Heparin Anticoagulation in Pediatric ECMO Patients

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Abstract

Extracorporeal membrane oxygenation (ECMO) is a high-risk, but highly successful intervention for the survival of critically ill neonatal and pediatric patients. Patients supported by ECMO require continuous infusions of anticoagulant medications to prevent clotting of the ECMO circuit, thrombotic events in the patient, and other bleeding complications. Close monitoring, care, and management of the ECMO circuit and its components, with specific focus on systemic anticoagulation, is vital as many factors may influence the efficacy of the anticoagulant and ultimately the patient condition. Globally accepted guidelines exist for the correct management of anticoagulation while supported on ECMO; however, health care centers frequently deviate from these recommendations. This project report synthesizes the most current literature on anticoagulation management in the pediatric ECMO supported population, discusses the limitations in current research, and demonstrates the necessity to use standardized anticoagulation protocols for the safest and most successful outcomes. To implement these findings, this project report suggests the need for an evidence-based project that focuses on the quality improvement of current ECMO anticoagulation guidelines.

Keywords: pediatric, extracorporeal membrane oxygenation, anticoagulation, anticoagulation protocol, heparin

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Heparin Anticoagulation in Pediatric ECMO Patients

Critically ill pediatric patients are surviving more severe diagnoses and disease processes since the first patient was supported with Extracorporeal Membrane Oxygenation (ECMO) in the 1970s. For the best chance of survival using this high-risk intervention, health care providers must administer systemic anticoagulation therapy and follow nationally recommended guidelines to prevent thrombotic events, ECMO circuit malfunction, or bleeding complications. Each patient must be closely monitored as many factors can influence the systemic anticoagulation effect. Deviation from standardized protocols and national recommendations allow for increased risk of error, incorrect dosing, unexpected outcomes, and fatal events.

Problem Statement

While patients are supported on ECMO, they have a significant risk for developing inappropriate bleeding, stroke, or clot formation. Patients receiving ECMO therapy are given a closely controlled, systemic, anticoagulation agent to reduce these risks and prevent clotting in the ECMO circuit itself. Many factors can influence how well these agents work, such as the age of the patient, weight, disease process, and other medications the patient is receiving. Despite accurate anticoagulation therapy, Cho et al. (2017) reports typically 15% of the pediatric ECMO patients develop circuit clots, 12% oxygenator clots, and 4% of the patients develop intracranial infarcts while receiving ECMO therapy. In a large eleven-year, retrospective review of the ELSO registry, 21,845 pediatric patients received ECMO support; during this time, 39% of those patients experienced hemorrhagic complications (Werho et al., 2015a). The goal during each ECMO run is to inhibit enough platelet and coagulation factor to prevent clot formation; however, maintain enough anticoagulation factor to prevent the patient from bleeding (Extracorporeal Life Support Organization [ELSO], 2014). Unfractionated heparin is the most

frequently used anticoagulant for patients supported by ECMO, and its level in the bloodstream is monitored frequently to maintain therapeutic levels. If heparin isn't sufficient to keep the patient's anticoagulation levels appropriate, other medications are considered.

Defining and adhering to proper anticoagulation strategies for pediatric patients receiving ECMO support can be challenging for critical care providers. The complexity of caring for critically ill neonatal or pediatric patients can influence providers' decision-making capabilities and deter them from adhering to policies or guidelines regarding anticoagulation therapy. Once a child is placed on ECMO, they need close attention and proper anticoagulation management that is evidence-based and follows national standards. Although ECMO has serious risks, it is a valuable intervention for the care of critically ill neonatal and pediatric patients. Strict adherence to recommended guidelines reduces the risk of further complications.

Purpose and Rationale

In the critical care setting, the neonatal and pediatric patients requiring ECMO support are some of the most fragile patients to manage. Close monitoring, care, and management of the ECMO circuit and its components, including systemic anticoagulation, are closely monitored to ensure the best chance of survival. If there is a standardized method to administer these anticoagulation medications, it must be used to reduce the risk of coagulopathies, thrombotic events, or inappropriate bleeding. This evidence-based literature review will demonstrate the current problems associated with anticoagulation while on ECMO, provide data and research to support the importance, and evaluate current issues with the anticoagulation management in local pediatric critical care units. The purpose of this project report is to evaluate the most current high-quality research available on anticoagulation for the pediatric patients receiving ECMO

therapy, explain the search strategies used on academic databases, and use the data to support adherence and management of heparin anticoagulation for pediatric patients on ECMO support.

Background and Significance

Pediatric Patients Receiving ECMO Support

The first uses of ECMO in the pediatric population began in the 1970s for infants undergoing congenital heart defect repair surgeries (Rodriguez-Cruz, 2017). Although there is more experience in the adult population with ECMO support, providers are managing the care of neonatal and pediatric patients with more complex diagnoses that are requiring ECMO intervention for survival. With high-acuity cardiovascular intensive care units (CVICU), neonatal intensive care units (NICU), and pediatric intensive care units (PICU), the need for ECMO in smaller and younger patients is increasing. The biggest contraindications for ECMO include any patient under 2 kg or less than 34 weeks of age (ELSO, 2017a). Other contraindications include life-limiting chromosome disorders, intraventricular hemorrhaging, irreversible multiple organ damage, or high probability of poor outcomes (ELSO, 2017a). If a patient is in respiratory or cardiovascular failure without improvement from other medical interventions and has no contraindications, ECMO may be the only remaining option for survival.

Anticoagulation Therapy on ECMO Support

Unfractionated heparin is an antithrombotic agent that is given continuously intravenously or through the ECMO circuit, to prevent clots in either the machine or patient. It is the most widely used anticoagulant for patients on ECMO; however other anticoagulation medications such as Bivalirudin have also been used (ELSO, 2014). Bivalirudin is a direct thrombin inhibitor which is a new class of anticoagulants that are particularly short-acting. This drug class has the potential to be effective in the pediatric population because they impact clot

bound thrombin and circulating thrombin in the bloodstream, which improves its overall anticoagulant effect (ELSO, 2014). Although ECMO support is necessary in certain instances for survival, the complications and risks can be life-limiting. In a review of global registry data Werho et al., found that out of 3,517 pediatric cardiac surgical patients, 12% developed strokes (2015b). Regardless of the drug being used for systemic anticoagulation, it must be continuously infused and closely monitored to therapeutic effect, to prevent thrombotic events or coagulopathies.

