Adjunctive Therapies for Treatment of Severe Respiratory Failure in Newborns

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Adjunctive Therapies for Treatment of Severe Respiratory Failure in Newborns

Additive Therapien in der Behandlung des schweren neonatalen Lungenversagens

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Key words
- adjunctive therapies
- ECMO
- mortality
- term or near term newborns

Schlüsselwörter
- additive Therapien
- ECMO
- Mortalität
- reifere Neugeborene

Abstract

Background: Severe respiratory failure of the newborn requires adjunctive therapies as application of surfactant, inhalation of nitric oxide (iNO), high frequency oscillatory ventilation (HFOV), or extracorporeal membrane oxygenation (ECMO). We designed this study to analyze the the usage and effectiveness of adjunctive therapies and the mortality of severe respiratory failure.

Patients and Methods: The survey in Germany was done in collaboration with the "Erhebungseinheit für seltene pädiatrische Erkrankungen" (ESPED). 397 patients within 2 years were included into the study. Effectiveness of each adjunctive therapy was judged by the treating physician.

Results: The most frequent diagnosis was respiratory distress syndrome (RDS) with 36.8%, followed by pneumonia sepsis (16.4%), meconium aspiration syndrome (MAS) and congenital diaphragmatic hernia (CDH). Surfactant was applied in 77.3% of all cases with a reported effectiveness of 71.6%. More than 40% of all patients were treated with iNO, which led to an improvement in every second case. HFOV was used in every third case with a response rate of about 60%. ECMO was performed on one in 7 patients and was sucessful with a survival rate of nearly 80%. The overall mortality was 10.3%. 29 patients in total died without ECMO. 10 of them might actually have been contraindicated, but 19 cases with a potential benefit from ECMO were not transferred for ECMO.

Conclusion: Our study-data suggests that more newborns suffering from respiratory failure should be transferred to centers offering ECMO.

Zusammenfassung

Hintergrund: Ein schweres neonatales Lungenversagen führt zum Einsatz von additiven Therapien, wie der Applikation von Surfactant, inhalativem Stickstoffmonoxid (iNO), der Hochfrequenz-Oszillationsbeatmung oder der extrakorporalen Membranoxygenierung (ECMO). Ziel dieser Studie war es Anwendung und Effektivität der additiven Therapien zu dokumentieren, und die Mortalität des schweren Lungenversagens zu analysieren.

Patienten und Methodik: Über die Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland (ESPED, Düsseldorf) wurden 397 Patienten innerhalb von 2 Jahren in die Studie aufgenommen. Die Effektivität der jeweiligen additiven Therapie wurde durch den behandelnden Arzt beurteilt.

Ergebnisse: Die häufigste Diagnose war der Surfactantmangel mit 36,8%, gefolgt von Pneumonie/Sepsis (16,4%), Mekoniumsaspirationssyndrom (MAS) und der kongenitalen Zwerchfellhernie (CDH). Surfactant wurde in 77,3% aller Fälle appliziert mit einer Effektivität von 71,6%. Mehr als 40% aller Patienten wurden mit iNO behandelt, mit einer Wirksamkeit von etwa 50%. HFOV wurde bei einem Drittel aller Fälle mit einer Wirksamkeit von 60% angewendet. Die ECMO-Therapie kam bei etwa jedem siebten Patienten zum Einsatz und war in fast 80% erfolgreich. Die Gesamtsterblichkeit innerhalb der Kohorte lag bei 10,3%. 29 Patienten starben ohne ECMO-Therapie. Davon konnten wir 10 Fälle ermitteln, welche für ECMO kontraindiziert gewesen wären. Die restlichen 19 Patienten, welche womöglich von einer ECMO-Therpaie profitiert hätten, wurden nicht an ein entsprechendes Zentrum überwiesen.

Schlussfolgerung: Die Daten legen nahe, dass mehr Neugeborene mit Lungenversagen an ECMO Zentren verlegt werden sollten.

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Introduction

Acquired pulmonary diseases of newborns at a gestational age of over 34 weeks are respiratory distress syndrome (RDS), pneumonia/sepsis, meconium aspiration syndrome (MAS) and transient tachypnea of the newborn (TTN). A variety of inborn conditions presents itself predominantly as pulmonary hypertension (PHT). Cases with severe respiratory failure may be difficult to treat and often require adjunctive therapies such as application of surfactant, inhalation of nitric oxide (iNO), high frequency oscillatory ventilation (HFOV), or extracorporeal membrane oxygenation (ECMO).

