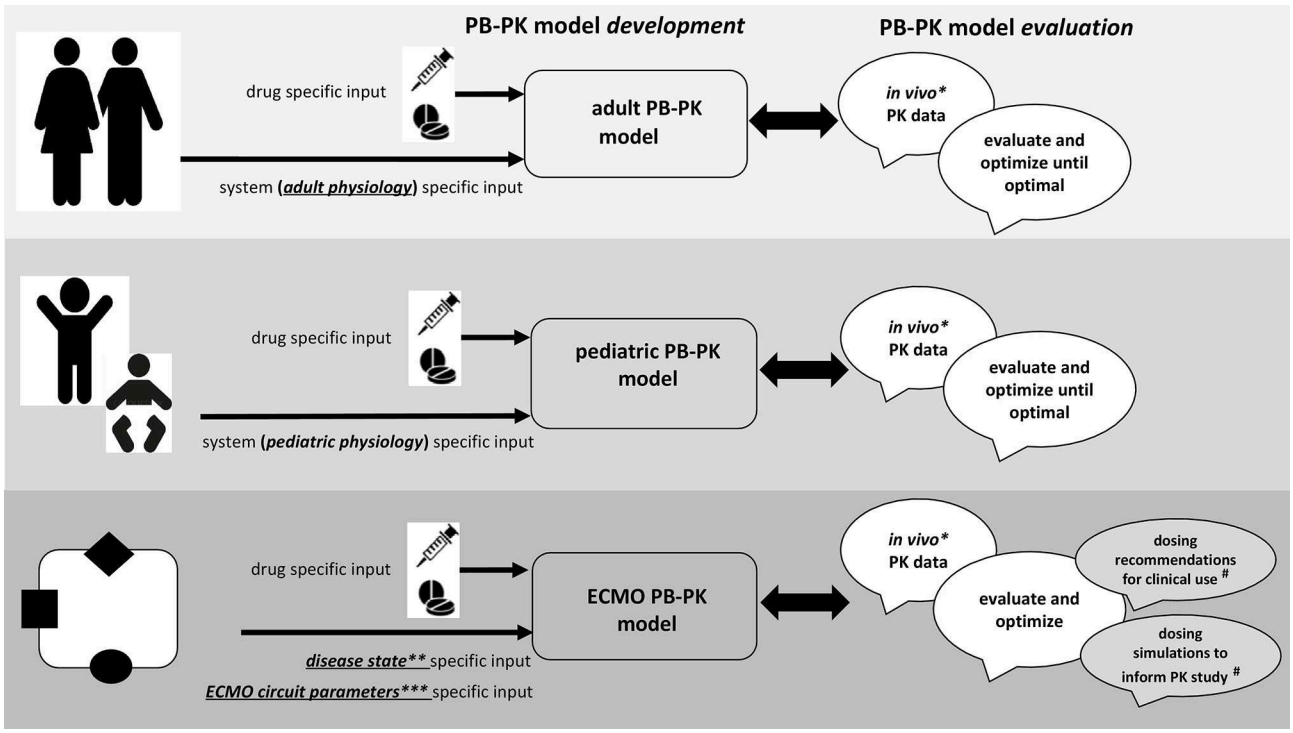

FIGURE 2 | Integrated approach for drug prediction through physiologically-based pharmacokinetic (PBPK) models during neonatal ECMO.

the models. So PK data sharing and collaboration is an obvious need, since the data already exist and can be used to predict PK for drugs not yet evaluated or even not yet marketed (169).

Data on Disease State (**, Figure 2)

Extracorporeal membrane oxygenation is a technique to treat life threatening conditions, so data on these underlying disease conditions are also needed to further develop ECMO related P'BPK models: *it's is not just the technique, but also the reason for the technique that matters.* To illustrate the feasibility to integrated (patho) physiology, we refer to PBPK models for carvedilol in children with cardiac failure (170) or intensive care adult patients with hypo-albuminemia (171). In the neonatal and pediatric ECMO, perinatal asphyxia, sepsis, or post resuscitation are common settings. It has been proven that disease affects drug PK (*refer to previous section on pre-ECMO disease*) (37, 67). Besides such observations, clinical researchers should also consider to build multi-center datasets (as part of the ongoing ELSO registry initiatives) on inter- and intra-patient trends of "real world" data. We hereby refer to trends in fluid retention, albumin, creatinine, heart rate, and cardiac output, energy expenditure or more specific issues like alfa-1 glycoprotein (**Table 4**). This is because such datasets can further feed and improve PBPK prediction, including intra-patient trends with time (8, 172). This has also recently been illustrated for e.g., alfa-1 glycoprotein maturation (173).

Data on ECMO Circuit Parameters (***)

Finally, equipment matters and data on newer extracorporeal technology need to be considered. PBPK modeling will generate further knowledge, which may guide both the development of new ECMO devices and the refinement of current technology at a biomedical engineering level.

CONCLUSIONS AND FUTURE DIRECTIONS

Extracorporeal membrane oxygenation has an established role in the care of critically ill neonates. The exposure to the extracorporeal circuit impacts on drugs' disposition, potentially leading to undertreatment or toxicity, especially for drugs with a narrow therapeutic index. Non-maturational determinants (such as asphyxia/hypoxia, sepsis/SIRS, MODS) during pre-ECMO predetermine large Vd for hydrophilic drugs due to the underlying disease, while superimposed ECMO may lead to larger Vd for lipophilic and, to a lesser extent, hydrophilic drugs. Therefore, LD adjustment may be recommended to achieve optimal drug levels in neonates on ECMO. CL is influenced by renal (hydrophilic, high renal clearance drugs) and/or hepatic functions (lipophilic, high liver clearance drugs) under sepsis, asphyxia and treatment modalities (HT, ECMO), and optimal maintenance dose adjustment should be achieved on an individual basis (development, disease, genetics). Therefore, TDM is suggested to optimize LD/MD in these critically ill neonates. As drug dosing needs to be guided by PK or PD or

PK/PD principles, the understanding of PK-PD changes during (pre-) ECMO will assist in the prescribing optimization and, eventually, contribute to improve patients' outcomes.

In this review we have provided an overview of the available evidence on the impact of both maturational and non-maturational determinants of PK in critically-ill neonates on ECMO. We subsequently have discussed the relevance of these determinants on the disposition of analgo-sedatives and antimicrobial and antiviral drugs during neonatal ECMO. Future efforts should be directed toward a more integrated approach, by combining existing knowledge to predict PK profile. *Sparse samplings* of three different periods (pre-, during, post-ECMO) may be adopted to better understand dynamically changing drug disposition. Further *PK in vivo*/*in vitro studies* will provide insights into the role of contemporary ECMO systems superimposed on maturational/non-maturational determinants.

Gathered knowledge into the maturational physiology-, illness-, and ECMO-related PK impact should be used to inform *PBPK modeling*, which is emerging as an alternative and powerful tool to provide bedside dosing guidance. Lastly, *a prospective validation of PK/PD studies* is needed by well conducted clinical trials to optimize dosing.

The final aim will be to apply pharmacotherapy in a goal-directed fashion, by reaching optimal PD outcomes through the *individualization* of the prescription, thus maximizing the therapeutical benefits in these vulnerable patients.

AUTHOR'S NOTE

PP and DT represent the section of Pharmacology of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC).

AUTHOR CONTRIBUTIONS

All authors contributed conception and design of the article. GR wrote the first draft of the manuscript. PP, KA, and DT wrote sections of the manuscript. All authors contributed to manuscript critical revision, read and approved the submitted version.

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REVIEW
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Anticoagulation in Neonatal ECMO: An Enigma Despite a Lot of Effort!

Katherine Cashen[1]*, *Kathleen Meert*[1] and *Heidi Dalton*[2,3]

[1] Division of Critical Care Medicine, Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit, MI, United States, [2] Division of Critical Care Medicine, Department of Pediatrics, INOVA Heart and Vascular Institute, Inova Fairfax Medical Institute, Falls Church, VA, United States, [3] Department of Surgery, George Washington University, Washington, DC, United States

Extracorporeal membrane oxygenation (ECMO) is a valuable modality used to support neonates, children, and adults with cardiorespiratory failure refractory to conventional therapy. It requires use of anticoagulation to prevent clotting in the extracorporeal circuit. Balancing bleeding from excessive anticoagulation with thrombotic risk remains a difficult aspect of ECMO care. Despite many advances in ECMO technology, better understanding of the coagulation cascade and new monitoring schemes to adjust anticoagulation, bleeding and thrombosis remain the most frequent complications in ECMO and are associated with morbidity and mortality. In neonates, ECMO is also complicated by the immature hemostatic system, laboratory testing norms which are not specific for neonates, lack of uniformity in management, and paucity of high-quality evidence to determine best practices. Traditional anticoagulation focuses on the use of unfractionated heparin. Direct thrombin inhibitors are also used but have not been well-studied in the neonatal ECMO population. Anticoagulation monitoring is complex and currently available assays do not take into account thrombin generation or platelet contribution to clot formation. Global assays may add valuable information to guide therapy. This review provides an overview of hemostatic alterations, anticoagulation, monitoring and management, novel anticoagulant use, and circuit modifications for neonatal ECMO. Future considerations are also presented.

Keywords: extracorporeal membrane oxygenation, neonate, anticoagulation, hemostasis, monitoring, thrombosis, bleeding

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***Correspondence:**
Katherine Cashen
kcashen@med.wayne.edu

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a valuable modality used to support neonates, children, and adults with cardiorespiratory failure refractory to conventional therapy. Neonatal ECMO has evolved over the past 50 years with more than 41,700 neonates undergoing this lifesaving modality (1). Survival in the neonatal ECMO population remains highest with 73% survival to hospital discharge in the respiratory cohort and 42% survival to discharge in the cardiac cohort (1). However, despite improvements in ECMO technology and institutional experience, bleeding and thrombosis remain significant complications and are associated with worse outcome (2–4). The most recent Extracorporeal Life Support Organization (ELSO) registry report found that 11% of neonates placed on ECMO for respiratory and cardiac indications suffered from an intracranial hemorrhage 7–26% suffered surgical site bleeding, and 1–2% had gastrointestinal hemorrhage. Neonates with bleeding complications had significantly increased mortality compared to neonates without bleeding complications (2). The Bleeding and Thrombosis During ECMO

(BATE) study performed by the Collaborative Pediatric Critical Care Research Network also found high rates of bleeding and thrombosis during neonatal ECMO. In the BATE study, 60–77% of neonates placed on ECMO for respiratory or cardiac indications suffered from bleeding events and 19–23% of these consisted of intracranial hemorrhage. Thrombotic events were recorded in 32–44% of the neonatal cohort. In the BATE study, 4–13% of these thrombotic events were patient-related (intracranial infarction, limb ischemia, aortopulmonary shunt clot, and other) and 25–40% were circuit-related. Both bleeding and thrombosis increased morbidity and mortality (3).

Titration of anticoagulation to limit bleeding and thrombosis remains challenging in neonates. The mechanisms of bleeding and thrombosis are complex and dynamic and involve multiple alterations in hemostatic factors. The developmental hemostatic system, increased risk for hemorrhage in the developing brain, heterogeneous disease processes that lead to initiation of ECMO, variability in anticoagulation strategies and lack of high-quality evidence to direct practice all contribute to the challenges in managing anticoagulation in the neonatal population. In this review, we provide an overview of developmental hemostasis, hemostatic alterations, anticoagulation, monitoring, management, and novel anticoagulant use as well as circuit modifications for neonatal ECMO.

DEVELOPMENTAL HEMOSTASIS

Hemostatic equilibrium involves both procoagulant and anticoagulant factors and evolves from fetal to adult life (5–9). Primary hemostasis which is dependent on platelet adhesion, activation, and aggregation is different in the neonatal period compared to the rest of childhood and adulthood. The platelet count of neonates is usually normal or elevated but platelet hyporeactivity is well-described (10–13). However, despite hyporeactive platelets the bleeding time and platelet closure time (a measure of platelet function) are shortened in neonates and do not normalize until the first month of life (11, 12). Higher levels of von Willebrand factor (VWF) and higher percentage of larger VWF multimers likely increase the adhesive activity of platelets in neonates despite the overall platelet hyporeactivity (11, 13, 14). Thus, in healthy neonates elevated VWF balances platelet hyporeactivity and normal hemostasis is maintained.

Secondary hemostasis which consists of the coagulation cascade and ultimately leads to the formation of fibrin factors is substantially different in neonates than adults. At birth, the plasma levels of most coagulation proteins are around half of those measured in adults. Prolonged prothrombin time (PT) and partial thromboplastin time (PTT) in neonates has been consistently reported (8, 9). Decreased anticoagulant factors including protein C and S, and antithrombin as well as decreased thrombin generation and reduced clot lysis have been reported in neonates (9, 15). In healthy neonates hemostatic equilibrium is maintained but in critically ill neonates on ECMO lack of reserve capacity and immaturity of the coagulation system interferes with this fine balance and disequilibrium with resultant bleeding or thrombosis is common.

HEMOSTATIC ALTERATIONS DURING ECMO—ECMO INDUCED COAGULOPATHY

The ECMO Circuit

The ECMO circuit consists of a mechanical blood pump, gas exchange devices, heat exchanger, tubing and cannulas. When blood is exposed to the non-biologic surfaces of the circuit, activation of the coagulation pathway and inflammatory response pathway occur (**Figure 1**). Exposure of blood to the non-endothelial surface of the extracorporeal tubing activates platelets, factor XII and kallikrein-kinin system, tissue factor, and von Willebrand factor, fibrinolysis and inflammation (16–20). Turbulent flow and shear stress from the pump, tubing, and cannula contributes to cellular damage and platelet activation. The continuous exposure of the blood to the non-endothelial surface shifts the normal hemostatic balance to a hypercoagulable state and requires systemic anticoagulation.

Our current understanding of the biomaterial interaction of the ECMO circuit and patient's blood involves surface contact and subsequent hemostatic activation. Fibrinogen binds to the ECMO circuit non-endothelial surfaces within minutes of contact followed by binding of coagulation factors, cellular adhesion and activation of platelets and polymorphonuclear (PMN) cells (21). Exposure of tissue factor and activation of circulating Factor VII then causes downstream thrombin generation. Activation of the complement system also leads to further activation of platelets and PMNs and increased adhesion and release of cytokines contributing to the pro-inflammatory hypercoagulable state (20–24).

To add even more complexity to the blood surface interaction some reports suggest distinct periods of activation in neonates. In the first 24 h of ECMO, contact activation and complement activation occur similar to the pattern of activation seen in

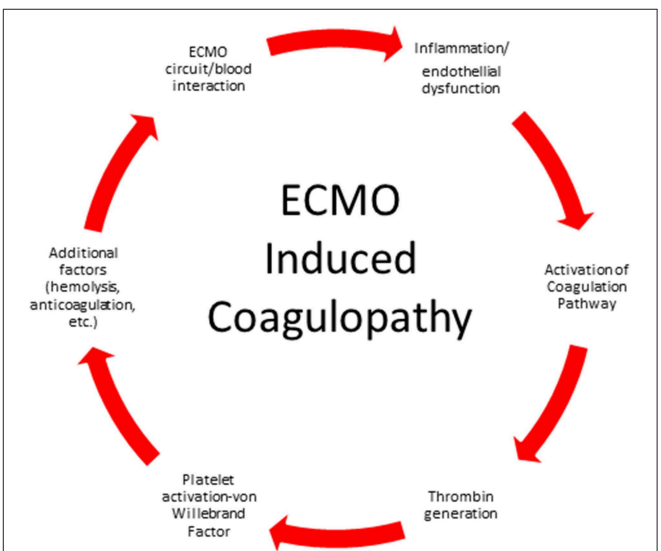

FIGURE 1 | Factors contributing to ECMO induced coagulopathy.

cardiopulmonary bypass. A second period of activation was observed 72 h after EMCO initiation and was characterized by clotting and fibrinolytic activity without activation of the complement system (25). Various strategies have been used to mitigate the contact and hemostatic activation of the ECMO surface and will be detailed in the management section.

Underlying Disease, Endothelial Dysfunction and Inflammation

The underlying disease process that leads to ECMO initiation plays an important role in ECMO induced coagulopathy. Neonates with a primary respiratory diagnosis such as meconium aspiration syndrome likely have very different coagulation profiles than neonates with sepsis or cardiac surgical patients who have undergone cardiopulmonary bypass. Thrombocytopenia also varies based on the pre-existing disease and platelet count prior to cannulation and may contribute to bleeding risk (26). On the other hand, continuous activation of the coagulation system during ECMO may lead to ongoing consumption of platelets and coagulation factors and contribute to a prothrombotic state.

Endothelial dysfunction during neonatal ECMO is also due to both the underlying disease process leading to ECMO initiation and the ECMO circuit itself (27–29). Damaged endothelium via expression of tissue factor activates procoagulant factors and contributes to ECMO induced coagulopathy (28–31). Critically ill neonates often have a generalized inflammatory response and associated coagulopathy. Underlying illness may lead to a hypercoagulable state or a hypocoagulable state and contributes to immune dysfunction and endothelial dysfunction and subsequent consumption of hemostatic factors (32–34). Many of the molecular mechanisms by which inflammation contributes to excessive activation of the coagulation cascade have been delineated and the cross-talk between innate inflammation and coagulation is well-described (35). This cross-talk between the systems may lead to unopposed amplification of the coagulation cascade in the setting of ongoing inflammation and may result in a hypercoagulable state and contribute to tissue damage and thrombosis.

Thrombin Generation

Thrombin is a key enzyme in coagulation that converts fibrinogen to fibrin, activates factor XIII, factor V, factor VIII, factor XI and activates platelets. Thrombin generation also occurs when endothelial injury causes exposure of tissue factor to factor VII (30). Thrombin has a large array of functions and formation occurs during different stages of hemostasis. Anticoagulation with unfractionated heparin (UFH) prevents clot formation but does not stop thrombin generation or coagulation within the circuit (36). Neonates show a persistent increase in thrombin generation and fibrinolysis activation despite anticoagulation in a distinctly different pattern than is seen with children and adults (37).

Platelet Activation and Von Willebrand Factor

Platelets adhere to the non-endothelial surfaces of the circuit and react with other activated components of the coagulation and complement systems increasing the risk of thrombotic complications. Both quantitative and qualitative platelet dysfunction has been described during ECMO and is associated with bleeding and mortality (31, 38) Thrombocytopenia is common during ECMO and more pronounced in neonates than older children (26). Severe thrombocytopenia from platelet consumption may lead to ongoing platelet transfusion, associated multiple organ dysfunction, microthrombi formation and immune dysregulation (39, 40). Platelets are also activated by shear stress from flow through the ECMO cannulas which is associated with decreased expression of platelet adhesion and structural molecules (41). Platelet microparticles, small circulating fragments of platelet plasma membranes, are produced by platelets during periods of shear stress and participate in thrombus formation (42). Platelet microparticles are increased in neonatal ECMO systems *in vivo* but no study to date has demonstrated that platelet microparticles contribute to a prothrombotic state *in vitro* (43).

Von Willebrand Factor (VWF) is a plasma glycoprotein that binds to FVIII, platelet surface glycoproteins and connective tissue. VWF forms a complex with FVIII that protects FVIII from degradation by activated protein C and localizes FVIII to sites of platelet plug and clot formation (44). Acquired VWF syndrome occurs during ECMO due to a loss of high molecular weight VWF multimers from shear stress. Disrupting VWF multimers is associated with increased bleeding complications (45, 46).

Additional Considerations

Hemolysis

Hemolysis measured by plasma free hemoglobin levels has been associated with increased morbidity and mortality during ECMO (47, 48). Increased hemolysis has been reported in neonates compared to older children likely due to increased shear stress from flow through smaller caliber cannulas, increased fetal red blood cells which show greater susceptibility to mechanical stress than adult red blood cells, and higher hemoglobin concentration in neonates with increased blood viscosity (47, 48). Of note, measurement of plasma free hemoglobin is not uniform across centers. When measured, hemolysis (plasma free hemoglobin $>$50 mg/dL) was present in over 50% of patients and was associated with need for subsequent ECMO component change within 3 days (3).

ANTICOAGULATION STRATEGIES

Unfractionated Heparin

Unfractionated heparin (UFH) remains the most commonly used anticoagulation agent during ECMO (49). UFH potentiates (up to 1,000 times) the anticoagulant effect of antithrombin III (ATIII) by forming a UFH-ATIII complex that inactivates free thrombin and prevents further thrombin generation. UFH also weakly inhibits factor Xa (50). UFH binds to endogenous plasma proteins or heparin binding proteins including platelet factor 4 and high molecular weight multimers of VWF (51). The advantages of UFH include its low cost, short half-life, reversibility, and familiarity with use. Other advantages of UFH are its non-anticoagulant effects. Heparin has anti-inflammatory

properties, inhibits reactive oxygen species generation, has tissue repair and protection properties and cardiovascular protective effects (52, 53). While most ECMO research focuses on limiting heparin exposure, higher heparin infusion dose was associated with decreased daily plasma free hemoglobin levels in neonates and children and improved survival in several studies (47, 54). UFH protocols usually include a bolus loading dose of UFH (50–100 units/kg) followed by an UFH infusion (10–51 units/kg/h) titrated for activating clotting time (ACT)or Anti-factor Xa assay activity (54). But, again the major benefit of UFH is the rapid reversibility.

The disadvantages of UFH include pharmacokinetic alterations depending on disease severity, renal failure, and increased volume of distribution in neonates (55).Variation in patient response to fixed dosing in part due to heparin binding proteins and the subsequent reduced anticoagulant activity of UFH especially in the neonatal population. As heparin requires a specific polysaccharide sequence to bind to ATIII, variability in activity between manufactured batches also exists and may help explain the individual responses noted. Another problem is heparin resistance related to reliance on ATIII levels which are lower in critically ill children and neonates and UFH's inability to inhibit factor Xa bound to platelets (56). Evidence suggests that ATIII activity often decreases over time in children on ECMO (57–60). Many centers routinely replace ATIII in an attempt to maximize heparin effect. ATIII can be supplemented by transfusion of fresh frozen plasma or by infusing ATIII concentrates. But, ATIII concentrates are expensive and studies in the neonatal and pediatric population have found mixed results when ATIII supplementation is utilized (57–60). A recent large observational report (including 5,360 neonates) found that ECMO patients supplemented with ATIII had an increased number of thrombotic and hemorrhagic events and longer hospital length of stay with no difference in mortality (61). A limitation of this study was that the rate of complications was not adjusted for exposure or illness severity. At this time, clear recommendations and indications for ATIII supplementation are lacking and use should be judicious.

Another potential disadvantage of UFH is development of heparin induced thrombocytopenia (HIT), an immune mediated adverse drug reaction caused by antibodies to complexes of platelet factor 4 and heparin. The risk of thrombotic events and associated morbidity and mortality is high. A recent systematic review on HIT in children found seroconversion in 0–1.7% of neonates but no cases of neonatal HIT. This could be due to challenges in defining HIT in the neonatal population, lack of studies in this population, or that HIT is indeed rare in neonates. Thus, while this is a disadvantage of heparin use in adults and pediatric patients it should not be a major concern for neonatal ECMO (62).

Direct Thrombin Inhibitors

Direct thrombin inhibitors have been rarely used in neonatal ECMO patients. Direct thrombin inhibitors such as bivalrudin, argatroban, and lepirudin directly bind to active sites on thrombin providing a greater reduction in thrombin compared to UFH. Direct thrombin inhibitors inhibit both free and bound thrombin, are ATIII independent, are not inhibited by platelet factor 4, and have more predictable dose effects because they do not bind to plasma proteins (63). Use of direct thrombin inhibitors are currently limited in children and reserved for those with allergy to UFH, HIT, and heparin resistance due to cost, safety and dosing concerns (31).

Of the direct thrombin inhibitors, bivalrudin has been utilized the most in the pediatric population but isolated reports of argatroban and lepirudin have been published. A handful of reports describe argatroban use in pediatric ECMO patients with HIT and are associated with good outcome (64–67). A prospective study of argatroban use in pediatrics as an alternative to UFH enrolled 18 pediatric patients and included 2 pediatric ECMO patients. Both of these patients had HIT and were treated with an initial bolus dose of 100 μg/kg followed by initial infusion of 2 μg/kg/min to reach a target ACT 180-220 (68). One of these patients died from progressive thrombosis and severe cardiac dysfunction during cardiac transplantation. In this report, argatroban in pediatric patients was used to achieve aPTT levels 1.5 to 3 times baseline with rapid achievement of therapeutic values however enrollment was limited, and complications persisted (68). Successful administration of lepirudin to treat HIT during ECMO has been reported in a 21-month-old child but two other children (a 15-year-old and a 4-year-old) ultimately died (69–71). In these studies, a lepirudin bolus dose was used ranging from 0.1 to 0.4 mg/kg loading dose followed by an infusion of 0.12 mg/kg/h and titrated in 0.01 mg/kg/h increments. Target aPTT levels were 1.5–2.5 times baseline values. Availability of lepirudin is currently limited.

The shorter half-life of bivalrudin (∼25 min) makes this agent more attractive compared to the longer half-life of argatroban (40 min) and lepirudin (78 min). Half-life may be increased in renal failure as roughly 20% is renally cleared while the remainder is degraded by proteases. Neonates compared to older children have more rapid clearance of bivalrudin and a lower average serum concentration than older children (72). Bivalrudin use and target aPTT and dosing is variable in reported case series of pediatric ECMO patients (72–74). Pediatric reports have used either no bolus or a small bolus of 0.5 mg/kg loading dose followed by an infusion of 0.05–0.15 mg/kg/h and targeting aPTT 1.5–2 times baseline (74–76). Others report a lower bolus 0.05–0.5 mg/kg loading dose followed by an infusion rate of 0.03–0.3 mg/kg/h and targeting aPTT 1.5–2.5 times baseline (54, 76). Ranucci and colleagues used bivalrudin in post-cardiotomy pediatric ECMO patients and reported less total blood loss and decreased transfusion needs (75). Direct thrombin inhibitor use is becoming standard in some centers, although little complete data on safety and efficacy is available in the literature except for single site reports.

Unlike UFH, direct thrombin inhibitors do not provide inhibition to the contact pathway which contributes to thrombus formation on ECMO (77). Safety and dosing concerns as well as lack of reversibility make direct thrombin inhibitors less attractive in the neonatal ECMO population as a first-line agent without additional systematic study.

Antiplatelet Agents

Platelet activation on ECMO is well-described however use of antiplatelet agents (aspirin, dipyridamole, clopidogrel) is rare (49). Experience from pediatric ventricular assist device (VAD) patients suggests that there may be utility in adding antiplatelet agents for anticoagulation. In the Berlin EXCOR Investigational Device Exemption trial the guideline for anticoagulation included use of aspirin, dipyridamole, and enoxaparin or warfarin (78). Although still substantial, pediatric VAD patients have decreased bleeding complications compared to pediatric ECMO patients and direct treatment comparisons to the neonatal ECMO population should not be made. In addition, thrombocytopenia is more pronounced in the neonatal ECMO population compared to older children. Neonates are at the highest risk for intracranial hemorrhage therefore antiplatelet agents are rarely used. This is another area in need of specific evaluation. Antihemostatic medications are shown in **Table 1**.