Recommended Unfractionated Heparin Goal Levels for Anticoagulation

Heparin is the primary medication used for ECMO anticoagulation in all age groups. The standard practice currently includes providers ordering activated clotting time (ACT) tests to measure the amount of time it takes for whole blood to begin clotting. The goal is one and one-half times the normal measured level (ELSO, 2017b). Tests are run hourly for immediate results with frequent medication adjustments/titrations to maintain accurate levels when correct equipment is available (ELSO, 2017b). Facilities may use other laboratory tests such as partial thromboplastin time (PTT) or activated thromboplastin time (aPTT) to measure the time it takes for clots to form, or anti-factor Xa (Anti-Xa) assay, which is a measurement of plasma heparin levels in the bloodstream. Both of these levels can be affected by other medications or blood products and may make these levels inaccurate (ELSO, 2017b). In local critical care units, anti-Xa levels are the diagnostic test used to titrate anticoagulation for ECMO supported patients. They also obtain thromboelastography (TEG) levels, which indicate how quickly and how dense clots are forming in the patients' blood.

One retrospective review of 604 pediatric patients receiving ECMO support, evaluated the survivability while maintaining an ACT range of 180-220 seconds, with increased heparin

levels (Baird et al., 2006). They found this ACT range might be inadequate anticoagulation, and the only predicted survival advantage was demonstrated in the patients who received increased amounts of heparin, independent from their ACT level (Baird et al., 2006). Another study conducted by Bingham et al. (2018), regarding anticoagulation measurements concluded PTT times greater than 64 seconds with TEG levels below 30 minutes, demonstrated no thrombus association. Knowing we have the ability to collect anticoagulation levels frequently, the ability to follow evidence-based guidelines and recommendations allows for the most appropriate and safe patient care.

Following Recommended Guidelines

In 1989 the development of ELSO helped shaped standards of practice, encouraged research, and developed a worldwide benchmark system that allows for shared data analysis to improve our care and current practice for patients requiring ECMO. This registry has developed multiple guidelines and recommendations based on the most current data. Still, there is no specific must-follow protocol for anticoagulation with patients requiring ECMO support and even less data on the outcomes and best protocols for the neonatal and pediatric populations.

Individual centers tend to develop guidelines based on ELSO data and their hospital-specific data. The high-risk state of these children makes it important to discuss with caregivers the potential adverse events that could happen from ECMO support, and significant education must be provided. In one single-center retrospective review, the children's hospital discussed the survival rate of patients supported by ECMO longer than 21 days and indicated worse overall outcomes and increased fatality (Ares et al., 2019). With very few evidence-based pediatric studies, and pediatric-focused anticoagulation therapy data or guidelines, this allows for a wide variety of center-based protocols that make it difficult to distinguish which therapy is best for the

pediatric population (Cho et al., 2017). Further research regarding overall long-term complications from ECMO is ongoing. Depending on the patients' initial diagnosis, their overall life quality may be significantly altered before, but especially after an ECMO run (Erdil et al., 2019).

Internal Evidence

From 2018-2019 a free-standing children's hospital in the Southwestern United States with several critical care units, 29 patients received heparin for their ECMO anticoagulation therapy. The hospital wide ECMO anticoagulation protocol is based on the most recent ELSO recommendations to maintain therapeutic heparin levels and limit the risk of bleeding or clotting events. According to this protocol, patients receive a loading heparin bolus upon initiation of ECMO based on their weight, and a continuous infusion of heparin is initiated at a designated age-related dose. If heparin levels are not therapeutic at the first anti-Xa, patients should receive another weight-based bolus and titrate their continuous infusion by either a 20%, 15%, or 5% increase based on their age. The goal for these patients per protocol is a therapeutic anti-Xa level of 0.3-0.7 units/mL. Of the 29 patients supported by ECMO, 23 had subtherapeutic heparin levels at the first anti-Xa result, and 20 had subtherapeutic levels at the second time. This information supports the need for reeducation regarding the current standardized protocol to maintain therapeutic and safe anticoagulation levels in ECMO supported patients. Lack of adherence to these guidelines will lead to further complications and can be life-threatening. However, using the most current data, based on global ELSO guidance, adherence to these protocols support the best outcomes for critically ill pediatric patients. This data from patients supported on ECMO from 2018-2019 at this local children's hospital, was used to understand how often the current ECMO anticoagulation policy was being followed and where deviations

usually take place. After this evaluation, a critical care provider survey was anonymously shared, for providers to voice their concerns, questions, and comments regarding current ECMO anticoagulation protocol.

PICOT Question

The objectives of this study were to evaluate personal bias, comments, and concerns with the current anticoagulation policy, identify themes of nonadherence to the current anticoagulation policy, and evaluate the need for further intervention to improve adherence to the current protocol. This project developed from the following study question; In pediatric patients receiving ECMO support, what intervention are necessary to improve adherence to current anticoagulation protocol? What provider concerns exist regarding the current protocol that could be addressed and update the protocol to improve patient outcomes?

Search Strategy

PubMed Database

The first search strategy on the PubMed database was the term “pediatric ECMO” with the Boolean phrase “AND” with the phrase “heparin anticoagulation”. Using these phrases initially ensured there was a narrow search window, without needing to add multiple search additions. This yielded a total of 122 results. The next step was to apply an inclusion criterion to these same phrases of articles published in the years 2014-2020 for the most current data and research. This narrowed the search further to 58 total results.

Cochrane Database

The Cochrane database seemed to be the most difficult to navigate and yield results. However, the initial search was very specific. The only phrase searched was “pediatric ECMO

anticoagulation" with the Boolean phrase "AND" with title abstract keywords to include "heparin". This yielded a total of five results.

CINAHL Plus with Full-Text Database

This database was used for multiple search terms. The first search included "pediatric ECMO", the Boolean phrase "AND", and "anticoagulation" which yielded eight results. The next search attempt included "pediatric ECMO", the Boolean phrase "AND", and "heparin" which resulted in eight results. Next, all three were combined- "pediatric ECMO", "heparin", "anticoagulation" with Boolean phrases "AND", and it yielded four results. The last search included "pediatric ECMO", the Boolean phrase "AND", and "anticoagulation policy" however, this yielded zero results.

ASU Library

Arizona State University's online library provided the last search database. The first search term was "heparin therapy" which yielded 2,029 results initially. The Boolean phrase "AND" was used with "pediatric ECMO" with the first phrase and this resulted in 1,111 results. An additional keyword of "policy" was then added to the previous phrases with the Boolean phrase "AND", which narrowed results to 449. The last step included excluding all publications with dates outside of a five-year time frame, which left a final yield of 81 results.

