Tandem Therapies in Extracorporeal Support

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Case Vignette

A 4-year-old (17 kg) previously healthy female presents to your hospital in acute respiratory failure due to pulmonary hemorrhage. She is intubated and brought to your intensive care unit requiring high conventional ventilator settings to maintain oxygenation and lung nodules are noted on chest X-ray. Initial labs obtained in the emergency department demonstrate anemia and hematuria. The patient has persistent hypoxia despite maximum ventilator support and she is cannulated onto veno-venous extracorporeal membrane oxygenation (VV-ECMO). Over the following day she is noted to have worsening fluid overload, and rising creatinine requiring CRRT to be started. Her anticoagulation for ECMO puts her at higher risk for line placement related bleeding complications, so the decision is made to run the CRRT hemofilter in line with your ECMO circuit. She continues to clot off hemofilters and membrane oxygenators requiring a change out of the full extracorporeal circuit. Autoimmune workup was sent, and on Day 3 of VV-ECMO the patient comes back positive for cytoplasmic staining anti-neutrophil cytoplasm antibodies (C-ANCA) confirming the diagnosis of granulomatosis with polyangiitis. After discussion with your apheresis physicians, you decide she meets criteria for therapeutic plasma exchange (TPE) due to severe renal vasculitis and a 7 day course is ordered.

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22.1 Tandem Extracorporeal Therapies

Patient acuity in the pediatric intensive care unit (PICU) is increasing. This has been attributed to multiple factors, including, but not limited to, improved survival of extreme premature infants, increased rates of technology dependent patients, and improved technology leading to longer hospital stays. While improved survival of many diseases is to be celebrated, many of these survivors have long term comorbidities associated with their initial disease or treatment of it. This has created a new population of pediatric patients who have chronic co-morbidities, and have increased utilization of the PICU. In addition to this increasing chronic population of patients, standardized management of acute life threatening diseases such as sepsis and septic shock have led to improved survival of patients who just a few years before were "certain to die." This combination has dramatically increased the number of patients with multiple organ failure who need to be supported in the PICU. Using individual extracorporeal therapies as a means for supporting individual organs have been a mainstay of PICU care for the last two decades. Using these techniques, we have seen improved survival (compared to historical controls) in patients supported with extracorporeal membrane oxygenation (ECMO), ventricular assist devices (VAD), and continuous renal replacement therapies (CRRT). For many of these therapies, the presence of multiple organ failure has been considered a contraindication for use. However, over in the last decade, centers have been willing to challenge that dogma, and have started using combinations of extracorporeal therapies to manage multiple organ failure patients and provide extracorporeal life support (ECLS).

This chapter will review the current state of the art of tandem use of multiple extracorporeal therapies for patients with multiple organ failure from the aspect of a patient who is already supported on ECMO. With that aim, several caveats should be stated. Progress in this field has been slow and difficult, because of multiple factors. From a very practical standpoint, these independent devices were never engineered or designed to work together and just achieving forward flow of blood in them can be a significant hurdle. Additionally, when looking at this problem worldwide, due to country specific regulations, there is a wide variety of devices that may or may not be available to any individual center. This vastly increases the number of permutations of choices that can be made when designing your multiple organ therapy platform, and makes a discrete review of all possibilities difficult. In this chapter, we will thus focus on the engineering, physics, and physiology that are commonly seen in currently available devices. We will leave it to the reader to determine how best to balance those factors based on the choices of devices that they have locally. Another important caveat to understand is that this field and these techniques are very young. There is little substantial medical literature that has been published, and what has been published tends to be from a small number of single centers, has been published in the last 5 years, and has small numbers of patients supported. Expert opinion remains a common source of information. Multiple clinical trials need to be conducted to evaluate optimal design aspects, as well as clinical outcomes and complications.

22.2 Acute Kidney Injury (AKI) During ECMO

AKI is commonly seen and has been demonstrated as a risk factor for death in critically ill patients of all ages in the ICU. As noted throughout previous chapters in this textbook, multiple assessments for this topic have spanned across neonatal, pediatric, and adult ICU patients [1–3]. Historically, AKI definitions have been highly variable, but now multiple standardized scoring systems exist which utilize both urine output and serum creatinine to allow classification of AKI [4–6]. Similar to variability in definitions, AKI during ECLS is highly variable and dependent on age, type of ECLS, and classification for AKI. Reports have demonstrated AKI in 19–71% of neonates, 20–72% of pediatrics, and up to >70% of adult ECMO patients [7–11]. Many of these studies show a correlation between AKI and mortality for ECMO patients. Kidney injury can be demonstrated beyond traditional definitions of urine output and serum creatinine through the concept of fluid overload (FO). The systemic deleterious effects of FO have been demonstrated through an increased mortality for ECMO patients with FO, impaired oxygenation and increased duration of extracorporeal support [12–20]. As both AKI and FO negatively affect outcomes, focus has shifted to treating these comorbidities as a goal to improve ECMO outcomes.

Both AKI and fluid overload have been treated in ECMO patients by the standard renal replacement therapies (acute intermittent hemodialysis, slow continuous ultrafiltration, peritoneal dialysis, etc.). However, the most common way that AKI and fluid overload is treated in ECMO patients is by adding CRRT to the ECMO circuit. The timing and indication for CRRT to treat AKI and FO are not well established in ECMO. Recent consensus guidelines were published by the Acute Dialysis Quality Initiative (ADQI) on pharmacological and mechanical fluid removal [21, 22] and these principles are, in general, followed for ECMO patients. The Extracorporeal Life Support Organization (ELSO) also publishes a series guidelines (found at https://www.elso.org/Resources/Guidelines.aspx) to assist providers in ECMO treatment. These guidelines discuss the importance of fluid management in order to reach a homeostasis similar to the patient's normal (dry weight) extracellular fluid volume. For ECMO patients, indications for CRRT are broadly divided into removal of drugs/toxins, FO, AKI and electrolyte imbalances refractory to medical therapy, with usage varying among institutions [12, 23]. The most comprehensive and up-to-date evidence-based review of tandem CRRT and ECMO use can be found in Chen et al. [24].

