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# Current practice and perceptions regarding pain, agitation and delirium management in patients receiving venovenous extracorporeal membrane oxygenation

Amy L. Dzierba [a,*], Darryl Abrams [b], Purnema Madahar [b], Justin Muir [a], Cara Agerstrand [b], Daniel Brodie [b]

[a] Department of Pharmacy, NewYork-Presbyterian Hospital, New York, NY, United States of America
[b] Division of Pulmonary and Critical Care Medicine, Columbia College of Physicians and Surgeons/NewYork-Presbyterian Hospital, New York, NY, United States of America

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ABSTRACT

*Purpose:* To characterize monitoring of pain, agitation, and delirium; investigate opioid and sedative choices; and describe prevention and treatment of delirium in adults receiving venovenous extracorporeal membrane oxygenation (vv-ECMO) for respiratory failure.
*Materials and methods:* International, cross-sectional survey distributed January 2018 to members of the Society of Critical Care Medicine.
*Results:* Respondents were predominately physicians (58%) from North America (89%). Fentanyl (77%) and hydromorphone (48%) were the most common intravenous opioids used to manage pain. A deep level of sedation was targeted in the first 24-h after initiation of vv-ECMO 64% of the time. When deep sedation was targeted, propofol (70%) and benzodiazepines (41%) were the most common sedatives. The most common sedatives for light sedation were dexmedetomidine (45%) and propofol (39%). Delirium prevention included avoidance of benzodiazepines (73%), whereas the most common treatment strategy was scheduled atypical antipsychotics (83%). Centers that extubated patients during vv-ECMO used dexmedetomidine as the second preferred sedative as compared to benzodiazepines at non-extubating centers ($p = 0.04$).
*Conclusions:* Most respondents use validated scales and protocols to assess and manage pain, agitation/sedation, and delirium. The majority of respondents reported targeting a deep level of sedation with propofol being used for both deep and light levels of sedation.



## 1. Introduction

Technological advances and improved outcomes with extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS) have resulted in increased use of this supportive therapy [1-5]. Conceptually, the management of pain, sedation, and delirium for patients receiving venovenous ECMO (vv-ECMO) for ARDS should be similar to other critically ill patients of equal severity of illness as set forth by international guidelines [6]. However, some differences may exist in this patient population including the initial depth of sedation and choice of opioid and sedative. Specifically, some recommendations from the guidelines, such as maintaining light sedation, exercising an analgosedation approach, and avoidance of benzodiazepines, may not be feasible or desirable at the commencement of vv-ECMO for patients with severe ARDS [6]. This, coupled with pharmacokinetic changes of intravenous opioids and sedatives during ECMO, make designing an effective analgesic and sedative regimen complicated [7,8]. As such, limited data exists on incorporation of guideline recommendations for the prevention and management of pain, agitation, sedation, delirium, immobility, and sleep (PADIS) in adult patients receiving ECMO [6].

The objectives of this survey were to characterize routine monitoring of pain, agitation, and delirium; investigate opioid and sedative choices in the setting of deep and light sedation goals; and describe strategies aimed at prevention and treatment of delirium in patients receiving vv-ECMO for ARDS. Additionally, we sought to make comparisons between higher and lower volume ECMO centers given that there may be an association between ECMO volume and practice patterns [9,10].

## 2. Materials and methods

We conducted an international, cross-sectional survey of physicians, nurse practitioners, physician assistants, pharmacists, physical therapists, respiratory therapists, and nurses to characterize practices in the

* Corresponding author at: Critical Care Clinical Pharmacy Specialist, NewYork-Presbyterian Hospital, Columbia University Irving Medical Center, 622 West 168th Street, VCB, New York, New York 10032, United States of America.
*E-mail address:* ald9012@nyp.org (A.L. Dzierba).

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monitoring of pain, agitation, and delirium, as well as sedative use and targets, in the management of patients receiving vv-ECMO for ARDS. We included providers who were involved in medication management of vv-ECMO patients beyond the initial cannulation. We used rigorous survey methodology to develop, test, and administer our questionnaire [11].

### 2.1. Questionnaire development

Survey sections consisted of questions about pain assessment and management, sedation assessment and management, and delirium assessment, management, and prevention. Survey items were generated with the intention of determining how closely providers adhere to international guidelines and statement recommendations from the 2013 pain, agitation, and delirium (PAD) guidelines [12].

### 2.2. Questionnaire testing

To test the questionnaire's comprehensiveness and clarity, we administered the questionnaire over electronic mail to 8 intensive care providers (2 nurse practitioners, 3 physicians, 3 pharmacists). Subsequently, we assessed clinical sensibility (ability to discriminate among responses, face validity, content validity, and ease of use) by administering the questionnaire and a structured assessment form to 7 individuals (4 physicians, 2 pharmacists, 1 nurse practitioner). We modified the questionnaire based on feedback obtained during testing.

### 2.3. Questionnaire formatting

The questionnaire was 9 pages in length, formatted in black and white, and prepared in English. The questionnaire included an introduction (purpose), descriptive information about prospective respondents (confirming providers are involved in the medication management of adult patients receiving vv-ECMO for ARDS beyond initial cannulation), demographic data, and a section each on pain assessment and management, sedation assessment and management, and delirium assessment, management, and prevention (Appendix I). Key demographic included geographical location and specialization of the intensive care unit (ICU), vv-ECMO case volume, years of experience managing patients receiving vv-ECMO, and respondents' primary specialty.

