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# Reduced Intracranial Hemorrhage with Anticoagulation Guideline Implementation

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**Abstract:** Hemorrhagic and thrombotic complications, including intracranial hemorrhage, embolic stroke, surgical bleeding, and circuit thrombosis, are common during extracorporeal membrane oxygenation (ECMO), occurring in up to 50% of patients. These complications have a significant impact on morbidity and mortality. Our objective was to implement standardized ECMO anticoagulation guidelines for the pediatric cardiothoracic intensive care unit (CTICU) to reduce the incidence of intracranial hemorrhage while on ECMO. All CTICU patients who received ECMO from January 2016 to December 2020 were retrospectively reviewed. Standardized ECMO anticoagulation guidelines were implemented in the fourth quarter of 2017. Variables and clinical outcomes before and after guideline implementation were compared. From January 2016 to December 2017, there were 22 separate ECMO runs. Eight of 22 (36%) suffered intracranial hemorrhage while on ECMO. Seven of 8 (88%) were withdrawn from ECMO secondary to bleed and expired prior to hospital discharge. From January 2018 to December 2020, there were 22 separate ECMO runs in the CTICU. Three of 22 (14%) suffered intracranial hemorrhage while on ECMO. One of 3 (33%) expired prior to hospital discharge. Implementation of standardized ECMO anticoagulation guidelines in the CTICU was successful in improving clinical outcomes as evidenced by reduction in the incidence of intracranial hemorrhage in this high-risk patient population. **Keywords:** pediatrics, ECMO, anticoagulation, outcomes. *J Extra Corpor Technol. 2022;54:318–23*

Exposure of blood to the extracorporeal membrane oxygenation (ECMO) circuit initiates the contact factor pathway, activates platelets, and induces an inflammatory response. Anticoagulation is necessary to prevent clotting in the circuit. Titrating the anticoagulation to prevent the ECMO circuit from clotting and prevent bleeding in the patient remains a major challenge (1). Hemorrhagic and thrombotic complications, including intracranial hemorrhage, embolic stroke, surgical bleeding, and circuit thrombosis, are common and occur in up to 50% of patients (2). These complications have a significant impact on morbidity and mortality.

Children are at a greater risk of imbalances in hemostasis with thrombotic or hemorrhagic complications, and a need for higher weight-based doses of anticoagulants to reach the same target anticoagulation level compared to adults. Unfractionated heparin is the most common anticoagulant used, but it requires antithrombin to exert its anticoagulant effects (1). Antithrombin levels are markedly reduced in children compared with adults which further complicates the issue (3).

Several coagulation assays can be used to monitor and titrate unfractionated heparin. To reduce high complication rates, many pediatric ECMO centers have incorporated these coagulation assays, including activated clotting time (ACT), partial thromboplastin time (PTT), heparin anti-Xa level, antithrombin activity, and thromboelastography (TEG), in their routine monitoring. Most centers have developed their own guidelines for managing anticoagulation; there is significant practice variation (4). General guidelines for managing anticoagulation in ECMO have been summarized and published by the Extracorporeal Life Support Organization (ELSO) (5). The objective of this quality improvement project was to implement standardized ECMO anticoagulation guidelines in the pediatric cardiothoracic intensive care unit (CTICU) to reduce

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the incidence of intracranial hemorrhage in this patient population.

## METHODS

### Ethical Issues

This quality improvement work (single center, retrospective review of the data) involved development of standardized ECMO anticoagulation guidelines in the CTICU. No interventions involved comparison of multiple devices or therapies, and patients were not subjected to randomization. Medical records were accessed by quality improvement team members as part of their normal responsibilities. Per institutional policy, this project does not meet the definition of human subject research. Therefore, institutional review board review was not required at our institution.

### Setting

Nationwide Children's Hospital is an academic, nonprofit, freestanding children's hospital located in Columbus, OH. The CTICU is a 20-bed unit with over 600 admissions per year. All cardiothoracic surgical patients undergoing repair or palliation of congenital heart disease are admitted to the CTICU for postoperative management. The CTICU staff includes a multidisciplinary team of critical care and cardiology physicians (n = 10), pediatric cardiac surgeons (n = 4), advanced practice nurse practitioners (n = 17), a dedicated clinical pharmacist (n = 1), registered nurses (n = 61), respiratory therapists (n = 21), cardiology and critical care physicians in fellowship training, clinical dieticians, physical and occupational therapists, child life specialist, and social worker.

