Supplemental Data

**List of collaborators**

**Africa**

Egypt, Arab Republic: Cairo, University of Cairo Hospital (Akram Abdelbary, M.D.; Ahmad Said, M.D.); Cairo, Air Force Specialized Hospital (Maged Salah, M.D.). South Africa: Johannesburg, Charlotte Maxeke Johannesburg Academic Hospital and Netcare Garden City Clinic (Ahmad Alli, M.D.; Stefan Bolon, M.D.).

**Asia**

China: Beijing, Anzhen Hospital Capital Medical University (Xiaotong Hou, M.D.); Beijing, The Seventh Medical Certer, PLA General Hospital (Xiaoyang Hong, M.D.); Beijing, Chaoyang Hospital, Capital Medical University (Bing Sung, M.D.); Foshan, Shunde Hospital of Southern Medical University (Changzhi Liu, M.D.); Wuhu, Yijishan Hospital, Wannan Medical College (Lu Weihua, M.D.). Hong Kong SAR, China: Hong Kong, Prince of Wales Hospital (Kai Man Chan, M.D.); Hong Kong, Queen Mary Hospital (Peter Chi Keung Lai, R.N.); Hong Kong, Tuen Mun Hospital (Kenny Chan, M.D.). India: Bangalore, Narayana Institute of Cardiac Science, Narayana Health City (Riyan S Shetty, M.D.); Bangalore, Vydehi Hospital (Sathyanarayan Jagannath, M.D.); Chennai, Apollo Hospital (Vignesh C, M.D.); Mumbai, Riddhi Vinayak Multispeciality Hospital (Pranay Oza, M.D.; Venkat S Goyal, M.D.); New Delhi, AIIMS Hospital (Poonam Malhotra Kapoor, M.D.). Israel: Ramat Gan, Safra Children's Hospital, Tel Hashomer (Uri Pollak, M.D.). Japan: Chiba, Chiba University Hospital (Yosuke Matsumura, M.D.); Hiroshima, Hiroshima University (Shinichiro Ohshimo, M.D.); Kagoshima, Kagoshima City Hospital (Eiji Hirakawa, M.D.); Saitama, Jichi Medical University Saitama Medical Center (Masamitsu Sanui, M.D.); Tokyo, Nippon Medical School Hospital (Shingo Ichiba, M.D.); Tokyo, Showa University (Toru Kotani, M.D.). Korea, Republic: Anyang, Hallym University Sacred Heart Hospital (Sunghoon Park, M.D.); Seong-nam, Seoul National University Bundang Hospital (Yeon-Joo Lee, M.D.); Seoul, Anam Hospital/ Korea University (Jae-Seung Jung, M.D.); Seoul, Samsung Medical Center, Sungkyunkwan University School of Medicine (Kyeongman Jeon, M.D.); Yangsan, Pusan National University Yangsan Hospital (Hye Ju Yeo, M.D.; Woohyun Cho, M.D.). Lebanon: Beirut, American University of Beirut Medical Center (Assi Jana, M.D.). Nepal: Kathmandu, Nepal Mediciti Hospital (Apurb Sharma, M.D.). Philippines: Muntinlupa City, Asian Hospital and Medical Center (Aaron Mark Hernandez, M.D.). Qatar: Doha, Hamad General Hospital (Tejas Mehta, M.D.; Ibrahim Fawzy Hassan, M.D.). Russian Federation: Moscow, Department of Internal Medicine, 52nd Hospital (Mikhail Ketskalo, M.D.); Moscow, State Budgetary Institution "Sklifosovsky Scientific Research Institution of Emergency Care” of Moscow Healthcare Department (Zhuravel Sergey, M.D.); Novosibirsk, National Medical Research Center (Kornilov Igor, M.D.). Saudi Arabia: Damman, Imam Abdulrahman Bin Faisal University (Mohamed El Tahan, M.D.). Singapore: Singapore, National University Hospital (Graeme MacLaren, M.D.). Sri Lanka: Galle, Teaching Hospital Karapitiya (Tolusha Harischandra, M.D.). Taiwan, China: Taipei, National Taiwan University Hospital (Yih-Sharng Chen, M.D.); Taoyuan, Chang Gung Memorial Hospital (Li-Chung Chiu, M.D.). Thailand: Bangkok, Bangkok Heart Hospital (Siriwasan Akanitthapichat, M.D.). Turkey: Ankara, Ankara University Hospital (Emel Okulu, M.D.); Bursa, Bursa State Hospital (Ahmet Yüksel, M.D.). United Arab Emirates: Dubai, Dubai Hospital (Fayaz Khazi, M.D.). Vietnam: Hanoi, International Vinmec Times City Hospital (Nguyen Quang Thang, M.D.).

