ORIGINAL ARTICLE

Predicting outcome in ex-premature infants supported with extracorporeal membrane oxygenation for acute hypoxic respiratory failure

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Objective: To identify predictors of outcome in ex-premature infants supported with extracorporeal membrane oxygenation (ECMO) for acute hypoxic respiratory failure.

Methods: Retrospective review of ex-premature infants with acquired acute hypoxic respiratory failure requiring ECMO support in the United Kingdom from 1992 to 2001. Review of follow up questionnaires completed by general practitioners and local paediatricians.

Results: Sixty four ex-premature infants (5–10 each year) received ECMO support, despite increased use of advanced conventional treatments over the decade. The most common infective agent was respiratory syncytial virus (85% of cases). Median birth gestation was 29 weeks and median corrected age at the time of ECMO support was 42 weeks. Median ECMO support duration was relatively long, at 229 hours. Survival to hospital discharge and to 6 months was 80%, remaining similar throughout the period of review. At follow up, 60% had long term neurodisability and 79% had chronic pulmonary problems. Of pre-ECMO factors, baseline oxygen dependence, younger age, and inpatient status were associated with non-survival ($p \leq 0.05$). Of ECMO related factors, patient complications were independently associated with adverse neurodevelopmental outcome and death ($p < 0.01$).

Conclusions: Survival rates for ex-premature infants after ECMO support are favourable, but patients suffer a high burden of morbidity during intensive care and over the long term. At the time of ECMO referral, baseline oxygen dependence is the most important predictor of death, but no combination of the factors considered was associated with a mortality that would preclude ECMO support.

Between 1992 and 2001, hospital survival in paediatric patients receiving extracorporeal membrane oxygenation (ECMO) support for respiratory failure was 50–60%, and, in neonates, it fell from 78% to 65%.¹ Since 1996, when the UK ECMO trial results showed reduced risk of death for neonates in the ECMO support group,² advances in conventional treatment have taken place,³ and the number of neonates supported per year has fallen world wide.¹ There have been no randomised trials comparing ECMO with conventional treatment in the paediatric group, because patient diagnoses are heterogeneous, numbers are small, and local practice patterns are variable.

Advances in perinatal care over the last decade have dramatically increased the number of survivors born at low gestational age and weight.^{4–6} Currently 1.8% of live births in the UK occur before 33 weeks.⁷ The most important secondary cause of respiratory morbidity for these infants is respiratory syncytial virus (RSV), which affects ex-premature infants with increased severity of illness.^{8–10} Available data indicate that the number of hospital admissions due to RSV rose from 484 in 1995 to 810 in 1998 in the West Midlands Region.¹¹ RSV prophylaxis has not been routinely administered to ex-premature infants in the United Kingdom,^{11–13} in contrast with North America where it is more widely used.^{14 15}

Ex-premature infants with acute hypoxic respiratory failure (AHRF) warranting ECMO support represent a formidable management challenge because they face the dual burden of prematurity and acquired acute lung injury. We aimed to evaluate immediate and long term outcomes for a cohort of ex-premature infants who were supported with

ECMO for AHRF and to assess potential predictors of outcome.

METHODS

Infants of gestational age less than 36 weeks who received ECMO support at the four UK ECMO centres between 1992 and 2001 were identified. Sixty four infants, who were born prematurely, survived the perinatal period, and subsequently re-presented with acquired acute respiratory failure requiring ECMO support, were included. Institutional ethics committee approval was obtained to perform a retrospective review of medical records and for completion of a follow up questionnaire by each subject's general practitioner and/or local paediatrician. Data on the following were collected:

- Neonatal factors: gestational age, birth weight, respiratory status, cranial ultrasound result (grade 1 intraventricular haemorrhage was not included as abnormal), neonatal intensive care unit (NICU) discharge age, and medical problems.
- Pre-ECMO factors: actual and corrected age, ECMO weight, virological or bacteriological diagnosis, baseline oxygen dependence, duration of ventilation, conventional treatment modalities (high frequency oscillation, surfactant, inhaled nitric oxide), inotrope requirement, and worst documented oxygenation index.

