Supplemental Data

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**Full version of the survey**

**Q1.** Your contact information and Institute

* Name and surname
* Institute
* City/Town
* Country
* E-mail address
* Do you work in a university hospital?
* Do you work in an ELSO-registered Centre?
* Number of subjects treated with VV-ECMO per year at your Centre

**Q2.** Which subjects are usually treated with VV-ECMO at your Centre? Neonates? Children? Adults?

**Q3.** Which drug is routinely used for systemic anticoagulation during VV-ECMO at your Centre?

* Unfractionated heparin
* Bivalirudin
* Argatroban
* Other (please specify)

**Q4.** Which test is routinely used to manage anticoagulation during VV-ECMO at your Centre? (please indicate *one* test, the preferred one, with the therapeutic target, and whether it is performed at the bedside or at the central laboratory).

**Q5.** Is circulating antithrombin activity routinely monitored during VV-ECMO at your Centre? If so, how often is it measured?

**Q6.** Which drug is routinely used to increase antithrombin activity during VV-ECMO at your Centre?

* Antithrombin concentrate
* Recombinant antithrombin
* Fresh frozen plasma (FFP)
* We routinely do not use any of these drugs to increase antithrombin activity

**Q7.** Are recombinant antithrombin or antithrombin concentrate routinely prescribed to subjects treated with VV-ECMO in your Centre?

* Yes, we automatically prescribe them when circulating antithrombin activity is lower than a minimum level (please specify the level)
* Yes, we routinely prescribe them according to the level of anticoagulation and/or the ongoing dose of anticoagulant; and not based on circulating antithrombin activity alone
* No; we do not routinely prescribe them
* No; we never prescribe them

**Q8.** How are recombinant antithrombin or antithrombin concentrate administered during VV-ECMO in your Centre?

* As a bolus (in few minutes)
* As extended infusion (in few hours)
* As continuous infusion (in 24 hours)
* Not applicable

**Q9.** If recombinant antithrombin or antithrombin concentrate are prescribed, what is the target? What is the rule for stopping the treatment?

* We stop the treatment when a minimum antithrombin activity (please specify) has been achieved
* We stop the treatment once the anticoagulation target has been achieved
* We infuse antithrombin when we consider it indicated, with no clinical or laboratory target (we simply give it!)
* Not applicable

**Q10.** What's the rationale for administering (or not administering) recombinant antithrombin or antithrombin concentrate during VV-ECMO? (multiple choices available)

* Administering – They prevent heparin resistance
* Administering – They correct heparin resistance
* Administering – They help achieve and maintain the anticoagulation target
* Not administering – They are too expensive or not available in my Centre
* Not administering – Anticoagulation is usually not an issue during VV-ECMO
* Not administering – I’m worried of possible side effects (bleeding, for example)
* Not administering – There is no robust scientific evidence to justify their use
* Other (please specify)

**Q11.** On average, how many patients treated at your Centre receive recombinant antithrombin or antithrombin concentrate during VV-ECMO? \*

* None of them (<10%)
* Some of them (10-50%)
* Most of them (50-90%)
* All of them (>90%)

\* This question was not included in the original survey. It was disseminated via e-mail to all participants afterwards, in February 2019. Response rate was 93.1%.

**Additional methods**

Definitions

The World Bank Group categorized the 2017 gross national income per capita as low (≤995 USD), lower-middle (996-3895 USD), upper-middle (3896-12055 USD) or high (≥12056 USD) [www.worldbank.org]. Due to data paucity (see below), however, we decided to group together low, lower-middle and upper-middle incomes, and referred to them as “non-high” income.

**Additional results**

Total number of contacts was not available as the link to the survey was disseminated not only via e-mail but also at scientific meetings, via newsletters and social networks (as detailed in the main manuscript). In addition, some participants in turn voluntarily disseminated the link to their contacts.