22.3 Technical Aspects of CRRT During ECMO

Three main methods exist for providing CRRT to an ECMO patient [25, 26]. The first method involves a second vascular access point which utilizes a commercially available CRRT device without any connection to the ECLS circuit. This approach is the simplest method of simultaneous CRRT and ECMO, but is limited to those patients with vascular access prior to cannulation, as placing a new vascular access

catheter for dialysis has an elevated severe bleeding risk once systemic ECMO anticoagulation has begun. Using this method, CRRT is run similar to non-ECMO patients, with the notable exception that systemic anticoagulation for ECMO precludes the need for local CRRT circuit anticoagulation.

The second method for CRRT on ECMO patients involves creating a shunt of blood post-pump from the ECMO circuit which flows through an isolated hemofilter. The pressure created by the extracorporeal pump drives blood through the hemofilter creating ultrafiltrate. The amount of ultrafiltrate produced is limited by using a standard intravenous (IV) pump programmed for the number of mL/h of ultrafiltrate desired and then this volume is measured with a bedside urimeter. The ultrafiltrate can be discarded to provide slow continuous ultrafiltrate (SCUF), or a replacement fluid with an appropriate electrolyte composition can be delivered back into the circuit via an additional standard IV pump to provide continuous veno-venous hemofiltration (CVVH). The now processed blood is returned to the ECLS circuit pre-pump (Fig. 22.1a). This method of "in-line" hemofiltration was the earliest form of tandem extracorporeal support therapies and is advantageous due to ease of use, simplicity for all ECMO specialists, and low cost of supplies. However, many disadvantages were noted with the use of this method. Notably, the creation of the shunt returning blood pre-pump creates a discrepancy between the blood flow listed on the ECMO pump and what is actually being delivered to the patient. The difference between ECMO pump flow and patient delivered flow must be monitored and represents the flow through the hemofilter circuit. Patient flow rates are now more accurately measured in the distal arterial limb of the ECMO circuit just prior to entry back into the patient. Additionally, the delivery of the blood exiting the hemofilter back pre-pump makes the CVVH less efficient due to recirculation of the already processed blood back through the hemofilter circuit. While this is a theoretical concern, clinically, the ECMO flow rates greatly exceed the hemofilter circuit flow rates, making clinically significant recirculation negligible. Also, using this method to provide SCUF for smaller children may create multiple electrolyte disturbances and is not recommended. The "in-line" circuit often has no pressure monitoring, which makes identifying hemofilter malfunction, thrombosis, or rupture more challenging. The most important disadvantage to "in-line" hemofiltration of CRRT during ECMO relates to inaccuracy of fluid balance. The IV pumps being used for control of ultrafiltrate and replacement fluid were not engineered for this therapy and truly function as flow restrictors (and not pumps), having an inherent error rate (~12.5%) when used in this setting [27]. An in vitro setup of "in-line" CRRT with ECMO, demonstrated a measured versus prescribed flow error of up to 34 mL/h (>800 mL/day), which in a small patient (5 kg) could equal their daily fluid goals (~150 mL/kg/day) [28]. Careful monitoring of the replacement fluid volume as well as ultrafiltrate volumes is essential to the ECMO specialist duties when providing these therapies concomitantly. This can be done either via volume measure (mL) or based off highly accurate scales (±1 g). The need for hourly monitoring increases ECMO specialist workload and is contributing to a reduction of use of this "in-line" technique.

The third and preferred method for CRRT on ECMO patients is via introduction of a commercially available CRRT device into the ECMO circuit. Multiple factors contribute to determining the optimal method to connect these separate extracorporeal support devices including, but not limited to, type and placement

of pressure monitors, CRRT device software limitations for variables such as pressure and flow, type of ECMO pump, and ECMO circuit design. In general, the roller head pump driven ECMO circuit has more positive pressures in the venous limb, allowing for pre-pump venous limb placement and return of the CRRT device (Fig. 22.1b). The sole driving pressure for the CRRT circuit is based off

