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# Defining The Difficult-To-Sedate Clinical Phenotype In Critically Ill Children

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# Defining The Difficult-To-Sedate Clinical Phenotype In Critically Ill Children

## **Abstract**

Each year thousands of critically-ill children receive sedation to help them tolerate intensive care therapies. A significant number of these children do not respond as expected to appropriately dosed sedation and remain agitated for some period, leading to iatrogenic injury and increased stress, as well as increased resource use. Children who remain under-sedated despite optimal therapy are considered “difficult-to-sedate”, but, to date, little data have been available to support an accurate description of this group of children. Recent attention to heterogeneity of treatment effect has spurred the development of clinical phenotypes that describe subgroups of patients within a disease process who differ in their clinical attributes and responses to therapy. Defining the difficult-to-sedate clinical phenotype in critically ill children is important because it will allow the use of sedation therapy targeted to the unique clinical, physiological, and developmental characteristics of the child.

The three papers developed in this dissertation study explored the concept of the difficult-to-sedate child clinical phenotype. A comprehensive review of the literature identified the lack of an operational definition and identified factors contributing to the clinical phenotype. These factors were used to develop an initial operational definition and to construct a conceptual model. Expert critical care clinicians validated the elements of the operational definition through an assessment of face and content validity and proposed additional factors for inclusion in the model. A refined definition was tested using data from the RESTORE study. Characteristics identified through latent class and classification and regression tree analysis were consistent with the conceptual model proposed.

Decreasing the ambiguity that currently exists around the concept of the difficult-to-sedate child clinical phenotype is a major achievement of this study. A clear operational definition of the concept promotes its consistent measurement and facilitates future investigation, and allows useful comparisons across studies. The conceptual model and operational definition require further investigation and refinement, as well as prospective validation by other investigators. This study suggests that a clinically meaningful population of difficult-to-sedate children requiring mechanical ventilation for a critical illness exists. Documentation of this phenotype promotes the development of evidence to support best practices in the care of these children.

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DEFINING THE DIFFICULT-TO-SEDATE CLINICAL PHENOTYPE  
IN CRITICALLY ILL CHILDREN

Ruth M. Lebet

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## DEDICATION

To the critically ill children and their families who require pediatric intensive care and the incredibly kind, creative, motivated, intelligent and patient-focused pediatric critical care clinicians who work as a team to provide that care

To Robert & Townsend Kent, who recognized the skill and value of pediatric critical care nurses through the care their daughter Louise (Noodle) received, and who continue to support the education of future nurses

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My very patient and understanding friends, especially Judy, Madeline, Deb, Mari, and Mary Grace

ABSTRACT

DEFINING THE DIFFICULT-TO-SEDATE CLINICAL PHENOTYPE  
IN CRITICALLY ILL CHILDREN

Ruth M. Lebet

Martha A. Q. Curley, PhD, RN

Each year thousands of critically-ill children receive sedation to help them tolerate intensive care therapies. A significant number of these children do not respond as expected to appropriately dosed sedation and remain agitated for some period, leading to iatrogenic injury and increased stress, as well as increased resource use. Children who remain under-sedated despite optimal therapy are considered “difficult-to-sedate”, but, to date, little data have been available to support an accurate description of this group of children. Recent attention to heterogeneity of treatment effect has spurred the development of clinical phenotypes that describe subgroups of patients within a disease process who differ in their clinical attributes and responses to therapy. Defining the difficult-to-sedate clinical phenotype in critically ill children is important because it will allow the use of sedation therapy targeted to the unique clinical, physiological, and developmental characteristics of the child.

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assessment of face and content validity and proposed additional factors for inclusion in the model. A refined definition was tested using data from the RESTORE study. Characteristics identified through latent class and classification and regression tree analysis were consistent with the conceptual model proposed.

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## **Chapter 1**

### **Introduction**

#### **The Problem**

Each year more than 115,000 critically-ill children receive sedation to help them tolerate intubation and mechanical ventilation.<sup>1</sup> A significant number of these children do not respond as expected to appropriately dosed sedation and remain agitated for some period of time, leading to iatrogenic injury and increased stress.<sup>2-5</sup> Over the course of the critical care admission, children who remain under-sedated despite optimal therapy are considered by the clinical team to be difficult-to-sedate, but little is known about this group of children to allow prospective identification. By the time the child is identified as difficult-to-sedate, excessive and potentially avoidable burden has been placed on the child and family; resource requirements to ensure the child's safety have increased; and injury may have occurred.

Prospective identification of these children has been hampered by a variety of factors. Intensive care sedation is a complex phenomenon, impacted by multiple variables. Easily implemented, valid and reliable instruments that describe sedation levels in children have only become available and widely used in the last decade. The age range of the patients cared for in the pediatric intensive care unit (PICU) is wide and encompasses enormous physiological and psychosocial differences. Although well studied in adults, there are limited data on the metabolism and elimination of drugs commonly used for sedation in children.<sup>6,7</sup> Organ maturation and critical illness also affect the rate at which sedation medications are metabolized and eliminated from the body. The influence of psychosocial development in response to sedation has not been thoroughly described. There may be a genetic basis<sup>8</sup> for the difficult-to-sedate child. Finally, the unit-specific context in which the sedation is provided is important. Each

PICU's environment influences how and when sedation is delivered, the specific agents used to provide sedation, as well as the definition of appropriate or optimal levels of sedation. Each of these factors combine to make studying the phenomenon of sedation in critically ill children challenging.

Defining sedation-related clinical phenotypes in critically ill children would facilitate better clinical management of these patients while avoiding harm. Specifically, accurate prediction of an individual child's response to sedation would allow the selection of individualized therapy and contribute to improved clinical outcomes. Jameson and Longo,<sup>9</sup> in their discussion of precision medicine, acknowledge the contribution of phenotype: "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations". High doses of sedatives, and the simultaneous use of multiple agents, as typically occurs in the difficult to sedate child, generally results in significant side effects. Identifying and providing targeted sedation strategies most effective for the difficult-to- sedate child will avoid these side effects.

To date, the difficult-to-sedate child clinical phenotype has not been described. In other populations, advanced statistical methods have been used to analyze large datasets and identify different phenotypes within a specific disease process. Howrylak and colleagues<sup>10</sup> provide one example. They examined clinical data from 1041 children with asthma using cluster analysis to identify differences between clusters in terms of pulmonary function and response to inhaled anti-inflammatory medication. Five patient clusters were identified based on differences in three features. They identified that membership in a specific cluster predicted the child's long-term asthma control and that two clusters which had the highest exacerbation rates responded differently to inhaled

corticosteroids. The authors concluded that phenotypic clustering effectively identified consistent and clinically relevant patient subgroups, with implications for targeted therapies.

Using latent class modeling, Calfee et al<sup>11</sup> analyzed data for 1022 subjects enrolled in two randomized controlled trials investigating acute respiratory distress syndrome. They identified two phenotypes within the population which had differing clinical and biological characteristics, differing responses to treatment, and differing outcomes. Members of phenotype 2 had severe shock, metabolic acidosis, high vasopressor use and higher levels of inflammatory biomarkers. They also had worse outcomes.

In the case of intubated and sedated children, the difficult-to-sedate child clinical phenotype might include a combination of demographic, physiological and developmental factors.<sup>12-14</sup> Concept analysis is an ideal methodology to identify candidate variables key to describing the clinical phenotype. The purpose of identifying a concept (what something is or how it works) is to develop a mechanism to describe and illuminate a phenomenon of interest. Walker and Avant<sup>15</sup> have developed and refined a process through several iterations which provides a systematic and thoughtful mechanism to achieve that goal. An important aspect of their method is that after a concept is identified, it must be clarified to clearly differentiate it from other concepts. This is done through careful examination of the structure and function of the concept. This requires examination of a concept's basic, essential elements in order to develop a clear, precise operational definition of the concept of interest.

This dissertation seeks to provide a comprehensive description of a clinical phenotype of critically ill children who demonstrate an under-sedation response, specifically, the difficult-to-sedate child clinical phenotype.



The specific aims for this dissertation are as follows:

- 1) To explore key variables thought to be associated with the difficult-to-sedate child, propose a conceptual model linking those variables in critically ill pediatric patients, and develop an operational definition of the difficult-to-sedate child. (Method: Concept analysis that includes a systematic review of the literature)
- 2) To assess both face and content validity of the candidate variables identified through the systematic review and incorporated in a preliminary model.  
(Method: Survey of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI Network and the Society of Critical Care Medicine (SCCM) Pediatric Sedation Study Group)
- 3) To build and test a statistical model describing the difficult-to-sedate child clinical phenotype. (Method: Statistical modeling of an existing clinical dataset of 2449 critically ill children)

Hypothesis: The difficult-to-sedate clinical phenotype can be described in critically ill children.

## **Approach**

The overall strategy for this dissertation will be: 1) to complete a concept analysis using the methodology described by Walker and Avant<sup>15</sup> that includes a systematic review of the pertinent literature resulting in a clear operational definition and framework of the difficult-to-sedate child clinical phenotype. The definition proposed in the current chapter will be modified based on the findings from the concept analysis. The operational definition and framework ultimately will be used to construct a statistical model which describes the key factors impacting the level of sedation achieved in critically ill children; 2) to establish face and content validity of the candidate variables

identified and explore additional unpublished variables to be incorporated in the model through a survey of expert pediatric critical care clinicians; and 3) to build and test the final model constructed using an existing clinical dataset of 2449 critically ill children. The methodology, and analyses to be used to accomplish the specific aims of this project are described below.

Three benchmarks for success have been identified as necessary to achieve the aims of this dissertation. The first is completion of the systematic literature review, which will direct the initial model design. The second benchmark will be achievement of a survey return rate of at least 50%, with attainment of an acceptable content validity index for at least half of the variables contained in the initial model and refinement of the initial model. The final benchmark will be the statistical model describing the difficult-to-date clinical phenotype.

## **Background**

Pediatric intensive care units (PICU) were developed to provide care to critically ill infants and children in a developmentally appropriate setting with a care team skilled in working with these patients. One of the most common therapies provided in the PICU is invasive mechanical ventilation.<sup>16-21</sup> It is difficult for children to understand and cooperate with this therapy, so they receive sedation to ensure safety, decrease fear and anxiety and promote comfort.<sup>22-27</sup> Doses for sedation agents have generally been extrapolated from adult doses and sedation practices vary greatly between PICUs.<sup>22,26-30</sup> A small number of studies have identified developmental differences in both the pharmacokinetics and pharmacodynamics of drugs in children.<sup>6,30-37</sup>

When children are sedated, effectiveness of sedation is generally assessed to ensure the target sedation level is achieved. Use of objective monitors of sedation level, such as the Bispectral index (BIS) monitor have not correlated well with clinical

assessment of sedation level in critically ill children, so observational sedation assessment tools are generally used.<sup>38-41</sup> Reliable and valid pediatric specific sedation assessment tools have been developed in the last ten years. Prior to their availability modified adult sedation assessment tools were used in most studies of critically ill children receiving sedation.<sup>42-47</sup> When sedation targets are not achieved, children are at risk for adverse events such as unplanned extubation.<sup>4,48</sup> Children who will be difficult-to-sedate cannot be prospectively identified based on current knowledge. One mechanism which shows promise is clinical phenotype identification. Clinical phenotypes group patients by presentation and response to therapy, and facilitate the delivery of individualized and effective therapy. In contrast, biological phenotypes consider specific, measurable biological abnormalities and may be determined by a single specific abnormality, such as rate of drug metabolism. Currently, there is no way to prospectively identify either the clinical or biological phenotype of the difficult-to-sedate child. Clinical phenotype identification is highly aligned with the National priority of Precision Medicine.

PICUs across the US are a very heterogeneous group. They vary dramatically on factors such as number of beds, availability of specialty services, ability to provide highly technical services such as renal replacement therapy or extracorporeal membrane oxygenation, and the educational preparation of nursing staff. However, one element universal to all PICUs is that all provide mechanical ventilation to patients on a daily basis. Each year thousands of children are admitted to PICUs in the United States due to a critical illness or injury which requires endotracheal intubation to facilitate mechanical ventilation.<sup>17-20</sup> At least 30% of children admitted to PICUs receive mechanical ventilation.<sup>1,17,18</sup> The majority of these children receive sedation therapy to keep them safe, prevent patient-ventilator dyssynchrony and minimize the negative

effects of painful procedures and the often unpredictable and frightening environment.<sup>22,23,25-27</sup> Appropriate levels of sedation change over the course of the child's illness and are impacted by both anticipated and unanticipated events for the patient, such as transport off of the unit for tests and procedures.

### Sedation Agents

Several surveys provide a description of the evolution of sedation practices in the PICU over time.<sup>23,24,26,27,29,49</sup> In 1989 Marx and colleagues<sup>24</sup> surveyed the directors of Pediatric Critical Care training programs in the United States and Canada to identify the sedative agents used and methods of delivery. In total, 35 surveys representing a 75% response rate, were received. At that point in time, opioids, benzodiazepines and chloral hydrate were identified as the most frequently used agents, and typically opioids and benzodiazepines were used in combination. The most frequent mode of administration was intermittent dosing on an as needed basis. Other adjunctive medications such as ketamine and barbiturates (e.g. thiopental, pentobarbital) were used less frequently, and generally for sedation related to procedures. Few units identified a written protocol for sedation (5.9%). The primary goals of sedation use were to increase comfort and prevent unplanned extubation. Interestingly, respondents reported the "biggest problem" with sedation to be inadequate efficacy.<sup>24</sup>

In 1997 Rhoney et al<sup>26</sup> surveyed all pediatric attending physician members of the Society of Critical Care Medicine on their use of sedative and neuromuscular blocking agents. The response rate was 51%, 145 pediatric critical care units were represented, and the findings were similar to those of Marx and colleagues. Opioids and benzodiazepines were the drugs most often used for sedation, given as continuous infusion or intermittent bolus dose. Drugs indicated as being "routinely" used for sedation, in order of frequency, included fentanyl, midazolam, morphine and lorazepam.

Adjunctive medications such as ketamine, chloral hydrate and propofol were “occasionally” used. The indications cited most often for use of sedation were management of anxiety and fear, amnesia, and facilitating mechanical ventilation. A sedation protocol was used in 13% of units. A sedation scale was used to monitor the level of sedation in 36% of units, almost equally divided between the COMFORT scale<sup>42</sup> and a scale developed by the respondent’s institution.

In 2003 Twite et al<sup>27</sup> surveyed Fellowship directors at 59 pediatric critical care training programs in the United States. The return rate was 60%; 35 surveys were received. Agents used for sedation were similar, but the ranking of those most frequently used sedatives had changed. Midazolam, rather than morphine was the most frequently used agent, with lorazepam second in frequency of use, and morphine third. These medications were most frequently delivered as continuous infusions, with both a sedative and analgesic being administered simultaneously. Chloral hydrate use had decreased from 68% of respondents reporting “frequent” use to 37% of respondents. Propofol and dexmedetomidine became available in the interval between the two surveys, and propofol in particular was used regularly. “Frequent” propofol use was reported by 29% of respondents, while only 3% of respondents reported frequent use of dexmedetomidine. Of note, 49% of units reported regular use of patient controlled analgesia. Use of adjunctive medications continued, most commonly to manage medication withdrawal symptoms. The number of units with a written sedation protocol increased from 5.9% to 66%. Overall satisfaction with the ability to provide optimal sedation increased compared to the previous survey, with respondents indicating that children were mainly “occasionally” difficult-to-sedate.

Kudchadkar<sup>23</sup> and colleagues surveyed an international sample of PICU intensivists, fellows, nurse practitioners and nurses. The majority of the respondents

(70%) were from North American and were pediatric intensivists (also 70%). Data were collected from July 2012 through January 2013. The authors separate out data for North American respondents (n= 225) and those data are reported here, as there was variability between North American sites and all other countries in primary agent used, sleep promotion techniques, frequency of delirium assessment, and the study population used in this dissertation is drawn from the United States. Availability of a sedation protocol was identified in this survey as 20% of PICUs, although this survey defined a sedation protocol as including a treatment algorithm, which is a more specific criterion than the two previous surveys. Fentanyl and midazolam were the two most frequently used agents, at 76% and 82% respectively, and were generally used in tandem. Continuous infusion as the method of delivery was by far the most frequent choice, at 80%. Scheduled intermittent dosing was used by 10% of units. The regular use of dexmedetomidine increased to 10%. This survey also reported on which team member managed the sedation protocol, and 58% of units reported using a nurse-managed protocol. A frequently identified frustration was inconsistency between team members in sedation goals. Although the method of distribution and roles of individuals completing the survey varied significantly from the previously reported surveys, comparison of sedation practices over time shows an increased use of synthetic opioids (i.e., fentanyl), increased use of midazolam, and continuous infusion as the strongly preferred mode of sedation medication delivery.

Review of the literature over this period demonstrates the continued use of adjunctive agents and the search for newer agents less likely to result in tolerance and iatrogenic withdrawal syndrome. Dexmedetomidine<sup>50-57</sup>, propofol<sup>58-61</sup>, and clonidine<sup>62</sup> have been the subject of a few clinical trials. Whalen<sup>57</sup> reported that dexmedetomidine was most frequently used when the desired sedation target was not able to be met using

opioids and benzodiazepines. Ketamine, clonidine and pentobarbital are also frequently added as additional sedatives when opioids and benzodiazepines have been escalated to high doses due to tolerance or when sedation targets have not been achieved. Other drugs which continue to be used as adjunctive sedation agents are diphenhydramine, lorazepam and chloral hydrate.

A major concern with the use of propofol in critically ill children is the significant incidence of propofol infusion syndrome, which manifests as bradycardia, renal failure and severe lactic acidosis. It is thought to be related to long-term use of the drug. Propofol infusion syndrome has resulted in several pediatric deaths.<sup>63</sup> As a result, the FDA required a Black Box warning, it's highest level of warning which indicates a serious or life-threatening risk, for propofol related to pediatric use. The propofol package insert indicates "Propofol injectable emulsion is not indicated for use in Pediatric ICU sedation since the safety of this regimen has not been established. (See PRECAUTIONS - Pediatric Use.)"<sup>64</sup> However both propofol and dexmedetomidine are often used as a bridge to extubation. For example, these drugs, which have a short half-life, are started as a continuous infusion in the hours prior to a planned extubation, allowing longer acting sedation agents to be weaned in preparation for extubation while maintaining an acceptable level of sedation.<sup>61,65,66</sup> This strategy is often used with children who do not tolerate being awake and mechanically ventilated. The duration of infusion in this situation is recommended to be 12 hours or less. Table 1 describes medications commonly used for sedation in the PICU

### **Developmental Issues and Child Characteristics Related to Sedation**

There have been a limited number of studies done to establish the pharmacokinetic and pharmacodynamics properties of most of the agents used to provide sedation to critically ill pediatric patients. Up to 80% of the drugs prescribed to

hospitalized infants and children are prescribed “off label,” meaning there is a lack of evidence to support their safety and efficacy in pediatric patients.<sup>7,28,29</sup> When identifying appropriate dosing of sedation agents, pediatric prescribers generally extrapolate a dose from the recommended adult dose. This practice assumes that the relationship between drug dose and drug concentration (i.e., pharmacokinetics [PK]) and drug dose and drug effect (i.e., pharmacodynamics [PD]) is the same in infants, children and adults.<sup>28,67</sup>

The PK and PD studies that have been carried out in both healthy and critically ill pediatric patients generally show that there is a difference in drug clearance, elimination, and response between neonates, infants, children and adolescents.<sup>6,30,31-37,68</sup> However the number of subjects enrolled in these pediatric studies is generally very small, limiting the generalizability of findings.<sup>57,67-69</sup> For example, four studies of midazolam PK and PD in critically ill infants and children reported in the period between 2002 and 2008 included a total of 15 pediatric subjects.<sup>33,34,68,70</sup> Factors related to changes in growth and maturation of organs and physiologic systems such as protein expression and protein function drive these differences.<sup>6,28,30</sup>

Maturation may increase or decrease drug receptor affinity for a particular drug and may alter signal transduction.<sup>6,71</sup> Changes in body composition, such as the decrease in total body water or increase in adipose stores that occur as a child grows, affect drug distribution and availability.<sup>30,71</sup> For example, neonates and young infants have lower adipose stores than older infants and children, and the adipose tissue of neonates has a higher ratio of water to lipid.<sup>6</sup> As a result, neonates and young infants have a decreased volume of distribution of lipophilic drugs such as midazolam or fentanyl. Thus, they will have a higher peak drug concentration than older children in response to the same dose.<sup>67</sup> Maturation of drug metabolizing enzyme pathways and



increasing renal function with greater age also account for variability in the PK or PD of specific drugs.<sup>6,30,67,71</sup>

Midazolam clearance is decreased in infants. The clearance rate increases with age, and a clearance rate similar to adults is seen at around 5 years of age.<sup>67</sup> deGast Bakker<sup>33</sup> and colleagues identified that one to four year olds required higher midazolam doses per kilogram of body weight than other age groups. Morphine clearance in infants is approximately 80% of that seen in adults. As a result, an increase in dose per kilogram from 5 mcg/kg at birth to 18 mcg/kg at 1 year is required to achieve steady state serum levels.<sup>31</sup> Fentanyl also has a higher clearance rate in infants and children.<sup>72</sup> Pentobarbital PD and PK are affected by both age and weight<sup>36</sup> and pentobarbital half-life is significantly longer in neonates and infants.<sup>72</sup> Critical illness compounds these developmentally driven effects. For example, Ince<sup>68</sup> and colleagues found decreased midazolam clearance in critically ill children compared with pediatric oncology patients receiving procedural sedation and healthy infants receiving postoperative sedation.

In addition, sedative use in infants and young children has been associated with long-term cognitive dysfunction. Few well-designed studies that can link specific sedation agents to cognitive outcomes have been completed to date, and results of some studies have been contradictory.<sup>73-78</sup> Studies of anesthetic agents are currently underway, as are studies examining cognitive outcomes in children who received sedation during a PICU admission. This will be an important area of investigation to follow as findings will impact sedation practices in the future.

Little research has been done in the area of psychosocial development and its relationship to sedation outcomes. A child's ability to manage negative stress and the coping strategies employed change as the child develops, and is linked to the child's ability to comprehend the current situation.<sup>79</sup> Innate child characteristics may also impact

response to sedation. A single study linking child temperament to sedation outcome in the setting of procedural sedation demonstrated that inflexible temperament was a predictor of sedation failure.<sup>80</sup> Although not commonly assessed, obtaining information on temperament or coping behaviors from parents of critically ill children could be an interesting area of investigation, and add to the characterization of the difficult-to-sedate child.

### **Sedation Assessment Tools**

Several pediatric sedation scoring tools have been developed, and are used in PICUs across the US and internationally. Commonly used tools include the State Behavioral Scale (SBS),<sup>43</sup> COMFORT Scale,<sup>42</sup> COMFORT-B scale,<sup>44</sup> Motor Activity Assessment Scale,<sup>81</sup> and the Pediatric Sedation-Agitation Scale.<sup>45</sup> The previously referenced sedation practices surveys demonstrated the development and increased use of validated pediatric sedation assessment tools over time.<sup>23,24,26,27</sup> The 1989 survey by Marx et al<sup>24</sup> did not reference an assessment tool at all. Clinical impression of the physician and nurse were the most frequent mechanism of assessment, with assessment of vital signs and response to procedures also considered. In the 2003 survey, Twite<sup>27</sup> et al included both analgesia and sedation scoring tools. Both adult and pediatric tools were being utilized. The pediatric specific COMFORT score was the most commonly used tool (49%), followed by the adult Motor Activity Assessment Scale (11%). The 2013 survey<sup>23</sup> is reflective of current practice. Pediatric specific sedation scoring tools are most commonly used, with 22% of PICUs reporting use of the State Behavioral Scale and 21% reporting use of the COMFORT scale, although 21% of PICUs continue to use the Richmond Agitation-Sedation Scale, a tool validated only in adult patients (e.g, RASS).<sup>82</sup> Table 2 provides a description of sedation tools commonly used in the PICU.