Abbreviations: AHRF, acute hypoxic respiratory failure; ECMO, extracorporeal membrane oxygenation; NICU, neonatal intensive care unit; RSV, respiratory syncytial virus

Table 1 Neonatal factors and survival to discharge after extracorporeal membrane oxygenation

Risk factor	Infants	Survivors
Ventilation at birth	48 (75)	40 (83)
Chronic lung disease	33 (52)	25 (76)
Medical problems of prematurity	15 (24)	12 (80)
Abnormal cranial scan	5 (8)	8 (80)
Discharged from NICU	52 (81)	44 (85)

Values in parentheses are percentage of the cohort in the case of the infants affected, and percentage of the affected infants in the case of the survivors.
NICU, Neonatal intensive care unit.

- ECMO related factors: type of ECMO support, duration of ECMO support, persistent arterial duct, renal support, and cranial ultrasound result. The following patient related complications were included: haemorrhage (either intracranial or other site) that required surgical intervention or discontinuation of ECMO support, major cannula related event (accidental decannulation or need for cannula change), circuit related septicaemia (culture positive), and more than three minutes of cardiopulmonary resuscitation. Major circuit related complications such as oxygenator failure or circuit rupture were also included.
- Outcome measures: survival to hospital discharge, number of ventilator days after ECMO support, respiratory problems, and neurodevelopmental problems resulting in disability (mild to severe) at follow up.

Follow up information

A questionnaire was sent to each patient's general practitioner and local paediatrician a minimum of six months after hospital discharge. An abnormal respiratory follow up score was awarded if there were symptoms requiring long term regular medical treatment such as inhaled steroids or supplemental oxygen. An abnormal neurological follow up score was awarded if there were neurodevelopmental problems resulting in functional impairment and requiring special assistance, aids, or long term treatment (mild to severe disability). These scores were not stratified further

Table 3 Pre-ECMO factors and survival to discharge after ECMO

Risk factor	Infants	Survivors
Oxygen dependent at baseline	22 (34)	14 (64)
NICU inpatient	12 (19)	7 (58)
Inotropes required	41 (64)	31 (76)
RSV positive	54 (85)	44 (81)
Culture negative bronchiolitis	7 (11)	6 (86)
<i>Bordetellapertussis</i>	3 (5)	1 (33)
Secondary bacterial pneumonia	8 (12)	6 (75)

Values in parentheses are percentage of the cohort in the case of the infants affected, and percentage of the affected infants in the case of the survivors.

ECMO, Extracorporeal membrane oxygenation; NICU, neonatal intensive care unit; RSV, respiratory syncytial virus.

because it was considered inappropriate to do so on the basis of the information available from a questionnaire.

Statistical methods

Cross tabulations of categorical variables were performed to investigate the relations between clinical and other factors. The importance of these relations was tested using a χ^2 test. T tests were used for continuous factors such as gestation. A logarithm transformation was used when investigating age at ECMO support because the distribution was positively skewed.

Univariate logistic regression was used to assess the importance of each of the neonatal, pre-ECMO, and ECMO factors in explaining the variability between patients in terms of three outcome measures, survival to hospital discharge, neurological problems, and respiratory problems (all coded as yes/no). Statistical significance was achieved when $p \leq 0.05$. Important factors on univariate analysis were incorporated into a multiple model. Interactions between factors were also considered.