The clinical phenotype of severe respiratory failure in newborns over 34 weeks of gestation presents like an ARDS (ARDS: acute respiratory distress syndrome), development respectively persistence of PHT, or a combination of both. PHT is triggered by a variety of acquired diseases for instance RDS, pneumonia and MAS [13]. Other underlying causes for PHT are inborn diseases such as pulmonary hypoplasia associated with oligohydramnion or the congenital diaphragmatic hernia (CDH) [8, 15]; both conditions result in hypoplastic pulmonary vasculature and alveoli [3]. PHT is idiopathic in newborns (iPPHN) wherever a direct causative factor cannot be found. A dysregulation of molecular mechanisms in pulmonary artery muscle cells are suspected [19].

We propose that the outcome of the severe respiratory failure in newborns crucially depends on the timing and sequence of administration as well as on the ideal combination of available adjunctive therapies based on the understanding the respective pathophysiology. We designed this study to address the following questions:

- What is the prevalence of the severe respiratory failure in neonates > 34 weeks of gestation that requires treatment with one or more of the adjunctive therapies like surfactant, iNO, HFOV and ECMO?
- What is the outcome of the severe respiratory failure related to the different underlying disorders?
- Which adjunctive therapies are in use for the different etiologies of severe respiratory failure and how effective are they?
- What is the mortality of severe respiratory failure and how many deceased patients were treated with ECMO?

Material and Methods

This study was performed in collaboration with the "Erhebungseinheit für seltene pädiatrische Erkrankungen" (ESPED) in Düsseldorf (http://www.esped.uni-duesseldorf.de/). The survey period started on July, 1st 2011 and ended on June 30, 2013. During the survey period a short information- "Expose" about the study goals was published by the ESPED and sent to all children's hospitals in Germany requesting them to report their neonatal case numbers corresponding to our criteria of record monthly to the ESPED using study specific questionnaires (see below). We defined a severe respiratory failure as the need for mechanical ventilation plus the need for usage of adjunctive therapies.

Our criteria of record were:

- gestational age > 34 + 0 weeks of gestation
- respiratory failure (defined as under mechanical ventilation and $FiO_2 > 0.4$)
- application of at least one of the following adjunctive therapies: Surfactant, iNO, HFOV, ECMO

We supposed that an adjunctive therapy is added earliest if the oxygenation index (OI) is above 10. That means mean airway pressure is higher than 12 cm H_2O and FiO_2 higher than 0.4 in order to reach a minimum of 50 mm Hg pressure of oxygen in the arterial blood. ECMO may perform as safety net for the other adjunctive therapies and is indicated if the OI is above 40 or earlier if the other therapies failed.

The questionnaires were sent to us for evaluation of the different items. Each questionnaire was anonymously but specifically connected to one case number by an identification number. The questionnaire addressed general items like the primary diagnosis, gender, gestational age at birth and survival. The reporting children's hospitals were asked which of the adjunctive therapies they had used had had the greatest influence on improvement of the patient's condition. Additionally they were asked for ventilator settings and arterial blood gases in order to calculate indices for severity of disease like the oxygenation index ($OI = \text{mean airway pressure} \times FiO_2 \times 100/PaO_2$) or the PaO_2/FiO_2-ratio (as used in adult ARDS) of the patients before and after the onset of treatment with adjunctive therapies. Effectiveness of an adjunctive therapy objectively means significant improvement of OI or PaO_2/FiO_2 ratio (at least 10 units decrease in OI or 50 units increase of the PaO_2/FiO_2 ratio). Because we anticipated that some questionnaires are incomplete concerning to data of ventilator settings and measurements of arterial blood gases we additionally asked for an individual judgment of the effect of each adjunctive therapy by the treating clinician. Therefore we defined: effectiveness [%] = cases with a positive effect of the respective adjunctive therapy/cases which received the respective adjunctive therapy × 100.

Descriptive statistics were performed using the program "Microsoft Excel v.2007". T-Tests as well as a multivariate data analysis were performed using the statistical program "SAS". The calculation of the confidence interval for the effectiveness of the adjunctive therapies in **Table 1** was done under the approximation of normal distribution.