Adequate and inadequate sedation exist along a continuum, and despite the development of valid and reliable instruments to assess sedation, assessment of adequacy of sedation is subjective. Although work is ongoing to develop an objective measure of level of sedation, such as the BIS monitor, SNAP II (Stryker, Kalamazoo, MI) or auditory-evoked potentials no objective measures have proved reliable and consistent in the PICU population.<sup>38-41</sup> There is strong evidence that sedation practices are influenced by personal, social, and professional factors.<sup>83-86</sup> Variability in assessment of level of sedation is frequently seen in children who are moderately to deeply sedated, and this is seen when raters are of the same or different provider categories.<sup>40</sup>

At the other end of the spectrum, assessment of children who are not well sedated and are in fact agitated generally shows more consistency. This is can be related to the use of sedation as a means to protect children who are unable to tolerate the intensive care environment and are perceived to be in an unsafe state. Terms such as refractory agitation, sub-optimal sedation, inadequate sedation and under-sedation are used to describe children at this end of the sedation spectrum.<sup>87-89</sup> The scales used to describe level of sedation use terms such as “intermittently unsafe” or “unsafe (biting endotracheal tube, pulling at catheters, cannot be left alone”,<sup>43</sup> “panicky”,<sup>42</sup> “pulls on or removes tube(s) or catheter(s) or has aggressive behaviors toward staff” or “cannot be left alone”,<sup>82</sup> “dangerously agitated, uncooperative- patient is pulling at tubes or catheters OR thrashing side to side OR striking at staff OR trying to climb out of bed”,<sup>81</sup> and “dangerous agitation- pulling at endotracheal tube, thrashing side to side, climbing over bedrails, hitting or kicking at staff, yelling or screaming at staff”.<sup>45</sup> Children who are at this end of the sedation spectrum raise significant levels of concern for parents, who worry that children will injure themselves and who also perceive their child as suffering. Agitated children increase the level of concern for care providers as well, who are

concerned that the child will suffer physical harm, physiologically decompensate, remove invasive tubes or catheters that will be difficult to replace, or possibly suffer long-term psychological consequences of their agitated state. Children who are inadequately sedated may remain in this state for significant amounts of time, despite regular adjustment and addition of medications, requiring increased staff resources to ensure all patients receive the needed attention.

Clinical states associated with ongoing agitation, such as hypoxia, pain, delirium and children near the end of life,<sup>88-91</sup> have been identified but there are very little data on factors which predict children who will become and remain agitated, despite aggressive treatment.

### **Adverse Events Related to Under-sedation**

Despite the best efforts of the care team, up to 24% of children fail to respond to usual sedation therapy and will require higher dosages and sedative drugs from three or more drug classes in order to achieve the desired level of sedation.<sup>89,92</sup> High dosages and the use of multiple sedative agents (i.e., polypharmacy) place these children at significant risk for sedation-related adverse events such as iatrogenic withdrawal syndrome, infection and pressure ulcers.

During the startup phase of the *RESTORE* study, Grant,<sup>4</sup> et al completed a systematic review in order to define and provide estimates of PICU specific sedation-related adverse events (AE). Of the eleven AE identified, five were directly related to agitation. Inadequate sedation management was defined as “Agitation defined by an SBS > 0 (or “assumed agitation present” in patients receiving neuromuscular blockade) for 2 consecutive hours not related to a planned extubation attempt” (p. 1318). Based on their systematic review the event rate for this AE was estimated as expected in less than 10% of patients. Clinically significant iatrogenic withdrawal was expected to occur

in less than 75% of patients. Unplanned endotracheal tube removal had an expected event rate of less than 3.0 per 100 ventilator days. Unplanned removal of any invasive tube could not be estimated but was tracked as an anticipated AE. Ventilator-associated pneumonia was identified as a sedation related AE with an expected event rate of less than 3.2 infections per 1000 ventilator days. New tracheostomies were tracked as a marker for extreme airway trauma secondary to agitation.

These sedation-related AEs are also supported by more recent work. Payen<sup>5</sup> et al identified the use of continuous intravenous sedation as a risk factor associated with prolonged invasive mechanical ventilation in critically ill children, which in turn is associated with increased morbidity and mortality. Gautam<sup>3</sup> and colleagues identified a relationship between ventilator-associated pneumonia and prolonged invasive mechanical ventilation in pediatric patients. Best<sup>2</sup> et al. identified duration and cumulative dose of opioid and benzodiazepine therapy as risk factors for iatrogenic withdrawal syndrome in critically ill pediatric patients.

After initiation of the *RESTORE* study, Grant<sup>48</sup> et al. completed a prospective observational study of 308 subjects from 22 PICUs who were enrolled in the baseline phase of the study, in order to test the previously developed operational definitions and estimate rates of occurrence of these sedation-related AEs. The most frequently occurring AE was inadequate sedation management. Agitation, identified as noted above, was documented in 30% of subjects and represented 41% of all AE. Clinically significant iatrogenic withdrawal was documented in 8% of subjects and represented 29% of all AE. The unplanned endotracheal tube extubation rate was 0.82 per 100 ventilator days.<sup>48</sup> These results clearly show that critically ill children who require intubation and mechanical ventilation experience a significant number of adverse events related to agitation, a key behavior observed in children labeled as difficult-to-sedate.

## Clinical Phenotypes

Clinical phenotypes have been developed as a way to describe patterns of presentation and response to therapy in an effort to provide the most appropriate and effective care in a timely way. Defining sedation-related clinical phenotypes in critically ill children would facilitate sorting these patients into subgroups, allowing specific therapies to be targeted to particular subgroups based on that subgroup's unique clinical and physiological characteristics.

In the last 10 years there has been a growing use of clinical phenotyping, sparked by completion of the Human Genome Project in 2004. Once the entire Human Genome had been sequenced, researchers began to investigate whether linking clinical phenotypes to variation in specific genes would facilitate identification of subgroups of patients with a particular disease process who would benefit most from tailored therapies or "precision medicine".

Precision medicine has become a priority for the nation. In his 2015 State of the Union address President Obama announced a \$215 million dollar line item for the Precision Medicine Initiative.<sup>93</sup> As defined by the Precision Medicine Working Group<sup>94</sup> "Precision medicine is an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle." The goal of this initiative is to "pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients." Stated simply, the goal of precision medicine is to "deliver the right treatment to the right patient at the right time."<sup>93</sup>

Having phenotype information would facilitate more effective ways to treat disease.<sup>95</sup> A defined clinical phenotype facilitates the classification of a patient into a

clearly identified sub-group of a specific clinical state that responds to specific therapies in a typical fashion for the sub-group. The utility of clinical phenotypes is that identification of these homogeneous subgroups of patients facilitates research specific to the phenotypic group to determine risk factors or unique response to particular therapies within the group.<sup>96</sup> This knowledge then guides targeted therapy, with the goal that members of the clinical phenotype receive the most appropriate and effective care in a timely way.

Descriptions of clinical phenotypes can be found in the biomedical literature beginning in the 1960s. Usually associated with specific disease entities, and therefore described in a clinical setting, clinical phenotypes describe patterns identified in a patient's presentation and response to therapies. The clinically observable characteristics used to identify these patterns may be morphological, physiological, or biochemical. Clinical phenotypes tend to be subsets of an overarching diagnosis: chronic obstructive pulmonary disease<sup>97</sup> and hypertension<sup>98</sup> are examples of diseases where specific clinical phenotypes have been well described.

The clinical dimensions of clinical phenotypes are most often described in terms of physical assessment findings. For example, type of wheezing is a key assessment finding in children with asthma. Depner,<sup>99</sup> et al. used wheezing types such as multitrigger wheeze, unremitting wheeze, recurrent unremitting wheeze, or episodic wheeze as an important way to characterize pediatric asthma clinical phenotypes. In sickle cell disease, benign or severely affected clinical phenotype assignment is based on clinical dimensions that include severity of pain crisis, frequency of hospital admissions, and complications.<sup>100</sup> Knowledge of these assessment findings and the resulting patterns suggested prompts the care provider to place the patient in a specific sub-group or category; that is, to assign a clinical phenotype. The usefulness of

identifying a clinical phenotype is that this categorization results in a meaningful benefit to the patient. Identifying the clinical phenotypes within a disease identifies groups of patients who may have an increased need for or respond differently to the typical therapies used to manage the disease. This guides the clinician in selecting the most appropriate therapies for that patient.

In order for clinical phenotypes to be useful in clinical practice, three elements must be present: a clinical condition or disease process, other patients who also have the clinical phenotype, and clinicians who can recognize the patterns of and identify the clinical phenotype.<sup>101</sup> Having knowledge of the clinical phenotype and the typical response to therapy can result in earlier treatment, more appropriate drug selection, and anticipation and avoidance of adverse outcomes. An important aspect of clinical phenotype is that it must be clearly articulated, so that it is readily applied by the clinician. If not, a patient could be misclassified, resulting in inappropriate treatment, or not receiving needed treatment.

Clinical phenotypes are clinical entities, and although the majority of the literature discusses specific disease processes, clinical phenotypes can also be identified as subgroups of patients that respond to specific therapies in a typical and consistent fashion for the subgroup. Knowledge of the sub-group's response allows the clinician to predict the trajectory of the clinical course and select appropriate therapies for the patient that result in beneficial outcomes.

It is known that patients have variable responses to sedation. Clinical phenotypes can be identified and used to categorize patients who require more or different sedation to promote best outcomes. Although there is thought to be a genetic underpinning to sedation response,<sup>8</sup> it is the clinical manifestations of the sedation clinical phenotypes that have immediate impact on the patient, family and clinician.



To date, data to allow prospective identification of the difficult-to-sedate child clinical phenotype do not exist. Identifying this phenotype may allow early identification of these patients and facilitate development of preventive strategies such as environmental manipulation and individualized sedation plans which could avoid adverse effects resulting from inadequate sedation. Latent class analysis, cluster analysis and classification and regression tree analysis are some of the advanced statistical methods that have been used to analyze large datasets and identify differentiating factors which describe different phenotypes within a specific disease process, such as asthma,<sup>99,102-104</sup> sepsis<sup>105</sup> or chronic obstructive pulmonary disease.<sup>101</sup> In the case of intubated and sedated children these differentiating factors might include demographic, physiological, developmental, and clinical factors.<sup>12-14</sup>

### **Significance**

A well articulated clinical phenotype for the difficult-to-sedate child would support further investigation related to sedation in critically ill pediatric patients by establishing a definition that could be used consistently by investigators. It also might allow early identification of the child at risk for under-sedation, which would facilitate more appropriate, targeted management. As a result the care team could ensure the child rapidly achieved the targeted sedation goal by selecting the most effective sedation agents at appropriate doses for that child, while minimizing the risk of adverse events. Identification of this clinical phenotype will assist in the development of personalized targeted therapy to minimize the negative effects of excessive sedation medications. Identification of this clinical phenotype will then inform future work on the identification of a genetic phenotype for this group of children.

### **Innovation**

Use of a clinical phenotype to describe response to sedation in a critically ill pediatric population is a novel way to approach the problem of under-sedation. To date no research has utilized this approach. Identifying the demographic, physiologic, and developmental characteristics associated with differing responses to sedation will assist the care team to provide specific and individualized sedation strategies for critically ill children. This goal is in keeping with current, innovative research in other areas, which seeks to identify targeted therapies. Additionally, identifying a group of children who fall into this clinical phenotype could facilitate an investigation for specific genetic phenotypes that underlie the clinical phenotype.

This study will take advantage of a unique data set from the Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) study<sup>16</sup> (ClinicalTrials.gov identifier NCT00814099.21), a previously developed data set containing highly detailed sedation-specific data in critically ill children to identify characteristics of this clinical phenotype. This approach is also innovative, and represents an effort to maximize the use of data and respect the contributions of over 2400 children and their families.

### **Introduction to the Dissertation Format**

The proposed dissertation consists of three papers, outlined in Table 3. The first paper will present the results of a concept analysis using the methodology described by Walker and Avant<sup>15</sup> that includes a systematic review of the pertinent literature resulting in a clear operational definition and framework of the difficult-to-sedate child clinical phenotype. The operational definition and framework will be used to construct a conceptual model, which describes the key variables impacting the degree of sedation achieved in critically ill children. Paper 2 will describe the process used to establish face and content validity of the candidate variables identified and seek additional factors to be

tested through a survey of expert pediatric critical care clinicians. Paper 3 will investigate a large cohort of children who received sedation while intubated for acute respiratory failure, building and testing the final model developed to identify subjects who are members of the difficult-to-sedate child clinical phenotype.

## **Paper 1**

Title: Describing the Difficult-to-Sedate Child: A Concept Analysis

Target Journal: Journal of Pediatric Nursing

Background:

Sedation is routinely used in pediatric patients requiring intubation to facilitate mechanical ventilation, decrease anxiety and stress, and minimize the likelihood of an adverse event.<sup>23,24,26,27</sup> Sedation targets are identified and sedation scores are utilized to determine if the desired target has been achieved.<sup>23,89</sup> Pediatric sedation scales have been developed and their psychometric properties have been carefully examined.(sedation scale references) The particular agents or combinations of agents used to achieve sedation in the PICU setting have been studied in order to identify the most effective agents which also have a good safety profile. The specific agents used have evolved over time as newer and safer agents have become available.<sup>23,24,26,27</sup>

A finding from these areas of investigation is that not all patients in the PICU achieve optimal sedation.<sup>23,45,49,89</sup> Some of the potential reasons for this fall within clinicians' control, such as inappropriate dosing of sedation agents, lack of environmental controls, uncontrolled pain, or the limitation of parental involvement in the child's care. However a portion of this patient population does not achieved the desired sedation target despite increased doses and the addition of agents. These patients have been identified as sedation failures or their level of sedation has been described as under-sedation. Although it is well documented that this subpopulation is routinely seen

in the clinical setting, there is little known about the risk factors for under-sedation. A clear mechanism does not exist for identifying which children will be difficult-to-sedate.

Paper 1 describes a systematic literature review, which identifies variables associated with pediatric sedation in the critical care setting, specifically variables associated with the difficult-to-sedate child. This information was synthesized using the concept analysis methodology of Walker and Avant.<sup>15</sup> The product of the concept analysis was a clear operational definition of the difficult-to-sedate child. This operational definition was used to frame a conceptual model of key factors impacting the level of sedation achieved in critically ill pediatric patients cared for in the PICU. The model describes potential variables to test in the development of a clinical phenotype of the difficult-to-sedate child. Table 4 lists other pertinent operational definitions.

Research Question: What individual, process or system variables are identified in the literature as associated with the difficult-to-sedate child?

Methods: A literature search of multiple databases, including PubMed, Medline, EMBASE, ISI Web of Science, Scopus, ProQuest Dissertations, CINAHL, and the Cochrane Database of Systematic Reviews and Central Register of Controlled Trials from January 1, 1985 through March 31, 2017 was completed in order to identify research articles specific to the topic of pediatric sedation in a critical care setting.

Inclusion criteria: The primary focus of the included studies was sedation for intubation or to facilitate mechanical ventilation in pediatric patients aged 2 weeks post conceptual age to 18 years cared for in a critical care setting.

Exclusion criteria: Studies primarily focused on dental sedation, procedural sedation, perioperative sedation or sedation for comfort care were excluded. Studies that do not report a measure of sedation effectiveness will also be excluded. Abstracts of papers published in languages other than English were translated.

Study procedures: A literature search was conducted as described. Additionally, reference lists of the articles retrieved were reviewed to identify additional studies for inclusion not identified in the initial search. A flow diagram describing identification of the final group of studies included in the systematic review is provided in Chapter 2.

Analysis Plan: A table of evidence was utilized to examine the studies reviewed. Data elements included in the table were: study population, setting, sample size, sedative agents used, sedation assessment mechanism and definition of under-sedation used in the study. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses<sup>106</sup> checklist was used to rate the quality of each included study. The table of evidence was used in the analysis of candidate factors for model construction, and a conceptual model was proposed and is described in Chapter 2.

## **Paper 2**

Title: Appraisal of Face and Content Validity of Variables Associated With the Difficult-to-Sedate Child in the Pediatric Intensive Care Unit: A Survey of Pediatric Critical Care Clinicians

Target Journal: Australian Critical Care

Background:

Face and content validity are used to determine if items in a scale or survey are important and relevant to the topic, clear and understandable. This assessment seeks to determine if there are adequate and appropriate items to represent the phenomenon or construct of interest.<sup>107</sup> Feedback from experts in the area under study is a method commonly used to assess face and content validity. A high level of consensus among the group of experts supports face and content validity.

Paper 2 describes the construction, deployment and results of a survey of pediatric critical care experts used to validate candidate model variables identified

through the systematic review and concept analysis. This group was asked to identify additional variables to consider for the model.

Methods: To establish face and content validity for criteria to be used in a subsequent study identifying the difficult-to-sedate child clinical phenotype, expert Pediatric ICU clinicians who are members of a research consortium, the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, and an expert study group, the Society of Critical Care Medicine (SCCM) Pediatric Sedation Study Group, were asked to complete a questionnaire using the Qualtrics (Provo, Utah) Survey platform. These groups were chosen because they include active, experienced critical care clinicians who provide pediatric sedation on a routine basis, and include a variety of providers including nurses, physicians, respiratory therapists and pharmacists. The SCCM Pediatric Sedation Study Group is tasked with developing sedation-specific recommendations for the pediatric critically ill patient. Recommendations on key elements to include when reporting surveys in publications generated by Duffett,<sup>108</sup> et al were followed in the write up of this study.

Inclusion criteria: All members of each group who are clinicians were included.

Exclusion criteria: Individuals who completed the survey but are not clinicians, determined by response to a question asking the respondent to identify their role, were excluded.

Procedures: The Institutional Review Board of the University of Pennsylvania determined that the study did not require informed consent from participants. A questionnaire was developed containing questions used to assess face validity of variables included in the initial model. Two additional questions asked for the respondent's clinical role and organization. No other demographic information was collected.

In order to avoid coercion and maintain confidentiality, the survey was distributed by a member of each groups' administrative staff to their email list. Investigators did not have access to the email list. Participation was voluntary. Submission of a survey was used as an assumption of consent.

Respondents were asked to answer the questions in relation to a patient's first four days of endotracheal intubation, with the assumption that the patient's pain was adequately controlled and that sedation medication doses were appropriate. Survey participants were instructed to score each of the variable items as not (1), somewhat (2), quite (3), or highly (4) relevant in identifying the difficult-to-sedate clinical phenotype.

Analysis: Descriptive statistics for the two demographic variables, including frequencies and percentages for nominal/binary variables were reported. All study data was examined carefully for invalid or outlying values, and distributional assumptions were assessed where appropriate.

Primary analysis involved calculation of a content validity index,<sup>107</sup> used to identify the factors which respondents felt best identified the difficult-to-sedate child. Items which scored a content validity index greater than or equal to 0.70 were retained in the model. The final model created was tested as described in Paper 3.

The primary limitation of survey research is a poor return rate for surveys.<sup>109,110</sup> In order to promote a high rate of return, survey responses were carefully tracked on a daily basis, and a reminder email was sent by the administrative staff one week after deployment of the original survey.

The survey site captures all responses in a survey, even if the survey is not completed, so any data provided in all surveys initiated was captured. However, the goal is to obtain complete surveys. The survey completion time was short, and the

survey site provided tools such as a completion bar and formatting for smartphones, which encouraged participants to complete the survey.

Because the survey will be distributed via email, it is important that the survey program used be stable and accessible throughout the data collection period. This survey site has been used extensively throughout the University of Pennsylvania, and has demonstrated good accessibility, stability and strong data protection and security.

### **Paper 3**

Title: Characteristics of the difficult-to-sedate child phenotype

Target Journal: Pediatric Critical Care Medicine

Background:

The aim of paper 3 is to characterize variability in sedation response within a cohort of 2,449 subjects enrolled in *RESTORE* and use data through the first three days after endotracheal intubation to operationalize and define the difficult-to-sedate child clinical phenotype.

Typical, over- and under-responders to sedation were compared on demographic, physiological, developmental and clinical characteristics, as well as patterns of opioid, benzodiazepine, and other sedative medication administration with the goal of identifying the characteristics of the difficult-to-sedate child clinical phenotype.

Methods: A secondary analysis of the *RESTORE* data set was completed to test the hypothesis that a phenotype for the difficult-to-sedate child can be described.

The *RESTORE* (Randomized Evaluation of Sedation Titration fOr Respiratory failure) study (U01 HL086622 and U01 HL086649) was a cluster randomized clinical trial designed to test an innovative approach to sedation management in pediatric patients supported on mechanical ventilation.<sup>16</sup> The trial intervention consisted of daily



assessment of illness trajectory, establishment of an individualized sedation goal and implementation of a nurse-directed comfort algorithm that guided the sedation/analgesic management. The sample consisted of 2449 critically ill infants and children supported on mechanical ventilation from 31 participating pediatric intensive care units (PICUs) between June 2009 and December 2013. The intervention tested in the trial sought to improve sedation management in pediatric critical care settings and to reduce the risk of sedation-associated complications such as failed extubation, iatrogenic withdrawal syndrome (IWS), and the development of ventilator associated pneumonia (VAP).

Inclusion criteria: All *RESTORE* subjects who contributed at least two days of data.

Exclusion criteria: None

Procedures: IRB approval for the parent study was obtained at all study sites. The parental permission document specifically allowed subsequent use of de-identified data. Data points extracted from the *RESTORE* data set were identified based on the variables included in the final model. A cohort of difficult-to-sedate subjects within the *RESTORE* trial data set was generated and then compared to typical response *RESTORE* subjects. This was done by developing a subset of patients who had both a sedation score indicating agitation and opioid and/or benzodiazepine doses above the standard dose range on the same day, during days 0 through 3, as this is likely the subset of patients that represent the difficult-to-sedate child clinical phenotype. Several iterations of models of the difficult-to-sedate child clinical phenotype were considered, as is standard for the type of analyses planned, in order to best define the phenotype.

Analysis Plan: Using the *RESTORE* data set, pertinent clinical factors were identified. Latent Class Analysis<sup>111</sup> was employed to characterize the difficult-to-sedate phenotype in children enrolled in the *RESTORE* trial. The analysis explored traits such

as number of inadequate sedation management events, number of sedative medication classes received, and standardized total daily sedation requirement to maintain target sedation goal.

Latent Class Analysis (LCA), a hypothesis-free statistical technique, has been used extensively in clinical phenotype development studies to identify unobserved (latent) classes by building typologies or clusters based on observable variables within a data set. We used LCA to analyze the *RESTORE* dataset, in order to characterize the difficult-to-sedate child clinical phenotype. LCA has been previously used to identify phenotypes in acute respiratory distress syndrome,<sup>11</sup> pulmonary hypertension,<sup>112</sup> COPD,<sup>101</sup> and wheezing phenotypes in young children.<sup>99,102,103</sup> The model developed and refined in Papers 1 and 2 was tested in order to develop a final model which used an appropriate set of demographic and clinical factors as well as agitation-related and sedation-related characteristics to predict membership in the latent classes. This allowed characterization of the difficult-to-sedate child clinical phenotype.

We also used Classification and Regression Tree (CART) analysis to identify risk factors for being difficult-to-sedate. CART methodology has been successfully used to identify risk in other populations, such as septic pediatric and adult patients,<sup>105</sup> and is useful in uncovering complex interactions when many potential predictor variables and patterns of relationship exist.<sup>113</sup> CART produces cut points and ordering of decision nodes that clearly discriminate between groups with high and low risk for the response variable.<sup>105,114</sup> We used a randomly selected sample of subjects from the *RESTORE* database as the learning dataset, which was used to build the initial classification tree using RStudio (Foundation For Open Access Statistics, Boston, MA). Cross validation was used to identify the most accurate and predictive tree. We used the remaining subjects as the test dataset to validate the initially derived tree. These approaches allow

characterization of the difficult-to-sedate child who does not respond to standard therapy and requires a treatment approach that deviates from the norm, as well as associated risk factors based on demographic and clinical factors.