### Planning the Intervention

Retrospective review of all patients in the CTICU who received ECMO in 2016–2017 revealed inconsistencies in the 1) starting time for anticoagulation; 2) starting dose of unfractionated heparin; and 3) coagulation assays used for anticoagulation management (ACT, PTT, Xa). All three assays were obtained and used differently by the practitioners for adjustments in heparin anticoagulation. The most frequent assay used was anti-factor Xa. Anti-factor Xa assay does not consider the role of platelets and fibrinogen in forming a stable clot. Underestimating the role of platelets and fibrinogen may lead to over-anticoagulation. Intracranial hemorrhage and mortality in this patient population was increased when compared to the ELSO database (pediatric CNS hemorrhage 5%; neonatal CNS hemorrhage 15%). It was felt that our patients were likely over anticoagulated given the high incidence of intracranial hemorrhage compared to ELSO and our management with anti-factor Xa. These issues led to a quality initiative to develop and implement standardized guidelines for ECMO anticoagulation. A multidisciplinary team was recruited to develop and implement standardized guidelines for ECMO anticoagulation in the CTICU. The team included physicians, ECMO team leaders, perfusionists, advanced practice nurse practitioners, a pharmacist, and representatives from the quality improvement team. A SMART (specific, measurable, achievable, realistic, timely) specific objective statement and key driver diagram was created (6, 7). Patient factors, lack of guidelines, staff education, staff accountability, and measurable outcome were identified as key drivers.

### Intervention

The interventions included development of standardized ECMO anticoagulation initiation and maintenance guidelines for CTICU patients on ECMO to reduce variation that were simple and minimally controversial; creation of electronic medical record order set for the initiation and maintenance of ECMO anticoagulation to simplify use; education and training of the CTICU staff regarding the guidelines and goals; obtaining CTICU staff buy-in and accountability; and development of outcome and compliance measures. The guidelines focused on 1) reducing the patient bolus heparin dose at ECMO initiation (from 200 units/kg to 100 units/kg); 2) following ACT for the first 24 hours rather than PTT or Xa; 3) following PTT rather than Xa for the subsequent time on ECMO; and 4) reducing our starting dose of heparin (Figure 1). Standardized ECMO anticoagulation initiation and maintenance guidelines for CTICU patients were instituted at the end of 2017.

### Method of Evaluation and Analysis

Once implemented, data on the compliance and specific clinical outcomes (intracranial hemorrhage and survival to hospital discharge) of the ECMO anticoagulation guidelines were tracked. Compliance and clinical outcomes data were reviewed following each ECMO run and at monthly ECMO staff meetings as part of a Plan-Do-Study-Act cycle to maintain buy-in with the new guidelines. Several patients in 2020 were anticoagulated utilizing bivalirudin (The Medicines Company, Parsippany, NJ) rather than unfractionated heparin (Hospira, Lake Forest, IL) per surgeon preference. These patients were excluded from analysis.

### Statistical Analysis

Retrospective review of ECMO anticoagulation guideline usage and outcome variables were performed with comparison of patients from January 2016 to December 2017 (before the standardization guidelines) and January 2018 to December 2020 (after the standardization guidelines). Data are expressed as median and ranges where

- After ECMO initiation, draw ACT Q15 min from Cardiohelp circuit
- When ACT < 225 seconds, call attending and APN to discuss bleeding and circuit status.
  - If **NOT** bleeding:
    - Prime Cardiohelp pre-oxygenator pigtail with 50 units Heparin (0.5 ml of 100u/ml Heparin, Yellow syringe) DO NOT FLUSH
    - Start Heparin drip at **10 u/kg/hr**
  - If **Bleeding**, continue to check ACT Q15 min.
    - Attending MD to consult with CT surgeon re: starting Heparin based on bleeding amount and circuit findings.
- After starting Heparin drip, check ACT Q1 hour x first 24 hours
  - Draw from the patient's A-line or CVL
  - Ensure appropriate waste is drawn from line (might be from a heparinized line)

