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## Dexmedetomidine Use in Critically-Ill Children with Acute Respiratory Failure

Mary Jo C. Grant, APRN, PhD, James B. Schneider, MD, Lisa A. Asaro, MS, Brenda L. Dodson, PharmD, Brent A. Hall, PharmD, Shari L. Simone, APRN, DNP, Allison S. Cowl, MD, Michele M. Munkwitz, MD, David Wypij, PhD, and Martha A.Q. Curley, RN, PhD for the **RESTORE Study Investigators**

Department of Pediatric Critical Care, Primary Children's Hospital, Salt Lake City (M.C.G.); Division of Pediatric Critical Care Medicine, Cohen Children's Medical Center, Hofstra-NSLIJ School of Medicine, New York (J.B.S.); Department of Cardiology, Boston Children's Hospital, Boston (L.A.A., D.W.); Department of Pharmacy, Boston Children's Hospital, Boston (B.L.D.); Department of Pharmacy, UC Davis Medical Center, Sacramento (B.A.H.); Department of Pediatric Critical Care, University of Maryland Medical Center, Baltimore (S.L.S.); Connecticut Children's Medical Center, Hartford (A.S.C.); Division of Pediatric Critical Care, Phoenix Children's Hospital, University of Arizona College of Medicine, Phoenix (M.M.M.); Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston (D.W.); Department of Pediatrics, Harvard Medical School, Boston (D.W.); School of Nursing (M.A.Q.C.) and the Perelman School of Medicine, University of Pennsylvania, Philadelphia (M.A.Q.C.); Critical Care and Cardiovascular Program, Boston Children's Hospital, Boston (M.A.Q.C.)

### Abstract

**Objective**—Care of critically-ill children includes sedation but current therapies are suboptimal.

To describe dexmedetomidine (DEX) use in children supported on mechanical ventilation for acute respiratory failure.

**Design**—Secondary analysis of data from the *RESTORE* clinical trial.

**Setting**—Thirty-one pediatric ICUs.

**Patients**—Data from 2449 children; 2 weeks to 17 years old.

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Address for reprints: Mary Jo C. Grant, APRN, PhD; Primary Children's Hospital Pediatric Critical Care; 100 North Mario Capecchi Drive; Salt Lake City, UT 84113 USA; maryjo.grant@imail.org; Office phone: 801.662.2442. No reprints will be ordered.

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**Interventions**—Sedation practices were unrestrained in the usual care arm. Patients were categorized as receiving dexmedetomidine as a primary sedative (DEXp), secondary sedative (DEXs), peritubation agent (DEXe), or never prescribed. DEX exposure and sedation and clinical profiles are described.

**Measurements and Main Results**—Of 1224 usual care patients, 596 (49%) received DEX. DEXp patients (N=138; 11%) were less critically ill (PRISM III-12 score median 6 [IQR 3–11]) and when compared to all other cohorts, experienced more episodic agitation. In the intervention group, time in sedation target improved from 28% to 50% within one day of initiating DEXp. DEXs usual care patients (N=280; 23%) included more children with severe PARDS or organ failure. DEXs patients experienced more inadequate pain (22% vs 11%) and sedation (31% vs 16%) events. DEXe patients (N=178; 15%) were those known to not tolerate an awake, intubated state and experienced a shorter ventilator weaning process (2.1 vs 2.3 days).

**Conclusions**—Our data support the use of dexmedetomidine as a primary agent in low criticality patients offering the benefit of rapid achievement of targeted sedation levels. Dexmedetomidine as a secondary agent does not appear to add benefit. The use of dexmedetomidine to facilitate extubation in children intolerant of an awake, intubated state may abbreviate ventilator weaning. These data support a broader armamentarium of pediatric critical care sedation.

### Keywords

Endotracheal intubation; extubation; analgesia; agitation; withdrawal; pediatric intensive care

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Sedation management is fundamental to the care of critically-ill children supported on mechanical ventilation. Although practice variation exists, the most common sedation strategy in pediatric critical care includes the concomitant administration of an opioid and benzodiazepine.<sup>1–4</sup> The use of these agents is associated with adverse effects contributing to intensive care morbidity, such as decreased spontaneous ventilation and prolonged mechanical ventilation. Further, gamma aminobutyric acid (GABA) agonists, such as benzodiazepines,<sup>3</sup> demonstrate neurotoxic apoptotic effects, and when used to provide anesthesia at a young age, may impact neurocognitive development.<sup>5,6</sup>

Dexmedetomidine (DEX) is an alpha 2-adrenoceptor agonist principally acting centrally in the locus ceruleus to produce sedation, as well as in the spinal cord resulting in analgesia. Unlike most sedatives used in intensive care, DEX preserves respiratory drive, allowing for sedation with maintenance of spontaneous breathing. In critically-ill adults, sedation with DEX has been shown to provide adequate levels of sedation while reducing the duration of delirium and/or coma and shortening the duration of mechanical ventilation.<sup>7–9</sup> Of particular interest to the pediatric population, animal models demonstrate a neuroprotective effect<sup>10–13</sup> that requires further clinical investigation.

Although not approved for use in children by the Food and Drug Administration (FDA), DEX has gained popularity in pediatric critical care. To date, data describing DEX use are derived from single-center retrospective cohort studies or case reports.<sup>4,14–18</sup> Most often, DEX has been used for short durations (<24 hours) and as an adjunct to other sedative

agents. Here we describe DEX use in pediatric intensive care units (PICUs) over a 4-year period using data prospectively collected in a large multicenter study of sedation practices. In addition to describing the change in DEX use over time, we describe the sedation and clinical courses of patients receiving DEX as a primary agent, as a secondary agent, or to facilitate endotracheal extubation in a cohort of children supported on mechanical ventilation for acute respiratory failure.

