Patient-Specific Factors Associated with Dexmedetomidine Dose Requirements in Critically Ill Children

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Abstract

The objective of this study was to evaluate patient-specific factors associated with dexmedetomidine dose requirements during continuous infusion. A retrospective cross-sectional analysis of electronic health record-derived data spanning 10 years for patients admitted with a primary respiratory diagnosis at a quaternary children's hospital and who received a dexmedetomidine continuous infusion ($n = 346$ patients) was conducted. Penalized regression was used to select demographic, clinical, and medication characteristics associated with a median daily dexmedetomidine dose. Identified characteristics were included in multivariable linear regression models and sensitivity analyses. Critically ill children had a median hourly dexmedetomidine dose of 0.5 mcg/kg/h (range: 0.1–1.8), median daily dose of 6.7 mcg/kg/d (range: 0.9–38.4), and median infusion duration of 1.6 days (range: 0.25–5.0). Of 26 variables tested, 15 were selected in the final model with days of dexmedetomidine infusion (β: 1.9; 95% confidence interval [CI]: 1.6, 2.3), median daily morphine milligram equivalents dosing (mg/kg/d) (β: 0.3; 95% CI: 0.1, 0.5), median daily ketamine dosing (mg/kg/d) (β: 0.2; 95% CI: 0.1, 0.3), male sex (β: −1.1; 95% CI: −2.0, −0.2), and non-Black reported race (β: −1.2; 95% CI: −2.3, −0.08) significantly associated with median daily dexmedetomidine dose. Approximately 56% of dose variability was explained by the model. Readily obtainable information such as demographics, concomitant medications, and duration of infusion accounts for over half the variability in dexmedetomidine dosing. Identified factors, as well as additional environmental and genetic factors, warrant investigation in future studies to inform precision dosing strategies.

Keywords
- sedation
- precision medicine
- dexmedetomidine

Introduction

Sedation is essential to promote safety and comfort in the care of critically ill children. Sedation management is commonly goal directed with the use of sedation scale scores and clinician intuition to guide dosing.[1] Medication choice and dose titration are widely variable across pediatric intensive care units (ICUs) worldwide.[2,3] Suboptimal sedation,

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including under- and oversedation, can result in negative sequelae such as increased anxiety, adverse events (e.g., unplanned extubation), drug tolerance and withdrawal, the development of delirium, increased costs, and negative long-term outcomes.[4–7] A recent systematic review found that critically ill children suffer from under- and oversedation for 11 and 32% of their ICU admission, respectively.[4] This highlights the challenges and complexities of sedation, heterogeneity of patient responses, and the opportunity to apply precision medicine to improve patient care through the identification of underlying factors that meaningfully contribute to dosing and, thus, response.

Dexmedetomidine is a highly selective α_2-agonist which confers favorable lighter levels of sedation with minimal respiratory effects.[8–10] It is suggested as a first-line sedative,[11] and its use has been demonstrated to decrease delirium prevalence, shorten time to extubation, and shorten the duration of mechanical ventilation compared with other sedatives.[12–14] Despite only being Food and Drug Administration approved in the adult population for short-term use with a maximum infusion rate of 0.7 mcg/kg/h,[10] dexmedetomidine is frequently used in pediatrics as a prolonged infusion and has been shown to provide safe and efficacious sedation.[15–20] However, dosing is highly variable, often exceeding two times the maximum approved infusion rate, and difficult to predict.[15–20] Drivers of dose variability have not been comprehensively evaluated to reflect the intricacies in the clinical care of critically ill children.[9,21] In addition, dexmedetomidine can be expensive compared with other sedatives and efficient titration to effective doses could mitigate excessive medication costs.

Given the opportunities to improve patient outcomes, large interpatient variability, and associated costs, we sought to comprehensively identify patient-specific factors associated with dexmedetomidine dose requirements in a cohort of critically ill children. We also aimed to quantify the variability in dose requirements and to identify the proportion of variability explained by factors identified in a large collection of real-world data.

