Impact of Changing Cannulation Strategies on Neurologic Injury in Infants with Respiratory Failure: HUM00236110

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Aims and Approach:
From 2019-2021, there was increased use of venoarterial (VA) extracorporeal membrane oxygenation (ECMO) for infants with respiratory failure, up to 92% of neonatal respiratory support in 2021. Our primary aim is to estimate the average effect on the rate of neurologic injury of VA ECMO versus venovenous (VV) among infants with respiratory failure over the period 2013-2018, during which clinicians could choose either cannulation strategy. We will estimate this causal effect using an inverse propensity weighted (IPW) approach. Secondarily, we will project this estimated treatment effect forward into the period 2019-2021. The beginning of this period roughly corresponds to start of increased use of VA ECMO. Under the assumption of a homogenous treatment effect across both study periods, we will estimate the rate of neurologic injury that *would have* occurred in 2019-2021, had the rate of VA ECMO *not* increased relative to pre-2019 levels. We hypothesize that our results will point to an increased rate of neurologic injury starting in 2019 due to the increased use of VA ECMO.

Outcome:
The outcome will be the composite occurrence of neurologic injury (ischemic stroke, intracranial hemorrhage, and brain death) that arises during critical illness supported by ECLS as reported to the Extracorporeal Life Support Organization (ELSO) registry, coded as a 0/1 variable (0 = no occurrence was reported during or after ECMO; 1 = one or more occurrence was reported).

Exposure:
The exposure / treatment of interest is the initial cannulation mode used, coded as a 0/1 variable (0= VV dual-lumen or two-site; 1= VA peripheral cannulation only).

Study Population:
We will analyze data from the ELSO registry. All runs satisfying the following inclusion and exclusion criteria will be included in our study population:

Inclusion criteria:
- Patient weighed less than or equal to 10kg at start of ECMO
- Pulmonary support was the indication for ECLS
- Initial cannulation strategy was VV or VA
- The run occurred during the period 2013-2023

Exclusion criteria:
- Patient had CDH
- Patient was post-cardiotomy
- Non-conventional initial cannulation strategies were employed, such as
    - Central Cannulation (surrogate for inability to achieve peripheral cannulation)
    - Veno-veno-arterial ECMO
    - Initial cannulation approach reported as “other”
- Patient was transported into or out of ELSO center on ECMO support
- Patient had pre-ECLS Cardiac Arrest
- Patient did not have subsequent ECMO runs in the ELSO registry

In addition, to the above criteria, all otherwise-eligible runs from centers that do not have at least one eligible run from each exposure group during the study period will be excluded.

Statistical Analysis Plan:

Step 1 will estimate the probability of being in the exposure group during a period when clinicians could choose either VV or VA ECMO. Among the subsample of patients from the period 2013 to 2018, we will fit a logistic regression model using pre-cannulation center and patient factors to predict the probability of a patient receiving VA ECMO.

We will include in this model factors that precede the start of ECMO and are posited to be associated with both the choice of cannulation strategy as well as the risk of neurologic injury.

We will include the following predictors in the propensity score model:
Unit Type- multinomial categorical
Admitted at birth -binary
Age at cannulation (days)- continuous
Gestational age (semi-continous to 38 weeks, term infants will older infants will be classified together)
Transfer into the ECMO center- binary
Weight (cont)
Sex- binary
Intubation to Time On (continuous)
Pre-ECLS pH (continuous)
Pre-ECLS pCO2 (continuous)
Pre-ECLS PO2 (continuous)
Pre-ECLS HCO3 (continuous)
Pre-ECLS FiO2 (continuous)
Pre-ECLS Mean Airway Pressure- oscillator (continuous)
Pre-ECLS Mean Airway Pressure- conventional (continuous)
Pre-ECLS Mean Arterial Pressure (continuous)
Pre-ECLS Pulse Pressure (continuous)
Pre-ECLS Renal Replacement Therapy- binary
iNO- binary
Inhaled epoprostenol- binary
Therapeutic Hypothermia- binary
Vasoactive Infusions- binary
Diagnoses

- Meconium Aspiration Syndrome- binary
- HIE- binary
- Pulmonary hypoplasia- binary
- Respiratory Distress Syndrome- binary
- Persistent Pulmonary Hypertension- binary
- Pulmonary Hypertension- binary
- Sepsis- binary
- Asthma- binary
- Bronchiolitis- binary
- Pneumonia - binary
- Pertussis- binary
- PDA- binary

We will also take into account each center's typical proclivity for VV versus VA ECMO, using either a mixed-effects modeling strategy or the surrogate indicator approach of Li, Zaslavsky, and Landrum (2007)

In **Step 2**, we will estimate the average treatment effect (ATE) of VA-ECMO in the period 2013-2018 using an IPW approach. We will estimate the ATE using an appropriate estimator that takes into account the clustered nature of the data (runs clustered within ELSO center).

Because the availability of VV ECMO cannulas appropriate for infants changed in 2019, we expect that at this point and afterward clinicians generally chose VA ECMO support more often than they otherwise would have. Using the propensity score model developed in Step 1, we will calculate propensity scores for patients cannulated during 2019-2021, estimating the propensity that a given patient would have received VA ECMO <u>had they received ECLS support in 2013-2018</u>. Using these estimated propensities, in **Step 3**, we will project this estimated ATE from the 2013-2018 cohort into the 2019-2021 cohort, thereby estimating what the rate of neurologic injuries would have been had the availability of VV ECMO cannulas not changed (and assuming a homogenous treatment effect of VA ECMO across periods). If there is a large enough sample size, we will perform a sensitivity analysis in a cohort from 2022-2023, during which there was increased availability of VV-ECMO cannulas and increasing use of VV-ECMO support.

<u>Missingness in the predictors</u>

We anticipate that there will be sporadic missingness in the predictors used to construct the propensity scores. We will use the approach recommended in Leyrat, et al. (2019) to incorporate the partial information available from observations with missingness. Specifically, we will create multiply imputed versions of the data, estimate a separate ATE for each of these completed datasets, and then combine the estimated ATEs across imputations to obtain a single estimated ATE.

<u>References</u>

Leyrat, C., et al. (2019). "Propensity score analysis with partially observed covariates: How should multiple imputation be used?" <u>Stat Methods Med Res</u> **28**(1): 3-19.

Li, F., et al. (2007). <u>Propensity score analysis with hierarchical data</u>. Proceedings of the American Statistical Association Joint Statistical Meetings.