## METHODS

We performed a secondary analysis of the Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) study dataset. *RESTORE* was a cluster randomized trial that compared usual care to a nurse-implemented goal-directed sedation algorithm in children with acute respiratory failure.<sup>19</sup> Thirty-one PICUs participated and were randomized to continued usual care (14 sites, 1224 patients) or to the intervention (17 sites, 1225 patients). Prior to randomization, all PICUs implemented the same pain (FLACC,<sup>20</sup> FACES,<sup>21</sup> Individualized Numeric Rating Scale<sup>22</sup>), sedation (State Behavioral Scale [SBS]<sup>23</sup>), and withdrawal assessment (Withdrawal Assessment Tool-Version 1 [WAT-1]<sup>24</sup>) instruments.

*RESTORE* enrolled children, 2 weeks to 17 years of age, who were expected to require mechanical ventilation for at least 24 hours for acute airways or parenchymal disease, between 2009 and 2013. The database includes demographic and medical history data, baseline Pediatric Cerebral Performance Category (PCPC) and Pediatric Overall Performance Category (POPC),<sup>25</sup> Pediatric Risk of Mortality (PRISM) III-12 scores,<sup>26</sup> pediatric acute respiratory distress syndrome (PARDS)<sup>27</sup> severity, daily clinical and organ function data, daily comfort assessments, and sedative dosing data from endotracheal intubation to 72 hours after the last opioid dose.

Most analyses focus on the usual care patients where DEX use was unrestrained. In the intervention group, DEX use per protocol was limited to the periextubation period in children assessed to be intolerant of an awake state. To facilitate data interpretation, patients were categorized into one of four DEX usage groups: 1) DEXe: DEX used as a periextubation agent, defined as DEX initiated on the day of, or day before, the first planned extubation, 2) DEXp: DEX used as a primary agent, defined as DEX initiated within the first 2 days of intubation and administered for 50% of intubated days and not used as a periextubation agent, 3) DEXs: DEX as a secondary agent, defined as DEX used but not as a periextubation or primary agent, and 4) DEX never prescribed.

Sedation profiles include opioid and benzodiazepine exposure, number of different sedative classes, measures of wakefulness, episodic pain and agitation, and sedation-related adverse events including inadequate pain management (2+ consecutive hours of pain scores 4), inadequate sedation management (2+ consecutive hours of SBS +1/+2), and clinically significant iatrogenic withdrawal (treatment of increased WAT-1 scores).<sup>28</sup> For patients in the intervention group, we report the percentage of time spent within the prescribed SBS target range.

## Statistical analysis

For the usual care arm, we describe the frequency of DEX usage groups by year. Site variability in DEX use was evaluated by calculating the percentage of patients managed with DEX by site and the intraclass correlation coefficient (ICC). The ICCs were derived from analysis of variance adjusting for age group, PRISM III-12 score, and baseline POPC>1 as performed in the primary trial publication, as well as study year to control for potential time trends in DEX use. Confidence intervals for the ICCs were constructed using Searle's method to adjust for unequal sample sizes across sites.<sup>29,30</sup> All usual care patients were used in calculating the DEXp ICC, all patients excluding DEXp patients were used in calculating the DEXs ICC, and DEXe and DEX never prescribed patients were used in calculating the DEXe ICC.

Baseline patient characteristics were compared across the four DEX usage groups using linear, logistic, multinomial logistic, and cumulative logit regression for continuous, binary, nominal, and ordinal variables, respectively. Analyses of sedation and clinical profile data used these methods as well as proportional hazards and Poisson regression for time-to-event and rate variables, respectively. Continuous variables except percentage of study days variables were log-transformed. For duration of mechanical ventilation, we adjusted for age group, PRISM III-12 score, and baseline POPC>1 as performed in the primary trial publication, as well as worst PARDS on days 0 to 1 to control for severity of lung injury.<sup>19</sup> All regression analyses except for primary diagnosis accounted for PICU as a cluster variable using generalized estimating equations. To reflect how decisions are made in clinical practice, sedation and clinical profiles were also compared between 1) DEXp vs all other patients, 2) DEXs vs all other patients excluding DEXp patients, and 3) DEXe vs DEX never prescribed, when the overall *P* value comparing across the four DEX groups was <0.05. Due to multiple comparisons, *P* values <0.01 were considered to indicate statistically significant differences for the additional comparisons. All data analyses were performed using SAS (Version 9.4, SAS Institute, Cary, NC).

## RESULTS

In total, 596 of 1224 (49%) usual care patients ever received DEX. DEXp and DEXs use increased each year; specifically, from 6% to 17% for DEXp and 17% to 32% for DEXs. DEXe use remained consistent throughout the 4-year enrollment period ranging from 13% to 17%. The percentage of patients managed with DEX varied by site: DEXp 8% (median; range, 0–37%), DEXs 23% (9–32%), and DEXe 12% (4–20%). The ICC indicated moderate variability by site: DEXp 0.081 (95% CI, 0.043–0.173), DEXs 0.050 (0.024–0.117), and DEXe 0.035 (0.012–0.092).