Results

According to the ESPED-List altogether 351 hospitals treating children in Germany were asked to report their cases. About 150 of them are perinatal centers at level I or II, which are responsible for our requested patients. In this prospective survey altogether 499 cases were reported by 102 different hospitals. 466 questionnaires (93.4%) were returned, but 69 of them were excluded because they did not fulfill the entry criteria of the study. Altogether 397 questionnaires were included into the analysis. The use of each adjunctive therapy and its effectiveness according to the clinician's judgment were listed by disease (**Table 1**). The most frequent diagnosis leading to severe respiratory failure and use of adjunctive therapies was RDS (36.8%). RDS was followed by pneumonia/sepsis (16.4%) and CDH (15.9%). MAS was reported as cause of severe respiratory failure in 15.9%, iPPHN in 4.0%, and transient tachypnea (TTN) in 2.5% of the cohort. 8.6% were summarized as "others" including perinatal asphyxia (n = 13), primary pulmonary hypoplasia (n = 7), pulmonary hemorrhage (n = 4), pneumothorax (n = 2), Surfactant-Protein disorders (n = 2), cystic malformations (CCAM) (n = 2), mediastinal teratoma (n = 1) and unclear diagnosis (n = 3). The mean gestational age of the total cohort was 37 + 4 weeks, it was lowest in the group of neonates suffering from RDS. 255 male neonates suffering from a severe respiratory failure were reported (64.2%).

Table 1 Distribution of diagnoses and rate of use as well as effectiveness in cases with use (judged by the treating clinician) of each adjunctive therapy in severe respiratory failure of the newborn > 34 + 0 weeks.

	Adjunctive therapy	rate of use (%)	effectiveness (%) ± confidence interval
	Surfactant	77.3	71.6 ± 4.4
total cohort	iNO	42.2	53.3 ± 4.9
n = 397	HFOV	33.3	61.4 ± 4.8
mean GA: 37 + 4	ECMO	14.9	81.4 ± 3.8
	Surfactant	96.6	88.0 ± 5.3
RDS	iNO	8.9	69.2 ± 7.5
n = 146	HFOV	17.8	73.1 ± 7.2
mean GA = 36 + 1	ECMO	2.1	100.0 ± 0.0
	Surfactant	89.2	67.2 ± 11.4
pneumonia/sepsis	iNO	38.5	72.0 ± 10.9
n = 65	HFOV	43.1	71.4 ± 11.0
mean GA = 38 + 2	ECMO	3.1	50.0 ± 12.2
	Surfactant	87.3	63.6 ± 11.9
MAS	iNO	58.7	75.7 ± 10.6
n = 63	HFOV	47.6	63.3 ± 11.9
mean GA = 40 + 1	ECMO	11.1	100.0 ± 0.0
	Surfactant	80.0	100.0 ± 0.0
TTN	iNO	10.0	0.0 ± 0.0
n = 10	HFOV	20.0	100.0 ± 0.0
mean GA = 36 + 3	ECMO	not used	not used
	Surfactant	14.3	11.1 ± 7.8
CDH	iNO	87.3	25.5 ± 10.8
n = 63	HFOV	27.0	17.6 ± 9.4
mean GA = 37 + 3	ECMO	65.1	85.4 ± 8.7
	Surfactant	56.3	33.3 ± 23.1
iPPHN	iNO	87.5	50.0 ± 24.5
n = 16	HFOV	56.3	55.6 ± 24.3
mean GA = 38 + 0	ECMO	18.8	33.3 ± 23.1
	Surfactant	79.4	37.0 ± 16.2
others	iNO	61.8	57.1 ± 16.6
n = 34	HFOV	55.9	63.2 ± 16.2
mean GA = 37 + 6	ECMO	8.8	33.3 ± 15.8

Table 2 Mortality, amount of used adjunctive therapies and ECMO use in severe respiratory failure.

	mortality (%)	amount of used adj. therapies (mean ± SD)	ECMO use (%)
total cohort n = 397	10.3	2.2 ± 1.2	14.7
RDS n = 146	4.8	1.5 ± 0.9	2.0
pneumonia/sepsis n = 65	6.2	2.5 ± 1.1	3.1
MAS n = 63	3.2	2.8 ± 1.3	11.1
TTN n = 10	0.0	1.3 ± 0.5	0.0
CDH n = 63	22.2	2.8 ± 1.0	65.1
iPPHN n = 16	25.0	2.9 ± 1.3	18.8
others n = 34	29.4	2.9 ± 1.0	8.8

