**SUPPLEMENTAL DIGITAL CONTENT (SDC) to the CLINICAL PRACTICE GUIDELINES FOR THE PREVENTION AND MANAGEMENT OF PAIN, AGITATION, NEUROMUSCULAR BLOCKADE, AND DELIRIUM IN CRITICALLY ILL PEDIATRIC PATIENTS** **WITH CONSIDERATION OF ICU ENVIRONMENT AND EARLY MOBILITY (Peds-PANDEM)**

## TABLE OF CONTENTS:

1. **Introduction –** p4
2. **Analgesia**

**B1.** Assessment of Pain – p5

**B1a.** SDC **TABLE 1**: Self-Report Pain Assessment Scales – p5

**B1b.** SDC **TABLE 2**: Observational Pain Assessment Scales – p6

**B2.** Pharmacologic Management of Pain – p7

**B2a.** Opioid Analgesics

**B2a1.** SDC **TABLE 3**: Opioid Analgesics – p8

**B2a2.** Unanswered Questions – p9

**B2b.** Opioid-sparing Strategies

**B2b1.** SDC **TABLE 4**: Non-Opioid Analgesics – p10

**B2b2.** SDC **TABLE 5**: Summary of Literature on the Impact of Non-Opioid Pain Management in Critically Ill Children – p11

**B2b3.** Unanswered Questions – p12

**B3.** Non-pharmacologic Management of Pain – p13

**B3a.** Unanswered Questions – p13

1. **Sedation**

**C1.** Assessment of Sedation – p14

**C1a.** SDC **TABLE 6**: Characteristics and Interpretation of Validated Sedation Scales in Critically Ill Children – p15

**C2.** Protocolized Sedation

**C2a.** SDC **TABLE 7**: Summary of Studies Assessing Impact of Protocolized Sedation – p16

**C3.** Daily Sedation Interruptions or Drug Holidays

**C3a.** SDC **TABLE 8**: Summary of Studies Discussing Daily Sedation Interruptions (DSI) – p18

**C4.** Peri-Extubation Strategies

**C4a.** SDC **TABLE 9**: Summary of Studies Discussing Peri-Extubation Strategies and Outcomes – p19

**C5.** Pharmacologic Provision of Sedation – p21

**C5a.** SDC **TABLE 10**: Pharmacology of Sedative Medications – p23

**C5b.** SDC **TABLE 11**: Summary of Studies Comparing Alpha-2 Agonists with Benzodiazepines – p25

**C5c.** SDC **TABLE** **12**: Summary of Studies Discussing Alpha-2 Agonists and Cardiovascular Surgery – p27

**C5d.** Adjunct Sedation

**C5d1.** Propofol

**C5d1**-- SDC **TABLE 13**: Summary of Studies Discussing Propofol Sedation in Critically ill Children – p29

1. **Neuromuscular Blockade**

**D1.** Neuromuscular Blocking Agent (NMBA) Pharmacology – p31

**D1a.** SDC **TABLE 14**: Pharmacology of Neuromuscular Blocking Agents – p32

**D1b.** SDC **TABLE 15**: Clinical Variables Affecting Pharmacodynamics of Non-depolarizing Neuromuscular Blocking Agents (NMBAs) – p33

**D1c.** Dosing NMBAs in Obese Pediatric Patients – p34

**D2.** NMBAs and Clinical Outcomes – p35

**D2a.** Oxygen Delivery

**D2b.** Respiratory Failure

**D2c.** Traumatic Brain Injury

**D3.** NMBA Rotation or Drug Holidays – p37

**D3a.** Unanswered Questions

**D4.** Nutrition During NMBA Use – p38

**D5.** NMBA Adverse Effects and Complications – p39

**D5a.** Unanswered Questions

1. **ICU Delirium**

**E1.** Delirium Epidemiology, Risk Factors and Outcomes – p40

**E1a.** Prevalence

**E1b.** Risk Factors

**E1b1.** SDC **TABLE 16**: Summary of Studies Discussing ICU Delirium Risk Factors in Pediatric Patients – p42

**E1c.** Outcomes – p45

**E2.** Delirium Monitoring

**E2a.** Feasibility of Delirium Monitoring – p46

**E2b.** Tools for Delirium Assessment – p47

**E2b1.** SDC **TABLE 17**: Pediatric and Preschool Confusion Assessment Methods for the ICU – p49

**E2b2.** SDC **TABLE 18**: Cornell Assessment of Pediatric Delirium (CAPD) – p50

**E3.** Delirium Prevention and Management in the PICU

**E3a.** SDC **TABLE 19**: Consideration for Possible Causes of Delirium (BRAIN MAPS) – p51

**E3b.** SDC **TABLE 20**: Summary of Studies Discussing Pharmacologic Management of Delirium in Pediatric Patients – p52