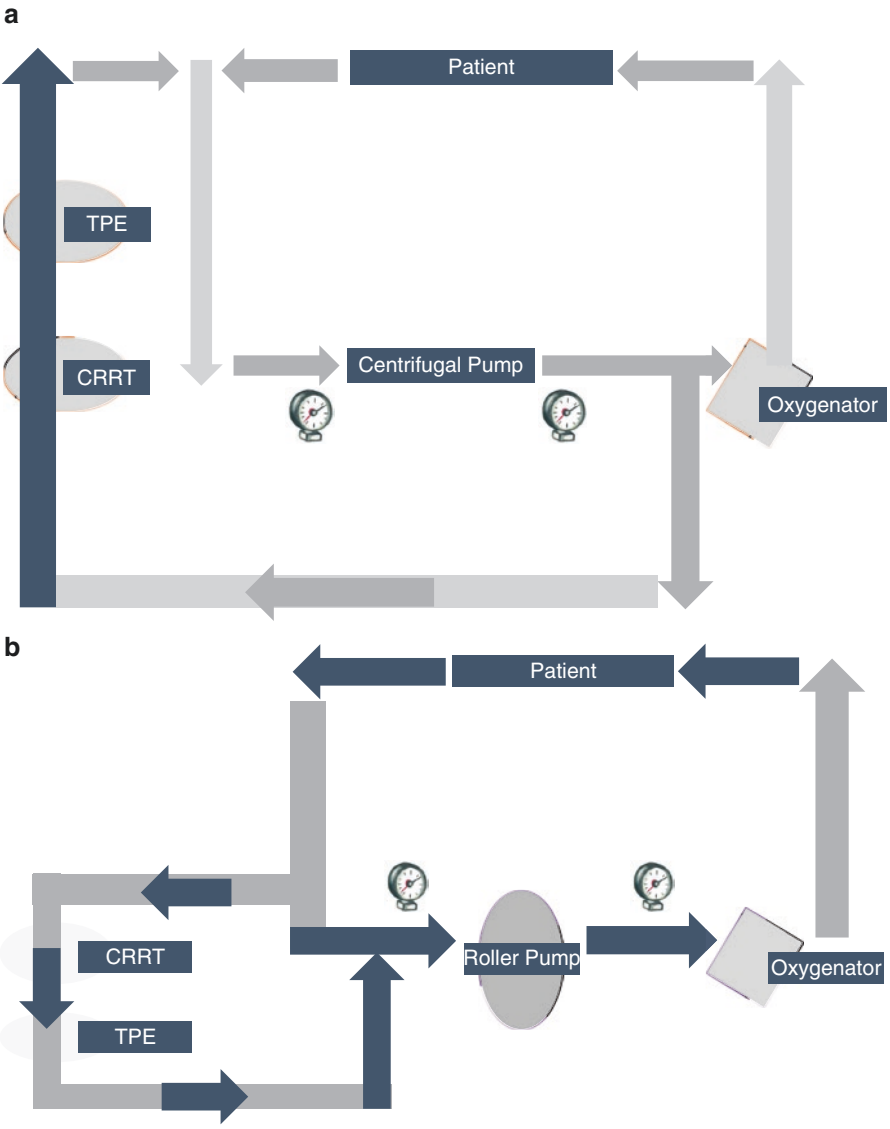

Fig. 22.1 Representative schematic diagram of multi-tandem extracorporeal procedures: ECMO, TPE and CRRT. *ECMO* extracorporeal membrane oxygenation, *TPE* therapeutic plasma exchange, *CRRT* continuous renal replacement therapy. ECMO, 3 way stopcock valve. Note: ECMO flow rates: 250 mL–5000 mL/min; TPE flow rates: 30 mL/min–70 mL/min; CRRT flow rates: 50 mL/min–150 mL/min

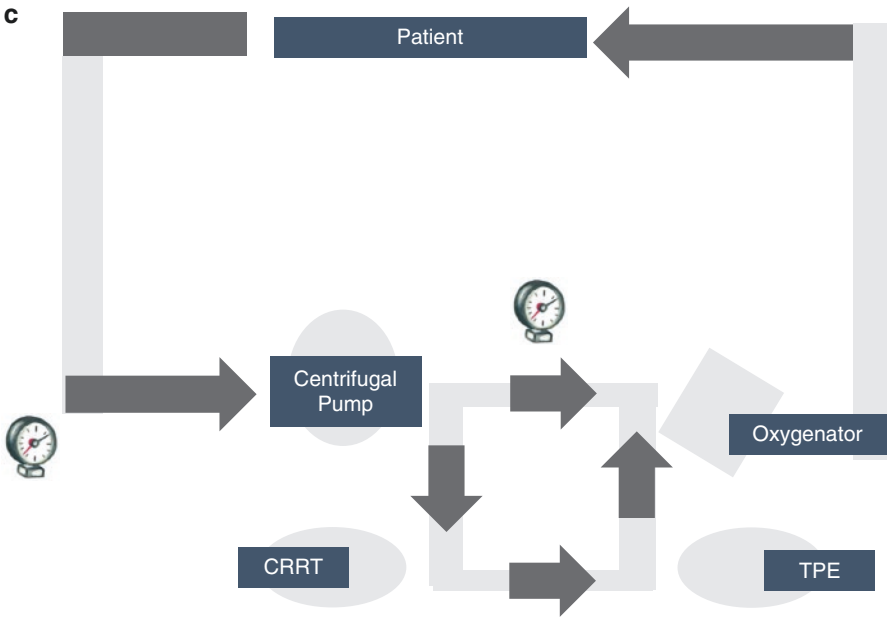

Fig. 22.1 (continued)

the CRRT device pump generating a negative pressure to pull blood from the ECMO circuit and then creating a positive displacement and pressure to drive it through the hemofilter and ultimately return it back to the ECMO circuit. The pressures in the venous limb of a roller head circuit are not very negative and are similar to what would be expected in a well-functioning dialysis catheter, thus allowing the CRRT device software to function in a normal fashion. Alternately, a centrifugal pump driven ECMO circuit has a much larger negative venous limb pressure, and so an alternative configuration is often required. A common issue is that the CRRT device's software pressure limits will typically not allow it to function with the magnitude of negative pressures seen on the pre-pump venous limb of a centrifugal circuit. Additionally, when making the physical connections of the CRRT device to the ECMO circuit in this highly negative pressure environment the risk of air entrainment is large. For a centrifugal ECMO system, recommendations include placing the CRRT device post-pump, but pre-oxygenator, to both move the CRRT device to a region of positive pressure where it is more likely to function more consistently, as well as decrease the risk of air entrainment (Fig. 22.1c). In this third configuration, the blood is returned from the CRRT device to the ECMO circuit post pump venous limb, just prior to the membrane oxygenator. Having both the CRRT drain and return post-pump but

pre-oxygenator is optimal because this configuration allows the oxygenator to act as a clot and air trap, and decreases the amount of recirculation through the CRRT circuit. When compared to the "in-line" method, this third method allows for more accurate fluid balance, a longer hemofilter life, standard pressure and flow monitoring of the CRRT circuit and the ability to use a CRRT device has been engineered for the purpose of providing CRRT [28–30]. It should be noted that all commercially available CRRT devices are not specifically approved or designed for use in ECMO patients. This method has the disadvantages of higher cost and additional training for the user.