Centre characteristics

242 (88.6%) responses were from high income and 31 (11.4%) from non-high income countries, including 20 (7.3%) responses from upper-middle income, 10 (3.7%) responses from lower-middle and 1 (3.7%) response from low income countries.

Primary patient population was adult-only in 166 (60.8%) centers, pediatric-only in 67 (24.5%) centers and mixed in 40 (14.7%) centers. Pediatric-only centers included 17 (6.2%) centers for children, 5 (1.8%) centers for adults and 45 (16.5%) centers for children and neonates. Mixed centers included 13 (4.8%) centers for adults and children, 2 (0.7%) centers for adults and neonates and 25 (9.2%) centers for all age groups.

On average (median and IQR), centers with low, intermediate or high ECMO patient volume treated 5 (4-6), 13 (10-18) or 40 (30-60) patients per year.

Anticoagulation management

Systemic anticoagulation was routinely prescribed in 264 (96.7%) centers, with unfractionated heparin being the drug of choice in 255 (96.6%) of them. Other anticoagulants included argatroban (in 3 [1.1%] centers), bivalirudin (in 4 [1.5%] centers) and nafamostat (in 2 [0.8%] centers).

The (mutually exclusive) preferred method to monitor anticoagulation was the aPTT in 114 (41.8%) centers, the ACT in 82 (30.0%) centers, the anti-Xa in 62 (22.7%) centers, thromboelastography in 3 (1.1%) centers, the prothrombin time (PT) in 1 (0.4%) center, the Fs actin in 1 (0.4%) center and unknown in 1 (0.4%) center. The aPTT was measured in the central laboratory in 103 (94.5%) centers and at the bedside (point-of-care testing) in 6 (5.5%) centers. The ACT was measured in the central laboratory in 4 (4.9%) centers and at the bedside in 77 (95.1%) centers. The anti-Xa was measured in the central laboratory in 62 (100%) centers. Six respondents did not specify where the anticoagulation monitoring test was performed. The aPTT was expressed in seconds in 87 (76.3%) centers or as ratio (relative to control) in 27 (23.7%) centers.

Antithrombin testing

Circulating antithrombin activity was routinely measured in 133 (48.7%) centers. Frequency of testing was once per week in 4 (3.0%) centers, more than once per week in 22 (16.5%) centers, once per day in 78 (58.6%) centers, and more than once per day in 27 (20.3%) centers. It was unclear or unknown for 2 (1.5%) centers. As shown in Supplemental Figure 2, antithrombin testing was more common in pediatric-only centers.

Antithrombin supplementation

203 participants reported their drug of choice for increasing antithrombin activity (either routinely or not): antithrombin concentrate in 102 (50.2%) centers, fresh frozen plasma in 79 (38.9%) centers and recombinant antithrombin in 32 (15.8%) centers. As shown in Table E1, use of fresh frozen plasma instead of recombinant antithrombin or antithrombin concentrate was significantly more common in centers from lower-income regions (probably because of difficult or impossible access to those other drugs); almost significantly more common in centers registered with ELSO; almost significantly less common in centers for children and/or neonates (probably because a concern about fluid overload).

134 participants provided details on the way recombinant antithrombin or antithrombin concentrate were administered at their sites: as a bolus (either drugs) in 74 (55.2%) centers, as extended infusion (either drugs) in 55 (41.0%) centers, or as continuous infusion (recombinant antithrombin only) in 5 (3.7%) centers. Goal of supplementation was reaching the anticoagulation target in 42 (31.3%) centers or increasing antithrombin activity above 80 [68-83] % in 61 (45.5%) centers. 29 (21.6%) respondents had no predefined clinical or laboratory target; 2 (1.5%) others did not report their treatment goal.

The proportion of patients treated with antithrombin was <10% in 10 (10.3%) centers, 10-50% in 35 (36.1%) centers, 50-90% in 36 (37.1%) centers and >90% in 16 (16.5%) centers where antithrombin supplementation was routine. It was <10% in 124 (79.0%) centers, 10-50% in 30 (19.1%) centers and 50-90% in 3 (1.9%) centers where antithrombin supplementation was not routine (p<0.001).