RESULTS

The number of ex-premature infants receiving ECMO support in the United Kingdom during 1993–2001 was 64, with 51 survivors to hospital discharge (80%). Over the period of review, the number supported remained relatively constant at

Table 2 Univariate analysis of neonatal, pre-ECMO, and ECMO associated factors related to the outcome measures: survival to discharge, neurodevelopmental problems, and respiratory problems at follow up

	Survival (n = 64)	Neurodevelopmental problems (n = 42)	Respiratory problems (n = 42)
Neonatal factors			
Birth weight (kg)	0.60 (0.36)	0.87 (0.83)	0.62 (0.53)
Gestation	0.97 (0.80)	0.91 (0.36)	0.99 (0.97)
Ventilation at birth	2.27 (0.22)	6.27 (0.04)	–
Home (yes versus no)	3.93 (0.05)	1.13 (0.89)	0.81 (0.85)
Abnormal head ultrasound	1.07 (0.96)	0.27 (0.31)	–
Chronic lung disease	0.60 (0.42)	1.13 (0.85)	1.78 (0.49)
Medical problems	1.08 (0.92)	1.07 (0.93)	2.61 (0.40)
Pre-ECMO factors			
Oxygen dependent	0.24 (0.03)	1.13 (0.86)	1.15 (0.89)
Age (log days)	3.11 (0.05)	1.35 (0.49)	1.06 (0.93)
Ventilator days pre-ECMO	0.97 (0.67)	1.13 (0.22)	0.92 (0.38)
ECMO factors			
ECMO duration (log days)	0.38 (0.13)	9.23 (0.012)	1.06 (0.49)
Abnormal head ultrasound	0.90 (0.88)	1.29 (0.72)	1.09 (0.93)
ECMO complications	0.06 (0.008)	5.93 (0.018)	–
Weight (kg)	1.15 (0.63)	1.46 (0.29)	0.83 (0.64)
VA versus VV support	0.28 (0.09)	2.2 (0.24)	0.43 (0.32)

Values are odds ratio (p value).

ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous.

Figure 1 Advanced conventional treatment modalities used before extracorporeal membrane oxygenation by era. HFOV, High frequency oscillatory ventilation; iNO, inhaled nitrogen oxide.

5–10 cases per annum, and the proportion of survivors did not change.

Neonatal factors

At birth, median gestation was 29 weeks (range 24–36) and median weight was 1300 g (range 600–3000). Table 1 presents further neonatal intensive care related factors with univariate analysis in table 2. Infants who had been discharged home from NICU before ECMO support were more likely to survive (odds ratio 3.93; 95% confidence interval 1.0 to 15.5; $p = 0.05$), and a requirement for ventilation at birth was associated with an increased chance of disability at follow up (odds ratio 6.3; 95% confidence interval 1.09 to 36.2; $p = 0.04$).

Pre-ECMO factors

At referral for ECMO support, median age was 81 days (range 16–360), median corrected gestational age was 42 weeks (range 34–78), and median weight was 3 kg (range 2.1–8.6). Median worst pre-ECMO oxygenation index was 39 (range 19–72); however, these data were only available in 40 (62%) case notes. Median number of ventilator days before ECMO was 6 (range 1–20). Table 3 presents further pre-ECMO related factors with univariate analysis in table 2. Survival was more likely for those infants of older corrected age (age log days ratio 3.11; 95% confidence interval 1.03 to 9.43; $p = 0.05$). Oxygen dependent infants were less likely to survive (odds ratio 0.24; 95% confidence interval 0.07 to 0.85; $p = 0.03$).

There was a considerable increase in the proportion of infants treated with high frequency oscillation, surfactant, and inhaled nitric oxide during the later half of the review (fig 1). From 1993 to 1997 there were 33 survivors (79%), and from 1998 to 2001 there were 31 survivors (81%). Figure 2 shows the distribution of patient presentation by calendar

Figure 2 Number of cases of extracorporeal membrane oxygenation by month.

Table 4 Factors related to extracorporeal membrane oxygenation (ECMO) and survival to discharge after ECMO

Risk factor	Infants	Survivors
Venovenous (VV) support	30 (47)	28 (90)
Venoarterial (VA) support	30 (47)	21 (72)
VV to VA conversion	4 (4)	2 (50)
Renal support	16 (25)	7 (44)
Major patient complications	33 (52)	21 (63)
Major circuit complications	2 (3)	1 (50)
Persistent arterial duct	4 (6)	3 (75)
Abnormal cranial scan	18 (29)	14 (77)

Values in parentheses are percentage of the cohort in the case of the infants affected, and percentage of the affected infants in the case of the survivors.