Surfactant was applied in 77.3% of all cases with a reported effectiveness of 71.6%. According to its pathophysiology the best effects turned out in RDS patients and in the 3 other acquired respiratory disorders sepsis/pneumonia, MAS and TTN. More than 40% of all patients were treated with iNO, which led to an observed improvement in every second case. The adjunctive therapy HFOV was used in every third case with a judged response rate of about 60%. Leading diagnoses for HFOV were iPPHN and the group of "others". ECMO as the safety net in cases in which all other adjunctive therapies failed was performed on one in 7 patients and was very sucessful with a survival rate of nearly 80%.

Mortality, the use of all adjunctive therapies including ECMO and the rate of ECMO were listed in **Table 2**. The overall mortality of severe respiratory failure was 10.3% and highest in the group of "others" with 29.4%. We found the highest number of adjunctive therapies in this group followed by patients with iPPHN. Using ECMO was done often in these 2 groups as well as in CDH cases.

In **Table 3** we focused on the correlation between outcome parameters (survival and need for ECMO) and the extent of therapies as well as the severity of disease by OI and PaO_2/FiO_2-ratio. As expected the survival rate was lower in the group of patients who received ECMO-therapy than it was in the group of those not receiving ECMO. On average more adjunctive therapies (ECMO included) were used to treat patients within the ECMO-group compared to those who did not need ECMO. The overall percentage of ECMO-use was 14.7%. The rate of ECMO in the group of non-survivors was only 29.3%. 29 patients in total died without ECMO. Out of these 29 patients we found 10 cases that might actually have had a contraindication for an ECMO therapy with present diagnoses such as severe asphyxia, surfactant protein disorders or severe pulmonary hemorrhage. We have to state, that 19 remaining severe cases with a potential benefit from ECMO were not transferred to an ECMO-therapy.

Finally we investigated factors influencing survival (**Table 4**). For this purpose we divided the cases into a group with acquired affections of the lung (group1: RDS, MAS, pneumonia/sepsis and TTN) and a group with innate or likely inborn conditions including iPPHN, pulmonary hypoplasia, CDH and "Other diagnoses" (group 2). All investigated factors (number of applied adjunctive therapies, use of ECMO and improvement by physician's judgment) were significantly different between survivors and non-survivors.

Multivariate analysis revealed that only the subjective evaluation of the clinical response to adjunctive therapies seems to be an indepent variable predicting the outcome regarding survival or death ($P < 0.0001$; Chi^2).

Discussion

Over a 2 year period about 200 cases were included annually into our survey of severe respiratory failure in near term and term infants in Germany. We received data from 102 hospitals, that means two third of about 150 perinatal centers at level I and II responded. Extrapolated we may expect up to 300 cases every year with need for adjunctive treatment while on mechanical ventilation. Despite this lack the cohort provided a valid information about the etiologies of severe respiratory failure. In a similar cohort focusing on respiratory failure of newborns with a gestational age above 34 + 0 weeks of gestation in the USA 2005 Clark et al. also concentrated on adjunctive therapies [6]. In his cohort of 1011 patients with need for mechanical ventilation 85% received an adjunctive therapy which he defined broader by

Table 3 Outcome criteria survival and ECMO in correlation to severity of disease by amount of adjunctive therapy and oxygenation indices.

	amount of used adj. therapies (mean ± SD)	paO2/FiO2 before therapy (mean ± SD)	paO2/FiO2 after therapy (mean ± SD)	OI before therapy (mean ± SD)	OI after therapy (mean ± SD)
total cohort n = 397	2.2 ± 1.2	68.1 ± 38.2 available: n = 241	152.3 ± 91.2 available: n = 229	23.6 ± 16.1 available: n = 224	12.1 ± 13.6 available: n = 186
non-survivors * n = 41	2.9 ± 1.2	59.9 ± 29.8 available: n = 25	77.6 ± 41.6 available: n = 23	32.7 ± 24.7 available: n = 22	30.9 ± 23.6 available: n = 17
survivors n = 356	2.2 ± 1.2	69.0 ± 39.0 available: n = 216	160.6 ± 91.5 available: n = 206	22.5 ± 14.7 available: n = 202	10.2 ± 10.6 available: n = 169
ECMO# n = 59	3.5 ± 1.0	65.1 ± 24.7 available: n = 27	145.9 ± 64.8 available: n = 20	25.9 ± 15.5 available: n = 24	14.4 ± 15.2 available: n = 14
non ECMO n = 338	2.0 ± 1.1	68.5 ± 39.6 available: n = 214	152.9 ± 93.4 available: n = 21	23.3 ± 16.2 available: n = 200	11.9 ± 13.5 available: n = 172