Materials and Methods

Study Design and Participants

We conducted a retrospective cross-sectional analysis of 10 years (January 1, 2009–December 31, 2018) of electronic health record (EHR)-derived data from patients admitted to UPMC Children's Hospital of Pittsburgh (Pittsburgh, PA, United States). To identify a cohort that received sustained exposure to dexmedetomidine for reasons other than agitation in the setting of primary neurological injury, patients were included if they received at least 6 hours of a dexmedetomidine continuous infusion and had a primary admission diagnosis of respiratory failure, distress, or insufficiency according to International Classification of Diseases, 9th Revision (ICD-9) and 10th Revision (ICD-10) codes. Patients with missing or unknown demographics as well as those with a primary admission diagnosis of respiratory insufficiency following trauma were excluded. A full list of ICD-9 and ICD-10 codes included can be found in ►**Supplemental Table S1**, available in the online version. Chart reviews were performed to verify the accuracy of data curation as appropriate (e.g., outliers). The University of Pittsburgh Institutional Review Board approved the study. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies.[22]

Outcome

The primary outcome was median daily dexmedetomidine dose (mcg/kg/d) during continuous administration, including continuous infusions plus any concomitant boluses, for up to 120 hours of infusion. Daily dose was chosen to capture dynamic dose titrations during infusions. Though average daily dose could better differentiate patient dose trajectories over time, median daily dose was selected to account for nonnormal distributions of cumulative doses over consecutive days and for its robustness to outliers. To meet the assumption of independence, only the first dexmedetomidine infusion for each patient was considered. The 120-hour endpoint was selected to encompass dose titration and focus on the initial indication for sedation.

Patient and Clinical Factors

Patient and clinical factors were comprehensively evaluated as independent variables. Factors included demographic and baseline admission information: age, sex, and reported race. The presence of a complex chronic condition (CCC) was obtained from the Pediatric Health Information Systems database.[23,24] Concomitant dosing of medications that have pharmacodynamic interactions with dexmedetomidine included opioid dosing (fentanyl, morphine, methadone, and hydromorphone in morphine milligram equivalents as calculated per LexiComp Pediatrics[25]), benzodiazepines (lorazepam, midazolam, and diazepam), and other sedatives (ketamine, propofol, clonidine, pentobarbital, etomidate, and chloral hydrate). Concomitant receipt of neuromuscular blockers (cisatracurium, vecuronium, and rocuronium) was evaluated (succinylcholine and atracurium were not used at our ICU during the study period).[26] Concomitant receipt of vasoactive medications (dobutamine, dopamine, epinephrine, milrinone, norepinephrine, phenylephrine, and vasopressin) was assessed as an indicator of illness severity. The number of concomitant medication classes was also determined using these medication data. Electronic pediatric logistic organ dysfunction-2 (e-PELOD-2) score was computed as a measure of the severity of organ dysfunction.[27,28] Mechanical ventilation during hospitalization was determined via documented ventilator type within the EHR, and ventilator settings (fraction of inspired oxygen [FiO_2] and mean airway pressure) were evaluated as indicators of respiratory illness severity. Extracorporeal membrane oxygenation (ECMO) during admission, minimum albumin level during infusion or hospitalization, and maximum alanine aminotransferase (ALT) level during hospitalization were assessed as factors or surrogates for altered dexmedetomidine pharmacokinetics.[9,10,29] Maximum creatinine during

hospitalization was included as a negative control since kidney function is not anticipated to affect dexmedetomidine pharmacokinetics.[9,10] Year of hospitalization was investigated to account for the potential effect of time on dexmedetomidine use and changes in sedation practices.[1,30] Additional infusion characteristics included length of therapy, percent of infusion at night (defined as after 7 pm and before 9 am), and proportion of infusion time occurring during the weekend.

Statistical Analysis

A sample size analysis was conducted using the four criteria and methods outlined by Riley et al.[31] Using combinations of an estimated adjusted R^2 ranging from 0.45 to 0.55 and 20 to 30 predictor parameters, a minimum sample size of 254 to 420 participants was determined. To mitigate collinearity prior to model development, only one variable was selected for evaluation in the model when a significant correlation ($p < 0.05$) was detected by Spearman's correlation. Descriptive statistics of median (interquartile range [IQR]) and frequencies with percentages were conducted for continuous and categorical variables, respectively.