### 2.4. Questionnaire administration

We used the Qualtrics platform (Qualtrics LLC, Provo, UT) to administer questionnaires, track respondents and non-respondents, and issue reminder questionnaires. The survey was distributed twice in a four-week period in January 2018 to 10,870 members of the Society of Critical Care Medicine (SCCM), whose membership consists of physicians, nurse practitioners, physician assistants, pharmacists, physical therapists, respiratory therapists, and nurses, only a subset of whom are involved in the care of patients receiving vv-ECMO for ARDS. This platform was chosen for maximal inclusion of ECMO centers and clinicians, allowing respondents to self-identify if they were involved in the care of ECMO patients and ending the survey if the participant was not involved in the medication management of adult patients receiving vv-ECMO for ARDS, or to simply not complete the survey. Participation was voluntary and all responses were confidential. We obtained Institutional Review Board approval prior to questionnaire administration.

### 2.5. Statistical analysis

Descriptive statistics were used to report the results. Data are presented as absolute numbers (percentages). Analyses were stratified by ECMO center volume, high ECMO volume was defined as centers performing >30 cases of vv-ECMO in the last year [9], and extubation practices. Categorical data were analyzed by Fisher's exact test or Chi-Squared test. Statistical significance was defined as a $p$-value of ≤0.05, using two-tailed tests of hypotheses. Analyses were performed in STATA, v14.2 (College Station, TX, USA).

## 3. Results

The survey was distributed to 10,870 members of SCCM, of whom 221 (2%) responded. Fifty-eight percent of respondents ($n = 128$) were physicians and 89% of respondents practice in North America (Table 1). Ninety-eight percent ($n = 216$) of respondents practice in ICUs with at least 1 year of experience managing vv-ECMO patients, with 33% of respondents practicing in ICUs that were characterized as having high ECMO volume. Being a high-volume center was associated with >5 years of experience with ECMO, as compared to low-volume centers (89% vs 53%, respectively; $p < 0.001$). When stratified by ECMO case volume, high-volume centers were more likely to manage patients receiving vv-ECMO in the cardiothoracic ICU or dedicated ECMO units.

Nearly all the respondents ($n = 219$, 99%) reported the use of some form of pain assessment in patients (Table 2). The most common intravenous opioid used to manage pain was fentanyl ($n = 171$, 77%) and the

**Table 1**
Respondent demographics.

| Characteristics | All Centers ($n = 221$) | High-volume Centers ($n = 73$) | Low-volume Centers ($n = 148$) | p-Value |
|---|---|---|---|---|
| Geographic practice location | | | | 0.06 |
| North America | 197 (89) | 68 (93) | 128 (87) | |
| Asia & Pacific | 12 (5) | 1 (1) | 11 (7) | |
| Europe | 8 (4) | 4 (6) | 4 (3) | |
| Central & South America | 4 (2) | 0 (0) | 5 (3) | |
| Provider role | | | | 0.61 |
| ICU Physician | 96 (43) | 31 (42) | 65 (44) | |
| Pharmacist | 57 (25) | 19 (26) | 38 (26) | |
| Anesthesiologist | 19 (9) | 9 (12) | 10 (7) | |
| Registered Nurse | 17 (8) | 7 (10) | 10 (7) | |
| Nurse Practitioner | 13 (6) | 2 (3) | 11 (7) | |
| Surgeon | 11 (5) | 2 (3) | 9 (6) | |
| Physician Assistant | 4 (2) | 2 (3) | 1 (1) | |
| Emergency Medicine | 2 (1) | 0 (0) | 1 (1) | |
| Respiratory Therapist | 2 (1) | 1 (1) | 2 (1) | |
| Practicing location for vv-ECMO | | | | 0.04 |
| Cardiothoracic ICU | 123 (56) | 49 (67) | 74 (50) | |
| Medical ICU | 40 (18) | 9 (12) | 31 (21) | |
| Mixed ICU | 33 (15) | 7 (10) | 26 (17) | |
| Surgical ICU | 10 (4) | 3 (4) | 7 (5) | |
| Cardiac Care Unit | 5 (2) | 1 (1) | 4 (3) | |
| Trauma ICU | 4 (2) | 0 (0) | 4 (3) | |
| vv-ECMO Unit | 4 (2) | 4 (6) | 0 (0) | |
| Neurological ICU | 2 (1) | 0 (0) | 2 (1) | |
| Years center managed vv-ECMO | | | | <0.001 |
| <1 | 5 (2) | 0 (0) | 5 (3) | |
| 1 to 5 | 64 (29) | 7 (10) | 57 (39) | |
| >5 | 144 (65) | 65 (89) | 79 (53) | |
| Not Sure | 8 (4) | 1 (1) | 7 (5) | |
| Annual number of patients managed with vv-ECMO | | | | |
| 1 to10 | 48 (22) | | | |
| 11 to 20 | 65 (29) | | | |
| 21–30 | 35 (16) | | | |
| 31–50 | 32 (14) | | | |
| >50 | 41 (19) | | | |
| Center extubates prior to decannulation | 120 (54) | 52 (71) | 68 (46) | 0.001 |

All data presented as n (%).
High-volume center is defined as managing >30 venovenous ECMO cases in the past year.
ICU = intensive care unit; vv-ECMO = venovenous extracorporeal membrane oxygenation.