Critical Appraisal and Synthesis

The following studies included for critical appraisal and synthesis, have been evaluated and described in detail (see Appendix A, Table 1). The studies can be evaluated based on their validity, reliability, and applicability according to Melnyk and Fineout-Overholt's rapid critical appraisal (2019). Almost all studies were retrospective reviews, with one randomized controlled trial, and one cohort study. Sample sizes ranged from small cohort groups to large national data

bank reviews including thousands of patients. These studies never reported bias, and only one reported funding from the National Institute of Health (Ares et al., 2019). Pediatric ECMO related research is limited; however, the large retrospective reviews allow clinicians to see what other interventions are working or are less effective on large scales.

Most testing subjects were of similar age, condition, and background and overall heterogeneity amongst the two pediatric and adult ECMO populations. This adds to their validity in critical appraisal inclusion. The reliability of the trails is varied, as many different variables were discussed in each study. Some researchers showed overall less patient risk to adverse outcomes with standardized anticoagulation treatment compared to other interventions. In contrast, other researchers discussed the little effect presumed changes to anticoagulation could be. Certain studies focused on the anticoagulation management itself, versus other studies who wanted to focus on other medications that may benefit the patient receiving ECMO. The variety of interventions, controls, and outcomes demonstrates how further studies should be conducted. Common major variables included- heparin use, using a variety of anticoagulation tests, evaluating for survivability and long-term outcomes, the incidence of bleeding and thrombotic events, and anticoagulation protocol use.

Although the studies covered multiple aspects of anticoagulation management for the pediatric population, all the studies apply to the proposed project. Three studies focused on the adult population patients receiving ECMO rather than the pediatric population, but the same principles being questioned apply to the pediatric world. Although there are large amounts of data on pediatric ECMO, actual high-level evidence is hardly available due to the lack of pediatric study opportunities. There also is limited specific data regarding anticoagulation in the pediatric population and suggests that more research should be conducted for proper evaluation.

The considerations for adequate pediatric anticoagulation protocols for ECMO are multifactorial and differ greatly from facility to facility; however, protocolization my help reduce variability in patient therapeutic range, provide organization, reduce the number of thrombotic events, decrease the amount of time spent inpatient in the hospital setting, and overall increase the survivability for the child. Pediatric ECMO is an area of study where more high-level research would benefit the population as a whole and allow for providers to routinely share universal knowledge regarding the most effective in reducing harm and providing most appropriate care. Overall, the evidence demonstrated the need for an organized system for anticoagulation management and finding the most effective anticoagulation medication that is most appropriate for pediatric ECMO. The project was conducted by an Advanced Practice Registered Nurse (APRN) student to prove the effectiveness of following evidence-based protocols after analyzing data regarding the most effectively used anticoagulation medications.

Theory Application

The knowledge to action framework (see Appendix B, Figure 1), focuses on gathering and understanding evidence-based knowledge, while also implementing the knowledge into action (Field et al., 2014). This is critical for the proposed project of anticoagulation management in pediatric ECMO supported patients. ECMO in the pediatric population has some available data and substantial evidence in its use, however specific to anticoagulation strategy and most effective management requires further research. Healthcare providers must be aware of the changes that could potentially take place regarding the most effective medication or strategy and make sure to safely implement them into practice once they have understood the new changes themselves. Having a framework that allows for constant fluctuation between stages of learning and implementation allows for providers to practice the most up-to-date evidence and

patients to receive the best care possible. Based on the evaluation of evidence (see Appendix A, Table A1), all studies concluded the need for further evaluation and research for further conclusive recommendations or best-practice development.

Implementation Framework

The implementation of this project would benefit from a structured model such as the Plan- Do- Study- Act improvement model (see Appendix B, Figure 2) (UIHC, 2017). This model provides a step-by-step plan to improve a health care concern, evaluate a need for change, create an intervention for the change, implement and review the overall success of the change, and determine if other changes need to be made for further improvement. This model fits especially well with the proposed project because of its continuous cycle. The "Plan" and "Do" areas of the model are currently being implemented. The data reflecting the providers' adherence to the policy over the past year is collected. Plans for reeducation or improving adherence continue. Once the "Act" area of the model is reached for the proposed project, interventions can be analyzed, and a plan will be implemented to continue to provide the best care for the pediatric ECMO supported patients.

Implications for Practice Change

Based on the external evidence evaluated (see Appendix A, Table A1) and from internal evidence already obtained, the next steps included meeting with key facility stakeholders such as the critical care pharmacist, critical care director, and all providers with ECMO initiation capabilities in the Neonatal Intensive Care Unit, Pediatric Intensive Care Unit and Cardiovascular Intensive Care Units to evaluate knowledge gaps, assess barriers to adherence, and to determine if there was a need to develop a more consistent approach for correctly prescribing the anticoagulation medications. Asking participation in an anonymous survey online

to evaluate their knowledge of the protocol, their concerns, and any comments they'd like to share, helped to determine where the providers felt the barriers lie. The collected data regarding adherence levels to the protocol, along with anonymous results of provider surveys helped to initiate important discussions regarding potential changes.

Methods

The project was conducted at a free-standing children's hospital in Southwestern U.S. The provider survey was sent to providers who worked in critical care areas only, where ECMO patients were managed. Local hospital IRB approval process was completed, however deemed a quality improvement project. Following hospital approval, expedited Arizona State University IRB approval was required and approved.

Inclusion criteria for this study included:

- Male or female pediatric patients (less than 21 years of age)
- Patients who have been supported on either veno-venous (VV) or veno-arterial (VA) ECMO between October 7th, 2018- October 7th, 2019, specifically on heparin anticoagulation continuous infusions
- Patients currently being supported on VV or VA ECMO meeting above criteria at

Exclusion criteria for this project included:

- ECMO supported patient not on heparin anticoagulation infusions.
- Patients not supported on ECMO
- Patients older than 21 years of age

Data collected on ECMO patients was documented on a Microsoft Excel sheet and included the following variables:

- Date ECMO heparin orders placed

- Patient age
- Patient weight in kilograms
- Dosage of heparin medication originally ordered
- Location (which unit) the patient was in when medication/ECMO was ordered
- When the patient was placed on/off ECMO
- If the heparin initiation bolus was given per protocol
- Dosage of initial heparin bolus
- What time the heparin continuous infusion started and at what dose
- The first Anti-Xa level date/time/result
- Whether an additional heparin bolus was given per protocol for not being therapeutic
- The number of heparin continuous infusion titrations
- The second Anti-Xa level date/time/result
- If the patient had a baseline antithrombin 3 level (AT3) drawn prior to ECMO initiation
- Whether or not AT3 was replaced prior to the second Anti-Xa level being drawn
- When the first therapeutic Anti-Xa level occurred
- If the patient was experiencing neurological outcomes

Project Procedure

1. De-identified data of ECMO supported patients from October 7th, 2018- October 7th, 2019 in aggregate form was provided by the agency. De-identified data was accessible via secure hospital network.
2. De-identified data for each patient meeting inclusion criteria, was documented regarding adherence to anticoagulation policy, pertinent laboratory data, and pertinent medical

outcomes on Microsoft Excel created document. This was not publicly accessible and was secured in the secure hospital network (See Appendix C).