### DEX as a primary agent

Baseline characteristics of usual care patients by DEX usage group are presented in Table 1. The DEXp cohort (N=138; 11%) included children with lower median PRISM III-12 scores and more children with asthma or reactive airway disease. When used as DEXp, the mean daily DEX dose was 0.6 mcg/kg/hr (median; IQR, 0.4–0.8), the peak daily DEX dose was 0.9 mcg/kg/hr (0.6–1.3), and the cumulative DEX dose was 77.0 mcg/kg (37.6–167.0). The

median duration of DEXp exposure was 6 days (IQR, 4–10) with 28% (N=39) receiving DEX postextubation for a median of 2 days (IQR, 1–3). Table 2 illustrates DEXp sedation profiles on the day DEX was initiated followed by two subsequent days. Most DEXp patients were awake and calm with modal SBS scores –1/0. Table 3 compares the sedation profiles by DEX usage group. Compared to all other patients, children receiving DEXp were exposed to significantly less opioids (median cumulative dose 12.4 vs 18.5 mg/kg) but more sedative classes (median 4 vs 3), propofol (18% vs 10%), and ketamine (38% vs 29%). Children receiving DEXp experienced significantly more study days with any episode of agitation (median 50% vs 38%). Table 4 compares the clinical profiles by DEX usage group. The duration of mechanical ventilation was significantly shorter in the DEXp group compared to all other patients (median 5.0 vs 6.8 days).

### **DEX as a secondary agent**

The DEXs cohort (N=280; 23%) included more children with severe PARDS and children with a greater number of organ dysfunctions on admission. When used as DEXs, the mean daily DEX dose was 0.5 mcg/kg/hr (median; IQR, 0.3–0.7), the peak daily DEX dose was 0.7 mcg/kg/hr (0.5–1.1), and the cumulative DEX dose was 49.8 mcg/kg (19.8–133.5). DEXs was initiated on Day 4 (median; IQR, 2–8) postintubation. The median duration of DEXs exposure was 4 days (IQR, 3–9) with 27% (N=75) receiving DEX postextubation for a median of 2 days (IQR, 1–3). Table 5 illustrates DEXs sedation profiles on the day DEX was initiated and up to two days before and after initiation. Most DEXs patients were awake and calm with modal SBS scores –1/0; on the first day of receiving DEX, 18% were agitated with modal SBS scores +1/+2. The percentage of patients receiving neuromuscular blockade was higher on the days before DEX was initiated. Compared to all other patients excluding DEXp patients, children receiving DEXs were exposed to significantly more opioids (median cumulative dose 53.2 vs 13.2 mg/kg), benzodiazepines (42.3 vs 9.5 mg/kg), and sedative classes (median 4 vs 3). DEXs patients experienced significantly more study days with any episode of pain (median 30% vs 20%) and agitation (52% vs 33%) compared to all other patients excluding DEXp patients. The DEXs group also experienced significantly more sedation-related adverse events, specifically, inadequate pain management (22% vs 11%), inadequate sedation management (31% vs 16%), and clinically significant iatrogenic withdrawal (15% vs 7%). The duration of mechanical ventilation was significantly longer in the DEXs group compared to all other patients excluding DEXp patients (9.9 vs 5.6 days). The DEXs group also experienced a significantly longer recovery from acute respiratory failure (median 4.7 vs 2.2 days), longer duration of weaning from mechanical ventilation (4.1 vs 2.2 days), and longer lengths of PICU and hospital stay (14.6 vs 8.3 days and 23 vs 14 days, respectively).

### **DEX as a periextubation agent**

The DEXe cohort (N=178; 15%) included fewer children with acute respiratory failure related to sepsis and more with asthma or reactive airways disease, patients known to not tolerate an awake, intubated state. When used as DEXe, the mean daily DEX dose was 0.3 mcg/kg/hr (median; IQR, 0.1–0.4), the peak daily DEX dose was 0.3 mcg/kg/hr (0.2–0.5), and the cumulative DEX dose was 11.2 mcg/kg (4.9–19.4). The median duration of DEXe exposure was 2 days (IQR, 1–2) with 22% (N=40) receiving DEX postextubation for a

median of 1 day (IQR, 1–2). Children receiving DEXe were exposed to significantly more sedative classes (median 4 vs 2), ketamine (29% vs 24%), and anti-delirium medications (4% vs <1%) compared to the DEX never prescribed group. The DEXe group experienced significantly more days with episodic pain (median 25% vs 17%) and agitation (median 50% vs 25%) and more inadequate sedation management events (19% vs 15% of patients). Patients prescribed DEXe experienced significantly shorter weaning from mechanical ventilation (2.1 vs 2.3 days).

### DEX use in the intervention group

As expected, DEX use was much lower in the intervention group, with 287 of 1225 (23%) intervention patients ever receiving DEX. When DEXp was prescribed as a protocol deviation (N=80; 7%), time in sedation target improved from 28% to 50% within one day of initiating DEX. No such improvements were noted when DEXs was prescribed as a protocol deviation (N=152; 12%). When compared to the DEX never prescribed cohort (N=938, 77%), patients in the intervention group who were prescribed DEXe per protocol (N=55; 4%) experienced a shorter duration of mechanical ventilation (median [IQR] 6.1 [3.6–9.7] vs 6.2 [4.0–10.5] days;  $P=0.002$ ). In addition, no DEX-related adverse events were reported in either arm of the *RESTORE* clinical trial.

