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Neonatal Hypoxic Respiratory Failure: Referral for ECMO

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Abstract: Background: Neonatal hypoxic respiratory failure (HRF) secondary to PPHN (persistent pulmonary hypertension of the newborn) is an uncommon but life-threatening complication. Despite advances in therapeutic interventions, there are neonates who may require ECMO (extracorporeal membrane oxygenation), which improves survival. In establishing the capability of ECMO in transport in New South Wales, significant variation in referral thresholds and management of PPHN in referring hospitals has been noted. **Aim**: To review cases referred to the Newborn and paediatric Emergency Transport Service (NETS) for consideration of ECMO due to HRF in neonates. The aetiology of HRF, the number of retrievals and their short-term outcomes were reported. **Methods**: A retrospective audit of referrals to NETS (January 2019 to December 2022) of infants aged <28 days with HRF for ECMO. Patient demographics, management, advice at the time of call and the outcome are described. **Results**: The mean weight was 3511 g, mean gestation was 37.1 weeks and 69% of the patients were male. The main diagnoses were MAS/PPHN (50%), and there was variation in inotropes and ventilation strategies at the time of the referral. Six (25%) of the fifteen babies who were transported by NETS to paediatric intensive care were placed on ECMO at the referring hospital. A further six babies were stabilised at the referral centre following NETS co-ordinated specialist advice and did not require retrieval or ECMO. All the babies who received ECMO and survived had normal early development (<6 months) with normal head US or MRI imaging. **Conclusions**: Optimising ventilation and inotrope management can eliminate the need for ECMO prior to or following retrieval. Early referral for the consideration of ECMO and a collaborative discussion can assist in optimising conventional therapy, thus eliminating the need for ECMO. Neonates requiring ECMO for HRF have good survival rates with good short-term neurological outcomes.

Keywords: neonate; hypoxia respiratory failure; ECMO; transport

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1. Background

Persistent pulmonary hypertension of the newborn (PPHN) is a condition of disruption in the normal transition from foetal to neonatal circulation where pulmonary vascular resistance remains elevated with subsequent hypoxic respiratory failure (HRF) [1]. It occurs in approximately 0.2% of live-births and is associated with a mortality of 7.6% of all babies in the first year of life [2,3]. The risk of associated significant morbidity for these infants includes readmission for respiratory disease and neurodevelopmental disability (15–25%) [4,5].

PPHN may be primary, i.e., without an apparent cause, or secondary, i.e., due to lung parenchymal pathology (meconium aspiration syndrome (MAS), congenital pneumonia, surfactant deficiency, or maternal medications in pregnancy. Critical congenital heart defects (CCHDs) are an important differential, and echocardiography or point of care ultrasound (POCUS) is beneficial to clarify these diagnoses early in the treatment pathway [6].

Conventional therapeutic options for severe PPHN include oxygen therapy, mechanical ventilation, adequate sedation, muscle relaxation, targeted inotropic support, inhaled nitric oxide, sildenafil, and optimising acid base and electrolyte status [7–14]. ECMO is reserved for cases where conventional therapy has failed. Only 5–10% of neonates with an oxygenation index >20 require ECMO. Complex congenital heart disease, myocarditis and airway anomalies are also indications for ECMO in the neonate [15,16].

A retrospective data analysis has demonstrated the benefit of ECMO vs. conventional care in increasing survival and reducing disability at one year in babies with HRF [17–19]. ECMO is lung-protective while correcting hypoxia and hypercarbia [20].

ECMO is life-support for patients with refractory cardiopulmonary failure. Blood is drained from the vascular system, circulated outside the body by a mechanical pump and then reinfused. ECMO may be delivered in a veno-veno (VV) or veno-arterial (VA) circuit, during which haemoglobin becomes fully saturated with oxygen and CO_2 is removed. Oxygenation is determined by flow rate and CO_2 elimination is controlled by adjusting the rate of counter-current gas flow through the oxygenator [21]. To maintain flows without clotting, the blood undergoes finely controlled anti-coagulation. In VV ECMO, patients must have stable haemodynamics; two venous cannulas are placed, one for drainage and one for infusion. VA ECMO provides respiratory and haemodynamic support as blood bypasses both the lungs and heart. Blood is extracted from the right atrium or vena cava and returned back in via the aorta. VA ECMO is the standard of care for any baby with left ventricular dysfunction [22].