### **Limitations, Assumptions, and Design Controls**

This study is a secondary analysis of an existing data set, which presents some potential limitations.<sup>91,115-120</sup> A key issue is that the question of interest in the secondary analysis must fit the data available from the parent study. Operational definitions and the unit of analysis must be congruent.<sup>117</sup> In this case a subset of the parent study data specifically matches information needed to answer the question of this study. For example several data points related to sedation levels, as well as daily amounts of sedation medications and the number of different agents used for sedation was collected in the parent study. The unit of analysis for this study will be the individual subject, which matches the parent study.

A potential problem is the inability to identify the difficult-to-sedate child phenotype. This may occur because the data may be too noisy and a group of characteristics may not be able to be identified. If this is the case, an alternative strategy is to calculate a cumulative difficult-to-sedate score for each subject, based on the previously identified variables and use linear regression and structural equation modeling to identify which variables predict the difficult-to-sedate child phenotype. A second potential limitation is that methodological issues may exist related to the parent study.<sup>116-118</sup> The parent study methodology was reviewed by Institutional Review Boards of the 31 sites which enrolled subjects, as well as the funding organization, the National Heart, Lung, and Blood Institute of the National Institutes of Health. A related potential methodological issue is that the parent study was a cluster-randomized trial, with sites being randomized to the intervention or control arms. The possibility exists that if there

were significant differences in sedation practices between the control sites, the data could be skewed. Careful evaluation of data considering treatment arm assignment will allow identification of any impact of this aspect of the study design.

When using a previously created data set, quality of the data is a potential limitation, specifically concerns that the data is outdated or inaccurate.<sup>116-120</sup> The parent data set in this case has a high level of quality. A key variable of interest in this study is sedation scores, obtained by direct assessment of subjects. Multiple procedures were implemented at each site to ensure accuracy. Medication data is another variable of interest, and this data was carefully reviewed by monitors over the course of the study to ensure data accuracy. The parent data set was carefully cleaned to minimize missing data. If questions arise about the data set, the study investigator will have ready access to the parent study principal investigators as well as the Data Coordination Center, which is where all data is held. In terms of concerns that the data is outdated, the parent data was collected over a five year period, from 2008 to 2014. Data analysis for the present study is anticipated to occur in 2016-2017. This represents a minimal time lag and reduces the risk that the data will be outdated.

If the parent data set is not representative of the population of interest, a concern arises that there will be limited generalizability. Entry criteria for the parent study and missing data, which may decrease power, are both potential concerns.<sup>115-120</sup> As noted, the parent data base was constructed to minimize missing data and was thoroughly cleaned. The parent study included children intubated specifically for respiratory causes, which limits generalizability to the entire PICU population. Although the most frequent diagnosis associated with intubation in the PICU is respiratory failure, children are also intubated for reasons such as control of intracranial hypertension, protection of a surgical incision, or manipulation of cardiopulmonary dynamics. The exclusion of

children with “Do not resuscitate” status also limits the ability to generalize to a group known to present sedation challenges.<sup>91</sup> The present study is exploratory and as a result, information gained in this study will provide direction for subsequent studies related to these populations.

A final concern related to secondary analysis on an existing data set is that the parent study may not contain the variables needed to answer the questions posed in the secondary analysis.<sup>116,117</sup> Because the variables of interest will be identified in papers one and two, this is a possibility, however, extensive data on variables likely to be of importance was collected in the parent study.

Some assumptions have been made in designing the present study. A key assumption is that when sedation levels were assessed, pain was controlled. This assumption is based on the agreement of all participating sites to assess pain using the same tools and at the same intervals, with minimal assessment intervals of every four hours. There are several additional assumptions. Factors known to be related to agitation have been appropriately managed; the environment is appropriate, ventilator settings are adequate; parent presence and participation in providing comfort to the child was facilitated; and initial starting doses of sedation medications were appropriate based on the child’s weight and clinical condition. It is assumed that sedation assessments were accurate, the sedation level scoring tool was used correctly,<sup>122</sup> and that medications were administered correctly and via an intact intravenous line or enterally, as appropriate.

## **Summary**

The three papers outlined in this discussion build progressively toward the goal of answering the primary question explored in this dissertation: Can specific clinical phenotypes be identified for the critically ill child receiving sedation and mechanical

ventilation? The systematic review of the literature and concept analysis in paper one resulted in construction of a model which proposes the key variables impacting the degree of sedation achieved in critically ill children. Paper 2 describes establishment of face and content validity for the factors included in the initial model and seeks additional factors to be tested through a survey of expert pediatric critical care clinicians. Paper 3 describes testing of the refined model using the *RESTORE* dataset.

The dissertation concludes by providing an in-depth discussion of the overall findings and significance of the completed work, the implications for research and practice stemming from the dissertation and how each of the three papers combine to contribute to the knowledge base of pediatric critical care.

## APPENDIX

Table 1:

Medications Frequently Used for Sedation in the Pediatric Intensive Care Unit

Drug Name	Therapeutic Class	Dose Range	Notes
<b>Sedatives</b>			
Midazolam	Benzodiazepine hypnotic sedative	0.06-1.2 mg/kg/hr	Max 7 mg/hr
Lorazepam	Benzodiazepine hypnotic sedative	0.025 mg/kg/hr	Max 2mg/hr
<b>Opioids</b>			
Morphine	Analgesic narcotic	.01-.06 mg/kg/hr	
Fentanyl	Analgesic narcotic	1-10 mcg/kg/hr	
<b>Adjunctive Medications</b>			
Chloral hydrate	Hypnotic sedative	25-75 mg/kg/dose	Max 2 gm/dose
Clonidine	Sedative $\alpha_2$ agonist	Oral: 3-6 mcg/kg/day Transdermal: 0.05-0.1 mg/d	Oral daily dose is given every 4-6 hours
Dexmedetomidine	Sedative $\alpha_2$ agonist	0.2-2.5 mcg/kg/hr	
Diphenhydramine	Sedative	0.5 – 1 mg/kg	
Ketamine	Dissociative general anesthetic	Intermittent: 0.5 – 2 mg/kg 5-20 mcg/kg/min	
Methadone	Narcotic analgesic	0.1 mg/kg/dose	
Pentobarbital	Barbiturate, hypnotic sedative, general anesthetic	1-2 mg/kg/dose	
Propofol	General anesthetic	125-300 mcg/kg/min	< 24 hour limit on infusion

Data compiled from references: 7, 22, 23, 25, 26, 52, 53, 55, 58, 61, 65, and 121

Table 2: Sedation Scoring Tools used in the Pediatric Intensive Care Unit

Tool	Author	Target Population	Descriptors	Indicators	Scale	Reliability & Validity Testing	Notes
COMFORT <sup>42</sup>	Ambuel et al	Pediatric ICU patients newborn to adolescent	8 scale dimensions are each graded 1-5 and summed to give a total score	Alertness Calmness Respiratory activity MAP HR Muscle tone Facial expression	8, unresponsive to 40, Hyper-alert and active  scores < 18 may be used as an indicator of deep sedation	Yes	Global measure of comfort/dis comfort, including pain; includes physiological measures
COMFORT-B <sup>44</sup>	Ista et al	Mechanically ventilated pediatric ICU patients, newborn to adolescent	6 of the COMFORT scale dimensions: HR and MAP removed	Alertness Calmness Respiratory activity Muscle tone Facial expression	6, unresponsive to 30, Hyper-alert and active	Yes	Validity has also been evaluated in young children with Down syndrome <sup>47</sup>
Pediatric Sedation Agitation Scale <sup>45</sup>	Lyden et al	Pediatric ICU patients newborn to adolescent	Level of responsiveness	Response to stimulus or movement	1, unarousable to 7, dangerous agitation	Face and content validity only	Adaptation of an adult scale
Ramsay Sedation-Agitation Scale <sup>81</sup>	Sessler et al	Adult ICU patients	Level of responsiveness, behavior	Response to stimulus or movement	-5, unresponsive to +4, combative	Adult population only	One of the earliest sedation assessment scales developed



State Behavioral Scale <sup>43</sup>	Curley et al	Mechanically ventilated pediatric ICU patients, 6 weeks to 6 years	Level of responsiveness	Level of alertness, respiratory activity, ability to calm	-3 unresponsive to +2 agitated	Yes	
University of Michigan Sedation Scale <sup>40</sup>	Malviya et al	Pediatric patients, newborn to 18 year	Level of responsiveness	Level of alertness, response to stimulus	0, awake to 4, unarousable	Validated for use with procedural sedation	Top of score is awake and alert- no indicators for agitation

MAP= mean arterial pressure

HR= heart rate

ICU= intensive care unit

Table 3: Manuscripts and Specific Aims

Chapter	Specific Aim
Chapter 2 The Difficult-to-Sedate Child: A Concept Analysis	To explore key variables thought to be associated with the difficult-to-sedate child, propose a conceptual model linking those variables in critically ill pediatric patients, and validate or refine the operational definition of the difficult-to-sedate child proposed in Chapter 1.
Chapter 3 Face and Content Validity of Variables Associated with the Difficult-to-Sedate Child in the Pediatric Intensive Care Unit: A Survey of Pediatric Critical Care Clinicians	To assess both face and content validity of the candidate variables identified through the systematic review and incorporated in a preliminary model.
Chapter 4	To build and test a statistical model describing the difficult-to-sedate child clinical phenotype.

Table 4: Operational Definitions

Term	Definition
Sedation Level	Child's observable response to physical and environmental stimuli during the administration of medications intended to decrease the level of response, measured with a valid and reliable sedation scoring tool
Sedation Goal	Desired sedation scoring tool value to be achieved identified by the care team; based on the child's illness trajectory and physiologic and psychosocial ability to tolerate activity, therapies, and environmental stimulation
Appropriate Sedation Dose	Dose of sedation medication which achieves the desired level of sedation, without causing physiologic instability
Optimal Sedation	Child consistently remains within the identified sedation goal range, without requiring frequent medication adjustments or additions
Tolerance	Decreasing clinical effect of a drug after prolonged exposure to it, requiring an increase in dose to achieve the same effect <sup>22</sup>

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## CHAPTER TWO

### The Difficult-to-Sedate Child: A Concept Analysis

Target Journal: Journal of Pediatric Nursing

#### Abstract

Critically ill children requiring mechanical ventilation receive sedation to promote their comfort and ensure their safety. Some children do not respond as expected to the usual sedative medications in typically adequate dosages and are considered “difficult-to-sedate”. A review of the literature indicated that the clinical characteristics of these difficult-to-sedate children have not been well described. The population of mechanically ventilated children examined was heterogeneous and included children from birth to 18 years of age with a variety of medical and surgical diagnoses. The reported incidence of undersedation in this population varied widely by cohort studied. Assessment instruments used to assess level of sedation also varied widely, with no agreement on the definition of undersedation. This paper provides a concept analysis of the phenomenon of the difficult-to-sedate child using the methodology of Walker and Avant. Analysis of the existing literature suggests the following operational definition: the difficult-to-sedate child is characterized as a mechanically ventilated critically ill child routinely requiring escalation of sedation doses beginning on day one of ICU care, as well as the routine administration of adjunctive medications, who reaches doses above the standard range within the first three days of intubation and remains above the target sedation goal. Given that these patients are seen in clinical practice, studies using valid and reliable measures are needed to test this definition in order to develop tailored treatment strategies.

#### Keywords

Child, pediatric intensive care, sedation, sedation assessment, concept analysis

## Highlights

- Children in pediatric ICUs receive sedation to ensure comfort and safety.
- A subset of children do not respond to sedation as expected.
- These children remain under-sedated despite receiving typically adequate sedative doses.
- This group of “difficult-to-sedate” children have not been well characterized.
- Effective characterization could lead to more appropriate targeted interventions.

## The Difficult-to-Sedate Child: A Concept Analysis

When a critically ill child remains agitated, despite providing adequate dosages of sedative agents, clinicians consider them “difficult-to-sedate”. More than 115,000 critically-ill children are admitted to pediatric intensive care units (PICUs) in the United States due to a critical illness or injury each year.(Agency for Healthcare Research and Quality, 2014) Sedation is routinely used in these patients to facilitate their comfort, to help them tolerate invasive therapies, to decrease their anxiety and stress, and to minimize the likelihood of an adverse event, including unplanned endotracheal extubation and removal of life-sustaining invasive catheters.<sup>2-5</sup>

Although sedation is a key element in pediatric critical care, not all patients in the PICU are able to be sedated and remain agitated despite receiving adequate dosages of sedative agents.<sup>2,6</sup> Some of the potential reasons for this fall within clinicians’ control, such as not controlling pain, lack of day-night cycling, or the limitation of parental involvement in the child’s care. However, a portion of these patients are not able to be sedated despite increased doses of multiple sedative agents. Multiple terms have been used to describe these patients, for example, sedation failures or under-sedated patients. This presents a problem because a clear operational definition of this phenomenon is necessary for systematic inquiry.

This paper will identify the individual, process and system variables that help characterize the critically ill difficult-to-sedate child. This information will be synthesized using the concept analysis methodology of Walker and Avant<sup>7</sup> to produce an operational definition of the difficult-to-sedate child. This definition will then be used to frame a conceptual model of key factors impacting the level of sedation achieved in critically ill pediatric patients cared for in the PICU, and ultimately to support further inquiry of the difficult-to-sedate child.

## **Methodology**

Walker and Avant's<sup>7</sup> concept analysis framework was developed to provide a methodical process for defining the core elements of a concept in order to develop an unambiguous operational definition which can then be tested. The purpose of identifying a concept (what something is or how it works) is to develop a mechanism to describe and illuminate a phenomenon of interest, in this case the difficult-to-sedate child. An important aspect of their method is that after a concept is identified, it must be clarified to clearly differentiate it from other concepts. Careful examination of the structure and function of the concept through concept analysis results in concept clarification and differentiation. This strategy requires examination of a concept's basic, essential elements in order to develop a clear, precise operational definition of that concept. The steps involved in concept analysis as described by Walker and Avant<sup>7</sup> are very specific, and are detailed in Box 1.

The concept of the difficult-to-sedate child is highly pertinent to the clinical setting and to the clinical work of nurses caring for critically ill children with respiratory failure who require mechanical ventilation. Benner, Kyriakidis, & Stannard<sup>8</sup> describe how nurses learn to identify patterns of patient responses as they provide care to multiple patients over time and become skilled at using pattern recognition to respond to evolving clinical situations. Nurses not only recognize and interpret these patient patterns but quantify the quality of the response for a particular group or sub-group of patients. This concept, difficult-to-sedate, describes specific patterns that exist in the presentation and behavior of a subset of critically ill children while they are receiving nursing care. Analyzing and clarifying the concept of the difficult-to-sedate child will result in the development of an operational definition that will facilitate incorporating this variable into a conceptual model and allow testing of the variable.

## **Uses of the Concept and Defining Attributes**

### **Uses of the Concept**

Patient sedation is pertinent to several disciplines, including nursing, medicine, pharmacy, and psychology. In order to identify as many relevant studies as possible, multiple data bases were searched to identify original research whose focus was mechanically ventilated critically ill children 2 weeks to 17 years of age receiving sedation. Table 1 provides details of the databases searched, inclusion and exclusion criteria and the search terms used. A table of evidence (see Table 2) was constructed to synthesize study data. Key areas of interest were sedation assessment method, definition of sedation categories used, incidence of undersedation, and any identified risk factors for undersedation. The literature review was conducted and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).<sup>9</sup> Figure 1 provides the PRISMA diagram outlining the search results. The literature review findings emphasize the need for an analysis of the concept of interest. A clear operational definition of the difficult-to-sedate child was not identified.

Sedation is widely used to indicate a calm, relaxed, cooperative state brought about by the administration of a sedative drug. The definitions provided in various sedation scales used in the studies reviewed demonstrate this well. A COMFORT scale score between 17 and 26 is frequently used to define optimal sedation. Descriptors in that range include drowsy, normal muscle tone, calm, occasional slight movement, heart rate at baseline.<sup>10</sup> The COMFORT-B scale is derived from the COMFORT score but eliminates the physiological parameters of heart rate and blood pressure. A score of 11-22 is used to define optimal sedation, and descriptors are similar to the COMFORT score.<sup>11,12</sup> An SBS score of -1, responsive to gentle touch or voice, or 0, awake and able to calm is generally used to describe optimal sedation. Descriptors in these categories

include able to calm with comforting touch or voice when stimulus removed, able to pay attention but drifts off after stimulation, occasional movement of limbs or shifting of position. Descriptors in the inadequate sedation range for the SBS include the following: does not consistently calm/unable to console, or unsafe (biting endotracheal tube, pulling at catheters, cannot be left alone).<sup>13</sup> The COMFORT and COMFORT-B descriptors include hyperalert, panicky, fights ventilator, coughing, choking, screaming, and facial muscles contorted, grimacing.<sup>10,11</sup> This depicts a clear and unambiguous difference in the state of optimal versus inadequate sedation.

It is also important to define difficult. The studies reviewed here describe treatment failure and persistent under-sedation, and the multiple strategies such as adjunctive medications used in an attempt to achieve optimal sedation when describing children who are difficult-to-sedate. Other PICU specific sedation literature supports this definition. The terms “refractory agitation” and “therapy-resistant” are used by van der Zwaan et al.<sup>14</sup> to describe the use of an alternative drug for sedation in a series of four critically ill PICU patients who did not achieve an acceptable level of sedation with usual management.

No studies were undertaken with the purpose of describing the incidence of undersedation in critically ill children or the difficult-to-sedate child. The purpose of the studies identified can be grouped into four categories. These include evaluation of sedation drug effectiveness, psychometric testing of sedation assessment instruments, comparison of sedation assessment instruments with a more objective measure, and evaluation of a sedation protocol. Multiple instruments were used to assess sedation. The definition of over, under and optimal sedation varied between studies, even when the same instrument was used. Incidence of undersedation was reported in a variety of ways and as a result, there was a wide range of reported incidence of undersedation.



Sedation failure was a frequently used term to describe children who were difficult-to-sedate, although the definition of the term was not consistent across studies. Many studies used reaching the maximum infusion dose of the sedation drug with sedation scores remaining in the undersedated range to define difficult-to-sedate children.<sup>15-17</sup> Studies of sedation assessment instruments generally used being unable to maintain sedation scores in the desired range as the definition of undersedation.<sup>10-13</sup> One study identified inadequate sedation management, defined as two or more hours with an SBS score of +1 or +2 despite the provision of appropriate sedation, as an adverse event.<sup>18</sup>

Two demographic characteristics were identified as possibly typical of difficult-to-sedate children; Trisomy 21<sup>11</sup> and young age.<sup>19,20</sup> In general, little information was provided about study subjects who were difficult-to-sedate, limiting the ability to identify characteristics these subjects have in common.

### **Defining Attributes of the Difficult-to-Sedate Child**

Systematic analysis supports considering the following attributes in a description of the difficult-to-sedate child. The child is critically ill and receiving sedation while mechanically ventilated. The child is assessed as undersedated despite reaching the maximum rate of sedative infusion as outlined in commonly accepted practice guidelines. The child requires adjunctive medications due to ongoing sedation scores in the undersedated range. The child is aged birth to 3 years. The child has a diagnosis of Trisomy 21.

The attribute of young age is well supported in the pharmacology literature. Pharmacokinetics and pharmacodynamics studies carried out in both healthy and critically ill pediatric patients show a difference in drug clearance, elimination, and response between neonates, infants, children and adolescents.<sup>21</sup> Factors related to

changes in growth and maturation of organs and physiologic systems drive these differences.<sup>22,23</sup> de Gast-Bakker et al.<sup>24</sup> identified that one to four year old children required higher midazolam doses per kilogram of body weight than other age groups. Morphine, fentanyl and pentobarbital are other sedation medications affected by both age and weight. Critical illness compounds these developmentally driven effects.<sup>25</sup> Ince et al.<sup>26</sup> found decreased midazolam clearance in critically ill children compared with pediatric oncology patients receiving procedural sedation and healthy infants receiving postoperative sedation.

Trisomy 21 as an attribute has limited support. While de Wildt et al.<sup>17</sup> describe treatment failure in a child with the diagnosis of Down syndrome, Valkenburg et al.<sup>27</sup> found similar COMFORT-B cutoff values when assessing pain and distress in children with and without Down syndrome.

Ista et al.<sup>11</sup> also noted that sedation scores trended higher in the day, so unit specific practices related to managing the environment, such as quiet time, may also be a variable to include.

### **Related or Similar but Non-equivalent Concepts**

There are several concepts related or similar to the difficult-to-sedate child.

*Optimal sedation* describes a calm, cooperative child who tolerates the PICU environment. An *oversedated* child is minimally responsive to the PICU environment and may require decreased drug doses. *Procedural sedation* involves a single sedation episode in order to complete a procedure. In this case, the goal is usually that the child receive short-term sedation which is stopped shortly before or at the time the procedure is completed, and the child returns to baseline status. Many children who receive procedural sedation do not require intubation and mechanical ventilation.

*Agitation* is another related concept. Agitation is usually described in terms of physical activity and makes up one element of the sedation assessment scales used here, but agitation alone does not define difficult-to-sedate. *Tolerance*, or the requirement for increasing drug doses over time is also a related but non-equivalent concept. Tolerance develops over time, where the difficult-to-sedate child generally requires steady increases in sedation doses beginning shortly after intubation and the initiation of mechanical ventilation. A study by da Silva et al.<sup>28</sup> identified that children who developed tolerance reached double their initial sedation medication dose between days three and five. Anand et al.<sup>29</sup>, in a multicenter clinical trial which enrolled 419 children found that 16% of the study population received double the initial opioid dose by day 7, which differs from the trajectory described for children who remained difficult-to-sedate in the reviewed studies.

Another related concept is *iatrogenic withdrawal syndrome (IWS)*. Agitation and restlessness are often seen in children experiencing IWS, and are also some of the descriptors of the difficult-to-sedate child. A systematic review by Best, Boullata, and Curley<sup>30</sup> described IWS and identified longer duration of therapy and higher cumulative dose of benzodiazepines and opioids as the two strongest risk factors for the development of IWS. Children we characterize as difficult-to-sedate receive multiple medications at increased doses, putting them at risk for IWS, but IWS develops later in the child's clinical course and the child typically has neurological and gastrointestinal symptoms in addition to agitation or restlessness.

*Delirium* is also a related concept. The European Society of Paediatric and Neonatal Intensive Care (ESPNIC) position statement on assessment of pain, sedation, withdrawal and delirium in critically ill infants and children<sup>31</sup> clearly demonstrates the overlap in presenting signs and symptoms when comparing delirium and the difficult-to-

sedate child. Delirium is a brain dysfunction, manifested as acute onset of disturbances in cognition and consciousness with inattention, altered cognition, and a fluctuating course, which develops over time but has an acute onset.<sup>31-33</sup> Opioids and benzodiazepines have been identified as an underlying cause of delirium in pediatric patients. Three types of delirium have been described in critically ill pediatric patients. Hypoactive delirium is the most common presentation and signs and symptoms are the opposite of the difficult-to-sedate child. The child is withdrawn, apathetic, and unable to focus or interact. Hyperactive delirium presents as agitation, an inability to focus, and inconsolability. The child has altered perception, which may include hallucinations. The severity of the hyperactive behavior fluctuates throughout the day, with the child often becoming more agitated in the evening or night.<sup>31-33</sup> In contrast, the difficult to sedate child is consistently agitated, often hyper alert, with short periods of calm occurring directly after the administration of additional sedatives, and appears to respond to the environment appropriately. The third type of delirium is identified as mixed, with the child fluctuating between a hypoactive and a hyperactive state. As opposed to the difficult-to-sedate child, this fluctuation is not necessarily related to the administration of sedatives, and periods of hypoactivity are variable in length.<sup>32</sup> The child who is difficult-to-sedate consistently has agitated behavior without altered mental status; actions are purposeful and goal directed, such as removal of the endotracheal tube. In a large multi-center point prevalence study of pediatric delirium, Traube et al<sup>34</sup> reported that children who were in the ICU 3 or more days were more likely to have a diagnosis of delirium. The difficult-to-sedate child generally would require escalating treatment in their first day of care.