**Europe**

Austria: Graz, University Hospital of Children and Adolescents (Friedrich Reiterer, M.D.); Innsbruck, Medical University of Innsbruck (Gerard Cortina, M.D.); Vienna, Medical University of Vienna (Michael Hermon, M.D.; Peter Schellongowski, M.D.; Thomas Staudinger, M.D.). Belarus: Minsk, Minsk Scientific and Practical Center for Surgery Transplantation and Hematology (Maryanna Hurava, M.D.). Belgium: Brussels, University Hospital Brugmann (Pierrakos Charalampos, M.D.); Brussels, Chirec Delta (Harald Engel, M.D.); Brussels, Hopital Erasme, Université Libre de Bruxelles (Fabio Silvio Taccone, M.D. Ph.D.; Leda Nobile, M.D.); Brussels, University Hospital Saint-Luc (Jacquet Luc, M.D.); Ghent, Ghent University Hospital (Harlinde Peperstraete, M.D.); Leuven, Leuven University Hospital (Dieter Dauwe, M.D.). Czech Republic: Olomouc, University Hospital in Olomouc (Martin Simek, M.D.); Ostrava, University Hospital in Ostrava (Peter Sklienka, M.D.); Prague, General University Hospital (Martin Balik, M.D.). Denmark: Copenhagen, Rigshospitalet (Andre Korshin, M.D.). France: Angers, Angers University Hospital (M Pierrot, M.D.); Besancon, University Hospital Jean Minjoz (Gilles Capellier, M.D.); Bordeaux, Haut Lévêque Bordeaux University Hospital (Hadrien Roze, M.D.); Brest, Brest University Hospital (Cecile Aubron, M.D.); Créteil, Henri Mondor University Hospital (Tommaso Maraffi, M.D.); Dijon, Dijon University Hospital (Pierre Gregoire Guinot, M.D.); Lille, University Hopital Salengro (Jourdain Mercè, M.D.); Lyon, Hospices Civils de Lyon, Université Lyon 1 (Jean-Christophe Richard, M.D.; Claude Guerin, M.D.); Marseille, University Hospital North (Christophe Guervilly, M.D.); Montpellier, Montpellier University Hospital (Philippe Gaudard, M.D.); Nancy, Nancy University Hospital (Bruno Levy, M.D.); Nantes, Nantes University Hospital (Pierre Bourgoin, M.D.); Paris, Armand-Trousseau Hospital, Sorbonne University (Jerome Rambaud, M.D.); Paris, Bichat Claude Bernard University Hospital (Jacob Lortat, M.D.); Paris, Hôpital Européen Georges Pompidou, Paris-Descartes (Nadia Aissaoui, M.D.; Romain Pirracchio, M.D.); Paris, Pitié-Salpetrière University Hospital (Alain Combes, M.D.); Rennes, Rennes University Hospital (Nicolas Nesseler, M.D.); La Réunion, University Hospital Nord (David Vandroux, M.D.); Strasbourg, Strasbourg University Hospital (Pierre-Emmanuel Falcoz, M.D.); Suresnes, Foch Hospital (Morgan Lee Guen, M.D.); Toulouse, Rangueil University Hospital (Clement Delmas, M.D.). Germany: Aachen, Aachen University Hospital, RWTH Aachen (Rolf Rossaint, M.D.); Berlin, Charité University Hospital (Steffen Weber-Carstens, M.D.); Bochum, Augusta-kliniken Bochum-Mitte (J.F. Heuer, M.D.); Bochum, BG University Hospital Bergmannsheil (Uwe Hamsen, M.D.); Bonn, Bonn University Hospital (Florian Kipfmueller, M.D.); Dortmund, Klinikum Dortmund (Ingolf