Circuit Modifications

In an attempt to mitigate the bleeding and thrombotic effects of ECMO, circuit modifications have been developed including surface modifications. Heparin-coated circuits are associated with reduced platelet, leukocyte and coagulation activation and decreased thrombin generation (79). Heparin-coated circuits were used by 59% of ECMO center respondents in a multicenter survey of ELSO centers (49). Nitric oxide embedded surfaces are also under development and are associated with local antiplatelet properties preventing platelet adhesion (80). Finally, modifications to the membrane oxygenator material and coating have also been made to decrease thrombotic risk. Newer generation oxygenators are made with polymethylpentene or polypropylene hollow fibers which are hydrophobic and allow gas exchange without allowing blood or protein absorption (80). The efficacy of surface coatings during prolonged ECMO runs is also unknown.

TABLE 1 | Antihemostatic agents. ATIII is antithrombin III, HIT is heparin induced thrombocytopenia, cAMP is cyclic adenosine monophosphate, ADP is adenosine diphosphate.

Drug	Mechanism of action	Onset of action	Half-life	Excretion	Pro	Con
Unfractionated Heparin	Potentiates the action of antithrombin III and inactivates thrombin (inactivates factors IXa, Xa, XIa, XIIa, and plasmin) and prevents the conversion of fibrinogen to fibrin	Immediate	Dose and age dependent: median 1.5 h, shorter in premature neonates	Renal, at therapeutic doses elimination occurs rapidly via non-renal mechanisms	Low cost, short half life, reversible	Variable patient response, variablility in activity, reliance on ATIII, HIT
DIRECT THROMBIN INHIBITORS						
Bivalrudin	Direct thrombin inhibitor	Immediate	25 min	Proteolysis 75–80%, Renal 20–25%	Not dependent on ATIII, inhibits free and bound thrombin, predictable dose effects, Used in HIT	No antidote, no inhibition to contact pathway
Argatroban		Immediate	39–51 min	Hepatic		No antidote, no inhibition to contact pathway
Lepirudin		Immediate	80 min	Renal		No antidote, no inhibition to contact pathway, unavailable
ANTIPLATELET AGENTS						
Aspirin	Irreversibly inhibits cyclooxygenase-1 and 2 enzymes which results in decreased formation of prostaglandin precursors and inhibition of thromboxane A2	Immediate release, non-enteric coated platelet inhibition within 1 h	Oral: Plasma concentration 15–20 min, 3 h at lower doses	Renal	Familiarity of use	Gastritis, normal platelet function only returns when new platelets are released, Reye syndrome with prolonged high dose aspirin
Dipyridamole	Inhibits the uptake and metabolism of adenosine in platelets, endothelial cells and erythrocytes, inhibits platelet cAMP	Peak plasma concentrations ~2 h	Oral tablets: Biphasic; initial half life 40–80 min and terminal half life 10–12 h.	Hepatic	Mediates coronary vasodilation	Variable absorption from gastrointestinal tract, headache, vasodilation
Clopidogrel	Irreversible blockade of the ADP receptor on the platelet surface	Dose dependent; 300–600 mg loading dose onset within 2 h, smaller doses within second day of treatment	6-8 h	Hepatic		Bleeding, decrease in white blood cell count, irreversibly inhibits platelet aggregation, normal platelet function only returns when new platelets are released

ANTICOAGULATION MONITORING

Anticoagulation monitoring is extremely variable and remains controversial in ECMO patients (49). Assessing coagulation in critically ill neonates is complex and limited by inability to standardize testing across laboratories. Center specific anticoagulation protocols have been developed with mixed results and the ideal monitoring tool is unclear. Almost 97% of centers reported using the ACT with many centers sending additional anticoagulation testing. There is no widely accepted gold standard in anticoagulation and tests developed *in vitro* may not always represent *in vivo* phenomena. While anticoagulation monitoring is complex, the number of tests and frequency of testing should be determined based on the individual patient's needs and expertise at each center.

Activated Clotting Time (ACT) Values and Limitations

The ACT is available in real time and measures the time for whole blood to clot when activated by kaolin, celite or glass beads. ACT is a global functional test of hemostasis and is low cost. ACT is prolonged with anticoagulant use but can also be prolonged by hemodilution, hypothermia, decreased coagulation factor levels, elevated d-dimer, hypofibrinogenemia and thrombocytopenia. These conditions could overestimate heparin effect (16, 31). ELSO guidelines suggest a target ACT of 180–220 in uncomplicated ECMO patients.

Activated Partial Thromboplastin Time (APTT)

The aPTT is the time for recalcified, citrated, platelet poor plasma to clot when activated with an intrinsic pathway activator. Baseline aPTT is prolonged in neonates and aPTT levels are affected by coagulation factor deficiency, hyperbilirubinemia, hyperlipidemia, anti-phospholipid antibodies and elevated C reactive protein. Variances in laboratory methods for measurement between sites also complicates aPTT interpretation.

Anti-factor Xa Concentration Assay

Anti-Xa assay measures the inhibition of factor Xa by heparin in plasma. This test is more specific to the assessment of heparin effect because it is not affected by other coagulation proteins or platelets. Anti-Xa measures the UFH-ATIII complex levels not the UFH concentration. Some laboratories add ATIII to their Anti-Xa assays to normalize the ATIII levels. In neonatal patients with lower ATIII the addition of ATIII to the assay can significantly impact the results. So, for neonates Anti-Xa assays without added ATIII are preferable. However, levels can be affected by elevated hemoglobin level, plasma free hemoglobin, lipids, and bilirubin. More centers are using Anti-Xa assays as part of their anticoagulation protocols and most target levels 0.3-0.7 IU/mL (54). Anti-Xa assay has a better correlation to UFH dose than ACT to UFH dose (81). But, while Anti-Xa assays may provide advantages over other laboratory testing this value alone cannot be used to determine hemostatic potential and a multifactorial approach is needed.

TEG or ROTEM Guided Algorithm

Global assays of coagulation measure the viscoelastic properties of blood and can provide information on clot dynamics and fibrinolysis. Like the ACT, thromboelastography (TEG) and rotational thromboelastography (ROTEM) can be performed in real time which would be a major advantage. Unfortunately, many centers do not have these capabilities. These assays use an activator Kaolin or tissue factor and are affected by thrombocytopenia and coagulation factor deficiencies. TEG can detect deficiencies in hemostasis throughout the coagulation cascade and provide information regarding fibrinolysis. The measurements of TEG can provide information about initial clot formation (R time), clot acceleration (α angle), maximum clot strength (MA), and fibrinolysis (Ly30) (**Figure 2**). Therapeutic ranges in the neonatal population are not well-established but recent studies have attempted to determine optimal values to minimize bleeding and thrombosis (82).

Novel Global Assays

Novel global assays of coagulation may have an application in the neonatal ECMO population. Clot formation and lysis assay (CloFAL) a global measure of fibrinolysis, global fibrinolytic capacity (GFC) in whole blood, and the thrombin generation assay (measured by calibrated automated thrombogram-CAT) are all novel assays that have been applied in the research setting and have not been applied clinically to the ECMO population. The CAT seems promising because this plasma-based assay can be performed with and without platelets and may give important information about thrombin generation and risk of bleeding and thrombosis.

Different combinations of laboratory monitoring have been proposed with mixed results. Initial reports suggested decreased blood product use, decreased hemorrhagic complications, and increased circuit life in a pediatric population of ECMO patients after initiation of a comprehensive monitoring protocol (83). However, others have reported no difference in outcomes when comparing a complicated vs. simple monitoring strategy (84). In the era of increasingly complicated patients, using only one anticoagulation laboratory test is likely ill-advised but the frequency of testing and ideal combination of anticoagulation monitoring tests is still unclear in the neonatal ECMO population. The impact of iatrogenic blood loss is especially concerning in the neonatal population and evidence comparing the different anticoagulation measurements with the risk of blood loss is lacking. Use of one measure with whole blood and one with plasma effect may seem a reasonable approach.

MANAGEMENT

Bleeding

Bleeding events occurred in 77% of the neonatal cardiac patients and 60% of the neonatal respiratory patients in the BATE study and were associated with increased mortality (3). Management of bleeding depends on the site of bleeding and primary cause. Initial management includes decreasing anticoagulant dose and using blood product replacement based on known deficiencies (i.e., platelet transfusion for thrombocytopenia). Target levels

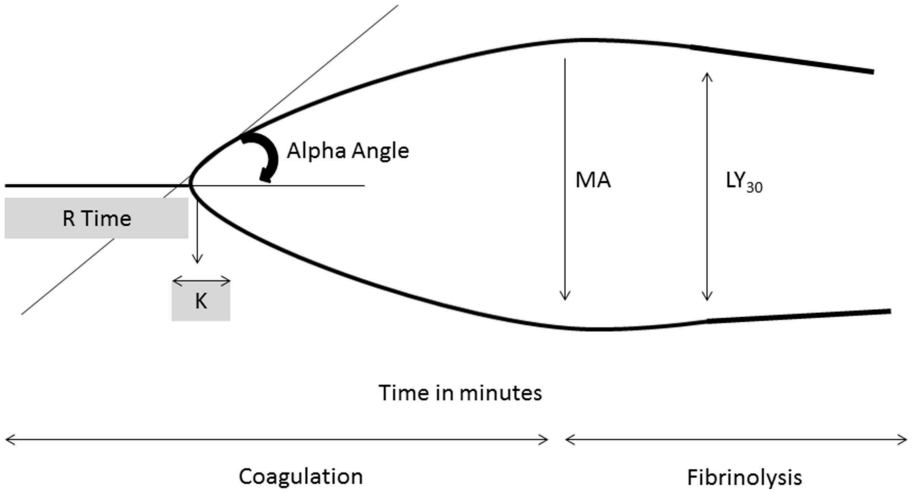

FIGURE 2 | Thromboelastography tracing with key parameters. R time, time of latency from start of test to initial fibrin formation; K, time taken to achieve a certain level of clot strength (amplitude of 20 mm); α angle (degrees), measures speed at which fibrin build up and cross linking takes place, rate of clot formation; MA, represents the strength of the fibrin clot; LY30 (%), percentage decrease in amplitude at 30 min post MA and gives measure of degree of fibrinolysis.

for hemoglobin, platelets, and fibrinogen may be changed in the setting of bleeding. In addition, acquired VWF deficiency and FXIII deficiency should be considered in bleeding patients with adequate fibrinogen and platelet counts. Cessation of anticoagulant use (mainly heparin) has also been employed, but the lower ECMO flow rates in neonates may make risk of circuit thrombosis higher than in older children and adults.

Antifibrinolytic agents like aminocaproic acid and tranexamic acid have been used to manage surgical site bleeding in pediatric patients. In pediatric ECMO patients, aminocaproic acid was associated with decreased incidence of surgical bleeding without an increase in thrombotic events (84). Tranexamic acid use was associated with decreased postoperative blood loss in infants with congenital diaphragmatic hernia repair while on ECMO (85).

Recombinant activated Factor VII (rVIIa) and Prothrombin Complex Concentrate (PCC) have been used to treat severe refractory bleeding on ECMO in adult and pediatric patients. rVIIa forms complexes with tissue factor and binds to platelet surfaces to generate thrombin and is given in doses of 40–90 ug/kg intravenously and may be repeated every 1–4 h in repeated doses (54). Reports of decreased bleeding and reduced need for transfusion must be balanced with reports of fatal thrombosis (86–88). PCC contains factor II, VII, IX, and X and some contain protein C and S and doses of 25–50 IU/kg have been used in pediatric cardiac surgical patients (89). An adult case report describes fatal circuit thrombosis when a man was treated with rVIIa and PCC for refractory bleeding (90). rVIIa and PCC needs additional study for treatment of severe refractory bleeding during ECMO before recommendations can be made in neonates.

Thrombosis

Thrombotic events were recorded in 32% of neonates on ECMO for respiratory indications and 44% of neonates on ECMO for cardiac indications in the BATE study (3). Thrombus formation, reportedly occurs during periods of low ECMO flow, at sites of stasis or turbulent flow, and during periods of inadequate anticoagulation (56). Thus, management first involves avoiding these states to prevent thrombosis. If thrombus formation has already occurred, then changing of circuit components may be necessary. Anticoagulation targets may be modified and if thrombotic events are ongoing or HIT is suspected then an alternate anticoagulant should be considered.

Transfusion Thresholds

The optimal threshold for transfusion of packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate are unknown with a paucity of data to guide clinical decision-making. Thresholds vary by center, location of ECMO care, and by clinical scenario. Multiple reports suggest that increased transfusion volume is associated with increased mortality (91, 92). Platelet transfusion thresholds are variable and volume of platelet transfusion is associated with mortality (26). While most centers focus on platelet count as the transfusion trigger, there is little to no data on platelet activity and associated platelet count in neonatal ECMO. Studies evaluating such associations and evaluating restrictive transfusion strategies are needed to guide therapy.

FUTURE STEPS

Additional Circuit Modifications

Research to develop fluid-repellent surfaces has been ongoing. This technology has been used to coat medical devices in the laboratory and in an animal model but has not been applied to the clinical setting (79). Endothelialization of ECMO surfaces via different techniques is another promising strategy currently being studied to inhibit thrombogenesis (79). Development of ECMO circuit modifications to prevent thrombosis and avoid bleeding associated with systemic anticoagulation could prevent many of the complications seen during ECMO.

Targeted Animal Studies

Factor XII-mediated activation and coagulation may contribute to thrombosis with biomaterial contact (92). Two studies in an animal model suggest that factor XII inhibition (via a monoclonal anti-factor XIIa antibody and a FXII inhibitor) decrease arterial and venous thrombus formation on ECMO but do not increase the rate of bleeding. Thus, this targeted therapy could decrease thrombotic risk without increased risk of bleeding and avoidance of systemic anticoagulation (92, 93).

Phenotyping and Genomics

One of the most perplexing aspects of ECMO is the fact that some patients with similar profiles, ECMO equipment, anticoagulation protocols and monitoring results bleed while others clot and others have neither complication. These facts suggest that individual variability may be important aspects in eliminating thrombotic risk and events. Genetic testing and variation in clotting and bleeding risk has been well-reported in multiple disease processes. In 1993, small endogenous nucleotides which were termed microRNAs (miRNAs) were identified as post-transcriptional regulators of gene expression. Further investigations have demonstrated that miRNAs are regulators of many biologic processes, including hemostatic function (94). miRNAs have been identified which affect many hemostatic factors in the coagulation cascade such as protein C and S production, tissue factor, platelets, fibrinogen and others. They have been shown to be associated with conditions of thrombosis, such as stroke and ischemic heart disease. Platelets, adams13, tissue factor, fibrinogen and proteins regulating fibrinolysis have all been suggested as important players in hemostasis during ECMO (95). The changes in miRNA production related to the hemostatic system on exposure to ECMO has not been evaluated, but establishing what changes in miRNA occur with ECMO may provide new data to develop these as biomarkers for thrombotic risk or even therapeutic intervention. The ability to determine what patients are most at risk for thrombosis may help tailor anticoagulation management, decrease or eliminate need for anticoagulation and improve outcomes. While promising, the connection between genetic variation and phenotypic expression in critically ill neonates on ECMO is not well-understood and needs further study.

CONCLUSION

Optimal anticoagulation in neonatal ECMO patients remains an enigma. Bleeding and thrombosis are common and involve multiple alterations in hemostatic factors. Neonatal anticoagulation is challenging due to the developmental hemostatic system, heterogeneous disease processes that lead to initiation of ECMO, variability in anticoagulation strategies and lack of high-quality evidence to direct practice. UFH remains the most commonly used systemic anticoagulant but there have been increasing reports of DTI use. Comprehensive assessments of hemostasis using more than one of the currently available assays (ACT, anti-Xa, PT, aPTT) is still variable across centers and suboptimal in isolation because these tests do not take thrombin generation or platelet contribution to clot formation into account. Global assays (TEG/ROTEM, CloFAL, CAT) may improve our anticoagulation management but still need to be studied in the neonatal population. A combination of whole blood and plasma assessment has also been suggested as optimal for anticoagulation management but no gold standard algorithm has been universally developed or accepted. Standard treatments for bleeding and thrombosis are lacking and case reports and expert opinion guides management. Optimal transfusion thresholds are unknown. Pragmatic multicenter trials randomizing neonates to restrictive vs. standard transfusion therapies are needed with well-defined endpoints. Detailed observational studies focused on sites with low neonatal rates of thrombosis and bleeding should be considered in order to compare anticoagulation algorithms. Then, with a protocol to standardize circuitry, transfusion thresholds, laboratory testing and clearly defined thrombotic and bleeding complications a trial to compare "best practice" anticoagulation strategy should be initiated. Finally, ongoing studies to develop new circuit modifications and targeted thrombotic factor inhibition are promising. Multicenter research focused on standardized anticoagulation protocols, monitoring and treatment are needed to improve our care of neonatal ECMO patients. Genomic investigation offers an exciting new area of research to achieve the "Holy Grail" of eliminating thrombotic risk and need for anticoagulation during extracorporeal support.

AUTHOR CONTRIBUTIONS

KC wrote the manuscript draft and finalized changes after revision and approval. KM and HD revised, read, and approved final manuscript.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Surgical Expertise in Neonatal Extracorporeal Membrane Oxygenation (ECMO): A Single Center Experience

Francesco Macchini[1], Antonio Di Cesare[1], Anna Morandi[1], Martina Ichino[1], Genny Raffaeli[2,3], Federica Conigliaro[2,4], Gabriele Sorrentino[2], Simona Neri[5], Fabio Mosca[2,3], Ernesto Leva[1] and Giacomo Cavallaro[2]*

[1] Department of Pediatric Surgery, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [2] Neonatal Intensive Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [3] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy, [4] Betamed Perfusion Service, Rome, Italy, [5] Pediatric Anesthesiology and Intensive Care Unit, Department of Anesthesia and Critical Care, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

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***Correspondence:**
Francesco Macchini
francesco.macchini@policlinico.mi.it

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Introduction: The surgical technique for peripheral cannulation aimed at providing extracorporeal membrane oxygenation (ECMO) is well described. Training methods for surgeons still need proper standardization, especially in newborn patients. This study aims to evaluate the surgical training outcomes of a neonatal ECMO team.

Materials and Methods: A 4 year training program (2014–2018) was developed to achieve the skills in the surgical technique for neonatal veno-arterial ECMO. Surgeons with experience in neonatal and vascular surgery were selected for the training. The training consisted of educational sessions, high-fidelity simulations, *in vivo* swine model procedures, international fellowship, and periodical simulations. The preliminary clinical experience in surgical neonatal ECMO management (2016-present) was analyzed by recording the following data: indications for ECMO and patients' data; effectiveness of cannulations (number; perioperative complications of cannulation; major surgical events during ECMO); efficacy of decannulation (number and perioperative complications).

Results: 12 neonates (5 females) fitted the ELSO criteria for ECMO. Nine newborns were affected by CDH; 1 by H1N1 flu-related pneumonia; 1 by meconium aspiration syndrome and one by Respiratory Syncytial Virus related bronchiolitis. Mean weight at cannulation was 3,281 g (range 2,330–3,840 g); mean gestational age was 36 weeks. No procedure was aborted, and no intra-operatory mortality was recorded. Mean operative time was 86 ± 30 min. The caliber of the carotideal cannulas ranged from 8F (8 patients) to 10F (2 patients); the caliber of the jugular cannulas were: 8F cannula (2 patients), 10F (6 patients), and 12F (2 patients). Four complications occurred: a case of air in the circuit, two cases of azygous vein cannulation and a partial dislocation of the venous cannula during the daily care maneuvers. All of them were promptly recognized and successfully treated. The mean ECMO duration was 7.1 ± 4.2 days (range 2–16 days). Seven patients (78%) were decannulated effectively. Mean decannulation time was

53 min (range 45–80 min). No complications occurred during the decannulation process. No ECMO–related deaths were recorded.

Conclusions: Neonatal respiratory ECMO still represents a challenge. Experienced neonatal surgeons can manage the neck vascular cannulation. The codified procedure must be adhered to after appropriate training and following a proper learning curve.

Keywords: neonatal, child, ECMO, surgery, training

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is an advanced life support therapy for life-threatening pulmonary and cardiac diseases in children (1). ECMO is a high-risk procedure and requires quick and effective decisions based on well-established knowledge as well as technical and organizational proficiency in an emergency setting (2). Despite the advances in equipment and technology, the adoption of standardized protocols and preventive strategies, and the increasing experience of providers, neonatal ECMO still remains a challenging procedure, due to its intrinsic high morbidity and mortality (3).

Accordingly, the Extracorporeal Life Support Organization (ELSO) strongly supports specific programs for education and training in order to improve patients' outcomes (4). Multidisciplinary team training has been previously described in the neonatal and pediatric ECMO setting (5, 6). Simulation-based cannulation curricula have been reported in the cardiac, pediatric setting (7).

Although the surgical technique for peripheral VA-ECMO cannulation is well-described (8), surgical training methods to acquire and master the procedure still need standardization.

Regarding neonatal respiratory ECMO, the most common indications are congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), pulmonary hypertension (PPHN), sepsis, and respiratory distress syndrome (RDS). The veno-arterial (VA) cannulation is the selected method in most Neonatal Intensive Care Units (NICU) (8).

ECMO-related mortality is still high in neonates, with only a 73% survival to hospital discharge (SHD) according to the ELSO registry reports (9) and a 57% according to a single center experience (3).

Mortality is particularly high for CDH, which have an SHD rate of 50%, as compared to MAS (92%) and PPHN (73%) (9). An early start of ECMO within 24 h after birth and a reduced time of ECMO duration (<7 days) seems effective in leading to SHD independently of other factors (3).

Next, with regards to survival rates, efforts are needed to be shifted toward the improvement of ECMO patients' outcomes (10).

The overall complication rate of ECMO in newborns is 49% (9). The ELSO registry reports 54.5% of surgical complications, with hemorrhagic ones accounting for 26.2%, mechanical ones for 16.2%, pulmonary ones for 10.6% and cardiovascular ones for 1.5% (9).

The aim of this study is to evaluate the clinical impact of surgical team training, in terms of technical performance of VA peripheral cannulation and decannulation in newborns treated by a single team of neonatal surgeons since the establishment of a new ECMO program.

MATERIALS AND METHODS

We conducted a retrospective, single-center, cohort study at the NICU of the Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan, Italy. No modifications were made to the standard of care for newborns requiring respiratory ECMO. Ethics committee approval was not required for this observational retrospective study on a small series of patients. Parents gave written informed consent for the publication of this series in accordance with the Declaration of Helsinki.

Training Curriculum

The ELSO guidelines, the "ELSO Redbook" and the "ELSO ECMO Specialist Training Manual" were selected as reference guidelines for our Institute (4, 8, 11).

The VA cannulation was selected as the preferred modality in our Institute for neonatal respiratory ECMO.

A 4-year training program (September 2014–2018) was delivered to achieve surgical skills in neonatal VA ECMO. The following multistep training program was designed for the whole ECMO team to reach full autonomy. Only surgeons with at least 2 years of experience and more than 100 procedures of neonatal and vascular surgery were selected for the training after being evaluated by the head of Department. The surgical training was supported by the implementation of a larger multi-disciplinary training program (5). As previously reported, the training process started with the delivery of educational material, attendance to national and international courses, and observership programs at ECMO referral centers. Next, with regards to the educational session, hands-on training was delivered through "wet labs," animal-based, and mannequin-based high-fidelity simulation sessions.

During the whole training process, attention was focused on both technical and behavioral factors that would impact the patient's outcome. Each session ended with extensive debriefing and immediate feedback.

The "wet labs" aimed to familiarize the participants with equipment and procedures. They consisted of hands-on training on a closed-loop ECMO circuit filled with saline. The animal laboratory consisted of isolating and cannulating neck vessels on anesthetized piglets to start a VA ECMO. During the ECMO

run, all members of the team, including pediatric surgeons, were involved in routine practices. According to the participants, this step appeared more similar to reality and crucial from a surgical point of view to develop adequate technical skills.

High-fidelity simulation sessions were performed with a neonatal mannequin (SimNewB® Laerdal). Tubes were inserted in the right side of the neck and distally connected to a reservoir bag, filled with fake blood.

Once the surgeon in training had completed the whole program, having effectively cannulated at least 10 piglets, they were considered for the clinical surgical approach (5). Simulations were carried on systematically even after treating the first patients in order to maintain a high level of technical ability.

Surgical Procedure

VA-ECMO was offered, based on ELSO criteria (11). Based on our institutional protocol, we considered neonates weighing over 2 kg and with a post-gestational age of 34 weeks (12) as eligible for ECMO.

Vascular access was obtained by a right neck incision and cannulation of the internal jugular vein and carotid artery. Cannulation was always performed in a dedicated and isolated room of the NICU. Adequate exposure of the neck was obtained by putting a small roll transversely beneath the shoulders of the neonate and by a minor contralateral rotation of the head. Deep sedation/anesthesia with muscle relaxation was required to prevent spontaneous breathing. After a transverse cervical incision, a complete exposition of the vessels was obtained. Titration of heparin occurred before placing the cannula every 3 min following boluses of 25 IU/kg, to achieve an activated clotting time of 220–250 s. The average dose was 50 IU/kg, while the maximum cumulative dose was 100 IU/Kg.

Cannula selection occurred after cut down with direct inspection of the vessels; the biggest caliber of both arterial and venous cannulas was chosen according to the patient's vessel sizes, maximal blood flow needed and the pressure drop of the cannula itself. Therefore, the Single Lumen Venous (8F, 10F, 12F, or 14F) and Arterial (8F, 10F, or 12F) cannulas (Bio-Medicus®, Medtronic), heparin-based coated (Carmeda® BioActive Surface), were selected for our neonates. Non-absorbable braided 4.0 ligatures were slid around the vessels above and below the cannulation site (**Figure 1A**). The cephalic ends of the vessels were ligated. The vessels were opened and the cannulas placed. The venous cannula was inserted for 6–9 cm while the arterial one for 3–5 cm, according to the size of the newborn (**Figure 1B**). Cannulas were then connected to the ECMO circuit, carefully avoiding air embolism (**Figure 1C**). Chest X-ray was performed to verify the position of the tip of the cannula after ECMO support was initiated, and minor cannula position adjustments were made (**Figure 1D**). Intraoperative echocardiography with Doppler flow was implemented to assess the position of the tip of the cannula in the right atrium. Once the correct position was confirmed, the cannulas were secured to the muscle insertions and to the retro-auricular skin to prevent dislocation.

At the time of decannulation, ligation of the neck vessels was the chosen option in our Center (8).

Surgical Outcome

To evaluate the impact of the surgical expertise on ECMO cannulation, we retrospectively analyzed our case-series from the establishment of the ECMO program (March 2016) to present (March 2019). We retrieved the following data: indications to ECMO and demographic data; effectiveness of cannulation; caliber of venous and arterial cannulas; perioperative complications of cannulation; major surgical events during ECMO; effectiveness of decannulation and perioperative complications of decannulation.

As reported by the ELSO Registry, complications are classified as (1) mechanical (oxygenator failure, raceway rupture, other tubing rupture, pump failure, circuit air, cannula-related problems); (2) hemorrhagic (cannulation site bleeding, surgical site bleeding); (3) cardiovascular (CPR required, cardiac arrhythmia, tamponade); (4) pulmonary (pneumothorax, pulmonary hemorrhage); (5) infectious (9). We considered only the surgical complications.