22.4 Outcomes of CRRT During ECLS

Although theoretical advantages and disadvantages of differing methods for providing simultaneous CRRT and ECLS exist, very little outcome data are available to compare methods. Prior studies which looked at "in-line," commercial CRRT devices and stand alone, found all methods to be adequate for fluid and electrolyte control. Although, data have shown increased fluid accuracy when using commercially available devices compared to an "in-line" system, and a decreased duration of use [29–31]. These studies also demonstrated a longer filter life when a CRRT device was incorporated into the ECLS circuit (138.4 h) compared to 36.8 h seen in non-ECLS children with stand-alone CRRT, and 27.2 h seen in CRRT during ECLS with citrate anticoagulation added [30, 31]. No difference was noted in intensive care unit (ICU) length of stay, hospital length of stay, or mortality.

Currently, the largest set of outcome data for concomitant CRRT on ECLS comes from the ELSO registry [32, 33]. "Renal Failure" is defined in the ELSO registry as a complication of ECLS, with three levels of injury coded: Creatinine (Cr) 1.5–3, Cr >3, and use of dialysis/hemofiltration/continuous arteriovenous hemodialysis. These definitions are very limited compared to modern scoring systems (e.g., KDIGO), and the registry only counts it once per run with no duration information available. This further complicates analysis of outcomes, because there is no way to differentiate a patient who, for example, received CRRT for their entire 14 day run versus someone who had it started 2 h before death. With those caveats, analysis of the ELSO registry demonstrates the presence of renal failure in each age category of respiratory failure has associated worse survival (Table 22.1) compared to the overall survivals of these categories (Neonatal 63%, Pediatric 58%, Adult 61%). Similar data is noted in the cardiac population. As coded in the ELSO registry, both kidney injury and the use of renal replacement therapy (RRT) are risk factors for increased mortality. A subset of six ELSO centers across North America came together and formed the Kidney Injury During Membrane Oxygenation (KIDMO) research network to further investigate relationships between RRT use, AKI, and survival in pediatric patients (<19 years old) [12, 23]. They evaluated a cohort of 835 ECLS patients at their centers from 2007 to 2011

Table 22.1 Renal complications and survival from ELSO Registry International Report 2016

Renal complication category	Neonatal respiratory failure n (% reported, % survival)	Pediatric respiratory failure n (% reported, % survival)	Adult respiratory failure n (% reported, % survival)
Creatinine 1.5–3	1927 (6, 50)	702 (9, 35)	1947 (16, 47)
Creatinine >3	378 (1, 37)	327 (4, 34)	1106 (9, 45)
Renal replacement therapy	6387 (23, 50)	3475 (43, 42)	4661 (38, 49)

Note: *ELSO* extracorporeal life support organization

using the modern KDIGO definition of AKI. The data showed that AKI affects the majority of pediatric ECLS patients (50–69%), it occurs early (99% within first 48 h) and it is associated with longer duration of ECLS (~48 h) and higher mortality (Odds Ratio = 2). There was a clear association in this data between increasing AKI stage being associated with increased risk of death. Fluid overload has also been assessed from this KIDMO cohort, and fluid overload of >10% is present in almost half (46.4%) and > 20% in almost one quarter (24.1%) of ECMO patients at the time of cannulation [34]. In this cohort, fluid overload was also found to worsen once a patient was placed onto ECMO. During extracorporeal membrane oxygenation, 84.8%, 67.2%, and 29% of patients had a peak fluid overload greater than or equal to 10%, 20%, and 50%, respectively. The magnitude of fluid overload was correlated with survival, with median peak fluid overload being lower in patients who survived to hospital discharge (24.8% vs. 43.3%; $p < 0.0001$). A multivariate model incorporating acute kidney injury score, pH at extracorporeal membrane oxygenation initiation, nonrenal complications, extracorporeal membrane oxygenation mode, support type, center and patient age, demonstrated that the degree of fluid overload at extracorporeal membrane oxygenation initiation, and the peak fluid overload on extracorporeal membrane oxygenation predicted duration of extracorporeal membrane oxygenation in survivors. Further analysis of this large KIDMO cohort is ongoing, with a focus on specific patient populations, such as the pediatric cardiac population. In previous work, five case series have reviewed CRRT during ECMO for the pediatric cardiac population. All but one showed statistically higher mortality when CRRT was used on ECMO, with a combined odds ratio of 6.19 [24].

