ORIGINAL ARTICLE

Nosocomial Infections in Neonates Supported by Extracorporeal Membrane Oxygenation: First French Retrospective Study

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Keywords: ECMO, Nosocomial infection
Indian Journal of Critical Care Medicine (2019): 10.5005/jp-journals-10071-23231

Introduction

Extracorporeal membrane oxygenation (ECMO) is a lifesaving technology widely used in neonatal population.[1–3] This procedure allowed a hemodynamic and/or respiratory support in case of refractory failure. Neonates under ECMO are a particularly exposed to secondary complication as hemorrhage, thromboembolism and oxygenator failure. Recent technology advance allowed to limits theses complications but nosocomial infections (NI) remained frequent in these very sick patients,[4] who probably are immunocompromised during ECMO.[5] Nosocomial infections are responsible for increased of mortality, mechanical ventilation, length of stay in intensive care.[6–8] To date, only few study report incidence and consequence of nosocomial infections in neonates under ECMO.[9–11] First objective of this study was to evaluate incidence rate of nosocomial infection in neonates under ECMO. Secondary end points were to find risk factors of NI and evaluated the outcome of the patients with NI.

Patients and Methods

Patients

This study was performed in Armand-Trousseau neonatal intensive care unit. We retrospectively reviewed all neonates who received ECMO for hemodynamic or respiratory refractory failure between January 2010 and June 2015. Venoarterial ECMO was initiated in case of refractory septic shock, congenital diaphragmatic hernia with severe pulmonary hypertension and right ventricular failure. Veno-Venous ECMO was initiated in case of meconium aspiration syndrome, congenital diaphragmatic hernia with pulmonary hypertension. Patients who had ECMO for less than 48 hours were excluded. All patients have almost two central venous lines, tracheal tube and a urinary tract catheter. All devices benefit from standard local infection prevention protocol.

Extracorporeal Membrane Oxygenation Implantation

ECMO was applied by trained vascular surgeons at bedside, with aseptic measure, because hemodynamic or respiratory instability makes it too dangerous to move the child. Cannulas are placed in the jugular vein and the carotid artery. The pumps used during this study were nonocclusive pumps with distensible tubing (A100, Sofracob®) and centrifugal pumps (Rotaflow, Maquet®). The membrane oxygenators used were the MedosHilite800LT® and Maquet Quadrox-iD pediatric®.

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How to cite this article: Rambaud J, Allioux C, Jean S, Guilbert J, Guellec I, Demoulin M, *et al*. Nosocomial Infections in Neonates Supported by Extracorporeal Membrane Oxygenation: First French Retrospective Study. Indian J Crit Care Med 2019;23(9):392–395.

Source of support: Nil

Conflict of interest: None

Definition of Nosocomial Infections

Neonatal nosocomial infection definition agreed with center for disease control recommendations. Central-line or ECMO cannula associated bloodstream infection is defined by at least one positive bloodstream culture associated with a positive culture of central line or cannula insertion site with the same microorganism. Two Positives bloodstream cultures were required in case of coagulase negative *Staphylococcus*, *Bacillus* spp, *Micrococcus* spp, *Corynebacterium* and *Propionibacterium*. Due to the temperature control during ECMO, bloodstream cultures were obtained each morning, in case of blood inflammatory syndrome or new hemodynamic failure. Ventilation acquired pneumonia (VAP) was defined by mechanical ventilation during more than 48 hours associated with new radiographic infiltrate and clinical deterioration (hypoxia or hypercapnia, fever >38°C or hypothermia, cardiac frequency higher than 170/min or lower than 100/min, white blood cells higher than 15,000/mm^3 or lower than 4000/mm^3, sputum alteration, majoration of respiratory distress and increased cough). No bacteriological data are necessary for ventilation-acquired pneumonia diagnosis in neonates. Nosocomial urogenital infection (UI) is defined by fever associated with leukocyturia (>10e4 leukocytes/mL) and positive uroculture (>10e5 microorganism/mL) in absence of ventilation-acquired pneumonia or central-line associated bloodstream infection. Urocultures were obtained in case of new systemic inflammation or hemodynamic failure.

Nosocomial infections under ECMO were defined by the diagnosis of a new infection after two days of ECMO.

Each patients chart's included sex, gestational age, birth weight, age at canulation, reason for ECMO initiation, SNAPPE II score (defined by birth weight, APGAR after 5 minutes of delivery, temperature, pH, median arterial pressure, PaO_2/FiO_2, urine output, seizures during the first twelve hours of life), inotropic score (defined by [epinephrine µg/kg/min x 100] + [norepinephrine µg/kg/min x 100]+ [dobutamine µg/kg/min x 10]), type of ECMO used, ECMO duration, time of onset of nosocomial infection, type of microorganism, type of nosocomial infection, central venous line duration and number of central venous line used, mechanical ventilation duration, used of continuous renal replacement therapy, intensive care unit lengths of stay, leukocytes count, initial and maximum CRP, red blood cells transfusion, platelets transfusion and fresh active plasma used per days of ECMO, survival rate.

Data for non-ECMO neonates come from a local database for critically ill neonates.