The severity of every complication was assessed according to the Clavien-Dindo Classification of Surgical Complications (**Table 1**). It is a morbidity scale based on the therapeutic consequences of complications, that constitutes a simple, objective, and reproducible approach for comprehensive surgical outcome assessment (13).

RESULTS

Three neonatal surgeons completed the training process after 3 years and were considered ready to start with the first patient. In the following year, they continued with the simulation sessions while other surgeons were selected to start the training program. Within the study period, 12 neonates (5 females) fitted the ELSO criteria for ECMO. Nine newborns were affected by CDH; 1 by H1N1 flu-related pneumonia; 1 by meconium aspiration syndrome and one by Respiratory Syncytial Virus (RSV) related bronchiolitis.

The main characteristics of the population are summarized in **Table 2**.

Mean weight at cannulation was 3,281 g (range 2,330–3,840 g); mean gestational age was 36 weeks. No procedure was aborted, and no intra-operatory mortality was recorded. Mean operative time was 86 ± 30 min (from draping to the skin closure including the external fixation of the cannulas and the radiological check). The caliber of the carotideal cannula ranged from 8F (8 patients) to 10F (2 patients); the caliber of the jugular cannula showed a wider range: 8F (2 patients), 10F (6 patients), and 12F (2 patients).

As for the complications, two grade I and two grade III complications occurred (**Table 3**). Among Grade I complications, a 30-day old male affected by RSV infection presented microbubbles of air in the circuit immediately after connection. The amount of air resulted minimal so that it was promptly fixed through the circuit, without any clinical consequence. The second one, a 1 day old male (GA 39 w; BW 3,280 g) with a right CDH, was cannulated with 8F arterial and 10F venous cannulas. The ECMO support was initiated, but the maintenance of adequate blood flow was impaired by worsening

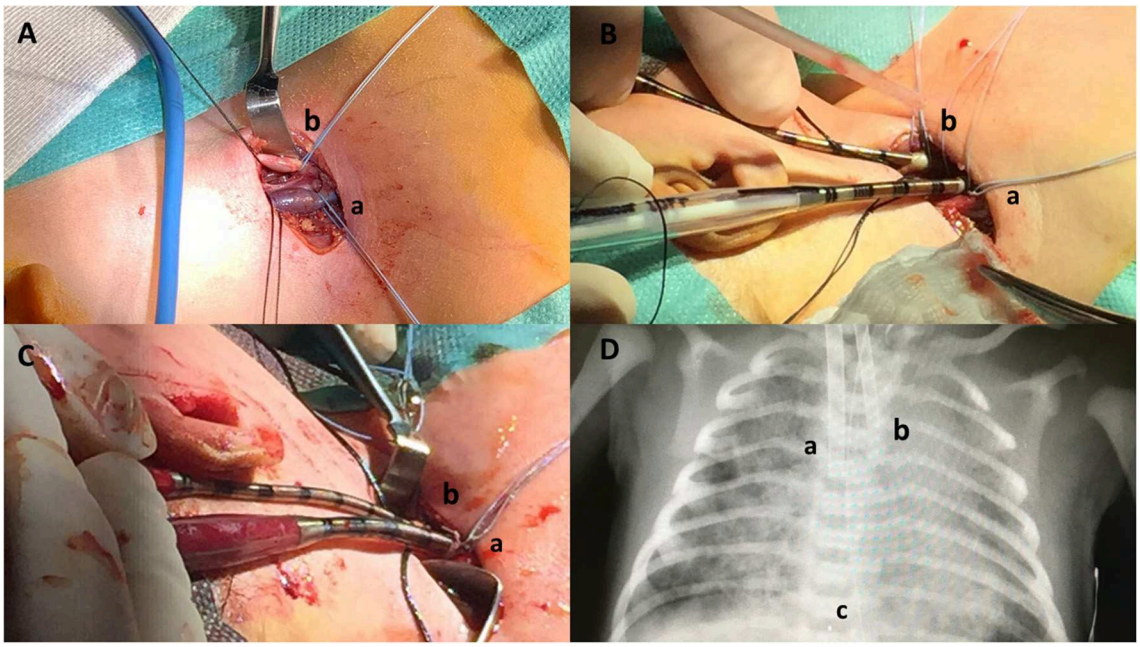

FIGURE 1 | Neonatal veno-arterial Surgical cannulation site in the neck for respiratory ECMO: surgical steps. **(A)** Neck skin incision and isolation of internal jugular vein **(a)** and carotid artery **(b)**. **(B)** Vascular cannulation. Drainage cannula (10 French) inserted in the jugular vein **(a)**, inflow cannula (8 French) inserted in the carotid artery **(b)**. **(C)** ECMO start. Drainage cannula (10 French) inserted in the jugular vein **(a)**, inflow cannula (8 French) inserted in the carotid artery **(b)**. **(D)** Chest X-ray. Drainage cannula (10 French) inserted in the jugular vein **(a)**, inflow cannula (8 French) inserted in the carotid artery **(b)**, and cannula tip **(c)**.

TABLE 1 | Classification of surgical complications grades definition (modified from Clavien-Dindo Classification).

Grade I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention Grade III-a: intervention not under general anesthesia
Grade III-b	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
Grade IV-a	Single organ dysfunction (including dialysis)
Grade IV-b	Multi-organ dysfunction
Grade V	Death of a patient

‡*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks (TIA); CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.*

drainage pressure. Despite the administration of multiple fluid boluses, we couldn't reach a satisfactory blood flow support. Echocardiography demonstrated the correct position of the arterial cannula, but the venous cannula was not visualized in the superior vena cava or the right atrium, thus raising the suspicion of azygous vein cannulation. Lateral X-ray of the thorax confirmed the diagnosis of cannula displacement. By modifying the head position, we could reach a 100 ml/kg blood flow, until the decannulation 3 days later.

As for grade III complications, a left CDH female (GA 36 w; BW 3,200 g) had a partial dislocation of the 10F venous cannula during the daily care maneuvers. The event was successfully treated, pushing the cannula back inside the jugular vein. ECMO support did not stop. The correct position of the cannula was subsequently confirmed by echocardiography. After this episode an increased level of attention was devoted to the securing of the cannulas.

The last complication occurred in a 1 day old male (GA 37 w; BW 2,530 g) with a right-sided CDH. A 10F venous cannula and an 8F arterial cannula were positioned without any difficulties. As in the previous patient with right CDH, we experienced high drainage pressure, which was not justified by the cannulation caliber and the clinical state of the neonate. Despite fluid therapy, repositioning of the head and multiple attempts to direct the venous cannula into the right atrium, we failed to support the neonate adequately. Consequently, caval cannulation via sternotomy was obtained on day 2 of life and ECMO was maintained for 16 days. The procedure was performed in association with a pediatric cardio-thoracic surgeon to offer the best multi-disciplinary approach.

No other minor or major complications were recorded during the procedure.

TABLE 2 | Population characteristics.

CDH	- Number of patients	9
	- Sex	Males: 5 Females: 4
	- GA (weeks)	36.5 ± 1.8
	- Birth weight (gr)	2.660 ± 383
	- Site	right: 3 left: 6
	- Defect size	B: 2 C: 5 D: 2
	- O/E LHR (%)	27 ± 17
	- Diaphragmatic patch (n pts)	7
	- Liver up (n pts)	9
	- Stomach up (n pts)	6
	- Age at ECMO (days)	8.5 (range 1–52)
	- Weight at ECMO (gr)	3.272 ± 632
	- ECMO duration (days)	6.6 ± 4.1
	- Age at CDH repair (days)	2.9 ± 1.9
	- Repair on ECMO (n pts)	3
H1N1 flu pneumonia	- Number of patients	1
	- Sex	Female
	- GA (weeks)	32
	- Birth weight (gr)	1.955
	- Age at ECMO (days)	53
	- Weight at ECMO (gr)	gr 3.310
	- ECMO duration (days)	12
Meconium aspiration syndrome	- Number of patients	1
	- Sex	Male
	- GA (weeks)	39
	- Birth weight (gr)	3.635
	- Age at ECMO (days)	3
	- Weight at ECMO (gr)	3.840
	- ECMO duration (days)	2
Respiratory Syncytial Virus bronchiolitis	- Number of patients	1
	- Sex	Male
	- GA (weeks)	34
	- Birth weight (gr)	2.400
	- Age at ECMO (days)	30
	- Weight at ECMO (gr)	2.850
	- ECMO duration (days)	6

Data are expressed as mean ± SD.

The mean ECMO duration was 7.1 ± 4.2 days (range 2–16 days). Seven patients (58%) tolerated the weaning trial of ECMO flow, and they were all decannulated effectively. Mean decannulation time was 53 min (range 45–80 min).

No intra-operative complications occurred during the decannulation process.

Finally, five patients survived to hospital discharge after ECMO treatment (42%). Among the causes of death of the other seven patients, none were ECMO–related. In the CDH population the survival rate was 22%.

DISCUSSION

ECMO is a well-established advanced life support therapy for critically-ill children with pulmonary or cardiac failure (1). It involves technically challenging procedures and extensive multidisciplinary coordination. Even with skilled providers, ECMO has significant risks of morbidity and mortality (3). Knowledge and routine training are essential to improve patient outcomes, as recommended by ELSO (4, 5).

TABLE 3 | Neonatal VA ECMO: classification of complications according to the Clavien-Dindo Classification.

Grade	**Cannulation**
I	2 Malposition Microbubble air in circuit
II	–
III	2 Malposition Dislocation
IV	–
V	–
Total (%)	4/12 (33%)

ECMO clinical specialists (CS) and technicians are the first line of defense in recognizing and responding to acute and potentially life-threatening complications. The ECMO-CS is defined as "the technical specialist trained to manage the ECMO system and the clinical needs of the patient on ECMO"; therefore, their ability to identify and appropriately react to a deteriorating patient is essential for optimal care. The education and training of the ECMO-CS are supported by ELSO, which requires the providers to complete didactics on circuit and patient emergencies (4).

While most centers rely on ECMO-CS to serve as first responders to circuit emergencies, there are no nationally established standards or certifications to provide ECMO care (2). Therefore, the CS, which may include surgeons, nurses, neonatologists, anesthesiologists, and perfusionists, may vary in training and experience depending on local institutional training standards.

As a result, there is wide variation amongst institutions in protocols used to address ECMO circuit emergencies (2).

Due to the different surgical approaches, ECMO for cardiac failure is generally managed by cardiothoracic surgeons with central cannulation, while ECMO for neonatal respiratory diseases is more frequently managed by pediatric surgeons with a neck approach. Respiratory diseases in newborns that may require ECMO include CDH, MAS, and PPHN. These conditions account for almost 75% of all neonatal respiratory ECMO cases. Other diagnostic categories that may constitute indications for ECMO are sepsis (10%) and RDS (5%) (14).

In addition, many Neonatal Departments treating children with pulmonary indications to ECMO are not equipped with pediatric cardiothoracic surgeons, so that different pediatric surgeons' teams have to be involved in the ECMO training and management. In particular, neonatal surgeons were identified

as suitable for the neonatal ECMO program in our Center. Only surgeons highly experienced in neonatal and vascular treatment were selected. A 4-year multi-step theoretical and practical training program was required. Only surgeons who completed the training program were considered suitable to manage the cannulation and decannulation procedures in newborns.

As previously described, according to most centers, a VA, as opposed to VV ECMO support, was employed for neonatal respiratory diseases (14).

According to our results, we believe that one of the keys of a successful ECMO cannulation in the neonatal period is based on the strict adherence to standardized surgical procedures. In our opinion, some techniques may help in increasing surgical effectiveness when applying a neck approach. Before surgery, the newborn has to be positioned supine, with neck extension under the shoulders and contralateral head rotation. This position must not be extreme in order to reduce the risk related to cannula progression and malposition at the end of the surgical procedure, when the newborn is placed back in a neutral position. A transverse cervical incision, approximately 3–4 cm in length to achieve a satisfactory exposure of the vessels, is made one finger's breadth above the clavicle over the lower aspect of the right sternocleidomastoid muscle. Direct handling of the vessels has to be minimized to avoid spasm. Finally, while connecting cannulas to the ECMO circuit, a member of the surgical team has to fill both ends of the tubes with saline to prevent air entrapment in the circuit, thus avoiding turbulences and embolism.

As for the decannulation procedure, a high degree of attention is required while managing the arterial cannula, as in newborns it is inserted in the carotid artery only for 3–4 cm and a spontaneous dislocation leading to major bleeding is not unlikely.

Although complications show decreasing trends over time, this therapy remains associated to a high percentage of morbidities and risks (14).

In our study, we decided to adopt a classification of surgical complications in order to make our results comparable to other series. We chose the Clavien-Dindo Classification because, even if it was designed for adults, it has been found to have high sensitivity for pediatric urology, oncology and also neonatal surgery. Its merit is that it moved the focus from the mere occurrence of complications to the grade of complication as a function of the resulting outcome (15).

Even in our preliminary series, complications occurred in 4/12 (33%) patients after cannulation.

In the first ones, two minor complications occurred (Grade I) and were managed without the need for pharmacological or surgical treatment. One of these complications consisted of air entrapment in the circuit, but the amount of air was minimal so that it was immediately fixed through the circuit, without any clinical consequence. Accurate filling of the connections between cannulas and ECMO circuit with saline may prevent such complications.

Clots may also be dangerous both for the circuit, leading to a mechanical obstruction, and the patient, with the risk of embolism. They represent the most common mechanical complication for neonatal respiratory and cardiac ECMO support (9). Clot development in the oxygenator, bridge, and bladder has decreased since 2000, while there has been an increased number in the "Other clots" category. Additional mechanical complications, such as air bubbles in the circuit and oxygenator failures, have been stable to decreasing over time (14). In our series, we did not experience any clot formation during cannulation time.

Also, two complications of medium severity occurred (Grade III), leading to surgery. However, in both cases, problems were effectively solved, with no need for ECMO interruption nor patient instability.

A special mention has to be given to one of the potential complications in the right CDH newborns. As described in a previous paper (16), misplacements of the venous cannulas were also recorded in group 2, with the tip located at the confluence of the azygous vein with the Superior Vena Cava (SVC).

Previous papers suggest that infants with right CDH experience higher morbidity and statistically borderline higher mortality than their left-sided counterparts (17).

Regarding ECMO, the anatomical distortion of the mediastinal vessels that develop as a consequence of right CDH is of particular concern. The combination of a leftward mediastinal shift, intrathoracic liver, and compression of the inferior vena cava (IVC) can perturb the orientation of the great vessels and interfere with venous cannulation. Correct diagnosis of this complication is not always easy, and signs may appear later in the course of ECMO. In our experience, a combination of impaired ECMO flow maintenance with increased drainage pressures, echocardiographic assessment, and cross-table lateral chest X-rays can help to confirm suspected azygous vein cannulation by demonstrating a posteriorly orientated venous cannula (18).

Direct cannulation of the right atrial appendage via sternotomy is an aggressive but feasible method to provide ECMO support in such cases, and may be the only available alternative. In such an occurrence, it may be advisable to seek the collaboration of a cardiothoracic team. Indeed, sternotomy is not frequently needed for respiratory ECMO and the availability of a multidisciplinary team may offer the best results.

The indication must be carefully evaluated according to the effectiveness of ECMO exchanges and the general conditions of the child. As previously suggested by Kuenzler et al., we agree that intraoperative ultrasound guidance can be effective in decreasing the ECMO catheter malposition rate and may prove to be a useful tool, especially in cases where an anatomical variance is suspected (19).

Furthermore, as previously mentioned, limited contralateral head rotation and neck extension may reduce the risks related to cannula progression and malposition at the end of the surgical procedure, when the newborn is placed back in a neutral position.

Our rate of surgical complications seems to be similar to other series (9). However, it is difficult to make a proper comparison because, as far as we know, other series considered surgical and medical complications together. We strongly recommend

adopting specific classifications for surgical complications, especially when evaluating the outcome of selected surgeries, such as the neonatal and oncological ones.

In our experience, SHD is lower than the mean value reported in the ECLS Registry Report 2019 (42 vs. 73%), especially considering the CDH population (22 vs. 50%). Nonetheless, no ECMO-related mortalities due to technical issues were recorded in our series. A possible explanation of the low survival rate may be found in the high number of severe CDH newborns in our series, as shown by the low O/E LHR. In fact, a Fetal Endo-Tracheal Occlusion (FETO) program is available in our center and therefore we frequently deal with severe conditions.

In the future, based on a larger population, we should evaluate SHD in different severity groups, according to pre-natal observed/expected lung-to-head ratio (O/E LHR), side and size of the defect.

Conversely, when considering the population other than CDH, the SHD was 100% in our population.

Despite the limited numbers, our results support the value of a standardized training program and a dedicated multidisciplinary team aimed to improve the management of severe cases.

In conclusion, neonatal respiratory ECMO represents a challenge even after prolonged dedicated training. Experienced neonatal surgeons can manage the neck vascular cannulation. The codified procedure must be adhered to after appropriate training and following a proper learning curve. This seems to provide adequate surgical skills, effective execution of ECMO in the neonatal period, and prompt intervention to manage the limited complications, with a positive impact on clinical prognosis.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FMa, GC, GR, AM, MI, EL, and FMo contributed conception and design of the review. FC, AD, SN, and GS collected and analyzed the data retrospectively. FMa, GC, GR, AM, and MI wrote the first draft of the manuscript. All authors contributed to manuscript critical revision, read, and approved the submitted version.

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REVIEW
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Neurocognitive Outcome After Treatment With(out) ECMO for Neonatal Critical Respiratory or Cardiac Failure

*Raisa M. Schiller and Dick Tibboel**

Department of Pediatric Surgery/IC Children and Child and Adolescent Psychiatry/Psychology, Erasmus MC-Sophia Children's Hospital, Rotterdam, Netherlands

Over the years, it has become clear that children growing up after neonatal critical illness are at high risk of long-term neurocognitive deficits that impact their school performance and daily life activities. Although the pathophysiological mechanisms remain largely unknown, emerging evidence seems to suggest that long-term neuropsychological deficits following neonatal critical illness are not associated with the type of treatment, such as extracorporeal membrane oxygenation (ECMO), but rather with underlying disease processes. In this review, neurocognitive outcome and brain pathology following neonatal critical respiratory and cardiac illness, either treated with or without ECMO, are described and compared in order to gain insight into potential underlying pathophysiological mechanisms. Putting these findings together, it becomes apparent that both children with complex congenital heart disease and children who survived severe respiratory failure are at risk of neurocognitive deficits later in life. Neurorehabilitation strategies, such as Cogmed working-memory training, are discussed. While prevention of neurocognitive deficits altogether should be strived for in the future, this is not realistic at this moment. It is therefore of great importance that children growing up after neonatal critical illness receive long-term care that includes psychoeducation and personalized practical tools that can be used to improve their daily life activities.

Keywords: ECMO (extracorporeal membrane oxygenation), Newborn, respiratory failure, circulatory failure, hippocampus

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****Correspondence:***
Dick Tibboel
d.tibboel@erasmusmc.nl

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) can be used as a lifesaving therapy in critically ill neonates with severe refractory respiratory and/or cardiac failure. As more and more of these patients survive to discharge (73% following respiratory illness and 42% after cardiac illness) (1), long-term outcomes become increasingly important. It has become clear that children growing up after neonatal critical illness are at high risk of long-term neurocognitive deficits that have a profound impact on school performance and daily life activities (2). Survivors are at risk of 'growing into deficit' as subtle brain injuries acquired at a young age only become functionally evident over time when demands on cognitive functioning increases (3). This phenomenon is nested within different developmental processes that occur in the brain [e.g., myelination, synaptic pruning, and neurogenesis (4)] during the period of critical illness.

The pathophysiological mechanisms underlying the long-term neurodevelopmental deficits remain largely unknown. Most likely, a complex interplay amongst different factors associated with the underlying disease (pharmacological), treatment and "iatrogenesis," further complicated by the child's genetic predisposition (5) and social economic status (6), determines a child's neurodevelopment. Emerging evidence seems to suggest that long-term neuropsychological deficits following neonatal critical illness are not associated with the type of treatment, such as extracorporeal membrane oxygenation (ECMO) (7), but rather with underlying disease processes, such as hypoxia-ischemia, stress, and neuroinflammation (2, 8, 9). However, whether this is similar between neonates with severe respiratory failure and neonates with cardiac anomalies remains largely unknown. Furthermore, whether brain alterations and its neurocognitive consequences are selective or generalized in these patients and differs between patients treated with and without ECMO is not yet clear.

In this review, long-term neurocognitive outcome and brain pathology following neonatal critical respiratory and cardiac illness, either in children treated with or without ECMO, will be described and compared. In light of this, potential common pathophysiological mechanisms across these patients will be explored. Finally, suggestions to improve long-term neurodevelopmental care, both through intervention and counseling, will be provided.

NEURODEVELOPMENTAL OUTCOME AFTER SEVERE RESPIRATORY FAILURE, TREATED WITH OR WITHOUT ECMO

There are relatively few studies that have compared outcome between ECMO and non-ECMO treated patients after severe respiratory failure (**Table 1A**). In one of the first studies comparing outcome between 7-year-old children treated with neonatal ECMO to children treated with conventional management (CM) in response to severe respiratory failure, global cognitive loss, poor spatial skills, difficulties with reading comprehension and deficits in visual and verbal memory were found equally in both groups (12). Madderom et al. (11) directly compared CDH survivors treated with ($n = 16$) or without ECMO ($n = 19$) on IQ, school performance and sustained attention at 8 years of age. Mean IQ significantly differed between the ECMO group [91.7 (19.5)] and non-ECMO group [111.6 (20.9)], but was normal in both groups compared to the general population. The proportions of children with above average, average and below average IQ did not differ significantly between both groups ($p = 0.052$), but there was a trend toward more children with below average IQ in the ECMO group compared to the non-ECMO group. In both groups, however, twice as many children needed extra help in school compared to healthy peers and both groups showed significantly impaired sustained attention compared to healthy peers (11). The difficulties experiences in school by these children therefore seem to be largely independent of IQ.

Indeed, when elaborate neuropsychological assessment was used to compare outcome between 8-year-old survivors of congenital diaphragmatic hernia (CDH) survivors treated with neonatal ECMO (CHD-ECMO), CDH survivors treated without ECMO (CDH-non-ECMO) and survivors of other types of severe respiratory failure treated with neonatal ECMO (ECMO-other), lower IQ in the CDH-ECMO group was found compared to the other groups. However, deficits in sustained attention and in verbal and visuospatial memory (both immediate and delayed recall) were found across all three groups, while other neuropsychological outcomes were normal (9). In all groups, the observed attention and memory problems were more severe than expected based on their IQ, indicating specific impairments in these domains that were independent of underlying diagnosis or ECMO treatment (9).

Behavioral problems have been compared between neonatal ECMO vs. non-ECMO treated survivors of respiratory failure as well. McNally et al. (12) found an increased risk of behavioral problems among 7-yearold children who had been treated conventionally, in particular hyperactivity. Madderom et al. compared self-perceived competence at 8 years of age and found no differences between groups. Furthermore, scores were similar to the general population. Behavioral problems did not differ between groups either, but the groups studied were small which makes the results less definitive (11). Future studies with large sample sizes are needed to gain a better understanding of how ECMO may or may not negatively influence behavioral outcome.

In recent years, studies have assessed long-term brain pathology and brain-function associations in these patient groups as well. Cooper et al. (10) assessed cognitive functioning and brain outcomes between 12-year-old survivors of acute hypoxemic respiratory failure (AHRF) who had either received treatment with neonatal ECMO or CM and were free of overt neurological impairment. In both groups, a similar degree of hippocampal atrophy was found at 12 years of age that positively correlated with memory outcome (10). The ECMO group was more impaired in Learning and Delayed Recognition relative to the CM subgroup, but their total IQ was lower as well (10). These findings thus seem to be similar to the results mentioned in the previous paragraph (9, 11), where specific neuropsychological deficits exist that are incongruent with their general intellectual abilities. Furthermore, the brain alterations seem to be specific as well. In another study, school-age survivors of neonatal ECMO and/or CDH, hippocampal volume reductions were observed, adjusted for total brain volume, that were associated with worse verbal memory delayed recall. This association was found both in children treated with and without ECMO (15). In the same cohort, white matter microstructure was assessed, showing alterations in the parahippocampal region of the cingulum, a white matter tract connecting the medial temporal lobe with the parietal and occipital lobes, to be associated with worse visuospatial memory (15). Again, these structure-function relationships existed in both the patients treated with and without ECMO (15).

Specific long-term neurodevelopmental deficits, particularly in memory and the hippocampus, seem to exist in survivors of critical illness, irrespective of ECMO treatment. Nonetheless,

TABLE 1 | Studies assessing neurocognitive outcome in ECMO vs. non-ECMO treated patients for severe respiratory failure or cardiac failure.

References	Participants	Assessed	Methods and materials	Findings
(A) SEVERE RESPIRATORY FAILURE				
Cooper et al. (10)	40 children treated for acute hypoxic respiratory failure: 27 treated with ECMO and 13 with conventional management. 64 healthy controls	8–15 years	Neuroimaging: Structural MRI 1.5 Tesla. Neurocognitive domains: intelligence, memory	Smaller left, right and bilateral hippocampal volume in patients. No difference in hippocampal volume between patients treated with ECMO and conventional treatment. The ECMO and CM subgroups differed consistently on Learning and Delayed Recognition, in both of which the ECMO subgroup scored below the CM subgroup
Leeuwen et al. (9)	65 survivors of severe respiratory failure: 35 treated with ECMO (CDH and other) and 30 treated with conventional management (CDH)	8 years	Neurocognitive domains: intelligence, attention, verbal and visuospatial memory, executive functioning, visuospatial processing	Patients had average intelligence (mean intelligence quotient ± SD, 95 ± 16), but significantly poorer sustained attention and memory than the norm population. ECMO-treated CDH patients had significantly lower mean IQ (84 ± 12) than other neonatal ECMO patients (94 ± 10) and CDH patients treated with conventional management (100 ± 20). Mean (SD) IQ for the ECMO
Madderom et al. (11)	35 survivors of congenital diaphragmatic hernia: 16 treated with neonatal ECMO and 19 with conventional management	8 years	Neurocognitive domains: Intelligence, concentration and attention	Mean (SD) IQ for the ECMO group was 91.7 (19.5) vs. 111.6 (20.9) for the non-ECMO group ($p = 0.015$). For all participants, problems with concentration (68%, $p < 0.001$) and with behavioral attention (33%, $p = 0.021$) occurred more frequently than in reference groups, with no difference between treatment groups
McNally et al. (12)	90 survivors of severe respiratory failure: 56 treated with neonatal ECMO and 34 with conventional management	7 years	Neurocognitive domains: Cognitive ability (verbal, nonverbal reasoning, and spatial abilities), number skills, spelling, word reading, reading comprehension and visual and verbal memory	76% recorded a cognitive level within the normal range. Learning problems were similar in the 2 groups, and there were notable difficulties with spatial and processing tasks.
Schiller et al. (13)	38 children with CDH and/or treated with neonatal ECMO. No controls	8–12 years	Neuroimaging: Structural MRI and DTI 3Tesla. Neurocognitive domains: intelligence, attention, verbal and visuospatial memory, executive functioning, visuospatial processing	Mean diffusivity (MD) in the left parahippocampal region of the cingulum (PHC) was negatively associated with visuospatial memory. MD in the left and right PHC were negatively associated with verbal memory. Bilateral hippocampal volume was positively associated with verbal memory. No differences between groups in the structure-function associations found
(B) SEVERE CARDIAC FAILURE				
Tindall et al. (14)	9 survivors of cardiac disease treated with ECMO compared to 13 controls matched for cardiac disease and age of surgery. 31 healthy controls	4–6 years	Neurocognitive domains: general cognitive ability, sustained attention, memory, spatial construction, verbal ability	Children treated with ECMO demonstrated significant impairment in general cognitive ability compared to normal controls. No group differences were found in impulsivity or sustained attention. On lateralized measures, children treated with ECMO demonstrated significant impairment in left-hand motor skill, visual memory, and spatial construction compared to both cardiac controls and normal controls. There were no group differences in general verbal ability, verbal memory, right-hand motor skills, or tactile perception

ECMO, extracorporeal membrane oxygenation; CDH, congenital diaphragmatic hernia; CM, conventional management; MRI, magnetic resonance imaging; DTI, diffusion tensor imaging; MRS, magnetic resonance spectroscopy.

more widespread neuropsychological impairment has also been reported in survivors of neonatal ECMO compared to those treated with CM (9–12). These differences may be due to more global brain alterations as a result of greater illness severity in the neonatal period. In line with this, in the study by Cooper et al. (10) an increase in CSF and trend toward reduced global white matter was observed in the ECMO group compared to the CM group. On the contrary, although global alterations in white matter microstructure were found in survivors of severe neonatal respiratory failure by others as well, these were independent of ECMO treatment (13). The explanation of this discrepancy remains speculative, but may be because the differences are small and are therefore difficult to detect in relatively small study populations.