**Table 2**
Pain practices.

| Survey questions | All Centers ($n = 221$) | High-volume Centers ($n = 73$) | Low-volume Centers ($n = 148$) | p-Value |
|---|---|---|---|---|
| Pain Assessment Methods | | | | 0.46 |
| Critical Care Pain Observation Tool | 93 (42) | 35 (48) | 58 (40) | |
| Behavioral Pain Scale | 79 (36) | 23 (32) | 56 (38) | |
| Nurse Assessment | 34 (15) | 13 (18) | 21 (14) | |
| Physician Assessment | 6 (3) | 0 (0) | 6 (4) | |
| Locally Developed Score | 3 (1) | 1 (1) | 2 (1) | |
| Other | 4 (2) | 1 (1) | 3 (2) | |
| No Routine Assessment for Pain | 2 (1) | 0 (0) | 2 (1) | |
| Initial Preferred Opioid | | | | 0.30 |
| Fentanyl | 171 (77) | 52 (71) | 119 (80) | |
| Hydromorphone | 36 (16) | 17 (24) | 19 (13) | |
| Morphine | 10 (5) | 3 (4) | 7 (5) | |
| Sufentanil | 3 (1) | 1 (1) | 2 (1) | |
| Remifentanil | 1 (1) | 0 (0) | 1 (1) | |
| Second Preferred Opioid | | | | 0.10 |
| Hydromorphone | 106 (48) | 34 (47) | 72 (49) | |
| Morphine | 48 (21) | 13 (18) | 35 (24) | |
| Fentanyl | 38 (17) | 17 (23) | 21 (14) | |
| Alfentanil | 2 (1) | 2 (3) | 0 (0) | |
| Sufentanil | 1 (1) | 0 (0) | 1 (1) | |
| Remifentanil | 1 (1) | 0 (0) | 1 (1) | |
| Other | 14 (6) | 6 (8) | 8 (5) | |
| None | 11 (5) | 1 (1) | 10 (6) | |
| Perception that opioid dosing is higher with vv-ECMO | 121 (55) | 44 (60) | 77 (52) | 0.32 |

All data presented as n (%).
High-volume center is defined as managing >30 venovenous ECMO cases in the past year.
vv-ECMO = venovenous extracorporeal membrane oxygenation.

second most common was hydromorphone ($n = 106$, 48%) in all centers. Regarding sedation, 94% of respondents used a validated ICU sedation assessment scale (Table 3) Eighty-three percent of respondents identified the existence of a sedation guideline or protocol for mechanically ventilated patients in their ICU but only 28% of guidelines specifically addressed sedation related to patients receiving vv-ECMO for ARDS. The frequency with which deep sedation (defined as a patient who is not responsive to voice or physical stimulation) was targeted in the first 24 h after initiation of vv-ECMO was characterized as 'very often' or 'always' 64% of the time. The most common intravenous sedative used to target deep sedation was propofol ($n = 155$, 70%) and the second most common was a benzodiazepine ($n = 90$, 41%) in all centers. The most common sedatives used when a light level of sedation was targeted were dexmedetomidine ($n = 100$, 45%) and propofol ($n = 85$, 39%).

Fifty-five percent of respondents perceived that opioid doses are higher in patients receiving vv-ECMO compared to patients with equally severe ARDS not managed with ECMO, and 59% of respondents noted a similar pattern with sedative dosing. Choice of initial opioids, sedatives, and perception of dosages and withdrawal were not significantly different between high- and low-volume centers. However, the choice of second-line sedative for deep sedation was more likely to be propofol in high-volume centers and benzodiazepines in low-volume centers.

Eighty-seven percent of respondents reported the use of a validated tool to detect delirium (Table 4). The most common strategies to prevent delirium in patients receiving vv-ECMO were the avoidance of benzodiazepines ($n = 161$, 73%), followed by the use of dexmedetomidine ($n = 58$, 26%) and initiation of scheduled atypical antipsychotics ($n = 44$, 20%). In patients recognized as having delirium, scheduled atypical antipsychotics were most commonly used ($n = 183$, 83%), followed by dexmedetomidine ($n = 155$, 70%) and as needed haloperidol ($n = 115$, 53%).

Fifty-four percent of respondents reported that they have extubated patients receiving vv-ECMO. More respondents from high-volume centers reported extubation during ECMO support than those from low-volume centers (71% vs 46%, $p = 0.001$). While propofol was the preferred first-line sedative in all centers targeting a deep level of sedation, dexmedetomidine was used more often as the second preferred sedative at centers that extubated compared to benzodiazepines at non-extubating centers ($p = 0.04$) (Table 5). Use of continuous infusion benzodiazepines for light sedation was less common at centers that extubate than at centers that do not extubate ($p = 0.02$), and extubating centers were less likely to always target deep sedation in the first 24 h post-cannulation ($p = 0.04$).