Missing data were imputed using multivariate imputation by chained equations.[32] Data were assumed to be missing at random and potential predictors of missing variables were included for imputation.[33,34] Convergence and observed versus imputed value plots were visually checked for quality control.[32]

A penalized linear regression method, least absolute shrinkage and selection operator (LASSO), was used for variable selection.[35–37] The imputed datasets were stacked for subsequent LASSO variable selection using standardized variables and 1-se lambda penalty.[35,38] Variables with nonzero coefficients in at least five of ten iterations were included in a pooled multivariable linear regression as a "relaxed LASSO" model.[37] Variables were also scaled to obtain standardized coefficients to estimate variable importance in the model. A *p*-value less than 0.05 was considered statistically significant. Pooled R^2_{adj} value was estimated. Regression assumptions were verified and high leverage/influential data points identified. Additional details regarding the statistical analysis can be found in the Supplemental Methods.

To confirm robustness of the final model, four sensitivity analyses were conducted: (1) omission of data points identified both as high leverage and influential, (2) with more strict inclusion criteria of age less than 18 years and patients who received invasive mechanical ventilation during hospitalization, and (3) a complete case analysis,[33] (4) with the exclusion of patients who developed bradycardia during infusion. Bradycardia was defined as heart rate less than the 1st centile for an age as per Fleming et al,[18,39] and development of bradycardia was determined by presence during infusion, but not within 72 hours prior to the infusion. This sensitivity analysis was to confirm that results are similar among this potential covariate given lack of independence of this pharmacodynamic endpoint with dosing. Wilcoxon rank-sum test, chi-square test of independence, and Fisher's exact test were used to compare the main analysis patient population to patient populations of the sensitivity analyses. Analyses were performed in R (v 4.0.5) (R Foundation for Statistical Computing, Vienna, Austria).[40]

Results

Patient and Clinical Characteristics

We identified 346 patients who met inclusion criteria over the 10-year study timeframe. Patient and clinical characteristics are summarized in ►**Table 1**. There was a general trend of

Table 1 Patient and clinical characteristics

Patient and clinical characteristics ($n = 346$)	
Median hourly dexmedetomidine dose (mcg/kg/h) (median [IQR])	0.5 [0.3–0.7]
Median daily dexmedetomidine dose (mcg/kg/d) (median [IQR])	6.7 [4.1–10.9]
Length of therapy (days) (median [IQR])	1.6 [0.8–2.9]
Length of hospitalization (days) (median [IQR])	14 [8–29]
Age (mo) (median [IQR])	18.0 [8.0–58.8]
Male, *n* (%)	202 (58.4%)
Reported race, *n* (%)	
White	237 (68.5%)
Black	70 (20.2%)
Other	17 (4.9%)
Unknown	22 (6.4%)
Complex chronic condition[a], *n* (%)	211 (61.5%)
Technology dependent	121 (35.3%)
Gastrointestinal	99 (28.9%)
Respiratory	85 (24.5%)
Cardiovascular	73 (21.3%)
Neurologic and neuromuscular	66 (19.2%)
Congenital or genetic	55 (16.0%)
Premature and neonatal	33 (9.6%)
Metabolic	28 (8.2%)
Renal and Urological	24 (7.0%)
Hematological or immunological	16 (4.7%)
Transplant	11 (3.2%)
Malignancy	7 (2.0%)
Received invasive mechanical ventilation	338 (97.7%)
Received ECMO	6 (1.7%)
e-PELOD-2 (median [IQR])	11.5 [10–14]
Number of concomitant medication classes (median [IQR])	3 [2–4]

Abbreviations: ECMO, extracorporeal membrane oxygenation; e-PELOD-2, electronic pediatric logistic organ dysfunction-2; IQR, interquartile range.

[a]Based on participants with data available ($n = 343$); patients can have multiple CCC flags.