NEURODEVELOPMENTAL OUTCOME AFTER SEVERE CARDIAC FAILURE—TREATED WITH OR WITHOUT ECMO

In neonates with congenital or acquired heart disease, ECMO is used as a perioperative bridge to recovery or temporary support. Although respiratory failure remains the most common indication for extracorporeal life support today, the proportion of cardiac ECMO cases has increased dramatically. ECMO has evolved into a standard therapy for support of cardiac failure refractory to medical care alone (16). Fortunately, this has led to lower mortality rates in these patients and improvement of short-term outcome (1, 16). Because of this, monitoring long-term neurodevelopment in these patients is of great importance.

Several long-term studies have shown that neonates with congenital or acquired heart disease are at risk of long-term deficits in multiple neurocognitive domains, such as visuospatial skills, executive functioning, attention and memory (17–22). Subsequently, just as in patients with severe respiratory failure, survivors of cardiac failure within the first weeks of life are at increased risk of academic difficulties (17–21). Whether patients treated with ECMO are at an even higher risk of these long-term neurodevelopmental problems remains largely unknown. Patients in need of ECMO obviously represent a negative case selection due to circulatory failure post-cardiac repair. In some patients, such as in selected patients with TGA and pulmonary hypertension, survival is even dependent on pre-surgery support by ECMO.

Studies comparing neurocognitive outcome after severe cardiac failure between ECMO and non-ECMO treated patients are very scarce (**Table 1B**). In an early study on this topic, Tindall et al. (14) compared neuropsychological outcome in 4–6 year-old children who were treated with ECMO following repair of congenital heart defects to patients not treated with ECMO and healthy controls. General cognitive ability was within the normal range in both patients groups, yet significantly lower in patients treated with ECMO when compared to healthy controls (14). On more specific neuropsychological tasks, the ECMO group scored significantly lower on left-hand motor skill, visual memory, and spatial construction compared to both cardiac controls and healthy children (14). No group differences were found in sustained attention, general verbal ability, verbal memory, right-hand motor skills, or tactile perception (14). Although providing some insight into long-term neuropsychological outcome in these patients, studies with older children are of interest as these patients may "grow into deficit." This phenomenon has been described in survivors of severe respiratory failure (2), in which early brain damage becomes only functionally evident at a school-age due to brain maturation and increasing demands on cognitive functioning (23, 24).

Both global and specific brain alterations have been described in survivors of congenital heart disease (25–27). In 8–16 year-old children with transposition of the great arteries that were treated with the arterial switch, significant memory impairment and abnormally small hippocampal volumes were found (20). These impairments were similar to those described previously in patients with acute hypoxemic respiratory failure by the same group (10). Although the neurocognitive deficits were found to be independent of surgical repair, no comparison was made between patients treated with and without ECMO (20).

PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING NEURODEVELOPMENTAL DEFICITS

Putting these findings together, it becomes apparent that children with complex congenital heart disease and children who survived severe respiratory failure are at risk of neurocognitive deficits later in life. In both groups, irrespective of ECMO treatment, these deficits lead to difficulties in school. This is highly problematic and underscores the need to understand the pathophysiological mechanisms underlying the long-term neurodevelopmental deficits.

Although some studies seem to suggest that patients treated with ECMO have worse outcomes than patients not treated with ECMO, this is not a consistent finding (9, 11, 14). Both global and specific brain alterations have been described in both of these patient groups. In patients with severe respiratory failure, these brain alterations were largely independent of the need for ECMO treatment (13, 15). However, in a study with school-age survivors of AHRF, patients treated with ECMO seemed to have more widespread brain alterations than patients not treated with ECMO (10). The question rises what pathophysiological mechanisms are underlying these long-term neurodevelopmental deficits. Severity of illness and factors associated with critical illness in general have been described to determine outcome following neonatal critical illness (2). In addition, ECMO treatment may further complicate neurodevelopment by affecting cerebral blood flow and subsequently cerebral autoregulation (28). However, a conclusive cause-effect relationship with ECMO has not been established (28). Moreover, despite lower IQ in patients treated with ECMO compared to patients treated without ECMO (11), the degree of neuropsychological deficits (i.e., specific memory and/or attention problems) and the extent to which these interfere with daily life are similar between these two groups

(9, 15, 29). Furthermore, in long-term imaging studies conducted by our group, no differences in (subtle) brain abnormalities were found either between ECMO vs. no-ECMO treated patients, nor between patients treated with veno-arterial and venovenous ECMO (15). These findings suggest that disease processes other than ECMO treatment are underlying the long-term neuropsychological deficits in these patients. An explanation for this may be that, while studies have shown major neurologic complications in about 20% of ECMO-treated patients (30), more subtle brain abnormalities that cannot be detected using standard neonatal MRI seem to be present in both ECMO and non-ECMO patients [12, 14, 28]. While major neurologic complications may lead to severe neurocognitive impairments such as generally lower intellectual ability, these more subtle brain injuries seem to be underlying the long-term neurocognitive deficits in the memory and attention domains observed in the survivors at school-age (29). Neuromonitoring before, during and after neonatal ECMO treatment in these patients is therefore of great importance. Future studies are needed in which neuromonitoring data from near-infrared spectroscopy (NIRS), transcranial Doppler, magnetic resonance imaging (MRI) and/or electroencephalogram (EEG) is coupled with neurodevelopmental outcome to see whether early predictors can be identified.

In survivors of perinatal cardiac failure, the effect of ECMO treatment on long-term brain alterations has, to our knowledge, not been studied. Comparing survivors of cardiac failure to survivors of severe respiratory failure shows both similarities in neurodevelopmental outcome, such as memory deficits with hippocampal alterations (10, 20), as well as differences. In survivors of CHD, multiple neurocognitive domains, such as visuospatial skills, executive functioning, attention and memory (17–21), are found to be compromised. Neurodevelopmental deficits therefore seem to be more widespread in these patient groups than in patients with severe respiratory failure. This may be due to the timing of brain injury. Several studies have shown that brain alterations in patients with CHD already exist prenatally, presumably due to lower oxygen tension in utero (31–33). In contrast, patients with severe respiratory failure are generally born at term and only exposed to deleterious conditions that may affect brain development postnatally. Although evidence from studies in patients with severe respiratory failure seem to suggest otherwise, ECMO treatment in patients with CHD may lead to an even increased risk of diffuse or global brain alterations and subsequent neuropsychological deficits due to its potential effect on cerebral autoregulation (28). However, future studies in CHD patients are needed to assess this notion.

Looking at similarities, we know that all patients described in this review are at risk of hypoxia-ischemia. Evidence has shown that white matter, in particular in the periventricular regions, and the hippocampus are particularly susceptible to hypoxic-ischemic insults (2, 34, 35). Using animal models, premyelinating oligodendrocytes (pre-OLs) in cerebral white matter have been found to be selectively targeted by oxidative stress. These cells account for ∼90% of the total oligodendroglial population at 28 weeks of gestation and ∼50% at term (35). Increased regional susceptibility of the periventricular white matter is suggested to be due to the distribution of these pre-OLs and relative underdevelopment of distal arterial fields to these areas (35, 36). In addition, studies using animal and *in vitro* models have demonstrated that the hippocampus shows more pronounced changes following hypoxia-ischaemia than other brain structures (34). Indeed, critically ill neonates exposed to hypoxic-ischemic injuries, irrespective of gestational age or underlying diseasse, have been shown to be at increased risk of periventricular white matter abnormalities and hipopcampal damage (2). Since white matter is important for high-speed transmission of neuronal signals between distant brain regions, aberrations in white matter development affects the orchestration of specific cognitive functions (13, 15). Furthermore, hippocampal alterations have shown to lead to significant memory deficits, which has been described as developmental amnesia in this population (37, 38). In line with this, our group previously found a specific negative association between the maximum dose of vasoactive medication received during first admission (measured by the Vasoactive Inotropic Score; VIS) and long-term verbal and visuospatial memory in survivors of neonatal ECMO and/or congenital diaphragmatic hernia. The association was found in both ECMO and non-ECMO treated patients (9). Although currently speculative, receiving high levels of vasoactive medication in the first period of life may be an indirect marker of temporarily (regional) inadequate brain perfusion. As the hippocampus, is particularly vulnerable for hypoperfusion and/or hypoxia, the association between the VIS and memory may be the indirect result of this pathophysiological mechanism. Future research in which dense and detailed data on continuous oxygen saturation and supplemental oxygen supply is combined with neurodevelopmental outcome is needed to gain further insight in this potential cause-effect relationship.

Finding ways to protect the brain against hypoxic-ischemic injury is therefore an important goal for future studies. The use of pharmacological agents that may have neuroprotective effects may be of great value in critically ill infants. Dexmedetomidine, used in particular for sedation in the pediatric ICU population, may have neuroprotective effects against hypoxic-ischemic damage (39). These effects have been suggested to result from an activation of α_2-adrenergic receptors by dexmedetomidine, which inhibits inflammation following brain ischemia (40). However, these findings are mostly based on animals models and studies in adult populations (39, 40). Future clinical trials that assess the efficacy and safety of dexmedetomidine in critically ill neonates are therefore needed.

FUTURE DIRECTIONS TO IMPROVE NEURODEVELOPMENT AFTER NEONATAL CRITICAL ILLNESS

Neurorehabilitation

Given the complex interplay of factors that are likely to affect the developing brain in critically ill infants, rehabilitation strategies aimed at improving impaired neuropsychological functions are of great interest in these patients. Our group has recently demonstrated short-term gains in verbal working-memory

and associated increased FA in the left superior longitudinal fasciculus (SLF) following Cogmed working-memory training (CWMT) in school-age survivors of neonatal ECMO and/or CDH (29). These findings are in line with the effects demonstrated in other clinical and non-clinical groups after CWMT (8, 41–46). One year after CWMT, neuropsychological follow-up showed that gains in visuospatial memory delayed recall persisted long-term (47). Unfortunately, MRI was not performed at this time, hampering our understanding of the neurobiological mechanisms that may be underlying these long-term changes. Nonetheless, as previous findings showed that over 50% of school-age survivors of neonatal ECMO and/or CDH have long-term visuospatial memory deficits (9), improving memory in these children is of great importance.

Ideally, intervention should take place before memory problems have interfered with school performance. In children with very low birth weight, memory improvements have been found 6 months after CWMT at preschool-age (41), suggesting earlier intervention may lead to similar results. However, these results need to be replicated in preschool survivors of neonatal ECMO and/or CDH with long-term visuospatial memory deficits, as well as in other survivors of critical illness such as following complex cardiac anomalies, before any definitive conclusions can be drawn. In future trials, neuropsychological assessment and neuroimaging should be conducted both immediately and 1 year post-intervention.

These studies demonstrate that neurocognition is malleable with CWMT in survivors of neonatal critical illness. However, it is not the (complete) answer to the long-term neuropsychological deficits observed in these children. Results described in this paper demonstrate that multiple neuropsychological domains are affected in both survivors of neonatal severe respiratory failure and complex cardiac anomalies, either treated with or without ECMO. It is therefore essential to conduct an elaborate neuropsychological assessment before initiating CWMT in survivors of neonatal critical illness to determine its clinical utility. Furthermore, if multiple domains are affected in a child, treatment strategies should ideally affect multiple domains as well. A combination of different intervention programs may therefore be of interest. Findings from both experimental and clinical studies have suggested that multimodal training leads to better results compared to a single training program (48, 49). Exercise training in children has been found to affect memory and learning by targeting the hippocampus (50). Combining such a physical program with cognitive training aimed at improving attention or memory, may strengthen the results and be beneficial in survivors of neonatal critical illness. However, these are future perspectives and of little use in today's clinical practice.

Currently, survivors of neonatal critical illness with long-term neuropsychological deficits may have to manage with practical tools to improve school performance and daily life activities. To improve long-term neurocognitive outcome in these children, we recommend that survivors of neonatal critical illness receive information on the practical implications of the deficits they may experience (e.g., difficulty remembering homework that is due tomorrow or appointments with friends), as well as learn about compensatory techniques or external (memory) aids that may be used to improve their activities of daily living [e.g., errorless learning, mental imagery to improve recall, writing important things down and using a schedule book (51)]. Ideally, this information is personalized to the patient's specific neuropsychological impairments and needs. Personalized information on neuropsychological deficits and practical tools can be realized by conducting neuropsychological assessment to evaluate the degree of neuropsychological deficits, as well as by evaluating the degree to which these deficits affect activities of daily living in the patient (51).

For all survivors of neonatal critical respiratory and cardiac illness, whether treated with or without ECMO, a long-term follow-up program with regular assessments across development that covers various medical and neurodevelopmental domains is recommended. It is important that follow-up continues until school-age and into adolescence, as these children seem to "grow into deficit" where early brain damage does not become functionally evident until cognitive functioning increases later in life (3). The neuropsychologist as such can play an essential role in (the improvement of) long-term outcome following neonatal critical illness (**Figure 1**). A multidisciplinary approach to long-term follow-up after neonatal critical illness should therefore be strived for. Please refer to IJsselstijn et al. (52) for more detailed recommendations on multidisciplinary age-appropriate follow-up programs in these patients.

Prevention

Ideally, the deleterious effects of neonatal critical illness on the neonatal brain should be prevented. This may be (partly) accomplished by fine-tuning therapy or treatment strategies, but may also be achieved with the use of neuroprotective agents in the future. While the specific pathophysiological mechanisms underlying the neurocognitive deficits are yet to be identified, we do know that the hippocampus is highly vulnerable in this population (2). The use of pharmacological agents that may have neuroprotective effects may therefore be of great value in

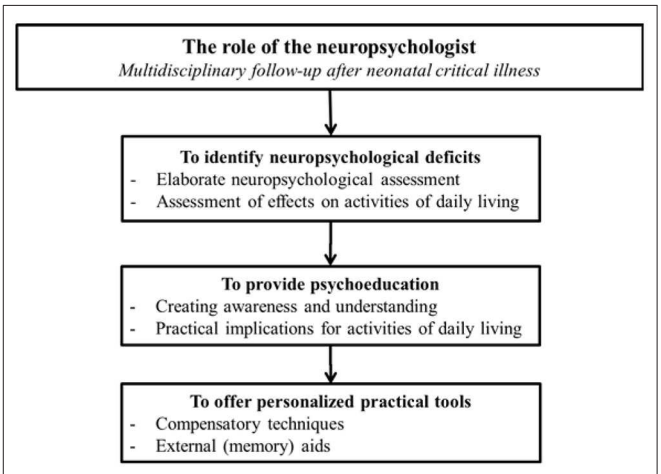

FIGURE 1 | The role of the neuropsychologist in multidisciplinary follow-up after neonatal critical illness.

critically ill infants. For instance, maternal allopurinol, which may protect the fetus against hypoxic-ischemic brain injury, is currently being conducted (53). Here, we mention two other potentially neuroprotective agents that are already commonly used in the neonatal intensive care unit (NICU).

Dexmedetomidine, used in particular for sedation in the pediatric ICU population, may have neuroprotective effects on the hippocampus, in particular against hypoxic-ischemic damage (39). These effects have been suggested to result from an activation of α_2-adrenergic receptors by dexmedetomidine, which inhibits inflammation following brain ischemia (40). As the hippocampus has been found to be vulnerable to both hypoxia-ischemia as well as inflammation (2), this specific mechanisms of action is of interest. However, these findings are mostly based on animals models and studies in adult populations (39, 40). Future clinical trials that assess the efficacy and safety of dexmedetomidine in critically ill neonates are therefore needed that also include neurobiological outcome parameters, such as hippocampal volume. Another agent that may be of interest in this respect is erythropoietin. Erythropoietin is produced by various cell types in the developing brain as a growth factor and as an endogenous neuroprotective response to hypoxia (54). As previously mentioned, in addition to hypoxia, high oxygen concentrations as a result of supplementary oxygen may lead to neonatal brain damage as well (34, 55–58). A recent study in 6-day-old rat pups showed that a single dose of erythropoietin at the onset of hyperoxia (24 h 80% oxygen) improved memory impairment and reduced acute oligodendrocyte degeneration up to the adolescent and adult stage (59). Given the vulnerability of pre-oligodendrocytes in the periventricular white matter during the perinatal period (35), which may potentially be (partly) underlying the attention and memory deficits observed later in life in survivors of neonatal critical illness (9, 11), reducing microstructural abnormalities in these fibers would have direct clinical benefits. In addition, studies have found that erythropoietin may have neurotrophic effects as well by increasing synaptic plasticity in the hippocampus and improving memory formation (59, 60).

The hippocampus shows a high degree of neuroplasticity, which means it has the unique ability to adapt and reorganize in response to internal or external stimuli (58). Although this unfortunately seems to result in more pronounced vulnerability than plasticity—the mechanisms underlying this (im)balance remaining largely unknown—its ability to generate new neurons throughout life does make it a promising target in this respect (58). Trials on potentially neurotrophic agents such as erythropoietin are therefore of interest. In infants with extreme prematurity, hypoxic-ischemic encephalopathy, perinatal stroke, and complex cyanotic heart disease, trials have demonstrated safety, and the potential for efficacy of erythropoietin (61). However, the optimal dose and regimen for neuroprotection in neonates remains largely unknown (62). Future clinical intervention trials assessing the effects of neuroprotective agents before, during or after exposure to both hypoxia and hyperoxia are needed in critically ill neonates.

CONCLUSIONS

Growing up after severe or cardiac respiratory failure in the neonatal period comes with an increased risk of neurocognitive deficits, which seem to be independent of ECMO treatment. In survivors of cardiac failure, widespread neurodevelopmental deficits are more often described than in survivors of respiratory failure, who seem to have more selective neurodevelopmental deficits in attention and memory. This may be due to the timing of brain injury, as brain alterations have been found to exist already *in utero* in patients with congenital heart disease. Nonetheless, academic failure has been reported in both groups. It is therefore of utmost importance that long-term outcome improves in these patient groups. Future studies are needed to identify early biomarkers or risk factors to improve early identification and intervention of children at risk. Furthermore, neuroprotective strategies should be explored. To improve outcome following neonatal critical illness in current practice, psychoeducation, compensatory techniques and external (aids) should become a standard part of (long-term) care following neonatal critical illness.

AUTHOR CONTRIBUTIONS

RS designed the manuscript and wrote the first versions while DT agreed upon the final version of the manuscript and provided editorial support.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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ECMO for Neonatal Sepsis in 2019

Warwick Wolf Butt [1,2,3]* *and Roberto Chiletti* [1,2]*

[1] *Paediatric Intensive Care Unit, Royal Children's Hospital, Melbourne, VIC, Australia,* [2] *Murdoch Children's Research Institute, Melbourne, VIC, Australia,* [3] *Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia*

Sepsis and septic shock in newborns causes mortality and morbidity depending on the organism and primary site. ECMO provides cardiorespiratory support to allow adequate organ perfusion during the time for antibiotics and source control surgery (if needed) to occur. ECMO mode and cannulation site vary depending on support required and local preference. Earlier and more aggressive use of ECMO can improve survival.

Keywords: sepsis, shock, ECMO, neonate, infection

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Timothy M. Maul,
Nemours Children's Hospital, United States
Neysan Rafat,
University Medical Center Mannheim, Germany

***Correspondence:**
Warwick Wolf Butt
warwick.butt@rch.org.au
Roberto Chiletti
roberto.chiletti@rch.org.au

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INTRODUCTION

Sepsis secondary to a bacterial, a viral, or a fungal infection during the first 28 days of life remains a significant cause of mortality and long-term morbidity. Despite advances in neonatal care and maternal antibiotic prophylaxis for group B streptococcus (GBS), the incidence of neonatal sepsis remains high with 1–4 cases every 1,000 live births in the USA with mortality and long-term disability affecting 40% of neonates with sepsis (1–3). Risk factors for the development of sepsis in the neonatal period can be maternal (prolonged rupture of membranes, poor or no antenatal care, meconium-stained liquor, premature labor and chorioamnionitis, GBS colonization) and neonatal (prematurity, low birth weight, APGAR 5 min <5, male gender, resuscitation at birth, neutropenia, lack of enteral feeding, need for vascular catheters and mechanical ventilation) (4). While GBS and Escherichia Coli are the most common bacteria involved, viral sepsis (Herpes Simplex Virus, HSV) and fungal infections are responsible for increased mortality and neurological sequelae, especially in the premature group. Mortality rates for neonatal sepsis vary between 10 and 30% across studies based on gestational age (term vs. birth weight <1,000 g, 52% vs. 72%, respectively) and pathogen (up to 73% for systemic candidiasis) (1, 5–7).

Neonatal sepsis is a heterogeneous entity with different clinical presentations depending on the time of onset and is classified as early (within the first 72 h of life) and late-onset (beyond 72 h of life). These differences correlate with the physiological changes the myocardium and vascular system undergo during the first weeks of life.

The definition of sepsis in neonates is adapted from the pediatric population complicating further diagnosis and management of neonatal sepsis; in a retrospective review of term neonates, only 53% of the cases of culture-positive early-onset sepsis were diagnosed by the consensus definition (8, 9).

Extracorporeal mechanical oxygenation (ECMO) is routinely used around the world to support children and adults with respiratory and/or cardiovascular dysfunction with increasing numbers of children supported over the last three decades (10). The American College of Critical Care Medicine, in their latest edition of the neonatal sepsis guidelines, recommends ECMO for refractory shock as last tier intervention when medical management has failed (11). Despite early reluctance of the ECMO community in supporting adults and children with septic shock due to high morbidity and mortality, ECMO has been routinely utilized for the neonatal population with reported survival rate of up to 70% (12–16).

TABLE 1 | Pathophysiological differences for sepsis/septic shock by ages and ECMO survival.

SEPSIS & SEPTIC SHOCK	Newborn	Child	Adult
Physiological differences	↓ myocardial mass ↓ compliance and contractility High baseline HR with poor compensatory capacity ↓ α-adrenergic receptors ↑ circulating catecholamines ↓ PMN recruitment and BM depletion ↓ phagocytic activity	Developmental transition from neonatal to adult features through first 5 years of life	Normal mass Normal compliance and contractility HR can double/triple to maintain DO2 Normal α-adrenergic receptors and circulating catecholamines PMN margination at infection site and inflammatory cascade activation
Incidence (USA)	1–5 cases per 1,000 live births	1 case per 1,000 person-year	13–78 cases per 100,000 person-year
Predominant cardiovascular status	↑PVR & ↓RV function ↓ LV function/CI	↓ LV function/CI & ↑or↓ SVR	↓ SVR and ↑ CI
Clinical features	PPHN & respiratory failure and/or cardiogenic shock	Cardiogenic shock and/or distributive shock	Distributive shock and/or cardiogenic shock
ECMO survival	50–77% (13, 16, 17)	31–74% (16, 18, 19)	22–78% (20–22)

HR, heart rate; DO2, oxygen delivery; PMN, polymorphonuclear cells; BM, bone marrow; PVR, pulmonary vascular resistance; RV, right ventricle; LV, left ventricle; CI, cardiac index; SVR, systemic vascular resistance; PPHN, persistent pulmonary hypertension on the newborn.

NEONATAL CARDIOVASCULAR PHYSIOLOGY VS. CHILDREN AND ADOLESCENTS

The neonatal myocardium has functional and structural features that differ markedly from the heart of older children and adults (**Table 1**). The myocardium has less contractile protein per 100 grams of tissue than an older child's heart; only half of the tissue is composed of contractile elements while the remaining 50% is made of connective tissue, large nuclei, and mitochondria (see **Figure 1**). Therefore, the mass of the myocardium is reduced, as well as its compliance and contractile capacity and reserve. Equally important is the "disorganization" of the neonatal myocardium as compared to the well-organized sheets of muscle of the older child's heart. The reduced compliance of the heart leads to higher filling pressure and reduced pre-load augmentation (23–25). These factors limit the reserve capacity of the neonatal heart, making it highly dependent on heart rate and susceptible to negative inotropic drugs or acidosis. While adults hearts can double or triple their heart rate to maintain oxygen delivery (high output shock), the high baseline rate of neonates limits this compensatory mechanism. Furthermore, differently from adult hearts, cardiac function is highly dependent on the resting beta-adrenergic stimulation leading to a reduced response to beta-agonist agents, meaning higher doses are required in neonates to achieve the same effect.

The neonatal myocardium expresses less alpha-adrenergic receptors which contribute to the reduced left ventricular function. To compensate for the reduced myocardial function, the concentration of circulating catecholamines is higher than in adults; therefore, the higher depressing effect in neonates on cardiac output by anesthetic agents. Calcium ion transport in the myocardial cells is fundamental to guarantee contraction and relaxation. Myocardial sarcolemma and T-tubular system is less well-developed and calcium entry into cells is compromised in the newborn. Also, neonatal myocytes have reduced mitochondrial calcium and rely mostly on extracellular calcium for contractility; volatile agents used in anesthesia, modulate calcium inflow and can lead to severe myocardial depression in neonates. Decreased kinetics of cytosol calcium contribute to delay in diastolic relaxation (26, 27).

During fetal life, the circulation is in parallel with equal right and left ventricular pressures, right ventricular (RV) predominance, and half of the cardiac output directed to the placenta circulation for its low vascular resistance. After cord clamping and initiation of ventilation, systemic vascular resistance (SVR) rises, and pulmonary vascular resistance (PVR) falls with rising in left atrial (LA) pressure and closure of the foramen oval (FO), and transition to a series circulation, finalized after several days by closure of the ductus arteriosus (through increase in oxygen tension, endothelin I and catechol amines and reduction in prostaglandins). Early infections during this transition period can interfere with this process leading to PPHN, right to left shunt via FO and persistent ductus arteriosus (PDA) (25).