## 4. Discussion

This international survey is the largest of its kind to assess provider practices in the monitoring and management of pain, agitation, and delirium of patients receiving vv-ECMO for ARDS. We found that most respondents who use vv-ECMO to manage patients with ARDS have implemented routine monitoring of pain, agitation, and delirium with validated tools, employed different sedative strategies depending on the level of desired sedation, and use pharmacologic management for prevention and treatment of delirium. This survey has important differences from previously published surveys on opioid and sedative use in patients receiving ECMO [9,16]. Our survey targeted bedside clinicians directly caring for patients receiving ECMO for ARDS beyond the initial cannulation, whereas previous surveys gathered responses from ECMO medical directors or program coordinators [9,16]. Additionally, this survey evaluated sedative use conditional on the goal level of sedation in a targeted adult patient population receiving vv-ECMO.

Respondents who manage patients receiving vv-ECMO for ARDS reported high rates of assessment of pain, agitation, and delirium in accordance with PADIS guidelines, consistent with recent ECMO and non-ECMO survey data [6,16,17]. Respondents confirmed a high frequency of sedation and delirium protocols to manage critically ill patients. This finding is not surprising given that PADIS guidelines are recommended for all critically ill patients, without comment on the use of ECMO, to minimize the duration of mechanical ventilation, decrease rates of delirium, and improve mortality [6]. However, very few respondents reported on having protocols in place specifically designed to address patients receiving vv-ECMO for ARDS. ECMO-specific deviations from general critical care protocols may include maintenance of deep sedation at the initiation of vv-ECMO for the management of ARDS, especially when neuromuscular blockade is necessary. Additionally, there may be a need for higher doses of lipophilic and moderately to highly protein bound drugs (known to be sequestered within extracorporeal circuits) to achieve adequate pain control and the desired level of sedation [8,12].

Sixty-four percent of respondents reported targeting a deep level of sedation in the first 24 h of ECMO, a number higher than reported from a recent survey in patients receiving ECMO for ARDS [16]. Patients receiving vv-ECMO for severe ARDS may initially require a deeper level of sedation than other critically ill patients in order to optimize patient comfort and ventilator synchrony, minimize catheter malposition or dislodgement, maximize ECMO blood flow, and decrease oxygen demand [18-22]. Targeting deep sedation may be warranted in these patients for a short period of time; however, the long-term effects of such practices remain unknown and should be studied in light of recent data suggesting lower mortality and delirium risk with low intensity sedation within the first 48 h of mechanical ventilation in non-ECMO patients [23].

When a deep level of sedation is targeted, propofol and benzodiazepines were the most common agents used as first and second choices for sedation, respectively. Previous surveys report high use of dexmedetomidine, propofol, and midazolam infusions. However, such practices had not been specifically linked to goal depth of sedation

**Table 3**
Sedation practices.

| Survey questions | All Centers (n = 221) | High-volume Centers (n = 73) | Low-volume Centers (n = 148) | p-Value |
|---|---|---|---|---|
| Sedation Assessment Methods | | | | 0.95 |
| Richmond Agitation Sedation Scale | 200 (90) | 69 (95) | 131 (88) | |
| Sedation Agitation Scale | 9 (4) | 2 (3) | 7 (5) | |
| Ramsay Sedation Scale | 5 (2) | 1 (1) | 4 (3) | |
| Nurse Assessment | 3 (1) | 1 (1) | 2 (1) | |
| Motor Activity Assessment Scale | 2 (1) | 0 (0) | 2 (1) | |
| Physician Assessment | 1 (1) | 0 (0) | 1 (1) | |
| Other | 1 (1) | 0 (0) | 1 (1) | |
| Sedation Protocol for Mechanically Ventilated Patients | 184 (83) | 62 (85) | 122 (82) | 0.86 |
| Sedation protocol specifically addresses vv-ECMO patients* | 51 (28) | 19 (31) | 32 (26) | 0.60 |
| Target Goal is Deep Sedation in First 24 Hours Post Cannulation | | | | 0.39 |
| Always | 43 (19) | 14 (19) | 29 (20) | |
| Very Often | 100 (45) | 28 (38) | 72 (49) | |
| Sometimes | 57 (26) | 24 (33) | 33 (22) | |
| Rarely | 19 (9) | 7 (10) | 12 (8) | |
| Never | 2 (1) | 0 (0) | 2 (1) | |
| Goal Sedation Achieved at Initiation of vv-ECMO | | | | 0.34 |
| Always | 41 (19) | 10 (14) | 31 (21) | |
| Very Often | 145 (65) | 48 (66) | 97 (66) | |
| Sometimes | 32 (15) | 14 (19) | 18 (12) | |
| Rarely | 3 (1) | 1 (1) | 2 (1) | |
| Never | 0 (0) | 0 (0) | 0 (0) | |
| Initial Preferred Sedative for Deep Sedation | | | | 0.14 |
| Propofol | 155 (70) | 48 (66) | 107 (72) | |
| Benzodiazepines | 54 (24) | 24 (33) | 30 (20) | |
| Dexmedetomidine | 9 (4) | 1 (1) | 8 (6) | |
| Ketamine | 2 (1) | 0 (0) | 2 (1) | |
| None | 1 (1) | 0 (0) | 1 (1) | |
| Second Preferred Sedative for Deep Sedation | | | | 0.03 |
| Benzodiazepines | 90 (41) | 21 (29) | 69 (47) | |
| Dexmedetomidine | 52 (23) | 17 (23) | 35 (24) | |
| Propofol | 41 (19) | 22 (30) | 19 (13) | |
| Ketamine | 27 (12) | 10 (14) | 17 (12) | |
| Other | 5 (2) | 1 (1) | 4 (2) | |
| None | 6 (3) | 2 (3) | 4 (2) | |
| Initial Preferred Sedative for Light Sedation | | | | 0.78 |
| Dexmedetomidine | 100 (45) | 32 (44) | 68 (46) | |
| Propofol | 85 (39) | 30 (41) | 55 (37) | |
| Benzodiazepine continuous infusion | 16 (7) | 4 (5) | 12 (8) | |
| Benzodiazepine as needed | 9 (4) | 2 (3) | 7 (5) | |
| Ketamine | 4 (2) | 2 (3) | 2 (1) | |
| Other | 4 (2) | 1 (1) | 3 (2) | |
| None | 3 (1) | 2 (3) | 1 (1) | |
| Second Preferred Sedative for Light Sedation | | | | 0.32 |
| Dexmedetomidine | 81 (37) | 25 (34) | 56 (38) | |
| Benzodiazepine as needed | 49 (22) | 20 (27) | 29 (20) | |
| Propofol | 45 (20) | 11 (15) | 34 (23) | |
| Ketamine | 12 (5) | 6 (8) | 6 (4) | |
| Benzodiazepine continuous infusion | 11 (5) | 2 (3) | 9 (6) | |
| Other | 13 96) | 4 (6) | 9 (6) | |
| None | 10 (5) | 5 (7) | 5 (3) | |
| Perception that Sedation Dosing is Higher with vv-ECMO | 131 (59) | 48 (66) | 83 (56) | 0.39 |
| Perception of Withdrawal from Opioids and Sedatives is Higher with vv-ECMO | 59 (27) | 23 (32) | 36 (24) | 0.52 |