Eichler, M.D.); Dresden, Dresden University Hospital (Peter Spieth, M.D.); Essen, Essen University Hospital (Clemens Aigner, M.D.); Essen, Elisabeth-Krankenhaus (Ingo Voigt, M.D.); Freiburg, Freiburg University Hospital (Dawid Staudacher, M.D.); Giessen, Giessen University Hospital (Matthias Hecker, M.D.); Göttingen, Göttingen University Hospital (Michael Quintel, M.D.; Federica Romitti, M.D.); Greifswald, Greifswald University Hospital (Sigrun Friesecke, M.D.); Hanau, Klinikum Hanau (Marco Gruss, M.D.); Hannover, Medical School Hannover (David Sascha, M.D.); Herford, Klinikum Herford, Ruhr University Bochum (Dietrich Henzler, M.D.); Homburg, University Hospital of Saarland (Philipp M. Lepper, M.D.); Langen, Asklepios Klinik Langen (Hans-Bernd Hopf, M.D.); Mannheim, Mannheim University Hospital (Alba Perez-Ortiz, M.D.); Munich, Barmherzige Brüder Hospital (Franz Brettner, M.D.); Munich, University Hospital, LMU Munich (Lorenz Frey, M.D.; Michael Irlbeck, M.D.; Tobias Kammerer, M.D.); Nuremberg, Paracelsus Medical University (Justyna Swol, M.D.); Regensburg, Regensburg University Hospital (Thomas Müller, M.D.); Stuttgart, Robert Bosch Hospital (Matthias Hansen, M.D.); Tübingen, Tübingen University Hospital (Matthias Kumpf, M.D.); Würzburg, Würzburg University Hospital (Markus Kredel, M.D.). Greece: Larissa, Larissa University Hospital (Dimitrios Magouliotis, M.D.). Hungary: Budapest, National Institute of Oncology (Ildikó Madurka, M.D.). Ireland: Dublin, St James's Hospital (Ignacio Martin-Loeches, M.D.); Dublin, Mater Misericordiae University Hospital (Edmund Carton, M.D.). Iceland: Reykjavik, Landspitali University Hospital (Sigurbergur Karason, M.D.). Italy: Bari, Policlinico Hospital, Bari University (Salvatore Grasso, M.D.); Bergamo, ASST Papa Giovanni XXIII (Luca Lorini, M.D.; Sergio Cattaneo, M.D.); Bologna, S.Orsola Hospital (Massimo Baiocchi, M.D.); Firenze, Careggi University Hospital (Giovanni Cianchi, M.D.); Genova, IRCCS Istituto Giannina Gaslini (Andrea Moscatelli, M.D.); Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan (Giacomo Cavallaro, M.D.; Mauro Panigada, M.D.); Milano, San Raffaele Hospital (Federico Pappalardo, M.D.); Monza, San Gerardo Hospital, University of Milan-Bicocca (Giacomo Bellani, M.D.); Padova, Padova University Hospital (Paolo Persona, M.D.; Angela Amigoni, M.D.); Palermo, Fondazione IRCCS ISMETT Hospital (Antonio Arcadipane, M.D.); Parma, Parma University Hospital (Sandra Rossi, M.D.); Pavia, Fondazione IRCCS Policlinico San Matteo (Mirko Belliato, M.D.); Roma, Fondazione Policlinico A. Gemelli IRCCS, Università Cattolica del Sacro Cuore (Giuseppe Bello, M.D.); Roma, Children's Hospital Bambino Gesù (Matteo Di Nardo, M.D.); Roma, Policlinico Umberto I, Sapienza University (Francesco Alessandri, M.D.); Sassari, Sassari University Hospital (Pierpaolo Terragni, M.D.); Torino, Molinette Hospital, University of Turin (Vito