* Rate of ECMO in non survivors was 29.3 %
#Rate of survival in ECMO was 79.7 %

Table 4 Factors influencing survival: Diagnoses, amount of adjunctive therapies, ECMO and subjective evaluation of the clinical response to therapy. Diagnosis-Group 1 contains: RDS, MAS, Pneumonia/Sepsis and TTN. Diagnosis-Group 2 contains: CDH, iPPHN, pulmonary hypoplasia and the group of "other diseases". Statistical p-values have been calculated performing TTests.

	survivors	non-survivors	p-value
Diag. group 1 n = 284	271	13	
Diag. group 2 n = 113	85	28	0.0008
one adj. therapy	208	15	
more than one	148	26	0.0119
ECMO	47	12	
no ECMO	309	29	0.0104
Response to therapy	353	8	
no response	3	33	< 0.0001

counting extra volume, alkalosis, vasopressors and neuromuscular blockade as adjunctive treatments. We found nearly the same distribution of diagnoses leading to respiratory failure. Ranking of the adjunctive therapies was also similar to our study. Nevertheless we assume that the group of children affected by CDH or children that received ECMO therapy might be slightly overrepresented within our total cohort, as the reporting rate from big centers was different.

Despite the high amount of RDS in near term infants and the widespread use of surfactant in these cases most studies concerning surfactant in this age group focused on conditions other than RDS. Controlled trials showed a positive effect of surfactant application in MAS and some uncontrolled trials showed a positive effect of surfactant therapy in MAS [14] by a reduction of air leaks [10] and need for ECMO. Mortality however was unchanged [4]. Furthermore data were published, that the application of surfactant may also be reasonable in treating pneumonia [11].

Especially the few non-responders to surfactant suffering of RDS should be considered as patients with inborn anomalies of the surfactant system. Generally, those infants with diffuse lung disease and no other cause of chronic respiratory symptoms should be evaluated for genetic abnormalities of the surfactant system (Surfactant protein B, Surfactant protein C; ATP-binding cassette A3, Thyroid transcription factor-1); if negative and continued symptoms, evaluation by lung biopsy for not yet molecularly defined surfactant dysfunction disorders, diffuse developmental disorders or interstitial lung disease due to deficient alveolarization should be performed [12].

Inhaled nitric oxide (iNO) is able to decrease pulmonary vascular resistance and thus pulmonary artery pressure by activating the intracellular guanylate cyclase [2]. By reducing the pulmonary artery pressure, iNO improves pulmonary blood flow and thus oxygenation in the lung and also reduces right to left shunting [18]. Any severe respiratory diseases in newborns (> 34 + 0 GA) which is associated with PPHN may be an indication for the use of iNO while on mechanical ventilation. A clear evidence was shown that iNO is able to reduce the need for ECMO in neonates > 34 + 0 weeks of gestation and respiratory failure [5]. On the other side non responders to iNO should be considered as ECMO candidates without any delay. Ongoing trials may determine if additional vasodilatation by drugs like sildenafil yields any benefit.

High frequency oscillatory ventilation (HFOV) is often used in order to facilitate CO_2 elimination without exposing the ventilated lung to otherwise harmful settings in conventional ventilation. The dynamics of gas exchange in the lung under HFOV are different from conventional ventilation and follows complex physical principles of convection and diffusion [16]. The wide use and positive clinical experience was reflected by our data and despite any proven evidence HFOV was judged to be effective by many clinicians. In fact, there are no studies showing a better survival by HFOV compared to conventional ventilation. But a single center study demonstrated, that HFO represents a promising ventilation technique in term neonates in whom conventional ventilation fails [7]. For instance, HFOV improves CO_2 elimination and may help avoiding respiratory acidosis, but there exists a risk of overdistention.