During sepsis, the difference between neonates, children, and adults have also been described at the level of endothelium and interaction between pathogen and immune system (28). Differently from adults, neonates have reduced recruitment of polymorphonucleate cells (PMN) to the site of infection, diminished phagocytic activity, and intracellular killing by reactive oxygen radicals, and a higher pathogen load per ml of blood as part as a "microbe-tolerant" strategy (29, 30). Furthermore, *in vitro* studies showed lower levels of circulating TNF, IL-1B, and IL10 (31).

CLINICAL FEATURES OF SEPSIS IN NEONATES VS. CHILDREN AND ADOLESCENTS

During the neonatal period, depending on gestation age, the timing of infection (early vs. late-onset), etiology

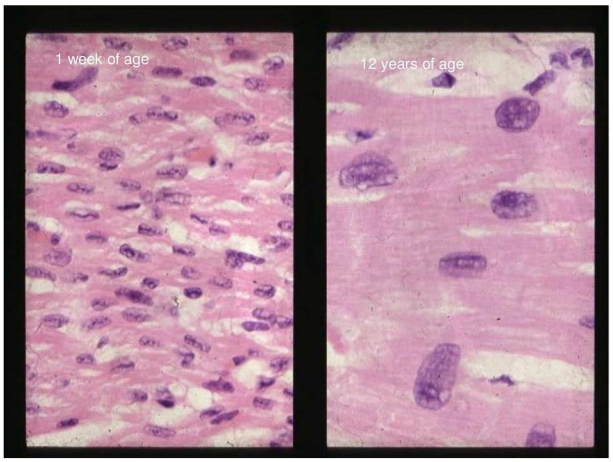

FIGURE 1 | Stained myocardial section in a neonate and a 12 year old at same magnification.

(bacterial, fungal, or viral), and primary focus (pneumonia vs. systemic), sepsis can present with different clinical features of cardiovascular disturbance.

Lack of transition from fetal to neonatal circulation with severe PPHN and persistent fetal circulation (PFC) is a frequent complication of early-onset sepsis. Therapeutic target remains agents that act on reduction of PVR and RV support.

Late-onset sepsis can have the same clinical features of early onset sepsis or can present with increased SVR and severely reduced left ventricular (LV) function and cardiac output, disseminated intravascular coagulation (DIC), and multiorgan failure (MOF). Older children with septic shock, or "cold shock," manifest the same features of severely depressed myocardial function.

Clinical features of septic shock in adults are reduced SVR (hypotension), standard or increased cardiac index, tachycardia and increased mixed venous saturations. This clinical presentation is also described as "warm shock" or distributive shock (32, 33). This is uncommon in children and very rare in neonates due to the developmental differences mentioned above.

INDICATIONS FOR ECMO IN NEONATAL SEPSIS

From 2012 to 2017, the Extracorporeal Life Support Organization (ELSO) reports that, of all neonates receiving ECMO, in <10% the indication was sepsis (34). In neonates where sepsis presents as RV failure, pulmonary hypertension and hypoxemia, indications for initiation of mechanical support do not differ from the ones for respiratory and/or cardiovascular failure secondary to meconium aspiration, congenital diaphragmatic hernia or pneumonia: oxygenation index >40 for more than 4 h, failure to wean from 100% oxygen despite maximal medical therapy, severe hypoxic respiratory failure and pulmonary hypertension with evidence of RV and/or LV failure. On the other hand, for neonates whose sepsis presents with systemic inflammatory response (SIRS), refractory septic shock (RSS), and MOF, the only indication for mechanical support provided by the latest ESLO guidelines is "pressor resistant hypotension" (34). At the current state, there is no consensus on level of inotropic/vasoactive support, level of organ dysfunction, time frame from onset to MOF or rapidity of medical therapy escalation that should trigger ECMO initiation for neonates with RSS. Validation of the septic shock scores for pediatric RSS in the neonatal population could potentially identify in future more targeted clinical parameters [vaso-inotrope score (VIS), arterial lactate and myocardial dysfunction] on the timing of ECMO (35).

ECMO MODALITY DURING NEONATAL SEPSIS

Depending on the critical clinical features of sepsis, neonates have been supported with different modalities of ECMO.

Veno-Venous ECMO

During veno-venous ECMO (VV-ECMO), blood is drained from the venous system [superior vena cava (SVC) or inferior vena cava (IVC)] or right atrium (RA) and returned into the venous system (SVC or IVC) or RA after carbon dioxide removal and oxygenation. Historically, this modality was deemed to provide only respiratory support although by decreasing ventilation, it can augment cardiac output by decreasing lung over-distension thus reducing PVR and increasing venous return to the LA, improve coronary blood oxygen content and LV performance, and diminish intrathoracic pressure. Neonates with severe pneumonia and sepsis, manifesting as severe PPHN, are the best candidates for VV-ECMO support. In clinical practice, there have been no predictors able to identify for which neonates VV-ECMO will provide sufficient myocardial support not to need veno-arterial support. Failing cardiovascular support with persistent acidosis, reduced lactate clearance and low mixed venous saturation (SvO2) on VV-ECMO should trigger early conversion to VA-ECMO via cannulation of the carotid artery. In an ELSO database review of ECMO in septic children, VV-ECMO was mostly used in the neonatal age (87%) compared to older children (13%) and associated with improved survival when compared to VA-ECMO (83% vs. 70%, respectively) (16). Both in adults and children supported for respiratory failure, VV-ECMO was associated with lower complications rates and improved survival (36, 37). In the 2019 report from the Karolinska Institute on ECMO for septic shock in adults, VV-ECMO was associated with reduced ECMO and hospital survival when compared to VA (60 vs. 85%, respectively); survival was also higher for adults with LV failure (90%) when compared to distributive shock (64.7%) (20). This study reinforces the concept of different outcomes for the same condition depending on clinical features and modality of support for it.

VV-ECMO has a safer profile than VA-ECMO not requiring arterial cannulation and subsequent potential risk of arterial embolic phenomena to the brain, to the splanchnic region, and to the peripheries. A major downside of veno-venous support

remains the potential for recirculation and hypoxemia. Since 2009, double-lumen cannulae were introduced, and have been widely utilized, to obviate for the risk of recirculation. Despite the positive aspect of requiring single vascular access, these devices are difficult to position correctly in neonates and children, and allow partial support when compared to a two cannulae strategy. In a single center review comparing complications of dual-lumen cannula vs. a two cannulae approach, children supported with a dual lumen-cannula had increased mechanical complications on ECMO and seizure episodes (38).

Veno-Arterial ECMO

Peripheral VA-ECMO

Septic neonates in whom the clinical presentation is dominated by severely depressed myocardial function with progressive left ventricular dilatation and increased systemic vascular resistance (SVR) require VA-ECMO. This modality provides the best level of cardiovascular support to the failing heart, ensuring adequate blood flow, and oxygen delivery to organs. It also allows a decrease of inotropic drugs and vasopressors with their potential complications. During peripheral VA-ECMO, blood is drained via a cannula in the SVC/RA and is returned through a cannula inserted in the carotid artery and tip positioned ideally at the junction with the aortic arch. Cerebrovascular accidents (cerebral infarction or hemorrhage) remain the more significant and severe complication. In an ELSO database review, 22% of neonates cannulated peripherally onto VA-ECMO developed a neurologic injury (39). Despite lack of evidence, carotid artery repair, and not ligation after decannulation could potentially limit long term neurological complication; many centers do this.

Left atrial (LA) dilatation due to poor myocardial function and /or myocardial stunning can delay left ventricular recovery and cause pulmonary hemorrhage; this is particularly likely in the settings of severe left ventricular failure pre-ECMO or differential ventricular function with right better than left. Signs of LA hypertension on echo, lack of native myocardial ejection, and LV dilatation should trigger ECMO flows and SVR manipulation; consideration should rapidly be given to LA decompression via percutaneous atrial septostomy, percutaneous cannulation of the LA via the Foramen Ovale or direct surgical LA cannulation. After ECMO initiation, an echo should also document the presence of a patent ductus arteriosus which might contribute to high pulmonary to systemic flow ratio (Qp:Qs), arterial diastolic steal (reverse flow in aorta during diastole) and pulmonary over circulation with increasing levels of lactate or lack of clearance, pulmonary oedema and hemorrhage, contributing to higher morbidity of this modality.

Central VA-ECMO

While peripheral VA-ECMO might be sufficient to ensure adequate cardio circulatory support for isolated cardiogenic or cold shock, in the presence of distributive shock or mixed shock (distributive and cardiogenic), higher ECMO flows may be required to maintain adequate end-organ oxygen delivery and function. Central cannulation is primarily utilized in the post-cardiotomy pediatric population and in ECMO centers with cardio surgical programs.

This modality is similar to what happens in a cardiac operating theater during cardiopulmonary bypass (CPB); the sternum is open, blood is drained via a large bore cannula placed directly into the RA and returned into the ascending aorta. Higher flows up to 200–250 ml/kg/min can be achieved to meet the circulatory needs during mixed cardiogenic/distributive shock. Rarely low dose vasopressors (Vasopressin or Noradrenaline infusions) might be required to achieve physiological blood pressure for age. Flows should be adjusted to guarantee the best oxygen delivery to tissue (SvO2 60–70%) and flow adequate to meet metabolic demand and clear lactate (lactate <2 mmol/L); counter to intuition, continuous infusion of systemic vasodilators (and not ECMO flow reduction) might be required to manage hypertension on this high flow. This is usual for the first 6 h of mechanical support. As time passes and organ resuscitation continues, flow reduction is possible and guided by SvO2, lactate, peripheral perfusion and individual organ function.

Left heart distention is a possible complication as for peripheral VA-ECMO, and direct drainage of LA or LV can be addressed during the cannulation process as well as the ligation of a PDA. Disadvantages remain the invasive nature of the procedure, the potential for secondary mediastinal infection and high risk of bleeding, especially in neonates with liver dysfunction, DIC, and coagulopathy. During the first 24–48 h of support aggressive blood products replacement with Platelets, Fresh Frozen Plasma (FFP), and Cryoprecipitate might be required. Chest exploration for mediastinal blood accumulation and inspection for secondary bleeding points is frequently needed and clot removal is mandatory to limit secondary fibrinolysis and consumptive coagulopathy which can worsen bleeding. Careful monitoring of inlet and outlet pressures are fundamental when high ECMO flows on centrifugal pumps are utilized, in order to avoid hemolysis or cavitation. High ECMO flows and excessively negative venous pressure (<-20 mmHg) can lead to hemolysis which is associated with increased odds of ICU and in hospital mortality (40).

Duration of ECMO

The duration of ECMO support for sepsis is generally 4–6 days and varies on the microorganism, clinical presentation (pneumonia vs. shock), timing of ECMO and pre-existing end-organ dysfunction. In the 2012–2016 ELSO registry report, 168 neonates received ECMO for sepsis, 41 of which had primary diagnosis of pneumonia and an average duration of support of 163 h (longest duration of 1,155 h) (34). Similar duration of mechanical support is reported in other single center studies on neonates and children with sepsis (18, 41, 42). Longer duration of ECMO might be expected for neonates with chronic or pre-ECMO lung disease and/or acute post-infective lung damage with cystic transformation to limit ventilator induced lung injury (VILI). The efficacy of antimicrobial therapy, the onset of any complications on ECMO, the development of other organ failures and the neonates' lung function all contribute to prolongation of ECMO; if lung disease is prominent and ECMO is needed for another 5–7 days, then conversion from VA to VV is common. Likewise, the adequacy of ECMO support has to be reassessed

TABLE 2 | Neonatal reports for ECMO and sepsis.

References	Study population	Neonates included	Method	Total survival (%)	Neonatal survival (%)	Predictors of mortality
Meyer et al. (13)	1,060 neonates (S)	1,060 (S)	ELSO registry retrospective	77	77	CPR pre-ECMO, low pH & high ventilatory rate
Reiterer et al. (14)	43 neonates resp. failure	9 (RSS)	SCR	65	44	–
Skinner et al. (16)	4,551 children (S)	3,645 (S)	ELSO registry retrospective	68	73	VA-ECMO compared to VV-ECMO
Chang et al. (19)	55 children (RSS)	4 (RSS)	SCR	31	25	Higher SOFA score
Rambaud et al. (15)	22 children (RSS)	14 (RSS)	ELSO registry retrospective	59	64	Higher inotropic requirement pre-ECMO
Sole et al. (17)	21 children (RSS)	12 (RSS)	SCR	43	50	Disease time before ECMO

S, sepsis; RSS, refractory septic shock; SCR, single center retrospective.

during the run and consideration placed on conversion to a different cannulation strategy. Conversion from VV to VA-ECMO might be required in neonates with early PPHN/PFC and worsening signs and symptoms of cardiogenic/distributive shock. Persistent lung disease and respiratory failure after the resolution of cardiovascular instability might trigger conversion from VA to VV-ECMO. Long term VV-ECMO for 3–6 months might be required for severe lung parenchyma injury (HSV cystic pneumonia or necrotizing pneumonitis, severe VILI). An alternative cannulation modality recently deployed in our center is transthoracic RA-PA ECMO which offers reduced mechanical complications (cannula migration, skin breakdown and site infection), no recirculation and RV support. Destination of therapy might involve lung transplant or withdrawal of active treatment in the face of no lung recovery and in countries where neonatal/infant lung transplant is not undertaken.

Furthermore, increased duration of ECMO can be expected in the presence of secondary acquired infections (43, 44). This risk is higher in previously septic neonates because of the immaturity of the immune system, because of the immunosuppression due to the initial pathogen leading to ECMO and the immunomodulatory effect of the circuit itself. In a 2018 report by Cashen, although not affecting outcome, 16% of neonates and children on ECMO acquired a secondary infection at a median time of 5.2 days from initiation (45).

RISK FACTORS AND OUTCOME

ECMO for neonatal sepsis has been utilized for over three decades with variable survival rates (**Table 2**). An ELSO registry report from 2014 to 2019 describes 119 neonates supported for sepsis with a survival rate of 51% (12). Survival rate for older children vary from to 43 to 74% based on local experience, while reported mortality for adults remains high, up to 75% (17, 18, 21, 46) (**Table 1**).

A multitude of factors influences the outcome after ECMO. Even a simple binary measure like survival or death is dependent on underlying pathogen and natural history of the disease, on clinical presentation and timing of support, on individual risk factors (age, weight, maturity of immune system, nutritional status), on the modality of support and the onset of complications.

Underlying etiological microorganism has been described as influencing outcome.

Survival with bacterial sepsis has been reported up to 75%; mortality for candida infection pre-ECMO remains very high in neonates (61%), children (69%), and adults (81%) (47).

Only one in four neonates supported with ECMO for herpes (HSV) survived, with sepsis/septic shock independently associated with mortality (OR 10.2) (42).

Similarly, survival after adenoviral infection for neonates supported with ECMO was only 11% (48). The high mortality for neonates on ECMO for disseminated viral infections might be correlated to the immaturity of the immune system, especially in premature babies, together with the invasive nature of the viral pathogen responsible for severe neurological and hepatic cytotoxic effect.

In a large ELSO review of 7,190 neonates supported on ECMO, the authors identified birth weight <3 Kg, gestational age <34 weeks and VA-ECMO as factors associated with neurological events, especially cerebral hemorrhage. In the same review, of 366 neonates supported for sepsis, 33% developed a neurological injury (49).

It remains difficult to ascertain if the onset of neurological events is solely due to ECMO or intrinsic to the natural history of the disease. In a retrospective cohort review of neonates with bacteremia, neurological complications were present in 19.4% of the study population who presented with septic shock and associated with a 57.1% mortality (50).

Similarly, intraventricular hemorrhage (IVH) grade III and IV were reported in 18% of premature babies with antenatal infection compared to 8.6% without infection (51).

Over the last two decades, as ECMO deployment has become standard of care for tertiary units, outcomes have improved, and complications have diminished, eligibility criteria have become less rigid. Gestational age lower than 34 weeks and birth weight under 2 Kg have become relative contraindications, while IVH grade III or IV and lethal chromosomal abnormality remained absolute contraindications. No significant difference in mortality for neonatal sepsis on ECMO were described for gestational age of 34 weeks (41%) and 29–33 weeks GA (46%) (52).

Timing of mechanical support for neonates with sepsis remains difficult to establish, but one can postulate that early reversal of tissue oxygen debt and organ dysfunction would

improve outcome. While no data are available in neonates, in an adult case series by Cheng, ECMO for sepsis within 96 h from admission was associated with better survival when compared to later support (60 vs. 19%), reflecting an earlier reversal of multiorgan dysfunction (53). Similarly, for septic adults, persistence of shock beyond 30.5 h before ECMO initiation was associated with no survival, accentuating the importance of timing of reversal of cardiovascular dysfunction (22). Higher lactate pre-cannulation, a pH < 7.2, higher VIS and the presence of a cardiac arrest pre-ECMO have been identified as predictors for increased ECMO mortality (19, 54).

While ECMO remains a supportive therapy, administration of adequate antimicrobial therapy remains fundamental to improve survival of septic neonates. Vast interest in ECMO research, for the last decade, has been the pharmacokinetic (PK) and the pharmacodynamics (PD) of medications, especially of antimicrobials, during ECLS. Neonates have an immature liver and kidney and their capacity of metabolizing and excreting drugs varies between individuals. Septic neonates represent even more a complex system because of fluid overload and changes in distribution volume (Vd), multiorgan dysfunction (kidneys and liver), hypoalbuminemia, capillary leak, and disruption in perfusion. Adding an ECMO circuit to the equation modifies further the Vd and allows for medications to be sequestered within its component (both polyvinylchloride of tubing and poly-methyl pentene of the oxygenator). Careful dosing and monitoring of the efficacy of antimicrobial therapy is fundamental for successful weaning off mechanical support. In a recent review, Raffaeli gives great insight in the pharmacotherapy of antimicrobials, sedatives and inotropic drugs for neonates supported with ECMO (55).

FUTURE DIRECTIONS

Earlier Use of ECMO With Better Technology and Less Sick Patients

Survival and long-term sequelae post-ECMO are multifactorial, only some of which are modifiable when a septic neonate is referred for ECMO. Early referral and/or transfer to an ECMO center might reduce the time neonates are exposed to high ventilatory pressures, and limit potential VILI, and excessive inotropic and vasopressor support. Established end-organ dysfunction pre-ECMO might not allow the deployment of "safer" ECMO modalities (VV vs. VA-ECMO) and could increase the complication rates on ECMO (bleeding and/or thrombosis, renal dysfunction, fluid overload, and need for RRT, high blood products requirements, neurological accidents). An ELSO review by Polito identified cardiac arrest and lower pH at ECMO initiation risk factors for neurological complications in neonates (cerebral hemorrhage, infarction, seizures, and brain death) (49). Several other pediatric series highlight the weight of pre-ECMO lactate on ECMO survival (18, 56, 57). Close collaboration with neonatologists and open discussion about local protocols and indications/inclusion criteria for ECMO could reduce the delay between clinical presentation and ECMO cannulation, and therefore improve outcomes.

Role of Adjunctive Extracorporeal Therapies

Despite limited data specific for the neonatal septic population, utilization of adjunctive extracorporeal techniques during ECMO has become standard practice. In a retrospective analysis of pediatric admissions for sepsis between 2004 and 2012 collected via Pediatric Health Information System (PHIS), 169 children under 1 year of age received both ECMO and renal replacement therapy (RRT) (58). Hypoxia, arterial hypotension, low cardiac output state, diastolic steal via PDA, and high vasoactive support can lead to acute kidney injury (AKI) in neonates with sepsis (59). In a mixed pediatric and neonatal report, the incidence of AKI on ECMO was of 60–74% while in a retrospective cohort study on neonates on ECMO, the presence of AKI was associated with a 3.2 Odds Ratio of death (60, 61). Renal replacement therapy (RRT) is commonly used in patients on ECMO to obviate for fluid overload and AKI, both associated with increased duration of circulatory support and mortality (60, 61). Furthermore, both *in vitro* and animal studies, have shown reduction of inflammatory mediators in sepsis and post cardio-pulmonary bypass (62, 63). In a case series by Blijdorp, the deployment of RRT in neonates on ECMO was associated with reduced duration of ECMO and ventilatory support (64).

Although the deployment and timing of RRT during ECMO remains controversial with non-neonatal studies showing either increased mortality or unaffected outcome, physiologically early renal support seems the best approach to reverse fluid overload and/or maintain even fluid balance, correct electrolyte disequilibrium, remove cytokines and enhance caloric intake (58, 61, 65, 66).

Thrombocytopenia-associated multi-organ failure (TAMOF) secondary to sepsis has been focus of interest over the last 5 years and has triggered utilization of plasma exchange (PE) techniques for patients off and on ECMO. In a clinical picture similar to thrombotic thrombocytopenic purpura (TTP), inflammatory mediators during sepsis can inhibit or inactivate ADAMTS-13, a metalloprotease whose deficiency leads to microangiopathic thrombosis, end-organ dysfunction and death. Children with TAMOF receiving PE have shown improved 28-days survival and reduction in end-organ dysfunction (67). In a case series of 14 children on ECMO for sepsis-related MOF and TAMOF, utilization of PE was associated with reduced organ failure index and VIS with a survival of 71.4% (68). Despite promising results of this technique in this subgroup of children, routine deployment should be balanced with the potential complications caused by it (hypotension, hypocalcaemia, coagulopathy, removal of protein-bound medications and antibiotics) (69).

Limited experience based on single case reports is available for extracorporeal blood purification techniques (EBPTs). Adsorptive therapies have been utilized mostly for hyperinflammatory syndromes (hemophagocytic lymphohystiocitosis, macrophage activation syndrome) or

toxin-mediated infections manifesting as SIRS/septic shock. Two clinical reports from Japan on non ECMO neonates with sepsis/toxic shock highlight the potential adoption of these techniques on ECMO (70, 71). Similarly, non ECMO studies on adults with septic shock treated with HA330 adsorption cylinder showed improved hemodynamic parameters and decreased mortality (72).

Adequacy of ECMO Blood Flow

In a multicenter study of children supported with ECMO for septic shock, VA-ECMO showed beneficial effect for children with a cardiac arrest and ECMO flows over 150 ml/kg/min were associated with higher survival compared to "standard" flows (survival 82 vs. 43%) (56).

Anticoagulation Is More Complex Than in Children/Adolescents

Anticoagulation for neonates on ECMO is difficult because of the immaturity of their clotting pathways and their hypercoagulable state, and propensity for cerebral hemorrhage. In a large prospective observational cohort study, bleeding and thrombotic events in neonates receiving respiratory ECMO were 60% and 43% respectively; furthermore, 22% of the events were cerebral hemorrhage while 3.3% were intracranial infarctions (73). Bleeding and thrombotic events are responsible for increased morbidity and mortality on ECMO (73–75).

Neonates present a unique and very fine balance between anticoagulant and procoagulant state. Neonatal platelet activity is reduced compared to children and adults compensating the increased level of von Willebrand factor. Plasma levels of clotting factors are reduced while there is reduced expression of anticoagulant factors (protein C and S and antithrombin III) (76). Sepsis with DIC and thrombocytopenia puts neonates at very high risk for both thrombotic and hemorrhagic complications and adds further complexities to the anticoagulation regimen.

Precipitant that disrupt the fine neonatal hemostatic homeostasis like sepsis and/or ECMO lead to platelet activation and secondary depletion, complement cascade activation, leukocyte margination and cytokine release, thrombin generation and subsequently secondary fibrinolysis are responsible for both hemorrhagic and/or thrombotic events and the difficulty of managing anticoagulation on ECMO. In a neonatal ECMO report by Doymaz, low fibrinogen (<150 mg/dL) and low platelet count (<50.000/μL) were associated with increased risk for intracranial hemorrhage (77).

Inconsistency of blood test results due to the small volumes of blood and reagents make goal setting for anticoagulation difficult and varied throughout the world. This is particularly relevant to APTT and ACT but less so with INR and Anti-Xa. Bedside tests such as TEG or Rotem are increasingly being evaluated. Exposure to the foreign surface of the ECMO circuits only accentuates the existing coagulopathy with further consumption of clotting factors and platelets (78, 79). Future biocompatible materials might limit the need for systemic anticoagulation or antiplatelet agents on ECMO limiting transfusion requirements and hemorrhagic or thrombotic events. Circuits that act as nitric oxide donors have been investigated for this purpose for the last decade (80–82).

CONCLUSIONS

High survival rates can be achieved for neonates with bacterial sepsis and septic shock and ECMO should be always considered in the absence of severe intracerebral pathology. Worse outcome is associated with non-bacterial sepsis, extreme prematurity, need for ECPR, higher lactate and severity of organ dysfunction pre-ECMO. Predominant pathophysiological features should dictate modality of support (VV-ECMO for right ventricular failure and PPHN, VA-ECMO for left ventricular failure and RSS). Future study is warranted to determine the optimal timing of support.

AUTHOR CONTRIBUTIONS

WB and RC contributed in equal parts at the development of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Sequestration of Voriconazole and Vancomycin Into Contemporary Extracorporeal Membrane Oxygenation Circuits: An *in vitro* Study

Genny Raffaeli[1,2,3]*, *Giacomo Cavallaro*[3], *Karel Allegaert*[4,5], *Birgit C. P. Koch*[5], *Fabio Mosca*[2,3], *Dick Tibboel*[1] and *Enno D. Wildschut*[1]

[1] Intensive Care and Department of Pediatric Surgery Erasmus MC–Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, Netherlands, [2] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [3] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NICU, Milan, Italy, [4] Department of Development and Regeneration and Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [5] Hospital Pharmacy, Erasmus MC, Rotterdam, Netherlands

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***Correspondence:**
Genny Raffaeli
genny.raffaeli@unimi.it

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Background: Bacterial and fungal infections are common and often contribute to death in patients undergoing extracorporeal membrane oxygenation (ECMO). Drug disposition is altered during ECMO, and adsorption in the circuit is an established causative factor. Vancomycin and voriconazole are widely used, despite the lack of evidence-based prescription guidelines.

Objective: The objective of this study was to determine the extraction of voriconazole and vancomycin by the Xenios/Novalung ECMO circuits.

Methods: We have set up nine closed-loop ECMO circuits, consisting of four different *iLAActivve*® kits for neonatal, pediatric, and adult support: three *iLA-ActivveMiniLung*® *petite* kits, two *iLA-ActivveMiniLung*® kits, two *iLA-ActivveiLA*® kits, and two *iLA-Activve X-lung*® kits. The circuits were primed with whole blood and maintained at physiologic conditions for 24 h. Voriconazole and vancomycin were injected as a single-bolus age-related dose into the circuits. Pre-membrane (P2) blood samples were obtained at baseline and after drug injection at 2, 10, 30, 180, 360 min, and 24 h. A control sample at 2 min was collected for spontaneous drug degradation testing at 24 h.

Results: Seventy-two samples were analyzed in triplicate. The mean percentage of drug recovery at 24 h was 20% for voriconazole and 62% for vancomycin.

Conclusions: The extraction of voriconazole and vancomycin by contemporary ECMO circuits is clinically relevant across all age-related circuit sizes and may result in reduced drug exposure *in vivo*.

Keywords: extracorporeal membrane oxygenation, pharmacokinetics, pharmacology, antibiotics, infection, antifungals, drug disposition

INTRODUCTION

Critically ill patients on extracorporeal membrane oxygenation (ECMO) are at high risk of serious infections, with rates of 15.4 per 1,000 ECMO days across all age groups (1). As the mortality of ECMO patients facing an infective event increases up to 68%, a timely and adequate antimicrobial therapy is essential to improve outcomes (1–3).