**Supplemental Table 1**. Description of our web survey.

|  |  |
| --- | --- |
| **Item category** | **Explanation** |
| * Design
 | This was an electronic survey disseminated via web sites and via e-mail. |
| * Institutional Review Board
 | Institutional ethics oversight was considered unnecessary. Responses were collected via SurveyMonkey.com®. Personal data were handled according to art. 13 of Regulation (UE) n. 2016/679 (General Data Protection Regulation) and Italian privacy legislation. |
| * Development and pre-testing
 | The survey was designed de-novo and informally tested by three experts in the field before being administered to the target population. |
| * Recruitment process and description of the sample having access to the questionnaire
 | The survey was announced at the 38th International Symposium of Intensive Care and Emergency Medicine and at the 7th European Chapter of the Extracorporeal Life Support Organization Congress. |
| * Survey administration
 | A presentation letter and the link to the survey were posted on the web site of the Extracorporeal Life Support Organization and on ResearchGate, a free social network service for scientists. They were also disseminated via e-mail to Directors and Coordinators of extracorporeal membrane oxygenation centers and to corresponding authors of publications on veno-venous extracorporeal membrane oxygenation. Participation to the survey was voluntary; no incentives were offered. The survey was open from March to December 2018. The text of the survey is reported above. Completeness and consistency of the questionnaires were checked by the authors; respondents were contacted for any related issue. |
| * Response rate
 | The total number of visitors in the web sites with the link to the survey and the total number of e-mails sent to potential respondents were not recorded. Therefore the response rate could not be determined.  |
| * Preventing multiple entries from the same individual
 | Respondents with same or very similar affiliations were contacted. Multiple respondents from the same institution were asked to provide a single common response. |
| * Analysis
 | Authors of incomplete responses were asked to provide missing data. Questionnaires that remained incomplete were included in the final analysis. Those with no data other than personal information of respondents were excluded.  |

Herein we describe our web survey according to the checklist for reporting results of internet e-surveys (CHERRIES) [Eysenbach G, J Med Internet Res 2004: 6;e34].

**Supplemental Table 2.** Factors associated with use of fresh frozen plasma instead of recombinant antithrombin and antithrombin concentrate to increase antithrombin activity during veno-venous ECMO.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **FFP preferred to other drugs** | **p** | **Unadjusted****OR (95%-CI)** | **p** | **Adjusted****OR (95%-CI)** | **p** |
| **Independent variable** | Yes (n [%]) | No (n [%]) |  |  |  |  |  |
| *University hospital* |  |  |  |  |  |  |  |
| * No
 | 16 (41.0) | 23 (59.0) | 0.704 | 1.00 (ref.) |  | 1.00 (ref.) |  |
| * Yes
 | 63 (36.2) | 111 (63.8) | 0.82 (0.40 to 1.66) | 0.704 | 1.37 (0.56 to 3.32) | 0.490 |
| *ELSO-registered* |  |  |  |  |  |  |  |
| * No
 | 20 (32.3) | 42 (67.7) | 0.436 | 1.00 (ref.) |  | 1.00 (ref.) |  |
| * Yes
 | 59 (39.1) | 92 (60.9) | 1.35 (0.72 to 2.52) | 0.436 | 2.17 (1.00 to 4.7) | 0.051 |
| *National income* |  |  |  |  |  |  |  |
| * High
 | 56 (30.3) | 129 (69.7) | <0.001 | 1.00 (ref.) |  | 1.00 (ref.) |  |
| * Non-high
 | 23 (82.1) | 5 (17.9) | 10.6 (3.83 to 29.3) | <0.001 | 12.0 (3.89 to 36.7) | <0.001 |
| *Primary patient population* |  |  |  |  |  |  |  |
| * Adult
 | 48 (42.5) | 65 (57.5) | 0.056 | 1.00 (ref.) |  | 1.00 (ref.) |  |
| * Mixed
 | 14 (42.4) | 19 (57.6) | 1.00 (0.46 to 2.19) | 0.846 | 0.74 (0.306 to 1.81) | 0.512 |
| * Pediatric
 | 17 (25.4) | 50 (74.6) | 0.38 (0.199 to 0.74) | 0.006 | 0.45 (0.196 to 1.03) | 0.058 |
| *Annual ECMO patient volume* |  |  |  |  |  |  |  |
| * >20
 | 26 (40.0) | 39 (60.0) | 0.366 | 1.00 (ref.) |  | 1.00 (ref.) |  |
| * 10-20
 | 22 (30.1) | 51 (69.9) | 0.65 (0.320 to 1.31) | 0.301 | 0.66 (0.287 to 1.50) | 0.319 |
| * <10
 | 30 (40.0) | 45 (60.0) | 1.00 (0.51 to 1.97) | 0.863 | 1.07 (0.47 to 2.40) | 0.878 |