ECMO is increasingly available for neonatal patients due to advances in cannula technology (better flows from smaller cannulae) and the evolution of high-income setting paediatric intensive care and retrieval services. ECMO is available in the retrieval environment in Victoria and Queensland, and NSW recently established a Model of Care and a formal ECMO referral service [23] to enhance previous ad hoc arrangements.

The aim of this audit is to review referrals to the Neonatal and paediatric Transport Service (NETS) for consideration of ECMO for HRF in babies and report short-term outcomes (Appendix A). It is anticipated that these data will inform referral criteria consensus and future service development.

2. Methods

2.1. Participants

This was a retrospective audit of prospectively collected data of babies <4 weeks of age (28 days) referred to the Newborn and paediatric Emergency Transport Service (NETS) NSW with HRF/PPHN for discussion regarding ECMO candidacy. The NETS serves 254 hospitals in New South Wales, Australia, providing clinical advice (to referring hospitals) and transport for newborns, infants and children requiring intensive care in nine tertiary neonatal intensive care units and three specialist children's hospitals. The NETS team comprises a highly skilled critical care nurse and doctor.

All babies referred between January 2019 and December 2022 were included in this study.

2.2. Data Collection

Infants were identified from the NETS NSW patient care database by searching the following terms: PPHN, HRF, MAS and ECMO. Data are entered in this database by clinical co-ordinators and clinical teams as routine documentation of patient care. De-identified data were retrieved from the database and the electronic medical records (EMR).

2.3. Statistics

Statistical analyses were performed using IBM SPSS Statistics version 27 (IBM Corp, Armonk, NY, USA). Patient characteristics were described using proportions, means or medians.

2.4. Ethics

Ethics approval was obtained from the Sydney Children's Hospital Network Ethics committee (2022/ETH01334).

3. Results

3.1. Demographics

Between January 2019 and December 2022, there were 24 referrals to NETS for babies with HRF requesting ECMO. Patient demographics are presented in Table 1. The mean gestation and birth weight were 37.1 weeks and 3511 g, respectively. The majority of babies were male, 16 (69.6%), with 9 (37.6%) being delivered by emergency LSCS (lower segment caesarean section). The mean age of referral was 41 h, 36 min. Most babies referred had PPHN with MAS (50%). There was one baby with undiagnosed CCHD (total anomalous pulmonary venous drainage).

Table 1. Patient demographics.

Demographic	*n* = 24	Percentage
Weight (g)	3511 (2010–4512(mean)	
Gender	Male—16 Female—8	69.6 33.4
Gestational age (mean)	37.1 (34–41) *n* = 23	
Mode of delivery	NVD—8 Elective LSCS—5 Emergency LSCS—9 Unknown—2	33.3 20.8 37.6 8.3
Age at referral (hours)	41.6 h (mean) (1–456 h)	
Primary diagnosis	12 MAS/PPHN (1 with associated pulmonary haemorrhage and 1 with HIE)	50
	2 CDH (1 post repair)	8.3
	1 Gram-negative sepsis (MAS)	4.2
	2 congenital pneumonia	8.3
	4 primary pulmonary HT	16.6
	1 TAPVR	4.2
	1 massive pulmonary haemorrhage	4.2
	1 pulmonary hypoplasia—anhydramnios (Posterior urethral valves))	4.2

NVD—normal vaginal delivery, LSCS—lower segment caesarean section, MAS—meconium aspiration syndrome, PPHN—persistent pulmonary hypertension of the newborn, CDH—congenital diaphragmatic hernia, TAPVR—total anomalous pulmonary venous drainage.