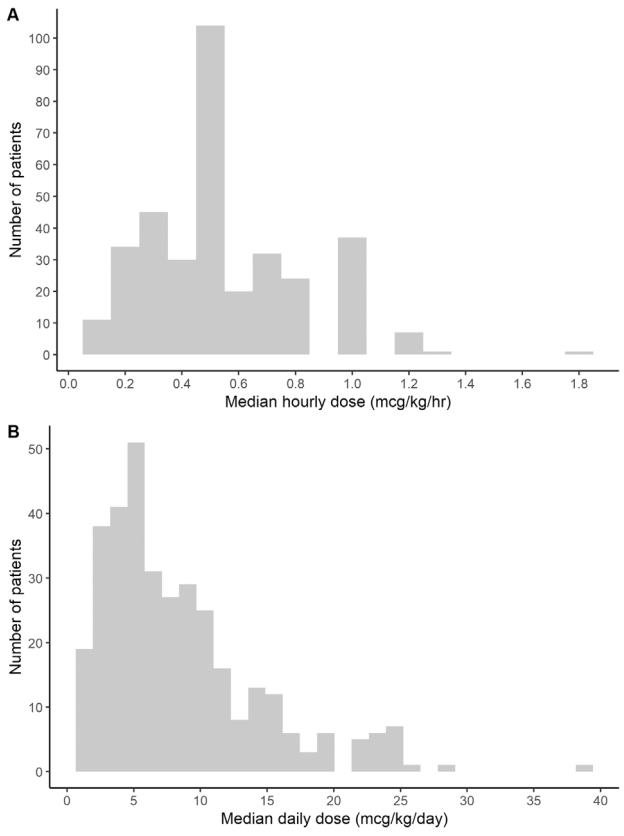

Fig. 1 Histogram of (**A**) median hourly dexmedetomidine dose requirements (mcg/kg/h) and (**B**) median daily dexmedetomidine dose requirements (mcg/kg/d) for patients with a primary admission diagnosis of respiratory failure, distress, or insufficiency ($n = 346$).

more patients receiving dexmedetomidine from 2014 to 2018 compared with years prior (data not shown). The median hospital length of stay was 14 days (IQR: 8–29, range: 1–260). Median age was 18 months (IQR: 8.0–58.8, range: 1.0–281.0). Most patients were male (58.4%). 338 of 346 patients were on invasive mechanical ventilation, while eight of 346 patients were on noninvasive support. Continuous infusion of dexmedetomidine was for a median 1.6 days (IQR: 0.8–2.9, range: 0.25–5.0). Median hourly dexmedetomidine dose was 0.5 mcg/kg/h (IQR: 0.3–0.7, range: 0.1–1.8) (►**Fig. 1A**). Because many patients received less than 24 hours of dexmedetomidine, median daily doses ranged from 0.9 to 38.4 mcg/kg/d (median: 6.8 mcg/kg/d; IQR: 4.1–10.9) (►**Fig. 1B**).

Dataset Comprehensiveness

Complete data were available for the primary outcome variable, and 54.1% (187/346) of patients had complete information for all variables. Independent variables of interest with missing data (percentage of missingness) were ALT (40.5%; 140/346), albumin (23.1%; 80/346), mean airway pressure (2.6%; 9/346), creatinine (2.3%; 8/346), and CCC flag (0.9%; 3/346). As mean airway pressure and FiO_2 were significantly correlated ($\rho = 0.34$, $p < 0.001$), mean airway pressure was included in the main model and FiO_2 was only retained for the imputation model. No patients received concomitant pentobarbital or etomidate during dexmedetomidine infusion which precluded evaluation of these variables. In total, 5, 11, and 19 patients received concomitant diazepam, propofol, and clonidine, respectively, and 6 patients received ECMO during hospitalization. These variables were included during multiple imputations and tested for variable selection.