3. Anonymous provider questionnaire (Appendix D) sent via SurveyMonkey to understand provider opinion and potential bias of current ECMO anticoagulation policy and provide reeducation of critical points of anticoagulation policy. Two weeks permitted to complete the survey, with goal of at least 15 provider responses.
4. The 2018-2019 ECMO patient data and provider opinion survey data were evaluated to determine if anticoagulation policy adherence was affecting overall anticoagulation outcomes of ECMO supported patients. This information was reviewed to provide support for a policy change and/or update in the future to current ECMO anticoagulation policy.

This project was qualified for waiver of consent because de-identified data was provided in aggregate form the hospital. Participants consented to the study by completing the provider survey via link sent through secure hospital email. Consent notification was included in the informative email. The project involved no more than minimal risk to the subjects and did adversely affect the rights and welfare of the subjects. A proposed budget was calculated and is attached (Appendix E) however, there was no actual financial compensation or cost for completion of this project. No funding was obtained for completion of this project.

Results

After data review of ECMO supported patients from October 2018-2019, overall 32 ECMO orders were placed however, 28 patients met inclusion criteria. One patient expired while being placed on ECMO support; however, was still included in initial calculations. The CVICU placed 19 orders, NICU placed five orders, and PICU placed eight orders for ECMO support. Of

the patients, 24 out of 28 patients received a heparin bolus prior to initiation of ECMO. Out of those 24 patients, four of them received a heparin bolus dose that was too high based on their age (per protocol). There were eight patients started on a heparin infusion that did not meet guideline standards - two of them being too high of a dose, six of them being too low. At the first Anti Xa level check, with a goal of 0.3-0.7, 23 patients out of 28 were subtherapeutic. At the second Anti Xa level check, six hours later, 20 patients were still subtherapeutic. However, two patients were transitioned to Bivalirudin anticoagulant, and four patients were above therapeutic range. Per protocol, if patients are not therapeutic at the first Anti Xa level, an additional heparin bolus may be given, and 20 eligible patients did not receive this bolus. On average, patients spent 21.2 hours subtherapeutic on continuous heparin infusions, and required an average of 4.5 titrations to get to therapeutic heparin anticoagulation levels.

Initially responses to the provider survey discuss the desire for alternative pathways for anticoagulation, because patients respond to heparin effect differently. Other comments suggest that initial labs need to me more frequent, should not solely rely on Anti Xa but also TEG evaluations, and 50% of providers so far think that Heparin is the most effective in maintaining an anticoagulated state while on ECMO.

Discussion

Initial results of this project demonstrate a need to make changes to the current hospital ECMO anticoagulation protocol. Providers initially agree that heparin can be an effective medication for anticoagulation but, the variety of its effect on patients should then determine other anticoagulation options. With patients in a subtherapeutic state for hours when initially placed on ECMO support, it’s only increasing the risk of bleeding complications, circuit failure, or other possible life-threatening complications. Standardized anticoagulation protocols have

shown to be associated with a decrease in hemorrhagic complications (Northrop et. al, 2015), and it's important that critical care providers can come to a consensus about a protocol that they agree with and will use. This will ensure best patient outcomes.

Limitations to this project included delays in IRB approval because of changes in the hospital quality improvement process. These delays severely limited the time frame of responses from key stakeholders such as ECMO management, and the COVID-19 pandemic made it impossible to host in-person meetings.

Potential Outcomes

Outcomes of this quality improvement project have the potential to be extensive. This project can provide the support and evidence necessary to warrant a local policy and ECMO anticoagulation protocol update. It can show improvement in thrombotic events and bleeding complications in pediatric patients supported by ECMO. It can support the need for a more comprehensive nationwide or global study regarding ECMO anticoagulation in the pediatric population. Evaluation of the most effective anticoagulant medication and management will improve survivability and overall risk for pediatric patients supported by ECMO. A future recommendation includes the implementation of a daily rounding checklist regarding ECMO anticoagulation goals to improve adherence to protocol. After this checklist is executed, repeat evaluation of protocol adherence should be completed one year later to determine if these interventions proved effective and overall adherence has improved. With a protocol already in place that is expected to be effective for therapeutic anticoagulation management, adherence to the current protocol and adjustments based on recommended changes as new evidence informs the care of pediatric patients supported by ECMO. Provider education and discussion of protocol improvement compared to current practice could affect patient therapeutic outcomes in the future

and will encourage participation in creating the most effective strategies for pediatric ECMO anticoagulation.

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Appendix A

Quantitative Studies

Table A1

Evaluation Table

Citation	Conceptual Framework	Design/ Method	Sample/ Setting	Variable and Definitions	Measurement	Analysis	Findings	Decision for Use
Ares et al., (2019). Outcomes and associated ethical considerations of long-run pediatric ECMO at a single center institution **Funding:** National Institutes of Health **Country:** USA **Bias/Conflicts:** Authors declare none	NR inferred ethical considerations for a conceptual framework	**Design:** Quantitative-Retrospective review and case analysis of all patients under 18 yrs from 2007-2017 who received ECMO support >/ 21 days **Purpose:** Hypothesize a decreased survival rate and increased number of long-term complications being supported on ECMO >/ 21 days	**N:** 175- pts in total **n:**14- pts being supported >/ 21 days. **Setting:** Ann & Robert H. Laurie Children's Hospital, Chicago, IL	**IV:** Long-term complications **IV2:** Survival rate **DV:** Length of ECMO run Chart reviewed each pt demographics, comorbidities, insurance, EGA, ECMO duration, age at ECMO initiation, type of ECMO, procedural year, indication for ECMO, and rationale for prolonging or discontinuing ECMO support	Primary Outcome- survival to hospital discharge Secondary outcome- LOS, medical comorbidities, ventilator dependence, neurologic outcomes Charts reviewed by two evaluators, with a third to look over final data	Fisher's Exact Test at $p < 0.05$	Overall survival for ECMO >/ 21 days (n = 14) = 36% Survival for ECMO < 14 days (n =141) = 72% Survival for ECMO 14-20 days (n = 20) = 50% Pts had higher survival rate if older Only 1/5 survivors made complete recovery with no neurological deficits	This is a level of evidence VI. Although this provides some insight to the survivability of pediatric pts specifically on ECMO support, and their potential adverse outcomes, there is no reference to anticoagulation therapies