1. **Sedative and Analgesic Tolerance**

**F1.** Unanswered Questions – p56

1. **Iatrogenic Withdrawal Syndrome (IWS) –** p58

**G1.** Opioid and Benzodiazepine IWS: Prevalence and Risk Factors

**G1a.** SDC **TABLE 21**: Summary of Studies Discussing Prevalence and Risk Factors for Opioid/Benzodiazepine Withdrawal – p59

**G1b.** Unanswered Questions – p62

**G2.** Alpha-2 Agonist IWS

**G2a.** SDC **TABLE 22**: Summary of Studies Discussing Prevalence and Symptoms of Alpha-2 Agonist Withdrawal – p64

**G3.** IWS Prevention and Management

**G3a.** SDC **TABLE 23**: Summary of Studies Discussing Sedation Weaning Protocols – p66

**G3b.** Unanswered Questions – p67

1. **Optimizing the ICU Environment** – p69

**H1.** Family Presence – p69

**H1a.** Unanswered Questions

**H2.** Sleep Hygiene and the ICU Atmosphere – p70

**H2a.** Unanswered Questions

**H3.** Early Mobility – p71

**H3a.** Unanswered Questions

1. **Search Strategy**: Appendix 1 – p73
2. **References** – p110

## A. INTRODUCTION

Supplemental digital content (SDC) consists of important yet “unanswered” PICO (Patient, Intervention, Comparison, Outcome) questions where available literature did not surmount to enough evidence to provide a recommendation. The SDC also highlights further information and resource tables for some answered PICO questions. Answers to all questions that were solely descriptive in nature are also presented in the SDC. Please utilize the table of contents as a guide for navigating the SDC.

## B. ANALGESIA

### B1. ASSESSMENT OF PAIN

#### B1a. SDC TABLE 1: Self-Report Pain Assessment Scales

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scale** | **Age Group** | **Numeric Scale** | **Assessment Procedure** | **Psychometric Properties** |
| **Visual Analog Scale (VAS)**1 | ≥ 8 years | 0 – 10 | Patients asked to mark their pain intensity on a line with a scale of pain from 0 (no pain) – 10 (worst pain) | **Validated**:  Acute and post-operative pain |
| **Numeric Rating Scale (NRS)**2 | ≥ 8 years | 0 – 10 | Patients asked to rate pain from  0 (no pain) to 10 (worst pain imaginable) | **Validated**:  Acute and post-operative pain |
| **Oucher3** | ≥ 3 years | 0 – 10 | 2 combined scales: a vertical line pain scale from 0 (no pain) to 10 (worst pain) and 5 photographic facial pictures depicting the general transition from no pain to severe pain | **Validated**:  Acute and post-operative pain |
| **Wong-Baker FACES**4 | ≥ 3 years | 0 – 10 | Patient asked to select one of six facial depictions that reflect varying levels of pain or distress | **Validated**:  Acute, chronic, and  post-operative pain |