22.5 Summary of Concomitant CRRT and ECMO

The ECMO community commonly uses CRRT for the treatment of AKI and FO in their population. Methods of providing these tandem extracorporeal support therapies are not standardized and no products are commercially designed for this use. In all critically ill patients, mortality of ECMO patients who develop AKI exceeds those patients without AKI. In contrast to previous thinking, it has now been

demonstrated that the presence and degree of AKI is the risk factor for death, not the use of the CRRT device. Additionally, in this population fluid overload has also been shown to be correlated to higher mortality and longer ECMO duration. Both AKI and fluid overload remain potential clinical targets to improve mortality in ECMO patients. However, the details for optimal treatment of AKI and fluid overload for ECMO patients are not well defined and therefore vary among institutions. Additional multicenter data and trials with standardized protocols are needed to better guide AKI management in ECMO patients.

22.6 Apheresis During ECMO

Therapeutic apheresis (TA) involves separating and removing individual constituents of blood. This is a well-established technology and many apheresis procedures are provided in the outpatient setting. Newer to the apheresis world, is providing TA to a critically ill population of children, especially those requiring ECMO. ECMO has often been considered a contraindication to TA as the patients were deemed "too sick/unstable." As the use of multiple extracorporeal therapies has grown, physicians are more regularly using TA procedures on ECMO patients and may even place patients on ECMO to achieve cardio-pulmonary stability in order to perform TA procedures. Details for indications and modalities of therapeutic apheresis are beyond the scope which will be covered in this chapter. The information in this chapter serves as a review for patients in multi-organ failure who require multiple tandem extracorporeal support therapies (TA, CRRT, and ECMO) and as a guide for how to provide these tandem procedures together successfully.

One method of therapeutic apheresis is via therapeutic plasma exchange (TPE). TPE is the separation, removal, and replacement of plasma from the blood. The goal of TPE is removal of large molecular weight constituents (e.g., antibodies, cytokines) or highly protein bound molecules while restoring depleted coagulation factors, and proteins to return homeostasis needed for recovery [35]. This is the most common form of TA utilized in ECMO patients, although no specific ELSO guidelines exist for indications of apheresis procedures while on ECMO. Instead, the decision to proceed is based on evidence of effectiveness for underlying disease based on the general guidelines set forth by the American Society for Apheresis (ASFA). Periodically, a set of evidence based guidelines are published by ASFA, with the last being in 2016 [36]. These guidelines review all medical evidence for apheresis by disease, and present a one-page summary with highlighted prescribed recommendations.

Regardless of indication, an anticoagulant is required to avoid excessive thrombosis due to the activation of blood through an apheresis device and its extracorporeal circuit. Although most patients on ECMO have systemic anticoagulation and no longer need local anticoagulation of either the apheresis and/or CRRT devices via citrate or other regional anticoagulation techniques However, one must be aware the effects of citrate toxicity may still be seen. Large amounts of plasma (which

contains citrate as an anticoagulant for storage) utilized in TPE potentially expose a patient to citrate toxicity, with depletion of free, ionized extracellular calcium. The ECLS patient's cardiac function (especially in the neonatal population) may be negatively affected by low ionized calcium. This could become a relative contraindication for TPE utilizing fresh frozen plasma replacement, and physicians may decide to utilize albumin replacement or forgo therapy altogether due to the hypocalcemia risks. Alternatively, either a continuous infusion of exogenous calcium or increasing veno-arterial ECMO flow rate during the procedure may mitigate these adverse effects of large citrate exposure.

22.7 Indications for TA with CRRT and ECLS

No ELSO guidelines currently exist for the use of therapeutic apheresis while on ECLS. Instead, the decision to proceed with TA should be made based on evidence of underlying disease and not based off ECLS and CRRT support for the patient. It should be understood that there is very little evidence presented in these guidelines for patients who are receiving ECMO. ECMO is only mentioned once in the 190 page guideline document, in the setting of describing a case series TPE use during ECMO of pediatric patients with sepsis-associated multiple organ failure. However, these guidelines remain the best summary of evidence for the effectiveness of therapeutic apheresis procedures to correct the underlying diseases that have caused the patient to need ECLS. As defined by the ASFA (7th Special Issue) Category I indications are for disorders where apheresis is first-line therapy either alone or in conjunction with other treatments. Category II indications are defined as second-line therapy either in conjunction with or as stand-alone treatment. Category III indications include disorders for which the optimum role of apheresis therapy is not established and decision making should be individualized. Category IV are considered harmful to the patient. As mentioned above, little data exist regarding the use of therapeutic apheresis in the setting of ECMO. In the largest cohort of 53 pediatric patients (<21 years old) receiving tandem TA with ECMO reported, Sirignano et al. found the vast majority of these 180 procedures were conducted for patients requiring solid organ transplant (51% cardiac, 13% renal) and sepsis induced thrombocytopenia-associated multiple organ failure (TAMOF) (26%) (Table 22.2) [37]. Other case series have similarly noted the use of TPE and CRRT during ECMO for the management of sepsis with multi-organ dysfunction syndrome (MODS) and TAMOF [35, 37].

As often occurs at the frontier of medical care, diseases and clinical scenarios will exist with either no or little evidence to support the use of therapeutic apheresis. Essentially all cases of multi-tandem extracorporeal support (TA, CRRT, and ECLS) fall into this category. Although guidance can be found through the ASFA guidelines, prior to starting any treatment for uncategorized diseases, the treatment clinicians should carefully document their reasoning behind a chosen apheresis procedure, provide a mechanism of action to address the current disease, how TA will improve the patient's condition, a proposed therapeutic plan and duration, and how the clinician will assess for efficacy of therapy.