Fanelli, M.D.). Lithuania: Vilnius, Vilnius University Hospital Santaros Klinikos (Robertas Samalavicius, M.D.). Netherlands: Groningen, Groningen University Medical Center (A. Oude Lansink, M.D.); Leiden, Leiden University Medical Center (Peter Roeleveld, M.D.); Maastricht, Maastricht University Medical Center (Thijs Delnoij, M.D.); Nijmegen, Radboud University Medical Center (Arno van Heijst, M.D.); Rotterdam, Erasmus University Medical Center (Dinis Reis Miranda, M.D.); ‘s Hertogenbosch, Jeroen Bosch Hospital (F. Polderman, M.D.); Utrecht, Utrecht University Medical Center (Dirk W. Donker, M.D.). Norway: Trondheim, St. Olavs Hospital (Kjetil Sundt, M.D.). Poland: Krakow, Jagiellonian University Medical College (Wojciech Szczeklik, M.D.); Lublin, Lublin University Hospital (Miroslaw Czuczwar, M.D.); Poznan, SKPP Poznan University of Medical Sciences (Mateusz Puslecki, M.D.); Wroclaw, Wroclaw University Hospital (Jakub Smiechowicz, M.D.). Portugal: Carcavelos, Centro Hospitalar Lisboa Norte, University of Lisboa (Francisco Abecasis, M.D.); Lisboa, Centro Hospitalar de Lisboa Central, EPE (Philip Pacheco Fortuna, M.D.). Spain: Barcelona, Hospital Vall d'Hebron (Jordi Riera, M.D.; Joan Balcells, M.D.); Barcelona, Bellvitge Hospital (Elisabet Periche Pedra, M.D.; Melinda Rita Koborzan, M.D.); Barcelona, Hospital Sant Joan de Déu, University of Barcelona (Susana Segura-Matute, M.D.); Madrid, Hospital General Universitario Gregorio Marañón (Patricia Santa Teresa, M.D.); Majadahonda, Hospital Universitario Puerta de Hierro (Verónica Guilló, M.D.); Santander, Hospital Universitario Marqués de Valdecilla (Marta López Sánchez, M.D. Ph.D.); Valencia, Hospital Universitari i Politècnic la Fe (Ricardo Gimeno, M.D.); Vigo, Alvaro Cunqueiro Hospital (Juan Chico, M.D.). Sweden: Gothenburg, Queen Silvia Childrens Hospital (Birgitta Romlin, M.D.); Stockholm, Karolinska University Hospital (L Mikael Broman, M.D.). Switzerland: Bern, Inselspital, University Hospital (Gabor Erdoes, M.D.); Lausanne, Centre Hospitalier Universitaire Vaudois (Gonzalez, M.D.); Zürich, University Children's Hospital (Bernhard Frey, M.D.); Zürich, Zürich University Hospital, Zürich (Marco Maggiorini, M.D.); Geneva, Geneva University Hospitals (Raphael Giraud, M.D.). United Kingdom: Aberdeen, Aberdeen Royal Infirmary (Ian Scott, M.D.); Cambridge, Royal Papworth Hospital (Alain Vuylsteke, M.D.); Glasgow, Royal Hospital for Children (Gillian Wylie, M.D.); Leicester, Glenfield Hospital (Chris Harvey, M.D.; Claire Westrope, M.D.); London, Great Ormond Street Hospital for Children (Aparna Hoskote, M.D.; Timothy Thiruchelvam, M.D.); London, Guy's and St. Thomas' Hospital (Nicholas Barret, M.D.; Luigi Camporota, M.D.); London, King's College Hospital (Georg Auzinger, M.D.); London, Royal Brompton Hospital (Paolo Bianchi, M.D.); Manchester, Manchester Royal Infirmary (Marc O. Maybauer, M.D.).