#### B1b. SDC TABLE 2: Observational Pain Assessment Scales

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scale** | **Age Group** | **Numeric Scale** | **Assessment Procedure** | **Psychometric Properties** |
| **Face, Legs, Activity, Cry, Consolability (FLACC)**5,6 | 2 months up to 7 years | 0 - 10 | Degree of facial grimace, leg position, agitation, crying and consolability assessed and each assigned a score of 0 – 2 points, a total score ranges from 0 (no pain or distress) to 10 (severe distress) | **Validated**:  Procedural and post-operative pain in ventilated and non-ventilated critically ill children |
| **rFLACC**7 | ≤ 10 years | 0 - 10 | Scored using same assessments as FLACC but assessor can adjust score to account for pain-related behaviors that may be observed in children with cognitive impairment | **Validated:**  Additional - non-verbal children with some degree of cognitive impairment |
| **COMFORT**8,9 | ≤ 10 years | 8 - 40 | Each of 8 categories scored from 1 to 5 based on blood pressure, heart rate, and degree of alertness, calmness, movement, facial tension, muscle tone and respiratory response/crying | **Validated:**  Pain in ventilated and non-ventilated critically ill children |
| **COMFORT-B**6 | ≤ 10 years | 6 - 30 | Each of 6 categories scores from 1 to 5 based on degree of alertness, calmness, movement, facial tension, muscle tone and respiratory response/crying for 2 minutes | **Validated:**  Pain in ventilated and non-ventilated critically ill children |
| **Hartwig**10,11 | ≤ 15 years | 5 - 25 | Each of 4 categories are scored from 1 to 5 based on reaction to ETT aspiration including motor response, mimic/grimace, eyes, and respirations | **Validated:**  Pain with ETT suctioning in critically ill children up to 15 years of age |
| **Cardiac Analgesia Assessment Score (CAAS)**12 | ≤ 19 years | 0 - 8 | Each of 4 categories are scores from 0 to 2 including 1 behavioral (respiratory/motor response) and 3 physiologic (pupil size, heart rate, blood pressure) symptoms | **Validated**:  Post-operative cardiac surgical patients up to 19 years of age |

### B2. PHARMACOLOGIC MANAGEMENT OF PAIN

Numerous agents are available for pharmacologic management of pain. Though initially developed as a guideline for analgesic escalation in adult cancer pain, the World Health Organization’s “pain ladder” became a landmark resource for the treatment of pain.13 A modification of this ladder for children with persisting pain was published in 2012, but retains a similar stepwise approach.14 In general, the ladder suggests the use of non-opioid enteral agents such as paracetamol/acetaminophen or non-steroidal anti-inflammatory agents (NSAIDs) for mild pain followed with the escalation to enteral opioids for moderate pain, and the judicious use of intravenous opioids for severe or persistent pain. While these recommendations do not specifically address the critically ill infant or child, the general framework for pain management remains applicable to this unique cohort of patients. A summary of analgesics commonly used in critically ill pediatric patients is found in **SDC TABLE 3 and TABLE 4**.

#### B2a. OPIOID ANALGESICS

##### B2a1. SDC TABLE 3: Opioid Analgesics†

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Class/Agent** | **Onset** | **Elimination Half-life** | **Metabolism‡** | **Active Metabolites‡** | **Intermittent Dose** | **Initial IV Rates\*** | **Adverse**  **Effects¥** |
| **Morphine**15,16  **IV**  **PO** | 5-10 min  30 min | Preterm:  12-20 h  Infant: 4.5h  >1 yo: 1-2h | **Hepatic**:  (G) | M6G  normorphine codeine | 0.05 – 0.1 **mg**/kg/dose  0.15 – 0.3 **mg**/kg/dose  (MAX 10 **mg**) | **< 50 kg**:  0.05 **mg**/kg/h  **≥ 50 kg**:  2 **mg**/h | (1)(2)(3)(4)  (5)(6)(7)(8) |
| **Hydromorphone**15,16  **IV**  **PO** | 5-15 min  15-30 min | 2-3h | **Hepatic**:  (G) | Unknown:  H3G - major H6H - minor | 5 – 10 **mcg**/kg/dose  (MAX 2 **mg**)  10 – 20 **mcg**/kg/dose | **< 50 kg:**  2 **mcg**/kg/h  (0.002 **mg**/kg/h)  **≥ 50 kg:**  0.3 **mg**/h | (1)(2)(3)(4)  (6)(7)(8)(9) |
| **Fentanyl IV**15,16 | 1-2 min | 2-4h | **Hepatic**: (DA)(HyD) CYP3A4 | None | 0.5 - 1.0 **mcg**/kg/dose  (MAX 100 **mcg**) | **< 50 kg:**  1 **mcg**/kg/h  **≥ 50 kg:**  50 **mcg**/h | (1)(2)(3)(4)  (6)(7)(10)(11) |
| **Remifentanil IV**17 | 1-2 min | 3-8 min | **Plasma esterase** | None | N/A | 0.1 **mcg**/kg/min | (3)(4)(6)(7)  (10)(11) |
| **Methadone**15,16,18  **IV**  **PO** | 10-20 min  (peak 36-48h)  30-60 min  (peak 3-5 d) | 30h  longest in neonates  (8-59 h) | **Hepatic**:  (DM)  CYP3A4  CYP2B6 CYP2C19  CYP2C9  CYP2D6 | None | * 1. **mg**/kg/dose   (MAX 5 **mg**)   * 1. **mg**/kg/dose   (MAX 5 **mg**) | **NA** | (4)(6)(7)(8)  (9)(11)(12) |