Table 22.2 ASFA (7th Special Issue) indications

Indication category	# Patients (% of Total)	# Procedures
Category I	8 (15)	42
Renal transplantation[a]	7	35
ANCA-associated RPGN	1	7
Category II	22 (42)	35
Cardiac transplantation desensitization	21	32
Hyperleukocytosis (Leukostasis)	1	3
Category III	23 (43)	103
Cardiac transplantation antibody mediated rejection	6	30
TAMOF	14	60
AIHA	1	7
Acute liver failure	2	6

Note: *ASFA* American Society for Apheresis, *ANCA* anti-neutrophil cytoplasmic antibody, *RPGN* rapidly progressive glomerulonephritis, *TAMOF* thrombocytopenia-associated multiple organ failure, *AIHA* autoimmune hemolytic anemia

[a]Antibody-mediated rejection and desensitization

22.8 Technical Aspects of TPE During Concomitant CRRT and ECMO

Similar to the concomitant CRRT and ECMO methods described above, apheresis procedures can be provided as stand-alone therapy through a separate vascular access or provided through the ECMO circuit. As seen with CRRT on ECMO the risks of bleeding for patients already anticoagulated on ECLS drive more providers to use TPE in line with ECMO circuit. No evidence suggests superiority to either stand-alone or in circuit use.

The first method of stand-alone therapy involves utilizing a second vascular access point for therapeutic apheresis for patients on CRRT and ECMO. As TA often has lower flower rates than CRRT, this can be achieved through two large bore peripheral catheters, or a preexisting apheresis compatible subcutaneous port but preferentially is done through a double lumen central venous line. As with all extracorporeal therapies, consideration must be made to the extracorporeal volume in relation to the patient's total blood volume. This is especially important in pediatric apheresis, where there often are not pediatric sized extracorporeal circuits. First, the apheresis device's extracorporeal volume (often being ~350 mL) needs to be accounted for in patients <20 kg, and in these patients a blood prime is preferred over crystalloid to avoid dilutional anemia. Blood prime could also be used in larger patients with inadequate oxygen delivery or unstable hemodynamics. In this stand-alone therapy, attention should be made to the temperature of the products being delivered as significant hypothermia can occur in smaller patients (<10 kg). Warming of the apheresis circuit to meet ECMO targets may also be required. The need of a regional anticoagulant during a therapeutic apheresis through a separate vascular is controversial, and no evidence exists to guide decision making. There is wide practice variation, with some centers relying only on the ECMO systemic anticoagulation, others who always

additionally provide regional anticoagulation, and those who assess each patient at the time of the procedure and determine a plan for that individual procedure only. As TPE is an intermittent procedure, when using a separate vascular access point, an anticoagulant solution should be used to lock the venous access points, per a center's usual policy, to avoid thrombosis.

The second method involves connecting the apheresis circuit to the ECMO circuit is done in a similar manner to CRRT as noted above (Fig. 22.1) [38]. Multiple configurations are possible, and dependent upon the type of ECMO pumping system. As with CRRT, none of the commercially available apheresis devices have been validated or designed for use concomitant with ECLS circuits. Similar to what is seen during CRRT during ECMO, a common complication includes a venous limb negative pressure alarm on the apheresis device. This can be ameliorated by adjustment of ECMO cannula position to improve drainage, reducing ECMO flow (if hemodynamically tolerable), changing parameters for alarms on the apheresis device, or altering the position of apheresis drainage from ECMO circuit (e.g., Fig. 22.1a, b). For patients already receiving concomitant ECMO and CRRT, a common configuration is that the apheresis device is placed in series to the CRRT device [26, 39]. Multiple three way stopcocks may be connected to the pigtail connection coming off the pre-pump venous limb of the ECLS circuit (Fig. 22.1b). During the procedure, the apheresis device pulls blood from the first stopcock and returns to the second one, where the blood then continues on into the CRRT circuit and ultimately back to the ECMO circuit (Fig. 22.2). In this configuration, it is important the

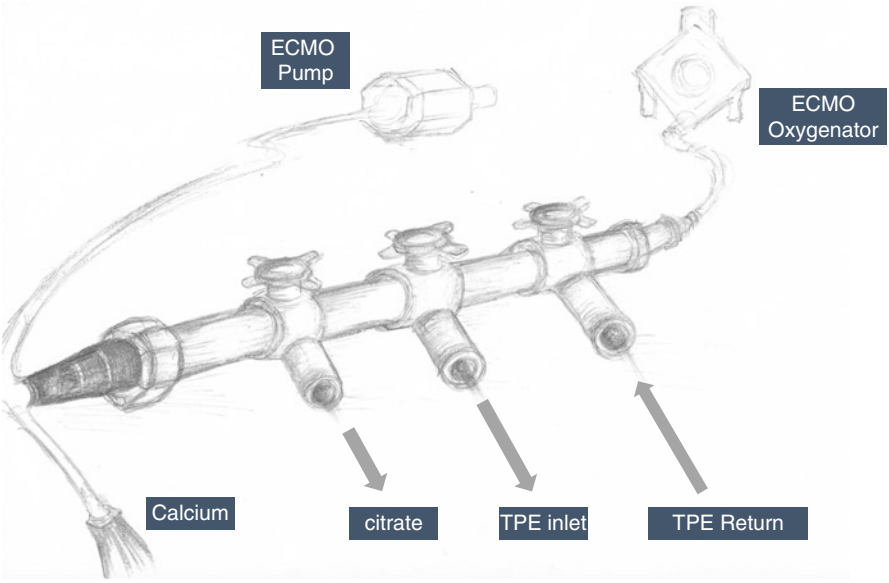

Fig. 22.2 Representative standardized connectors to TPE and CRRT from ECLS circuit. *TPE* therapeutic plasma exchange, *CRRT* continuous renal replacement therapy, *ECLS* extracorporeal life support

apheresis device and CRRT devices which are run in series, have matching flow rates to avoid pressure alarms and recirculation.