**Heparin management:**

- First 24 hours:
  - If ACT < 180 seconds, give one hour Heparin bolus and increase drip 10%
  - If ACT 180-220 seconds, no change
  - If ACT > 220 seconds, decrease Heparin drip 10%
  - If ACT > 250 seconds, turn Heparin off x 1 hour and restart drip at 50% of current Heparin rate
- After 24 hours:
  - Discontinue ACT
  - Draw PTT Q4 hours
    - Titrate Heparin dose based on PTT results, NOT Anti Xa
    - Ensure Heparin is at 'steady state' prior to drawing lab (minimum of 3 hours after any heparin drip change or Heparin bolus)
  - If PTT < 60 seconds, give one hour Heparin bolus, and increase Heparin drip by 10%
  - If PTT 60-80 seconds, no change
  - If PTT > 80 seconds, decrease Heparin drip by 10%
  - If PTT > 100 seconds, turn Heparin off x 1 hour and restart at 50% of current Heparin rate

**Other labs:**

- Draw daily Unfractionated Anti-factor Xa @ 0400, use to guide PTT management
  - Ensure Heparin is at 'steady state' prior to drawing lab (minimum of 3 hours after any heparin drip change or Heparin bolus)
- Draw daily Anti-thrombin III level at 0400
  - Do not treat before morning rounds

**Figure 1.** Standardized ECMO anticoagulation initiation and maintenance guidelines.

appropriate. Statistical analysis was performed by using Fisher's exact test or Chi squared test where appropriate. Statistical significance was defined as a $p$-value $< .05$.

## RESULTS

### Compliance

Table 1 shows compliance with following ACT and starting dose of heparin as written in the guidelines. Compliance during the last half of 2019 was poor secondary to semantics as heparin was started when ACT was 225 seconds rather than less than 225 seconds. This negatively affected monitoring of guideline compliance. Two patients were started on heparin dosages higher than 10 units/kg/h per surgeon's request. Neither patient suffered intracranial hemorrhage. All patients were treated in compliance with the guidelines in regards to management utilizing PTT as the coagulation assay rather than Xa.

### Clinical Outcomes

All patients both pre guidelines and post guidelines were on VA ECMO secondary to cardiac failure. Median age of our ECMO patients pre guidelines was 3 months (range: .25–108); post guidelines was 2 months (range: .25–552) (Table 2). There were six neonates (<30 days of age) in both groups (highest risk for intracranial hemorrhage). Two of the six suffered intracranial hemorrhage in both groups (30%). Pre guidelines both

**Table 1.** Compliance data.

| | Number of ECMO Patients | Start Heparin When ACT <225 | Start Heparin Dose of 10 units/kg/h | PTT as Coagulation Assay |
|---|---|---|---|---|
| January–June 2018 | 6 | 5 (83%) | 4 (67%) | 6 (100%) |
| July–December 2018 | 1 | 1 (100%) | 1 (100%) | 1 (100%) |
| January–June 2019 | 5 | 4 (80%) | 5 (100%) | 5 (100%) |
| July–December 2019 | 2 | 1 (50%) | 2 (100%) | 2 (100%) |
| January–June 2020 | 3 | 3 (100%) | 3 (100%) | 3 (100%) |
| July–December 2020 | 4 | 4 (100%) | 2 (50%) | 4 (100%) |

ECMO, extracorporeal membrane oxygenation; ACT, activated clotting time; PTT, partial thromboplastin time.

patients died. Post guidelines one of the two patients died. The median time on ECMO was 2 days (range: .8–14) pre guidelines; 3 days (range: .13–148) post guidelines. There was a difference in extracorporeal cardiopulmonary resuscitation (ECPR) between the two groups: pre guidelines 11 of 22 (50%) ECPR vs. 5 of 22 (23%) post guidelines. Of interest, 4 of the 11 (36%) of ECPR patients pre guidelines suffered intracranial hemorrhage whereas, none of the post guideline ECPR patients had intracranial hemorrhage. This did not reach statistical significance ($p = .11$).

The incidence of intracranial hemorrhage decreased from 36% to 14% following guideline implementation (Table 2). While this did not reach statistical significance; it is clinically relevant. Pre guideline two patients with intracranial hemorrhage were neonates (30% of neonates) and six patients were older than 1 month of age (37% of pediatric patients). Post guidelines two patients with intracranial hemorrhage were neonates (30% of neonates) and one patient was older than 1 month of age (6% of pediatric patients). Our post guideline intracranial hemorrhage results in the pediatric age group is now closer to what is reported by ELSO (5.1%). However, in the neonatal age group our intracranial hemorrhage results remains greater than what is report by ELSO (15%). This may be due to small neonatal patient numbers in this quality study (n = 6).

