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## Defining Sedation-Related Adverse Events in the Pediatric Intensive Care Unit

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# Defining Sedation-Related Adverse Events in the Pediatric Intensive Care Unit

## Abstract

### Background

Clinical trials exploring optimal sedation management in critically ill pediatric patients are urgently needed to improve both short- and long-term outcomes. Concise operational definitions that define and provide best-available estimates of sedation-related adverse events (AE) in the pediatric population are fundamental to this line of inquiry.

### Objectives

To perform a multiphase systematic review of the literature to identify, define, and provide estimates of sedation-related AEs in the pediatric ICU setting for use in a multicenter clinical trial.

### Methods

In Phase One, we identified and operationally defined the AE. OVID-MEDLINE and CINAHL databases were searched from January 1998 to January 2012. Key terms included sedation, intensive and critical care. We limited our search to data-based clinical trials from neonatal to adult age. In Phase Two, we replicated the search strategy for all AEs and identified pediatric-specific AE rates.

### Results

We reviewed 20 articles identifying sedation-related adverse events and 64 articles on the pediatric-specific sedation-related AE. A total of eleven sedation-related AEs were identified, operationally defined and estimated pediatric event rates were derived. AEs included: inadequate sedation management, inadequate pain management, clinically significant iatrogenic withdrawal, unplanned endotracheal tube extubation, post-extubation stridor with chest-wall retractions at rest, extubation failure, unplanned removal of invasive tubes, ventilator-associated pneumonia, catheter-associated bloodstream infection, Stage II+ pressure ulcers and new tracheostomy.

### Conclusions

Concise operational definitions that defined and provided best-available event rates of sedation-related AEs in the pediatric population are presented. Uniform reporting of adverse events will improve subject and patient safety.

### Keywords

patient safety, pediatric care, adverse event, respiratory failure

### Disciplines

Critical Care Nursing | Medicine and Health Sciences | Nursing | Pediatric Nursing

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## Defining Sedation-Related Adverse Events in the Pediatric Intensive Care Unit

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### Keywords

patient safety; pediatric critical care; adverse event; respiratory failure

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The majority of critically ill infants and children supported on mechanical ventilation receive some form of sedative therapy; most often various combinations of opioids and benzodiazepines<sup>1,2</sup>. Although there are clear benefits in using sedation in critically ill pediatric patients<sup>3</sup> sedative use may also be associated with iatrogenic injury<sup>4-6</sup>. Clinical trials exploring optimal sedation management in mechanically ventilated pediatric patients are urgently needed to improve short and long-term outcomes in this vulnerable patient population.

Fundamental to any clinical trial is patient safety. During the study design phase, anticipated adverse events (AEs), specific to the patient population and the intervention studied, are operationally defined and event rates estimated based on best available evidence. Operational definitions for each AE should be clear and reproducible across multiple clinical sites. Expected AEs are also incorporated into the study's risk-benefit profile and informed consent process. Adverse events are continuously monitored by the investigative team and Data and Safety and Monitoring Board (DSMB). If an AE rate exceeds that expected then the study's risk-benefit burden is reevaluated.

Here, we describe the process used to identify and operationalize sedation-related AEs for the *RESTORE* clinical trial. *RESTORE* (Randomized Evaluation of Sedation Titration for

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Respiratory Failure; U01 HL086622 and U01 HL086649) is a multicenter clinical trial evaluating the impact of a nurse-implemented goal-directed sedation protocol on clinical outcomes in pediatric patients with acute respiratory failure. Our objective was to develop concise operational definitions that defined, and provided best-available event rates, of sedation-related AEs in the pediatric population.

## Methods

We conducted a multiphase systematic review of the literature. Sedation-related AEs were first identified and operationally defined. Next, each of the operational definitions and event rates were estimated specific to the pediatric intensive care unit (PICU) population. Adverse events were defined as “any untoward or unfavorable medical occurrence, including any abnormal sign or symptom, temporally associated with the use of ICU sedation”<sup>7</sup>.