Dexmedetomidine Dose Requirements Modeling

Out of the 26 variables tested, 15 variables were selected via LASSO regression following multiple imputation procedures (►**Supplementary Table S2**, available in the online version) and input into the relaxed LASSO model (►**Table 2**). Factors significantly associated with increased median daily dexmedetomidine dose requirements were days of dexmedetomidine infusion (β: 1.9; 95% CI: 1.6, 2.3), median daily morphine milligram equivalents dosing (mg/kg/d) (β: 0.3; 95% CI: 0.1, 0.5), and median daily ketamine dosing (mg/kg/d) (β: 0.2; 95% CI: 0.1, 0.3). Factors significantly associated with decreased median daily dexmedetomidine dose requirements were male sex (β: −1.1; 95% CI: −2.0, −0.2) and non-Black reported race (β: −1.2; 95% CI: −2.3, −0.08) (►**Supplementary Fig. S1**, available in the online version). Based on the standardized regression coefficients, days of dexmedetomidine infusion (β: 0.5; 95% CI: 0.4, 0.6), receipt of mechanical ventilation (β: 0.2; 95% CI: −0.3, 0.7), opioid dosing (β: 0.2; 95% CI: 0.07, 0.3), reported race (β: −0.2; 95% CI: −0.4, −0.01), and sex (β: −0.2; 95% CI: −0.3, −0.04) were estimated to have the greatest importance in the model. Approximately, 56% (95% CI: 49–63%) of variability within dexmedetomidine daily dose was explained by variables included in the model. Similar results were found with average daily dexmedetomidine dose as the outcome variable (►**Supplementary Tables S3** and **S4, available in the online version).**

For multiple imputation quality control, overlapping chains without trends showed healthy convergence (►**Supplementary Fig. S2A**, available in the online version).[32] All imputed values were within the range of observed values (►**Supplementary Fig. S2B**, available in the online version). Linear regression assumptions were acceptable based on visual checks of residuals versus fitted, components plus residual, normal Q-Q, and scale-location plots (►**Supplementary Fig. S3**, available in the online version).

Sensitivity Analyses

Results from the sensitivity analyses are shown in ►**Table 3**. Patient population characteristics were not significantly different from the main analysis in each of the four sensitivity analyses with the exception "complete case," which had more patients with CCCs (71 vs. 62% in main analysis, $p < 0.05$) and higher median e-PELOD-2 scores (12 vs. 11.5 in main analysis, $p = 0.01$).

Overall, results were similar to the main analysis. For "high leverage/influential points removed" ($n = 343$), we found almost identical coefficient values and consistent significant associations with the addition of chloral hydrate dosing. For "age < 18 years and mechanically ventilated" ($n = 327$), selected variables were consistent except for

Table 2 Relaxed LASSO regression

Variable	β (95% CI)	Standardized β (95% CI)	*p*-Value[c]
Diazepam dosing[a]	−8.5 (−23.8, 6.8)	−0.04 (−0.1, 0.03)	0.273
Non-Black reported race	−1.2 (−2.3, −0.08)	−0.2 (−0.4, −0.01)	0.036
Male sex	−1.1 (−2.0, −0.2)	−0.2 (−0.3, −0.04)	0.015
Midazolam dosing[a]	−0.3 (−0.7, 0.09)	−0.06 (−0.1, 0.02)	0.124
% Infusion at night	−0.02 (−0.05, 0.01)	−0.05 (−0.1, 0.03)	0.205
Age (months)	−0.006 (−0.01, 0.001)	−0.06 (−0.1, 0.01)	0.102
Chloral hydrate dosing[a]	0.02 (−0.001, 0.04)	0.08 (−0.004, 0.2)	0.062
Year[b]	0.06 (−0.1, 0.2)	0.03 (−0.05, 0.1)	0.460
Ketamine dosing[a]	0.2 (0.1, 0.3)	0.1 (0.07, 0.2)	<0.001
MME dosing[a]	0.3 (0.1, 0.5)	0.2 (0.07, 0.3)	0.001
Receipt of NM blocker	0.6 (−0.4, 1.6)	0.1 (−0.06, 0.3)	0.215
Minimum albumin level (g/dL)	0.7 (−0.2, 1.5)	0.07 (−0.02, 0.1)	0.120
Mechanically ventilated	1.5 (−1.5, 4.4)	0.2 (−0.3, 0.7)	0.335
Lorazepam dosing[a]	1.8 (−1.9, 5.6)	0.04 (−0.04, 0.1)	0.329
Length of infusion (days)	1.9 (1.6, 2.3)	0.5 (0.4, 0.6)	<0.001