**Table 2.** Clinical outcomes.

| | Pre Guidelines January 2016–December 2017 | Post Guidelines January 2018–December 2020 | *p*-Value |
|---|---|---|---|
| Number ECMO runs | 22 | 22 | |
| ECPR (%) | 11 (50%) | 5 (23%) | .11 |
| Age (months) Median (range) | 3 (.25–108) | 2 (.25–552) | |
| Length of ECMO (days) Median (range) | 2 (1–14) | 3 (.25–148) | |
| Intracranial hemorrhage (%) | 8 (36%) | 3 (14%) | .16 |
| Pediatric patients (%) | 6 (37%) | 1 (6%) | .08 |
| Component changes per ECMO run | | | |
| One (%) | 8 (36%) | 2 (9%) | .07 |
| Greater than one (%) | 4 (18%) | 7 (32%) | .48 |
| Survived to hospital discharge (%) | 7 (32%) | 11 (50%) | .34 |

ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation.
*p*-Value ≤ .05.

Two of the three patients post guidelines who suffered intracranial hemorrhage were neonates. One was following an arterial switch operation and the second following repair of total anomalous pulmonary venous connection. Both patients were compliant with the guidelines for ACT and initial unfractionated heparin dose. None of the three had ECPR. The third patient was a 2 years old with septic shock and myocarditis. This patient was compliant with unfractionated heparin starting dose, but ACT was >225 seconds at start of unfractionated heparin. Two of the three survived to hospital discharge.

Survival to hospital discharge improved from 32% to 50% following guideline implementation. While, again, this did not reach statistical significance; it is also clinically relevant.

### Balancing Measures

As a balancing measure, ECMO circuit component change outs were tracked (Table 2). Component changes outs of greater than one per ECMO run were increased post guidelines (18% vs. 32%). This was felt to be acceptable given the decrease in intracranial hemorrhage and improvement in survival to hospital discharge.

## DISCUSSION

Practice guidelines are systematically developed management protocols intended to assist with decisions regarding appropriate care for certain medical situations (6). These guidelines are intended to improve decision making and optimize patient outcomes (6, 8). With the development and implementation of guidelines for ECMO anticoagulation in the CTICU, the incidence of intracranial hemorrhage and mortality was reduced with

only minimal impact on thrombus formation as evidenced by minimal increase in ECMO component changeouts following guideline implementation.

Following review of patients from 2016 to 2017, it was felt that our patients were likely over anticoagulated given the high incidence of intracranial hemorrhage. The guidelines for ECMO anticoagulation were developed with this in mind; reduce the incidence of over anticoagulation and resultant intracranial hemorrhage. The choice of anticoagulant was clear, as unfractionated heparin is currently the most common anticoagulant used in this patient population. The starting dose of unfractionated heparin was lower post guidelines (10 units/kg/h) compared to pre guidelines (20 units/kg/h) given the goals of this quality improvement project. The titration of unfractionated heparin in the guidelines was clear and minimally controversial.

Next step was anticoagulation monitoring. This was less straight forward and more controversial. There are several coagulation assays, including ACT, PTT, and heparin anti-factor Xa level that are used in routine anticoagulation monitoring on ECMO; each with benefits and drawbacks. PTT evaluates not only the efficacy of unfractionated heparin therapy but also, congenital and acquired factor deficiencies. Thus, there can be many reasons for a prolonged PTT, such as factor deficiencies, vitamin K deficiency, liver disease, and disseminated intravascular coagulation (9). PTT does not take into consideration antithrombin levels, platelet count, or platelet function (10). There is high inter- and intrapatient variability, and a poor association with unfractionated heparin dose (10). Therefore, it may not be the best method to monitor unfractionated heparin (9); but an acceptable method to measure clotting ability.

ACT is another coagulation test used to monitor unfractionated heparin (11). ACT is a convenient, reproducible test that requires small volumes of blood and can be performed by the bedside ECMO specialist. A limitation of using ACT is its dependency on user technique. Variability in ACT may be due in part to poor technique; hemolysis and clotted samples may also be causes of result variability (12). ACT does not account for other factors that may prolong the clotting time. There is also a poor association with unfractionated heparin dose (10).