### Search Strategy

In Phase One we searched the OVID-MEDLINE and CINAHL databases from 1998 – 2008. Search terms included “sedation”, “intensive care unit” and “critical care”. We limited our search to English language data-based articles, involving Human subjects across the age spectrum from neonatal to adult. We included randomized clinical trials, prospective observational, or pre/post implementation study designs but excluded quality improvement projects, case reports, surveys, pharmacokinetics studies, and studies evaluating a single agent. We limited our search to include adverse events related to sedation management and not those related to a specific sedative or analgesic agents. Reference lists of retrieved articles were also reviewed. For each publication, we abstracted into data tables: methods, study population, results, reported operational definitions and event rates for each AE. Data pooling was not possible because of study heterogeneity. Data saturation was achieved when no further unique AE or rates of occurrence were identified.

Phase Two replicated our previous search strategy to search terms that included all AEs identified in Phase One, limited to data-based articles in the pediatric population. Unpublished data from the *RESTORE* pilot study (R21 HD045020)<sup>8</sup> and available event rate data from participating sites were added. Pediatric-specific definitions and event rates were then added to the data table.

### Data Extraction and Synthesis

The *RESTORE* Core Investigator team that included 2 adult and 3 pediatric intensivists, 3 PICU nurses and 1 PICU pharmacist reviewed the data table and, by consensus, made a recommendation that operationally defined each AE with an expected rate of occurrence. Excluded from further review at this stage were several phenomena uncommon in pediatrics (myocardial infarction, delirium), not specific to sedative use (multisystem organ failure), related to administration techniques (hypotension), unit-based standards of care (urinary tract infection, restraint use) or evaluated after ICU discharge (post-traumatic stress). Of note, delirium has not been fully explicated in the pediatric population, valid and reliable pediatric-specific assessment instruments have only recently been published for verbal cognitive-capable pediatric patients.

The *RESTORE* Steering Committee, that included 22 voting pediatric intensivist or advanced practice nurses representing each participating PICU, then reviewed the data tables and approved the final terms and rates with 100% agreement. These were then reviewed and approved by the *RESTORE* DSMB (see Table One). A replicated systematic review in January 2012 demonstrated no new AEs that would impact our findings. Institutional review board was not obtained for this review.

## Results

In Phase One we screened 245 papers (see Figure 1). Of these, 32 articles were retrieved for more detailed evaluation and 20 met Phase One inclusion/exclusion criteria<sup>9-28</sup> [ENREF 9](#) [ENREF 9](#). As anticipated, none included pediatric patients. 9 were reported as RCTs, 8 prospective before/after, and 3 prospective, observational. The majority of studies were conducted in medical ICUs (N=12). Most studies evaluated the effect of guideline directed sedation management on patient outcomes (N=10).

In Phase Two we included 62 papers to refine our definitions and determine the rates of each AE in the PICU population. A summary of the sedation-related AEs is provided below. Anticipated rates for these events are presented in Table One. .

### Inadequate sedation management

Achieving adequate and effective sedation levels, and controlling agitation, was evaluated by most studies in Phase One of this review. In pediatric patients, Fonsmark et al<sup>29</sup> described the efficacy of sedation as "the quality of sedation assessed by the nursing staff; specifically, the patient is asleep, tolerating mechanical ventilation and able to show a slight response to nursing procedures". The COMFORT scale<sup>30</sup> was designed to assess distress in ventilated children but distress was operationalized to include the constructs of both pain and agitation. From a clinical perspective, separate valid and reliable pain and agitation assessment tools would allow more targeted therapeutic management.<sup>31</sup> In 2006, Curley et al<sup>32</sup> developed then validated State Behavioral Scale (SBS) for use in ventilated pediatric patients aged 6 wks to 6 yrs. The SBS range is -3 unresponsive to +2 agitated.

In the *RESTORE* trial, inadequate sedation management was defined as an SBS<sup>32</sup> of +1 (restless and difficult to calm) or a SBS of +2 (agitated) for 2 consecutive hours, not related to a planned extubation attempt.