## DISCUSSION

We present the sedation and clinical profiles of mechanically ventilated children receiving dexmedetomidine over a four-year period within a large multicenter clinical trial. Our data indicate that dexmedetomidine use is increasing as both a primary and secondary agent in pediatric critical care. We report that clinicians are prescribing DEXp more often in children who are less critically ill, and, in the intervention group, DEXp resulted in more time within the prescribed sedation target. Adding DEXs into an existing sedative regime does not appear to add benefit. Dexmedetomidine as a periextubation agent is prescribed more often in patients who experienced a difficult sedation course (more episodic pain and agitation and inadequate sedation management) or in those known not to tolerate an awake, intubated state; specifically, patients with reactive airways disease or asthma. When prescribed, DEXe shortened the ventilator weaning process.

The ideal sedation agent in pediatric critical care would effectively produce anxiolysis in a wide range of patient age and developmental levels, preserve spontaneous ventilation, and exhibit a short half-life. In addition, the ideal sedation agent would not be associated with physiological tolerance with continued use or produce adverse effects including the potential for long-term neurocognitive dysfunction. While the pharmacologic and pharmacodynamics properties of DEX meet most of these criteria, symptoms characteristic of sympathetic over-activity including tachycardia, hypertension, emesis, agitation and seizures have been reported in children upon DEX discontinuation and warrant further study.<sup>18,31–34</sup>

Data supporting the use of DEXp in pediatrics are limited.<sup>35</sup> In adult critical care, multiple large randomized controlled clinical trials support DEXp as an effective sedation agent that shortens the duration of mechanical ventilation and length of intensive care unit stay.<sup>7,8</sup> Here we report a large cohort of critically-ill children who were adequately sedated with DEXp



for a median of 6 days. In our cohort, children prescribed DEXp were less critically ill with a short anticipated length of mechanical ventilation, such as children with asthma but without multisystem organ failure.

DEXp was opioid-sparing but was associated with the use of more sedative classes. With light levels of sedation, it is not surprising that those receiving DEXp experienced more intermittent episodes of agitation. Importantly, despite an increase in episodic agitation, we did not identify an increase in unplanned removal of medical devices. Of note, when prescribed in the intervention group as a protocol deviation, DEXp was associated with a rapid achievement of targeted sedation scores.

Even after adjusting for severity of illness, DEXp was associated with a shorter duration of mechanical ventilation, possibly due to the more awake state and use of less opioids known to depress spontaneous respiration. Literature describing the use of DEX in children after cardiac surgery also suggests that DEX is effective as a primary agent and may facilitate earlier extubation.<sup>36,37</sup> Pending further investigation, data may support the use of DEXp as a superior sedative agent in pediatric populations where the duration of mechanical ventilation is expected to be short.

As a secondary agent, however, DEX did not improve the patient's sedation profile. Adding DEXs into the sedative regime of complex PARDS patients with a median of two or more organ dysfunctions did not result in an appreciable improvement in patient comfort nor did DEXs reduce other sedative dosing. This finding is in contrast to that of others who report a reduction<sup>4</sup> or plateau<sup>18</sup> in opioid and benzodiazepine dosing after starting a DEX infusion. The profile and characteristics of the pediatric patient most likely to have either a comfort or reduced sedative burden benefit remain unclear, but this analysis suggests it is not useful as a secondary agent in complex pediatric patients.

The use of DEXe was stable over our 4-year enrollment. We found that patients receiving DEXe were weaned from mechanical ventilation earlier but, again, did not experience less opioid or benzodiazepine exposure as previously reported in pediatric cohort studies<sup>14,37-40</sup> and case reports.<sup>41-45</sup> Similar to difficult-to-extubate adult patients,<sup>46</sup> DEXe improves the rate of successful extubation

Our analyses are vulnerable to design flaws and bias. Unmeasured factors may have impacted a clinician's decision to prescribe DEX. Without patient-level randomization one cannot evaluate the impact of DEX on clinical outcomes. In addition, delirium was not systematically assessed in the parent trial and its presence may have impacted both the dose and number of sedative classes administered. Also, non-pharmacologic interventions which may impact sedation were not captured. Since DEX use was not the objective of the parent study there may have been an underreporting of DEX side effects. Evaluation of DEX safety, as well as the potential benefit of DEX in facilitating restorative sleep, requires prospective study.<sup>47-49</sup> Finally, we studied pediatric patients with acute respiratory failure. These data may not apply to other critically-ill pediatric cohorts.

## CONCLUSIONS

Our data support the use of dexmedetomidine as a primary sedative agent in low criticality children because it offers the benefit of rapid achievement of targeted sedation scores and awake patients whose comfort levels can be better assessed and rapidly managed. Prescribing dexmedetomidine as a secondary sedative agent in a cohort of high criticality children did not appear to add clinical benefit. Finally, using dexmedetomidine to facilitate extubation in children who are intolerant of an awake, intubated state may abbreviate ventilator weaning. These data allow us to broaden our armamentarium of pediatric critical care sedation and inform the design of future randomized controlled clinical trials investigating how dexmedetomidine can be best used in pediatric critical care.