**†Abbreviations**: (**d**) day(s), (**h**) hour(s), (**IV**) intravenous, (**kg**) kilogram, (**mcg**) microgram(s), (**min**) minute(s), (**mg**) milligram(s), (**PO**) enteral/oral, ( (**yo**) years old

**‡Metabolism**: (**DA**) N-dealkylation, (**DM**) N-demethylation, (**G**) glucuronidation, (**H3G**) hydromorphone-3-glucuronide, (**H6H**) hydromorphone 6-hydroxy, (**HyD**) hydroxylation, (**M6G**) morphine-6-glucuronide

**¥Adverse Effects** may include the following: (**1**) drowsiness, (**2**) sedation, (**3**) respiratory depression, (**4**) hypotension, (**5**) headache, (**6**) constipation, (**7**) nausea/vomiting, (**8**) pruritis, (**9**) asthenia, (**10**) chest wall rigidity, (**11**) confusion/dizziness, (**12**) diaphoresis

**\***Doses should be titrated up or down as needed to clinical effect, desired sedation depth, and/or based on presence of adverse effects

##### B2a2. UNANSWERED QUESTIONS

**Unanswered Question:**

**What opioid provides a therapeutic advantage for critically ill pediatric patients?**

**Discussion*:*** Data do not demonstrate greater quality of analgesia with any intravenous opioid in critically ill pediatric patients. Surveys of practices across PICUs in the United States, Canada, and the United Kingdom have consistently reported that morphine is the most commonly used analgesic, followed by fentanyl.19-21 Multiple observational and randomized trials have evaluated IV opioids in the PICU setting,22-27 although often in specialized populations (i.e. cardiac, post-operative, neurosurgical). Generally, equivalent analgesia quality with no difference in adverse event rates are consistently reported when using morphine, fentanyl, and remifentanil.22,24,26 Amongst opioids, morphine may be associated with a higher incidence of pruritis and urinary retention but similar incidences of nausea and ileus.28 More serious adverse effects include respiratory depression, hypotension, in addition to rigid chest syndrome with synthetic opioids. Morphine and hydromorphone should be chosen cautiously in patients with renal failure as active metabolites (morphine-3-glucuronide, morphine-6-glucuronide, hydromorphone-3 glucuronide) may accumulate and prolong duration of effects.29,30 While morphine-3 glucuronide may confer anti-analgesic activity,29 morphine-6-glucuronide is a potent  receptor agonist and contributes to prolongation of the duration of morphine-based analgesia.30 Due to lack of active metabolites, fentanyl may be the preferred opioid in the setting of renal dysfunction.

In critically ill pediatric patients fast-tracking towards extubation or in whom frequent awakening is necessary for neurological exam, remifentanil may optimize patient readiness because of its favorable pharmacokinetics. The unique short context-sensitive half-life of remifentanil allows for expedient weaning and recovery from drug effect regardless of length of time of exposure.22,24,27 However, there is a dearth of evidenced based literature regarding use of remifentanil in the pediatric ICU and consideration of known rapid tolerance and rebound pain with synthetic opioids.31

#### B2b. OPIOID SPARING STRATEGIES

##### B2b1. SDC TABLE 4: Non-opioid Analgesics†

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Class/Agent** | **Onset** | **Elimination Half-life** | **Metabolism‡** | **Active Metabolites‡** | **Dose** | **Adverse**  **Effects¥** |
| **Acetaminophen**59,60  **IV**  **PO** | 5-10 min  <1 h | 3-4 h | **Hepatic**:  (G)(O)(S)  CYP2E1 | Highly active metabolite  NAPQI | 15 **mg**/kg/dose Q4-6 h  (MAX 60 **mg**/kg OR 4 **g**/d)  15 **mg**/kg/dose Q6H  (MAX 60 **mg**/kg OR 4 **g**/d) | (7)(13)(14)(17) |
| **Ibuprofen**61  **IV**  **PO** | 2-4 min  30-60 min | 1.5 h  ~2 h | **Hepatic**:  (O) | None | 10 **mg**/kg/dose Q6–8 h  (MAX 40 **mg**/kg OR 2400 **mg**/d)  Same as IV | (15)(16)(18)(19)(20) |
| **Naproxen**62 | 30-60 min | 8-17 h | **Hepatic**:  (G)(O) | None | 5 - 6 **mg**/kg/dose Q12 h  (MAX 1000 **mg**/d) | (6)(7)(11)(19)  (20)(21)(22) |
| **Ketorolac**63-65  **IV**  **PO** | 30 min    30-60 min | 4-6 h | **Hepatic**:  (G)(O) | None | 0.2-0.5 **mg**/kg/dose Q6H for 5 d (*Only* 3 d course if < 2 yo)  (MAX 30 **mg**/dose) | (19)(20)(23)(24)  (25)(26)(27) |