### Inadequate pain management

While a number of studies reported daily or total administration of sedatives and analgesics<sup>6,17,19,20,23,25,26,33-35</sup> few systematically evaluated the effect of the sedation/analgesia regimen on a patient's pain level. A variety of instruments were used to assess pain. The incidence of pain varied in adult studies ranging from 6-42%<sup>21,25</sup>.

No pediatric study defined or reported the incidence of inadequate pain management in mechanically ventilated children. Pain scores of 4 on a 0-10 scale equate to a moderate level of pain infrequently experienced in nonsurgical patients supported on mechanical ventilation. Pain assessment tools were based on a 10-point scale. The validated pain assessment tool depended upon the age and verbal capacity of the subject: infant to 7 years and nonverbal: FLACC (Facial expression, Leg movement, Activity, Cry, and Consolability)<sup>36,37</sup>; 3+ years of age and verbal: Wong-Baker FACES<sup>38</sup>; 5+ yrs of age and verbal: Numeric Rating Scale; and 8 yrs and nonverbal: Individualized Numeric Rating Scale (INRS)<sup>39</sup>. The *RESTORE*'s pilot study<sup>8</sup> showed the highest median daily pain score on a 0-10 scale to be 1 (IQR: 1-4).

In the *RESTORE* trial, inadequate pain management was defined as a pain score > 4 on a 0-10 age appropriate pain scale for 2 consecutive hours, not related to a planned extubation attempt..

### Clinically significant iatrogenic withdrawal

Iatrogenic withdrawal syndrome related to opioid and or benzodiazepine use has not been thoroughly described in critically ill adult patients. In contrast, iatrogenic withdrawal syndrome has been reported to occur in up to 57% of PICU patients<sup>40</sup>. Iatrogenic withdrawal is influenced by the length and total exposure to opioids and benzodiazepines, increasing to over 50% after 5 days of continuous infusion or around-the-clock administration<sup>40,41</sup> and by the rate of weaning<sup>29,40,42</sup>.

Several assessment instruments have been used to describe iatrogenic withdrawal syndrome<sup>29,42-49</sup>. The Finnegan Neonatal Abstinence Score<sup>50</sup> (NAS) has been used in pediatric patients<sup>40,43,51,52</sup> defining withdrawal as a NAS of  $\geq 8$  of 39 for three consecutive scores obtained every 2 hours<sup>51,52</sup> or a NAS of  $>12$  of 39<sup>43</sup> or agitation requiring opioid rescue<sup>52</sup>. Franck et al. developed the pediatric-specific Withdrawal Assessment Tool 1 (WAT-1)<sup>53,54</sup>. WAT-1 score of  $> 3$  of 12 is associated with iatrogenic withdrawal.

In the *RESTORE* trial, clinically significant iatrogenic withdrawal was defined any patient receiving rescue therapy to manage an increase in WAT-1 score.

### Unplanned endotracheal tube (ETT) extubation

Numerous randomized controlled<sup>12,13,16,20,24,28,55,56</sup> [ENREF 36](#) and comparative observational studies<sup>9,18,57-60</sup> report unplanned extubation as a sedation-related AE in adult patients. Unplanned/self extubation rates in these studies ranged from 1-6 per 100 airway days.

[ENREF 53](#) Factors associated with unplanned extubation in pediatrics include the presence of agitation<sup>61-64</sup> [ENREF 55](#) [ENREF 58](#), high patient/nurse and patient acuity/nurse ratios<sup>64,65</sup>, younger age<sup>63,66,67</sup>, medical vs. surgical patients<sup>63</sup>, sedation not administered in the two hours before event<sup>62</sup>, lack of two-point or more restraints<sup>62</sup>, and performance of a patient procedure at the bedside<sup>62,63</sup>. Patients with a longer length of mechanical ventilation and children in the weaning phase were at a higher risk of unplanned extubation<sup>63</sup>. Unplanned extubation rates in pediatrics range from 0.2 to 1.7 per 100 airway days<sup>62-70</sup>. Overall, 14-22% of pediatric patients who self-extubate require re-intubation<sup>63,71</sup>.