**North America**

Canada: Alberta: Edmonton, University of Alberta (Laurance Lequier, M.D.). British Columbia: Vancouver, St. Paul’s Hospital (Ansong Cheung, M.D.). Ontario: London, University Hospital (Dave Nagpal, M.D.); Toronto, University of Toronto (Lorenzo Del Sorbo, M.D.). Québec: Montreal, Hopital du Sacré-Coeur de Montréal (Martin Albert, M.D.); Montreal, Montreal Children's Hospital (Samara Zavalko, M.D.). United States of America: Arizona: Tucson, University of Arizona (Jarrod Mosier, M.D.). Arkansas: Little Rock, Arkansas Children's Hospital/University of Arkansas for Medical Sciences (Matthew P. Malone, M.D.). California: Irvine, Children's Hospital Orange County (Yigit Guner, M.D.); La Jolla, University of California San Diego (Robert L. Owens, M.D.); Los Angeles, Children's Hospital Los Angeles (Rachel Chapman, M.D.; David Bliss, M.D.); Orange County, Children's Hospital Orange County (Joanne Starr, M.D.); Palo Alto, Lucile Packard Children’s Hospital (Vamsi Yarlagadda, M.D.); San Francisco, Benioff Children’s Hospital/University of California San Francisco (Peter Oishi, M.D.). Colorado: Aurora, Children's Hospital of Colorado (Sara Sullivan, M.D.). Delaware: Nemours AI duPont Hospital for Children (Mark Ogino, M.D., Curtis Froehlich, M.D.). District of Columbia: Washington, Children's National Health System (Billie Short, M.D.); Washington, George Washington University Hospital (Mel Ricks, R.N.). Florida: Gainesville, University of Florida (Ravi Samraj, M.D.); Miami, Holtz Children's Hospital/University of Miami (Gwenn E. McLaughlin, M.D.); Miami, University of Miami (Mehdi Mirsaeidi, M.D.); Orlando, Nemours Children's Hospital (Timothy M. Maul, C.C.P. Ph.D.). Georgia: Atlanta, Children's Healthcare of Atlanta (James Fortenberry, M.D.); Augusta, Children's Hospital of Georgia at Augusta University (Brian Stansfield, M.D.; Linda Wise, M.S.N.); Savannah, St. Joseph's/Candler Health System (Amanda Norris, F.N.P.). Hawaii: Honolulu, Kapiolani Medical Center for Women and Children (Len Tanaka, M.D.). Indiana: Indianapolis, Riley Hospital for Children/Indiana University School of Medicine (Brian Gray, M.D.; Michael Hobson, M.D.). Iowa: Iowa City, University of Iowa Children’s Hospital (Aditya Badheka, M.D.); Iowa City, University of Iowa (Jennifer Crumley, M.D.). Kansas: Kansas City, Children's Mercy Hospital (John Daniel, M.D.). Kentucky: Lexington, University of Kentucky (Sean Skinner, M.D.). Louisiana: Shreveport, LSU Health Sciences Center (Steven Conrad, M.D. Ph.D.); St. Louis, St. Louis Children's Hospital/Washington University (Ahmed Said, M.D.). Massachusetts: Boston, Boston Children's Hospital/Harvard Medical School (Ravi Thiagarajan, M.D.). Maryland: Baltimore, Johns Hopkins Children's Center (Melania Bembea, M.D.); Baltimore, University