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Citation	Conceptual Framework	Design/ Method	Sample/ Setting	Variable and Definitions	Measurement	Analysis	Findings	Decision for Use
Baird et al., (2007). Anticoagulation and pediatric extracorporeal membrane oxygenation: Impact of activated clotting time and heparin dose on survival. **Funding:** None **Country:** USA **Bias/Conflicts:** None listed	NR but inferred best relationship between heparin dose and survivability	**Design:** Quantitative-Retrospectively reviewed 604 pediatric ECMO patients, multiple regressions used to see impact of survival rate **Purpose:** The purpose of this review was to show the relationship of heparin dosing, heparin levels and ACT levels, on patient survivability. It also included other influential factors on these outcomes such as age, weight, diagnoses, and history of previous surgery.	**N:**604 **n:**349 survivors **Setting:** Children's Hospital of Pittsburgh from 1980-2001.	**IV:** ACT, heparin, age, weight, diagnosis, previous surgery **DV:** Impact of survivability	Previous surgery, hours on ECMO, ACT level, heparin level Relationships between heparin levels and ACT levels to survivability Recommended ACT level 180-220 seconds.	Normality testing used Kolomogorov-Smirnov statistic. 2-sample t-test used for survivors versus non-survivors. Values of P <0.05 in 2-tailed study is considered statistically significant. Pearson correlation coefficient was used to summarize association between ACT and heparin dose. SPSS 14.0 software used.	Increased heparin levels indicative of survival (P < 0.0001) independent of all other variables. ACT was not indicative of survival. Previous surgery associated with increased likelihood of ECMO death (P <0.001). ACT may be too insensitive to maintain adequate systemic heparin levels.	This is level VI evidence but is a large retrospective study that is specific to pediatric ECMO and heparin affect that indicated the importance of correct heparin levels and patient survivability. One large flaw of this study is date of study. However, because of the data sample and being one of the first large studies on the topic that is still similar to other studies conducted more recently, it is valuable to include.
Bingham et al., (2018). Anticoagulation	NR but inferred best practice theory	**Design:** Quantitative-Retrospective	**N:** 35 pts supported longer	**IV:** Anticoagulation variables (heparin	Goal aPTT level 60-80 seconds.	Regression and (ROC)	ROC analysis demonstrated aPTT > 60	This is VI evidence. This was a

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Citation	Conceptual Framework	Design/ Method	Sample/ Setting	Variable and Definitions	Measurement	Analysis	Findings	Decision for Use
management during first five days of infant-pediatric extracorporeal life support. **Funding:** None **Country:** USA **Bias/Conflicts:** Author declares none		case review and analysis of 35 ECMO supported patients from January 2013-February 2016. **Purpose:** Hypothesized anticoagulation levels are influenced by AT- maintaining a specific AT level would continuously achieve a therapeutic aPTT. Goal to determine optimal aPTT level and heparin dose rate and AT level needed to maintain these levels	than 3 days on ECMO **Setting:** Mayo Clinic Institutional Review Board-Center for Cardiovascular Services	dose rates, aPTT, ACT, INR, blood loss, thrombus formation in circuits, AA, kaolin thromboelastograph reaction time, anti Xa, bivalirudin dose rate, circuit interventions, argatroban dose rate, and blood product transfusions **DV:** AT level	Anticoagulation medications delivered directly to oxygenator	Probability of <0.1 were considered significant	seconds; AT level must be > 42% Strongest ROC values came with aPTT of 64 seconds (p <0.001) No relationship between Anti-Xa and ACT levels which demonstrates inconsistency with these values during pediatric ECMO ROC analysis displayed multiple correlations that may benefit future protocols	nonrandomized review with a small sample size. However, this review was conducted specifically on various anticoagulation therapies and a proposed intervention to improving patient outcomes and patient anticoagulation that is related to the PICOT question
Colman et al., (2019). Evaluation of a heparin monitoring protocol for	NR but inferred quality improvement after systematic process implementation	**Design:** Quantitative-Retrospective chart review of 18-year-old or older patients,	**N1:** 72 pre-protocol **n2:** 51post-protocol	**IV:** Heparin monitoring protocol **DV:** Clinical outcomes such as	Heparin monitoring protocol in place my checking TEG levels twice a day and aPTT	Pre-protocol group, 69.4% had major bleeding events, post-protocol 66.7% (P=0.85),	Variation among centers is very apparent.	This is level VI evidence. This was a nonrandomized retrospective review with a

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extracorporeal membrane oxygenation and review of literature. **Funding:** None **Country:** USA **Bias/Conflicts:** Author declares none		pre-protocol (January 2016-March 2017) and post-protocol March 2017- December 2017). **Purpose:** Would a heparin monitoring protocol using aPTT and TEG studies improve clinical outcomes	**Setting:** Baylor St. Luke's Medical Center, Houston, TX	major bleeding or thrombosis events	levels every 6 hours Goal levels were aPTT of 60-80 sec, a TEG reaction time of 2-4 times baseline, and an anti-Xa of 0.3-0.7 units/ mL	pre-protocol 8.3% had minor bleeding evets, post-protocol 9.8% (P=0.78), pre-protocol 15.3% had peritoneal bleeds versus post-protocol 2% (P= 0.01), and pre-protocol mortality on ECMO 56.9% versus post-protocol 33.3% (P= 0.01)	Although major bleeding and minor bleeding were not statistically significant, specific bleeds such as peritoneal and overall mortality were. Protocol adaptation provides a more streamlined anticoagulation management approach to increase efficiency and reduces variability	smaller sample size which limits this study however its relevance to the PICOT question is helpful as it demonstrates some benefits to implementing an anticoagulation protocol. This study is also limited to adults.
Kessel et al., (2017). The impact and statistical analysis of a multifaceted anticoagulation strategy in children supported on ECMO:	NR but inferred improving anticoagulation protocol to fit best practice	**Design:** Quantitative-Retrospective chart review of 18pts. Collected ACT, aPTT, anti-Xa, prothrombin time, INR, and AT3 levels for both studied groups.	**n:** 18 pts, 9 new anticoagulation protocol, 9 old anticoagulation protocol **Setting:** Tertiary care, academic Children's hospital-Alexandra	**IV:** HID and new versus old anticoagulation protocol used influencing anticoagulation studies **DV:** Anticoagulation therapeutic range based on	Measured percentage of in-range anticoagulation levels, probability of becoming in range, average HID between groups, and correlations between HID and	Generalized linear mixed model (GLIMMIX), mixed model analysis of variance (ANOVA) and correlational studies. All data analysis	Significant inverse correlation between the ACT and the HID in both the groups. Significant positive correlation between the aPTT and the	This is level VI evidence. This was a nonrandomized retrospective review with a small sample size. Due to positive correlation of HID and aPTT in the old