All data presented as n (%).
High-volume center is defined as managing >30 venovenous ECMO cases in the past year.
vv-ECMO = venovenous extracorporeal membrane oxygenation.
* $n = 184$ for all centers; $n = 62$ for high-volume centers; $n = 122$ for low-volume centers.

[9,16]. Our survey reports a high use of propofol, as compared to previous surveys (70% vs 19%), despite the lipophilic properties and greater potential for sequestration within the ECMO circuit [16,24]. Propofol is associated with a shorter time to light sedation and shorter time to extubation when compared to benzodiazepines [25-27] and has not been associated with a decrease in oxygenator lifespan [28]. In contrast, benzodiazepines have been associated with prolonged ICU stay, higher rates of short- and long-term neuropsychological impairment, and increased mortality [12,23,29].

When a light level of sedation is targeted, dexmedetomidine was reported to be the preferred agent. Existing data has concluded that dexmedetomidine is associated with a shorter duration of mechanical ventilation compared to benzodiazepines, with the caveat that benzodiazepines are commonly administered as continuous infusions rather than intermittent boluses [30-32]. More than half of respondents reported extubating patients during vv-ECMO support for ARDS. Centers that extubated patients while receiving vv-ECMO used more propofol and dexmedetomidine and were less likely to use continuous infusions of benzodiazepines, likely contributing to a trend toward lower levels of sedation and increased mobilization, in-line with PADIS guidelines [6].

Adult patients receiving ECMO for ARDS appear to have increased requirements of analgesia and sedation over time [20,21]. In our survey

**Table 4**
Delirium practices.

| Survey questions | All Centers (n = 221) | High-volume Centers (n = 73) | Low-volume Centers (n = 148) | p-Value |
|---|---|---|---|---|
| Delirium assessment methods | | | | 0.62 |
| Confusion assessment method for the intensive care unit | 177 (80) | 59 (80) | 118 (80) | |
| Intensive care delirium screening checklist | 16 (7) | 4 (6) | 12 (8) | |
| Nurse assessment | 16 (7) | 4 (6) | 12 (8) | |
| Physician assessment | 8 (4) | 4 (6) | 4 (3) | |
| No routine assessment for delirium | 4 (2) | 2 (2) | 2 (1) | |
| Delirium protocol for all patients | 141 (64) | 48 (66) | 93 (62) | 0.24 |
| Delirium protocol specifically addresses vv-ECMO patients* | 8 (6) | 5 (10) | 3 (3) | 0.19 |
| Delirium prevention strategies used | | | | |
| Avoid benzodiazepines | 161 (73) | 55 (75) | 106 (72) | 0.56 |
| Dexmedetomidine | 58 (26) | 23 (32) | 35 (24) | 0.21 |
| Scheduled atypical antipsychotics | 44 (20) | 16 (22) | 28 (21) | 0.60 |
| Scheduled haloperidol | 12 (5) | 5 (7) | 7 (5) | 0.51 |
| No pharmacologic intervention | 72 (33) | 27 (37) | 45 (30) | 0.33 |
| Other | 10 (5) | 2 (3) | 8 (5) | 0.50 |
| Delirium Treatment Strategies Used | | | | |
| Avoid benzodiazepines | 161 (73) | 54 (74) | 107 (72) | 0.79 |
| Scheduled atypical antipsychotics | 183 (83) | 67 (92) | 116 (78) | 0.01 |
| Dexmedetomidine | 155 (70) | 53 (73) | 102 (69) | 0.57 |
| Haloperidol as needed | 115 (52) | 34 (47) | 81 (55) | 0.25 |
| Atypical antipsychotics as needed | 84 (38) | 29 (40) | 55 (37) | 0.71 |
| Scheduled haloperidol | 38 (17) | 10 (14) | 28 (19) | 0.33 |
| No pharmacologic intervention | 7 (3) | 4 (6) | 3 (2) | 0.17 |
| Other | 4 (2) | 0 (0) | 4 (3) | 0.31 |
| Perception that Risk for Delirium is Higher with vv-ECMO | 104 (47) | 43 (59) | 61 (41) | 0.013 |