**†Abbreviations**: (**d**) day(s), (**g**) gram(s), (**h**) hour(s), (**IV**) intravenous, (**kg**) kilogram, (**mcg**) microgram(s), (**min**) minute(s), (**mg**) milligram(s), (**PO**) enteral/oral,

(**Q**) every, (**yo**) years old

**‡Metabolism**: (**G**) glucuronidation, (**NAPQI**) N-acetyl-p-benzoquinone imine, (**O**) oxidation, (**S**) sulfation

**¥Adverse Effects** may include the following: (**1**) drowsiness, (**2**) sedation, (**3**) respiratory depression, (**4**) hypotension, (**5**) headache, (**6**) constipation, (**7**) nausea/vomiting, (**8**) pruritis, (**9**) asthenia, (**10**) chest wall rigidity, (**11**) confusion/dizziness, (**12**) diaphoresis, (**13**) increased alkaline phosphatase (ALP), (**14**) increased bilirubin, (**15**) increased alanine aminotransferase (ALT), (**16**) increased aspartate aminotransferase (AST), (**17**) hepatotoxicity, (**18**) decreased hemoglobin, (**19**) renal dysfunction, (**20**) gastritis, (**21**) edema, (**22**) abdominal pain, (**23**) GI perforation, (**24**) GI hemorrhage, (**25**) thrombotic events, (**26**) myocardial infarction, (**27**) hemorrhagic stroke

