A case of antithrombin replacement using recombinant human antithrombin in an adult patient supported with extracorporeal membrane oxygenation

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Key Clinical Message
In the critically ill patient on extracorporeal life support, antithrombin production and activity can be decreased and may require replacement to therapeutic levels in order to maintain appropriate anticoagulation and prevent thrombosis.

Keywords
Antithrombin III, extracorporeal membrane oxygenation, recombinant human antithrombin.

Introduction
Major advances in the use of extracorporeal membrane oxygenation (ECMO) have been reported for both cardiac and pulmonary support with an improved outcome and positive risk benefit ratio [1-4]. These advances in positive outcomes have led to greater use of ECMO worldwide [5,6]. Due to hemodilution, blood loss and coagulation cascade activation acquired antithrombin-III (ATIII) deficiency often exists in patients receiving ECMO support. ATIII replacement therapy with fresh frozen plasma (FFP) or ATIII concentrate has been used to address this deficiency. FFP requires preparation time and is not immediately available. Furthermore, FFP carries a known risk of viral transmission and allergic reactions not to mention the volume load required to achieve ATIII supplementation; therefore, ATIII concentrate is used as an alternate supplementation. We report the use of recombinant human ATIII concentrate to achieve normal ATIII activity level in an adult patient receiving venovenous (VV)-ECMO support for respiratory failure.

Case Presentation
A 39-year-old man (height, 5’9” [175 cm]; weight, 210.1 lbs [95.3 kg]; body mass index, 31.0 kg/m²) presented to the emergency department (ED) with a 3-day history of malaise, shortness of breath, cough, and fever. On physical examination, he exhibited tachypnea, diffuse rhonchi and wheezing, and extensive accessory respiratory muscle use. Pulse oximetry revealed that his initial saturation of peripheral oxygen (SpO₂) was 60% on room air. Workup in the ED revealed extensive bilateral pulmonary infiltrates on chest radiograph, and a respiratory virus panel was positive for influenza A. He was intubated in the ED and placed on mechanical ventilation. In spite of sedation, muscle relaxation, and an escalation in mean airway pressures, including a positive end-expiratory pressure of 15 cm H₂O and a fraction of inspired oxygen of 1.0, the patient’s SpO₂ remained at 75%. He was then admitted to the medical intensive care unit where a consultation was conducted with the extracorporeal life support service regarding ECMO support.

After determining that the patient was a suitable candidate for ECMO, he was initially cannulated. The femoral cannulas included a 23 Fr Biomedicus cannula in the right femoral vein and a 23/25 Fr Estech venous cannula in the left femoral vein. VV ECMO was initiated through these cannulas using a Rotaflow centrifugal pump and Quadrox oxygenator (Maquet-Cardiopulmonary-AG, Hirrlingen, Germany) with pump flows of 4 lpm, sweep...
gas flow of 3.5 lpm, and an FiO₂ of 0.8. After 5 days of ECMO support, the patient was converted to a right internal jugular 31 French double lumen catheter (Avalon Laboratories, LLC, Rancho Dominguez, CA), and ECMO support was continued utilizing the CardiOHelp system with a HLS Set Advanced 7.0 (Maquet-Cardiopulmonary-AG). This was a heparin-coated circuit with heparin used during priming. The patient was anticoagulated with unfractionated heparin according to the protocol to achieve an activated clotting time between 160 and 180 sec. The protocol called for initiation of heparin infusion at 15 units/kg/h was adjusted according to hourly assessment of the activated clotting time.

As per our institutional management guidelines, AT levels were checked daily or whenever heparin requirements rose by 25%. After 36 h of extracorporeal support, the patient’s ATIII activity was 47%. The decision to use recombinant human antithrombin (rhAT) (ATryn® [antithrombin (recombinant)], rEVO Biologics, 175 crossing Blvd. Framingham, MA 01702, United States.) was made to increase ATIII activity. Guidance for dosing of rhAT in adult patients receiving ECMO support is lacking; therefore, the dosage of rhAT was individualized as for ATIII-deficient patients undergoing a surgical procedure. This was based on a pretreatment functional activity level and body weight while using therapeutic drug monitoring as shown in Figure 1 and Table 1 [7].

ATIII replacement with rhAT in this particular patient was initiated with a bolus of 2100 IU followed by an infusion of 480 IU/h. The follow-up ATIII levels while on the infusion are shown in Figure 2. Using this dosing schedule, the target ATIII level (70%) was reached in just under 2 h. Administration of rhAT was halted on Day 4 because both bolus and continuous infusion achieved an ATIII activity level >70% for 4 consecutive days with no dosage adjustments. Although there was a decline in ATIII activity after stopping the infusion, the patient’s heparin requirement did not fluctuate. The patient received plasma infusions while on rhAT to support blood pressure and provide intravascular volume expansion. No bleeding complications or evidence of thromboembolism were noted during treatment with rhAT, nor were any significant clots identified in the circuitry. The patient was ultimately decannulated from ECMO and eventually tapered from mechanical ventilator support. He was transferred for inpatient rehabilitation, and was discharged home after 1 week.

Discussion

This case demonstrates the use of rhAT to successfully restore ATIII activity to >70% in an adult receiving VV-ECMO support. ATIII levels were normalized over a relatively short period of time. This case begins to elucidate the dose of rhAT required to achieve acceptable ATIII activity levels. The current case differs significantly from the four previously published case study reports involving adult ECMO patients [8–11] in several important aspects. Three of the cases [8–10] involved adult patients with heparin-induced thrombocytopenia (HIT) on ECMO and were not focused on AT replacement, but rather described the use of direct thrombin inhibitors as alternative anticoagulation agents. The remaining case [11] also described

Table 1. Antithrombin activity monitoring and dose adjustment protocol [7].

| Initial monitor time | Antithrombin level | Dose adjustment | Recheck antithrombin level |
|---------------------|--------------------|----------------|---------------------------|
| 2 h after initiation of treatment | <80% | Increase 30% | 2 h after each dose adjustment |
|                     | 80%–120% | None | 6 h after initiation of treatment or dose adjustment |
|                     | >120% | Decrease 30% | 2 h after each dose adjustment |

Figure 1. Recombinant human antithrombin dosing formula for surgical patients [7].

Figure 2. Follow-up antithrombin III levels while on recombinant human antithrombin infusion. The infusion was discontinued on Day 4 (open arrow).
the use of a direct thrombin inhibitor as an alternative anticoagulation agent, however, the patient did not have HIT, but instead had heparin resistance attributable to ATIII deficiency. This case was unique in demonstrating a relatively rapid restoration of ATIII activity in an adult patient on ECMO receiving unfractionated heparin and ATIII replacement therapy with rhAT. Additionally, this case describes a safe and successful rhAT- dosing regimen based on continuous infusion, as well as an effective ATII activity monitoring strategy. The results of this case can serve as a guidance for ATIII replacement in a patient undergoing ECMO support. This dosing regimen provided acceptable ATIII activity levels throughout the ECMO run.

Conclusions
Acceptable ATIII activity level can be achieved in adult patients receiving ECMO support using the standard surgical dosing of rhAT using a continuous infusion protocol.

Conflict of Interest
None declared.

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