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Table 1

## Baseline Characteristics of Usual Care Patients by DEX Usage Group

Characteristics	DEXp (N=138)	DEXs (N=280)	DEXe (N=178)	DEX Never Prescribed (N=628)	P Value Across All Groups <sup>d</sup>
Age at PICU admission, median (IQR), y	2.5 (1.1–9.0)	2.6 (0.7–8.7)	3.1 (0.9–8.1)	2.6 (0.4–9.8)	0.26
Female sex, No. (%)	44 (32)	138 (49)	78 (44)	283 (45)	0.01
Non-Hispanic white, No./total no. (%)	61/136 (45)	152/279 (54)	87/176 (49)	302/619 (49)	0.045
Cognitive impairment (baseline PCPC score >1), No. (%) <sup>b</sup>	26 (19)	71 (25)	43 (24)	161 (26)	0.38
Functional impairment (baseline POPC score >1), No. (%) <sup>b</sup>	35 (25)	94 (34)	50 (28)	183 (29)	0.37
PRISM III-12 score, median (IQR)	6 (3–11)	9 (5–13)	8 (4–13)	9 (5–15)	<0.001
Percent risk of mortality based on PRISM III-12 score, median (IQR)	2.9 (1.0–7.7)	5.9 (1.7–15.0)	3.8 (1.7–11.7)	5.8 (1.7–20.8)	<0.001
Primary diagnosis, No. (%)					<0.001
Pneumonia	49 (36)	99 (35)	58 (33)	227 (36)	
Bronchiolitis	23 (17)	54 (19)	34 (19)	117 (19)	
Acute respiratory failure related to sepsis	13 (9)	40 (14)	18 (10)	141 (22)	
Asthma or reactive airway disease	26 (19)	29 (10)	28 (16)	37 (6)	
Aspiration pneumonia	9 (7)	19 (7)	14 (8)	37 (6)	
Other <sup>c</sup>	18 (13)	39 (14)	26 (15)	69 (11)	
PARDS based on worst OI or OSI on Days 0 to 1, No. (%) <sup>d</sup>					<0.001
At risk (OI <4.0 or OSI <5.0)	24 (17)	21 (8)	26 (15)	117 (19)	
Mild (OI 4.0–7.9 or OSI 5.0–7.4)	36 (26)	57 (20)	44 (25)	127 (20)	
Moderate (OI 8.0–15.9 or OSI 7.5–12.2)	40 (29)	89 (32)	55 (31)	174 (28)	
Severe (OI 16.0 or OSI 12.3)	38 (28)	113 (40)	53 (30)	210 (33)	
Any past medical history, No. (%)					
Prematurity (<36 weeks post-menstrual age)	19 (14)	47 (17)	27 (15)	82 (13)	0.29
Asthma (prescribed bronchodilators or steroids)	34 (25)	53 (19)	43 (24)	80 (13)	<0.001
Seizure disorder (prescribed anticonvulsants)	7 (5)	26 (9)	11 (6)	68 (11)	0.03
Cancer (current or past diagnosis)	13 (9)	26 (9)	10 (6)	60 (10)	0.02
Trisomy 21	3 (2)	10 (4)	7 (4)	13 (2)	0.27
Number of organ dysfunctions on Days 0 to 1, median (IQR) <sup>e</sup>	2 (1–2)	2 (2–3)	2 (1–3)	2 (1–3)	<0.001

Abbreviations: DEX, dexmedetomidine; DEXe, DEX used as a periextubation agent; DEXp, DEX used as a primary agent; DEXs, DEX used as a secondary agent; IQR, interquartile range; OI, oxygenation index; OSI, oxygen saturation index; PARDS, pediatric acute respiratory distress syndrome; PCPC, Pediatric Cerebral Performance Category; POPC, Pediatric Overall Performance Category; PICU, pediatric intensive care unit; PRISM III-12, Pediatric Risk of Mortality score from first 12 hours in the PICU.

<sup>a</sup> *P* values for the comparison between groups were calculated using linear, logistic, multinomial logistic, and cumulative logit regression for log-transformed continuous, binary, nominal, and ordinal variables, respectively. All regression analyses except for primary diagnosis accounted for PICU as a cluster variable using generalized estimating equations.

<sup>b</sup> PCPC and POPC scores range from 1 to 6, with higher categories indicating greater impairment.

<sup>c</sup> Other primary diagnoses include pulmonary edema, thoracic trauma, pulmonary hemorrhage, laryngotracheobronchitis, acute respiratory failure after bone marrow transplantation, acute chest syndrome/sickle cell disease, pertussis, pneumothorax (nontrauma), acute exacerbation lung disease (cystic fibrosis or bronchopulmonary dysplasia), acute respiratory failure related to multiple blood transfusions, pulmonary hypertension (not primary), and other.

<sup>d</sup> Oxygenation index was calculated as  $(\text{FIO}_2 \times \text{mean airway pressure}) / (\text{PaO}_2 \times 100)$ . When an arterial blood gas measurement was not available,  $\text{SpO}_2$  was used to estimate  $\text{PaO}_2$  in order to calculate OSI  $(\text{FIO}_2 \times \text{mean airway pressure}) / \text{SpO}_2 \times 100$ . Lower scores reflect better oxygenation.

<sup>e</sup> All patients had respiratory dysfunction. Cardiovascular dysfunction based on vasoactive medication use (single or multiple), Neurologic dysfunction based on worst level of consciousness (stupor or coma) or pupillary response (one or both pupils non-reactive), Hematologic dysfunction based on platelet threshold ( $<80 \text{ K}/\mu\text{L}$ ), Renal dysfunction based on age-specific creatinine thresholds. Hepatic dysfunction based on age- and gender-specific ALT thresholds or total bilirubin thresholds.