3.2. Ventilation, Sedation and Inotropes (Table 2)

Table 2 summarises the respiratory and inotropic care at the time of referral. Three patients had a microcuffed endotracheal tube and fifteen patients were on high-frequency oscillatory ventilation at the referral unit. Twenty-one patients referred from an NICU were receiving iNO (20 ppm); three babies referred from centres without NICU capabilities were not. Variations in dosage and targeting choice of inotropes were noted with dobutamine and noradrenaline being the two commonest choices. The majority of babies were receiving at least two inotropes; six babies (24%) were on milrinone. Seven babies (29%) had received a dose of hydrocortisone.

Twenty-three (95%) of the patients who were intubated were sedated with morphine at the time of the call. In addition, three of these patients had a midazolam infusion running. One patient was sedated with fentanyl.

Table 2. Therapeutic management at the time of referral.

Therapy	Yes	No	Unknown
Oxygen FiO_2 > 60%	24	0	
Cuffed endotracheal tube	3	13	8
HFOV *	15	9	
Inspiratory time > 0.4 s	0	24	
Sedated with opiates	23	1	
Muscle relaxation	13	10	1
iNO	21	3	
Adrenaline	7	17	
Noradrenaline	9	15	
Dobutamine	16	8	
Milrinone	8	16	
Hydrocortisone	7	17	

* HFOV—high-frequency oscillatory ventilation; iNO—inhaled nitric oxide.

3.3. ECMO

Of the 24 referrals, 2 (8.3%) were not considered candidates due to irreversible lung hypoplasia (Table 3). Six patients (25%) improved following clinical advice coordinated by NETS and did not require retrieval. The initial clinical advice is provided by a neonatologist or paediatric intensive care consultant. Fifteen patients were retrieved by NETS, six were placed on VA ECMO at the referring hospital and connected directly to the mobile ECMO system on the modified NETS paediatric stretcher. The modifications include an additional securing arm with the console, pump and oxygenator securely attached. The heater is strapped to the floor of the ambulance or helicopter. It was the cardiothoracic surgeon's preference to place all the babies on VA as opposed to VV ECMO despite haemodynamic stability. One baby received ECMO at the receiving paediatric intensive care unit following retrieval, and one baby with severe MAS and perinatal asphyxia (not undergoing therapeutic hypothermia) died at the referring hospital prior to establishment of ECMO.

Table 3. Retrieval, ECMO and overall mortality.

	***n* = 24**	**Percentage**
Retrieved	On ECMO 6	25
	To an ECMO centre 9	37.5
	Improved at referring hospital 6	25
	Died 3	12.5
ECMO	Yes: 7	29.2
	No: 15	62.5
	Not a candidate: 2	8.3
Mortality overall	Total deaths 4/24 1 died awaiting ECMO (late referral) 2/2 died—not candidates as irreversible conditions 1/1 died after decannulation—severe recurring PPHN (alveolar capillary dysplasia with misalignment of pulmonary veins)	16.67

ECMO—extracorporeal membrane oxygenation; PPHN—persistent pulmonary hypertension of the newborn.

The mean time to place the baby on ECMO and stabilise to move was 5 h and 18 min. Four babies (66.8%) were transported by road ambulance, one was transported (16.6%) by rotary wing, and one was moved on foot via the connecting corridor between the perinatal centre and paediatric intensive care (Table 4).

Table 4. Details of the patients who received ECMO on retrieval.

	Description	Number of Patients
Retrieved (n = 24)		15
Location established on ECMO (n = 7)	Referring unit Receiving unit	6 1
ECMO mean stabilisation time (n = 6)	5.11 (4:13–5:55)	
Type of ECMO (n = 7)	VA ECMO VV ECMO	7 0
Mode of transport (n = 7)	Rotary wing Road ambulance Walk (connecting corridor) Unknown	1 4 1 1
Survival in ECMO patients (n = 7)		6 ^
Neurodevelopmental outcomes (n = 6)	Head ultrasound/MRI brain Normal development (<6 months)	6 6

^ One died following decannulation—capillary alveolar dysplasia. MRI—magnetic resonance imagings.