##### B2b2. SDC TABLE 5: Summary of Literature on the Impact of Non-opioid Pain Management in Critically Ill Children†

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(Year)** | **Design** | **Cohort** | **Intervention** | **Control** | **Outcomes** | **Limitations** | **Risk of Bias** |
| Zhu  (2017)66 | **SR** | Postoperative General and PICU | Non-opioid analgesia pre/intraop | Pre/intraoperative opioid or placebo | 11 APAP studies:  **↓** opioid use in 5/11 studies  **↓** pain scores in 4/11 studies  3 ibuprofen studies:  **↓** postop opioid/adjunct analgesia all studies  **↓** pain scores in 2/3 studies | Control group analgesia differed.  Studies with multiple NSAIDs. | **M** |
| Wong  (2013)67 | **SR** | Postoperative General and PICU | Opioids + NSAIDs and/or APAP  (n=1636) | Opioids only  (n=988) | **↓** opioid consumption 21/31 studies  No difference 4/31 studies  Variable results 6/31 studies  **↓** pain scores in 14 studies | Overlapping use of NSAIDs/APAP  Hard to separate medication classes.  Variable study methodology. | **M** |
| Ceelie  (2013)68 | **RCT** | PICU < 1 years  Post-thoracic or abdominal surgery | Paracetamol Q6h x 48h postop  (n=35) | Placebo (saline)  Q 6h + MSO4 infusion x 48h postop (n=39) | 66% **↓** cumulative morphine (p<0.001)  No differences in pain scores (p=0.8)  No differences in adverse effects  (27% vs 34%, OR 0.9, 95% CI 0.3 – 2.6) | Single center study.  Limited external validity.  Not powered for safety assessment.  Limited age group. | **M/H** |
| Munro  (2002)69 | **RCT** | 11-17 years  Post-scoliosis surgery | IV KT Q 6h for 6 doses + morphine PCA (n=20) | IV Placebo Q 6h x  6 doses + MSO4 PCA (n=15) | **↓** pain scores on POD 1 and 2 (p<0.05)  **↓** morphine consumption by 33%  No differences in side effects  Earlier physical activity on POD 1 (p<0.05) | Small sample size  Long-term follow-up in ~40% of the cohort | **M** |
| Sutters  (1999)70 | **RCT** | PICU  Post-orthopedic surgery | IV KT Q6h x 48h  + MSO4PCA (n=36) | IV placebo Q6h x 48h + MSO4 PCA (n=32) | Improved analgesia  **↓** in opioid use by 47% in first 24 h | Small sample size  Lack of details on additional adjunctive therapies | **M** |
| Olbrecht  (2018)71 | **PCS** | 10-18 years  Post-scoliosis surgery | IV APAP 15 mg/kg Q 6h x 12 doses  + opioid PCA, diazepam, KT, methocarbamol (n=44) | Opioid PCA with diazepam, KT and methocarbamol (n=70) | **↓** MSO4 equivalent consumption  POD 1 (25% reduction, p<0.001) and  POD 2 (30% reduction, p<0.001)  Earlier PO intake (2 vs 2.9 d p=0.01)  Postop MSO4 consumption mediates IV APAP and LOS association by ~79% | Non-randomized.  Intraop remifentanil and postop KT differences between groups.  Unmeasured confounders.  No liver function monitoring. | **H** |
| Dawkins  (2009)72 | **RS**  **CCS** | < 6 months CICU | KT (n=19) | No KT (n=19) | No differences in adjunctive use of  MSO4 (p=0.97) or fentanyl (p=0.2) | Selection bias (CV only).  Retrospective chart review.  Only biventricular repair.  Opioid use secondary objective. | **H** |
| Inoue  (2009)73 | **RS** | 5 mo – 18 years PCICU | KT + opioid analgesia  (n=108) | Opioid analgesia alone  (n=140) | **↓** opioid exposure on Day 0 and 1 (p<0.05)  LOMV: 6.1 vs 7.2h, (p=0.07)  Failed extubation: 0 vs 5% (no p value)  ICU LOS: 23 vs 24h (p=0.004) | Detection/selection bias  (low risk CV surgeries).  Primary outcome renal function.  Possible monitoring bias in KT group causing early termination of use | **M** |

**†Abbreviations**: (**APAP**) acetaminophen, (**CCS**) case-control study, (**CV**) cardiovascular, (**d**) day(s), (**H**) high, (**h**) hour(s), (**IBP**) ibuprofen, (**intraop**) intraoperatively, (**IV**) intravenous, (**kg**) kilogram, (**KT**) ketorolac tromethamine, (**L**) low, (**LOMV**) length of mechanical ventilation, (**LOS**) length of stay, (**M**) moderate, (**mcg**) microgram(s), (**mg**) milligram(s), (**mo**) months, (**MSO4**) morphine sulfate, (**NSAIDs**) non-steroidal anti-inflammatory drugs, (**PCA**) patient-controlled analgesia, (**PCS**) prospective cohort study, (**PO**) enteral/oral, (**POD**) post-op day, (**postop**) postoperative, (**Q**) every, (**RCT**) randomized controlled trial, (**RS**) retrospective cohort study, (**SR**) systemic review, (**yo**) years old

##### B2b3. UNANSWERED QUESTIONS

**Unanswered Question:**

**Do low dose opioid antagonists alleviate opioid-induced adverse effects or have opioid-sparing effects?**

**Discussion*:*** Literature suggests that a low dose opioid-antagonist may be efficacious in critically ill pediatric patients experiencing significant opioid-related adverse effects such as pruritus, and nausea/vomiting. Addition of a low dose naloxone infusion has been associated with a reduction in symptoms of pruritus and nausea related to morphine analgesia in both a prospective dose-finding study32 and an interventional RCT.33 There are conflicting studies reporting no difference in opioid-related adverse events with use of naloxone,34 however the primary study opioid used in another RCT was fentanyl which may cause less pruritis at baseline.35

**Unanswered Question:**

**Does the adjunct use of neuraxial or regional analgesia in critically ill pediatric patients shorten the duration of mechanical ventilation (MV) or ICU length of stay (LOS)?**