Quantitative measurement of unfractionated heparin is done by anti-factor Xa assay. This test has decreased sensitivity in the presence of plasma free hemoglobin, bilirubin, and triglycerides. The anti-factor Xa assay is a plasma-based test which does not consider the role of platelets and fibrinogen in forming a stable clot. Thrombocytopenia and platelet dysfunction are common features in ECMO patients. Underestimating their role may lead to over-anticoagulation should only anti-factor Xa assays be used to adjust the unfractionated heparin dose (10). Unlike ACT and PTT, there is a correlation between anti-factor Xa and unfractionated heparin dose (13).

Several studies have demonstrated poor correlation of ACT with anti-factor Xa level and PTT in pediatric patients on ECMO (14, 15). Maul et al. in a retrospective study that compared ACT with PTT in pediatric ECMO patients, suggested that management of patients using PTT resulted in fewer bleeding complications, a reduction in mortality, but required more circuit changes (15). In a prospective study, Bembea et al. evaluated the correlation among ACT, anti-factor Xa level, and PTT (14). This study showed a poor correlation of ACT and anti-factor Xa; as well as a weak correlation of PTT with anti-factor Xa (14). While there is no consensus regarding the perfect test to monitor unfractionated heparin anticoagulation; some feel that PTT is, overall, a more reliable test than ACT (16). However, most feel that no single laboratory test can be used alone to monitor unfractionated heparin anticoagulation (16).

In our ECMO anticoagulation guidelines, we chose to initially follow ACT as it is a convenient, reproducible test requiring a small volume of blood with a fast turn-around time. Immediately following ECMO cannulation, especially in a CTICU, there may be confounding factors contributing to post procedural bleeding. Therefore, we start heparin once the ACT falls below 225 seconds. We chose to follow ACT for unfractionated heparin adjustments for 24 hours following ECMO cannulation; then switch to following PTT for adjustments in anticoagulation. We do not use anti-factor Xa levels secondary to the risk of over anticoagulation and hemorrhage. Anti-factor Xa levels do not consider the many other factors important in clot formation. In our patient population we struggled with increased intracranial hemorrhage leading to mortality. We sought to reduce the risk of over anticoagulation while accepting potential increase in circuit clot burden.

ECMO component change outs secondary to potential increase in circuit clot burden were tracked as a balancing measure. We hypothesized that negative effects of the new guidelines might result in inadequate anticoagulation and thereby increase thrombus formation in the ECMO circuit. Increased thrombus formation in the ECMO circuit would likely lead to an increase in component change outs. The incidence of ECMO component changeouts was increased somewhat following institution of the guidelines. We felt this was acceptable clinically.

## Lessons Learned

Key components that contributed to the successful process included involving a multidisciplinary team to question and explore current practice variability; developing and implementing simple guidelines to reduce variation and change the practice pattern; holding staff accountable

for implementation and outcomes; monitoring to ensure the intervention was successful; and sharing the results with the staff of the CTICU. The reduction in intracranial hemorrhage was noticeable to the staff as a "quick win" which helped buy in. Next steps include the use of multimodal anticoagulation monitoring as additional tests for anticoagulation (e.g., ROTEM) as they become more readily available. No single laboratory test will be used alone to monitor Unfractionated Heparin anticoagulation.

## LIMITATIONS

This manuscript was intended as a quality project with the goal of presenting the process of creating guidelines, introducing guidelines, measuring compliance with the guidelines, and reporting the results. It was written according to Squire guidelines which is appropriate for reporting quality manuscripts. It was not intended as a scientific paper with research methodology. Limitations to this quality project was the low number of patients in the groups (n = 22). While there was no additional "official practice changes" during this time frame, we strive for continued improvement in the care that we provide. In addition, there were fewer ECPR patients in the post guideline group. Therefore, we cannot say that the clinical improvement (decreased mortality) demonstrated above was not multifactorial.

## CONCLUSIONS

Implementation of standardized ECMO anticoagulation guidelines in the CTICU was successful in improving clinical outcomes as evidenced by reduction in the incidence of intracranial hemorrhage in this high-risk patient population. Increased circuit clot burden and component change outs, our balancing measure, was felt acceptable given the clinical improvement.

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