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Performance and pitfalls. **Funding:** None **Country:** USA **Bias/Conflicts:** Author declares none		Developed new protocol for HID **Purpose:** Demonstrate the new HID protocol can maintain therapeutic levels of anticoagulation longer, and demonstrate utility of different anticoagulation studies	Cohen Children's Medical Center of New York	anticoagulation studies	anticoagulation studies	performed using SAS 9.3 statistical analysis software 2-tailed P < .05- considered significant for all tests	HID in the old protocol group (r = .25, P < .0001), but no correlation between the aPTT and the HID in the new protocol group. The anti-Xa level showed a significantly positive correlation with the HID in the new protocol group	protocol but no correlation in new protocol may indicate study design flaws. This study also is trying to analyze the dependent variables based on independent variables while the independent variables are also being studied in comparison with the old versus new protocol.
Khaja et al., (2010). Evaluation of heparin assay for coagulation management in newborns undergoing ECMO. **Funding:** None **Country:** USA	NR but inferred comparing anticoagulation level relationships improving current practice to best practice	**Design:** Quantitative-Retrospective review of 21 pts, group data was plotted and analyzed to find correlation coefficient between anticoagulation parameters **Purpose:** Identify	**N:** 24 neonatal pts underwent ECMO **n:** 21 neonatal pts included in study **Setting:** NICU pts at Texas Children's Hospital, Houston, TX	**IV:** Anti-Xa, ACT, or aPTT levels **DV:** Anticoagulation effect relationship	316 total heparin levels of ECMO pts plotted and compared to aPTT levels and ACT levels, in how they were related/if they correlated or not	Control (r)= 0.5386 from a group of adult patients Positive correlation between heparin and aPTT and ACT. (r)= 0.364 heparin to PTT vs. (r)= 0.125 heparin to ACT showing heparin and PTT have	PTT and ACT still are not perfectly reliable in demonstrating heparin effect PTT is more reliable than ACT however multifactorial anticoagulation studies are necessary for adequate	This is a level of evidence VI. This was a nonrandomized review with a small sample size. This data is beneficial to the PICOT question because it shows what other labs could be used to determine adequate anticoagulation

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Bias/Conflicts: Author declares none		usefulness of Anti-Xa assay vs. aPTT or ACT.				slightly stronger relationship	anticoagulation treatment in neonates	levels and demonstrates the potential need for more frequent studies. This study lacks a large sample size but explains thoroughly the results of the included sample size.
Mazzeffi et al., (2019). Bleeding, thrombosis, and transfusion with two heparin anticoagulation protocols in venoarterial ECMO patients. **Funding:** None listed **Country:** USA **Bias/Conflicts:** None listed	NR but inferred comparison of protocol for best practice and quality improvement	**Design:** Quantitative-Retrospective cohort study of adult VA ECMO patients during a 6-year period **Purpose:** Find a protocol that distinguishes which anticoagulation study is more accurate, and which protocol reduces incidence of bleeding, transfusions, or thrombotic events	**n**=121 total included. 50 belonged to ACT guided heparin anticoagulation, 71 had aPTT guided heparin anticoagulation **Setting:** Tertiary care, academic medical facility	**IV:** ACT-guided heparin anticoagulation protocol **IV2:** aPTT-guided heparin anticoagulation protocol **DV:** Thrombosis or bleeding incidence	Demographic, medical, transfusion, and ECMO history were collected on all patients Primary outcomes included bleeding and thrombosis, secondary outcomes included stroke and in hospital mortality	SAS 9.3 statistical analysis software was used. Chi-square test or Fisher exact test for categorical variables and Wilcoxon tests for continuous variables For all tests, >P=0.05 were considered statistically significant	No difference in bleeding or thrombosis between either group but ACT guided heparin anticoagulation required more blood transfusions	This is level VI evidence as it is a retrospective cohort study. It is a small sample size however discusses implementation of anticoagulation protocol supports the PICOT question. This study is also limited by the misclassification of bleeds or thrombotic events. This study is also

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								limited to adult patients.
McQuilten et al., (2016) Low-dose heparin in critically ill patients undergoing extracorporeal membrane oxygenation-The HELP-ECMO pilot randomized controlled trial. **Funding:** None listed **Country:** Australia **Bias/Conflicts:** Author declares none	NR but inferred that the randomized controlled trial is evaluating efficacy of heparin dose for ECMO patients.	**Design:** Quantitative-Randomized, controlled, unblinded trial at two ICUs in Australia. Between May 2014- March 2016, any patient on VA or VV ECMO. **Purpose:** Determine feasibility of putting patients on lower anticoagulation levels versus normal therapeutic levels to prevent from adverse bleeding	**n:** 31 pts (9 VA ECMO, 22 VV ECMO) 16 pts randomized to low dose heparin, 15 to therapeutic dose heparin **Setting:** Australian ICUs	**IV:** Feasibility of low dose heparin administration **IV2:** Adverse events- bleeding or thrombotic **DV:** Low or therapeutic dose heparin administration	Primary feasibility included the difference in mean heparin dose, aPTT, and anti-Xa. It also measured number of thrombotic and bleeding events.	Repeat measures ANOVA. CI: 95%	Significant difference in daily mean aPTT P= 0.03, daily mean anti-Xa P=0.00, and daily mean heparin dose P=0.0004 in the low dose heparin group. Low dose heparin was not associated with a decrease in bleeding events or increase in thrombotic events. Overall this supports feasibility of administration of low dose heparin.	This is level III evidence being a randomized control trial, however of small sample size. This study is beneficial into understanding the maintenance of heparin for patients on ECMO however doesn't fully support one protocol versus the other. It sets up a good foundation for a larger more influential randomized controlled trial. This study is also limited to adult patients.
Saini et al., (2019). Anti-factor Xa-Based	NR but retrospective review of	**Design:** Qualitative-Single-center,	**n:** 95 pts	**IV:** Anti- Xa nomogram, titration	Median of 2 anti-Xa measurements a	SAS 9.2 statistical analysis	Median anti-Xa dose required to reach	This is level VI single-center observational