Statistical Analysis

Continuous variables are expressed as means ± standard deviations and were compared with a t test of student. Categorical variables were compared with a Pearson Chi-2 and are expressed as percentages. Statistical significance was defined by $p < 0.05$. All statistics were performed with SSPS software.

This study was approved by the Institutional Review Board of our hospital as an observational study.

Results

Patients

Ninety-one patients underwent ECMO during the study period. One patient had been excluded due to ECMO lengths <48 hours. Clinical and demographical patients' characteristics were not significantly different and are reported in Table 1. Reason for ECMO initiations are reported in Table 2.

Nosocomial Infections

Forty patients presented a NI (40/90: 44%), corresponding to a rate of 13.8 infections per 1000 days of intensive care hospitalization. Furthermore, the number of nosocomial infections corresponding to a rate of 30.3 Nis per 1000 days of ECMO (number of nosocomial infection during ECMO for 1000 days of ECMO). Mean time to the first infection was 15.3 days after ECMO starting. Patients suffering from Nis presented a significantly higher white blood cells count ($p = 0.002$) and CRP ($p = 0.001$). CRP at ECMO initiation was higher in the non-infected groups ($p = 0.004$). No significant difference was noticed for lymphocytes, polynuclear neutrophils.

The most frequent microorganism responsible for Nis was the *Staphylococcus* (42.5%). The other microorganisms are reported in Table 3. The most frequent nosocomial infection was central-line or ECMO cannula associated bloodstream infection. Twenty-six patients (65%) presented this kind of complication representing a rate of 12.9 infections per 1000 days of central line. Fifty-three percent of the bloodstream infections were related with a

Table 1: Population characteristics.

	No Ni (N = 50)	*Ni (N = 40)*	*p*
Male. N (%)	30 (60)	16 (40)	0.075
Gestational age (weeks)	39 ± 2	39 ± 2	0.411
Birth weight (g)	3277 ± 368	3212 ± 638	0.567
SNAPPE II	41 ± 19	33 ± 19	0.048
Inotropic score (µ/kg/min)	150.3 ± 167.2	90.2 ± 106.1	0.051
Antibiotherapy before Ni N (%)	49 (98)	36 (90)	0.095
Initial leukocytes count (G/L)	12717 ± 8179	19992 ± 12527	0.002
Polynuclear neutrophiles (G/L)	8930 ± 6821	12800 ± 9623	0.074
Lymphocytes (G/L)	3157 ± 3626	3203 ± 2422	0.955
Initial CRP (mg/L)	55.7 ± 73.4	28.9 ± 32.8	0.044
Age at ECMO implantation (days)	4.9 ± 5	5.7 ± 5.4	0.44
V-A ECMO N (%)	30 (58.8)	26 (65)	0.548
V-V ECMO N (%)	21 (41.2)	14 (35)	0.548

CRP, C = reactive protein; V-A ECMO, venoarterial extracorporeal membrane oxygenation; V-V ECMO, venovenous extracorporeal membrane oxygenation; Ni, nosocomial infection; SNAPPE II, score for neonatal acute physiology and perinatal extension II

Table 2: Reason for ECMO initiations

Initial disease	*No Ni N (%)*	*Ni N (%)*	*Overall N (%)*
Meconium aspiration syndrom	14 (15.6)	20 (22.2)	34 (37.8)
Congenital diaphragmatic hernia	17 (18.8)	10 (11.1)	27 (30)
Septic shock	2 (2.2)	12 (13.3)	14 (15.5)
ARDS	7 (7.8)	6 (6.7)	13 (14.5)
Cardiac disease	0	2 (2.2)	2 (2.2)

ARDS, acute respiratory distress syndrome; Ni, nosocomial infection

Table 3: Microorganism responsible for nosocomial infections.

Ventilation acquired pneumonia		*Bloodstream infection*		*Urogenital infection*	
Organism	*N (%)*	*Organism*	*N (%)*	*Organism*	*N (%)*
Escherichia coli	3 (28)	*Staphylococcus epidermidis*	14 (53.8)	*Escherichia coli*	2 (66)
Stenotrophomonas	2 (18)	*Pseudomonas aeruginosa*	3 (11.4)	*Candida albicans*	1 (34)
Staphylococcus epidermidis	1 (9)	*Staphylococcus aureus*	2 (7.7)		
Enterobacter aerogenes	1 (9)	*Stenotrophomonas*	2 (7.7)		
Collibacille	1 (9)	Polymicrobial	1 (3.8)		
Acinetobacter baumani	1 (9)	*Enterobacter cloacae*	1 (3.8)		
Candida albicans	1 (9)	*Klebsiella pneumoniae*	1 (3.8)		
Unknown	1 (9)	*Aspergillus*	1 (3.8)		
		Candida parapsilosis	1 (3.8)		

Staphylococcus epidermidis and 11% to *Pseudomonas aeruginosa*. The other microorganisms are related in Table 3. Ventilation-acquired pneumonias were responsible for 27.5% of Nis, representing a rate of 4.3 VAP per 1000 days of mechanical ventilation. *Escherichia coli* represented 46% of the microorganism implicated in VAP. The other microorganisms are related in Table 3. Urogenital infections are involved in 7.5 % of Nis representing a rate of 1.7 (UI) per 1000 days of urinary catheter. *Escherichia coli* and *Candida albicans*, respectively represented 66% and 34% of the microorganism.