**Table 2**

Sedation Profiles of Usual Care Patients in Primary DEX Usage Group By Day

Variables	Day First Received DEXp (N=138)	1 Day Later (N=138)	2 Days Later (N=137)
Opioid dose, median (IQR), mg/kg <sup>a</sup>	1.5 (0.4–2.9)	2.4 (0.7–3.8)	1.9 (0.5–3.6)
Benzodiazepine dose, median (IQR), mg/kg <sup>b</sup>	1.0 (0.4–2.3)	1.8 (0.5–2.9)	1.5 (0.4–3.3)
Secondary sedatives, No. (%)			
Propofol	8 (6)	2 (1)	3 (2)
Barbiturates	1 (<1)	3 (2)	8 (6)
Ketamine	29 (21)	17 (12)	18 (13)
Clonidine	1 (<1)	2 (1)	3 (2)
Methadone	3 (2)	3 (2)	4 (3)
Chloral hydrate	7 (5)	12 (9)	13 (9)
No. of different sedative classes received, median (IQR) <sup>c</sup>	3 (3–3)	3 (3–3)	3 (3–3)
Modal pain score, No. (%)			
0–3	119 (86)	123 (89)	119 (87)
4	2 (1)	1 (<1)	1 (<1)
N/A patient chemically paralyzed entire day	16 (12)	12 (9)	14 (10)
Not assessed	1 (<1)	2 (1)	3 (2)
Modal SBS score, No. (%)			
–3/–2	27 (20)	26 (19)	22 (16)
–1/0	61 (44)	82 (59)	86 (63)
+1/+2	12 (9)	10 (7)	9 (7)
N/A patient chemically paralyzed entire day	16 (12)	12 (9)	14 (10)
N/A not intubated	0	1 (<1)	1 (<1)
Not assessed	22 (16)	7 (5)	5 (4)

Abbreviations: DEX, dexmedetomidine; DEXp, DEX used as a primary agent; IQR, interquartile range; SBS, State Behavioral Scale.

<sup>a</sup>Opioid doses were calculated as morphine equivalents in mg/kg. Opioids (morphine equivalents) include morphine (1), fentanyl (0.015), methadone (0.3), enteral codeine (20), hydromorphone (0.15), enteral oxycodone (3), and remifentanyl (0.015).

<sup>b</sup>Benzodiazepine doses were calculated as midazolam equivalents in mg/kg. Benzodiazepines (midazolam equivalents) include midazolam (1), clonazepam (0.2), lorazepam (0.3), and diazepam (2).

<sup>c</sup>Different sedative classes include opioids, benzodiazepines,  $\alpha$ 2-adrenergic agonists, ketamine, chloral hydrate, propofol, and barbiturates.



**Table 3**

Sedation Profiles of Usual Care Patients by DEX Usage Group

Variables	DEXp (N=138)	DEXs (N=280)	DEXe (N=178)	DEX Never Prescribed (N=628)	P Value Across All Groups <sup>d</sup>	P Value DEXp vs All Other Patients <sup>d</sup>	P Value DEXs vs DEXe or Never Prescribed <sup>d</sup>	P Value DEXe vs Never Prescribed <sup>d</sup>
<b>Sedatives administered</b>								
Opioid exposure, median (IQR) <sup>b</sup>								
Cumulative dose, mg/kg	12.4 (4.9–38.6)	53.2 (23.3–111.4)	12.8 (4.8–39.6)	13.3 (3.9–36.6)	<0.001	0.003	<0.001	0.24
No. of exposure days	7.5 (4–18)	19 (12–29)	7 (4–15)	7 (4–18)	<0.001	0.34	<0.001	0.33
<b>Benzodiazepines exposure, median (IQR)<sup>c</sup></b>								
Cumulative dose, mg/kg	13.1 (4.1–33.7)	42.3 (17.7–86.2)	9.7 (3.7–27.3)	9.3 (2.8–26.3)	<0.001	0.17	<0.001	0.16
<b>Secondary sedatives, No. (%)</b>								
Propofol	25 (18)	51 (18)	15 (8)	46 (7)	<0.001	<0.001	<0.001	0.07
Barbiturates	25 (18)	104 (37)	29 (16)	68 (11)	<0.001	0.70	<0.001	0.01
Ketamine	53 (38)	116 (41)	51 (29)	148 (24)	<0.001	0.009	<0.001	<0.001
Clonidine	22 (16)	82 (29)	23 (13)	36 (6)	<0.001	0.25	<0.001	0.07
Methadone	49 (36)	135 (48)	38 (21)	146 (23)	<0.001	0.08	<0.001	0.98
Chloral hydrate	29 (21)	61 (22)	28 (16)	63 (10)	<0.001	0.97	0.01	0.07
No. of different sedative classes received, Median (IQR) <sup>d</sup>	4 (3–5)	4 (3–5)	4 (3–4)	2 (2–3)	<0.001	<0.001	<0.001	<0.001
Antideliirium medications, No. (%)	4 (3)	10 (4)	7 (4)	5 (<1)	0.005	0.50	<0.001	0.007
<b>Measures of wakefulness, pain, and agitation, median (IQR)</b>								
Study days awake and calm (modal SBS score –1 or 0), %	75 (56–100)	71 (50–88)	68 (40–100)	75 (50–100)	0.002	0.049	0.82	0.02
Days to first awake/calm state	2 (1–3)	2 (1–5)	2 (1–3)	2 (1–5)	<0.001	0.03	0.89	<0.001
Study days with an episode of pain (highest pain score 4), %	29 (7–55)	30 (16–50)	25 (0–50)	17 (0–40)	<0.001	0.02	0.001	<0.001
Study days with an episode of agitation (highest SBS score +1 or +2), %	50 (33–73)	52 (29–75)	50 (20–67)	25 (0–51)	<0.001	<0.001	<0.001	<0.001
<b>Sedation-related adverse events</b>								
Inadequate pain management, No. (%)	22 (16)	61 (22)	27 (15)	64 (10)	<0.001	0.22	<0.001	0.02