of Maryland School of Medicine (Jay Menaker, M.D.). Michigan: Ann Arbor, University of Michigan (Ryan P. Barbaro, M.D.); Detroit, Children's Hospital of Michigan (Katherine Cashen, M.D.); Royal Oak, Beaumont Hospital (Kathy Swartz, M.D.). Minnesota: Rochester, Mayo Clinic (J. Kyle Bohman, M.D.). New York: Buffalo, University of Buffalo Jacobs School of Medicine and Biomedical Sciences (Amanda Hassinger, M.D.); New York, Cohen Children's Medical Center (James Schneider, M.D.); New York, Columbia University Medical Center/New York Presbyterian Hospital (Daniel Brodie, M.D.; Darryl Abrams, M.D.); Syracuse, Crouse Hospital (Edward Darling, M.D.). North Carolina: Chapel Hill, University of North Carolina Children’s Hospital (Katherine Clement, M.D.; Anthony Charles, M.D.); Durham, Duke University (Christopher Cox, M.D.). Ohio: Cincinnati, Cincinnati Children’s Hospital (Jonathan Byrnes, M.D.); Cleveland, Cleveland Clinic (Kenneth McCurry, M.D.). Oregon: Portland, Doernbecher Children's Hospital (Amit Mehta, M.D.); Portland, Oregon Health & Science University Hospital (David Zonies, M.D.). Pennsylvania: Danville, Geisinger Medical Center (Evan Gajkowski, M.D.); Hershey, Penn State Hershey Children's Hospital (Gary D Ceneviva, M.D.); Philadelphia, Children's Hospital of Philadelphia/University of Pennsylvania (Leslie Raffini, M.D.); Philadelphia, Hospital of the University of Pennsylvania (Robert Rice, M.D.); Philadelphia, Thomas Jefferson University (Hitoshi Hirose, M.D.); Philadelphia, Temple University (Shigemura, M.D.); Pittsburgh, University of Pittsburgh Medical Center (Penny Sappington, M.D.). South Carolina: Charleston, Medical University of South Carolina (Luca Paoletti, M.D.). Tennessee: Memphis, LeBonheur Children’s Hospital (Morgan Melancon, M.D.); Nashville, Vanderbilt Children's Hospital (Brian Bridges, M.D.). Texas: Dallas, Baylor University Medical Center (Sara Kearns, R.N.); Dallas, Children's Medical Center/UT Southwestern (Ali McMichael, M.D.); Houston, Baylor St. Luke's Medical Center (Meredith Reyes, M.D.); Houston, Texas Children's Hospital (Jun Teruya, M.D.); Houston, Baylor College of Medicine (Ayse Arikan, M.D.); San Antonio, US Army Institute of Surgical Research, Fort Sam (Craig R. Ainsworth, M.D.); San Antonio, University Health/UT Health (Andrew D. Meyer, M.D. M.S.; Veronica Armijo-Garcia, M.D.). Utah: Salt Lake City, University of Utah Hospital (David Bailly, M.D.). Virginia: Falls Church, Inova Fairfax Medical Center (Heidi Dalton, M.D.; Erik Osborn, M.D.); Norfolk, Sentara Heart Hospital (David A. Baran, M.D.). Washington: Seattle, Seattle Children's Hospital/University of Washington (Wayne Chandler, M.D.). Wisconsin: Milwaukee, Children's Hospital of Wisconsin/Medical College of Wisconsin (Robert A. Niebler, M.D.).