Herein we compare the drug of choice for increasing (routinely or not) antithrombin activity between centers classified according to the following criteria: (1) university hospital or not; (2) ELSO-registered or not; (3) 2017 gross national income per capita, categorized as high (≥12056 USD) or non-high (<12056 USD); (4) primary patient population, categorized as adult-only, pediatric-only or mixed; (5) annual ECMO patient volume, categorized as low (<10 cases per year), intermediate (10-20 cases per year) or high (>20 cases per year). From left to right, p values refer to the overall Chi-squared test, univariate (unadjusted) regression analysis and multivariable (adjusted for the independent variables listed above) regression analysis. As for multivariable logistic regression analysis, responses with missing values were deleted; significant correlation between covariates was excluded (all variance inflation factors were < 2.0). ECMO: extracorporeal membrane oxygenation; ELSO: Extracorporeal Life Support Organization; FFP: fresh frozen plasma; OR: odds ratio; CI: confidence interval. Ref.: reference. Please note that this analysis was designed a posteriori.

**Supplemental Table 3.** Factors associated with routine antithrombin supplementation during veno-venous ECMO in Europe and North America.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Routine AT supplementation** | **p** | **Unadjusted****OR (95%-CI)** | **p** | **Adjusted****OR (95%-CI)** | **p** |
| **Independent variable** | Yes (n [%]) | No (n [%]) |  |  |  |  |  |
| *University hospital* |  |  |  |  |  |  |  |
| * No
 | 15 (50.0) | 15 (50.0) | 0.855 | 1.00 (ref.) |  | 1.00 (ref.) |  |
| * Yes
 | 80 (46.2) | 93 (53.8) | 0.86 (0.40 to 1.87) | 0.855 | 0.91 (0.384 to 2.15) | 0.829 |
| *ELSO-registered* |  |  |  |  |  |  |  |
| * No
 | 25 (39.7) | 38 (60.3) | 0.226 | 1.00 (ref.) |  | 1.00 (ref.) |  |
| * Yes
 | 70 (50.0) | 70 (50.0) | 1.52 (0.83 to 2.78) | 0.226 | 0.80 (0.362 to 1.75) | 0.568 |
| *Country* |  |  |  |  |  |  |  |
| * Europe
 | 60 (46.9) | 68 (53.1) | 0.907 | 1.00 (ref.) |  | 1.00 (ref.) |  |
| * North America
 | 35 (46.7) | 40 (53.3) | 0.99 (0.56 to 1.76) | 0.907 | 0.42 (0.187 to 0.92) | 0.031 |
| *Primary patient population* |  |  |  |  |  |  |  |
| * Adult
 | 38 (32.8) | 88 (67.2) | <0.001 | 1.00 (ref.) |  | 1.00 (ref.) |  |
| * Mixed
 | 15 (51.7) | 14 (48.3) | 2.48 (1.09 to 5.6~~4~~) | 0.047 | 2.97 (1.18 to 7.5) | 0.021 |
| * Pediatric
 | 42 (72.4) | 16 (27.6) | 6.1 (3.05 to 12.1) | <0.001 | 9.0 (3.40 to 23.6) | <0.001 |
| *Annual ECMO patient volume* |  |  |  |  |  |  |  |
| * >20
 | 26 (36.6) | 45 (63.4) | 0.027 | 1.00 (ref.) |  | 1.00 (ref.) |  |
| * 10-20
 | 34 (46.6) | 39 (53.4) | 1.51 (0.78 to 2.94) | 0.297 | 0.95 (0.45 to 2.01) | 0.899 |
| * <10
 | 35 (60.3) | 23 (39.7) | 2.63 (1.29 to 5.4) | 0.012 | 1.30 (0.57 to 2.95) | 0.530 |