### **Sample Cases**

The model case presented here is a composite of many patients described in the clinical setting. Susie is an eighteen-month old who has had a developmentally appropriate course. She was admitted to the PICU last night with pneumonia. She was initially managed on non-invasive ventilation but her respiratory failure progressed and she required intubation and mechanical ventilation. Her respiratory status has stabilized. The unit has in place a nurse-managed sedation protocol, which includes sedation assessment using the SBS at least every four hours and with any sedation infusion adjustments, which the nurse implements following the protocol. Susie was started on continuous infusions of midazolam and morphine after receiving bolus doses at the time of intubation. Over the last 8 hours she has required five increases in her midazolam infusion and multiple bolus doses, as her SBS score is consistently +1 (restless and difficult to calm) to +2 (agitated). Susie's mother is at the bedside and is providing appropriate soothing strategies. Susie's nurse has determined that Susie is not in pain, that her intravenous line is patent, and that she is not hypoxic. After Susie sits bolt upright in bed which threatens the security of her endotracheal tube, the nurse calls the nurse practitioner to the bedside to request an evaluation of Susie's sedation plan. Pentobarbital is ordered and given as an adjunctive medication. Susie doses off, and her nurse and mother breathe a sigh of relief. Thirty minutes later Susie is again awake and agitated, with an SBS score of +1. In this model case, Susie demonstrates the attributes identified through the concept analysis. On her first day of intubation, Susie's medications are rapidly escalated per the sedation protocol, but she remains agitated. She requires adjunctive medications, but does not achieve optimal sedation for more than a short time. There are no underlying causes such as pain or hypoxia that would explain her agitation. Her mother is present at the bedside and providing appropriate support. She does not reach a state of optimal sedation.

A borderline case contains some but not all of the required attributes. Sam is a 6 month old admitted from the emergency department to the PICU intubated and mechanically ventilated with respiratory failure due to respiratory syncytial virus. Morphine and midazolam infusions are begun per protocol. Sam's SBS score fluctuates between 0 (awake and able to calm) and +1, and he requires bolus doses of midazolam about every 2 hours. He has required one increase in his midazolam infusion in the course of a 12 hour shift. His mother is at the bedside providing appropriate support. In this case, Sam has required a single increase of his infusion, but does not require adjunctive medications, and reaches the desired level of sedation for a significant portion of the time.

A related case contains some of the attributes of the identified concept. John is a three year old, admitted to the PICU intubated and mechanically ventilated after abdominal surgery. He is begun on the sedation protocol, and over the course of a 12 hour shift, his nurse increases his morphine infusion twice, his midazolam infusion once, and he receives a total of 9 bolus doses. John's SBS score is 0 to -1 (responsive to gentle touch or voice), but his pain score is consistently 4 or 5/10, until 20 minutes after the second increase in his morphine infusion, when it decreases to 2/10. In this case, increases in the medication infusions were required, as well as additional bolus doses, but John did not have an elevated SBS score. Once his pain was well controlled, he did not require further increases. He also did not require any adjunctive medications.

Contrary cases are cases that clearly do not represent the concept described, and in fact are the opposite of model cases. For example, Justine is a five year old admitted to the PICU with respiratory failure, intubated after failing a trial of hi-flow nasal cannula. She is begun on the sedation protocol, and her first SBS score assessment is -3 (unresponsive). Her nurse attributes this to the medications she received to facilitate

intubation. After 4 hours Justine is again assessed, and her SBS score remains -3. Per protocol, the nurse decreases Justine's midazolam infusion, but her SBS score remains -3 to -2 (responsive to noxious stimuli). Her sedation infusion continues to be decreased per protocol until Justine's SBS score reaches -1. Justine's response to the sedation medication differed in that she required a much smaller dose than usual, and in fact was oversedated for a period of time. As her infusion dose was decreased she became less sedated, but remained in the optimal sedation range.

These clinical cases all involve PICU patients receiving sedation to facilitate mechanical ventilation, but demonstrate each patient's individual response to sedation. Susie, John, and Justine represent different patterns of response to sedation. Justine is oversedated in response to the typical sedation dose, John achieves optimal sedation, and Susie represents the difficult-to-sedate child.

### **Identify Antecedents and Consequences**

Antecedents are events that must take place prior to the occurrence of the concept.<sup>7</sup> A significant antecedent for the difficult-to-sedate child is that the child requires sedation for ICU therapies. Others include a care team knowledgeable about standard sedation dosing and administration, a valid and reliable instrument for measuring level of sedation, and an identified sedation score goal for the patient. Another is that no other reason exists which could cause the child to remain agitated, for instance hypoxia, untreated pain, technology issues such as a malfunctioning IV pump or catheter, or incorrectly mixed sedation medication solutions. Unit culture may be another antecedent of this concept. It is possible that local practices may influence identification of children as difficult-to-sedate, as some subjectivity occurs with the use of assessment instruments. Over time, there may be practice drift, and more children may be scored as undersedated. For example, a unit with a high rate of unplanned extubation may

interpret any activity as concerning, score children as undersedated and as a result increase medication doses, or more readily utilize adjunctive medications.

As described by Walker and Avant<sup>7</sup>, consequences are the outcomes of a concept. In the case of the difficult-to-sedate child, having knowledge of this pattern of response to sedation therapy might result in earlier treatment, more appropriate drug selection, and anticipation and avoidance of adverse outcomes. It would also guide interactions and communication with the family, to help them understand how management will be tailored to their child based on the child's response to therapy. There is also the possibility of negative consequences. If the clinician inaccurately identifies the child as difficult-to-sedate, the therapy and care provided may be excessive, or an underlying condition such as hypoxia may not be identified and treated. This would result in harm the patient.

### **Empirical Referents**

The final step in the concept analysis is defining empirical referents. Walker and Avant<sup>7</sup> define empirical referents as ways in which the concept is measured or determined. There are several empirical referents of the difficult to sedate child, and not all of them must be present at any one time. Sedation scores are a primary empirical referent. Empirical referents include other clinical signs and symptoms, for example agitation, response to medication, ventilator dysynchrony or inability to achieve the target sedation goal despite multiple medication adjustments. Patient characteristics such as age, gender, weight, strength or mobility are also empirical referents. Physiologic measures include heart rate and blood pressure, sweating, and response to usual therapies administered.

### **Operational Definition**



As a result of the iterative process of analyzing the concept of the difficult-to-sedate child this operational definition is provided: the difficult-to-sedate child is characterized by a mechanically ventilated critically ill child routinely requiring escalation of sedation doses beginning on day one of ICU care, as well as the routine administration of adjunctive medications who reaches doses above the standard range within the first three days of intubation and remains above the target sedation goal. It is likely that this child is young, and possible that the child has a diagnosis of Down syndrome. This classification facilitates prediction of trajectory, selection of appropriate therapies on the part of the provider and improved and clinically meaningful outcomes.

### **Conceptual Model**

Themes identified through the literature review point to three types of factors to consider in constructing a conceptual model of sedation in the critically ill child. Demographic and medical history factors include age, severity of illness, and coexisting diagnoses, such as Down syndrome. Weight or body-mass index, unique genetic code and the child's physiology may also be important as these impact drug distribution and clearance. Factors specific to the environment where care is provided may include unit practices related to parent presence and maintaining normal day/night cycles, as well as staffing ratios, interrater reliability for sedation assessment instruments used and the degree of adherence to sedation protocols. Factors specific to the process of providing and managing sedation include the sedation assessment instrument selected, use of a sedation protocol, whether the protocol is nurse-driven, standard and adjunctive medications used and local standards for maximum allowable dose. Figure 2 provides a depiction of the model developed.

### **Discussion**

The existing literature does not present a clear operational definition of the critically ill, difficult-to-sedate child requiring sedation. The current literature identifies the use of multiple sedation assessment instruments, several of which have not been tested for validity or reliability. Difficult-to-sedate is not consistently defined in the studies reviewed, and the incidence of difficult-to-sedate is reported in a variety of ways. Few characteristics of the difficult-to-sedate groups were reported. It is evident from the literature that difficult-to-sedate children are routinely seen in clinical practice, and require a different approach to sedation.

The benefit of identifying difficult-to-sedate children early in their treatment course is clear. The clinical manifestations seen in this group of children have an immediate impact on the patient, family and clinician. Sustained periods of agitation impact the child's psychologic and physiologic health. Parents may feel less confident in the care team if they perceive the team is unable to manage their child's clinical state.

The goal of identifying children who have the difficult-to-sedate pattern of response to sedation is also very much in keeping with the National Precision Medicine initiative. The goal of this initiative is to identify which treatments will work best for which patients. Stated simply, the goal of precision medicine is to deliver the right treatment to the right patient at the right time to facilitate more appropriate, targeted management.<sup>35</sup> Clearly describing the population of children who are difficult-to-sedate could facilitate rapidly achieving the targeted sedation goal in this group, by identifying that these children need a different sedation approach than the "typical" child and require different sedation agents at different doses. This could also minimize the risk of adverse events and the negative effects of excessive sedation medications.

## **Future Directions**

The model developed identifies several variables appropriate to investigate in validating the operational definition of the difficult-to-sedate child. The validated definition can then be used in further studies with the goal of early patient identification, early intervention, and the development of effective treatment strategies, both pharmacologic and non-pharmacologic. There is also the opportunity to test the economic impact of early identification of the difficult-to sedate child population, as caring for these children increases the need for nursing resources, there are increased drug costs, and the current management strategies may increase both PICU and hospital length of stay.

The difficult-to-sedate child describes a patient population that presents challenges to the care team, and increases the stress of the child and family at an already stressful time. Studies are needed to validate the characteristics of the difficult-to-sedate child in order to describe this group of children who consistently demonstrate a particular pattern of response to sedation. This would support the development of tailored treatment strategies and more effective management. Identifying the demographic, physiologic and developmental characteristics associated with differing responses to sedation will assist the care team to provide specific and individualized sedation strategies for critically ill children. This goal is in keeping with current, innovative research in other areas, which seeks to identify targeted therapies.

The next step in moving this work forward will be a survey of PICU clinicians in order to establish face and content validity of the factors outlined in the model as characteristic of the difficult-to-sedate child. Those characteristics that are identified as valid can then be solidify the proposed operational definition of the difficult-to-sedate child clinical phenotype. The proposed clinical phenotype can then be tested prospectively and if found to be valid can then be used as the basis for further

investigation to establish additional characteristics this group of difficult-to-sedate children have in common. Once the clinical phenotype is well described, a further step would be to search for an associated genotype. Clarification of the concept of the difficult-to-sedate child identifies that different sedation strategies are needed for different subgroups of critically ill pediatric patients. PICU nurses, as the members of the care team who spend the most time with these children, have a vested interest in understanding this patient population and play a key role in moving this research forward.

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Table 1: Search Strategy

- PubMed, EMBASE, Web of Science, SCOPUS, CINAHL, and the Cochrane Database of Systematic Reviews and Central Register of Controlled Trials were searched.
- Inclusion criteria: original research on the topic of sedation to facilitate intubation and mechanical ventilation in pediatric critical care patients 2 weeks to 17 years of age from January 1, 1985 through March 31, 2017.
- Additional inclusion criteria:
  - level of sedation was measured with a scale
  - the study included a definition of under, over, and optimal sedation.
  - Papers published in languages other than English which had an abstract translated into English were screened, and two articles were subsequently translated for review.
- Exclusion criteria: studies focused on dental sedation, procedural sedation, perioperative sedation, sedation for comfort care, pain, studies in the neonatal intensive care population, and studies including non-intubated patients.
- Reference lists of articles included in the review were examined to identify additional studies for inclusion.
- A research librarian was consulted to ensure an effective search strategy.

Search terms:

1. ventilator\* OR ventilation\* OR respirator\* OR Respiration, artificial OR artificial respiration OR Intubation OR endotracheal OR mechanically ventilate OR ventil\* OR artificial ventilation
- AND

2. infant\* OR neonate\* OR newborn\* OR pediatric OR paediatric OR child OR children OR teen\* OR adolescent\* OR youth OR juvenile  
AND
3. sedation quality\* OR quality of sedation OR sedation level OR level of sedation  
AND
4. pediatric critical care OR paediatric critical care OR paediatric intensive care OR pediatric intensive care OR PICU  
AND
5. measur\* OR evaluat\* OR tool\* OR battery OR instrument\* OR inventor\* OR checklist OR indicator OR score\* OR scoring OR questionnaire OR series OR scale\* OR protocol\* OR appraisal OR assessment OR behavior\* OR guideline OR algorithm OR sedation scale OR sedation assess\* OR sedation protocol  
AND
6. nurs\* OR nursing assess\* OR nursing assessment  
AND
7. pharmacodynamic OR sedat\* OR midazolam OR lorazepam OR diazepam OR benzodiazepine\* OR fentanyl OR remifentanyl OR morphine\* OR ketamine OR dexmedetomidine OR clonidine OR pentobarbital OR opioid\* OR propofol OR hypnotic OR depressant OR narcotic\* OR \*drug therapy OR drug utilization

Table 2: Studies Evaluated

Study	Site	Design/Testing	Sample Size	Age	Sedation Assessment Scale	Under, over, optimal Sedation Definition	Undersedation Incidence (%)
Dreyfus et al (2017) <sup>36</sup>	PICU France	Prospective observational  Sedation protocol	n= 200	0 to 18 years	COMFORT-B	<b>Under &gt;17</b> Optimal 11-17 <i>Over &lt;11</i>	4% pre-protocol 8% post-protocol
Gaillard-Le roux et al (2017) <sup>37</sup>	PICU France	Prospective observational  Sedation protocol	n= 194	28 days to 18 years	COMFORT-B	<b>Target 1</b> <b>Under &gt;17</b> Optimal 11-17 <i>Over &lt;11</i> <b>Target 2</b> <b>Under &gt;11</b> Optimal 8-11 <i>Over &lt;8</i>	Not reported
Beytut et al (2016) <sup>38</sup>	PICU Turkey	Prospective observational  Sedation protocol	n = 37	2 to 9 years	COMFORT	<b>Under &gt;26</b> Optimal 17-26 <i>Over &lt;17</i>	Not reported
da Silva et al (2016) <sup>28</sup>	PICU Brazil	Pragmatic RCT  Drug	n = 112	3 to 14 months	COMFORT-B	<b>Under &gt;22</b> Optimal 11-22 <i>Over &lt;11</i>	257 episodes of agitation reported
Curley et al (2015) <sup>15</sup>	PICUs US	RCT  Sedation protocol	n= 2449	2 weeks to 17 years	SBS	<b>Under +1/+2</b> Optimal -1/0 <i>Over -3/-2</i>	547 events SBS +1/+2 for 2 hours despite treatment
Neunhoeffler et al (2015) <sup>39</sup>	PICU Germany	Non-randomized intervention trial	n = 172	0 to 18 years	COMFORT-B NISS	<u>COMFORT-B</u> <b>Under &gt;22</b> Optimal 12-18 <i>Over &lt;12</i>	COMFORT-B 2168 observations 18% NISS

		Sedation protocol				<u>NISS</u> <b>Under 1</b> Optimal 2 <i>Over 3</i>	2168 observations 11%
Wolf et al (2014) <sup>17</sup>	PICUs UK (10)	RCT  Drug	n = 125	1 month to 15 years	COMFORT	<b>Under &gt;26</b> Optimal 17-26 <i>Over &lt;17</i>	Treatment failure 19/125 (15.2) Percent of time undersedated 0-54
Silva et al (2013) <sup>40</sup>	PICU Brazil	Prospective observational  BIS monitor	n = 11	1 month to 16 years	COMFORT-B	<u>COMFORT-B</u> <b>Under &gt;23</b> Optimal 11-23 <i>Over &lt;11</i> <u>BIS</u> <b>Under &gt;80</b> Optimal 40-79 <i>Over &lt;40</i>	COMFORT-B 5.7-11.5% BIS 14.3%
Amigoni et al (2012) <sup>41</sup>	PICU Italy	Prospective observational  BIS monitor	n = 46	Birth to 6 years	COMFORT-B	<u>COMFORT-B</u> <b>Under &gt;22</b> Optimal 11-22 <i>Over &lt;11</i> <u>BIS</u> <b>Under &gt;80</b> Optimal 40-80 <i>Over &lt;40</i>	COMFORT-B 0 BIS 2/46 (4.3)
Ista et al (2009) <sup>42</sup>	PICU The Netherlands	Non-randomized intervention trial	n = 131	0 to 3 years	COMFORT-B NISS	<u>COMFORT-B</u> <b>Under &gt;22 OR 11-22 with NISS 1</b> Optimal 11-22 with NISS 2 <i>Over &lt;11</i>	461/3573 observations identified as undersedated (12.9)



		Sedation protocol				<i>OR 11-22 with NISS 3</i> <u>NISS</u> <b>Under 1</b> Optimal 2 <i>Over 3</i>	
Darnell et al (2008) <sup>43</sup>	PICU US	RCT  Drug	n = 72	1 day to 18 years	MMAAS	<b>Under +3</b> Optimal +2 to -2 <i>Over -3</i>	Reported mean number of times subjects undersedated without a denominator: 16.7 naloxone group, 14.6 placebo group.
Bustos Bu et al (2007) <sup>44</sup>	PICU Chile	Prospective observational  BIS monitor	n = 9	9 months to 14 years	COMFORT	<b>Under &gt;26</b> Optimal 17-26 <i>Over &lt;17</i>	7/90 BIS observations (7.8)
Curley et al (2006) <sup>13</sup>	PICUs US	Prospective observational  Sedation Scale metrics	n = 91	6 weeks to 6 years	SBS	<b>Under +1/+2</b> Optimal -1/0 <i>Over -3/-2</i>	8/198 (4)
De Wildt et al (2005) <sup>11</sup>	PICU The Netherlands	Prospective observational  Drug	n = 21	2 days to 17 years	COMFORT	<b>Under &gt;26</b> Optimal 17-26 <i>Over &lt;17</i>	14/242 episodes of COMFORT score > 26 (5.8) Note: Could not reach target sedation in one patient with Trisomy 21
Ista et al (2005) <sup>14</sup>	PICU The Netherlands	Prospective observational  Sedation Scale metrics	n = 78	Birth to 18 years	COMFORT-B NISS	<u>COMFORT-B</u> <b>Under &gt;22</b> Optimal 11-22 <i>Over &lt;11</i> <u>NISS</u> <b>Under 1</b> Optimal 2 <i>Over 3</i>	93/843 (11)  Note: Daytime scores consistently higher

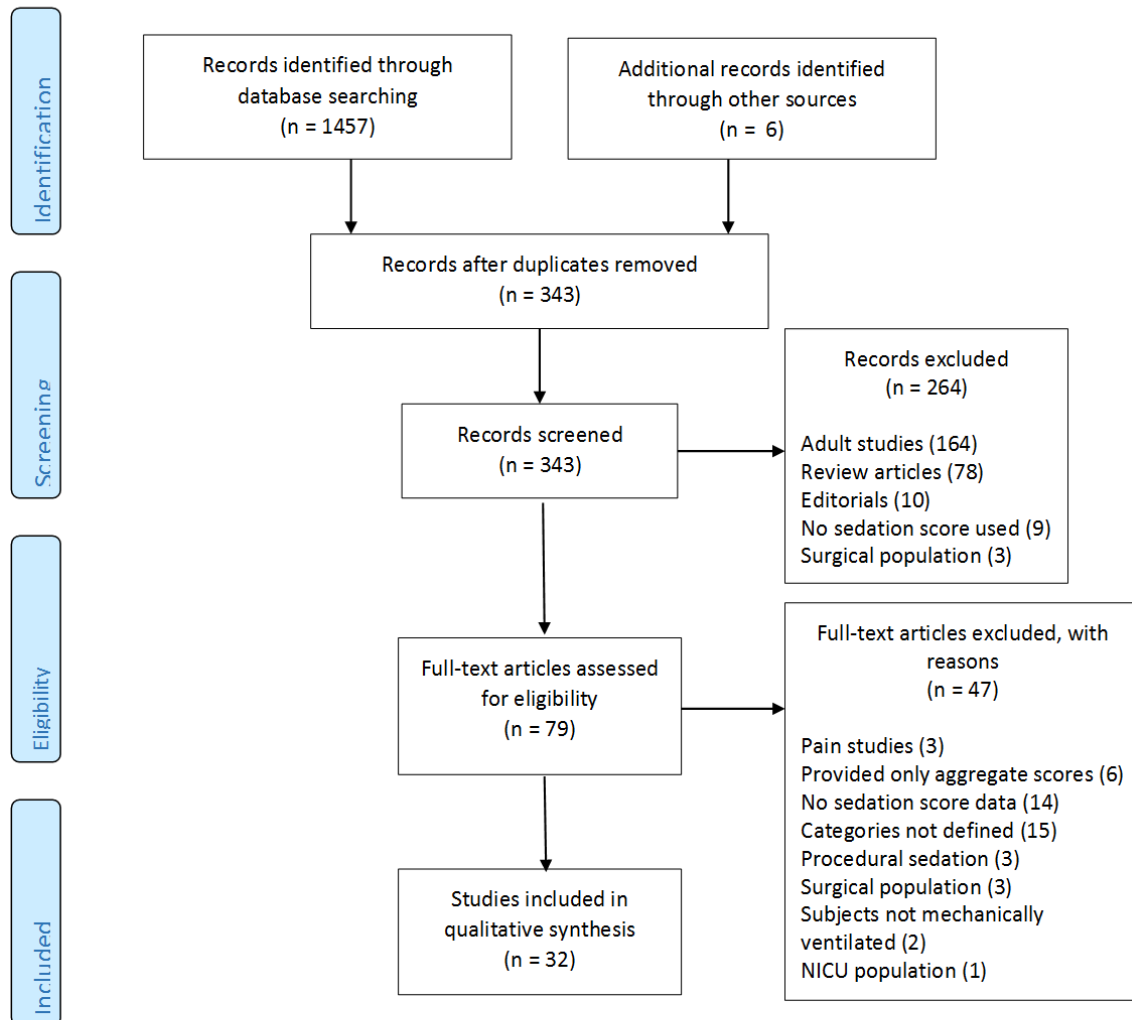
Triltsch et al (2005) <sup>45</sup>	PICU Germany	Prospective observational  BIS monitor	n = 40	3 weeks to 16 years	COMFORT	<u>COMFORT</u> <b>Under &gt;26</b> Optimal 17-26 <i>Over &lt;17</i>	0/40 (0)
Twite et al (2005) <sup>5</sup>	PICU US	Prospective observational  BIS monitor	n = 75	1 month to 12 years	COMFORT	<u>BIS</u> <b>Under &gt;80</b> Optimal 61-79 <i>Over &lt;61</i>	9.5% of observations
Arenas-Lopez et al (2004) <sup>10</sup>	PICU UK	Prospective observational  Drug	n = 14	1 month to 3 years	COMFORT	COMFORT <b>Under &gt;23</b> Optimal 13-23 <i>Over &lt;13</i>	110/1022 hours (10.8) Treatment failure 3/24 (12.5)
Tobias & Berkenbosch (2004) <sup>46</sup>	PICU US	RCT BIS monitor  Drug	n = 30	2 months to 8 years	Ramsay BIS	<u>Ramsay</u> Under 1	12/30 subjects had at least one episode of undersedation Total number of episodes not provided
Aneja et al (2003) <sup>47</sup>	PICU US	Prospective observational  BIS monitor	n = 48	3 months to 18 years	Ramsay	<b>Under 1</b> Optimal 2-5 <i>Over 6</i>	42/458 observations (9.2)
Courtman et al (2003) <sup>48</sup>	PICU UK	Prospective observational  BIS monitor	n = 43	1 month to 16 years	COMFORT BIS	<u>BIS</u> <b>Under &gt;80</b> Optimal 40-80 <i>Over &lt;40</i>	49/373 observations (13.1)
Alexander et al (2002) <sup>49</sup>	PICU Canada	Retrospective observational  Sedation protocol	n = 10	children	COMFORT	<b>Under &gt;18</b> Optimal 14-18 <i>Over &lt;14</i>	11/14 episodes (78.6)
Berkenbosch et al (2002) <sup>50</sup>	PICU US	Prospective observational	n = 24	1 month to 20 years	PICU scale Tracheal suctioning scale	<u>Ramsay</u> <b>Under 1</b> Optimal 2-4	37/426 observations (8.7)