Vancomycin is widely used as the first-line treatment for both the empiric and targeted treatment of blood stream infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative staphylococci (CONS), and ampicillin-resistant enterococci (1, 4–6). Although bacteria remain the most common causative agents, fungi contribute to the healthcare burden being the second cause of nosocomial infection during ECMO (1), with a prevalence ranging from 0.04 to 5%, and differences based upon age and timing of infection (2, 5). Voriconazole is a second-generation triazole and a synthetic derivative of fluconazole, acting against *Candida* and *Aspergillus* spp., which are the most frequently isolated fungi in ICU (7). Indeed, the azole class is pivotal in the prevention and treatment of invasive fungal infections in critically ill patients (7, 8). While the pharmacology of fluconazole, which is the recommended first-line treatment against *Candida* spp., has been extensively addressed in the pediatric ECMO population (9–11), scanty evidence is available for voriconazole, a first-line treatment for invasive aspergillosis (7, 12, 13).

Besides the choice of the proper agent, the selection of the right dose to attain target exposure is crucial for therapeutic success (14). Drug dosing is known to be complex in critically ill patients, and it is further complicated in specific populations, in which pathology-related factors sum up to physiologic age-specific PK changes (15). The need for an extracorporeal support adds interfering mechanisms, which are responsible for further PK variability (16).

ECMO is increasingly spreading, especially across adult intensive care settings, to support potentially reversible cardiac or respiratory failure, unresponsive to conventional treatment (17). This procedure requires the addition of fluids and exogenous blood products to prime the circuit, thereby increasing the circulating volume. As a consequence of hemodilution, priming compositions, and organ dysfunction, both the volume of distribution (Vd) and clearance (Cl) of drugs are altered (18). A certain degree of sequestration into the circuit may be expected based on the physicochemical characteristics of a drug, such as molecular size, plasma protein binding, degree of ionization at physiological pH, and lipophilicity, as all are based on the characteristics of the circuits and oxygenators (18–21). Moreover, the exposure of blood to the exogenous surface triggers a systemic inflammatory response, further contributing to altered antimicrobial disposition and overall therapeutic efficacy (16, 20, 22).

Despite the wide use of antimicrobial agents during ECMO (23), PK data related to newer systems are limited and heterogeneous, resulting in a poor level of evidence-based pharmacotherapy (22, 24). Previous pharmacological knowledge (25–27) needs to be updated according to the recent advances of extracorporeal technology to prevent altered antimicrobial exposure during ECMO. Furthermore, the optimization of pharmacotherapy is required to limit the burden of microbial resistance (28, 29).

The aim of this study was to provide new insights into the disposition of voriconazole and vancomycin in contemporary neonatal, pediatric, and adult ECMO circuits.

MATERIALS AND METHODS

The study was carried out at the Intensive Care Unit of the Sophia Children's Hospital—ECMO Center, Erasmus MC in Rotterdam, the Netherlands. The need for the institutional review board approval was waived as ethical approval was not required, according to the Dutch Law of research on human subjects. In particular, the fact that no patients were used in this *in vitro* study determined this decision. Study circuits were provided by the Xenios® company as part of an unrestricted research grant.

In vitro ECMO Model

The *in vitro* ECMO model has been previously published (28). Here, we present a brief overview of the setting. We have set up nine different *in vitro* ECMO circuits, consisting of four *iLAActivve*® kits: *iLA-ActivveMiniLung*® petite kits ($n = 3$), *iLA-ActivveMiniLung*® kits ($n = 2$), *iLA-ActivveiLA*® kits ($n = 2$), and *iLA-Activve X-lung*® kits ($n = 2$). They were made up of hollow fiber oxygenators with a diffusion membrane for neonatal, pediatric, and adult patients. All circuits were whole blood primed, connected to a 100-ml reservoir bag and run for 24 h at a flow rate of 500 ml/min (neonatal), 700 ml/min (infant), 2.5 L/min (pediatric), and 3.5 L/min (adult) with an estimated circuit volume of 225, 280, 360, and 400 ml, respectively. Anticoagulation was provided by administering a bolus of heparin 500 UI to maintain activated clotting times over 200 s. Experimental conditions (temperature, pH, hematocrit) have been maintained stable throughout the study period, as previously described (30).

Drug Selection and Administration

We selected voriconazole and vancomycin for their clinical relevance in the Intensive Care Unit (ICU) practice and as illustrative examples of different chemical properties and their drug classes. Dosing for neonatal circuits was based on a standardized neonatal weight (3.5 kg), while for the other systems, we have increased the dose in proportion to the rise of volume to achieve similar theoretical concentrations. We injected voriconazole 35 mg/40 mg/52.5 mg/68 mg (neonatal/infant/pediatric/adult) followed by vancomycin 45 mg/54 mg/67.5 mg/91.8 mg through a line connected to the tubing right after the reservoir bag (P1), with 5-s intervals in-between injections. We flushed the line with 1 ml of physiological saline solution (0.9%) after voriconazole administration to avoid crystallization or pooling effects.

Samples

A line attached to the tubing prior to the reservoir bag was used as a pre-membrane (P2) sample-drawing site. For each system, we

collected samples before a single-bolus drug administration (T0) and during the circuit run at the following time intervals: 2 (T2), 10 (T10), 30 (T30), 180 (T180), 360 (T360) min, and 24 h (T24) after injection. At T2, a control sample was collected and analyzed at 24 h (T2-24) to determine spontaneous drug degradation. The T2–24 samples were stored in ethylenediaminetetraacetate (EDTA) sample tubes, which were maintained at the same temperature as the tested systems until 24 h. For all other samples (T0–T24), whole blood was collected in polypropylene EDTA tubes and stored at 4°C for a maximum of 12 h until further processing. Afterward, all blood samples were centrifuged (3,000 rounds/min for 6 min), and the plasma supernatant was transferred to labeled polypropylene cryogenic vials with polyethylene screw caps (Nalgene Labware, Rochester, NY, USA). Plasma samples were maintained at −80°C until measurement.

Quantification of Drugs in Plasma Samples

Voriconazole and vancomycin were analyzed by means of ultrafast liquid chromatography–mass spectrometry (LC-MS/MS) in the pharmacy laboratory of Erasmus MC, as previously described (30) with regard to voriconazole or a validated immune-assay (Architect, Abbott) for vancomycin. Methods were validated according to the US Food and Drug Administration guidelines for bioanalytical method validation (31).

Reference values are reported [including lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ)]. Intra- and inter-assay means were within 15% of the target range value, as requested by the FDA. For voriconazole, the linear calibration range was 0.1–10 ng/ml. For vancomycin, the linear calibration range was 0.6–50 mg/L.

Spontaneous Drug Degradation and Expected Drug Levels

Spontaneous drug degradation was defined as the amount of drug left after 24 h of spontaneous decay, and it was calculated as a difference in drug recovery between T2 and T2–24. Expected blood drug levels were calculated, accounting for the amount of drug administered and the total circulating volume. Mean recovery of each circuit category at 24 h was corrected by the average drug spontaneous degradation.

Data Analysis

We performed a comparative evaluation of drug disposition between four different ECMO circuits (MiniLung® petite: MLP, MiniLung®: ML, iLAActivve®: iLA, Xlung®). We calculated the average recovery corrected by spontaneous drug degradation at 2, 10, 30 min and 3, 6, and 24 h across all circuit categories. The trend over time is presented for the entire study period for each drug (see **Figures 1**, **2**). Data are expressed as mean (±SD) or percentage. All analyses were performed using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In vitro ECMO models were maintained under physiological conditions for 24 h. Throughout the experimental time, we did not experience any circuit complications. A total of 72 samples (eight for each circuit) were analyzed, in triplicate, for each drug. All baseline plasma samples were free of study drugs.

The recovery of drugs after a 24-h exposure to the extracorporeal circuit has been corrected for average drug spontaneous degradation, and it is graphically reported in **Figures 1**, **2**. The mean percentage of drug recovery at 24 h was 20% for voriconazole and 62% for vancomycin. While the loss of voriconazole was similar across all age circuits, vancomycin levels decreased by 38% in the miniLung petite, by 25% in the minilung, by 38% in the ILA active, and by 50% in the XLung circuits (**Table 1**). Drug physicochemical properties, namely, lipophilicity and protein binding, were derived from the Drug Bank online database (32) and are summarized in **Table 1**.

DISCUSSION

Suboptimal antimicrobial exposure may be associated with therapeutic failure, toxicity, antimicrobial resistance, and, ultimately, worsened patient outcomes (2, 3). In this *in vitro* study, we provide the equipment-related disposition of voriconazole and vancomycin in contemporary ECMO circuitry with *iLAActivve*, contributing insights into circuit- and drug-specific determinants of PK changes during ECMO. Voriconazole was largely sequestered in the circuits, with no distinction across the different circuit sizes. Vancomycin was absorbed slightly more in the neonatal (miniLung petite), pediatric (ILA active), and adult (XLung) circuits than in the infant ones (miniLung). Spontaneous drug decay over 24 h was limited for both study drugs.

We consider these drugs as representative for the pharmacological classes they belong to, thus extending the relevance of our findings.

As expected, based on its lipophilicity and high protein binding (32), voriconazole was largely sequestered in the systems, uniformly across all size groups. Our data confirm those by Mehta et al., who reported a dramatic loss of 60% of voriconazole within 3 h from administration, in an *ex vivo* silicone membrane-based model of blood primed circuit (33). Similarly, the altered PK profile of voriconazole has been observed in pediatric and adult case series (34, 35), showing a drop of voriconazole plasma levels immediately after ECMO initiation or membrane change (36). Higher initial loading and daily doses have been suggested, with an intense therapeutic drug monitoring (TDM) to allow the attainment of therapeutic serum concentrations (37).

Vancomycin is a hydrophilic and moderately protein-bound agent and, given the narrow therapeutic window and the risk of nephrotoxicity, its PK profile has been extensively evaluated both in *in vitro* and *in vivo* settings (25–27). Indeed, targeting the ratio of the area under the vancomycin concentration–time curve over a 24-h period to the minimum inhibitory concentration of the bacteria is crucial, especially among critically ill patients (1, 38). Based on previous neonatal studies, vancomycin has shown an increased volume of distribution (Vd) and a decreased clearance (Cl) during ECMO, resulting in prolonged half-life (25–27). However, these findings were related to older roller

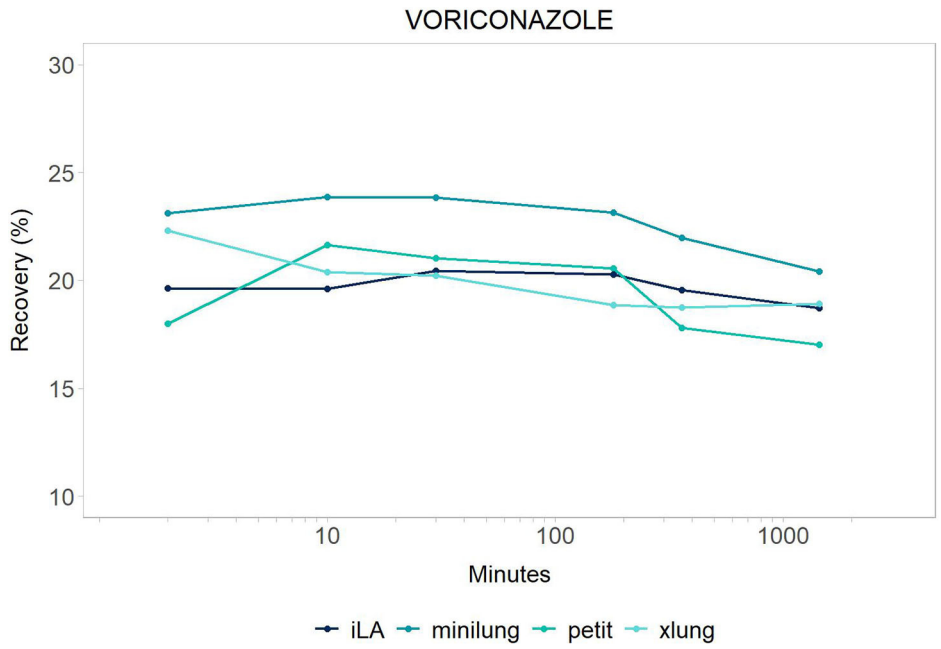

FIGURE 1 | Voriconazole: mean drug recovery (%) plotted vs. time (min) over 24 h for antimicrobial across the four different categories of systems tested: *Minilung petite* (green), *MiniLung* (blue), *iLaActivve* (dark blue), and *XLung* (light blue).

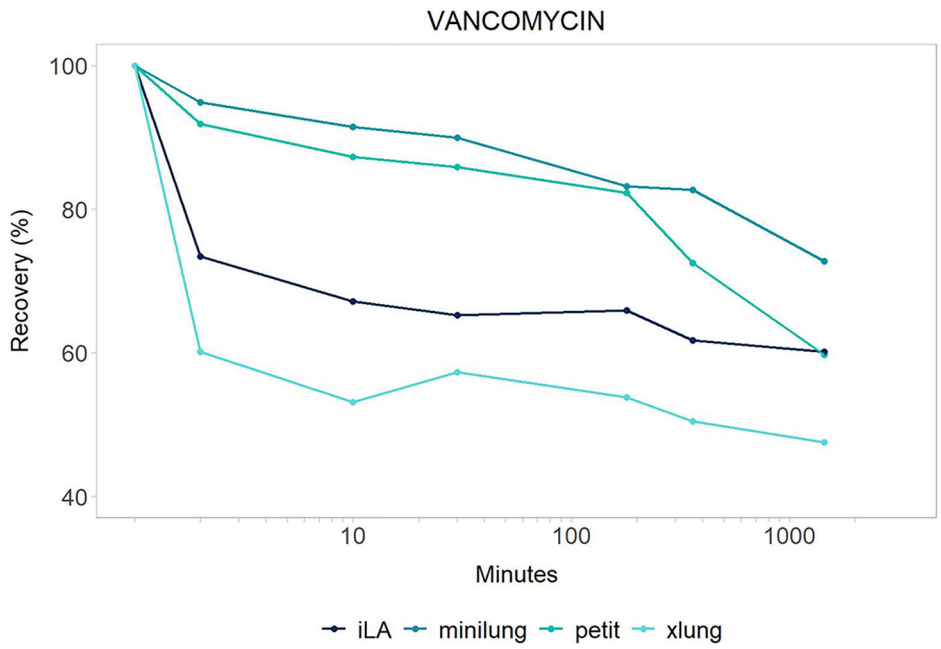

FIGURE 2 | Vancomycin: mean drug recovery (%) plotted vs. time (min) over 24 h for antimicrobial across the four different categories of systems tested: *Minilung petite* (green), *MiniLung* (blue), *iLaActivve* (dark blue), and *XLung* (light blue).

pump-based systems, whereas data on centrifugal pump-based circuits are limited. *In vitro* studies on adult contemporary circuits have revealed either steady vancomycin levels or minimal loss over 24 and 48 h (22, 39). In contrast, we have observed a substantial decay of vancomycin, especially within the first 30 min. These results are in line with our previous *in vitro* findings on neonatal centrifugal-based circuits (18) (**Table 2**). The discrepancy among these results may reflect the

TABLE 1 | Mean drug recovery (mg/L; ±SD) after 24 h of circulation in the study testing circuits (r), corrected for spontaneous drug degradation compared to expected drug levels (e).

Drug	e-MLP	r-MLP ($n = 3$)	e-ML	r-ML ($n = 2$)	e-iLA	r-iLA ($n = 2$)	e-XL	r-XL ($n = 2$)	Spontaneous degradation	LogP	PB
VOR	140	24.9 (±3.5)	117.1	25 (±0.3)	134.7	26.3 (±0)	143.2	28.2 (±4.6)	0.8%	1.8	58
VAN	180	112 (±31.6)	177.1	133.2 (±49.7)	173.2	108.5 (±4,4)	193.7	96.5 (±13.5)	2.4%	−3.1	50

iLA, iLAActivve®; MLP, MiniLung® petite; ML, MiniLung®; PB, protein binding; VAN, vancomycin; VOR, voriconazole; XL, Xlung®. LogP values and protein binding (PB) of study drugs are derived from Drug Bank.

TABLE 2 | Comparison of mean drug recovery at 24 h (%) between centrifugal pump-based *in vitro* studies.

Drugs	Current experiment					Evidence from centrifugal-based systems			Physico-chemical data		
	MLP $n = 3$	ML $n = 2$	iLA $n = 2$	Xlung $n = 2$	Spontaneous drug degradation	Medos n Wildschut (18) $n = 2$ 180 min	Quadrox a Shekar (22) $n = 4$ 24 h	Quadrox a Lemaitre (39) $n = 3$ 24 h	LogP	PB %	Vd L/kg
VOR	17	20	19	19	0.8	-	-	-	1.8	58	4.6
VAN	60	73	60	48	2.4	67.1*	90	100	−3.1	50	0.4–1
Volume (ml)	250	310	400	480	-	200	670	800			

**Recovery at 180 min. iLA, iLAActivve®; MLP, MiniLung® petite; ML, MiniLung®; PB, protein binding; VAN, vancomycin; Vd, volume of distribution, VOR, voriconazole, XL, Xlung®.*

heterogeneity of experimental settings and highlights the need for a better understanding of drug–circuit interactions, as new materials and coatings become available. A matched-cohort study conducted in adult critically ill patients on ECMO receiving continuous infusion of vancomycin showed comparable drug concentrations between ECMO and non-ECMO patients (40). Similarly, other clinical studies showed no PK differences of vancomycin between ECMO adults and critically ill patients not on ECMO (41, 42). The inconsistency between neonatal, pediatric, and adult findings may originate from either ECMO circuit-related factors or (patho-) physiological determinants, as the priming fluid impacts more on neonatal circulating blood volume compared to adults. Pending new data from pediatric clinical PK of vancomycin, it is currently recommended to increase the loading dose and to perform TDM, with target trough plasma levels between 15 and 20 μg/ml (24, 37, 43–45).

Although spontaneous drug degradation was negligible for both voriconazole and vancomycin, it is methodologically rigorous to collect a dedicated sample on purpose, as the degradation may be relevant for certain drugs undergoing high spontaneous decay over time, such as midazolam (30). Moreover, according to standard practice, we have measured the total concentration of drugs, while in ECMO patients, the detection of free drug concentration could be worth exploring.

We acknowledge that our findings are not directly transferable to the bedside for a number of reasons. The number of circuits tested, which is limited by the high costs of the equipment required, calls for caution when interpreting the results to adapt the *in vitro* PK knowledge to clinical practice. Owing to the *ex vivo* setting, patient- and disease-related variables of drug disposition have not been taken into account. However, exploring the impact of circuit-related non-maturational covariates on antimicrobial PK variability is suitable to inform the ECMO compartment within the physiologically based PK modeling to develop a targeted dosing regimen during ECMO (24). Given the dearth of data related to antimicrobial drug disposition into contemporary ECMO circuits, our findings might be valuable to fill this knowledge gap in pharmacotherapy. Further efforts should be made to integrate both preclinical and clinical evidence to optimize pharmacotherapy in this vulnerable patient population by taking into account different ECMO circuit types provided by various manufacturers.

CONCLUSIONS

These results highlight the specific impact of contemporary extracorporeal technology on antimicrobial therapy in critically ill ECMO patients. Sequestration of voriconazole in newer circuits was significant and similar to older silicone-based ones. Although to a lesser extent than voriconazole, adsorption was relevant for vancomycin. As suboptimal antibiotic therapy may lead to treatment failure, maturational toxicity, and antimicrobial resistance, TDM should be performed where available.

Meanwhile, further research is required to improve dosing accuracy and move toward tailored pharmacotherapy with the aim to deliver safe and effective ECMO management, across all age groups.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The need for the institutional review board approval was waived as ethical approval was not required, according to the Dutch Law of research on human subjects. In particular, the fact that no patients were used in this *in vitro* study determined this decision.

AUTHOR CONTRIBUTIONS

GR was involved in the performance of experiments, acquisition, analysis, interpretation of data, writing of the first draft, and critical revision of the manuscript. GC and FM contributed to analysis, interpretation of data, and critical revision of the article. KA contributed to planning of the study, interpretation of the data, and critical revision of the article. BK performed the pharmacological analysis and critically revised the article. DT was involved in the conception and planning of the study, supervision of data collection, interpretation of the data, and critical revision of the article. EW was involved in the conception and planning of the study, performance of experiments, acquisition, analysis, interpretation of data, and critical revision of the manuscript. All authors revised the manuscript, gave final approval of the version to be submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Surgery in Neonatal and Pediatric ECMO Patients Other Than Congenital Diaphragmatic Hernia Repair: A 10-Year Experience

*Casper M. Kersten, Sergei M. Hermelijn, René M. H. Wijnen, Dick Tibboel, Robert J. M. Houmes and J. Marco Schnater**

Department of Pediatric Surgery and Intensive Care, Erasmus University Medical Center Sophia Children's Hospital, Rotterdam, Netherlands

Aim of Study: The use of extracorporeal membrane oxygenation (ECMO) has increased as a result of technological developments and the expansion of indications. Relatedly, the number of patients undergoing surgery during ECMO is also rising, at least in the adult population. Little is known on surgery in children during ECMO-therapy. We therefore aimed to assess the frequencies and types of surgical interventions in neonatal and pediatric patients on ECMO and to analyze surgery-related morbidity and mortality.

Methods: We retrospectively collected information of all patients on ECMO over a 10-year period in a single tertiary and designated ECMO-center, excluding patients undergoing cardiac surgery, and correction of congenital diaphragmatic hernia. Chi-squared test and Mann-Whitney U test were used to analyze data.

Main Results: Thirty-two of 221 patients (14%) required surgery when on ECMO. Common interventions were thoracotomy (32%), laparotomy (23%), fasciotomy (17%), and surgical revision of ECMO (15%). Complications occurred in 28 cases (88%), resulting in a 50% in-hospital mortality rate. Surgical patients had a longer ICU stay and longer total hospital stay compared to those not receiving surgery during ECMO. No significant difference in mortality was found when comparing surgical to non-surgical patients (50 vs. 41%).

Conclusions: Approximately one in seven neonatal or pediatric patients required surgical intervention during ECMO, of whom almost 90% developed a complication, resulting in a 50% mortality rate. These results should be taken into account in counseling.

Keywords: extracorporeal membrane oxygenation, surgery, outcome, complications, pediatric, neonate, critical illness, post-surgical complications

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****Correspondence:***
J. Marco Schnater
j.schnater@erasmusmc.nl

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) has been proven to be an efficient and cost-effective addition to conventional ventilator support in both children and adults (1–3). In the last decades, the use of ECMO has increased as a result of technical developments and an extension of indications, especially beyond the neonatal period. Relatedly, the number of patients undergoing

surgery on ECMO is increasing. This increase is accompanied by higher complication rates in adults (4, 5). To date, complication rates and risks of surgical procedures in children on ECMO are still unknown, apart from those undergoing congenital diaphragmatic hernia (CDH) repair (6, 7).

Current indications for ECMO in the neonatal and pediatric populations include preoperative stabilization, post-surgical recovery, bridge to transplantation, bridge to recovery of organ function, and emergency cardiopulmonary resuscitation, so-called ECPR (8–10). Atkinson et al. (11) reported that 19 of 135 adults (14%) treated with ECMO underwent surgery while on ECMO in the years 1987 through 1989. Twenty-three years later, Taghavi et al. (5) reported a corresponding proportion of 269/563 (48%); an increase possibly demonstrating the effect of the extension of indications following new techniques and more experience. Surgical intervention during ECMO has not been associated with higher mortality rates in general (5, 11). Nevertheless, higher incidences of hemorrhage-related complications, due to the necessary anticoagulation during ECMO, have been reported (4, 5). The study of Taghavi et al. (5) found a significantly higher mortality rate in patients requiring blood transfusion because of hemorrhage.

In neonatal and pediatric patients, ECMO is often used as a bridge toward elective surgery of congenital abnormalities. Well-known examples are CDH, cardiac defects and bronchopulmonary abnormalities (4, 12–15). The role of ECMO in the management of CDH is debated and still subject of ongoing research (16). Although, clinical trials and subsequent systematic reviews have reported improved outcomes in CDH patients with the use of ECMO (2, 17, 18), repair of CDH on ECMO can lead to hemorrhage due to the necessary anti-coagulation (6, 7). Considering this, we decided not to include correction of CDH in this study.

To our knowledge, outcomes of neonatal, and pediatric patients undergoing surgical procedures on ECMO have not been published so far, apart from one abstract describing a cohort of 98 neonatal and pediatric patients on ECMO, 36 of whom (37%) underwent surgery. In-hospital mortality was not higher in the surgical group, but a longer median length of stay, a longer intensive care unit (ICU) stay and more blood transfusions were required following surgery (19). The exact complication rate of surgery on ECMO in neonatal and pediatric patients is unknown. Consequently, clinical decision making is mostly subjective and based on expert opinion rather than evidence. The aim of our study was to analyze the frequencies and types of surgical interventions in neonatal and pediatric patients on ECMO as well as the surgery-related morbidity and mortality.

METHODS

We searched our center's electronic patient database as well as the national Extracorporeal Life Support Organization (ELSO) database for patients who had received ECMO-treatment between January 2009 and January 2019 in our center. This University center is one of two neonatal and pediatric ECMO centers in the Netherlands, executing more than 30 ECMO runs each year. Data of all patients who had undergone one or more surgical intervention on ECMO—apart from insertion and removal of cannulas—were analyzed in detail. Patients undergoing CDH repair and cardiac surgery during ECMO represent a distinctly different population with electively planned surgery. This population was therefore found to be beyond the scope of this article and was excluded. In addition, patients undergoing surgery in another hospital were excluded due to missing data.

We collected the following information: the child's sex, gestational age at birth, and weight at start of ECMO, indication for ECMO, type of ECMO, and duration and number of ECMO-runs. Indication for ECMO was categorized into ECPR and respiratory or cardiac support, broken down for neonatal (<28 days age) and pediatric patients (≥28 days age), as is customary in the ELSO registry (10). Type of ECMO was categorized into veno-venous double lumen (VVDL), veno-arterial (VA), veno-venous (VV), a combination of types (hybrid), or multiple consecutive types (multiple).

Surgical procedures were categorized as thoracic, abdominal, and vascular. Only the surgical removal, replacement or placement of additional ECMO cannulas apart from primary installation of ECMO was counted as a surgical procedure. The number of days on ECMO elapsed at the time of the surgery was noted. Furthermore, we distinguished between therapeutic and diagnostic surgical procedures and elective vs. emergency surgery. The following outcome parameters were recorded: total length of hospital stay, total days at ICU and complications including mortality. Complications were categorized as hemorrhage, ischemia, compartment syndrome, mortality, and other. Cause of death was categorized as futility, neurological, cardiovascular, pulmonary, therapy failure, or directly related to surgery. Deaths were measured up until discharge from our center.