ASFA guidelines help determine the indication, duration, and dose of therapy required for therapeutic plasma exchange, however certain alterations are required when doing in tandem to CRRT and ECMO circuits. According to guidelines, dosing is presented as based off a multiplier of "plasma volume" (PV) or "whole blood volume" [36]. Typically these volumes are based off equations calculating from weight or body surface area and standard hematocrit (Nadler's equation). However, these equations are not valid when concomitant to other extracorporeal support systems. During ECLS, you must calculate both the total blood volume of the patient as well as the total extracorporeal circuit(s) volume. The total extracorporeal circuit includes a sum of each individual circuit, in this case, CRRT + Apheresis + ECMO . Failure to account for these volumes will under calculate the plasma volume involved and provide inadequate dosing of TPE. For example, using the standard calculations our 17 kg case report would have a total blood and plasma volume of 1700 mL and 714 mL. But if we accounted for an ECLS volume of 400 mL, CRRT volume of 250 mL, and apheresis volume of 350 mL, with a recent hematocrit of 40%, the same child has a total blood and plasma volume of 2700 mL and 1755 mL. Not accounting for the volumes of each of the extracorporeal circuits would lead to 40% underdosing in this child.

Depending on the indication of TPE, the ASFA guidelines recommend processing of 1–1.5 PV, which are replaced with either fresh frozen plasma (FFP) or albumin [36]. Strict dosing by mL is not necessary, and it can be rounded to the nearest unit of product. This is because for a solely plasma based molecule removed by TPE, you remove 63.2% with 1 PV, 77.7% with 1.5 PV, and 95% with 3 PV. Recommendations do not call for a full removal of 3 PV on the first therapy because many of the targeted molecules are not solely confined to the blood compartment, and redistribute with time necessitating repeat therapies. When providing TPE, one must be mindful that although the removal target is removed, many other blood components are removed simultaneously. Drug dosing is particularly challenging with the use of multiple extracorporeal elimination methods such as ECMO, CRRT, and TA in tandem. While some pharmacokinetics data exists, much additional work is needed in this field and careful, repeated, clinical assessment of the effect of each prescribed drug is required to evaluate for signs of sub- or supra-therapeutic dosing [40, 41].

Similar to CRRT, local anticoagulation with citrate can be utilized of the apheresis circuit during ECMO, however complications of hypotension and hypocalcemia have been described in both adults and children [38] due to citrate toxicity. The systemic anticoagulation (e.g., heparin or direct thrombin inhibitors) required for ECMO is typically sufficient for anticoagulation of all extracorporeal support devices. Although, as discussed prior, pharmacokinetics can alter significantly pre- and post-therapeutic plasma exchange and close monitoring is recommended both during and immediately after TA. As these procedures are being performed as an "off label" use of these devices in a setting they were not designed for, complications can and do arise. For example, many commercially available apheresis devices are engineered to only work when an anticoagulant solution is hung and running. As systemic

anticoagulation for ECLS precludes the need for local anticoagulation, a bag of crystalloid solution can be substituted for citrate allowing the apheresis device to function in the ECMO setting. Similarly, many of the commercially available apheresis devices utilize Nadler's formula to calculate the prescribed volumes required for TPE based off of inputted height and weight of patient. As noted above, much large volumes are required for patients on tandem extracorporeal circuits, and the devices will often alarm over concern that a very large exchange has been ordered. They may fail to run, or default to providing the procedure over extended periods of time (>8 h). In this scenario, the provider may choose to run therapy over an extended period, or more commonly, adjust the patient's weight programmed to reflect a patient with similar native (non-ECLS) blood volume. For example, our 17 kg patient was calculated to have 2700 mL of total blood volume (all circuits accounted) could be programmed as a 39 kg patient and this would allow processing of a similar volume of plasma over a shorter time course (~2 h). Whenever an institution is considering over-riding or altering a manufacturer's recommended practices, a formal written protocol should be established and closely followed, with multiple independent practitioners checking calculations and adherence to the protocol prior to initiating the procedure.

22.9 Use and Outcomes of Therapeutic Apheresis with CRRT During ECMO

Upon review of the current literature, the published experience is comprised of 67 patients across the world have received TPE simultaneous to CRRT and ECMO (Table 22.3). No randomized clinical trials have been published on disease process for the use of therapeutic apheresis on these extracorporeal support systems. All literature is currently based off individual case report and case series. The most common indications for use were sepsis with either thrombocytopenia-associated multi-organ failure (TAMOF) or multi-organ dysfunction syndrome [35, 37, 41, 43, 45, 47, 54]. Rationale for the use of TPE in this cohort of patients is best summarized by Nguyen et al., which includes removing ultra-large von Willebrand factor multimers, removal of antibodies to ADAMTS13, and replacement of ADAMTS13 with fresh frozen plasma [55]. The next most prevalent category is for antibody removal in active autoimmune diseases [26, 37, 42, 48–53, 55, 56] and organ transplantation [37]. Individual case reports exist for ingestions/poisonings [46] as well.

Significant heterogeneity exists in case reports for tandem extracorporeal supports due to the variety of rare diseases, differentiation in technique for TA, differences in technique for ECMO, and lack of severity of illness scoring. Together, these factors make commenting about complications and survival difficult. While center specific and regional registries exist, there is no international registry for these patients. As has been done with the ELSO registry for ECMO, capturing data about device related factors, therapy prescribed and patient related factors to an international database would allow for accrual of data which would be required to make definitions of best practices and improve outcomes for the patients with multiple extracorporeal therapy needs.