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monitoring of unfractionated heparin: Clinical outcomes in a pediatric cohort. **Funding:** None listed **Country:** USA **Bias/Conflicts:** Author declares none	physician-titrated, computerized nomogram for patients receiving unfractionated heparin	observational cohort study over 20 months including pediatric pts < 21 years old, being treated with unfractionated heparin and following an anti-Xa-based nomogram **Purpose:** Assess clinical outcomes of anti-Xa nomogram and assess correlation between aPTT and anti-Xa.	**Setting:** Quaternary Nationwide Children's Hospital, Columbus, Ohio	of heparin administration **DV:** Maintain anti-Xa of 0.35- 0.7 units/mL,	day and median of 1 heparin infusion rate change to maintain therapeutic anti-Xa.	software was used. Mean, median, and Spearman correlation coefficient were used	therapeutic range was significant higher in infants than older children (P < 0.0001), median time to reach therapeutic anti-Xa rage was 10 hrs and much shorter in those who received initial bolus, 5.3% experienced a major bleeding event, and moderate correlation between aPTT and anti-Xa was noted (r= 0.75, CI: 72-77%)	cohort study. The sample size was small and was limited to one facility. This study although was good in providing data about following a specific nomogram, and in the pediatric population, was not studied on ECMO patients.
Werho et al., (2015). Hemorrhagic complications in pediatric cardiac patients on extracorporeal membrane oxygenation: An analysis of the	NR but inferred best practice and quality improvement	**Design:** Quantitative-Retrospective review of the Extracorporeal Life Support Registry of patients less than 18 years	**N:**21,845- total pts supported on ECMO during study period **n:** 8,480- had hemorrhagic complications	**IV:** Hemorrhagic risk **DV:** Cardiac disease versus non cardiac disease processes	Measured cardiac versus noncardiac disease patient complications. Not explicitly explained, reviewed data from multiple	"Multivariable analysis" is all that is stated. CI**:** 95% Factors associated with hemorrhagic complications in	Higher rates of hemorrhagic complications in pts with cardiac disease versus those without 49% vs 32% (p < 0.0001)	This is level IV evidence with a large study sample size. This study lacks specific study details such as methods of collecting data

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extracorporeal life support organization registry. **Funding:** None listed **Country:** N/A Worldwide **Bias/Conflicts:** Author declares none		old from 2002-2013. **Purpose:** Review patient data from 2002-2013 from ELSO centers. Not explicitly explained.	**Setting:** Participating ELSO centers		participating centers	cardiac surgical pts: Pre-ECMO mediastinal exploration, surgical complexity, early post-operative cannulation, and longer bypass times.	In all pts, hemorrhagic complications were more prevalent if the child was greater than 1 year of age and had an extended ECMO run.	and analysis of data. Discusses hemorrhagic risk which can affect anticoagulation and ultimately adverse outcomes for pediatric pts supported on ECMO. The large number of pts analyzed can offer some support in ECMO complication risk and the need to mitigate that as much as possible, related to the PICOT question.

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Table A2

Synthesis Table

	Ares et al.	Baird et al.	Bingham et al.	Colman et al.	Kessel at al.	Khaja et al.	Mazzeffi et al.	McQuilten et al.	Saini et al.	Werho et al.
Year	2019	2007	2018	2019	2017	2010	2019	2016	2019	2015
Level of Evidence	VI	VI	VI	VI	VI	VI	IV	II	IV	IV
Design	QRR, single center	QRR	QRR	QRR	QRR	QRR	QRR of cohort study	Randomized, controlled, unblinded trial	Observational cohort study	QRR
Conflicts	None	None	None	None	None	None	None	None	None	None
Funding	NIH	None	None	None	None	None	None	None	None	None
Location of Study	USA	USA	USA	USA	USA	USA	USA	Australia	USA	Global
Demographics										
Sample Size	14	604	35	72-pre group 51-post group	18	21	121	31	95	21, 845
Age Included	Birth- 18 yrs	NR	NR	Adult	NR	NR	Adult	Adult	< 21 yrs	< 18 yrs
Median Age	1.5yr +/- 2.2	3 days	39 days	56-pre group 60-post group	NR	2 days	57- ACT group 54- aPTT group	41- low dose hep 43- therapeutic hep	8 yrs	NR
Gender	9 m 5 f	346 m 258 f	NR	46%-m pre group 34%- m post group	NR	12- m 12- f	33% f 66% m	68% m low dose hep 80% m therapeutic hep	60% m	NR

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Ethnicity	5 white 7 black 2 Hispanic	NR	NR	NR	NR	NR	NR	NR	NR	NR
VA/VV ECMO	VA and VV	NR	NR	VA	NR	NR	VA	VA and VV	NR	VA and VV
Heparin use	NR	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Other Anticoagulant use	NR	**X**	**X**		**X**					
DV										
Survivability	**X**	**X**								
Long Term Complications	**X**									**X**
Different anticoagulant tests		**X**	**X**	**X**	**X**	**X**	**X**		**X**	
Bleeding				**X**			**X**	**X**	**X**	**X**
Thrombotic events				**X**			**X**	**X**		**X**
IV										
Length of ECMO use	> 21 days 14-20 days < 14 days	182 hrs +/- 134 (cardiac pts less hours compared to respiratory)	NR	6 +/- 6 days	NR	10.8 days	5-6 days	9.33 days- low dose hep 9.79 therapeutic hep	NR	NR
Clinical outcomes	**X**	**X**		**X**				**X**		**X**
Therapeutic ranges		**X**		**X**	**X**		**X**		**X**	
Weight		**X**								
Gestational Age		**X**								
Conditions		**X**						**X**		
Anticoagulant protocol				**X**	**X**	**X**	**X**			

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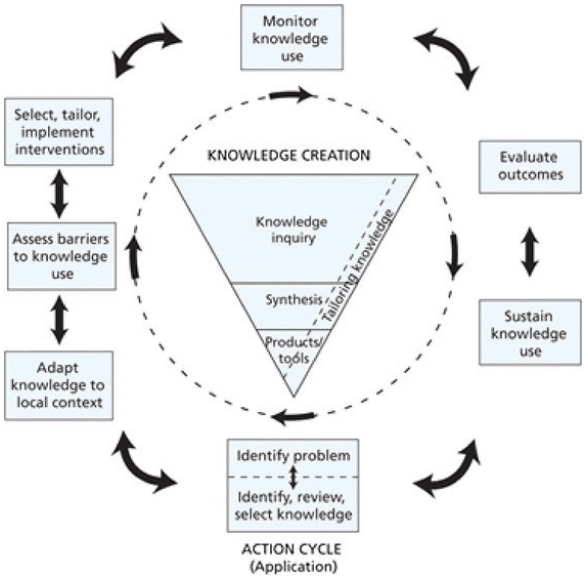
Appendix B