**South America**

Argentina: Buenos Aires, Clinica Bazterrica (Fernando Palizas, M.D.); Buenos Aires, Favaloro Foundation (Daniel Absi, M.D.); Buenos Aires, Hospital Italiano de Buenos Aires (Manuel Tisminetzky, M.D.). Brasil: Porto Alegre, Santa Casa (Sadi Marcelo Schio, M.D.); Rio de Janeiro, Hospital e Maternidade Santa Lucia (Rodrigo Amancio, M.D.); Sao Paulo, Hospital das Clinicas da Faculdade de Medicina da Universitade de Sao Paulo (Marcelo Park, M.D.; Eduardo Leite Vieira Costa, M.D.). Chile: Santiago, Clinica Las Condes (Rodrigo Diaz, M.D.); Santiago, Pontificia Universidad Catolica de Chile (Alejandro Bruhn, M.D.). Colombia: Bogota, Clinica Shaio (Otto Mauricio González Pardo, M.D.); Floridablanca, Fundacion Cardiovascular de Colombia (Leonardo Salazar, M.D.).

**Oceania**

Australia: Brisbane, Lady Cilento Children's Hospital/University of Queensland (Adrian Mattke, M.D.); Brisbane, The Prince Charles Hospital (Kiran Shekar, M.D.; John Fraser, M.D.); Geelong, University Hospital of Geelong (Joe McCaffrey, M.D.); Melbourne, Royal Children’s Hospital (Warwick Butt, M.D.); Melbourne, Alfred Hospital (Vincent Pellegrino, M.D.); New Lambton Heights, John Hunter Hospital (Jorge Brieva, M.D.); Perth, Fiona Stanley Hospital (Edward Litton, M.D.); Sydney, St. Vincent’s Hospital (Hergen Buscher, M.D.); Sydney, St. George Hospital (Konstantin Yastrebov, M.D.); Sydney, Royal Prince Alfred (Paul Forrest, M.D.); Gold Coast, Gold Coast University Hospital (James Winearls, M.D.). New Zealand: Auckland, Auckland Hospital (Andrew McKee, M.D.); Auckland, Starship Children’s Hospital (David Buckley, M.D.).

**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.

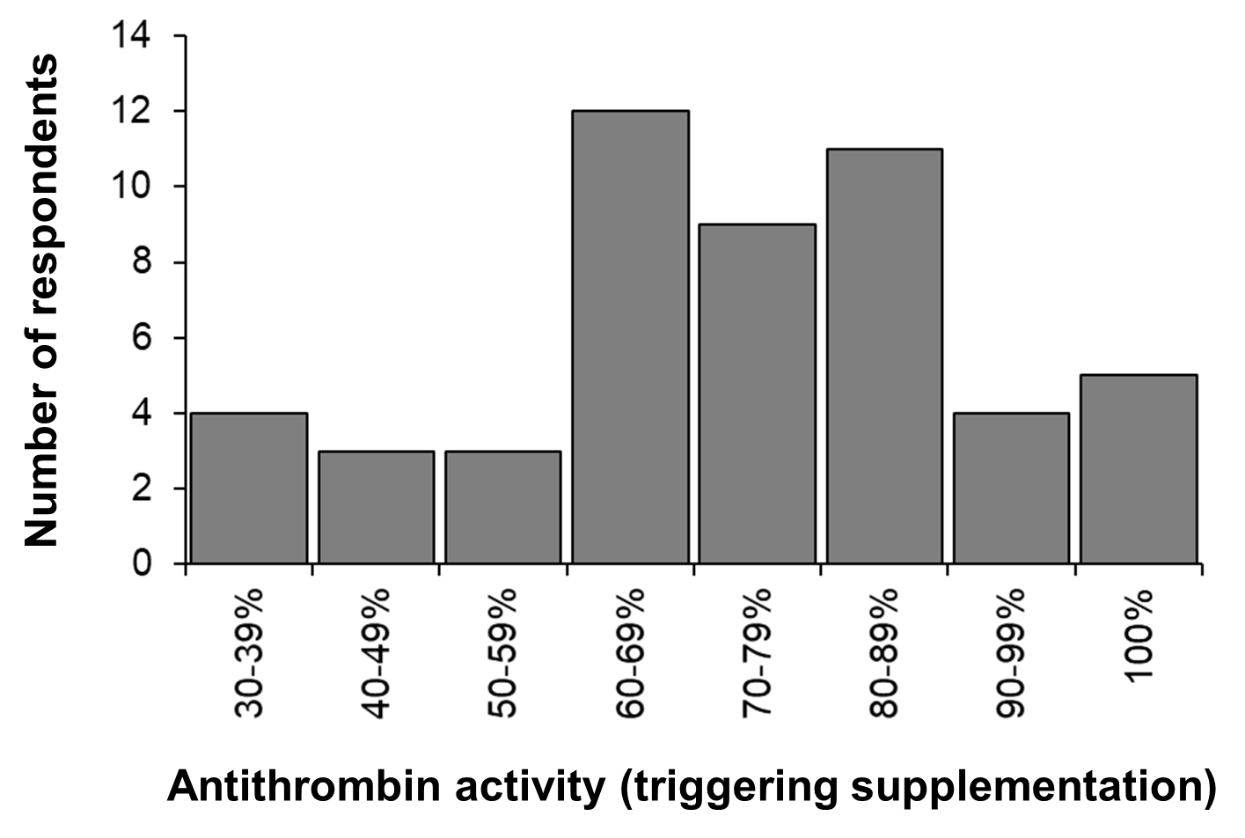
**Supplemental Table 4.** Cost of antithrombin in different regions of the world.

|  |  |  |  |
| --- | --- | --- | --- |
| **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.