		BIS monitor				Over 5-6	
Crain et al (2002) <sup>51</sup>	PICU US	Prospective observational BIS monitor	n = 31	1 month to 5 years	COMFORT	<u>COMFORT</u> <b>Under &gt;26</b> Optimal 17-26 <i>Over &lt;17</i> <u>BIS</u> <b>Under &gt;80</b> Optimal 40-80 <i>Over &lt;40</i>	5/62 observations (8.1%)
Ambrose et al (2000) <sup>9</sup>	PICU UK	Prospective observational  Drug	n = 30	1 day to 3 years	0 – 10 sedation scale	<b>Under &lt;2</b> Optimal 2-7 <i>Over &gt;7</i>	2/30 treatment failure (6.7)
Playfor et al (2000) <sup>52</sup>	PICU UK	Prospective observational  Drug	n = 28	1 month to 16 years	Ratcliff scoring system	1, 2, 4 = acceptable 3, 5 = unsatisfactory	8/81 observations (9.8)
Brunow de Carvalho et al (1999) <sup>53</sup>	PICU Brazil	Prospective observational  Sedation Scale metrics	n = 18	2 weeks to 5 years	COMFORT Hartwig	<u>COMFORT</u> <b>Under &gt;26</b> Optimal 17-26 <i>Over &lt;17</i> <u>Hartwig</u> <b>Under &gt;18</b> Optimal 15-18 <i>Over &lt;15</i>	COMFORT 2/30 (6.7) Hartwig 5/30 (16.7)
Parkinson et al (1997) <sup>16</sup>	PICU UK	RCT  Drug	n = 43	0 to 15 years	1 – 5 descriptive scale	<b>Under 3, 5</b> Optimal 2, 4 <i>Over 1</i>	294/799 observations (36.8) Treatment Failure 2/43 (4.7)
Reed et al (1996) <sup>54</sup>	PICU US	Non-randomized	n = 28	1 week to 15 years	COMFORT	<b>Under &gt;26</b> Optimal 17-26 <i>Over &lt;17</i>	5/28 subjects (17.9)

		intervention trial					
		Drug					
Marx et al (1994) <sup>3</sup>	PICU US	Prospective observational  Sedation Scale metrics	n = 85	0 to 8 years	COMFORT  Descriptive scale	<u>COMFORT</u> <b>Under &gt;26</b> Optimal 17-26 <i>Over &lt;17</i> <u>Descriptive</u> <b>Inadequately sedated = 3</b> <i>Too sedated = 1</i>	COMFORT 14/110 observations (12.7) Descriptive 18/110 observations (16.4)
Arnold et al (1993) <sup>55</sup>	PICU US	Prospective observational Drug	n= 10	3 weeks to 19 years	Clinical Sedation Score	<b>Under 1</b> Optimal 2-5 <i>Over 6</i>	21% of total administration time
Rosen & Rosen (1991) <sup>56</sup>	PICU US	Retrospective observational  Drug	n = 55	Birth to 19 years	Five point activity scale	<b>Under &gt; 3</b> Optimal 2-3 <i>Over 1</i>	<10% of total infusion time

BIS = bispectral index; COMFORT = Comfort scale; COMFORT-B = COMFORT behavioral scale; MMAAS = Modified Motor Activity Assessment Scale; NISS = Nurse Interpretation of Sedation Scale; RCT = randomized controlled trial; SBS = State Behavioral Scale; UK = United Kingdom; US = United States.

**Figure 1: PRISMA Flow Diagram**  
**PRISMA Flow Diagram**



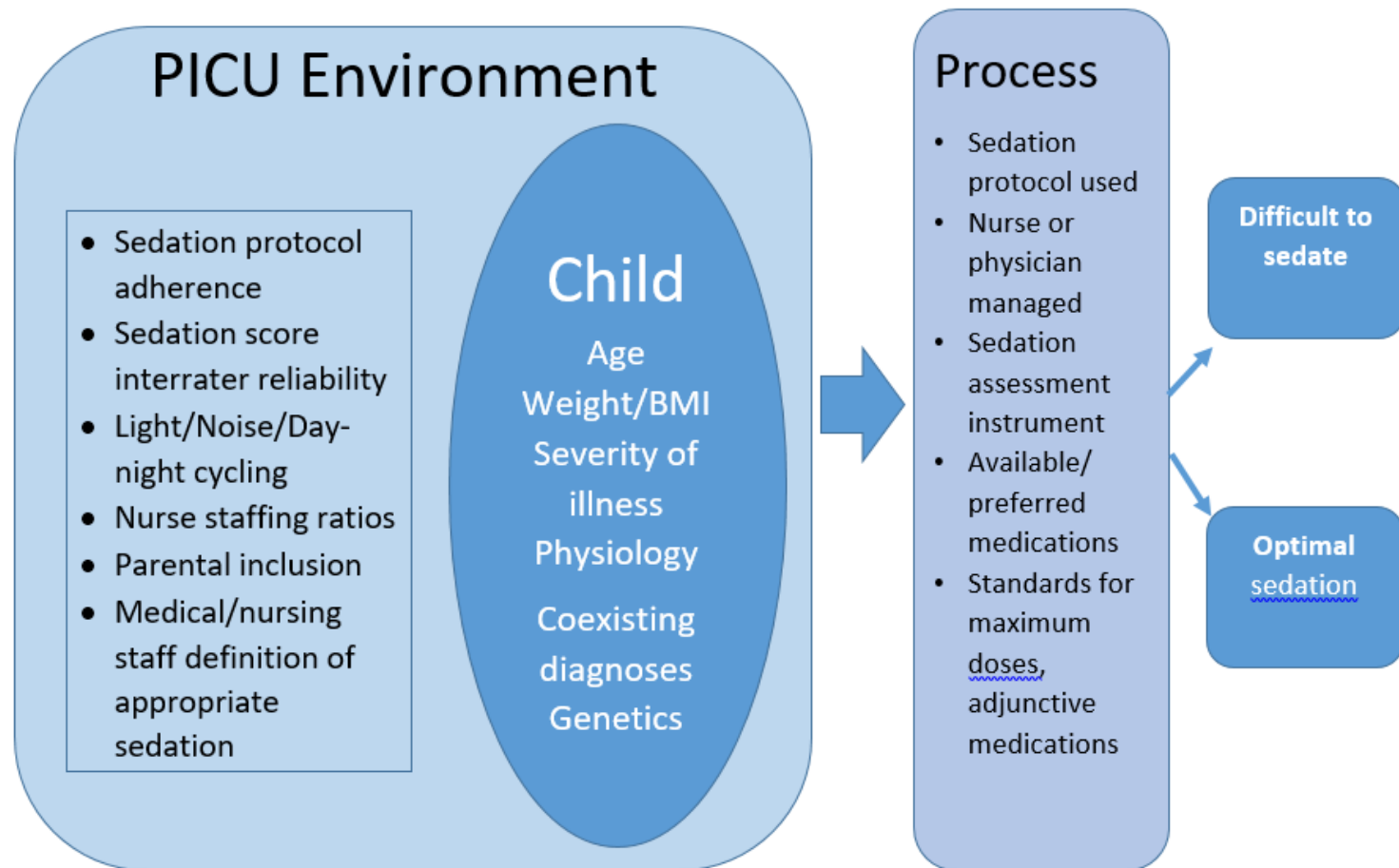
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Box 1: Sequential Steps in the Walker & Avant Method of Concept Analysis

1. Identify the concept for analysis; the phenomenon of interest
2. Determine the aims of the analysis, such as clarify the meaning of a concept or create an operational definition
3. Identify all uses of the concept, including dictionary definitions and use of the concept in fields other than nursing
4. Review all uses identified to determine the concept's defining attributes; characteristics that appear consistently in all sources reviewed
5. Identify related or similar, but non-equivalent concepts
6. Identify a model case; a "real world" case that includes all defining attributes
7. Identify borderline (many but not all defining attributes are present), related (a few of the defining attributes are present), and contrary (cases that are the opposite of the described concept)
8. Identify antecedents (events that must occur prior to the concept occurring) and consequences of the concept
9. Identify empirical referents (how a concept is measured or determined)

Walker, L.O., & Avant, K.C. (2011). *Strategies for theory construction in nursing*. (5th ed.). Boston, MA: Prentice Hall.

Figure 2: Conceptual Model



## CHAPTER 3

### Face and Content Validity of Variables Associated with the Difficult-to-Sedate Child in the Pediatric Intensive Care Unit: A Survey of Pediatric Critical Care Clinicians

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## Abstract

Background: Clinicians recognize that some critically ill children are difficult-to-sedate. It may be possible to identify this unique clinical phenotype for sedation response using statistical modeling techniques adopted from machine learning. This requires identification of a finite number of candidate variables to include in the statistical model.

Objective: To establish face and content validity for 17 candidate variables identified in the literature as characteristic of the difficult-to-sedate child phenotype.

Methods: Pediatric critical care clinicians rated the relevance of 17 candidate variables characterizing the difficult-to-sedate child using a four-point scale ranging from not (1) to highly relevant (4). Face and content validity of these variables were assessed by calculating a mean score for each item and computing an item-level content validity index. Any item with a mean score  $>1$  was rated as having adequate face validity. An item-level content validity index  $\geq 0.70$  indicated good to excellent content validity.

Setting and Participants: Web-based survey emailed to members of the Pediatric Acute Lung Injury & Sepsis Investigators Network or the Society of Critical Care Medicine Pediatric Sedation Study Group.

Results: Of 411 possible respondents, 121 useable surveys were returned for a response rate of 29%. All items had a mean score  $>1$ , indicating adequate face validity. Ten of 17 items scored an item-level content validity index  $\geq 0.70$ . The highest scoring items were requiring three or more sedation classes

simultaneously, daily modal sedation score indicating agitation, sedation score indicating agitation for 2 consecutive hours, receiving sedatives at a dose >90th percentile of the usual starting dose and receiving intermittent paralytic doses for sedation.

Conclusions: Computation of an item-level content validity index validated candidate variables to include in statistical modeling of the difficult-to-sedate phenotype. The results indicate consensus among pediatric critical care clinicians that the majority of candidate variables identified are characteristic of the difficult-to-sedate child.

## Introduction

Each year, more than 115,000 critically ill children receive sedation to help them tolerate intubation and mechanical ventilation.<sup>1</sup> A substantial number of these children do not respond as expected to appropriately dosed sedation and remain agitated for some period of time, leading to iatrogenic injury and increased stress.<sup>2-5</sup> These children, who remain agitated despite receiving usual doses of sedation, or who eventually reach their target sedation goal but require much larger amounts of sedative drugs, are considered by the clinical team to be difficult-to-sedate. Little is known about the reasons contributing to this phenomenon in these children, preventing early identification of the child who will be difficult-to-sedate. The child is often identified as difficult-to-sedate at the time care providers are actively administering sedative drugs, resulting in a delay in the attainment of therapeutic concentrations and the desired clinical effect. This experience causes excessive and potentially avoidable burden on the child and family, and increases the chances that the child's safety has been compromised, and injury may have occurred. Developing a mechanism to identify the difficult-to-sedate child could allow for early identification, and prepare the care provider with *a priori* knowledge that the child may require more than the typical sedation needs. However, the first step towards the goal of early identification is consensus on the characteristics defining the difficult-to-sedate child.

## Background

Many factors hamper identification of the difficult-to-sedate child. Sedation in the pediatric intensive care unit (PICU) is a complex phenomenon,

impacted by multiple variables. Easily implemented, valid and reliable instruments that describe sedation levels in children have only become available and widely used in the last decade.<sup>6,7</sup> Patients cared for in the PICU vary widely in age and encompass enormous physiological and psychosocial differences. Although well-studied in adults, there are limited data on the metabolism and elimination of drugs commonly used for sedation in critically ill children.<sup>8,9</sup> Organ maturation and critical illness affect the rate at which sedation medications are distributed, metabolized and eliminated from the body. The influence of psychosocial development in response to sedation is not thoroughly described. There may be a genetic basis for the difficult-to-sedate child, due to polymorphisms in the genes that encode drug metabolizing enzymes as well as pertinent receptors.<sup>3,10</sup> Finally, each PICU's individual sedation management plan dictates how and when sedation is delivered, the specific agents and doses used to provide sedation, as well as the definition of optimal levels of sedation. These factors contribute to the challenge of studying sedation in critically ill children.

Defining sedation-related clinical phenotypes in critically ill children would facilitate better clinical management of these patients while decreasing potential harm. Specifically, insight into an individual child's response to sedation would allow the selection of personalized therapy and potentially contribute to improved clinical outcomes. Phenotype identification supports treatments geared to the needs of individual patients by considering each individual's unique genetic, biomarker, phenotypic or psychosocial characteristics that distinguish them from other patients with similar presentations.<sup>11</sup> High doses of sedatives and the

simultaneous use of multiple sedative agents, as typically occurs in the difficult-to-sedate child, generally results in adverse effects such as hypotension, bradycardia, propofol infusion syndrome and iatrogenic withdrawal syndrome.<sup>12</sup> Based on recent evidence that prolonged or repeated use of sedative and anesthetic drugs may negatively affect the developing brain by causing brain cell death, the United States Food and Drug Administration has required a warning be added to drug labels indicating that brain development in children three and under may be affected by exposure to these drugs. Included in this group are some of the most commonly used pediatric sedation drugs including midazolam, lorazepam, pentobarbital, ketamine and propofol.<sup>13</sup> Identifying and providing targeted sedation strategies most effective for the difficult-to-sedate child could minimize these effects.

An operational definition of the difficult-to-sedate child clinical phenotype does not exist. In other populations, advanced statistical methods including cluster, classification and regression tree, and latent class analysis have been used to analyze large datasets and create an operational definition of specific phenotypes within a disease process such as childhood asthma, pediatric sepsis or acute respiratory distress syndrome.<sup>14-16</sup> These statistical methods require identification of candidate variables likely to be associated with the concept under investigation. In the case of intubated and sedated children, the difficult-to-sedate child clinical phenotype might include a combination of demographic, physiologic, genetic and developmental factors.<sup>17-19</sup>

We sought to create an operational definition of the difficult-to-sedate clinical phenotype using a large data set from the Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) study (clinicaltrials.gov identifier: NCT00814099).<sup>20</sup> This data set of 2,449 children with acute respiratory failure contains hundreds of variables and millions of data points, requiring a thoughtful approach to identifying candidate variables. Completion of a concept analysis using the methodology described by Walker and Avant<sup>21</sup> was the first phase in identifying candidate variables from those available in the *RESTORE* database.

The next phase in creating our operational definition involved assessing face and content validity of the candidate variables identified in order to substantiate their appropriateness and ensure all possible candidate variables were included. Face and content validity are generally used in instrument assessment. Face validity assesses whether an instrument seems to measure what it purports to measure. It assesses the relevance of an item to a construct in the opinion of experts.<sup>22</sup> Content validity is generally used to assess whether the content of an instrument is inclusive and representative of the domain of interest; i.e., do the items completely measure the domain.<sup>23-25</sup> Polit and Beck<sup>25</sup> note that content validity assesses if the items in the tool, when considered as a group, provide a reasonably complete operational definition of the construct being measured. Although not intended to be a formal instrument for repeated use, our survey was constructed to include what we had identified as the characteristics of the difficult-to-sedate child phenotype. Here we report on the

face and content validity of candidate variables potentially characteristic of the difficult-to-sedate phenotype in children based on our survey of expert pediatric critical care clinicians.

## **Methods**

### **Design and Data Collection**

This study consisted of a web-based survey sent to a purposive sample of experts, practicing pediatric critical care providers, and is described here using the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).<sup>26</sup> The survey link was sent via e-mail to all members of the Pediatric Acute Lung Injury & Sepsis Investigators (PALISI) network and to all members of the Society of Critical Care Medicine (SCCM) Pediatric Sedation Study Group. These groups were chosen because members are practicing critical care clinicians with extensive experience in pediatric critical care and sedation. PALISI members are clinical researchers from PICUs across North America who collaborate to conduct multi-center research studies concerning pediatric critical illness, with a focus on interventions and outcomes.<sup>27</sup> Members of the SCCM Pediatric Sedation Study Group are critical care clinicians from the United States with a strong interest in pediatric sedation and knowledge of best practices. The group's primary charge is to develop guidelines related to pediatric sedation. The Institutional Review Board of the University of Pennsylvania reviewed the study and determined it to be exempt from full board review. No personal information was collected and data was stored on a password-protected drive, to which only the investigators had access.



As described above, we developed the list of candidate variables included in the survey through a literature review and concept analysis. A pediatric critical care nurse scientist and a pediatric intensivist reviewed an initial draft of the survey for clarity and completeness. Prior to deployment, the research team tested the technical functionality of the survey, which used the Qualtrics (Washington, DC, USA) survey platform. In order to avoid coercion and ensure anonymity, the PALISI Network Coordinator and SCCM Quality and Guidelines Specialist forwarded an email containing an introduction, instructions and the survey link (Appendix A) to their membership. A unique survey link was set up for each group in order to better describe participants. The survey link was sent to 389 PALISI members, representing 78 centers on April 6, 2015, with reminder emails sent one and two weeks later. SCCM task force members (24 members representing 14 centers) received the initial email on April 22, 2015, with a reminder sent one week later. Two individuals were members of both groups and received both sets of emails. The survey was closed to responses on May 8, 2015.

The survey (Appendix B) was a voluntary, self-administered web-based survey consisting of five screens in total, including an introductory page, a page displaying questions concerning 17 candidate variables and an “Other (please list)” free-text question, a respondent demographics page, a page with a single free-text question, and a final thank you page. The first question in the SCCM survey asked if the respondent had previously completed the survey. A “yes” response closed the survey. There were no mandatory items. To encourage

initial participation, an estimate of the time required for survey completion (“a few minutes”) was included in the introductory text. To encourage continued participation once started, a progress bar at the bottom of the screen displayed the participant’s progress, along with text indicating percent completed. Forward and back buttons allowed respondents to review and change their answers prior to survey submission. The survey platform captured all responses entered, even if the full survey was not completed. To provide context, respondents were instructed to answer each question in relation to a patient’s first four days of endotracheal intubation, assuming that the patient’s pain was adequately controlled and that sedation medication doses were appropriate. Each item related to the candidate variables was scored as not (1), somewhat (2), quite (3) or highly (4) relevant in identifying the difficult-to-sedate phenotype.

### Data Analysis

Data was downloaded from the survey management site to a password-protected drive as an Excel spreadsheet and was analyzed using IBM SPSS Statistics 24 (IBM, Armonk, NY, USA). Thirteen surveys (11 from PALISI and 2 from SCCM respondents) which were opened but had no data entered were deleted during data cleaning. All surveys with any data concerning characteristics of the difficult-to-sedate child were included in the analysis, even if they were incomplete. Descriptive analysis of the two respondent demographic questions consisted of calculation of frequencies and percentages. In order to determine face validity, we calculated the mean score for each item. A mean score greater than 1 was considered an indicator of acceptable face validity. We

also calculated an item-level content validity index (I-CVI) for each candidate variable. The I-CVI is a way to measure interrater agreement of each item in an instrument, and to identify items that should be retained or deleted from the instrument. In order to calculate the I-CVI, the number of experts who ranked an item as quite or highly relevant is divided by the total number of experts.<sup>21</sup> A threshold of 0.70 (at least 70% of respondents rated these items as quite (3) or highly (4) relevant) was considered an indication of good to excellent content validity for the item. In order to ensure accuracy and account for missing data, we used the number of complete responses to the item as the denominator in our calculations.

## **Results**

One hundred twenty-one clinicians, 113 (95%) physicians, 3 (2%) advanced practice nurses, 4 (3%) nurse scientists and 1 (<1%) respiratory therapist responded to the survey sent to 411 individuals for a response rate of 29%. Table 1 provides further detail about response rates and sample demographics. Of the 89 clinical sites represented by PALISI and SCCM groups, members from 61 sites (69%) responded, with a mean of 1.6 individuals per site (range of 1 to 4) completing the survey. Twelve of 17 items related to candidate variables had a 100% response rate, four had 99%, and one item had a 98% response rate. Six of 2,040 data points related to the candidate variables were missing, resulting in a missing data rate of 0.3%. All variables had a mean score >1, ranging from 1.5, midway between not and slightly relevant, to 3.5, midway between quite and highly relevant. Table 2 summarizes the I-CVI for each item.

Ten of seventeen items met the threshold of 0.70. Those items include requiring three or more sedation classes simultaneously, a daily modal State Behavioral Scale (SBS) score indicating agitation (SBS +1/+2), an SBS score indicating agitation for 2 consecutive hours, receiving sedatives at a dose >90th percentile of the usual starting dose, receiving intermittent paralytic doses for sedation, suspected delirium, unplanned endotracheal extubation, unplanned removal of an invasive device, paradoxical response to sedation, and Trisomy 21. At 0.65, the I-CVI for the item previous sedation exposure did not quite meet the threshold. The six items which had a low I-CVI were all demographic or diagnostic characteristics, including not able to verbally communicate, body mass index >90th percentile, an oncologic diagnosis, moderate or severe cerebral disability, moderate or severe overall disability, and bronchiolitis.

Responses from the PALISI and SCCM groups were similar. This would be expected as the members of both groups are practicing clinicians with experience in pediatric sedation, and the SCCM group was added to increase the pool of experts. Two items which met the I-CVI threshold in the PALISI group were just under 0.70 in the SCCM group (both 0.67), paradoxical response to sedation and sedation doses >90<sup>th</sup> percentile of the usual starting dose. The highest-rated item for both groups was requiring three or more sedation classes simultaneously. The SCCM group ranked suspected delirium and unplanned endotracheal extubation second and third. The PALISI group ranked daily modal SBS indicative of agitation and SBS indicative of agitation for two consecutive hours second and third. The results for the six items which clearly did not meet

the I-CVI threshold were ranked in the same order by both groups, and each of these items had an I-CVI <0.50.

Several respondents identified characteristics not listed. Table 3 summarizes the 17 responses provided when the “Other (please list)” option was selected for the question “Typically has the following demographics/diagnoses/characteristics”. Young age was listed as a characteristic by 5 respondents, the remaining characteristics were identified by single respondents. Table 3 also summarizes the 61 free-text responses listing other criteria characterizing the difficult-to-sedate child. Twelve respondents identified age  $\leq 4$  years, 8 identified multiple drugs/bolus doses, 5 identified medical diagnosis, sleep/day-night cycling issues or psychiatric diagnosis, and anxious parents and rapid change in sedation level were each identified by 4 respondents.

## **Discussion**

There is currently no operational definition of the difficult-to-sedate child in the pediatric critical care literature. This study assessed face and content validity of candidate characteristics, derived from a literature review and concept analysis, to be used in constructing an operational definition of the difficult-to-sedate child phenotype. The majority of items met the threshold we set for good to excellent content validity. The items that did not were all related to demographic or diagnostic characteristics, and the mean scores for these items were in the somewhat relevant range. The results support including all candidate variables evaluated in this survey when developing the model in the next phase

of our project, as all variables had a mean score  $>1$ , indicating adequate face validity.

