Neonatal Sepsis and Extracorporeal Membrane Oxygenation Support: Pushing the Envelope

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Dr. Robert Bartlett was the first to support a neonate with extracorporeal membrane oxygenation (ECMO) in 1975. Esperanza, a 1-day-old infant with severe meconium aspiration syndrome (MAS) was failing conventional medical therapy. Dr. Bartlett placed her on ECMO, supported her heart and lungs for 3 days, and then was able to wean her back to conventional medical therapy [1]. Since that first neonatal success story, improvement in equipment, changes in medical management and available therapies, and the patient population for which ECMO is used, have tremendously transformed.

There are three clinical trials to support the use of ECMO in neonates. The first one in 1985 was conducted by Bartlett et al. [2] using a randomized play-the-winner design. This study included 12 patients, 11 of whom were randomized to ECMO. All 11 survived and the one patient treated with conventional medical therapy died.

The second study was a larger trial published by O'Rourke et al. in 1989 [3], also using an adaptive randomization scheme. Thirty-nine neonates with persistent pulmonary hypertension of the newborn (PPHN) and/or respiratory failure with an estimated 85% mortality risk were included. The overall survival rate of ECMO patients in this study was 97%.

The UK Collaborative ECMO Trial Group published a large, definitive randomized controlled trial in 1996 [4]. In total, 185 neonates were randomized to conventional medical therapy or to transfer to an ECMO center (78 of 93 in this group received ECMO). This study showed a relative risk of death of 0.55 when comparing the ECMO group to the conventional medical therapy group. The study was terminated early due to a clear survival advantage in the ECMO group [5].

Neonatal sepsis is a heterogeneous entity with different clinical presentations. During the neonatal period, depending on several factors, sepsis can present with different cardiovascular clinical features. Lack of transition from fetal to neonatal circulation with severe persistent pulmonary hypertension of the newborn (PPHN) and persistent fetal circulation is a frequent complication of early onset sepsis (0–3 days). Late onset sepsis (4–28 days) can have the same clinical features of early onset sepsis or can present with increased systemic vascular resistance (SVR) and severely reduced left ventricular (LV) function and cardiac output, disseminated intravascular coagulation, and multiple organ failure (MOF). These differences in presentation correlate with the physiological changes the myocardium and vascular system undergo during the first weeks of life [6].

Despite early reluctance of the ECMO community in supporting adults and children with septic shock due to high morbidity and mortality, ECMO has been utilized routinely for the neonatal population with reported survival rate of up to 70% [7-10].

From 2012 to 2017, the Extracorporeal Life Support Organization (ELSO) reported that, of all neonates receiving ECMO, in less than 10% the indication was sepsis [11]. In neonates where sepsis presented as right ventricular (RV) failure, pulmonary hypertension, and hypoxemia, indications for initiation of mechanical support did 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 hours, 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. However, for neonates whose sepsis presented with systemic inflammatory response (SIRS), refractory septic shock (RSS), and MOF, the only indication for mechanical support provided by the latest ELSO guidelines was pressor resistant hypotension [11]. Currently, there is no consensus on level of inotropic/vasoactive support, degree of organ dysfunction, period from onset to MOF, or frequency of medical therapy escalation that should trigger ECMO initiation for neonates with RSS [6].

As skills, experience, and technology have rapidly advanced, the use of ECMO in extreme scenarios has become common practice over the years, with significant modifications of the contraindications for ECMO support [Table 1].

In this issue of the *Israeli Medical Association Journal* (*IMAJ*), Rabinowicz and colleagues [12] reported on the case of a neonate with *Listeria monocytogenes* refractory septic shock who, at the age of 24 hours, was successfully supported by veno-arterial ECMO. The manifestations were PPHN and RSS. The infant was decanulated after 84 hours and converted to conventional treatment. Hospital discharge at the age of 6 weeks and neurologic follow-up at 8 months of age was normal except for mild

Table 1. Contraindications to ECMO according to the ELSO guidelines [17]

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: • The condition is irreversible and/or • There is no timely, reasonable therapeutic option and/or • High likelihood of poor neurological outcome
2. Absolute contraindications: • Extremes of prematurity or low birth weight (< 30 weeks gestational age or < 1 kg) • Lethal chromosomal abnormalities (e.g., Trisomy 13 or 18) • Uncontrollable hemorrhage • Irreversible brain damage
3. Relative contraindications: • Intracranial hemorrhage • Less extreme prematurity or low birth weight in neonates (< 34 week gestational age or < 2.0 kg) • Irreversible organ failure in a patient ineligible for transplantation • Prolonged intubation and mechanical ventilation (> 2 week) prior to ECLS

ECLS = extracorporeal membrane oxygenation support, ELSO = Extracorporeal Life Support Organization

hypotonia and gross motor developmental delay. This case is an impressive example of a prompt and efficient utilization of a legitimate technology.