month. Most cases occurred in the bronchiolitis season between October and March.¹¹

ECMO related factors

Median support duration was 229 hours (range 43–667). Six infants, of whom three survived, were supported for more than 504 hours. Support duration was related to the incidence of ECMO related complications, which represented a major source of morbidity. Table 4 shows further ECMO related factors with univariate analysis in table 2. ECMO complications affecting the patient considerably reduced the chance of survival (odds ratio 0.06; 95% confidence interval 0.007 to 0.48; $p = 0.008$) and increased the risk of neurodevelopmental problems (odds ratio 5.93; 95% confidence interval 1.36 to 26.0; $p = 0.02$). Duration of ECMO support was not related to survival, but was associated with neurodevelopmental problems at follow up as shown in fig 3 (log days odds ratio 9.23; 95% confidence interval 1.62 to 52.6; $p = 0.012$).

There were no significant differences in outcome between infants who received venoarterial and venovenous ECMO support. Those who received venovenous support had a mean pre-ECMO oxygenation index of 38, and 16 (53%) required inotropes. Twenty eight (90%) of these infants survived, and 15 (50%) had disability. Infants on venoarterial support had a mean pre-ECMO oxygenation index of 36, and 21 (70%) required inotropes. Of these, 21 (70%) survived and 20 (67%) had disability.

Patient outcome

Of 13 infants who died, the cause was multiple organ failure in six (9%), respiratory failure in five (8%), and intracranial

Figure 3 Duration of extracorporeal membrane oxygenation (ECMO) support and patient outcome in terms of survival and neurodisability.

haemorrhage in two (3%). Three (5%) late deaths occurred at 17 months, 49 months, and 59 months after ECMO support.

Multiple analyses of statistically important univariate factors indicated that the only independently important factors were: occurrence of ECMO complications affecting the patient (odds ratio 0.06; 95% confidence interval 0.007 to 0.49; $p = 0.01$) and oxygen dependence at initiation of ECMO support (odds ratio 0.23; 95% confidence interval 0.06 to 0.95; $p = 0.04$).

Data obtained on the number of ventilator days after ECMO support were inadequate for statistical analysis, because many infants were transferred between several hospitals after discharge from the ECMO centre. This information was available for 49 (77%) patients, in whom total duration of mechanical ventilation in the NICU ranged from 216 to 2441 hours and the mean NICU stay was 29 days.

Follow up data were obtained on 42 (82%) of the 51 hospital survivors, and nine (18%) patients were lost to follow up. Median time to follow up was 32 months (range 6–106), and median age was 35 months (range 9–113). Thirty three of 42 (79%) were receiving regular medical treatment for pulmonary problems. These included 12 (29%) who required long term home oxygen and 21 (50%) with asthma symptoms requiring regular medical treatment. No factor predicted the development of respiratory problems at follow up. Twenty five (60%) had disability, although the severity of this could not be stratified on the basis of the data available. Only two of the survivors traced (3% of the cohort) were described as free of both neurological and respiratory problems in the long term.

DISCUSSION

Patient outcome in terms of survival to hospital discharge (80%) compares favourably for this cohort of ex-premature infants with other respiratory ECMO data.¹ However, the long term information indicates that this superficially encouraging figure could be misleading, if taken out of context. Despite the advent of advanced conventional treatment modalities for AHRF and a worldwide reduction in neonatal ECMO support numbers,^{1–3} no change occurred in the number of ex-premature infants supported annually (or the survival rate) during the period of review. If this unchanging pattern reflects the increase in survivors of premature birth, then this group may remain a challenge in future years.^{4–6} Although a wealth of long term outcome data are available on survivors of neonatal respiratory ECMO support,¹⁶ there is a relative paucity of information on paediatric respiratory ECMO patients. Furthermore, as far as we are aware, this is the first study to provide predictors of outcome for this challenging group of infants who have experienced the double burden of prematurity and acquired acute lung injury.