Because content validity also considers whether all important elements of a domain are represented, we were particularly interested in the number of additional characteristics identified in the free-text responses. A few characteristics were consistently identified, including young age, sleep or day/night cycling issues, requiring multiple bolus doses, a psychiatric diagnosis or parental anxiety. Although not all of these variables were measured in the *RESTORE* data set, those that were measured such as age, received medication to facilitate sleep, received medication to treat delirium, received multiple bolus doses and medical diagnosis will be added to the list of candidate variables to be evaluated in the next phase of this project.

In general, there was remarkable consistency between the PALISI and SCCM responders, despite the small number of respondents and small population of the SCCM group. Aside from organizational affiliation, there was minimal missing data, which further supports the consistency of the findings. No single center was over-represented in the sample, so it is unlikely that responses were skewed by regional differences such as differing patient populations or local sedation practices.

As with any survey, several factors may have introduced bias. The survey was voluntary and participants self-selected, so the results may represent the viewpoint of clinicians who have a specific point of view related to this topic. The sample population was drawn from a research network and an expert sedation

workgroup, and may not be representative of the PICU clinician population in general. It is also possible that a respondent from either of the groups, who only received one invitation to complete the survey, may have taken the survey multiple times or that the two individuals who were members of both groups and received two invitations may have taken the survey more than once. We collected minimal respondent demographic data and respondents were not assigned any type of identifier, so there was no way to identify multiple surveys from a single individual. Because the survey link was sent via email, it is also possible that the link may have been provided to an individual not included in the original sample frame. We attempted to prevent this by including a request that the survey link not be forwarded in the email sent to the SCCM group, but did not include this in the PALISI email request. Although no respondent listed an organization not included in the PALISI or SCCM lists provided by those organizations, 16% of respondents did not identify their organization. Finally, 95% of the respondents were physicians. Nurses, who are consistently at the bedside, may have a different perception of the characteristics of the difficult-to-sedate child. It would be interesting to solicit the expert opinion of this group of providers, to see if any additional characteristics are identified.

## **Conclusions**

This survey asked practicing clinicians to assess whether the items identified through a theoretical concept analysis agreed with their practice experience. The results of this survey indicate consensus among expert PICU clinicians, primarily physicians, that the items included in this survey are consistent characteristics

exhibited by the child who is difficult-to-sedate. They will be used in phase three of this project to create a statistical model of the difficult-to-sedate child phenotype. Additional characteristics identified by the expert panel will also be added to the list of candidate variables to be included in the model. Developing a mechanism to prospectively identify the difficult-to-sedate child would allow sedation tailored to the individual child, avoiding the burden placed on the child and family and decreasing the potential for injury.

### **Authors' Contributions**

All authors (RL, LA, AZ, and MAQC) contributed to the study design. RL and LA completed data analysis, and all authors contributed to data interpretation and manuscript preparation. All authors approve the final manuscript for publication.

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**Table 1. Survey Response Details**

	<b>Total</b>	<b>PALISI</b>	<b>SCCM</b>
	<b><i>n</i> (%)</b>	<b><i>n</i> (%)</b>	<b><i>n</i> (%)</b>
Center Representation <sup>1</sup>	61/89 (69) <sup>2</sup>	59/78 (76)	7/14 (50)
Respondents	121/411 (29) <sup>3</sup>	112/389 (29)	9/24 (39)
Role <sup>4</sup>			
Attending Physician	115 (95)	106 (95)	9 (100)
Advanced Practice	3 (3)	3 (3)	0
Nurse			
Nurse Scientist	2 (2)	2 (2)	0
Respiratory Therapist	1 (<1)	1 (<1)	0

PALISI, Pediatric Acute Lung Injury & Sepsis Investigators; SCCM, Society for Critical Care Medicine.

<sup>1</sup> Nineteen of 121 respondents (16%) did not indicate organizational affiliation.

<sup>2</sup> Due to overlap in organizations represented by PALISI and SCCM members, total center representation does not equal the sum of PALISI plus SCCM center representation.

<sup>3</sup> Two potential respondents were members of both the PALISI and SCCM groups, so number of total possible respondents does not equal the sum of PALISI plus SCCM respondents.

<sup>4</sup> Pediatric ICU Fellow (physician-in-training), Research Assistant, and Pharmacist were other options but none participated.

**Table 2. Difficult-to-Sedate Criteria: Mean Score and Item-level Content**

**Validity Index (I-CVI)**

	<u>Mean</u>	<u>I-CVI</u>		
	<u>Score</u>	Total	PALISI	SCCM
	Total			
	(n=121)	(n=121)	(n=112)	(n=9)
Sedation Characteristics				
Requires 3 or more sedation	3.51	0.93	0.92	1.00
classes simultaneously		(112)	(103)	(9)
Daily modal SBS +1/+2	3.21 <sup>1</sup>	0.82	0.83	0.75
		(98) <sup>1</sup>	(92) <sup>2</sup>	(6) <sup>3</sup>
SBS +1/+2 for 2 consecutive	3.09 <sup>4</sup>	0.79	0.80	0.75
hours		(95) <sup>4</sup>	(89)	(6) <sup>3</sup>
Doses >90th percentile of usual	3.24 <sup>4</sup>	0.78	0.78	0.67
starting dose		(93) <sup>4</sup>	(87) <sup>2</sup>	(6)
Intermittent paralytic doses for	3.13	0.74	0.74	0.78
sedation		(90)	(83)	(7)
Sedation-related Events				
Suspected delirium	3.15	0.79	0.78	0.89
		(95)	(87)	(8)
Unplanned endotracheal	3.13	0.72	0.71	0.89
extubation		(87)	(79)	(8)

Unplanned removal of an invasive device	3.13	0.71 (86)	0.71 (79)	0.78 (7)
Paradoxical response to sedation	2.94	0.70 (85)	0.71 (79)	0.67 (6)
Demographic/Diagnostic Characteristics				
Trisomy 21	2.98	0.71 (86)	0.71 (79)	0.78 (7)
Previous sedation exposure	2.82	0.65 (79)	0.65 (73)	0.67 (6)
Not able to verbally communicate	2.36	0.43 (52)	0.41 (46)	0.67 (6)
>90th percentile for BMI	1.96	0.24 (29)	0.23 (26)	0.33 (3)
Oncologic diagnosis	1.91 <sup>4</sup>	0.23 (28) <sup>4</sup>	0.23 (26) <sup>2</sup>	0.22 (2)
Moderate or severe cerebral disability	2.05	0.22 (27)	0.22 (25)	0.22 (2)
Moderate or severe overall disability	1.93	0.17 (20)	0.16 (18)	0.22 (2)
Bronchiolitis	1.55 <sup>4</sup>	0.09 (11) <sup>4</sup>	0.10 (11) <sup>2</sup>	0

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PALISI, Pediatric Acute Lung Injury & Sepsis Investigators; SCCM, Society for Critical Care Medicine; SBS, State Behavioral Scale; BMI, Body mass index.

Data presented as mean or I-CVI (*n* of respondents who ranked item as quite or highly relevant).

<sup>1</sup> Total *n*=119.

<sup>2</sup> Total *n*=111.

<sup>3</sup> Total *n*=8.

<sup>4</sup> Total *n*=120.

**Table 3. Summary of Free-Text Responses**

	<i>n</i>
“Other” demographics/diagnoses/characteristics that the difficult-to-sedate child typically has ( <i>n</i> =17)	
Infant/toddler	5
Lengthy PICU stay	1
Prior history of delirium	1
Airway repair	1
Intoxicated	1
Parents’ expectations	1
>5 days of sedation	1
Autism Spectrum Disorder	1
ECMO/ECLS or CRRT	1
ADHD, anxiety disorder, other psychiatric diagnosis	1
Transplant recipient	1
Multi-organ dysfunction	1
Prematurity	1
Other criteria that characterize the difficult-to-sedate child phenotype ( <i>n</i> =61)	
Age ≤4 years	12
Multiple drugs/bolus doses	8
Diagnosis	5
Psychiatric diagnosis (e.g., anxiety, autism, ADHD)	5
Sleep/day-night cycling issues	5
Anxious parents	4
Rapid change in sedation level	4
Nursing factors (e.g., experience, nurse/patient ratio)	3
Patient instability limits sedation doses	3
Activity limited by technology or instability	2
Adolescent	2

History of negative sedation experience	2
Other	6

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PICU, pediatric intensive care unit; ECMO, extracorporeal membrane oxygenation; ECLS, extracorporeal life support; CRRT, continuous renal replacement therapy; ADHD, attention-deficit/hyperactivity disorder.

## **Appendix A. Text of PALISI and SCCM Survey Participation Request Emails**

Dear PALISI Network Colleagues,

We are interested in establishing face validity for criteria that will be used in a study identifying the "difficult to sedate child" phenotype, and would appreciate your expert opinion. Please take a few minutes to answer 8 questions on our Qualtrics survey <https://upenn.co1.qualtrics.com/XXXXXXXX>

Data are encrypted and results will be reported in aggregate. You will have an opportunity to add a comment at the end of the survey. Thank you for taking the time to review and respond.

Dear SCCM Pediatric Sedation Study Group Colleagues,

We are interested in establishing face validity for criteria that will be used in a study identifying the "difficult to sedate child" phenotype, and would appreciate your expert opinion. Please take a few minutes to answer the following 8 questions. NOTE: If you have previously taken this survey, distributed to you as a PALISI member, thank you for your participation. We request that you please answer question 1.

To start the survey please click on this link: <https://upenn.co1.qualtrics.com/XXXX>

Please do not forward to your colleagues, as we would like to know your opinion as a member of the SCCM Task Force.

Data are encrypted and results will be reported in aggregate. You will have an opportunity to add a comment at the end of the survey. Thank you for taking the time to review and respond.

## **Appendix B. Difficult to Sedate Survey (SCCM Version)**

Have you completed this survey as a PALISI member?

- ☐ 1- Yes
- ☐ 2- No

NOTE: If "Yes" was selected, the survey skipped all remaining questions and the text "Thank you for your previous participation" was displayed

The "difficult to sedate child"... (assuming pain is adequately controlled and sedation medication doses are appropriate)

1. Exhibits a State Behavioral Scale (SBS) score of +1 (restless and difficult to calm) or +2 (agitated) for two consecutive hours

- ☐ 1- Not Relevant
- ☐ 2- Somewhat Relevant
- ☐ 3- Quite Relevant
- ☐ 4- Highly Relevant

2. Exhibits a consistent pattern of agitation, demonstrated by a daily modal (most frequently occurring) SBS score of +1 (restless and difficult to calm) or +2 (agitated)

- ☐ 1- Not Relevant
- ☐ 2- Somewhat Relevant
- ☐ 3- Quite Relevant
- ☐ 4- Highly Relevant

3. Requires intermittent paralytic doses for sedation management

- ☐ 1- Not Relevant
- ☐ 2- Somewhat Relevant
- ☐ 3- Quite Relevant
- ☐ 4- Highly Relevant

4. Requires sedation medication doses above the 90th percentile of usual starting doses (e.g. >0.2 mg/kg/hour for morphine or midazolam)

- ☐ 1- Not Relevant
- ☐ 2- Somewhat Relevant
- ☐ 3- Quite Relevant
- ☐ 4- Highly Relevant

5. Requires three or more sedative classes simultaneously to achieve target sedation

- ☐ 1- Not Relevant
- ☐ 2- Somewhat Relevant
- ☐ 3- Quite Relevant
- ☐ 4- Highly Relevant

6. Experiences sedation-related events that include the following:

	1- Not Relevant	2- Somewhat Relevant	3- Quite Relevant	4- Highly Relevant
a) Unplanned endotracheal extubation				
b) Unplanned removal of any invasive device				
c) Reports of a paradoxical response to sedation				
d) Suspected of having delirium				

7. Typically has the following demographics/diagnoses/characteristics:

	1- Not Relevant	2- Somewhat Relevant	3- Quite Relevant	4- Highly Relevant
a) >90th percentile for BMI				
b) History of previous sedative exposure				
c) Bronchiolitis				
d) Oncologic diagnosis				
e) Trisomy 21				
f) Moderate or severe cerebral disability				
g) Moderate or severe overall disability				
h) NOT able to verbally communicate				
i) Other (please list):				

8. Please list any other criteria that you feel characterizes the "difficult to sedate child" phenotype.

9. Please select what best describes your role:

- ☐ Attending Physician
- ☐ Pediatric ICU Fellow
- ☐ Advanced Practice Nurse
- ☐ Nurse Scientist
- ☐ Respiratory Therapist
- ☐ Research Assistant
- ☐ Pharmacist
- ☐ Other (please list) \_\_\_\_\_

10. Please use the drop down menu to provide the name of your organization. If your organization is not listed please select "other" (last item in the drop down box).

11. Please provide any closing thoughts that you think may be important to consider with regard to the "difficult to sedate child" phenotype.

Thank you .... The END!! Please click the Next (>>) button to submit your survey.

## CHAPTER 4

### Characteristics of the Difficult-to-sedate Child Clinical Phenotype

Target Journal: Pediatric Critical Care Medicine

Key Words: child; classification and regression tree; critical care; latent class analysis; phenotypes; sedation;



## **Abstract**

**Objective:** To characterize the difficult-to-sedate child clinical phenotype in a cohort of children intubated and ventilated for acute respiratory failure.

**Design:** Secondary analysis of prospectively collected data from the Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) clinical trial. Latent Class Analysis was used to characterize the variability in sedation response through the first three days after endotracheal intubation to operationalize the difficult-to-sedate child clinical phenotype. Classification and Regression Tree methodology was used to develop branching algorithms that identified the characteristics of patients at high-risk for being difficult-to-sedate.

**Setting:** Thirty-one PICUs in the U.S.

**Patients:** 2,449 patients 2 weeks to 17 years old receiving mechanical ventilation for respiratory failure.

**Interventions:** None.

**Measurements and Main Results:** Latent Class Analysis identified a two-class model as the best fit, with need for adjunctive medications, less organ failure, occurrence of inadequate sedation events, and normal cognitive state identified as being indicative of the difficult-to-sedate child latent class. Classification and Regression Tree analysis produced a tree with 9 nodes. The best fitting model classified 18% of children as likely to be difficult-to-sedate. The most important sorting variable was need for adjunctive medications.

**Conclusions:** Latent Class and Classification and Regression Tree analysis were useful techniques in identifying likely phenotypic characteristics and clinical risk factors of the difficult-to-sedate child clinical phenotype. Further prospective study, with the inclusion of genetic markers, will be useful in validating these findings.

Patients admitted to the Pediatric Intensive Care Unit (PICU) are a heterogeneous group on many factors including age, diagnosis, severity of illness, and medical history. One of the most common therapies children admitted to the PICU receive is mechanical ventilation. To help them tolerate this invasive therapy, the majority of children receive sedation, primarily benzodiazepines, but there is great variability in practice and many classes of sedation medication are routinely used.(1,2,3). Response to sedation is also heterogeneous. The majority of children respond as anticipated to appropriately dosed sedation, and are considered to be adequately sedated.

However, there are children who do not respond as expected. Some children are over sedated and require less drug than expected. A more challenging group are those children who are persistently agitated, requiring higher than anticipated doses and sedation medications from multiple classes.(4) These children may be referred to as refractory to sedation, sedation failures, or difficult-to-sedate, and are at risk for adverse events such as unplanned endotracheal tube extubation or removal of other critical devices such as central venous catheters.(5)

In addition to sedation-related adverse events, the requirement for higher doses and multiple classes of sedative agents may cause hypotension, bradycardia, drug-specific iatrogeneses such as iatrogenic withdrawal syndrome.(6,7) Also concerning is recent data that suggests many of most commonly used sedation medications may negatively impact a young child's neurocognitive development.(8) Midazolam, lorazepam, pentobarbital, ketamine and propofol labeling now carry an FDA required Black Box warning indicating that brain development in children three and under may be affected by exposure to these drugs.(9)

Aside from noting that this group of difficult-to-sedate children exists within the heterogeneous PICU population, there is very limited data describing them. Clinical phenotypes have been useful in characterizing patients identified as having a heterogeneous disease process into groups with similar characteristics. This approach has stimulated research aimed at identifying effective phenotype specific treatment strategies and has been a successful strategy for patient populations with asthma, sepsis, and Acute Respiratory Distress Syndrome.(10-12) Two statistical modeling approaches are frequently used to describe clinical phenotypes. Latent class analysis (LCA) characterizes subgroups within a particular patient population based on clinical and biological data. Classification and regression tree analysis (CART) has been used as a way to predict a particular outcome for a subgroup of patients. The purpose of this study was to characterize the difficult-to-sedate clinical phenotype in a cohort of children intubated and ventilated for acute respiratory failure using these two machine learning techniques.

## **Materials and Methods**

This is a secondary analysis of data from the *RESTORE* (Randomized Evaluation of Sedation Titration fOr Respiratory failure; U01 HL086622) study.(18) *RESTORE* was a cluster randomized clinical trial designed to test a nurse-implemented goal-directed approach to sedation management in pediatric patients supported on mechanical ventilation. The study captured a large amount of prospectively collected and validated sedation data in a cohort of 2,449 children from 31 participating pediatric intensive care units. Data collection occurred between June 2009 and December 2013. Inclusion and exclusion criteria as well as specifics of the protocol are detailed in the study report.(18) The institutional review board of each participating center approved the

*RESTORE* trial. Parental permission was obtained for each enrolled child. When feasible, assent was also obtained from children 8 years and older.

For this secondary analysis, we examined data from the first three days of study enrollment only. We chose these days because it is likely the subset of patients that represent the difficult-to-sedate child clinical phenotype demonstrate this characteristic early in their treatment course. We also sought to avoid possible confounding effects related to sedation tolerance or iatrogenic withdrawal syndrome (IWS). We examined demographic, physiological, developmental and clinical characteristics, as well as patterns of opioid, benzodiazepine, and other sedative medication administration with the goal of identifying the characteristics of the difficult-to-sedate child clinical phenotype. We included all *RESTORE* subjects who contributed at least two days of data. There were no exclusion criteria aside from those of the parent study.

We identified an initial list of variables for inclusion in the LCA and CART models based on a review of the literature and concept analysis.<sup>(20)</sup> We then surveyed pediatric critical care clinicians to establish face and content validity of these variables and to identify other variables to consider for inclusion in the model.<sup>(21)</sup> Based on the results of our survey, additional unpublished variables were added to our initial list. The complete list of variables used in the models is available as Supplement Table 1 but included baseline demographics, sedation characteristics such as classes of sedation agents received on study day 0-3, as well as the incidence of sedation related events on study day 0-3 such as unplanned device removal. The majority of the variables included in the models were ordinal or categorical, but continuous variables are appropriate for use in CART analysis, so age, weight, body mass index (BMI), blood urea nitrogen (BUN), or alanine amino transferase (ALT) were included as continuous variables in the CART analysis.

We used an exploratory LCA to analyze the *RESTORE* data, with the goal of characterizing the difficult-to-secure child clinical phenotype. Forty demographic and clinical variables were included in the initial analysis as possible class defining variables in the LCA model. For this analysis, we converted all but one variable into a binary categorical variable. We created a dummy variable for each diagnosis group, resulting in six diagnoses variables. The Pediatric Risk of Mortality version III (PRISM III-12) score was converted to a standardized z-score with a mean of 0 and a standard deviation of 1. The complete data set was randomly divided into a training (n= 1,470) and validation set (n= 979), with 60% of cases assigned to the training set and 40% to the validation set. The CART training and validation sets were compared using the t test or chi-squared test, as appropriate (see Table 1) using IBM SPSS Statistics 24 (IBM, Armonk, NY, USA). As is appropriate in LCA, clinical outcomes were not included in identifying the number of latent classes. We used mixture modeling to test a series of 2, 3, 4 and 5 class latent class models using the discovery data set. We used recommended criteria for model evaluation and selection, including the sample-size adjusted Bayesian information criterion (ABIC), Aikake information criterion (AIC), the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (VLMRLRT), and the degree of entropy, used to assess classification quality.(23, 24) We assessed the parametric Bootstrapped Likelihood Ratio Test, but it remained low for all models, so is not included here. MPlus, version 7.4 (Muthén & Muthén, UCLA) was used for the LCA.(13,14) MPlus uses full-information maximum likelihood in latent class model estimation, which allows use of all subjects, including those with missing data.(25) Each model fitted was evaluated using the criteria listed above, and the best fitting model which established the number of latent classes was selected. We then repeated these analyses with the validation data set, to evaluate model stability across the two groups.

We used CART analysis to classify patients into risk categories for being difficult-to-sedate. Unlike LCA, CART requires an outcome variable. Using the operational definition of difficult-to-sedate child clinical phenotype developed from our review of the literature and survey of expert PICU clinicians, we created a composite difficult-to-sedate categorical outcome variable, which was positive if the subject had a State Behavioral Scale (SBS) score of +1/+2 (agitated) and was receiving at least two times the usual starting dose of an opioid or benzodiazepine continuous infusion on any study day from day 0-3. CART uses a branching algorithm to classify patients into groups, starting with 2 groups at the first decision node, using a chi-square statistic for each possible predictor variable. The algorithm then assigns the predictor variable with the highest calculated logworth statistic as the candidate for splitting the group into two additional nodes.(26) We used the entire *RESTORE* dataset to build the classification tree using the *rpart* package in RStudio (Foundation For Open Access Statistics, Boston, MA). We used an unsupervised approach to model development. Cross validation was used to identify the most accurate and predictive tree. We used the process of pruning to remove nodes with few observations by setting a complexity parameter, in order to minimize the cross-validation error rate and identify a workable model. Finally, we ran the same model by control or intervention group to assess stability of the tree.

## **Results**

Table 1 compares the cohort of difficult-to-sedate subjects, identified as positive for the outcome variable (n= 473) to those identified as not difficult-to-sedate (n= 1503) using the t test or chi-squared test, as appropriate. There were significant differences between the usual care and protocol groups in the parent study on several variables. Children classified as difficult-to-sedate had a younger age, were less likely to have a primary diagnosis of asthma, were more likely to be premature or have previous

exposure to opioids or benzodiazepines and were more likely to have received fentanyl as their primary opioid. In addition, the difficult-to-sedate children were less likely to have elevated blood urea nitrogen or alanine aminotransferase levels.

#### Latent Class Analysis

The training and validation cohorts for the LCA were randomly generated, and the only statistically significant difference between the groups was that patients in the training group were more likely to have an elevated ALT. A 2-class model was identified as the best fit in both the training and validation cohorts, based on both fit statistics and interpretability of the model. Although the AIC and ABIC continued to decrease in the 3 class model, the VLMRLRT demonstrated a non-significant p-value of 0.76 in the training and 0.78 in the validation cohort, indicating the smaller, 2 class model was a better fit. The best log likelihood was replicated in >25% of 1000 iterations. Table 2 lists the fit statistics for the various models estimated in the LCA.

The children who make up the difficult-to-sedate phenotype identified here have less overall organ failure. They are less likely to require vasoactive medications, do not have hepatic or renal failure, have normal ratings for Pediatric Outcome Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC), and are not likely to have an abnormal level of consciousness. This group is more likely to require neuromuscular blockade to manage agitation, occurrences of an inadequate sedation management event (SBS +1 or +2 for 2 consecutive hours, not associated with an extubation attempt), and having a daily SBS high score of +1/+2. Figure one provides a comparison of the difficult-to-sedate and not difficult-to-sedate groups by phenotype characteristic. Of note, the probability of class membership differed between the training and validation groups, with the training cohort having a 43% probability of belonging to

the difficult-to-sedate class, and the validation cohort having a 19% chance of belonging to the difficult-to-sedate class.