Table 22.3 Case Reports of Therapeutic Plasma Exchange (TPE) and CRRT during ECLS

Reference	n	Outcome Measure	Result	Year(s)/Center	Apheresis device	Anti coagulation	Apheresis complications
Sirignano et al. [37]	30 pediatric 24 CRRT + ECLS 6 CRRT + TPE + ECLS 180 procedures	Survival	79% survival	2012–2015 USA—CHOA	Optia	ECLS heparin only	Air in line Clot formation Pump malfunction Hypocalcemia
Kawai et al. [35]	14 pediatric 12 CRRT + TPE + ECLS 2 TPE + ECLS 51 procedures	PICU survival Organ failure index Vasoactive score	71% survival Improvement in organ failure and vasoactives	2005–2013 USA—University of Michigan	If on CRRT, Prisma/ PrismaFlex No CRRT, spectra or Optia	ECLS heparin Apheresis citrate	Transient hypotension New onset rash
Laverdure [26]	5 adult CRRT + TPE + ECLS 5 procedure	Hemofilter half life	Improved	2017 France	Prismaflex	ECLS heparin	
Bridges et al. [40]	3 pediatric CRRT + TPE + ECLS 16 procedures	ADAMTS-13 level and platelet count before and after	Rise in ADAMTS-13 and platelet counts in all	2012 USA—Vanderbilt	Spectra	ECLS heparin Apheresis citrate	
Kolovos et al. [42]	3 pediatric CRRT + TPE + ECLS ? Procedures	Survival	Survived	1991–2000 USA—Michigan	Spectra	ECLS heparin only	
Patel et al. [43]	1 pediatric CRRT + TPE + ECLS 3 procedures	Pediatric logistic organ dysfunction scores, FiO_2 and vasopressor requirements	Reduction in all 3 after two exchanges	2009 USA—Shreveport, LA	Prisma	ECLS heparin only	
Tabbutt et al. [44]	1 pediatric CRRT + TPE + ECLS 2 procedures	CK and myoglobin levels	Reduction in CK and myoglobin	2004 USA—CHOP	Spectra		

(continued)

Table 22.3 (continued)

Reference	n	Outcome Measure	Result	Year(s)/Center	Apheresis device	Anti coagulation	Apheresis complications
Mok et al. [45]	1 pediatric CRRT + TPE + ECLS 1 procedure	Survival	Survived	1985–1992 Australia—Melbourne			
Maclaren et al. [46]	1 adult CRRT + TPE + ECLS 1 procedure	Survival	Survived	2004 Australia—Melbourne	Spectra		
Nasir et al. [47]	1 adult CRRT + TPE + ECLS 4 procedures	Survival	Died after 4 days	2013 Turkey			
Hofenforst et al. [42]	1 adult CRRT + TPE + ECLS 25 procedures	Survival Proteinase 3 titers	Survived Titers were effectively reduced	2011 Greece		ECLS coated circuit and argatroban Apheresis citrate	Heparin induced thrombocytopenia
Barnes et al. [48]	1 adult CRRT + TPE + ECLS 1 procedure	Survival	Survived	2011 Australia			
Ahmed et al. [49]	1 adult CRRT + TPE + ECLS 5 procedures	Survival	Survived	2004 USA—MUSC		ECLS heparin	
Yusuff et al. [50]	1 adult CRRT + TPE + ECLS 8 procedures	Survival PR3 levels	Survived PR3 levels dropped	2015 UK		ECLS heparin only	
Joseph et al. [51]	1 pediatric CRRT + TPE + ECLS 5 procedures	Survival	Survived	2011 USA—UNC		ECLS heparin	
Di Maria et al. [52]	1 pediatric CRRT + TPE + ECLS 5 procedures	Resolution of pulmonary hemorrhage	Within 3 days	2008 USA—Denver		ECLS heparin Apheresis citrate	
Dalabih et al. [53]	1 pediatric CRRT + TPE + ECLS 6 procedures	Survival	Survived	2012 USA—Vanderbilt		ECLS heparin Apheresis citrate	

22.10 Summary of TA During ECMO

Use of TA during ECMO technologically is feasible although is rarely used. Guidance related to the appropriateness of TA, timing, and prescribed therapy should be supported based on the underlying disease through the ASFA guidelines. When evidence is lacking, reliance on knowledge of the underlying pathophysiology of the disease is necessary to guide and support treatment options. Variation exists on how and when to perform TA during CRRT and ECLS, including variable anticoagulation strategies. A worldwide registry approach is needed to describe the potential harms and benefits of this rare combination of extracorporeal support.

Box: Key Learning Points of Extracorporeal Tandem Therapies
Key Learning Points

- A growing number of pediatric patients meet criteria for multiple extracorporeal support therapies (e.g., ECMO, CRRT, TPE).
- Multiple permutations exist to connect extracorporeal devices together. Knowledge of the pump flow and device pressure limitations can help guide optimal placement for each circuit.
- Size of patient and volume of extracorporeal circuits must be accounted for when calculating total body volume for therapeutic apheresis.
- The systemic anticoagulation required for ECLS can be utilized for CRRT and TPE, and supercedes the need for individual local circuit anticoagulation.

Note: *ECMO* extracorporeal membrane oxygenation, *CRRT* continuous renal replacement therapy, *TPE* therapeutic plasma exchange, *ECLS* extracorporeal life support

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