### Post-extubation stridor with chest-wall retractions at rest

No sedation articles in adults discussed this AE. However, excessive movement of the ETT within the airway is thought to precipitate airway trauma in the agitated pediatric patient. The reported pediatric incidence of post-extubation stridor requiring treatment ranges from 15% to 41%<sup>72-74</sup>. The frequency of pediatric reintubation for stridor ranges from 2% to 52%<sup>72-77</sup>. Other variables related to stridor included the number of racemic epinephrine treatments<sup>73,76-80</sup>, use of a helium-oxygen gas mixture<sup>73</sup>, and stridor requiring some form of intervention<sup>74,77</sup>. Two RCTs evaluating the use of dexamethasone to prevent post-extubation stridor reported reintubation in 11%<sup>73</sup> and 25%<sup>74</sup> of patients with stridor.

The *RESTORE* trial defined stridor (high-pitched or harsh inspiratory noise) with chest-wall retractions at rest after ETT extubation to be phenomena of concern.

### Extubation failure

In adults, extubation failure was defined as reintubation occurring within 24-48 hours of extubation<sup>16,18,81</sup>. The criteria for reintubation was not reported or left to the discretion of the treating physician. There were significant differences in reintubation rates across study groups<sup>10,13,18</sup>. Subjects treated with continuous IV sedation were more likely to require

reintubation<sup>10</sup>. Subjects managed with a nurse-implemented sedation protocol were less likely than the control group to require reintubation<sup>18</sup>. Weaning parameters were also found to be poor predictors of successful extubation<sup>82,83</sup>.

Reintubation rates in electively extubated pediatric patients ranged from 4-14%<sup>67,71,84-86</sup>. Patients who failed extubation were typically younger<sup>67,85,86</sup>, experiencing a longer PICU length of stay and length of mechanical ventilation<sup>67,76,84-86</sup>, were receiving inotropic support with a low PaO<sub>2</sub><sup>87</sup>, or were chronically ill with a respiratory or neurologic condition<sup>77</sup>.

### **Unplanned removal of any invasive tube**

Six prospective adult observational studies reported the frequency of unplanned removal of any invasive tube/catheter<sup>16,21,24,58,60,88</sup>. Devices removed included vascular catheters, bladder catheters, and gastric tubes. Studies implementing systematic pain and sedation assessments<sup>21</sup>, daily sedation interruption<sup>24</sup> and protocolized sedation<sup>16</sup> noted low rates of device removal. Similar pediatric data were not identified. Unplanned removal of any invasive tube in *RESTORE* trial was defined as removal of the device per 100 device days.

### **Ventilator Associated Pneumonia (VAP)**

Five adult studies reported an association between sedation practices and VAP rates<sup>9,18,21,56,89</sup>. The incidence of VAP has been reported to be significantly lower in nurse-implemented sedation protocol vs. control groups<sup>21,18</sup>. *RESTORE* adopted the National Nosocomial Infections Surveillance System (NNIS)<sup>90,91</sup> definition of VAP

### **Catheter Associated Bloodstream Infection (CA-BSI)**

CA-BSI rates may be affected by the use of continuous versus intermittent sedation and/or the need to enter a central line to administer rescue sedation doses. One adult study reported a significantly lower rate of CA-BSI in patients managed with a sedation protocol<sup>21</sup>. *RESTORE* adopted the NNIS<sup>91,92</sup> ENREF 79 definition of CA-BSI.

### **Stage two pressure ulcers**

Sedated patients cannot communicate nor respond to pressure-related discomfort and thus are at high risk for pressure ulcers. Adult patients managed with a sedation algorithm experienced fewer pressure ulcers<sup>9</sup>. Using the National Pressure Ulcer Advisory Panel guidelines<sup>93</sup>, Curley et al<sup>94</sup> ENREF 83 reported that 27% of critically ill pediatric patients developed pressure ulcers. Predictors of pressure ulcers included mechanical ventilation and lower Braden Q<sup>95</sup> ENREF 97 scores. *RESTORE* used the National Pressure Ulcer Advisory Panel guidelines<sup>93</sup> and defined Stage II<sup>93</sup> pressure ulcer (or worse) as reportable.