### CART Analysis

The group classified as difficult-to-sedate for the CART analysis were younger, more likely to receive fentanyl as the primary opioid, received more classes of sedation medications, be admitted with a diagnosis of pneumonia, and have a history of prematurity and previous exposure to sedation medications. Patients classified as not difficult-to-sedate were more likely to be admitted with a diagnosis of asthma or acute respiratory failure related to sepsis. The final pruned decision tree produced by the CART analysis of all subjects had nine splitting nodes, with the primary node predicated on whether or not the child received any adjunctive sedation medications, and is displayed in Figure 2. Other important splitting nodes were daily modal SBS score, occurrence of an inadequate sedation management event, presence of an elevated blood urea nitrogen level, age, weight, and race. Supplement Figure 1 presents variable importance for the top ten variables.

The prevalence of the difficult-to-sedate child phenotype in this sample was 18.6% (386/2078 subjects), based on the outcome variable developed for the CART analysis. Due primarily to missing data related to SBS scores, only 821 subjects were included in the CART analyses. Accuracy to correctly predict a child who was difficult to sedate was 0.83 (CI, 0.798- 0.851). The sensitivity for the model was low at 21%, with a high level of false positives and false negatives. The decision tree was highly specific, correctly identifying 97% of difficult-to-sedate child cases. Table 3 reports the test characteristics of the CART analysis.

### Discussion



The difficult-to-sedate child in our sample **had less organ failure, less cognitive impairment, higher modal SBS scores and required more than two agents to manage agitation, including in some situations neuromuscular blockade.** This study was exploratory and identified the clinical characteristics of the difficult-to-sedate child phenotype proposed in our operational definition and conceptual model. We used two different machine-learning methodologies in this analysis, to evaluate if any characteristics were supported in both types of models. Regardless of the methodology used, sorting points included **the requirement for adjunctive medications, presence of organ failure, particularly renal failure, occurrences of inadequate sedation events, high daily modal SBS scores and need for vasoactive medications.**

There were some differences noted when comparing the results of each analysis. The LCA is a descriptive model, which assigns each subject to a single class and for each indicator variable included in the model provides the probability that any member of the class will demonstrate that variable. LCA is atheoretical; it does not assess the data based on an outcome, but rather looks for and reports patterns in the data. The results of this LCA also provide a more descriptive picture of a child who is **not** difficult-to-sedate being likely to have renal or hepatic failure, an altered level of consciousness, a history of alterations in cerebral and overall performance, and a requirement for vasoactive medications. The finding that children with organ failure were more likely to be in this class is supported by a study which found that midazolam clearance was decreased in critically ill children.(28) In order to assess the strength of our findings, we randomly divided our data set, and the findings were very similar across the two groups, supporting the characteristics identified here for the difficult-to-sedate child clinical phenotype.

The CART analysis predicts the likelihood of an outcome, so takes a different approach to data analysis. The data is also analyzed for patterns, but at each node or sorting point, there are only two options for assignment. However, many different paths may lead to the outcome of interest. The tree shown in Figure 2 has three terminal nodes positive for the difficult-to-sedate outcome and the difficult-to-sedate outcome was reached through three paths along the decision tree. Important variables in the CART analysis included primary diagnosis; age, with young age being more predictive of the outcome; weight, with weight > 8 and < 22 kg being predictive of the outcome; and requirement for adjunctive sedation medication as an important predictor. The weight range reported here is typical of the toddler and pre-school age range, which was one of the characteristics identified in our survey of PICU experts. It is also a finding supported in the literature. For example, de Gast Bakker et al. identified that in a population of mechanically ventilated children, children 1-4 years of age required a significantly higher dose of midazolam, starting on their first day of intubation, and other studies have identified that age impacts both the pharmacokinetics and pharmacodynamics of medications.(29-31)

This is one of the first studies to attempt to determine the incidence of this clinical phenotype. Approximately 18% of subjects in the CART analysis demonstrated the difficult-to-sedate outcome. Although this was one point on which the training and validation data sets differed in the LCA, occurrence of the difficult-to-sedate child phenotype was at a minimum 19%. This finding demonstrates that this clinical phenotype is not rare. Combining the finding of the CART analysis that these children tend to be young, and the concern that sedation medications may negatively impact cognitive development, exploration of this clinical phenotype warrants further investigation. Both the LCA and the CART analysis demonstrated these children require

more classes of medication, and still are less likely to reach their target sedation goal as demonstrated by the higher modal SBS scores for this group and the more frequent incidence of inadequate sedation management events.

There are limitations to consider in this study. Although we used a rigorous process to identify variables to include in the model, it is possible that we omitted an important variable. The outcome variable used in the CART analysis was a composite of two sedation related variables. It is possible that a different outcome variable would be more appropriate. Secondary analyses of existing data sets presents some limitations. Data collected may not include variables important to the question being investigated. However, our question of interest generally fit the data available from the parent study.

The parent study was a cluster-randomized trial, with sites being randomized to the intervention or control arms, so significant differences in sedation practices between the control sites would impact study results. We carefully evaluated our data considering treatment arm assignment and did find some significant differences, which could have affected our findings. Young age, primary diagnosis, and primary opioid received were important predictor variables in the CART analysis and there were significant differences seen between the usual care and protocol groups in the parent study on these variables. Subsequent prospective studies could address this limitation.

Sedation scores and medication data are key variables of interest in this study. Low interrater reliability in sedation scoring would bias our results, particularly for the CART analysis, as our outcome variable was a composite variable, which included a sedation score. The parent trial assessed interrater reliability routinely throughout the study, and demonstrated strong agreement with no difference in Fleiss's kappa for the SBS based on unit size or timing of assessment (earlier or later in the study).(32) The parent study population included only children with acute respiratory failure, a subset of

the PICU population, which limits generalizability of our findings. Missing data, which may decrease power, was a concern, as approximately 9% of SBS scores were missing for the study days in question and in the control group. This was particularly true in the CART analysis, as SBS scores were part of the composite outcome variable. In addition, other missing data points also decreased the final sample size.

Finally, other clinical entities, particularly tolerance, iatrogenic withdrawal syndrome and delirium share some of the characteristics seen in the difficult-to-sedate child. We felt that by examining data from days early in the clinical course, we would avoid overlap with these potent confounders. We found that children were identified as being positive for the difficult-to-sedate outcome variable beginning on their first day of intubation and on average this group met the difficult to sedate criteria on two of the days studied.

This study included primarily clinically observable characteristics in describing this clinical phenotype, such as medication classes and doses received, sedation scores, episodes of agitation, and level of consciousness. BUN and ALT were included in the model, but no other biomarkers or genetic samples were included. This clinical phenotype has not been previously described and the goal of this study was to characterize the phenotype. However, it is likely that there is a genetic basis underlying the clinical phenotype of the difficult-to-sedate child. There is emerging evidence that polymorphisms in the cytochrome p450 enzymes may influence the metabolism of benzodiazepines(33), and identifying a population at risk would facilitate investigation of the genetic basis of this phenotype. The utility of characterizing this phenotype is that it identifies a group of patients to target in a genome-wide association study. Understanding the underlying genetic basis of the difficult-to-sedate clinical phenotype would support early and appropriate medication selection and dosing.

## **CONCLUSIONS**

This study tested a model characterizing the difficult-to-sedate child and identified that these children are typically young, require more adjunctive medications, are more likely to have inadequate sedation management events, have high daily modal SBS scores despite receiving high doses of opioids and benzodiazepines, have less organ failure, particularly renal failure, and less need for vasoactive medications. In this cohort of critically ill children, the incidence of this clinical phenotype was approximately 18%, indicating that this phenotype deserves further investigation. The next step would be to test and refine this model using prospectively collected data.

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Table 1: Demographic and Patient Characteristics of Sample by Outcome First Three Days of Therapy for the LCA & CART

	LCA n = 2449	CART (N=2224)		
		DTS	Not DTS	P value
		473 (21)	1976 (79)	
Intervention group, No. (%)		240 (51)	985 (50)	0.72
Age at PICU admission, median (IQR), years	1.9 (0.4-8)	1.6 (0.6-4.5)	2.0 (0.3-9.3)	<.001
Female, No., (%)	666 (46)	221 (47)	880 (45)	0.294
Non-Hispanic white, No., (%)	725 (51)	227 (48)	1006 (51)	0.25
Baseline PCPC = 1, No., (%)	1094 (76)	362 (77)	1503 (76)	0.049
Baseline POPC = 1, No., (%)	1024 (71)	329 (70)	1418 (72)	0.235
PRISM III-12 score, median (IQR)	8 (3-13)	7 (2-12)	7 (3-13)	0.645
Primary diagnosis, No., (%)				
Pneumonia	493 (34)	179 (38)	647 (33)	0.03
Bronchiolitis	424 (30)	110 (23)	547 (28)	0.05
Acute respiratory failure related to sepsis	200 (14)	49 (10)	308 (16)	0.003
Asthma or reactive airway disease	121 (8)	59 (13)	148 (8)	<0.001
Aspiration pneumonia	75 (5)	25 (5)	124 (6)	0.417
Other	122 (9)	51 (11)	202 (10)	0.718
Past medical history, No., (%)				
Prematurity	206 (14)	89 (18)	280 (14)	0.032
Previous exposure to opioids/benzodiazepines	221 (15)	94 (20)	300 (15)	<0.001
Oncology diagnosis	100 (7)			
Chromosomal abnormality	58 (4)	30 (6)	161 (8)	0.113
		22 (5)	86 (4)	
Weight for age > 95 <sup>th</sup> percentile, No., (%)	324 (13)	61 (13)	263 (14)	0.164
Pt characteristics PICU Days 0-3				
Primary opioid agent, No., (%)				
Morphine	487 (34)	105 (22)	728 (37)	<0.001
Fentanyl	918 (64)	362 (77)	1204 (69)	
At least one modal SBS score +1/+2, No., (%)	218 (15)	166 (36)	221 (11)	0.243
Opioid dose ≥0.2 mg/kg/hour morphine equivalents any day, No., (%)	343 (24)	358 (76)	240 (12)	<0.001
Benzodiazepine dose ≥0.2 mg/kg/hour midazolam equivalents any day, No., (%)	274 (17)	296 (63)	194 (10)	<0.001
Highest number of secondary sedative agents received any day, median (IQR)	0 (0)	1 (0-2)	0 (0-1)	<0.001

Unplanned removal of any device, No. of events, (%)	38 (3)	15 (3)	42 (2)	0.255
Inadequate sedation management event	141 (10)	166 (35)	122 (6)	<0.001
Received neuromuscular blockade for agitation, No., (%)	247 (17)	128 (27)	320 (16)	<0.001
BUN > 20, No., (%)	233 (16)	55 (12)	328 (17)	0.026
ALT > 55, No., (%)	356 (25)	69 (15)	440 (22)	0.001

Table 2: Fit Statistics for Latent Class Models For 2 to 4 Class Models By Group

	AIC	ABIC	Entropy	VLMR LRT for k vs k-1 classes (p-value)	Percent of cohort per class			
					1	2	3	4
Training Cohort								
2 Classes	56799.9	57007.9	0.84	-29520.9 ( $<0.001$ )	57	43		
3 Classes	54865.0	55177.1	0.91	-28302.0 (0.76)	17	42	41	
4 Classes	57007.9	55177.1	0.88	-27285.5 (0.78)	29	22	33	16
Validation Cohort								
2 Classes	37066.8	37233.4	.99	-19257.5 ( $<0.001$ )	19	81		
3 Classes	35966.6	36216.5	0.91	-18435.4 (0.78)	19	36	45	
4 Classes	53894.6	35716.6	0.88	-17836.3 (0.78)	28	24	18	30

AIC= Akaike Information Criteria; ABIC= Sample-size Adjusted Bayesian Information Criteria;

VLMR LRT= Vuong-Lo-Mendell-Rubin Likelihood Ratio Test; Parametric BLRT= Parametric Bootstrapped Likelihood Ratio Test.

Table 3: Test Characteristics of the Decision Tree

Characteristic	
Number of subjects included	2078
Subjects positive for DTS	386
Number of true positives	32
Number of true negatives	646
Number of false positives	23
Number of false negatives	120
Accuracy (% , CI)	82.6 (0.799, 0.851)
Sensitivity	0.211
Specificity	0.966
Positive predictive value	0.582
Negative predictive value	0.843
Positive likelihood ratio	6.21
Negative likelihood ratio	0.82
Prevalence	0.067

CI= confidence interval; DTS= difficult-to-sedate

## Figures

Figure 1: Comparison of Latent Class and Classification and Regression Tree Methodologies

Latent Class Analysis is a hypothesis-free statistical technique that uses mixture modeling, and has been used extensively in clinical phenotype development studies to identify unobserved (latent) classes by building typologies or clusters based on observable variables within a data set. In comparison to other statistical analyses, no outcome variable is included in the analysis. The algorithm seeks previously unobserved patterns in the data by looking for patterns between the variables included in the analysis, and produces groups of patients that are as different as possible from each other. LCA works best with categorical or ordinal data. (13,14)

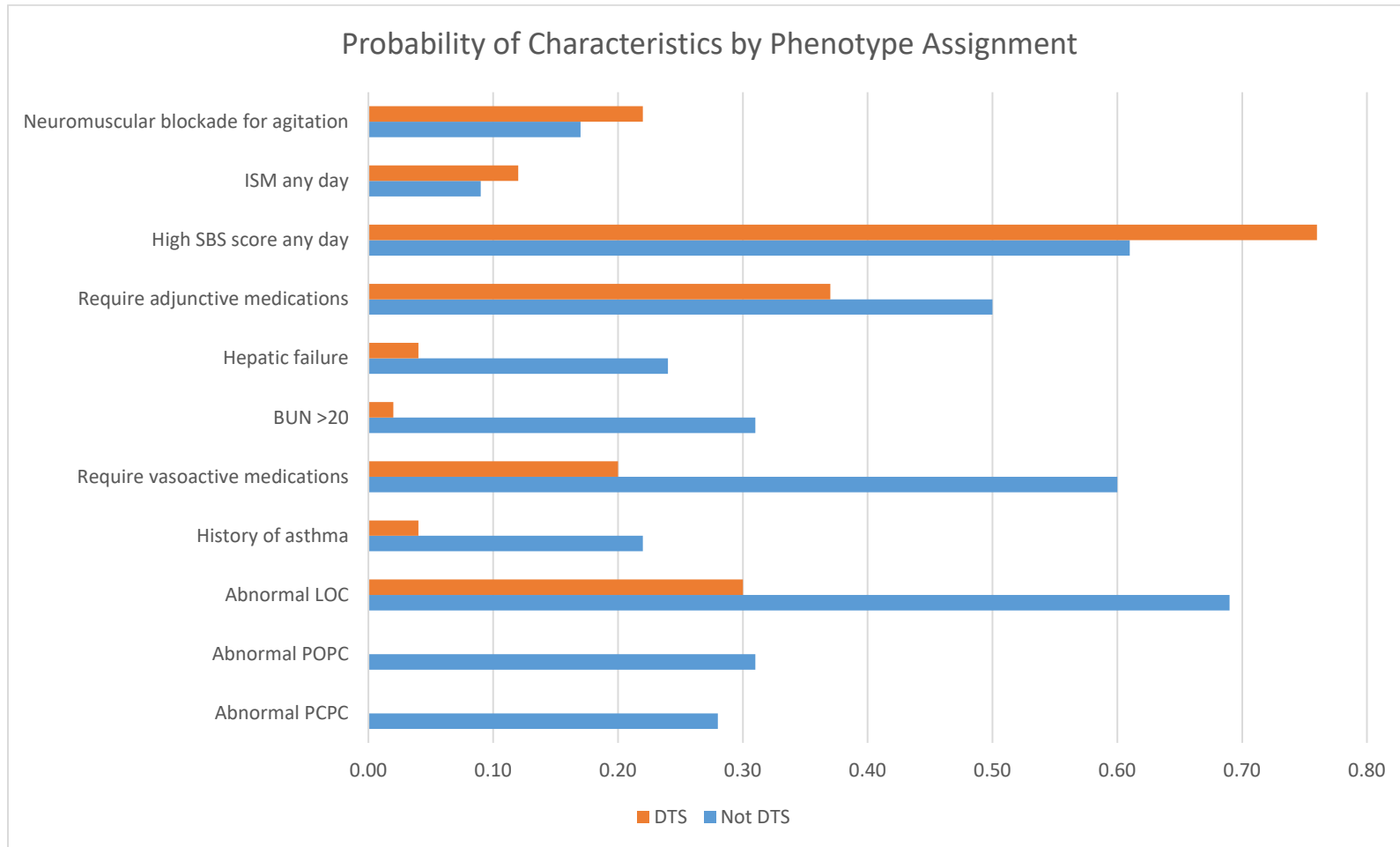
CART methodology is an exploratory data mining technique that searches large data sets looking for meaningful patterns. It classifies populations into clinically meaningful risk categories, and is useful in uncovering complex interactions when many potential predictor variables and patterns of relationship exist. CART can use categorical, ordinal and continuous data. Unlike LCA, CART does require an outcome or response variable, which can be categorical or continuous. CART produces cut points and ordering of decision nodes that clearly discriminate between groups with high and low risk for the response variable. The CART output includes a diagram of the tree produced by the analysis, which looks very similar to many algorithms used in clinical care. (15-17)

LCA and CART are both non-parametric tests that do not require normally distributed data. Both LCA and CART test statistical models, so multiple variations of the proposed model are analyzed. The final best fitting model is selected based on model

fit statistics and interpretability of the model. The model must then be validated by testing the model in other groups to see if it is reproduced.(13-17)

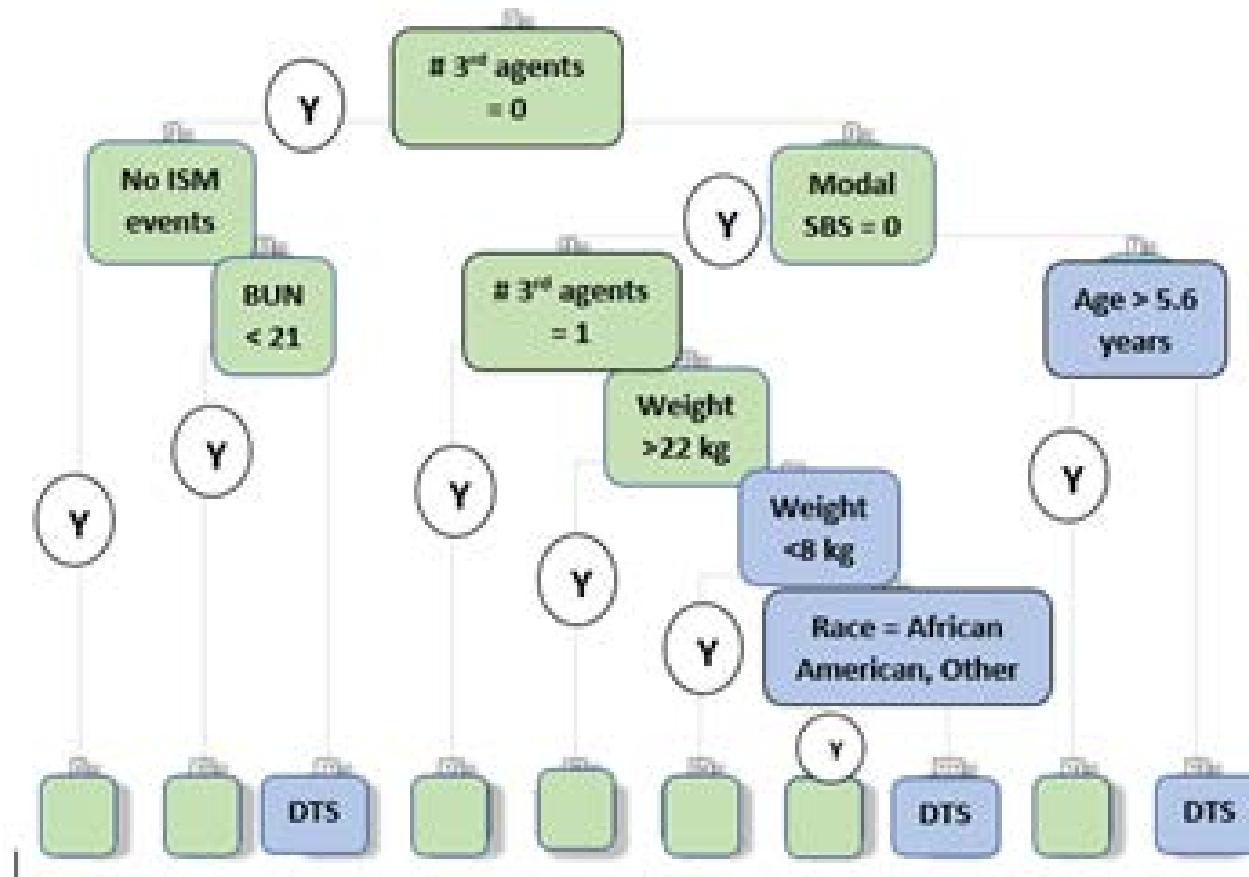


Figure 2: Latent Class Analysis Findings: Probability of Characteristics by Phenotype Assignment



BUN= blood urea nitrogen in mg/dL; ISM= inadequate sedation management event; LOC= level of consciousness; PCPC= Pediatric Cerebral Performance Category; POPC= Pediatric Overall Performance Category

Figure 3: Classification and Regression Tree Decision Tree for Difficult-to-Sedate Child Clinical Phenotype



BUN= blood urea nitrogen; DTS= difficult-to-sedate; ISM= inadequate sedation management event; # 3<sup>rd</sup> agents= number of classes of adjunctive medications received; SBS= State Behavioral Scale Score.