Figure 1

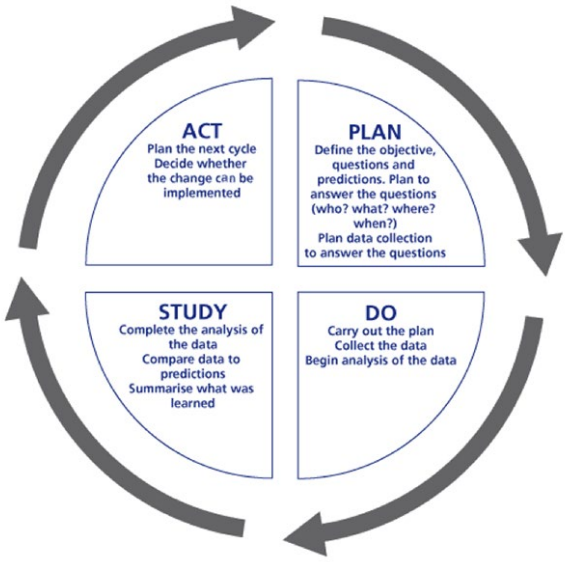
Knowledge to Action Framework



Field et al. (2014).

Figure 2

PDSA Cycle



UI Healthcare Marketing and Communications (2017).

Appendix C

Data Collection Sheet

PHOENIX CHILDREN'S Hospital

Start Date: 10/7/2018
End Date: 10/7/2019
ECMO Heparin IV Drip

Date of orders	Pt Age	Weight KG	Dosage	Location When Ordered	Order Requested	On/Off ECMO	Initiation Heparin dose per guideline? Y/N	Initial Heparin bolus Dose	ECMO Heparin Drip Start Date/Time	Initial Dose H: higher L: lower C: correct	First anti-Xa level (Date/Time)	First anti-Xa level result	Heparin Bolus Y/N	Heparin Bolus Dose (units/dose)	Heparin gtt Dose change (Date/Time)	Second anti-Xa level (Date/Time)	Second anti-Xa level result	AT3 level at baseline	AT3 repleted before second antiXa level? (Y/N)	First therapeutic anti-Xa level (goal: 0.3-0.7) Date/Time	Neurological Concerns	Notes

KEY:
AT3=
Y= Yes
N= No
gtt= Drip
kg= kilograms

Appendix D

Provider Survey Questions

1. How confident are you in following the anticoagulation protocol currently in place, for our ECMO patients?

   (Likert scale 1-5, 1= Not confident, 5= Extremely confident)
2. What would you change about the current anticoagulation protocols for ECMO patients?

   (Text entry response)
3. Per hospital protocol, what is the ECMO heparin infusion initiation guidelines based on?

   (Text entry response)
4. What is the initial Heparin loading dose for ECMO patients? Does this differ between weight and age? (Text entry response)
5. Heparin drips are titrated by percentage- 5%, 10%, 20% based on the anti Xa or PTT result. Are these percentages sufficient to therapeutic effect? (Yes, No, Other)
6. When is it appropriate to give a heparin bolus to an ECMO patient? (Text entry response)
7. Do you think Heparin is the most effective in proper anticoagulation for ECMO supported patients? (Yes, No, Other)
8. Please add any other additional comments that you would like, regarding our protocol, Heparin, or ECMO anticoagulation. (Text entry response)

Appendix E

Heparin Anticoagulation in Pediatric ECMO Patients: Budget Proposal

Potential Funding: Extracorporeal Life Support Organization, Phoenix Children's Hospital Family Advisory Council, Agency for Healthcare Research and Quality

Revenue/ Savings: Adequate anticoagulation while on Extracorporeal Membrane Oxygenation (ECMO) prevents adverse patient events which could require higher levels of care/additional interventions, and possibly prevent patient expiration.

Phase	Activities	Estimated Cost	subtotal	Total
Preparation	Chart review of the past years qualifying pediatric ECMO patients ($15/hr x 24 hours)	$360		
	Meetings with project champion- Allison Mruk, CVICU pharmacist ($50/hr x 1hr each meeting)	$200		
	Meetings with project mentor- Dani Sebbens ($45/hr x 1hr each meeting)	$180		
	Meeting with Critical Care Director- Joshua Koch, MD ($60/hr x 1hr each meeting	$120		
	Design and print badge reference cards (200 count) ($0.50 each)	$100		
	Design and share electronic protocol evaluation/survey	$50		
	Design and print ECMO Anticoagulation rounding checklist to be used for each patient bedside each shift (500 count) ($0.10 each)	$50		
	Internet accessibility	$80/year	$1140	
Delivery	Meeting/ education review session with critical care providers (estimate $60/hr for at least 20 providers)	$1200		

	Light refreshments for educational meeting	$75		
	ECMO Anticoagulation protocol rounding review sheets on a yearly basis	$50		
	IT/EMR specialist time and compensation to develop notification window/ link to incorrect dosing (	$1500		
	Rented meeting space	$0- considering open access to rooms or Zoom meetings with COVID restrictions	$2825	
Evaluation	Intellectus statistical software for data review	$0- already accessible by student		
	Review and analysis of results ($15/hr x 24 hrs)	$360	$360	**$4325**

Budget Justification

The purpose of this quality improvement project is to ensure adequate dosing of Heparin anticoagulation medication is being administered to pediatric patients supported by ECMO. Incorrect dosing of Heparin while being supported on ECMO has significant risk that may lead to inappropriate bleeding, stroke, or clot formation.

Preparation

Computer and internet use is necessary for chart review, chart review and data collecting will need to be completed to evaluate current adherence to protocol and identify areas of improvement, resources must be designed and printed for ECMO technicians, bedside ECMO nurses, and prescribing physicians may have access to reference the protocol in an easy and clearly described way.

Delivery

For this project to be successful, a meeting must be held to review the current protocol for anticoagulation administration and obtain a baseline knowledge of the current protocol. If this could be held in an organized meeting space with light refreshments, it would entice higher attendance. If possible, it would also be beneficial to make an electronic medical record update to make a warning flag if a provider prescribes an inappropriate dose of anticoagulation medication based on the protocol.

Evaluation

To make sure the protocol is still being followed, annual chart review and annual provider remedial training of our current anticoagulation protocol would make sure that we are providing the most appropriate evidence-based care. Tracking our results and statistics of following this protocol will help train providers further and allow for a goal to maintain. Continuous improvement goals will make sure we are performing to the best of our ability.