Variables	DEXp (N=138)	DEXs (N=280)	DEXe (N=178)	DEX Never Prescribed (N=628)	P Value Across All Groups <sup>a</sup>	P Value DEXp vs All Other Patients <sup>a</sup>	P Value DEXs vs DEXe or Never Prescribed <sup>a</sup>	P Value DEXe vs Never Prescribed <sup>a</sup>
Inadequate sedation management, No. (%)	33 (24)	87 (31)	34 (19)	92 (15)	<0.001	0.03	<0.001	0.003
Clinically significant iatrogenic withdrawal, No. (%)	14 (10)	41 (15)	14 (8)	45 (7)	<0.001	0.64	<0.001	0.21
Extubation failure (reintubation within 24 h), No. (%)	13 (9)	37 (13)	17 (10)	37 (6)	0.02	0.72	0.01	0.15
Unplanned endotracheal tube extubation, No. of events/100 ventilator days	1.07	0.56	0.45	0.33	0.28	-	-	-
Unplanned removal of any invasive tube, No. of events/100 device days	0.12	0.11	0.12	0.13	0.86	-	-	-

Abbreviations: DEX, dexmedetomidine; DEXe, DEX as a perextubation agent; DEXp, DEX as a primary agent; DEXs, DEX as a secondary agent; IQR, interquartile range; SBS, State Behavioral Scale.

<sup>a</sup> *P*-values for the comparison between groups were calculated using linear, proportional hazards, logistic, and Poisson regression for log-transformed continuous variables (except percentage of study days variables), time-to-event variables, binary variables, and rate variables, respectively. All regression analyses accounted for PICU as a cluster variable using generalized estimating equations.

<sup>b</sup> Opioid doses were calculated as morphine equivalents in mg/kg. Opioids (morphine equivalents) include morphine (1), fentanyl (0.015), methadone (0.3), enteral codeine (20), hydromorphone (0.15), enteral oxycodone (3), and remifentanyl (0.015).

<sup>c</sup> Benzodiazepine doses were calculated as midazolam equivalents in mg/kg. Benzodiazepines (midazolam equivalents) include midazolam (1), clonazepam (0.2), lorazepam (0.3), and diazepam (2).

<sup>d</sup> Different sedative classes include opioids, benzodiazepines,  $\alpha_2$ -adrenergic agonists, ketamine, chloral hydrate, propofol, and barbiturates.

Table 4

## Clinical Profiles of Usual Care Patients by DEX Usage Group

Variables	DEXp (N=138)	DEXs (N=280)	DEXe (N=178)	DEX Never Prescribed (N=628)	P Value Across All Groups <sup>d</sup>	P Value DEXp vs All Other Patients <sup>d</sup>	P Value DEXs vs DEXe or Never Prescribed <sup>e</sup>	P Value DEXe vs Never Prescribed <sup>d</sup>
Duration of mechanical ventilation, median (IQR), <sup>d</sup> <sup>b</sup>	5.0 (3.1–8.6)	9.9 (6.4–16.5)	4.4 (2.5–7.0)	6.0 (3.5–12.1)	<0.001	0.005	<0.001	<0.001
Adjusted for age group, PRISM III-12 score, POPC score >1, and worst PARDS on days 0 to 1					<0.001	0.01	<0.001	<0.001
Time to recovery from acute respiratory failure, median (IQR), <sup>d</sup> <sup>c</sup>	1.7 (1.0–4.0)	4.7 (1.7–9.0)	1.9 (1.0–4.1)	2.3 (1.0–4.6)	<0.001	0.07	<0.001	0.13
Duration of weaning from mechanical ventilation, median (IQR), <sup>d</sup> <sup>d</sup>	3.0 (1.2–5.3)	4.1 (2.0–7.0)	2.1 (0.7–3.4)	2.3 (1.1–4.5)	<0.001	0.74	<0.001	0.006
Neurological testing, No. (%)	20 (14)	66 (24)	21 (12)	123 (20)	<0.001	0.18	0.06	<0.001
Length of stay, median (IQR), <sup>d</sup> <sup>e</sup>								
PICU	8.6 (5.5–14.1)	14.6 (9.4–22.7)	7.1 (4.5–12.4)	8.7 (5.1–15.3)	<0.001	0.16	<0.001	0.002
Hospital	13 (8–24)	23 (14–37)	12 (7–21)	15 (9–27)	<0.001	0.09	<0.001	<0.001
In-hospital mortality, No. (%)								
At 28 d	2 (1)	12 (4)	1 (<1)	48 (8)	0.002	0.03	0.33	0.007
At 90 d	4 (3)	21 (8)	1 (<1)	62 (10)	<0.001	0.02	0.90	0.003

Abbreviations: DEX, dexmedetomidine; DEXe, DEX as a pentextubation agent; DEXp, DEX as a primary agent; DEXs, DEX as a secondary agent; IQR, interquartile range; PARDS, pediatric acute respiratory distress syndrome; PICU, pediatric intensive care unit; POPC, Pediatric Overall Performance Category; PICU, pediatric intensive care unit; PRISM III-12, Pediatric Risk of Mortality score from first 12 hours in the PICU.