Perioperative anticoagulation was administered according to local protocol, which was updated in 2015. Preoperatively thrombocytes were required to be above 150×10^9/L. Thirty minutes before start of the surgery Tranexamic acid was administered with a loading dosage of 4 mg/kg intravenously, followed by a continuous infusion of 1 mg/kg/h for 24 h or longer, depending on the extent of post-operative hemorrhage. Before 2015 Heparin was continued during surgery to maintain an activated partial thromboplastin time (APTT) of either 50–75 or 60–85 s depending on a normal or high thrombosis risk. After 2015 Heparin was stopped preoperatively, except when the risk of thrombosis was deemed high. Furthermore, fibrinogen levels were kept >1 g/L for 24 h after the surgical procedure (12, 20).

Analysis

Statistical analysis was performed using SPSS (version 25, IBM Corp., Armonk, NY, USA). Differences in medians and percentages were assessed using the Mann-Whitney U test for continuous variables and the $\chi 2$ test for categorical variables.

RESULTS

In the 10-year study period, a total of 307 patients received ECMO-treatment in our center. Eighty-six patients were excluded; i.e., 58 (67%) who underwent cardiac surgery, 27 (31%) who underwent CDH repair, and one who underwent surgery elsewhere. Of the remaining 221 patients, 32 (14%) underwent surgery whilst on ECMO. See **Figure 1** for the corresponding flowchart.

Surgery vs. No Surgery ($n = 221$)

An overview of patient and ECMO characteristics is presented in **Table 1**. None of the baseline characteristics (sex, gestational age at birth, and birth weight) differed significantly between the surgical and non-surgical group.

ECMO Characteristics

Age and weight at start of ECMO were significantly higher in the surgical group compared to the non-surgical group. Furthermore, surgical patients had a significantly longer duration of ECMO compared to non-surgical patients.

Outcome

Both the length of stay on the ICU and the total length of hospital stay were significantly longer for the patients who underwent surgery on ECMO. However, the in-hospital mortality was not significantly different between the surgical and non-surgical group (41 vs. 50%, $p = 0.327$). While the mortality rate during ECMO was 38% in the surgical group compared to 28% in the non-surgical group, the mortality rate after cessation of ECMO was comparable between the two groups. Both differences were not statistically significant.

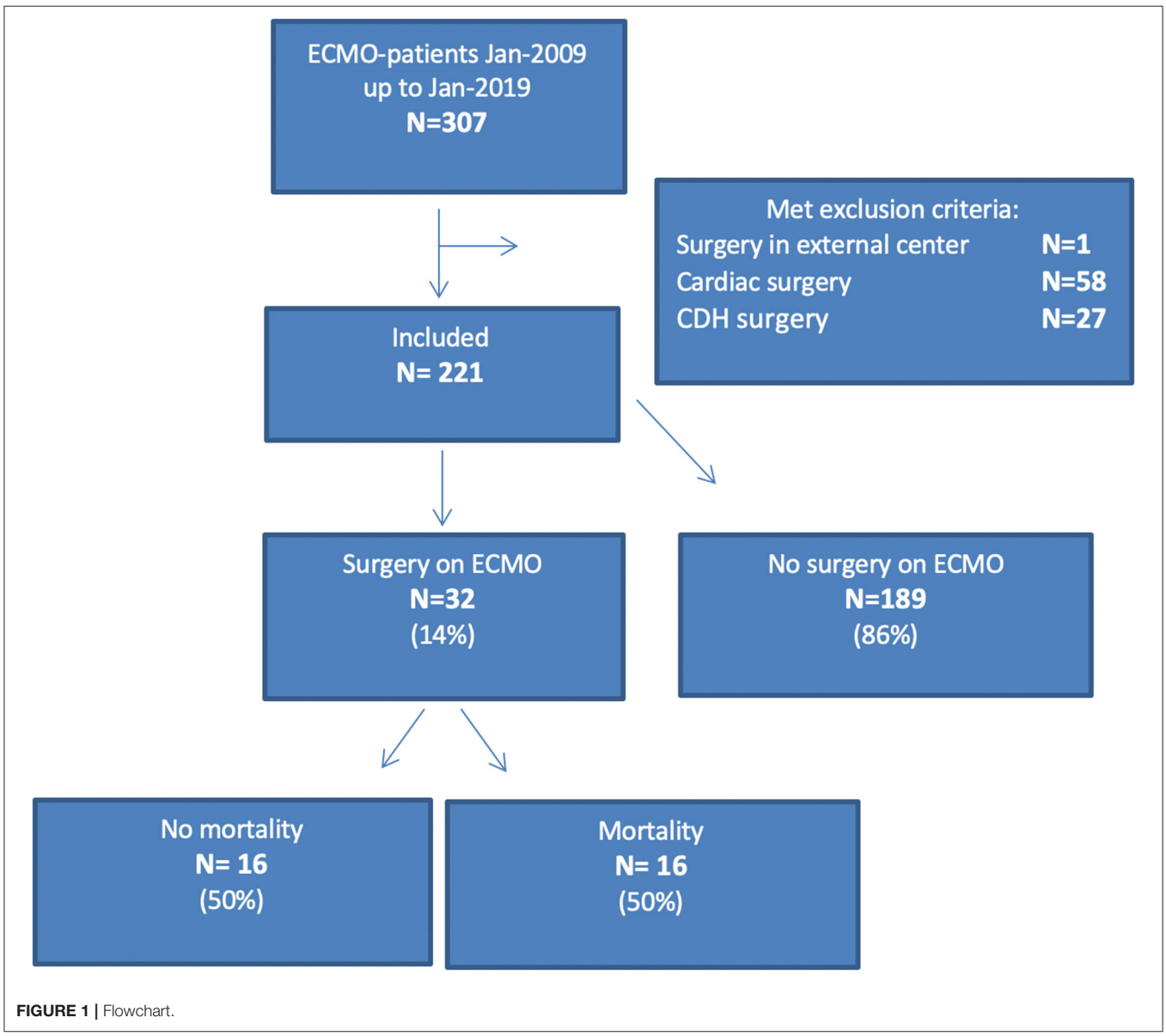

FIGURE 1 | Flowchart.

TABLE 1 | Baseline, ECMO, and outcome characteristics of surgical and non-surgical patients.

	Surgery *N* = 32 (14)	No surgery *N* = 189 (86)	*P*-value
Male	18 (56)	106 (62)	0.986
Gestational age at birth	38.79 (31.71–41.71)	38.64 (25–42.43)	0.531
Birthweight	2700 (1800–4134)	3225 (500–5100)	0.356
Weight at start of ECMO†	14 (2.55–75)	4.2 (1.94–120)	0.005*
Age at start of ECMO categorical†			0.005*
premature <28 days	0	9 (5%)	
At term <28 days	7 (22%)	70 (37%)	
28 days−2 years	4 (13%)	47 (25%)	
>2 years	21 (66%)	63 (33%)	
ECMO indication†			0.144
Neonatal-respiratory	6 (19%)	61 (32%)	
Neonatal-cardiac	0	9 (5%)	
Neonatal-ECPR‡	1 (3%)	7 (4%)	
Pediatric-respiratory	13 (40%)	78 (41%)	
Pediatric-cardiac	3 (9%)	9 (5%)	
Pediatric-ECPR‡	9 (28%)	25 (13%)	
ECMO type†			0.127
VVDL	8 (25%)	80 (42%)	
VA	16 (50%)	85 (45%)	
VV	2 (6%)	9 (5%)	
Multiple	6 (19%)	15 (8%)	
ECMO duration†			0.006*
<7 days	12 (38%)	120 (64%)	
7–20 days	13 (41%)	55 (29%)	
>20 days	7 (22%)	14 (7%)	
ECMO run(s)†			0.707
1	30 (94%)	179 (95%)	
2	2 (6%)	6 (3%)	
3	0	3 (2%)	
4	0	1 (1%)	
ICU days§	22 (2–179)	12 (1–275)	0.003*
Total hospital days	24 (0–179)	15 (0–300)	0.023*
Complications			
Compartment syndrome	5 (16%)		
Other	3 (9%)		
Hemorrhage	2 (6%)		
Ischemia leg	2 (6%)		
Mortality on ECMO†	12 (38%)	53 (28%)	0.278
Mortality post-ECMO†	4 (13%)	24 (13%)	0.975
Complications total (including mortality)	28 (88%)		
Total in hospital mortality	16 (50%)	77 (41%)	0.327
Reason of death			0.69
Futility	8 (25%)	31 (16%)	
Neurological	2 (6%)	8 (4%)	
Cardiovascular	3 (9%)	19 (10%)	
Pulmonary	3 (9%)	13 (7%)	
Therapy failure	0	4 (2%)	
Surgical	0	1 (1%)	

Data are reported as n (%) and median (minimum-maximum).
**Indicates significance ($p < 0.05$).*
† Extracorporeal membrane oxygenation.
‡ Extracorporeal cardiopulmonary resuscitation.
§ Intensive care unit.

Surgical Group

Thirty-two (14%) patients required surgery whilst on ECMO, 17 of whom (53%) received more than one intervention.

Types of Procedures

Thoracic surgery accounted for 40% of procedures, followed by vascular surgery (38%), and abdominal surgery (23%) (**Table 2**). In total 53 surgical procedures were performed in these 32 patients; thoracotomy was most frequently performed ($n = 17$, 32%), followed by laparotomy ($n = 12$, 23%), fasciotomy ($n = 9$, 17%), and surgical revision of ECMO ($n = 8$, 15%) (**Figure 2**).

Six out of the 17 thoracotomies were performed to obtain a lung biopsy, five for intra-thoracic hemorrhage, two for pleural effusion and two for empyema. One emergency thoracotomy was performed for a tension pneumothorax, and one for secondary closure of the thorax following a tracheal reconstruction.

Six out of the 12 laparotomies were indicated for suspicion of an abdominal compartment syndrome. In one case, a second-look laparotomy was performed 2 days later following elevated lactic acid; this revealed extensive bowel ischemia. One patient required two laparotomy procedures on the same day because of hemorrhage 9 days after CDH correction. In this case ECMO was not started until 4 days after the CDH repair had taken place, following the development of fulminant sepsis. One laparotomy was performed for an anastomotic leakage of the bowel. The remaining two cases concerned acute laparotomy. In one case an abdominal compartment syndrome was suspected, in the other a volvulus was discovered.

Comparing survivors with non-survivors, it appeared that neither the categorical type of surgery nor the number of surgical procedures per patient was significantly different (**Table 2**).

Indications and Planning

Most surgical interventions were therapeutic (87%), as opposed to 13% being diagnostic (**Table 2**). One diagnostic laparotomy was performed following an ECPR ECMO procedure, and this revealed a volvulus. This patient did not survive. The other six diagnostic surgical procedures were lung biopsies; three were indicated to identify the cause of pneumonia, the other three intended to investigate the cause of pulmonary hypertension. In one case, the result of the lung biopsy led to immediate cessation of therapy because of alveolar capillary dysplasia. Four out of the other five patients who underwent a lung biopsy procedure did not survive (**Table 2**). Death was in these cases

TABLE 2 | Baseline, ECMO, and surgical characteristics of surgical patients.

	Total (*N* = 32, 14%)	**Mortality (*N* = 16, 50%)**	**No mortality (*N* = 16, 50%)**	***P*-value**
Male	18 (56%)	6 (38)	12 (75)	0.033*
Gestational age at birth	38.79 (31.71–41.71)	38.57 (34.14–40.14)	38.71 (31.71–41.71)	0.482
Birthweight	2700 (1800–4134)	2670 (2075–3690)	2705 (1800–4134)	0.862
Weight at start of ECMO†	14 (2.55–75)	14.3 (2.55–60)	16.10 (2.84–75)	0.577
Age at start of ECMO categorical†				0.909
Premature <28 days	0	0	0	
At term <28 days	7 (22%)	4 (25%)	3 (19%)	
28 days−2years	4 (13%)	2 (12.5%)	2 (13%)	
>2 years	21 (66%)	10 (62.5%)	11 (69%)	
ECMO indication†				0.242
Neonatal-respiratory	6 (19%)	4 (25%)	2 (13%)	
Neonatal-cardiac	0	0	0	
Neonatal-ECPR‡	1 (3%)	0	1 (6%)	
Pediatric-respiratory	13 (40%)	8 (50%)	5 (31%)	
Pediatric-cardiac	3 (9%)	0	3 (19%)	
Pediatric-ECPR‡	9 (28%)	4 (25%)	5 (31%)	
ECMO type†				1
VVDL	8 (25%)	4 (25%)	4 (25%)	
VA	16 (50%)	8 (50%)	8 (50%)	
VV	2 (6%)	1 (6.3%)	1 (6%)	
Multiple	6 (19%)	3 (19%)	3 (19%)	
ECMO duration†				0.758
<7 days	12 (38%)	5 (31%)	7 (44%)	
7–20 days	13 (41%)	7 (44%)	6 (38%)	
>20 days	7 (22%)	4 (25%)	3 (19%)	
ECMO run(s)†				1
1	30 (94%)	15 (94%)	15 (94%)	
2	2 (6%)	1 (6%)	1 (6%)	
3	0	0	0	
4	0	0	0	
Number of surgical interventions per patient				0.524
1	15 (47%)	6 (38%)	9 (56%)	
2	13 (40%)	8 (50%)	5 (31%)	
3	4 (13%)	2 (13%)	2 (13%)	
Total	53	28	25	
Thoracic surgery	21 (40%)	14	7	0.241
Abdominal surgery	12 (23%)	7	5	0.465
Vascular surgery	20 (38%)	7	13	0.389
Day in ECMO-run 1st intervention	6 (1–38)	6 (1–18)	6 (1–38)	0.422
Day in ECMO-run 2nd intervention	10 (2–42)	8 (2–19)	12 (2–42)	0.567
Day in ECMO-run 3rd intervention	19 (9–41)	17 (14–19)	21 (9–41)	0.653
Reason of surgery				0.061
Therapeutic	46 (87%)	22 (79%)	24 (96%)	
Diagnostic	7 (13%)	6 (21%)	1 (4%)	
Elective/emergency surgery				0.361
Elective	8 (15%)	6 (21%)	3 (12%)	
Emergency	45 (85%)	22 (79%)	22 (88%)	

Data are reported as n (%) and median (minimum-maximum).

**Indicates significance ($p < 0.05$).*

† Extracorporeal membrane oxygenation.

‡ Extracorporeal cardiopulmonary resuscitation.

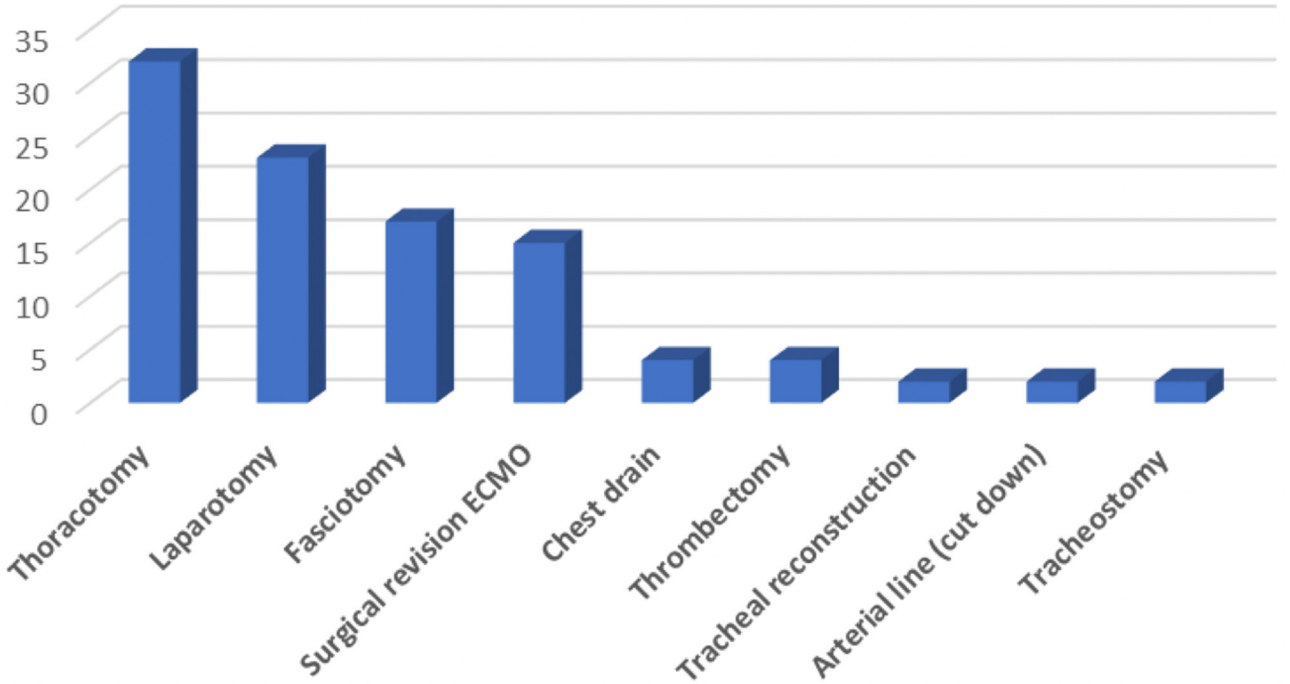

FIGURE 2 | Surgical interventions during ECMO.

not directly related to the surgical procedure. Comparison of the mortality rate related to either diagnostic or therapeutic surgical procedures did not show a significant difference. The majority of surgical procedures took place in an emergency setting (85%), as opposed to 15% being elective. Six of these procedures were the abovementioned diagnostic lung biopsies. In one case a tracheal reconstruction took place on ECMO due to an obstructive trachea and in one case an arterial line was placed by surgical cut down. The mortality rate was not significantly different between elective and emergency surgical cases (**Table 2**).

Outcome

Complications after surgery, including mortality, were seen in 88% of cases. The total in-hospital mortality was 50% in the surgical group. One quarter of deaths occurred after cessation of ECMO. Futility was the most reported reason of death (22%), resulting in cessation of therapy after multidisciplinary consensus was reached. Pulmonary failure was noted as reason of death in 13% of cases, and cardiovascular failure accounted for 9% of cases. Additional information concerning cause of death in the surgical cases can be found in the **Supplementary Material**.

DISCUSSION

To our knowledge, this is the first study describing outcomes of neonatal and pediatric patients undergoing a surgical intervention while on ECMO, apart from CDH repair, and cardiac surgery.

We found that 14% of the patients who received ECMO-treatment in the study period had undergone a surgical intervention while on ECMO, of whom more than half required multiple interventions. Thoracotomy was the most frequent intervention, followed by laparotomy, fasciotomy and surgical revision of ECMO cannulas. Complications occurred in 88% of surgical patients, associated with death in half of the cases. Other frequent complications included compartment syndrome and hemorrhage. The most common reason of death was futility, resulting in cessation of therapy. Patients who underwent surgery on ECMO had a significantly longer ICU stay and total hospital stay compared to non-surgical patients.

These results suggest that patients who undergo surgery while on ECMO have a higher risk of complications compared to those not operated on. In our cohort, this risk did not lead to a significantly higher in-hospital mortality in surgical patients (50 vs. 41% $p = 0.327$). This may be related to the relatively small sample sizes, as is also seen in literature in adults (5). In the present study, one quarter of deaths in surgical patients occurred after cessation of ECMO-treatment, which demonstrates that the critical period of patients in need of surgery while on ECMO does not end with decannulation.

The proportion of neonates and children on ECMO in our cohort receiving surgery (14%) is relatively low in comparison with studies in adults, reporting incidences from 14 to 48% (5, 11). We hypothesize that this relatively low proportion is related to the relatively large group of neonates in our cohort who need ECMO for respiratory support directly post-partum, few of whom require surgical intervention during ECMO.

When comparing the ECMO-indication in surgical and non-surgical patients, a larger proportion within the non-surgical group is represented by neonates who are in need of ECMO due to respiratory failure (32% non-surgical vs. 19% surgical, $p = 0.144$). This patient group is known to have a relatively favorable prognosis (10). However, in our cohort we did not find a significant difference in mortality between the surgical and non-surgical group (50 vs. 41%, $p = 0.327$). We hypothesize that this is due to the fact that the neonatal-respiratory group represents a minority within our cohort (in total 68 out of 221 patients), and therefore does not significantly influence the mortality of either of the groups.

Various studies have focused on specific surgical interventions on ECMO such as cardiac catheterization, CDH correction and lung biopsies (13, 20, 21). We, however, investigated the surgical interventions in children on ECMO in general, and found a high complication rate as well as a high mortality rate in this group of patients. These findings can help improve the quality of counseling.

We searched the ELSO-registry but could not identify data on surgical interventions during ECMO. Though, complications including surgical site hemorrhage, cannulation site hemorrhage, and compartment syndrome were reported, numbers of surgical procedures appear not to be documented systematically (10). As we found that in our center approximately one in seven neonatal and pediatric patients on ECMO undergoes surgery—associated with a distinctly high complication rate—we advocate for the systematic registration of surgical interventions during ECMO in the future. Centralized registration will possibly lead to new insights and thereby influence clinical practice.

The retrospective nature of this study accounts for the possibility of missing data. The quality of data was especially poor concerning coagulation complications and transfusions in the perioperative period. Due to the large portion of missing data, analysis of these parameters was not possible. Colleagues Erdem et al. described coagulation complications on ECMO, however the relationship of these complications to surgical interventions during ECMO was not further analyzed in this study (22).

Follow-up was limited to either death or first hospital discharge after ECMO-treatment; we did not inventory whether complications had occurred thereafter. IJsselstijn et al. already stressed the importance of multidisciplinary long-term follow-up with a standardized approach, which is now being implemented in our center (23). Even though our cohort stems from the largest neonatal and pediatric ECMO-center in the Netherlands, we found it to be too small and heterogeneous for a clinically significant prediction model. In order to achieve a cohort fit for a prediction model, a multi-center study design will be necessary in order to include a sufficient number of patients. Large multi-center studies have reported high rates of complications due to either bleeding or thrombosis, warranting future studies exploring new coagulation strategies during ECMO (24, 25). Likewise, future multi-center studies focusing on surgical procedures during ECMO could lead to identification of possible predictive variables for surgical outcome. ECMO-treatment is an evolving field of medical practice in which new instruments and techniques are frequently introduced. Consequently, it is plausible that during the 10 years of inclusion in the present study ECMO techniques, practice and the supportive care have changed, although, recent results suggest that the transition from roller to centrifugal pump techniques has not significantly influenced outcome (22).

In conclusion, approximately one in seven neonatal and pediatric patients required a surgical intervention during ECMO-treatment, 88% of them developed complications. In-hospital mortality after surgery on ECMO was 50%, which was not significantly higher than in non-surgical patients. These results should be taken into account in counseling.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Daily Board of the Medical Ethics Committee Erasmus MC. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JS and RH contributed to conception and design of the study. CK organized the database, performed case study, and wrote the first draft of the manuscript. CK and SH performed data analysis. CK, SH, JS, and RH drafted the manuscript for important intellectual content. JS, RW, and DT contributed to revising the manuscript and gave final approval. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.660647/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Assessing Anticoagulation in Neonates With Congenital Diaphragmatic Hernia During Extracorporeal Membrane Oxygenation: Does Anti-Factor Xa or Thromboelastometry Provide Additional Benefit?

Alba Perez Ortiz[1], Carl E. Dempfle[2], Toni Jung[1], Thalia Doniga[1], Christel Weiß[3], Svetlana Hetjens[3], Thomas Schaible[1] and Neysan Rafat[1]*

[1] Department of Neonatology, University Children's Hospital Mannheim, University of Heidelberg, Mannheim, Germany, [2] IMD Coagulation Center Mannheim, Mannheim, Germany, [3] Department for Medical Statistics and Biomathematics, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

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Aparna Hoskote, Great Ormond Street Hospital for Children NHS Foundation Trust, United Kingdom

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Uri Pollak, Hadassah-Hebrew University Medical Center, Israel

***Correspondence:**
Alba Perez Ortiz
alba.perez-ortiz@umm.de

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Objective: The optimal management of anticoagulation in neonatal/pediatric patients during extracorporeal membrane oxygenation (ECMO) has not been established yet and varies greatly among ECMO centers worldwide. Therefore, we aimed to assess whether the use of anti-factor Xa assay and/or thromboelastometry correlate better than activated clotting time with heparin dose in newborns with congenital diaphragmatic hernia during ECMO. We also examined whether these coagulation assays correlate with thrombotic and/or hemorrhagic complications, when the management of anticoagulation is based only on activated clotting time values.

Methods: A prospective observational study in a neonatal ECMO center was conducted. We included all neonates with congenital diaphragmatic hernia born in our institution between March 2018 and January 2019 and requiring support with venoarterial ECMO. A total of 26 ECMO runs were analyzed. During the study, the heparin dose was still adjusted according to activated clotting time values. Measurements of anti-factor Xa assay, activated partial thromboplastin time, and a thromboelastometry from the same blood specimen were performed twice a day.

Results: Anti-factor Xa levels showed a moderate correlation with heparin dose, whereas the other tests showed a weak correlation. Four patients (17.4%) had thrombotic complications, 2 patients (8.7%) experienced life-threatening bleeding, and in 11 patients (47.8%) disseminated intravascular coagulation (DIC) occurred. Anti-factor Xa levels were lower in the group with thrombotic complications (0.23 vs. 0.27 IU/ml; $p = 0.002$), while activated partial thromboplastin time was higher in the group with hemorrhagic complications (69.4 s vs. 59.8 s; $p = 0.01$). In patients experiencing DIC,

heparin dose and anti-factor Xa levels were lower, while no difference in activated clotting time and clotting time in INTEM and INTEM-HEPTEM were shown.

Conclusions: Anti-factor Xa levels correlate better to heparin dose than activated clotting time. The use of anti-factor Xa assay instead of activated clotting time for dosing of unfractionated heparin could reduce thrombotic complications in neonates with congenital diaphragmatic hernia on ECMO support. The thromboelastometry showed no additional benefit for this purpose.

Keywords: extracorporeal membrane oxygenation, congenital diaphragmatic hernia, thromboelastometry, anti-factor Xa, heparin

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is an extracorporeal technique used to support patients with respiratory and/or cardiac failure refractory to conventional treatment. Since the first reported use of ECMO in a newborn in 1975, over 40,000 newborns worldwide have been treated with ECMO (1). Congenital diaphragmatic hernia (CDH) is nowadays the most common indication for ECMO in neonates with respiratory failure (2).

Despite increasing clinical practice and technical improvements, the optimal management of anticoagulation in patients during ECMO is still controversial and varies greatly among the various ECMO centers worldwide (3). The rate of hemostatic complications, including life-threatening bleeding and thrombotic events, remains high (10–33%) and represents a major cause of morbidity and mortality in these patient populations (1, 3, 4). Maintaining an optimal balance of hemostasis can be particularly challenging in neonates due to their immature hemostatic systems, with decreased plasma concentrations of most procoagulants and many anticoagulant factors and the resulting lack of reserve capacity (1, 4). Furthermore, these physiological differences may influence the monitoring and efficacy of the anticoagulation required during ECMO (1).

Although there is no standardized protocol, unfractionated heparin (UNFH) is the most commonly used anticoagulant during ECMO (1, 3, 5). Several tests to monitor coagulation and anticoagulation during ECMO have been developed over time, but the ideal test or combination of tests to adequately manage anticoagulation still remains to be established (1, 6–9).