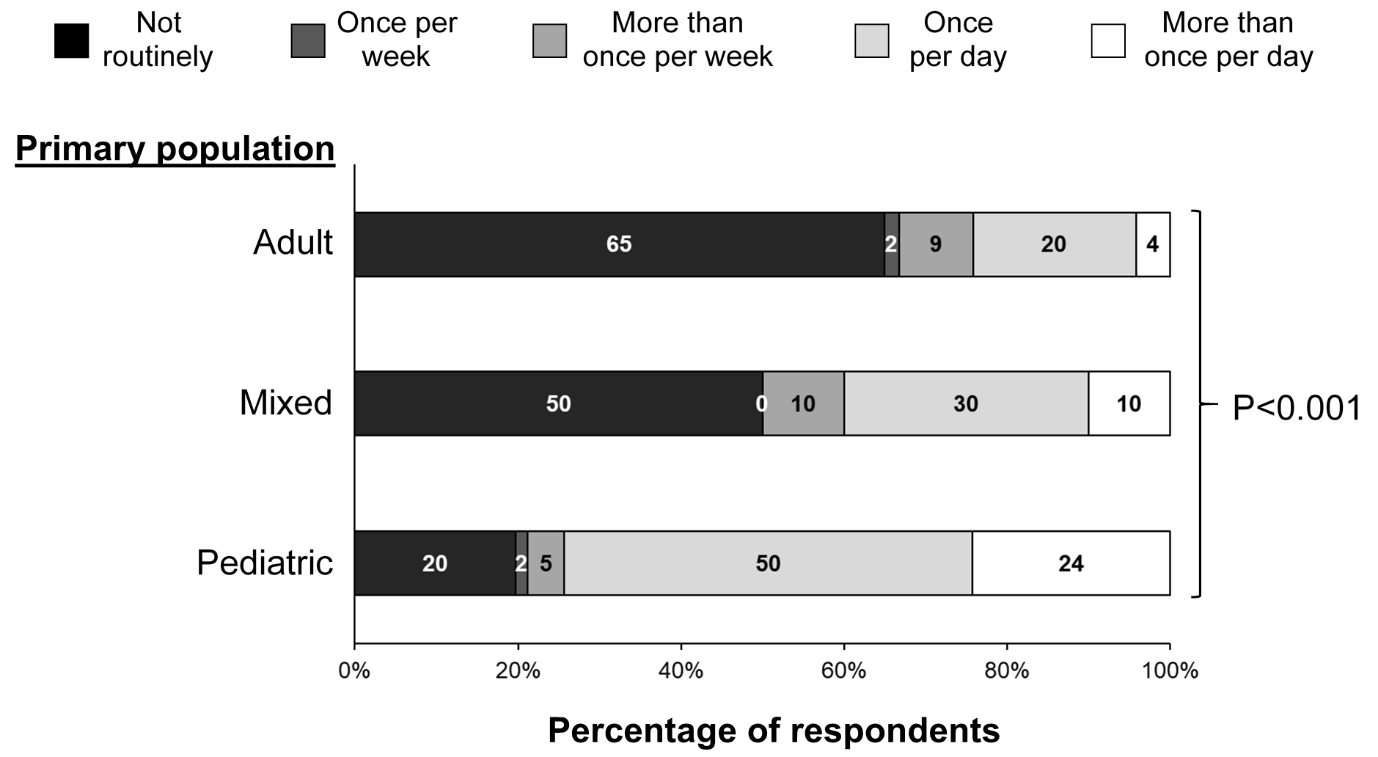
Antithrombin cost significantly differed between regions (p<0.001 at one way analysis of variance on ranks) and was not linearly associated with 2017 gross regional income (R2 0.37; p=0.276 at linear regression analysis). As for other drugs, the cost of antithrombin was particularly high in the US (3.21 [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.