3.4. Outcomes

Six of the seven babies who received ECMO in this audit survived (85.7%) (Table 4). The baby who died developed severe PPHN following decannulation from ECMO and received palliative care. The autopsy confirmed alveolar capillary dysplasia. All babies who survived had normal early development (<six months) with a normal head US or MRI imaging.

4. Discussion

This study was a retrospective audit of prospectively collected neonatal patient referrals made between January 2019 and December 2022 to the recently established NETS NSW ECMO retrieval service [21]. Of the 24 patients referred, the most common reason for ECMO candidacy consideration was PPHN with MAS, followed by primary pulmonary hypertension, congenital pneumonia and congenital heart disease. This pattern of referral is consistent with previously reported neonatal ECMO referral cohorts [24,25]. In the systematic review by Bryner et al., the majority of neonatal cases had congenital cardiac disease (compared with PPHN/MAS in the NSW cohort) and similarly there was a male predominance [26].

Data relating to the cardio-respiratory management of NSW neonatal patients at the time of ECMO referral demonstrated notable variation between patients with regards to ET tube choice (cuffed vs. uncuffed), ventilatory mode and strategy (e.g., HFOV vs. conventional MV with long IT), sedation and muscle relaxation therapies, and circulatory support treatments. According to a recent survey of neonatologists and paediatric intensivists, these practice variations are consistent with neonatal PPHN management and treatment preferences between the subspecialist groups [27].

In response to the variation in ECMO-referred patient profiles, Sydney Childrens' Hospital Network and NETS NSW has subsequently developed a statewide referral process (Appendix A) to facilitate generally earlier and more consistent access to paediatric ECMO services.

Following NETS NSW ECMO referral and the resultant facilitation and provision of expert peri-ECMO teleconference advice by retrieval and receiving paediatric intensivist consultants, 25% of this cohort were stabilised locally and thus high-risk medical retrieval and ECMO was avoided. A further 37.5% of the cohort avoided ECMO treatment following retrieval to and stabilisation in the receiving intensive care unit. ECMO-avoidance amongst survivors in this patient group of around 50% is typical amongst reported cases and

likely results from a combined package of optimised expert retrieval and intensive care therapy [28]. Heulitt et al. emphasised that ECMO is resource intensive, and early referral, discussion and transport to an ECMO centre remain crucial [29].

Survival outcomes between patients transported on ECMO and those receiving ECMO in an ECMO centre are comparable [30–35]. Bryner et al. describes a 76% survival in 29 neonates with respiratory failure requiring ECMO in transport compared with 75% in the ELSO registry during the same period [26]. For babies with cardiac conditions, the survival was 67%. Survival has improved significantly over the years, with studies in the 1980s reporting survival rates of 31% in neonates with respiratory failure transported on ECMO; these improved to 91% in the 1990s [31]. In this audit, we, like others have shown previously, established that it is feasible and safe to transport babies on VA ECMO with an 85.7% overall survival rate. Concerning longer-term outcomes, Graziani et al. reports a 20% rate of cerebral palsy in 181 babies treated with VA ECMO. An additional 7% had sensorineural hearing loss [36]. The short-term neurodevelopmental outcomes at 6 months of age in this cohort for babies who received ECMO were good; they also had normal brain MRI and head ultrasounds. Although cognitive outcomes are likely to be normal for most survivors of ECMO support, visual–spatial ability, reading comprehension, communication, neuromotor deficits and school difficulties are common [36].

This study was predominantly limited by the retrospective nature and small cohort size, typical of critical care studies of infrequent intervention types. In addition, some data not collected at the time of initial referral, for example, PaO2 and oxygenation index, may be useful in assessing disease severity, which may have impacted the decision making regarding the timing of retrieval.

5. Conclusions

Mortality and morbidity outcomes following neonatal ECMO retrieval in NSW in this small cohort are comparable to published international data. Early referral for ECMO initiation is crucial for optimising care in HRF. A centralised expert multi-disciplinary ECMO referral teleconferencing service provides timely case management advice that may avert the need for ECMO.