The activated clotting time (ACT) is the most frequently used test to monitor UNFH activity in patients supported on ECMO, because it is available in real time at the bedside (4, 6). However, recent studies suggest that managing ECMO anticoagulation solely based on ACT measurements may lead to sub-optimal anticoagulation in these patients (4, 9–12). The activated partial thromboplastin time (aPTT) is the second most frequently used test to monitor UNFH during ECMO (1). The anti-factor Xa assay does not provide a direct measurement of the UNFH concentration but of the UNFH effect instead (6). Its value appears to be more specific than ACT values for heparin control, as it is not affected by coagulopathy, thrombocytopenia, coagulation factor deficiency, or dilution (6). Thromboelastometry (ROTEM®; Tem Innovations GmbH, Munich) is a whole blood viscoelastic point-of-care coagulation test that provides information on the overall kinetics of hemostasis, as well as on the interactions between coagulation factors, erythrocytes, platelets, and coagulation inhibitors (6). Such information makes the use of viscoelastic tests in ECMO patients compelling.

The objectives of this study were to examine the correlations between ACT, aPTT, anti-factor Xa assay, and two ROTEM® parameters that detect the UNFH effect (CT-INTEM and CT-INTEM–CT-HEPTEM) and the dose of UNFH in neonates with CDH during venoarterial ECMO. Furthermore, we were interested in assessing whether the different measurements of anticoagulation correlate with thrombotic and/or hemorrhagic complications when the management of anticoagulation is based only on ACT values.

MATERIALS AND METHODS

Subjects

Neonates with CDH requiring venoarterial ECMO ($n = 23$) were selected directly after birth between March 2018 and January 2019 from the neonatal intensive care unit (NICU) of the Department of Neonatology of the University Children's Hospital Mannheim, University of Heidelberg. The indication for and the allocation to ECMO was performed based on the recommendations made by the CDH EURO Consortium Consensus Team (2015 Update) (13). All gestational ages were included. Exclusion criteria were congenital heart defects (except patent ductus arteriosus and persistence of the foramen ovale), inborn errors of metabolism, other anatomical pulmonary anomalies, and severe pneumonia/sepsis. We selected only CDH patients in order to have a homogenous patient population for this study. This study was approved by the local ethics committee of the Medical Faculty Mannheim of the University of Heidelberg (Ethics Committee II), and informed consent was obtained from the parents of all study subjects.

Extracorporeal Membrane Oxygenation and Anticoagulation

All patients received an ECMO circuit consisting of a Jostra HL20 roller pump (Maquet Cardiopulmonary AG, Hirrlingen, Germany), a QUADROX-i Neonatal Oxygenator (Maquet

Cardiopulmonary AG, Hirrlingen, Germany), and a heparin-coated system Maquet Bioline (Maquet Cardiopulmonary AG, Hirrlingen, Germany). Anticoagulation was performed with a continuous infusion of UNFH. The circuits were all primed with gas (carbon dioxide) following a prime with Ringer's solution with UNFH (0.5 IU/ml), an albumin prime (50 ml 20% Albumin), and finally a blood prime with one packed red blood cells, 50 ml fresh-frozen plasma, and 200 IU UNFH. During ECMO circuit prime, a continuous infusion of UNFH at 500 IU/h was started. After finishing the blood prime, an ACT measurement was taken, and if it was greater than 999 s, the UNFH infusion was reduced to 300 IU/h until connection to the patient. No bolus of UNFH was given to patients prior to cannulation. After cannulation and start of ECMO, continuous infusion of UNFH was decreased to 100 IU/h and gradually reduced until ACT values were within target range (160–180 s). During the study, UNFH was still titrated according to ACT values measured hourly. Target range from ACT was increased from 160–180 to 180–200 s in case of the presence of thrombosis in ECMO circuit. According to our protocol, antithrombin (AT) activity was measured daily, and values below 60% were systematically supplemented. Transfusion requirement was monitored twice a day: platelet transfusions (15 ml/kg) were administered to achieve platelet counts higher than 80,000 cells/μl during the first 72 h of ECMO and greater than 60,000 cells/μl thereafter. Fresh-frozen plasma (15 ml/kg) was also administered to keep fibrinogen level above 100 mg/dl and Quick test value higher than 40%.

Monitoring of Anticoagulation

Measurements of ACT, anti-factor Xa assay, aPTT, and thromboelastometry from the same blood specimen were performed twice a day (7 a.m. and 7 p.m.). The ACT was measured at the bedside using ACT Plus® (Medtronic Biologic Therapeutics and Diagnostics, Minneapolis, USA). Both aPTT and anti-factor Xa were collected in citrated tubes and measured at the Institute of Clinical Chemistry of the University Hospital Mannheim. The aPTT was measured using a coagulometric test with addition of Actin FS and calcium chloride (Sysmex® CS-5100, Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). The assessment of anti-factor Xa was performed with a chromogenic test without addition of exogenous ATIII (INNOVANCE® Heparin test, Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). The thromboelastometry was performed as a point-of-care examination using ROTEM® delta (Tem Innovations GmbH, Munich, Germany). In each ROTEM® analysis, four tests were performed simultaneously: EXTEM, INTEM, FIBTEM, and HEPTEM. Since the effect of heparin can be specifically demonstrated by comparing INTEM (reflects the intrinsic coagulation pathway) and HEPTEM (it includes heparinase and reflects the intrinsic coagulation pathway in the absence of UNFH), both the coagulation time for INTEM (CT-INTEM) and the difference between the coagulation time for INTEM and HEPTEM (CT-Diff) were used to analyze the heparin effect.

Data Collection

Demographic, clinical, and laboratory data were collected, including demographic variables, duration of ECMO support, UNFH dosing, transfusion requirement, the presence of disseminated intravascular coagulation (DIC), and thrombotic and hemorrhagic complications as defined by the Extracorporeal Life Support Organization (ELSO) registry (6). In the absence of ECMO-specific, validated DIC scores (14), DIC was defined as a composite of thrombocytopenia (<50,000 cells/μl), d-dimer >20 g/l, fibrinogen <100 mg/dl, and Quick test <39%. Laboratory values were collected twice a day and included platelet count, hemoglobin, ACT, Quick test, aPTT, fibrinogen, anti-factor Xa, and ROTEM® values. AT and d-dimer levels were measured once a day.

As described above and according to our protocol, the solution and the blood products used for the priming of the ECMO circuit contained UNFH, and a continuous infusion of UNFH (100 IU/h) was started after cannulation. Due to this high infusion rate of heparin, the values of the coagulation assays were outside the range of measurement in the first hours after initiation of ECMO support, and the UNFH infusion rate had to be significantly reduced until ACT values were within the target range. To guarantee that this situation did not affect the results, these outliers of the values from the coagulation tests (ACT levels >200 s in the first 2–12 h after cannulation until ACT target range of 180–200 s was reached for the first time) as well as the corresponding UNFH dose and associated bleeding complications (such as cannula site bleeding directly after cannulation) were excluded from the statistical analyses.

Statistical Methods

Statistical analysis was performed with SAS® Version 9.4 (SAS Institute GmbH, Heidelberg, Germany). Descriptive statistics were used to describe the demographic characteristics of the patients and to analyze the distribution of UNFH infusion rates and coagulation tests. Each ECMO course was divided into 12-h periods daily, and each laboratory value and UNFH infusion rate was recorded within its corresponding time point. Spearman correlation coefficients were used to assess correlations between heparin dose and values from the different coagulation assays. The Wilcoxon–Mann–Whitney test was used to compare the values from the coagulation assays and the heparin dose between groups with and without clinical complications. A p-value of 0.05 or less was considered significant.

RESULTS

Demographic and Clinical Characteristics of the Study Cohort

Twenty-three newborns (7 female and 16 male) were included in our study, of which two patients (8.7%) were late preterm infants (34^{+5} and 36^{+0} weeks). The remaining patients were term neonates (37^{+1}-39^{+4} weeks). The median birth weight was 2,894 g (range 2,160–3,890 g). All patients were placed on ECMO in the first 48 h after birth. After 10 days, three patients required

TABLE 1 | Median values of the different coagulation assays.

Coagulation assay	Median (IQR)
ACT (s), $n = 500$	181 (118–301)
aPTT (s), $n = 496$	59.9 (35.6–135.6)
Anti-factor Xa (IU/ml), $n = 455$	0.26 (0.09–0.68)
CT-INTEM (s), $n = 409$	277 (164–856)
CT-Diff (s), $n = 380$	56 (−148 to 560)

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CT-INTEM, clotting time in INTEM; CT-Diff, clotting time in INTEM minus clotting time in HEPTEM; IQR, interquartile range.

TABLE 2 | Spearman correlation coefficients between heparin dose and the different coagulation tests.

	ACT	aPTT	Anti-factor Xa	CT-INTEM	CT-Diff
r_s	0.19	0.20	0.38	0.03	0.17
***p*-value**	**<0.0001**	**<0.0001**	**<0.0001**	0.46	0.0006

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CT-INTEM, clotting time in INTEM; CT-Diff, clotting time in INTEM minus clotting time in HEPTEM; r_s, Spearman's rank correlation coefficient.
The bold values symbolize that the value is statistically significant.

a second ECMO run; hence, a total of 26 ECMO runs were analyzed. The median duration of ECMO support was 10.3 days (range 1–20 days). Nine patients (39.1%) died prior to discharge, four of them (17.4%) died while on ECMO support.

With regard to hemostatic complications, four patients (17.4%) showed significant thrombosis in the ECMO circuit, requiring an unplanned replacement of the circuit or an unplanned termination of the ECMO support. No patient experienced a clinically noticeable thrombotic complication. Eight patients (34.8%) had hemorrhagic complications, of which six developed immediate bleeding at cannulation site, and three required surgical revision. Two patients (8.7%) experienced life-threatening hemorrhagic complications (one pulmonary and one cerebral) after the first 24 h of ECMO support. None of the patients experienced lethal bleeding. DIC occurred in 11 patients (47.8%).

Monitoring of Anticoagulation

The median values of the different coagulation tests are shown in **Table 1**. None of the coagulation assays showed a strong correlation with the heparin dose (**Table 2**). Anti-factor Xa assay showed a positive moderate correlation with the heparin dose, whereas the other tests correlated only weakly (**Table 2**). No significant correlation was found between heparin dose and CT-INTEM (**Table 2**). In **Figure 1**, the correlation of heparin dose to the values from the analyzed coagulation tests are displayed. The gently slanted horizontal lines shown in **Figures 1D,E** indicate a lack of sensitivity of the analyzed thromboelastometric tests in response to a change in heparin dose. In contrast, an increase in heparin dose increased the values of ACT, aPTT, and anti-Xa assay (**Figures 1A–C**), while the steeper regression line and the fewer outlying values in the case of anti-Xa assay indicated a stronger correlation of this test to heparin dose in comparison with ACT and aPTT.

Thrombotic Complications

Table 3 shows the median values of the analyzed coagulation assays in the group of patients with thrombotic complications compared to the group of patients without thrombotic complications. Anti-factor Xa assay was the only test which was statistically significant between the groups and was lower in the group with thrombotic complications.

Hemorrhagic Complications

A comparison of the median values of the different coagulation tests between the group of patients who experienced a bleeding complication and the patients without bleeding complication is shown in **Table 4**. aPTT was the only test that was statistically significant between the two groups and was higher in the group with clinically relevant hemorrhagic complications.

Disseminated Intravascular Coagulation

The median values of the coagulation assays when DIC occurred compared to median values of the tests in the absence of DIC are represented in **Table 5**. No statistically significant differences in ACT values were found, whereas the median values of anti-factor Xa test were significantly lower when DIC occurred. The same could be observed with the heparin dose. In contrast, the median values of aPTT were significantly higher. No differences in the thromboelastometric tests were shown.

DISCUSSION

In the present study, we evaluated the correlation of an administrated heparin dose to different coagulation assays in newborns with CDH undergoing venoarterial ECMO and assessed whether the different coagulation assays correlated with thrombotic and/or hemorrhagic complications, when the management of anticoagulation was based only on ACT values. Anti-factor Xa assay showed a moderate correlation with heparin dose, whereas the other tests correlated only weakly. The levels of anti-factor Xa were lower in the group with thrombotic complications, while aPTT was higher in the group with hemorrhagic complications. In patients experiencing DIC, heparin dose and anti-factor Xa levels were lower, while no differences in ACT and CT-INTEM and CT-Diff were seen.

The ACT, which is our standard assay to manage heparin administration on ECMO, showed only a weak correlation to heparin dose. This finding is consistent with prior studies of pediatric patients on ECMO (4, 11, 14–16) and may suggest that management of anticoagulation during ECMO based only on ACT measurements leads to sub-optimal anticoagulation in these patients. Although pediatric patients and neonates have physiologically prolonged aPTT values, several publications have shown a better correlation of heparin dose to aPTT compared to ACT, suggesting that the aPTT could be a more accurate test than the ACT to measure heparin effect in pediatric patients including neonates during ECMO (4, 14, 17, 18). Our findings

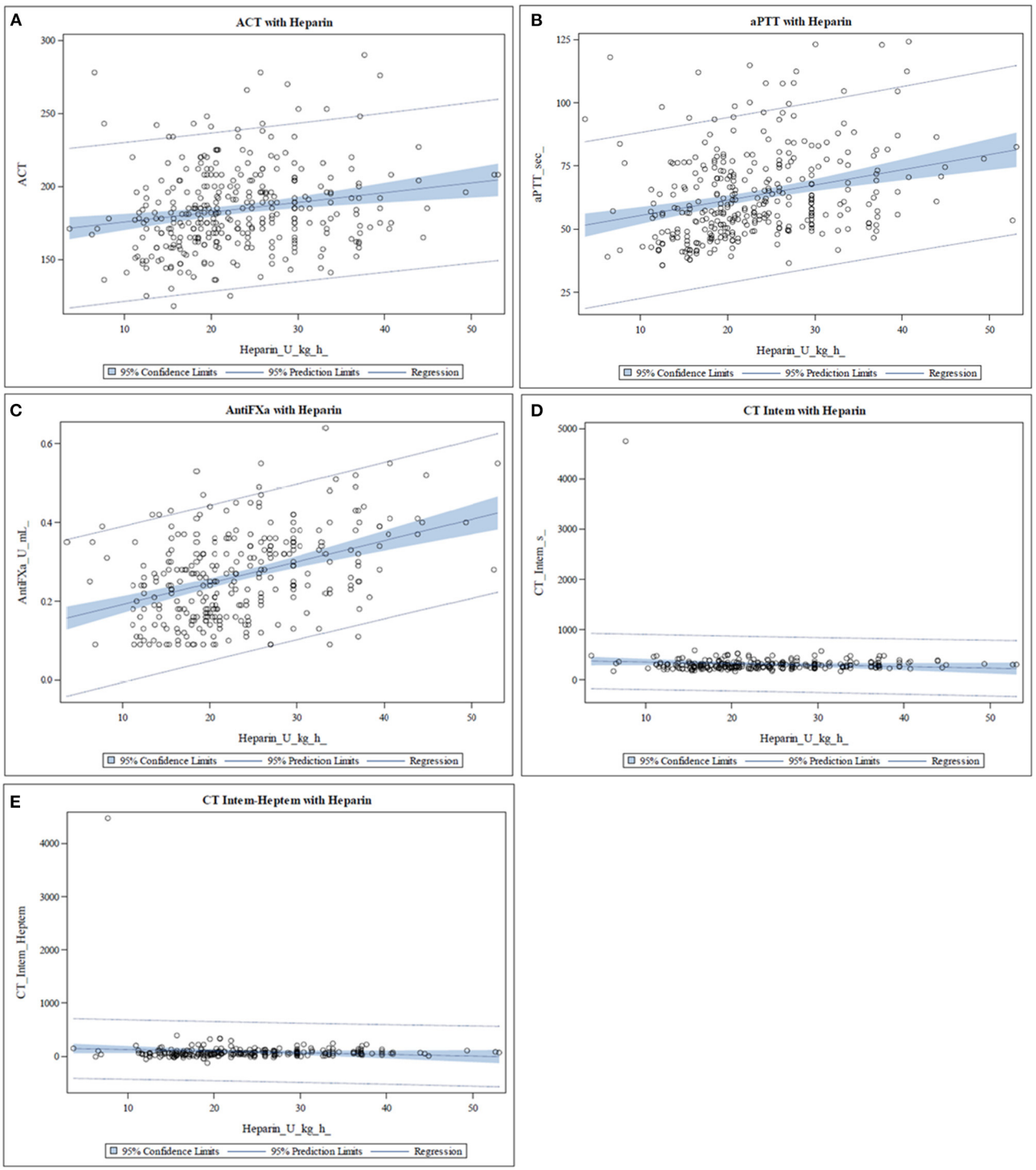

FIGURE 1 | Scatter plots representing the relationship between heparin dose and the different coagulation assays. The blue area represents the 95% confidence limit of the mean predicted values of the regression line. (**A–C**) The values of activated clotting time (ACT), activated partial thromboplastin time (aPTT), and anti-Xa assay increase with increasing heparin dose. In the case of anti-Xa assay, fewer outlying values and a steeper regression line are seen. (**D,E**) The slightly slanted horizontal line indicates a lack of sensitivity of the clotting time in INTEM (CT-INTEM) and INTEM-HEPTEM (CT-Diff) in response to a change in heparin dose.

do not support this hypothesis: the correlation of heparin doses to aPTT was only weak and not stronger than the correlation to ACT. Several studies have shown a more significant correlation of heparin dose to anti-factor Xa assay values in pediatric patients and neonates during ECMO, compared to ACT and aPTT values (4, 11, 15, 19). In our study, the anti-factor Xa assay showed the

TABLE 3 | Comparison of the median values from heparin dose and coagulation assays in the group of patients with and without thrombotic complications.

	Thrombotic complications[a]	No thrombotic complications[a]	*p*-value
Heparin dose (IU/kg/h)	21.2 (0–60.6)	20.6 (0–161.3)	0.39
ACT (s)	185 (125–999)	182 (118–999)	0.85
aPTT (s)	57.6 (36.7–151)	60.8 (28.7–151)	0.89
Anti-factor Xa (IU/ml)	0.23 (0.09–0.78)	0.27 (0.09–1.9)	**0.002**
CT-INTEM (s)	267 (195–1881)	286 (154–5126)	0.14
CT-Diff (s)	49 (−148 to 1597)	60 (−126 to 4785)	0.07

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CT-INTEM, clotting time in INTEM; CT-Diff, clotting time in INTEM minus clotting time in HEPTEM.
[a]*Median values and interquartile ranges.*
The bold values symbolize that the value is statistically significant.

TABLE 4 | Comparison of the median values from heparin dose and coagulation assays in the group of patients with and without bleeding complications.

	Bleeding complications[a]	No bleeding complications[a]	*p*-value
Heparin dose (IU/kg/h)	26.3 (0–44)	20.6 (0–161.3)	**0.03**
ACT (s)	185 (141–999)	182 (118–999)	0.90
aPTT (s)	69.4 (35.1–151)	59.8 (28.7–151)	**0.01**
Anti-factor Xa (IU/ml)	0.28 (0.09–0.75)	0.27 (0.09–1.9)	0.42
CT-INTEM (s)	297 (204–1235)	279 (154–5126)	0.15
CT-Diff (s)	61 (−46 to 960)	58 (−148 to 4785)	0.6

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CT-INTEM, clotting time in INTEM; CT-Diff, clotting time in INTEM minus clotting time in HEPTEM.
[a]*Median values and interquartile ranges.*
The bold values symbolize that the value is statistically significant.

TABLE 5 | Comparison of the median values from heparin dose and coagulation assays in the presence and absence of disseminated intravascular coagulation.

	DIC[a]	Absence of DIC[a]	*p*
Heparin dose (IU/kg/h)	15.1 (0–37.2)	20.8 (0–161)	**0.004**
ACT (s)	189.5 (143–289)	182 (118–999)	0.27
aPTT (s)	64.7 (47.4–151)	60.2 (28.7–151)	**0.04**
Anti-factor Xa (IU/ml)	0.16 (0.09–1.2)	0.27 (0.09–1.9)	**<0.0001**
CT-INTEM (s)	298 (237–1157)	278 (154–5126)	0.13
CT-Diff (s)	56 (−148 to 788)	58 (−126 to 4785)	0.60

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CT-INTEM, clotting time in INTEM; CT-Diff, clotting time in INTEM minus clotting time in HEPTEM; DIC, disseminated intravascular coagulation.
[a]*Median values and interquartile ranges.*
The bold values symbolize that the value is statistically significant.

strongest correlation to heparin dose. Nankervis et al. (11) found a strong correlation of anti-factor Xa assay to the administered heparin dose ($r = 0.75$), whereas the correlation in our study was only moderate ($r = 0.38$) and comparable to the findings of Bembea et al. (15) ($r = 0.33$). In the study of Nankervis et al. (11), the median heparin dose was 42.2 IU/kg/h, and the median value of anti-factor Xa assay was 0.7 IU/ml. These values are considerably higher in comparison with the median values reported by Bembea et al. (15) (34 IU/kg/h and 0.4 IU/ml) and our values (21.2 IU/kg/h and 0.26 IU/ml). This could suggest that the correlation of anti-factor Xa assay to heparin is stronger when higher heparin doses are administered.

Although the use of viscoelastic tests to monitor coagulation on ECMO is not widespread, the literature reports benefits of their use (20). Major obstacles for the use of thromboelastometry for coagulation management in neonatal ECMO are the scarcity of data on reference ranges for ROTEM® parameters in neonates and the lack of established therapeutic ranges for monitoring anticoagulation (19, 21). Panigada et al. concluded in a study of an adult population that the use of a thromboelastography-driven protocol to manage heparin anticoagulation during venovenous ECMO seemed to be feasible, not associated with an increased rate of complications, and even allowed the administration of lower heparin doses compared to the use of an aPTT-driven protocol (22). Northrop et al. (10) showed that the use of a protocol which included anti-factor Xa assays, AT measurements, and thromboelastometry was associated with a reduction of thrombotic and hemorrhagic complications in pediatric patients on ECMO. Henderson et al. (19) showed a feasible management of heparin administration using the thromboelastography in a study of pediatric patients and neonates on ECMO and established the optimal target for one thromboelastographic parameter for predicting a significant thrombotic event. In contrast to these findings, we did not find a strong correlation of the evaluated thromboelastometric parameters to heparin dose. CT-Diff correlated only weakly, and no significant correlation of CT-INTEM to heparin dose was found. The graphical representation of the obtained thromboelastometric values showed a lack of sensitivity of the tests in response to a change in the heparin dose.

Showing the strongest correlation to heparin dose is not enough to demonstrate a superiority of one coagulation assay to manage the anticoagulation during ECMO. The goal of anticoagulation during ECMO is to minimize thrombotic complications in patients and the ECMO circuit without increasing hemorrhagic complications. Therefore, in a study that compares different coagulation assays, these clinical complications should be considered.

Irby et al. (23) published the first study in 2014, which linked anti-factor Xa concentrations with clinically relevant thrombotic complications in pediatric patients during ECMO. This study suggested that higher anti-factor Xa activity levels were associated with a lower probability of requiring a change of the ECMO circuit. In our study, only anti-factor Xa assay out of the evaluated tests showed statistically significant values between groups with and without thrombotic complications. Because heparin was still being administered according to ACT values, median values of anti-factor Xa assay were below 0.3 IU/ml in both groups. According to the current literature, such values are in a sub-therapeutic range (3). Nevertheless, the median value of anti-factor Xa assay was significantly lower in the group with clinically relevant thrombotic complications in comparison with the group without thrombotic complications.

This observation would potentially suggest that dosing heparin according to anti-factor Xa assay values would not only lead to higher anti-factor Xa assay values but also to a greater difference in terms of thrombotic complications.

When considering hemorrhagic complications, only aPTT out of all evaluated coagulation assays was significantly higher in the group with clinically relevant bleeding in comparison with the group without hemorrhagic complications. The median dose of heparin infusion was also significantly higher in the group with hemorrhagic complications. This finding could suggest that monitoring aPTT could be important to prevent bleeding complications. In a systematic review, Willems et al. (24) compared time-guided vs. anti-factor Xa-guided anticoagulation strategies for UNFH titration in patients on ECMO. This meta-analysis showed that an anti-factor Xa-based anticoagulation strategy was associated with fewer hemorrhagic complications without an increase in thrombotic events, when compared to a time-based anticoagulation strategy (24). In contrast to these findings, we found no differences regarding anti-factor Xa values, when comparing the groups with and without bleeding events. However, we did not compare two different anticoagulation strategies. Nevertheless, the results shown in the study by Willems et al. (24) could suggest that an anti-factor Xa-based UNFH titration strategy could also reduce bleeding complications in neonatal patients on ECMO.

Values of ACT and aPTT are typically elevated in the setting of DIC. If heparin is titrated according to ACT values, it will need to be reduced to keep ACT in the target values. This finding is demonstrated in our study: while median values of ACT showed no significant differences, the median of the heparin dose and the median value of anti-factor Xa assay were significantly lower in the setting of DIC. In contrast, the median value of aPTT was significantly higher. No difference was observed by the thromboelastometric parameters CT-INTEM and CT-Diff. This finding supports that anti-factor Xa assay correlates better to heparin dose than ACT, aPTT, and the two evaluated parameters of the thrombelastometry. The clinical correlations of ACT, aPTT, and anti-factor Xa in the setting of DIC are relatively unknown and should be investigated in future studies (4).

Our homogenous study population, comprising only CDH patients, offered several advantages. First, confounders derived from the differences in hemostatic system between neonates and older children were avoided. Furthermore, general inflammation, as present in sepsis or pneumonia, which might affect coagulation, interfering and influencing the anticoagulation management during ECMO, was excluded.

There are several limitations to our study. First, even though we have a number of measurements conducted, the sample size is still small. Also, results may not be applicable to older children supported by ECMO, because of developmental hemostasis in neonates. A second issue is that the design of the study does not allow declaration of superiority and/or inferiority of one of the coagulation assays. In our study, anticoagulation was managed based on ACT values, and the other assays were only measured but not used for the management of anticoagulation. However, our results are consistent with prior studies in pediatric patients on ECMO. A prospective study to evaluate if managing anticoagulation based on anti-factor Xa assay measurements instead of ACT could reduce thrombotic and bleeding complications in neonates during ECMO is currently being conducted at our institution.

CONCLUSIONS

Anti-factor Xa correlates stronger to heparin dose than ACT and could be a more accurate method to dose anticoagulation with heparin in neonates during ECMO. Moreover, managing ECMO anticoagulation based on anti-factor Xa assay measurements instead of ACT could reduce thrombotic and bleeding complications in these patients. Nevertheless, the moderate correlation of anti-factor Xa assay to heparin dose indicated that it is not the ideal test. Furthermore, the anti-factor Xa assay does not provide any information about the status of the patient's hemostasis. To allow an optimal management of the anticoagulation during ECMO and to avoid complications, additional tests which can assess the status of the patient's hemostasis are probably necessary. The use of thromboelastometry does not seem to have any additional benefit for dosing heparin in neonates supported with ECMO. However, due to the potential information that viscoelastic tests can provide, the use of thromboelastometry in pediatric and neonatal ECMO should be further explored.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the Medical Faculty Mannheim of the University of Heidelberg (Ethics Committee II). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AP, CD, CW, SH, TS, and NR contributed to the concept and design, acquisition, interpretation of data, and drafting of the article. TJ and TD contributed to the interpretation of data and revised the article for important intellectual content. All authors approved the final version of the article.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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