All data presented as n (%).
High-volume center is defined as managing >30 venovenous ECMO cases in the past year.
vv-ECMO = venovenous extracorporeal membrane oxygenation.
* $n = 1141$ for all centers; $n = 48$ for high-volume centers; $n = 93$ for low-volume centers.

more than half of the respondents perceived that opioid and sedation requirements were higher in this patient population as compared to patients with equal ARDS severity not receiving ECMO. A survey published in 2013 reported that 58% of respondents felt sedatives were 'generally much more' or 'generally more' in patients receiving ECMO compared to other patients in the ICU with similar target sedation goals.[9] This observation is supported by many reports that have observed increased opioid and sedative requirements in patients receiving ECMO [18-22,33]. It has yet to be determined whether the increased opioid and sedative requirements observed in patients receiving ECMO are a result of circuit-related factors alone or whether other important elements such as drug-metabolism, tolerance, age, or organ function influence the doses needed to achieve desired sedation goals.

Pain management in critically ill patients can be quite complex. Careful selection and titration of analgesics are influenced by pharmacokinetic alterations and potential adverse effects. Our survey reports that fentanyl and hydromorphone were the most common IV opioids used to treat pain in patients receiving vv-ECMO for ARDS. Previous surveys report a high use of fentanyl and morphine [9,16]. Hydromorphone and morphine have low levels of lipophilicity that correspond to a reduced potential for sequestration within the ECMO circuit, potentially making them preferred agents if high doses of fentanyl are unsuccessful in achieving adequate pain control [8,34]. However, morphine use may be limited by its potential hypotensive effects and accumulation of the active metabolite, specifically in the setting of renal failure.

Delirium in the intensive care unit is common, with a reported prevalence of approximately 50% in patients receiving ECMO [19,33,35]. The prevention of delirium is of paramount importance in order to minimize the associated consequences, including higher in-hospital mortality and long-term functional impairment [35-37]. The two most common interventions reported in our survey to prevent delirium include the avoidance of benzodiazepines and use of dexmedetomidine, strategies supported by PADIS guidelines and a recent clinical trial [6,38]. The routine use of typical or atypical antipsychotics for the prevention of delirium was reported 25% of the time in our survey, despite not being supported by the PADIS guidelines. Conflicting results have been published regarding the effectiveness of pharmacologic agents in the treatment of ICU delirium [39-43]. Despite these conflicting results, more than half of respondents reported the use of haloperidol and atypical antipsychotics in the treatment of delirium. Though its efficacy remains questionable [6], haloperidol was reported to be used 52% of the time when delirium was present.

Our study has a number of limitations. First, the overall low response rate may limit the generalizability of the conclusions. However, the survey was distributed broadly to critical care clinicians without the ability to target recipients who manage ECMO patients. Therefore, we cannot estimate the percent of eligible ECMO providers who responded (i.e. the desired response rate). Second, the survey may only be indicative of perceived management of pain, agitation, and delirium in patients receiving ECMO for ARDS and not reflective of actual practice at the center caring for patients receiving ECMO or at the clinician level. Since the name of the center was not collected, it is unknown how many centers are represented or whether there were multiple respondents from the same center. Additionally, all respondents, regardless of provider role were analyzed together. Responses may be differ depending on the perception of the role of the provider, particularly at centers that are routinely staffed with a clinical pharmacist, or other non-physician practitioners. Given that most respondents were from North America, the results from this survey may not be generalizable to other ICUs, particularly those outside North America.

## 5. Conclusion

To our knowledge, this international survey is the largest study to date that assesses clinician practices regarding the monitoring and management of pain, agitation, and delirium in adult patients receiving vv-ECMO for severe ARDS beyond initial cannulation. Most respondents

**Table 5**
Preferred Choice of Sedatives & Perceptions of Delirium and Withdrawal Stratified by Centers that Extubate Prior to Decannulation in ARDS.