<sup>a</sup> P-values for the comparison between groups were calculated using proportional hazards and logistic regression accounting for PICU as a cluster variable using generalized estimating equations for time-to-event and binary variables, respectively.

<sup>b</sup> Patients were assigned 28 days of mechanical ventilation if they remained intubated or were transferred or died prior to day 28 without remaining extubated for 24 hours, therefore making the outcome equivalent to ventilator-free days.

<sup>c</sup> Time to recovery from acute respiratory failure was defined as the duration from day 0 start (endotracheal intubation, initiation of assisted breathing for chronically trached patients, or PICU admission for patients intubated at an outside hospital) to the time that the patient first met criteria to be tested for extubation readiness (spontaneously breathing and oxygenation index > 6). Excludes nonsurvivors who did not meet criteria prior to death. For survivors who never met criteria, the duration of recovery was set equal to the duration of mechanical ventilation if the patient was successfully extubated or to 28 days if the patient was still intubated on day 28 or transferred to another PICU still intubated. Calculated for 135 DEXp, 267 DEXs, 177 DEXe, and 577 DEX never prescribed patients.

<sup>p</sup>Duration of weaning from mechanical ventilation was defined as the duration from the time that the patient first met criteria to be tested for extubation readiness to successful endotracheal extubation (remained extubated for >24 hours) or successful removal of assisted breathing for tracheated patients. Excludes nonsurvivors who were not extubated for >24 hours prior to death. Also excludes survivors who never met criteria or were still intubated on day 28. Calculated for 111 DEXp, 212 DEXs, 159 DEXe, and 478 DEX never prescribed.

<sup>g</sup>PICU and hospital length of stay exclude all nonsurvivors. Patients still in the PICU or hospital on day 90 were censored at day 90.

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**Table 5**  
Sedation Profiles of Usual Care Patients in Secondary DEX Usage Group By Day

Variables	2 Days Earlier (N=244)	1 Day Earlier (N=257)	Day First Received DEXs (N=280)	1 Day Later (N=278)	2 Days Later (N=276)
Opioid dose, median (IQR), mg/kg <sup>a</sup>	3.2 (1.5–6.0)	3.9 (2.4–6.4)	4.3 (2.0–6.9)	4.2 (1.6–6.7)	3.8 (1.3–6.5)
Benzodiazepine dose, median (IQR), mg/kg <sup>b</sup>	2.5 (1.1–5.2)	3.2 (1.5–6.1)	3.2 (1.3–6.7)	3.0 (1.4–6.3)	2.8 (1.0–5.8)
Secondary sedatives, No. (%)					
Propofol	6 (2)	7 (3)	8 (3)	3 (1)	6 (2)
Barbiturates	27 (11)	42 (16)	50 (18)	50 (18)	49 (18)
Ketamine	43 (18)	45 (18)	46 (16)	26 (9)	26 (9)
Clonidine	10 (4)	12 (5)	17 (6)	21 (8)	24 (9)
Methadone	24 (10)	29 (11)	35 (13)	46 (17)	52 (19)
Chloral hydrate	14 (6)	23 (9)	31 (11)	32 (12)	29 (11)
No. of different sedative classes received, median (IQR) <sup>c</sup>	2 (2–3)	2 (2–3)	3 (3–4)	3 (3–4)	3 (3–4)
Modal pain score, No. (%)					
0–3	187 (77)	207 (81)	244 (87)	236 (85)	236 (86)
4	5 (2)	6 (2)	6 (2)	4 (1)	5 (2)
N/A patient chemically paralyzed entire day	46 (19)	41 (16)	22 (8)	30 (11)	32 (12)
Not assessed	6 (2)	3 (1)	7 (3)	7 (3)	2 (<1)
Modal SBS score, No. (%)					
–3/–2	45 (18)	43 (17)	45 (16)	35 (13)	30 (11)
–1/0	110 (45)	126 (49)	152 (54)	162 (58)	151 (55)
+1/+2	19 (8)	32 (12)	50 (18)	40 (14)	43 (16)
N/A patient chemically paralyzed entire day	46 (19)	41 (16)	22 (8)	30 (11)	32 (12)
N/A not intubated	4 (2)	5 (2)	2 (<1)	4 (1)	13 (5)
Not assessed	20 (8)	10 (4)	8 (3)	6 (2)	6 (2)

Abbreviations: DEX, dexmedetomidine; DEXs, DEX used as a secondary agent; IQR, interquartile range; SBS, State Behavioral Scale.

<sup>a</sup>Opioid doses were calculated as morphine equivalents in mg/kg. Opioids (morphine equivalents) include morphine (1), fentanyl (0.015), methadone (0.3), enteral codeine (20), hydromorphone (0.15), enteral oxycodone (3), and remifentanyl (0.015).

<sup>b</sup>Benzodiazepine doses were calculated as midazolam equivalents in mg/kg. Benzodiazepines (midazolam equivalents) include midazolam (1), clonazepam (0.2), lorazepam (0.3), and diazepam (2).

Different sedative classes include opioids, benzodiazepines,  $\alpha$ 2-adrenergic agonists, ketamine, chloral hydrate, propofol, and barbiturates.

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