Follow up at 6–106 months after ECMO support revealed three (5%) late deaths, long term respiratory disease in 33 (79%), and disability in 25 (60%) of the infants. The severity of respiratory morbidity was greater than that observed in survivors of RSV infection¹⁷ or the general population of NICU graduates born at 29 weeks, which was the median gestational age for the cohort.¹⁸ This concurs with the higher rates of disability for birth gestation found in preterm infants with a history of bronchopulmonary dysplasia¹⁹ and reported high levels of respiratory and neurological morbidity in a single institution review of outcome in nine infants with bronchopulmonary dysplasia who received ECMO support.²⁰

It is difficult to ascertain what proportion of the long term morbidity was a consequence of the NICU course and what proportion was attributable to the subsequent acquired critical illness. Certainly, the proportion of patients with

respiratory morbidity was greater in the available group who survived ECMO support (33; 79%) than in the whole cohort beforehand (33; 52%). Neurological status before ECMO was deemed within normal limits in all but one patient, who died, but this assessment was made at a median corrected age of only 42 weeks and should be viewed with caution.

Interpretation of our long term data is limited by several further factors, the most significant of which is the loss of nine (18%) patients to follow up. Considerable efforts were made to trace families who had moved to different parts of the country. This is an inherent limitation of a retrospective review of this kind. It was not possible to perform first hand medical and neurodevelopmental assessment of subjects and therefore the level of disability was not quantifiable. The young age at which some of our patients were followed up will have influenced our findings.

Of the factors considered, oxygen dependence at baseline was found to represent the only independently identifiable risk factor for death at the time of referral for ECMO support. However, even this risk factor was associated with a survival rate of 64%. Oxygen dependent infants experienced particularly high respiratory morbidity at follow up, with nine (64%) survivors requiring home oxygen and five (36%) discharged home in room air after prolonged stays in hospital. Younger corrected age and NICU inpatient status were associated with non-survival on univariate analysis, but multiple analyses indicated that these were related to the more important factor, baseline oxygen dependence.

Eleven (17%) infants, of whom nine (82%) survived, received 10–20 days of mechanical ventilation before ECMO support was initiated. These lengths of ventilation before ECMO fall outside the previously reported range compatible with acceptable survival rates.²¹ It is possible that a measure of pre-ECMO ventilation that takes account of cumulative mean airway pressure and fraction of inspired oxygen (oxygenation index days) would clarify its relation to recovery potential.

Statistically, the most important adverse risk factor for disability and death was the occurrence of ECMO related complications. Ex-premature infants with AHRF typically require long and challenging ECMO runs, the duration depending on the severity of lung disease. The average ECMO run for the ex-premature cohort was 11.3 days, which exceeds the average of 10.1 days for the paediatric respiratory category and 7.2 days for the neonatal respiratory category.¹ Inevitably, long ECMO runs result in prolonged exposure to the associated risks. If this ex-premature cohort is compared with the ECLS Registry report for all paediatric respiratory patients, the incidence of culture proven sepsis was 23% in ex-premature infants versus 21% in all paediatric patients, the incidence of cardiopulmonary resuscitation was 8% versus 5.9%, the incidence of surgical bleeding was 17% versus 17.3%, and the incidence of major intracranial bleeding was 8% versus 3.9%. Surprisingly, the development of cranial ultrasound abnormalities during ECMO support, which occurred in 18 (29%) of the cohort, did not appear to be associated with long term neurological outcome. The incidence was higher than the average of 21% observed in a large neuroradiology study of ECMO patients.²²

In conclusion, given the favourable long term survival rate, we believe that ECMO support should be offered to this cohort of patients. However, families and doctors should be informed of the considerable NICU and long term morbidity involved. Our current approach is to consider ECMO support for those with potentially reversible pulmonary disease, who have failed a trial of advanced conventional management and have an oxygenation index in the region of 40 or severe barotrauma. ECMO support is contraindicated for infants who have received more than 10–14 days of high pressure,

high fraction of inspired oxygen ventilation, have established pulmonary hypertension at baseline, or have major intracranial pathology.

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