Abbreviations: CI, confidence interval; LASSO, least absolute shrinkage and selection operator; MME, morphine milligram equivalents; NM, neuromuscular.
Note: Pooled R^2_{adj} (95% CI) = 56% (49–63%).
[a]Median daily dosing (mg/kg/d).
[b]Year was adjusted such that zero is equal to 2009 and each year thereafter increased by one.
[c]*p*-Values are equivalent in both unstandardized and standardized relaxed LASSO regression analyses.

midazolam dosing, year, and receipt of vasoactive medications. Similar coefficients and statistical significance were retained in all variables except reported race. For "complete case" ($n = 187$), four variables were selected and all remained statistically significant. Finally, for "bradycardia developed during infusion excluded" ($n = 259$), similar variables were selected apart from lorazepam, clonidine, and propofol dosing, and the presence of at least one CCC. Coefficients were comparable for common variables. Reported race, opioid dosing, length of infusion (all the same as the main analysis), and receipt of a neuromuscular blocker were significant factors, but sex and ketamine dosing were no longer significant.

Discussion

Our findings demonstrate profound variability of dexmedetomidine dose requirements in a large cohort of critically ill children who had a primary admission diagnosis of respiratory failure, distress, or insufficiency over a 10-year timeframe. Length of dexmedetomidine therapy, concomitant dosing of opioids and ketamine, reported race, and sex were independently associated with dosing intensity. Altogether, the model was able to explain approximately 56% of variability within dosing requirements. To the best of our knowledge, this represents the largest and most comprehensive study to evaluate the combined effect of patient and clinical factors on dexmedetomidine dose requirements.

Our results are complementary to a smaller study by Tillman et al who highlight the high dosing variability of medications within sedative regimens for 130 mechanically ventilated critically ill children under 3 years of age.[41] Specifically, for patients who received dexmedetomidine, they found a mean (standard deviation) hourly dose of 0.59 (0.28) mcg/kg/h. Median hourly dexmedetomidine dose in our study was 0.5 mcg/kg/h (IQR: 0.3–0.7, range: 0.1–1.8). This range of dosing is also consistent with studies which have collectively reported doses ranging from 0.1 to 2.5 mcg/kg/h.[15–20]

Overall, a longer duration of infusion was significantly associated with increased dexmedetomidine dosing and this was estimated to be the most important factor in the model based on standardized coefficients. This finding may be reflective of tolerance. Time to development of tolerance to dexmedetomidine is ill defined,[19,42–44] and may be important as it has been linked to withdrawal upon discontinuation. Haenecour et al found withdrawal is more likely to occur after a cumulative dose of 107 mcg/kg in critically ill children, which corresponds to 1 mcg/kg/h for 4 days, though an infusion duration cutoff could not be determined.[19] Escalating doses of dexmedetomidine may also reflect emerging tolerance to other concomitantly administered sedatives.

Concomitant medications, encompassing both boluses and infusions, that have pharmacodynamic interactions and are used in a multimodal approach to achieve adequate analgesia/sedation were also evaluated. Dexmedetomidine was used predominantly in conjunction with other sedatives. We found that increased doses of opioids and ketamine were significantly associated with increased dexmedetomidine