## Supplement 1

Table 1: Variables included in the Difficult-to-Sedate Analysis Linked to Survey of Expert PICU Clinicians

Sedation Characteristics	LCA Variable	CART Variable
Requires 3 or more sedation classes simultaneously	Received 3 <sup>rd</sup> class of sedation medication	Number of classes of additional sedation medication received
Daily modal SBS +1/+2	Modal SBS score +1/+2 any day 0-3	Modal SBS score +1/+2 any day 0-3
SBS +1/+2 for 2 consecutive hours	Inadequate sedation management event	Inadequate sedation management event
Doses >90th percentile of usual starting dose	Morphine or midazolam equivalents $\geq 0.2$ mg/kg/hour	Element in composite outcome variable
Intermittent paralytic doses for sedation	Received neuromuscular blockade for agitation	Received neuromuscular blockade for agitation
Sedation-related Events		
Suspected delirium	Number of events too small to include in analysis	Number of events too small to include in analysis
Unplanned endotracheal extubation	Unplanned device Removal	Unplanned endotracheal tube removal

Unplanned removal of an invasive device	Unplanned device removal	Unplanned device removal
Paradoxical response to sedation	Number of events too small to include in analysis	Number of events too small to include in analysis
Demographic/Diagnostic Characteristics		
Trisomy 21	PRISM III-12 chromosomal abnormality	PRISM III-12 chromosomal abnormality
Previous sedation exposure	Past medical history of previous exposure	Past medical history of previous exposure
Not able to verbally communicate	PCPC GCS LOC	PCPC GCS LOC
>90th percentile for BMI	Overweight for age Normal BMI	BMI Weight for Age
Oncologic diagnosis	PRISM III-12 cancer diagnosis	PRISM III-12 cancer diagnosis
Moderate or severe cerebral disability	PCPC	PCPC
Moderate or severe overall disability	POPC	POPC
Bronchiolitis	Admission Diagnosis	Admission Diagnosis
Additional Variables Suggested by Experts		
Prematurity	History of prematurity	History of prematurity

Infant or toddler	Age category	Age
Patient instability	PRISM III-12 Z-score Vasoactive medications Cardiovascular, hepatic, renal, neurologic failure Elevated BUN or ALT	PRISM III-12 Z-score Vasoactive medications Cardiovascular, hepatic, renal, neurologic failure Elevated BUN or ALT
Diagnosis specific	Admission diagnosis Asthma diagnosis Seizure disorder	Admission diagnosis Asthma diagnosis Seizure disorder
Additional factors suggested in the literature		
Gender	Gender	Gender
Race/ethnicity	Race, ethnicity	Race, ethnicity
Primary opioid (morphine vs. fentanyl)	Primary opioid days 0-3	Primary opioid days 0-3

GCS= Glasgow Coma Scale score; LOC= level of consciousness; PRISM III-12 =  
PCPC= Pediatric Cerebral Performance Score; POPC= Pediatric Overall Performance  
Score;

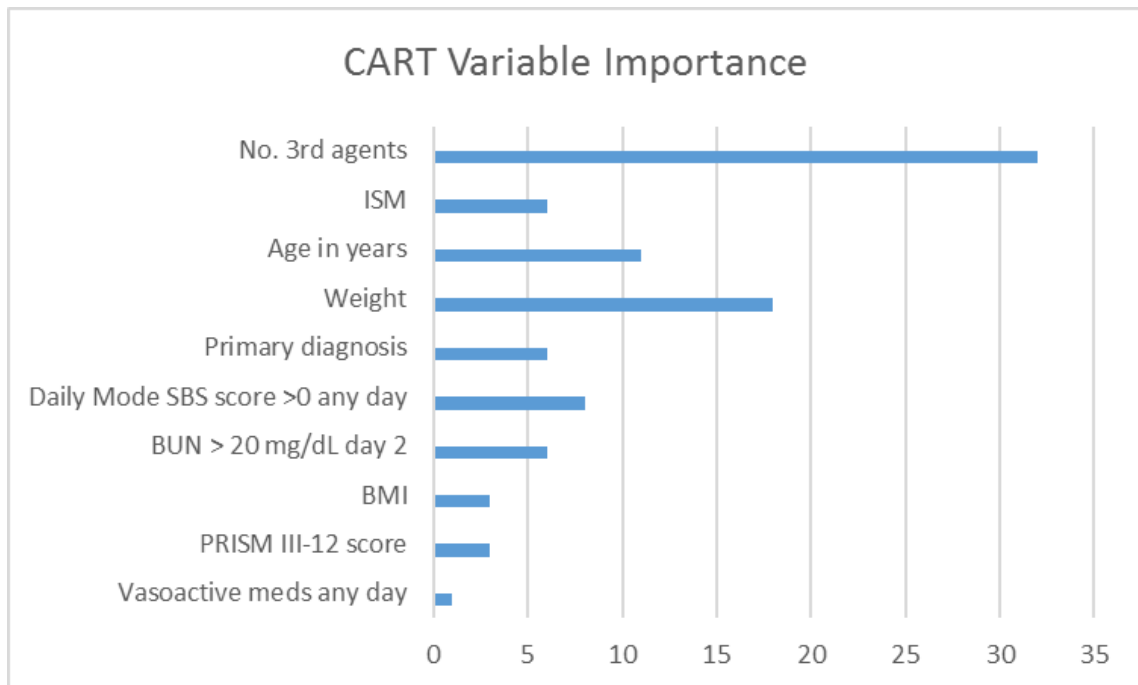
Supplement Table 2: Characteristics of the Parent Study Cohort by Group

Admission Characteristics	Total	Control	Intervention	p value
	n = 2449	n = 1224	n = 1225	
Age at PICU admission, median (IQR), years	1.8 (0.4-8.2)	2.6 (0.6-9.2)	1.4 (0.3-7.0)	0.002
Female, No. (%)	1,101 (45)	543 (44)	558 (46)	0.53
Non-Hispanic white, No. (%)	1,233 (50)	602/1210 (50)	631/1215 (52)	0.81
Baseline PCPC = 1, No. (%)	1,865 (76)	923 (75)	942 (77)	0.41
Baseline POPC = 1, No. (%)	1,747 (71)	862 (70)	885 (72)	0.51
PRISM III-12 score, median (IQR)	7 (3-13)	8 (5-13.5)	6 (3-11)	0.005
Primary diagnosis, No. (%)				<0.001
Pneumonia	827 (34)	433 (35)	394 (32)	
Bronchiolitis	656 (27)	228 (19)	428 (35)	
Acute respiratory failure related to sepsis	357 (15)	212 (17)	145 (12)	
Asthma or reactive airway disease	207 (8)	120 (10)	87 (7)	
Aspiration pneumonia	149 (6)	79 (6)	70 (6)	
Other	253 (10)	152 (12)	101 (8)	
Past medical history, No. (%)				0.37
Prematurity	369			
Previous exposure to opioids/benzodiazepines	394			0.31
Oncology diagnosis	197 (8)	109 (9)	88 (7)	
Chromosomal abnormality	108 (4)	48 (4)	60 (5)	0.24
Weight for age > 95 <sup>th</sup> percentile, No. (%)	307 (13)	144 (12)	163 (13)	0.132
Pt characteristics PICU Days 0-3				
Primary opioid agent, No. (%)				<0.001
Morphine	992 (41)	210 (17)	782 (64)	
Fentanyl	1,420	989 (81)	431 (35)	
Other	(58)	10 (<1)	3 (<1)	
None	13 (<1)	15 (1)	9 (<1)	
	24 (1)			
At least one modal SBS score +1/+2, No. (%)	387 (16)	242 (20)	145 (12)	0.002
Opioid dose ≥0.2 mg/kg/hour morphine equivalents any day, No. (%)	588 (24)	334 (28)	254 (21)	0.001
Benzodiazepine dose ≥0.2 mg/kg/hour midazolam equivalents any day, No. (%)	490 (20)	276 (23)	214 (17)	0.002
Highest number of secondary sedative agents received any day, median (IQR)	0 (0-1.0)	0 (0-1.0)	0 (0-1.0)	<0.001
Unplanned removal of any device, No. of events, (%)	59 (2)	31 (3)	28 (2)	0.685
Inadequate sedation management event, No., (%)	547 (22)	246 (20)	301 (25)	0.93
Received neuromuscular blockade for agitation, No., (%)	616 (25)	326 (27)	290 (24)	0.66
BUN > 20, No., (%)	403 (16)	233 (19)	170 (14)	<0.001

ALT > 55, No., (%)	404 (16)	230 (19)	174 (14)	<0.001
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ALT= alanine amino transferase; BUN= blood urea nitrogen in mg/dL; IQR= interquartile range; PCPC= Pediatric Cerebral Performance Category; POPC= Pediatric Overall Performance Category; PRISM III-12= Pediatric Risk of Mortality version III score for first 12 hours of PICU admission; SBS= State Behavioral Scale score.

Supplement Figure 1: CART Variable Importance



BMI= body mass index; BUN= blood urea nitrogen; ISM= inadequate sedation management event; No. 3<sup>rd</sup> agents= number of classes of adjunctive medications received; SBS= State Behavioral Scale Score.



## CHAPTER 5

### DISCUSSION AND CONCLUSIONS

Sedation of critically ill children is one of the most commonly provided therapies in PICUs, yet clinicians continue to search for the optimal way to provide this therapy. It requires a delicate balance between providing sufficient sedation to ensure the child is comfortable and able to tolerate needed interventions such as endotracheal intubation and mechanical ventilation, yet not so much that the child is at risk for iatrogenic injury and a prolonged length of mechanical ventilation or stay due to oversedation. The majority of sedative drugs used in the PICU are used off-label. They have not been studied extensively in children, and dosing guidelines are often extrapolated from adult studies.(1) Chapters 1 and 2 of this dissertation describe variability of current practice, nationally and internationally, in terms of sedative agents used, methods of assessment of the level of sedation, and the use of non-pharmacologic techniques such as noise reduction and promoting normal day/night cycling.(2,3)

PICU patients are a very heterogeneous population and this increases the complexity of providing optimal sedation to all patients. Patients range in age from birth to 18 years with a wide variety of diagnoses, and evidence suggests that age and critical illness impact the pharmacokinetics and pharmacodynamics of sedation medications. (4,5) Young children do not yet have the developmental skills needed to cognitively appraise and understand the PICU environment. In addition, there is recent evidence suggesting that sedatives routinely used in the PICU may have a negative impact on neurodevelopment in young children.(6,7) As a result, clinical practice is trending toward setting sedation goals of a more awake state, and the decreased use of benzodiazepines, with the concomitant increase in the use of other sedative agents.

These concerns are descriptive of the PICU population as a whole, but there is an added level of complexity in providing sedation to patients in the PICU, due to

significant inter-patient variability in response to sedation medications. In particular, some children remain consistently agitated despite receiving high doses and multiple classes of sedative agents. These children are frequently labeled difficult-to-sedate. Studies have acknowledged the existence of this population, but this group has not been well described or studied. This dissertation contributes to the existing knowledge of sedation for critically ill children by creating and testing an operational definition of the difficult-to-sedate child clinical phenotype, which will be useful in future research.

### **Overall Goals**

The purpose of this study was to explore and define the phenomenon of the difficult-to-sedate child clinical phenotype within a population of critically ill children. This is one of the first studies attempting to operationalize this concept and identify its prevalence. The study had three specific aims: (1) to explore key variables thought to be associated with the difficult-to-sedate child and propose a conceptual model linking those variables in critically ill pediatric patients; (2) to assess both face and content validity of the candidate variables identified in the difficult-to-sedate conceptual model; and (3) to build and test a statistical model describing the difficult-to-sedate child clinical phenotype. The conceptual model, described in Chapter 2, served as the foundation for the subsequent analyses. Chapter 3 details the process of establishing face and content validity of the variables included in the model, and Chapter 4 details the modeling process. In this exploratory analysis, the majority of variables included in the statistical model performed consistently across the two methods of analysis, providing further support for the conceptual model. The results of this study show that the difficult-to-sedate child clinical phenotype is a stable concept, and may represent 18% of the PICU patient population.

### **Major Findings: Operational Definition**

The difficult-to-sedate child is one who requires routine and repeated escalation of sedation doses beginning on the first day of intubation, routine administration of adjunctive sedation medications over and above the increased opioid and benzodiazepine doses, and reaches opioid and benzodiazepine doses above the unit's standard range for the drug within the first three days of intubation without achieving the target sedation goal.

Prior to the definition proposed in this dissertation, no clear operational definition of the difficult-to-sedate clinical phenotype existed in the pediatric critical care literature. Variability in practice is one of the main reasons for this. There are several different assessment instruments used to identify the child's level of sedation, many of which lack sufficient reliability and validity testing. Some tools, such as the COMFORT B (8) assess both pain and agitation, using a single score. This can be problematic for the clinician at the bedside who must use a single score to determine whether pain or anxiety is the cause of a child's distress and then select the appropriate intervention for the child receiving both analgesics and opioids.

Another reason an operational definition is lacking is that routine establishment of a daily sedation goal does not occur in most PICUs. Kudchadkar et al. surveyed an international group of pediatric intensivists in 2014 and identified that although 70% of units reported using a specific sedation assessment instrument, less than half of those units used them regularly to establish a daily sedation goal to guide therapy.(3) More recently, Garcia Guerra et al. (2) surveyed Canadian pediatric critical care intensivists on the same topic and found that 74% of PICUs did not routinely identify a daily sedation goal. Without designation of a goal and routine assessment of goal achievement, there is no objective way to determine when a child is optimally or sub optimally sedated.

The studies included in the literature review detailed in Chapter 2 consisted of seven that assessed the effectiveness of a sedation protocol, 12 that compared two different sedation medications or assessed the effectiveness of a single drug and 10 that assessed the accuracy of an “objective” sedation measure, most commonly the Bispectral index monitor. All but two of the studies described patients who were undersedated, but used a wide variety of metrics. A frequently used metric was the number of observations where a child was above the desired sedation goal. As detailed in Chapter 2, number of episodes of agitation, removal of a patient from study due to “treatment failure”, percent of total drug administration time the child was in the target sedation range and percent of time a child was undersedated based on a set sedation goal were other metrics described. The variability seen here clearly identifies the lack of a consistent operational definition. It is interesting that the studies evaluating drug effectiveness and the effectiveness of sedation protocols did not use a consistent metric to report the observed rate of undersedation, as this limits the ability to compare treatment protocols.

The operational definition created through the process of concept analysis included several characteristics: routine and repeated escalation of sedation doses beginning on the first day of intubation, routine administration of adjunctive sedation medications over and above the increased opioid and benzodiazepine doses, and reaches opioid and benzodiazepine doses above the unit’s standard range for the drug within the first three days of intubation without achieving the target sedation goal. Young age and Trisomy 21 were the two demographic characteristics identified through the literature review. When considering use of this operational definition, it is important to note that obtaining sedation scores, setting a sedation score goal, knowledge of the standard dose specific to the PICU where the child is receiving care, and knowledge of

adjunctive medication are key elements that must be in place. Utilization of this definition across studies in this population will facilitate comparison of results.

### **Major Findings: Face and Content Validity of the Operational Definition**

Chapter 3 describes the process used to establish face and content validity for the 17 candidate variables identified through the literature review. The survey was distributed via email to 411 expert pediatric critical care clinicians, primarily physicians, from 61 centers across the U.S. The response rate was 29%, and 69% of sites were represented. The amount of missing data was minimal, at 0.3%. Respondents scored each of the candidate variables using a rating of 1 (not at all relevant) to 4 (highly relevant). An item level content validity index (I-CVI) was calculated for each variable, and items with an I-CVI $\geq$ 0.70 were considered important and retained in the model.

The participants agreed that the majority of candidate variables proposed were characteristic of the difficult-to-sedate child. The 10 variables confirmed for inclusion in the final model were as follows: requiring three or more sedation classes simultaneously, a daily modal State Behavioral Scale (SBS) score indicating agitation (SBS +1/+2), an SBS score indicating agitation for 2 consecutive hours, receiving sedatives at a dose >90th percentile of the usual starting dose, receiving intermittent paralytic doses for sedation, suspected delirium, unplanned endotracheal extubation, unplanned removal of an invasive device, paradoxical response to sedation, and Trisomy 21. Six items which had a low I-CVI were demographic characteristics: not able to verbally communicate, >90th percentile for BMI, oncologic diagnosis, moderate or severe cerebral disability, moderate or severe overall disability, and bronchiolitis. The highest-rated item was requiring three or more sedation classes simultaneously. Additional characteristics were proposed by the respondents, with young age being most consistently cited. Additional variables included in the final model based on expert feedback were medical diagnosis

and required multiple sedative agents. In summary, expert clinicians validated that the majority of variables extracted from the literature were appropriate to include in the final model, along with two additional variables.

### **Major Findings: Characteristics of the Difficult-to-sedate Clinical Phenotype**

Latent Class Analysis (LCA) was used to identify the model which best divided the group into clinically meaningful classes. LCA provides a description of members of each class by indicating the probability that they will be positive for any variable. High probability supports inclusion of the variable as class-defining. Evaluation of model fit statistics and interpretability identified a two-class model as the best fitting model, with classes identified as difficult-to-sedate and not difficult-to-sedate. Variables which had a high probability of being true for the class were identified as characteristic of the difficult-to-sedate class. Variables with the highest probabilities and the widest separation from the not difficult-to-sedate class included the need for adjunctive medications, less organ failure, higher incidence of inadequate sedation events, and normal cognitive state. The not difficult-to-sedate class had a low probability for each of these variables. Repeating the analysis using the validation cohort demonstrated that the model was stable across the cohorts. The probabilities identified in the testing cohort were found to be similar in the validation cohort, with the exception of probability of class membership. Individuals in the testing cohort had a 43% probability of belonging to the difficult-to-sedate class, while individuals in the validation cohort had a 19% chance of belonging to the difficult-to-sedate class. The characteristics of the difficult-to-sedate class are consistent and supported in both cohorts. The proportion of individuals belonging to the difficult-to-sedate class were different across the two cohorts, and further testing using different sized training and validation cohorts would better define the size of the difficult-to-sedate population.

### **Major Findings: Variables Indicating Risk for the Outcome of Difficult-to-sedate**

CART analysis was used to identify patients at risk of being difficult-to-sedate. As detailed in Paper 3 (Chapter 4), CART sorts patients on each of the predictor variables included in the model. Unlike LCA, CART requires an outcome variable. Based on the literature review and I-CVIs established by the group of critical care experts, a composite difficult-to-sedate binary categorical outcome variable was created. In order for a subject to be scored as positive for the outcome, two criteria had to be met: the SBS score had to be +1/+2 and the subject had to have received at least two times the starting dose of an opioid or benzodiazepine continuous infusion on any study day from day 0-3.

The output of a CART analysis includes a decision tree and various fit statistics, which are described in detail in Chapter 4. Variables which identified a patient as at risk for being difficult to sedate included need for adjunctive sedation medications, daily modal SBS score of +1/+2, occurrence of an inadequate sedation management event, presence of an elevated blood urea nitrogen (BUN) level, age, weight, and race.

Sensitivity and specificity are important indicators of a useful decision tree, as they indicate whether a subject was placed into the appropriate category. Each of the analyses demonstrated good specificity, correctly identifying difficult-to-sedate patients 94% of the time. However sensitivity was low, resulting in patients being classified as difficult-to-sedate when in fact they were not positive for any of the indicator variables.

### **Major Findings: Characteristics Identifying the Difficult-to-sedate Clinical Phenotype**

Regardless of the methodology used, some characteristics were important indicators of this group, and aligned with expert opinion. The requirement for adjunctive medications, presence of organ failure, particularly renal failure, occurrences of

inadequate sedation management events, high daily modal SBS scores and need for vasoactive medications were sorting characteristics in both CART and LCA. CART also identified young age and primary diagnosis as important predictor variables, which align with our conceptual model and the opinion of experts. The results of these analyses provide support for the operational definition proposed in Paper 1. Approximately 18% of patients demonstrated the difficult-to-sedate outcome, based on the operational definition of difficult-to-sedate. This is one of the first studies attempting to determine the incidence of this clinical phenotype. Although it is difficult to extrapolate an expected rate of incidence from the literature reviewed, our finding does not seem excessively high.

### **Limitations**

This study was a secondary analysis of an existing data set, and it is likely that characteristics important to our concept were not included or available in the RESTORE data set. Missing data had an impact on the data analysis. Sedation assessment was a key variable, and 9% of subjects were missing SBS scores on all days. Because SBS scores contributed to the composite outcome variable created for the CART analysis, subjects who did not have SBS scores recorded on days 0 - 3 could not be included in the CART analysis. As a result, the incidence of the difficult-to-sedate clinical phenotype reported here might have been mis-estimated. It is important to note that overall, the data from RESTORE was of high quality, as sites routinely assessed inter-rater reliability for the SBS score and demonstrated high reliability.

A major assumption of this study was that pain was adequately controlled in this population. It is possible that this was not the case, especially early in the patient's course of treatment which was the timeframe evaluated in this study. The patients enrolled in RESTORE primarily had medical diagnoses, as opposed to surgical diagnoses, so it is less likely that pain was a highly significant issue for this group.



However, because patients did have medical diagnoses, the generalizability of our findings is limited.

Achieving optimal sedation is a very complex process, involving more than the child's clinical phenotype. The conceptual model described in Paper 1 indicates that in addition to child specific factors, process and environmental factors also influence sedation outcomes. This study focused exclusively on patient level factors in describing the difficult-to-sedate clinical phenotype, which is a simplistic approach given that phenotype is a set of observable characteristics created through the interaction of the individual's genotype with the environment. In future studies, it will be important to evaluate the impact of environmental and process factors.

Finally, this exploratory study employed a very straightforward approach to machine learning techniques. Testing a more complex model using covariates might help to refine the model and improve sensitivity.

### **Directions for Future Research**

The majority of critically ill children in PICUs require mechanical ventilation, and therefore receive sedation. Establishing the clinical phenotype of the difficult-to-sedate child and its incidence in a cohort of children supports the necessity for continued work in this area, as there are physiologic, developmental, psychosocial and economic impacts resulting from undersedation. This study raises many new questions and suggests multiple areas for investigation.

It is necessary to replicate the findings from this study prospectively in other populations. For example, this study identified the incidence of the difficult-to-sedate child clinical phenotype as approximately 13%. It will be important to examine this statistic in other patient populations, in order to determine the true incidence. It will also

be important to validate the characteristics and risk factors described in this study in other cohorts of critically ill children.

The characteristics included in this model were theoretically determined and then validated through a survey of practicing PICU clinicians, primarily physicians, prior to testing. Nurses are also intricately involved in providing sedation to critically ill children and monitoring the outcome. It would be useful to explore this model with nurses experienced in providing sedation to critically ill children, in order to continue to develop and refine the model.

An important area for future investigation is exploring a genetic basis for this phenotype. Phenotypes are observed characteristics of the individual that result from the interaction of the genotype, the environment, and other factors. Clinical phenotypes are useful specifically because they are observable. Examining the genomes of a group of individuals presenting with a particular observed trait such as an unexpected response to sedation increases the likelihood that a genome-wide association study (GWAS) could identify genetic variants that contribute to the altered drug response. A well-defined phenotype that clearly identifies affected individuals enhances the effectiveness of a well-designed GWAS.

Examining the genomes of phenotypic individuals through a GWAS has been used successfully to identify specific families of genes in the cytochrome P450 enzyme system, which characterize individuals in terms of their metabolism of codeine and other pain and sedation medications (9). Genetic polymorphisms cause intra-individual variation in enzyme activity, resulting in varying rates of drug metabolism, expressed as different phenotypes. Two groups of particular concern have been labeled poor metabolizers and ultra-rapid metabolizers as those individuals do not process drug in the “typical” way and are at risk for adverse drug reactions. Commercially available assays

that test for these specific polymorphisms exist and are becoming more affordable, and as a result are beginning to be utilized in clinical practice.(10).

The CYP3A4 enzyme, part of the cytochrome P450 enzyme system has been linked to the action of midazolam and other benzodiazepines.(11) Identifying the particular genetic variant responsible for differing action in different individuals would support clinical care in a variety of ways. Clinicians currently base initial drug dosing of sedatives on a standard dose known to be effective for the majority of patients and adjust the dose as needed based on the patient's response. Multiple dose adjustments over an extended period may be required to achieve the target sedation level in a patient with an atypical response. The undersedated child remains at risk for iatrogenic injury until the correct drug and dose are identified. Knowledge of the patient's genotype specific response to sedation medications would allow individualization of both the drug selected and the appropriate dose. In addition to quickly achieving the desired sedation level, the patient would not be exposed to drugs known to be ineffective for their genotype. This is particularly important in light of the current concern related to neurotoxic effects of sedatives on the developing brain.(12,13)

## Conclusion

The three papers developed in this dissertation study explored the concept of the difficult-to-sedate child clinical phenotype and accomplished three objectives. A comprehensive review of the literature identified the lack of an operational definition and facilitated extraction of possible factors contributing to the clinical phenotype. These factors were used to provide an initial operational definition and construct a conceptual model. A panel of expert critical care clinicians validated the elements of the operational definition through an assessment of face and content validity and proposed additional factors to be included in the model. A refined definition was tested using data from the

RESTORE study. The characteristics identified through latent class analysis were similar to risk factors identified through classification and regression tree analysis, and consistent with the conceptual model proposed.

Decreasing the ambiguity that currently exists around the concept of the difficult-to-sedate child clinical phenotype is a major achievement of this study. A clear operational definition of the concept promotes its consistent measurement and facilitates future investigation. This definition can be utilized by other researchers, allowing useful comparisons across studies. The conceptual model and operational definition developed in this study require further investigation and refinement, as well as validation by other investigators. This study suggests that a clinically meaningful population of difficult-to-sedate children requiring mechanical ventilation for a critical illness exists. Documentation of this phenotype promotes the development of evidence on the best way to support these children. Critically ill difficult-to-sedate children and their families will benefit from future research exploring this question.

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