Herein we compare practice between European and North American centers, classified according to the following criteria: (1) university hospital or not; (2) ELSO-registered or not; (3) 2017 gross national income per capita, categorized as high (≥12056 USD) or non-high (<12056 USD); (4) primary patient population, categorized as adult-only, pediatric-only or mixed; (5) annual ECMO patient volume, categorized as low (<10 cases per year), intermediate (10-20 cases per year) or high (>20 cases per year). From left to right, p values refer to the overall Chi-squared test, univariate (unadjusted) regression analysis and multivariable (adjusted for the independent variables listed above) regression analysis. As for multivariable logistic regression analysis, responses with missing values were deleted; significant correlation between covariates was excluded (all variance inflation factors were < 2.0). ECMO: extracorporeal membrane oxygenation; ELSO: Extracorporeal Life Support Organization; AT: antithrombin (recombinant or concentrate) OR: odds ratio; CI: confidence interval. Ref.: reference. Please note that this analysis was designed a posteriori.

**Supplemental Table 4.** Cost of antithrombin in different regions of the world.

|  |  |  |  |
| --- | --- | --- | --- |
| **Region** | **Respondents (n)** | **Antithrombin cost (USD per unit)** | **Gross regional income per capita (USD)** |
| North America | 22 | 3.20 (3.00-3.60) | 58270 (58270-58270) |
| Oceania | 6 | 0.98 (0.94-1.46) | 51360 (48263-51360) |
| South America | 5 | 0.84 (0.44-1.35) | 13040 (10810-13610) |
| Europe | 60 | 0.57 (0.30-0.65) | 40530 (31020-43490) |
| Asia | 12 | 0.50 (0.40-0.87) | 33465 (28380-38550) |
| Africa | 0 | NA | NA |

Herein we report the cost of recombinant antithrombin or antithrombin concentrate in different areas of the world, as referred by 105 participants to the survey. Results are presented as median (IQR). Gross regional income was computed from the 2017 gross national income of the country of origin of respondents.

Antithrombin cost significantly differed between regions (p<0.001 at one way analysis of variance on ranks) and was not linearly associated with 2017 gross regional income (R2 0.37; p=0.276 at linear regression analysis). As for other drugs, the cost of antithrombin was particularly high in the US (3.21 [3.15-3.79] USD per unit; 19 respondents), where government does not control medicine costs. In most of other countries, with national health insurance systems, governments negotiate with drug makers to limit what their state-funded health systems pay [Kesselheim AS, Avorn J, Sarpatwari A: The high cost of prescription drugs in the United States: origins and prospects for reform. *JAMA* 2016; 316:858-71].

**Supplemental Figure 1.** Circulating antithrombin activity as trigger for supplementation.



Fifty-one respondents specified the circulating antithrombin activity that triggered antithrombin supplementation during veno-venous extracorporeal membrane oxygenation at their institution. Herein we report the corresponding frequency distribution.

**Supplemental Figure 2.** Frequency of antithrombin testing during veno-venous extracorporeal membrane oxygenation.

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Herein we compare the frequency of antithrombin testing between centers classified according to their primary patient population. Bars and labels are (rounded) percentages of respondents. P value refers to Chi-squared test.