Table 3 Sensitivity analyses

	High leverage/ influential points removed		Age < 18 y and mechanically ventilated		Complete case		Bradycardia developed during infusion excluded	
	(*n* = 343)		(*n* = 327)		(*n* = 187)		(*n* = 259)	
Variable	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
Diazepam dosing[a]	−8.7 (−43.0, 25.5)	0.616	−7.5 (−23.2, 8.1)	0.345			−17.0 (−34.8, 0.8)	0.061
Non-Black reported race	−1.2 (−2.3, −0.1)	0.029	−1.0 (−2.1, 0.2)	0.102			−1.3 (−2.4, −0.07)	0.038
Male sex	−1.0 (−1.9, -0.2)	0.019	−1.0 (−1.9, −0.1)	0.03			−0.8 (−1.7, 0.2)	0.101
Midazolam dosing[a]	−0.4 (−0.9, −0.02)	0.042					−0.3 (−0.7, 0.09)	0.126
% Infusion at night	−0.02 (−0.05, 0.01)	0.275	−0.02 (−0.05, 0.01)	0.182			−0.01 (−0.04, 0.02)	0.406
Age (months)	−0.005 (−0.01, 0.002)	0.158	−0.005 (−0.01, 0.003)	0.205			−0.004 (−0.01, 0.003)	0.217
Chloral hydrate dosing[a]	0.02 (0, 0.04)	0.048	0.02 (−0.003, 0.04)	0.094			0.008 (−0.02, 0.03)	0.498
Year[b]	0.06 (−0.1, 0.2)	0.464					0.1 (−0.07, 0.3)	0.255
Ketamine dosing[a]	0.2 (0.1, 0.3)	<0.001	0.2 (0.07, 0.3)	0.001	0.3 (0.1, 0.5)	<0.001	0.1 (−0.006, 0.2)	0.063
MME dosing[a]	0.3 (0.1, 0.5)	0.001	0.3 (0.1, 0.5)	0.001	0.3 (0.06, 0.6)	0.014	0.4 (0.2, 0.6)	<0.001
Receipt of NM blocker	0.7 (−0.3, 1.6)	0.184	0.7 (−0.3, 1.7)	0.168			1.1 (0.03, 2.1)	0.044
Minimum albumin level (g/dL)	0.7 (−0.2, 1.5)	0.13	0.7 (−0.2, 1.7)	0.13			0.5 (−0.4, 1.3)	0.282
Mechanically ventilated	1.5 (−1.5, 4.5)	0.321					1.3 (−1.7, 4.3)	0.392
Length of infusion (days)	1.9 (1.6, 2.3)	<0.001	1.9 (1.6, 2.3)	<0.001	2.0 (1.6, 2.5)	<0.001	1.8 (1.4, 2.4)	<0.001
Lorazepam dosing[a]	2.3 (−1.5, 6.0)	0.233	1.7 (−2.0, 5.5)	0.365	5.2 (0.3, 10.2)	0.038		
Receipt of inotropes or pressors			−0.7 (−1.9, 0.5)	0.277			−0.8 (−2.1, 0.5)	0.212
CCC present							−0.4 (−1.5, 0.6)	0.408
Clonidine dosing[a]							−0.4 (−0.9, 0.2)	0.162
Propofol dosing[a]							0.04 (−0.06, 0.1)	0.437
Pooled R^2_{adj} (95% CI)	56% (49–63%)		55% (47–62%)		56%		55% (47–63%)	

Abbreviations: CCC, complex chronic condition; CI, confidence interval; MME, morphine milligram equivalents; NM, neuromuscular.
[a]Median daily dosing (mg/kg/d).
[b]Year was adjusted such that zero is equal to 2009 and each year thereafter increased by one.

doses. Our findings align with a secondary analysis of the RESTORE trial, which specifically evaluated dexmedetomidine use within a large clinical trial that included 31 pediatric ICUs and 2,449 children with acute respiratory failure.[30,45] Patients in the usual care arm who received dexmedetomidine as a secondary agent had significantly more exposure to opioids, benzodiazepines, other secondary sedatives, including ketamine, and number of different sedative classes compared with patients who received dexmedetomidine only during the periextubation period or who were never prescribed dexmedetomidine.[30]

Patients who reported as non-Black race required significantly lower dexmedetomidine doses. Conflicting evidence exists on associations of reported race with dexmedetomidine response for sedation efficacy and cardiovascular effects. Tellor et al found non-Black adult participants were significantly more likely to experience dexmedetomidine failure or intolerance,[46] but sedation efficacy did not differ with race in work by Smithburger et al.[47] Kurnik et al investigated differences in blood pressure and norepinephrine concentrations in Black and White participants and found no significant difference, though Black participants had significantly higher dexmedetomidine plasma concentrations in a secondary analysis.[48] This contrasts with our findings of increased dosing needs which suggest lower plasma exposure. However, the reported race is a coarse factor that requires improved specificity to identify more precise predictors, such as potential socioeconomic, environmental, or genetic differences. Race and ethnicity data collected from EHRs can be inaccurate.[49] Genetic variability within pharmacogenes that may impact dexmedetomidine pharmacokinetics and/or pharmacodynamics has been reported and varies across ethnicities.[21,50–53] Differences in dexmedetomidine pharmacokinetics have also been reported between children from different countries.[54] Taken together, these findings require further research to better understand their precise impact on dosing needs.