### **New tracheotomy**

Tracheotomy practices differ between adult and pediatric critically ill patients. There is conflicting evidence on the rate of new tracheotomy in adult patients managed with a sedation protocol<sup>13,14,27,56</sup> ENREF 27. There were no pediatric studies reporting the rate of new tracheotomy in sedated critically ill patients. We elected to follow all new tracheotomies as a tracer for extreme airway trauma secondary to agitation.

## **Discussion**

We conducted this systematic literature review to operationally define, summarize and present a sedation-related AE monitoring plan for the *RESTORE* multi-institutional clinical trial. AE definitions and estimated event rates were derived through a multilayered

consensus process using best available evidence. While clear and concise operational definitions and estimated rates of specified AE are paramount to the safe conduct of clinical trials, these data may also be useful to those evaluating patient safety initiatives.

Because of the paucity of pediatric data, pediatric clinicians frequently use data that are available from adult care. When relevant anatomical or maturational differences exist between adult and pediatric patients we based our definitions strictly on pediatric literature. For example, whereas extubation failure is universal, post-extubation stridor is unique in the pediatric population because of anatomical differences.

Our recommendations must be interpreted in light of several important limitations. The etiology of sedation related AE appear multi-factorial, and each may be associated with different risk or protective factors. Sedation practices are rapidly evolving and many papers now pre-date the trend towards a more awake ICU patient population. Not all tools are validated to the entire pediatric age spectrum; specifically the SBS was validated in 6 wk to 6 yr olds. While AE rates seem to vary with the use of a sedation protocol, there is significant heterogeneity among studies and different operational definitions of AE made comparisons across studies difficult. Careful consideration of the complex interaction between, age, development, sedation level and exposure, use of protocols and organizational factors will be fundamental to understanding the factors that alter patient risk. The proposed definitions and event rates represent a consensus evidence based opinion. Finally, although our search methods were quite comprehensive, we may have overlooked a relevant paper that should have been included in our review.

## Conclusion

In this article, we propose operational definitions and recommendations for reporting sedation-related AE in critically ill ventilated pediatric patients. While this work provides the necessary foundation for the safe conduct of sedation clinical trials, we anticipate continued dialogue on this topic. These standard definitions may help us communicate, share results and advance the field.

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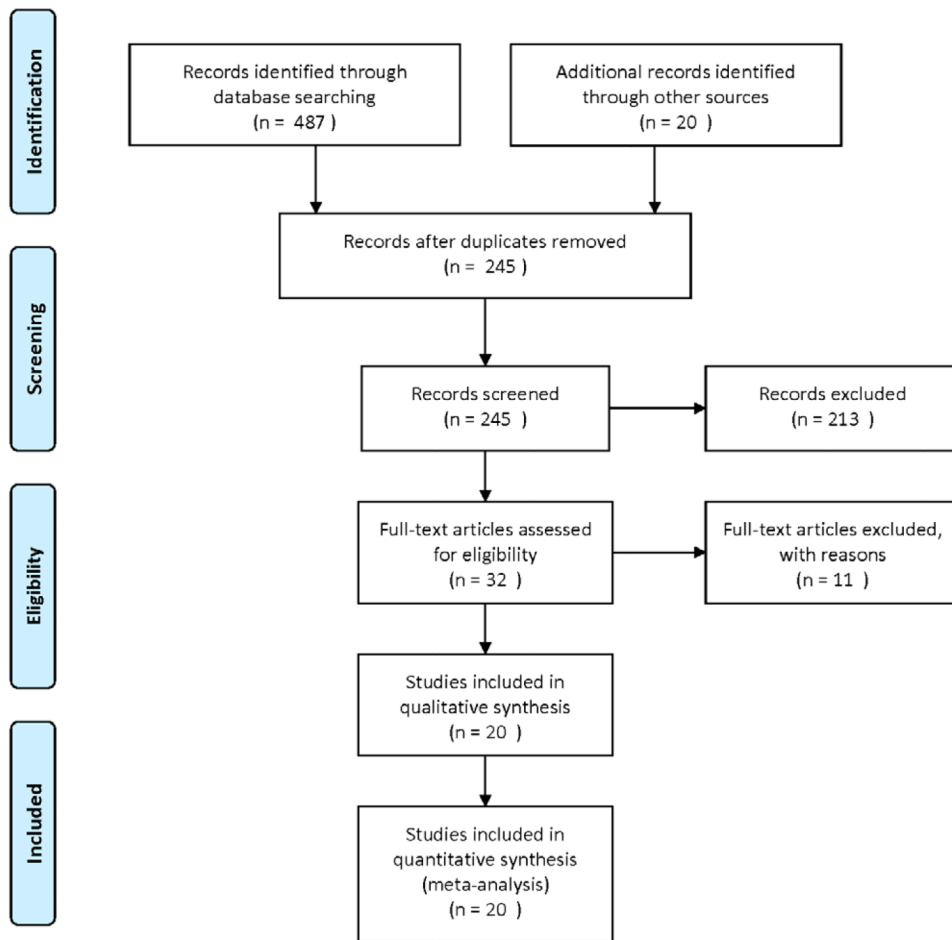
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**Figure One.**  
Phase One Flow Diagram