Outcomes

Global survival rate was 55.6%. Survival rates in infected and non-infected patients were respectively 62.7% and 47.5%, without significant difference. Survival was not significantly different considering the type of Nis. Extracorporeal membrane oxygenation support (10.7 ± 5.5 vs 19.4 ± 10, $p < 0.0001$), duration of mechanical ventilation (21.2 ± 11.5 vs 37 ± 21.4, $p < 0.0001$), central line (17.6 ± 12.3 vs 28 ± 17.8, $p < 0.0001$) and length of stay in intensive care (24.6 ± 15.9 vs 41.1 ± 25.7 days, $p < 0.0001$) were significantly longer in infected patients. Renal replacement therapy was not significantly different in both groups. Consumption of red blood cells (2.6 ± 2.3 vs 5.4 ± 3.8, $p < 0.0001$) and platelets (7.6 ± 7.1 vs 16.1 ± 10.9, $p < 0.0001$) were significantly higher in infected patients but daily adjusted, consumption of apheresis and red blood cell were not different in both groups.

Discussion

We describe the infectious complications and outcome in neonates under ECMO for respiratory or hemodynamic refractory failure. In our study, rate of nosocomial infections in neonates under ECMO is significantly higher than non ECMO neonates (13.8 vs 8.8 per 1000 days of intensive care hospitalization). Adjusted with the length of ECMO, the risk of Nis in our population is 30.3 per 1000 days of ECMO. To date, only few studies have reported Nis in neonates under ECMO.[11] Bizzarro et al.[12] retrospectively described in neonatal population a lower risk (10.1 per 1000 days of ECMO) but Schmidt et al.[6] and Sun et al.[13] reported higher rate of Ni between 55 and 30 per 1000 days of ECMO. This difference could be explained by the characteristics of the studied population. Indeed, Bizzarro et al[12] excluded all patients with infection before ECMO implantation. In our study, 14 nosocomial infections occurred in patients under ECMO for refractory septic shock.

We first describe precisely all different types of Nis with the ecological status and outcomes for each kind of infection. Central line bloodstream infections, ventilation-acquired pneumonias and urogenital infections occurred in 65%, 27.5 % and 7.5% with a rate of 12.9 per 1000 days of central line, 4.3 per 1000 days of mechanical ventilation and 1.7 per 1000 days of urinary catheter, respectively. Surprisingly, ventilation acquired pneumonia are not more frequent in our neonates under ECMO but central line infections occurred more frequently than neonates without ECMO. This difference could be explained by the implantation of two ECMO catheters in the cervical zone. Indeed, multiplication of exogenous materiel is significantly associated with a higher risk of nosocomial infection. As previously described,[12] the probability of remained Ni-free decreased with the duration of ECMO. In our study, the mean delay of Ni occurrence was 15 days. These result comforts us in using an aggressive weaning strategy to prevents some case of Nis. We confirmed the severe consequences of Nis with longer duration of ECMO, mechanical ventilation, central line and intensive care unit hospitalization. Due to the small size of our population, we were not able to perform a cost study of Nis under ECMO but longer duration of ECMO, mechanical ventilation, and intensive care unit hospitalization probably had substantial consequences for financial cost of each hospitalization.

Recently, studying of the immune system in septic shock underlie the possibility of immune dysfunction after septic shock which may be responsible for nosocomial infections.[14] We can hypothesize that neonates under ECMO, which is already responsible for hemolysis and thrombopenia, may also suffered from impairment of white blood cells function. Indeed, monocytic HLA has been tested in intensive care patients and seems to be associated with prognosis and secondary infection.[15,16] To date, evaluation of HLA DR in neonate under ECMO had only been reported once[5] but suggest dysfunction of this immune system. Neutrophils dysfunction in neonates under ECMO had been reported in 1993 by DePuydt et al.[17] with significant phagocytosis impairments. Furthermore, Seeburger et al.[18] reported alteration of genes expression in leukocytes depending on the type of coating for ECMO circuits which resulted in an increasing of inflammatory genes expression. Further studies are needed to explain this "dysimmunity" and better identifying patients with potential immune failure. Monitoring the immune response[19] during ECMO could provide useful data and allow immune-modulatory treatment for the more severe patients.[15,20]

Conclusion

Nosocomial infections during neonate ECMO remain severe complications with impairment of patient outcome. Care bundle to prevent ventilation acquired pneumonia and central line bloodstream infections are a strongly recommended. The "dysimmune approach" seems to be a promising research program requiring prospective study in neonates under ECMO to confirm the first data.

What we know:

- Patients under ECMO often suffer from nosocomial infection

What needs to be studied:

- Immune response of neonates under ECMO
- Immune response of critically ill neonates

What can we do today:

- Strongly monitored infectious parameters during neonatal ECMO
- Systematic protective isolation for neonate under ECMO

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