Males required significantly less dexmedetomidine after holding other variables in the model constant. Dexmedetomidine pharmacokinetics have not been found to differ between males and females,[10] and sex has not been significantly associated with sedation medication requirements in a previous study.[41] Our contrasting finding may be related to reported differences in resting heart rates between males (i.e., lower) and females (i.e., higher) which could limit dose escalation strategies.[55]

To overcome the shortcomings of stepwise regression which selects variables based on *p*-values, we used LASSO regression to improve prediction accuracy and interpretation.[37] While this method identified the above variables that achieved statistical significance, it also identified additional important variables including concomitant dosing of diazepam, midazolam, lorazepam, and chloral hydrate, receipt of a neuromuscular blocker, mechanical ventilation, percent of infusion at night, year, minimum albumin level, and age. Year captures changes in sedation practices[11] and differences in use or comfort with dexmedetomidine[30] across the 10 years of data. Higher dose needs in younger patients (<1 year) have been reported[15] and pediatric pharmacokinetic models of dexmedetomidine have demonstrated age-related changes.[9,56–58] Though the understanding of the effect of age on relevant pharmacokinetic and pharmacodynamic pathways remains incomplete, maturation of metabolic pathways, receptor expression, and receptor functionality have been postulated to contribute.[56] In contrast to age, few pharmacokinetic studies have evaluated albumin as a covariate. Dexmedetomidine is eliminated primarily by the liver, has a reported hepatic extraction ratio of 0.7, and is highly protein bound (94%).[9,10] Despite being reported as a high extraction drug, previous studies in adults have suggested that hypoalbuminemia increases the volume of distribution and therefore slows the elimination rate.[59,60] While not statistically significant, we noted coefficients for benzodiazepines had opposite directionalities. More work is needed to determine if these findings may reflect patient class (e.g., diazepam use in orthopedics) or differences in administration (e.g., midazolam is often a continuous infusion, while lorazepam is bolus). Both ECMO and ALT levels were not included in our final model, likely owing to a low number of patients and limitations as a marker of liver dysfunction, respectively. As anticipated, renal creatinine was not in the final model given kidney impairment does not alter dexmedetomidine pharmacokinetics.[10] Finally, surrogates of illness severity were not selected in our final model, similar to results from Tillman et al who found no association between PELOD score and sedation requirements.[41]

Limitations of this study should be considered. First, this study is a retrospective analysis of EHR-derived data. This limits data availability, has the potential for miscoding, and hinders an ability to draw causal inferences. Second, patients are assumed to be dosed to an equivalent sedation goal level. Sedation goals or other indicators of sedation levels were not captured in these data. These are likely to have high within- and between-patient variability given the heterogeneity and dynamic nature of critical illness. Further, lack of explicit knowledge of the indication for sedation increases ambiguity in sedation goals. To account for potential changes in sedation goals broadly over time, we evaluated year as an independent variable, which was retained in the final model. Third, the study included patients with specific admission diagnoses from a single center which may limit generalizability of findings as other variables may be important for dexmedetomidine dose requirements in different populations of critically ill children.[17,56] Fourth, the common choice of dexmedetomidine as an adjuvant agent rather than first-line in sedation regimens for critically ill children confounds the interpretation of dose adjustments in the setting of concomitantly administered sedative agents.

A major strength of this study was the vast number of demographics, clinical characteristics, and medications evaluated through a comprehensive approach to determine their collective impact on dexmedetomidine dose requirements. Our model took into consideration many variables encountered throughout clinical care that may shape dosing intensity for each patient. We leveraged a rich dataset with low

missingness, included a large number of patients in our analysis, and applied emerging statistical methodologies (e.g., multiple imputation, LASSO) toward this goal.

Conclusions

Readily obtainable information such as demographics, concomitant medications, and duration of infusion accounted for over 50% of the variability in dexmedetomidine dosing. These findings advance understanding of patient-specific factors associated with dose intensity. Factors identified in the present work, as well as additional environmental and pharmacogenomics factors, warrant further investigation in future prospective studies toward a precision dosing strategy for dexmedetomidine.

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Conflict of Interest

None declared.

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