If a neonate > 34 + 0 weeks of gestation suffers from severe respiratory failure and is refractory to ventilator therapy then ECMO may represent a potentially live-saving therapy [1]. Evidence for ECMO is mainly based on the data from the UK ECMO collaborative study group. Not only is gas exchange secured by the oxygenator but ECMO can treat some circulatory problems at their root. As blood is removed from the right atrium in veno-arterial ECMO therapy, ECMO is also able to reduce right to left shunting due to PHT and may also unload the right ventricle and the pulmonary vascular bed. This is why the veno-arterial mode is used most often in infants suffering from diseases associated with suprasystemic pulmonary hypertension.

We observed an improvement in mean PaO_2/FiO_2 ratios and OI in the course of treatment regarding each diagnosis. Yet the values were not available in every case. We assume that a reason for this might be that not every children hospital in Germany uses arterial lines in every ill neonate. In congruence with the positive effects of adjunctive therapies we generally found a high

rate in response judged by the treating clinician. Failure of response to adjuctive therapies in contrast was shown to be a strong independent factor for a poor prognosis by multivariate analysis. The other factors for poorer prognosis like inborn disorders of the lung (diagnosis group 2), use of more than one adjunctive therapy or need for ECMO are probably more closely. The observed mortality of 10.1 % in severe respiratory failure of the newborn > 34 + 0 weeks of gestation indicates how serious underlying diseases may proceed. Especially the development of a pulmonary hypertension worsens the prognosis of the respective child. Many of the reported cases of death are found in CDH (22.2 % mortality in CDH). Primary pulmonary hypoplasia even shows a mortality of 71.4 %. Both CDH and pulmonary hypoplasia are diseases in which pulmonary hypertension develops due to vascular remodeling. As we demonstrated that this pathogenesis of pulmonary hypertension only shows a weak response to iNO therapy. This is why ECMO as the "last line" rescue therapy is used more often in these diseases. Mortality of patients who received ECMO-therapy was higher than in the overall cohort. This finding must not lead to the premature conclusion that ECMO raises mortality as an independent factor. The need for ECMO rather indicates the severity of the underlying condition since it should only be performed, if the respective child meets the ECMO-inclusion criteria and other forms of therapy are exhausted and/or it is foreseeable that they will not further improve the situation.

It is notable that only 12 cases of the 41 neonates who did not survive respiratory failure were moved onto ECMO therapy. This raises a central question of this study: Can mortality be reduced in severe respiratory failure of the newborn > 34 + 0 weeks of gestation if each child that might benefit from ECMO therapy would be transferred to an experienced ECMO-center in a timely manner. Given the survival rate of nearly 80 % after ECMO therapy in our cohort it seems safe to assume that most of the 19 patients who had no contraindication for ECMO might have survived with ECMO.. This is why we conclude that the mortality of the severe respiratory failure of the newborn can possibly be reduced by offering ECMO more offensively. Clark et al. only counted 4 deceased cases in Florida in which ECMO was not performed although his cohort was much larger [6]. Availability of ECMO and logistics for transfer in good time seem to be better established in Florida than in Germany. Concerning to our data we suggest a need of more runs of ECMO in Germany. As formerly reported, expertise in the method ECMO may arise by treating a minimum amount of 6 cases per year [9]. To our knowledge there are enough centers (6) offering ECMO for respiratory disorders in the newborn in Germany, but most of them with a significantly lower number than recommended. Therefore timing of contact, trust in expertise and possibilities for transfer should be reconsidered.

In summary we can state that only ongoing effort in the complex treatment of newborns with severe respiratory failure will lead to reduction in infant mortality. In a second step further studies concerning to morbidity need to be performed. Adjunctive therapies are very helpful in order to reduce ventilator associated lung injury by improving oxygenation and ventilation. They should be used according to the pathophysiology of the underlying disease in early phases of the clinical course and should be ready for use in all perinatal centers at level I and II. While using these therapies poor responders or non-responders should be offered to an ECMO centre without any delay [17]. The view on the widespread use of adjunctive therapies shows that there is need for a specialised transport service which provides these adjunctive treatment options especially during the transfer period.

Contributor's Statement

Patry C: data aquisition, drafting the manuscript Demirakca S; Hien S, Reinhard J, Majorek M: interpretation of data Brade J: Analysis of data Schaible T: revising the manuscript.

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