| Survey questions | Extubate ($n = 120$) | Do not Extubate ($n = 91$) | p-Value |
|---|---|---|---|
| Initial Preferred Sedative for Deep Sedation | | | 0.30 |
| Propofol | 89 (74) | 61 (67) | |
| Benzodiazepines | 23 (19) | 26 (29) | |
| Dexmedetomidine | 5 (4) | 4 (4) | |
| Ketamine | 2 (2) | 0 (0) | |
| None | 1 (1) | 0 (0) | |
| Second Preferred Sedative for Deep Sedation | | | 0.04 |
| Benzodiazepines | 45 (38) | 42 (46) | |
| Dexmedetomidine | 35 (29) | 15 (17) | |
| Propofol | 19 (16) | 18 (20) | |
| Ketamine | 15 (12) | 12 (13) | |
| Other | 1 (1) | 4 (4) | |
| None | 5 (4) | 0 (0) | |
| Initial Preferred Sedative for Light Sedation | | | 0.02 |
| Dexmedetomidine | 58 (48) | 40 (44) | |
| Propofol | 46 (38) | 33 (36) | |
| Benzodiazepine Continuous Infusion | 3 (3) | 12 (13) | |
| Benzodiazepine IV Push | 4 (3) | 5 (6) | |
| Ketamine | 4 (3) | 0 (0) | |
| Other | 3 (3) | 0 (0) | |
| None | 2 (2) | 1 (1) | |
| Second Preferred Sedative for Light Sedation | | | 0.58 |
| Dexmedetomidine | 44 (37) | 33 (36) | |
| Benzodiazepine IV Push | 29 (24) | 19 (21) | |
| Propofol | 24 (20) | 18 (20) | |
| Ketamine | 7 (6) | 5 (5) | |
| Benzodiazepine continuous infusion | 3 (2) | 7 (8) | |
| Other | 5 (4) | 7 (8) | |
| None | 8 (7) | 2 (2) | |
| Target Goal is Deep Sedation in First 24 Hours Post Cannulation | | | 0.04 |
| Always | 14 (11) | 26 (28) | |
| Very Often | 54 (45) | 40 (44) | |
| Sometimes | 38 (32) | 18 (20) | |
| Rarely | 13 (11) | 6 (7) | |
| Never | 1 (1) | 1 (1) | |
| Perception that Risk for Delirium is Higher with vv-ECMO | 53 (44) | 43 (47) | 0.33 |
| Perception of Withdrawal from Sedatives is Higher with vv-ECMO | 36 (30) | 21 (23) | 0.39 |

All data presented as n (%).
vv-ECMO = venovenous extracorporeal membrane oxygenation.

reported use of validated scales to assess pain, agitation/sedation, and delirium along with protocols in place to help guide sedation and delirium management; although very few protocols addressed management of patients receiving vv-ECMO for ARDS. The majority of respondents reported targeting a deep level of sedation with propofol being used for both deep and light levels of sedation. More than half of the respondents reported extubating patients with during ECMO support more commonly in high-volume centers. Future research should focus on how these practices affect long-term outcomes.

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## Conflicts of interest

Dr. Brodie is on the medical advisory board for Baxter, past medical advisory board member for ALung Technologies, anticipated future medical advisory board member for BREETHE. Currently on the Trial Steering Committee for the VENT-AVOID trial sponsored by ALung Technologies.

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## Appendix A. Appendix I

### *A.1. Part 1: inclusion question*

1. Are you involved in medication management of adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome (beyond the initial cannulation)?
(respondent will only be able to choose one answer)
    a. Yes
    b. No

**If answer "a" to question 1, will go on to rest of survey.**
**If answer "b" to question 1, will end the survey.**

### *A.2. Part 2: demographics*

1. What geographical region is your hospital/ICU located in?
(respondent will only be able to choose one answer)
    a. Africa
    b. Asia and Pacific
    c. Australia and New Zealand
    d. Central and South America
    e. Europe
    f. North America
2. How many years has your hospital/ICU provided venovenous ECMO (vv-ECMO) to adult patients?
(respondent will only be able to choose one answer)
    a. <1
    b. 1–5
    c. >5
    d. Not sure
3. In the past year, how many adult patients have been treated with vv-ECMO in your hospital?
(respondent will only be able to choose one answer)
    a. 1–10
    b. 11–20
    c. 21–30
    d. 31–50
    e. >50
4. What is your primary specialty?
(respondent will only be able to choose one answer)
    a. Pharmacist
    b. Surgeon
    c. Intensive care physician
    d. Anesthesiologist
    e. Cardiologist
    f. Nurse
    g. Nurse practitioner
    h. Physician assistant
    i. Perfusionist
    j. Respiratory therapist
    k. Other (please specify)

5. What type of ICU do you primarily practice in when caring for vv-ECMO patients?
(respondent will only be able to choose one answer)

    a. Cardiothoracic
    b. Cardiac Care
    c. Medical
    d. Neurological/neurosurgical
    e. Surgical
    f. Trauma
    g. Mixed Medical-Surgical
    h. Other (please specify)

6. Do you ever extubate adult patients receiving vv-ECMO for ARDS prior to decannulation?
(respondent will only be able to choose one answer)
    a. Yes
    b. No
    c. Not sure

*A.3. Part 3: pain management*

**All questions in this section refer to adult patients receiving vv-ECMO for acute respiratory distress syndrome (ARDS) unless otherwise specified.**

1. How is pain primarily assessed when the patient is unable to self-report and when motor function is intact and behaviors are observable?
(respondent will only be able to choose one answer)

    a. Behavioral Pain Scale
    b. Nurse opinion
    c. Critical-Care Pain Observation Tool
    d. Physician opinion
    e. Locally developed score
    f. Other (please specify)
    g. Do not routinely assess for pain