**Table 1****RESTORE Specified Events Operational Definitions and Event Rates**


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**Inadequate sedation management:** 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. Event Rate: < 10% of patients

**Inadequate pain management:** Pain score > 4 (or “assumed pain present” in patients receiving neuromuscular blockade) for 2 consecutive hours not related to a planned extubation attempt. Event Rate: < 20% of patients

**Clinically significant iatrogenic withdrawal:** In patients weaning from 5 days of continuous infusion or round-the-clock narcotics, any patient receiving rescue therapy (defined as an opioid or benzodiazepine bolus or an increase in opioid or benzodiazepine infusion) to manage an increase in WAT-1 (59) symptoms after the start of weaning and not for treatment of new pain or sedation needs. Available evidence identifies iatrogenic withdrawal as a WAT-1 Score of 3. Event Rate: <75% of patients

**Unplanned endotracheal tube (ETT) extubation:** Unplanned extubation. Event Rate < 3.0 per 100 ventilator days

**Post-extubation stridor with chest-wall retractions at rest:** Stridor (defined as a high-pitched or harsh inspiratory noise) with chest-wall retractions after ETT extubation. Event Rate: < 30%

**Extubation failure:** Reintubation within 24 hours. Less than 10% of patients electively extubated should require reintubation. Event Rate: < 10% of patients

**Unplanned removal of any invasive tube:** Unplanned removal of any invasive tube (e.g., arterial access, central venous access, peripheral venous access, nasogastric drainage tube, bladder catheter, chest tube, “other” tube). Denominator data are required to determine accurate rates per 100 days. Event Rate: Unknown

**Ventilator-associated pneumonia VAP:** Pneumonia occurring 48 hours after the initiation of mechanical ventilation (104) VAP rate as the number of VAP per 1000 ventilator days (92). VAP rates should be zero. All cases of suspected VAP are to be adjudicated by the local infectious disease officer using a standardized process (105) and National Healthcare Safety Network definition (106) Event rate: < 3.2 per 1,000 ventilator days

**Catheter-associated bloodstream infection CA-BSI:** Defined using The National Nosocomial Infections Surveillance System (NNIS) (100) as the number of CA-BSI per 1,000 days of IV sedative use. CA-BSI rates should be zero. All cases of suspected CA-BSI are to be adjudicated by the local infectious disease officer using National Healthcare Safety Network definition (106) Event Rate: < 4 per 1,000 central line days

**Stage 2+ pressure ulcers:** Stage II (or worse) partial thickness loss of skin layers involving epidermis and possibly penetrating into but not through dermis. May present as blistering with erythema and/or induration; wound base moist and pink; painful; free of necrotic tissue (107). Assign attribution using the Braden Q scale (102). Event Rate: <30%

**New tracheostomy:** Track all new tracheostomy as a tracer for extreme airway trauma secondary to agitation.

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