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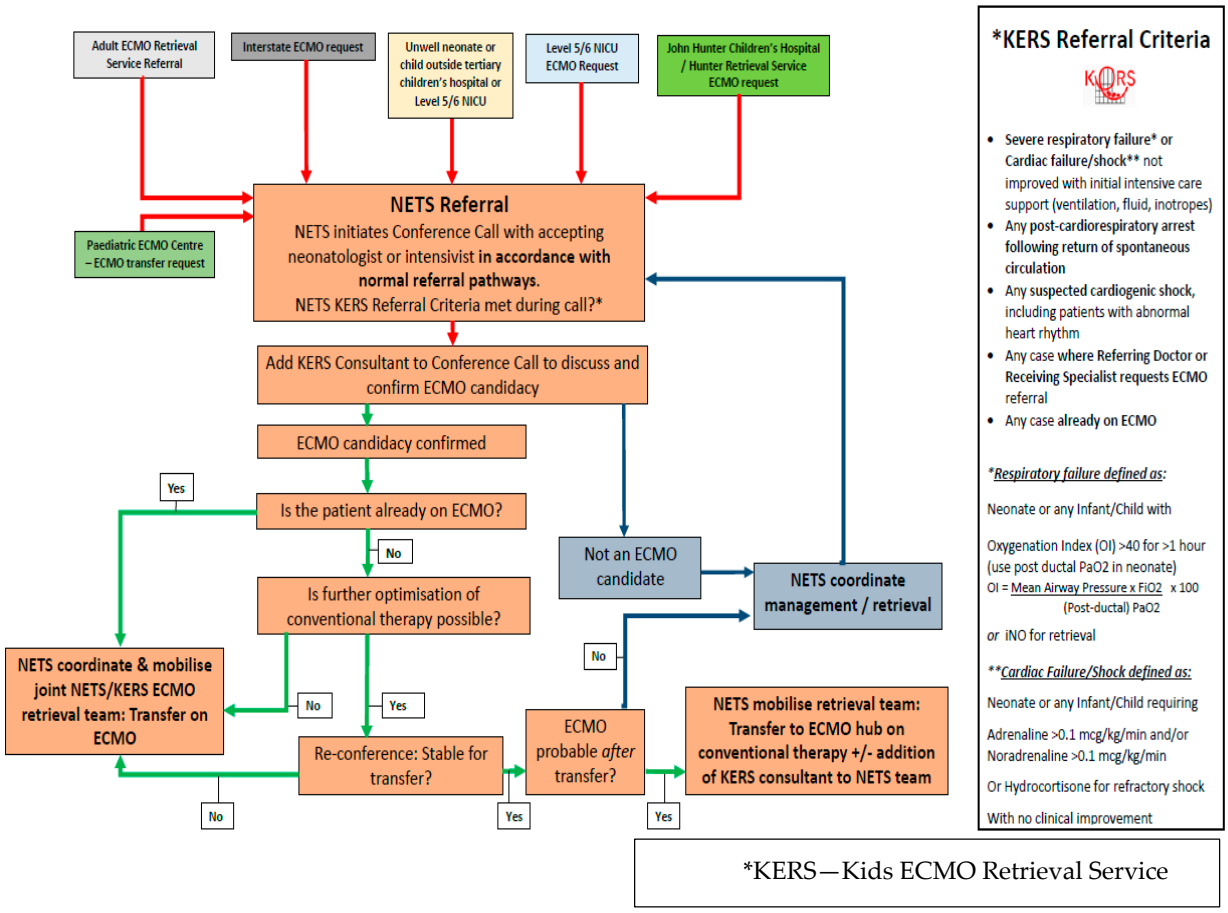
Informed Consent Statement: Patient consent was waived as this was a retrospective de-identified audit.

Data Availability Statement: Data are stored on a password protected database. The data presented in this study are available on request from the corresponding author due to privacy.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A. ECMO Referral Flow Chart



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