2. Which intravenous opioid is most commonly and second most commonly used to treat pain in your ICU:
(respondent will only be able to choose one answer)

    a. Alfentanil
    b. Fentanyl
    c. Hydromorphone
    d. Morphine
    e. Remifentanil
    f. Sufentanil
    g. Other (please specify)
    h. None

3. In general, do you feel that opioid doses are higher in these patients as compared to patients with equal severity of ARDS not receiving vv-ECMO?
(respondent will only be able to choose one answer)

    a. Yes
    b. No
    c. Not sure

*A.4. Part 4: sedation management*

**All questions in this section refer to adult patients receiving vv-ECMO for acute respiratory distress syndrome (ARDS) unless otherwise specified.**

1. How is the level of sedation usually assessed?
(respondent will only be able to choose one answer)

    a. Adaptation to the Intensive Care Environment (ATICE)
    b. Motor Activity Assessment Scale (MAAS)
    c. Nurse opinion
    d. Ramsay sedation scale
    e. Richmond sedation agitation scale (RASS)
    f. Sedation agitation scale (SAS)
    g. Physician opinion
    h. Locally developed score
    i. Other (please specify)
    j. Do not routinely assess level of sedation

2. Does your ICU have a sedation guideline/protocol for all mechanically ventilated patients?
(respondent will only be able to choose one answer)

    a. Yes
    b. No
    c. Not sure

**If answer "a" to question 2, will be asked question 3.**
**If answer "b or c" to question 2, will move on to question 4.**

3. Does your ICU sedation guideline/protocol address sedation related to adult patients receiving vv-ECMO for ARDS?
(respondent will only be able to choose one answer)

    a. Yes
    b. No
    c. Not sure

4. In general, do you feel that sedative doses for a given sedation goal are higher in these patients as compared to patients with equal severity of ARDS not receiving vv-ECMO?
(respondent will only be able to choose one answer)

    a. Yes
    b. No
    c. Not sure

**For questions 5 and 6, deep sedation refers to a patient who is not responsive to voice or physical stimulation.**

5. In the last year, please estimate how frequently your target sedation goal was deep sedation in the first 24-h after of vv-ECMO cannulation:
(respondent will only be able to choose one answer)

    a. Always
    b. Very often
    c. Sometimes
    d. Rarely
    e. Never

6. When targeting deep sedation, which sedative is most commonly and second most commonly used in your ICU:
(respondent will only be able to choose one answer)

    a. Dexmedetomidine
    b. Benzodiazepines
    c. Propofol
    d. Ketamine
    e. Other (please specify)
    f. None

7. When NOT targeting deep sedation, which sedative/strategy is most commonly and second most commonly used in your ICU:
(respondent will only be able to choose one answer)

   a. Dexmedetomidine
   b. Benzodiazepine infusion
   c. Benzodiazepine as needed
   d. Propofol
   e. Ketamine
   f. Other (please specify)
   g. None

8. How frequently are you able to achieve goal sedation at initiation of vv-ECMO?
(respondent will only be able to choose one answer)

   a. Always
   b. Very often
   c. Sometimes
   d. Rarely
   e. Never

9. In general, do you feel that the incidence of withdrawal from opioids and sedatives is higher during weaning in these patients as compared to patients with equal severity of ARDS not receiving vv-ECMO?
(respondent will only be able to choose one answer)

   a. Yes
   b. No
   c. Not sure

*A.5. Part 5: delirium management*

**All questions in this section refer to adult patients receiving vv-ECMO for acute respiratory distress syndrome (ARDS) unless otherwise specified.**

1. Which delirium-screening tool is used in these patients?
(respondent will only be able to choose one answer)

   a. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)
   b. Nurse opinion
   c. Intensive Care Delirium Screening Checklist (ICDSC)
   d. Physician opinion
   e. Locally developed score
   f. Other (please specify)
   g. Do not routinely assess for delirium

2. In general, do you feel that these patients are at higher risk for experiencing delirium as compared to patients with equal severity of ARDS not receiving vv-ECMO?
(respondent will only be able to choose one answer)

   a. Yes
   b. No
   c. Not sure

3. Does your ICU have a delirium guideline/protocol that applies to all patients?
(respondent can choose more than one answer)

   a. Yes
   b. No
   c. Not sure

**If answer "a" to question 3, will be asked question 4.**
**If answer "b or c" to question 3, will move on to question 5.**

4. Does the delirium guideline/protocol recommend treating adult patients receiving vv-ECMO for ARDS differently than other ICU patients?
(respondent will only be able to choose one answer)

   a. Yes
   b. No
   c. Not sure

5. In patients **WITHOUT** delirium, what **pharmacologic** delirium prevention strategies are used (select all that apply)?
(respondent choose more than one answer)

   a. Avoid benzodiazepines
   b. Initiate scheduled atypical antipsychotic
   c. Initiate scheduled haloperidol
   d. Initiate dexmedetomidine
   e. No pharmacologic prevention is used
   f. Other (please specify)

6. In patients **WITH** delirium (with or without agitation), what **pharmacologic** strategies are used (select all that apply):
(respondent choose more than one answer)

   a. Schedule atypical antipsychotic
   b. As needed atypical antipsychotic
   c. Scheduled haloperidol
   d. As needed haloperidol
   e. Avoid benzodiazepines
   f. Dexmedetomidine
   g. No pharmacologic strategies are used
   h. Other (please specify)

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