Depending on the clinical features of sepsis, neonatal support can be achieved with either venovenous ECMO or veno-arterial ECMO. Historically, venovenous ECMO 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 left atrium, 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 venovenous ECMO support. In clinical practice, there have been no predictors able to identify for which neonates venovenous ECMO will provide sufficient myocardial support, thus eliminating the need for venoarterial support. Failing cardiovascular support with persistent acidosis, reduced lactate clearance and low mixed venous saturation on venovenous ECMO should trigger early conversion to venoarterial ECMO via cannulation of the carotid artery [6]. In an ELSO database review of ECMO in septic children, venovenous ECMO was mostly used in the neonatal age (87%) compared to older children (13%) and associated with improved survival when compared to venoarterial ECMO (83% vs. 70%, respectively) [10].

Septic neonates in whom the clinical presentation is primarily depressed myocardial function with progressive LV dilatation and increased SVR require venoarterial ECMO. This modality provides the best level of cardiovascular support to the failing heart, ensuring adequate blood flow, and oxygen delivery to organs with simultaneous decrease of inotropic/vasopressors agents with their potential complications [6].

Cerebral infarction or hemorrhage remain the more significant and severe complications. In an ELSO database review, 22% of neonates cannulated peripherally onto venoarterial ECMO developed a neurologic injury [13]. The duration of ECMO support for sepsis is generally 4 to 6 days and varies on the microorganism, clinical presentation (pneumonia vs. shock), timing of ECMO, and pre-existing end organ dysfunction [6]. In the 2012–2016 ELSO registry report, 168 neonates received ECMO for sepsis, 41 of whom had primary diagnosis of pneumonia and an average duration of support of 163 hours (longest duration was 1155 hours) [11]. Similar duration of mechanical support is reported in other single-center studies on neonates and children with sepsis [14-16]. In neonates with chronic or pre-ECMO lung disease and/or acute post-infective lung damage with cystic transformation, longer duration of ECMO might be expected to limit ventilator-induced lung injury.

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 pre-ECMO organ dysfunction. Predominant pathophysiological features should dictate modality of support, venovenous ECMO for right ventricular failure, and PPHN or venoarterial ECMO for left ventricular failure and RSS.

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Capsule

Heat seeking in mosquitoes

Mosquitoes seek hosts using several cues, one of which is body heat. **Greppi** et al. hypothesized that cooling-activated receptors could be used for locating mammalian hosts if they were rewired downstream for repulsion responses. A gene family conserved in insects and known to be responsible for sensing changes in temperature in fruit flies was the starting point. Genome-wide analyses and labeled CRISPR-Cas9 mutants allowed visualization of the receptor in neurons of *Anopheles gambiae* mosquitoe antennae and assessment of adult female mosquitoes with a disrupted copy of the receptor. This ancestral insect temperature regulatory system has been repurposed for host-finding by malaria mosquitoes.

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Capsule

A weird way to recognize phosphoantigens

In contrast to the well-studied αβ T cells, which recognize peptide antigens presented by major histocompatibility complex (MHC) and MHC-like molecules, how γδ T cells recognize antigens remains largely a mystery. One major class of γδ T cells, designated $V\gamma9V\delta2^+$, is activated by small, phosphorylated nonpeptide antigens, or phosphoantigens, produced by microbes and cancer cells. **Rigau** and co-authors found that these cells needed the combination of two immunoglobulin superfamily members, butyrophilin 2A1 (BTN2A1) and BTN3A1, on their cell surface to recognize these phosphoantigens. BTN2A1 directly binds the $V\gamma9^+$ domain of the T cell receptor (TCR), whereas a second ligand, potentially BTN3A1, binds the Vδ2 and γ-chain regions on the opposite side of the TCR. A better understanding of this unexpected form of T cell antigen recognition should inform and enhance future γδ T cell–mediated immunotherapies.

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Capsule

Rewiring the adolescent brain

As children go through adolescence, many undergo profound and occasionally disruptive changes in behavior. How does this map onto changes in the developing brain? Using functional magnetic resonance imaging in healthy young people (14 to 26 years old), **Váša** and colleagues observed two modes in functional connectivity between brain regions. By 14 years of age, conservative regions, often specialized for basic sensory and motor functions, are already strongly connected and consolidate further as an adolescent reaches adulthood. By contrast, disruptive regions, activated by complex tasks, show shifts in connectivity as a person transitions between the ages of 14 and 26. The disruptive maturation of connectivity between cortex and subcortex may reflect metabolic remodeling that underpins development of sophisticated adult faculties, such as socializing, mentalizing, and executive skills.

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"The first principle is that you must not fool yourself - and you are the easiest person to fool"

Richard Feynman, (1918–1988), Nobelauriate in physics. American theoretical physicist known for his work in the path integral formulation of quantum mechanics, the theory of quantum electrodynamics, and the physics of the superfluidity of supercooled liquid helium, as well as in particle physics