**Discussion:** The use of adjunct neuraxial or regional analgesia in appropriate perioperative pediatric patients (cardiac, thoracic, abdominal, and spine surgery) may shorten duration of MV and decrease ICU LOS. Neuraxial or regional analgesia (anesthesia) offers the potential benefit of reducing the need for systemic analgesia and sedation. Commonly used methods of neuraxial anesthesia in infants and children include epidural, caudal and spinal approaches. Several observational case series have demonstrated the feasibility and safety of providing neuraxial and/or regional anesthesia and analgesia for prolonged periods in children in a wide variety of perioperative settings.36-47 In children undergoing cardiac, thoracic, major or minor abdominal, and spinal fusion procedures, earlier extubation occurred with intraoperative addition of neuraxial techniques among numerous studies,48-56 whereas few studies report no difference.57,58 In cardiac surgical patients, addition of neuraxial analgesia was associated with reduced ICU and hospital LOS.55,56 Postoperative opioid requirement was reduced following regional/neuraxial analgesia resulting in less postoperative opioid use with similar or improved pain scores.53,57 There is no literature on the potential benefits of regional analgesia in the management of pain among critically ill pediatric patients with non-surgical pain. There have been numerous studies that demonstrate feasibility of neuraxial analgesia in critically ill infants and children, with few catheter-related adverse effects reported and no reports of catheter-associated complications (i.e., epidural hematoma or infection), even in the presence of anticoagulation for cardiac surgery.49-52

### B3. NON-PHARMACOLOGIC MANAGEMENT OF PAIN

#### B3a. UNANSWERED QUESTIONS

**Unanswered Question:**

**Does the addition of acupuncture impact outcomes including a decrease in postoperative or procedural pain, decrease in duration of MV, or reduction in PICU LOS?**

**Discussion:** Acupuncture has been utilized in the operative room, emergency room and PICU to assist with painful procedures, treat agitation and withdrawal, and aid in weaning of sedative infusions. Multiple acupuncture modalities (needle acupuncture, acupressure, application of magnets, laser acupuncture, application of electricity to inserted acupuncture needles, transcutaneous electrical nerve stimulator (TENS), cutaneous stimulation at acupuncture points, burning of warm herb at acupuncture points and electrical stimulation at acupuncture points) have been safely used in children.74 An RCT in pediatric postoperative cardiac surgical patients reported that TENS application resulted in decreased C-reactive protein and troponin levels, faster extubation, and decreased ICU LOS.75 In non-ICU patients undergoing tonsillectomy or tympanostomy, acupuncture following induction of anesthesia was associated with less pain at 24 and 36 hours, and improved oral intake at 72 hours postoperatively compared to controls,76 with increased time to first postoperative analgesic dose requirement.77 A case series in the Emergency Department also demonstrated reduction in perception of pain following acupuncture.78 Acupuncture and acupressure application in NICU patients prior to necessary heel stick lancing were both associated with shorter procedural time and duration of crying.79,80 No studies were found evaluating non-procedural pain control with acupuncture in the PICU setting.

**Unanswered Question:**

**Does the direct application of heat or cold aid in pain management for critically ill pediatric patients?**

**Discussion:**Heat and cold are commonly used for management of outpatient pain associated with muscle aches and strains, but there is no data on similar applications in acutely ill hospitalized or critically ill pediatric patients. There is support for the use of local cooling of acute burn injuries, but this is focused primarily on limitation of ongoing tissue destruction.81 Other data regarding the use of cooling or heating for management of pain is limited to specific disease states and not generally applicable to the PICU environment. Trials are underway evaluating the use of heat or cool therapies to decrease pain associated with intravenous cannula placement.82

## C. SEDATION

### C1. ASSESSMENT OF SEDATION

As with pain assessment, it has become well recognized that formal assessment of sedation depth should be a routine part of critical care provision. Four scales have been formally validated in the PICU.(**SDC TABLE 6**) The COMFORT Score is an observational instrument validated for the assessment of level of sedation in patients 0-16 years of age.9,83,84 The COMFORT-B Score is an adaptation of this tool in which alterations in physiologic variables (heart rate and blood pressure) have been removed due to concerns that they may be significantly impacted by factors other than sedation and/or comfort.85,86 The State Behavioral Scale (SBS) was initially validated to assess sedation and agitation in mechanically ventilated children aged 6 weeks to 6 years87 and has subsequently been validated in children up to 17 years of age.88 The Richmond Agitation-Sedation Scale (RASS) has been validated in critically ill children aged 2 months to 21 years.89 Although less well studied, use of the RASS is likely to continue to grow as it is the score which both the pediatric Confusion Assessment Method for the ICU (pCAM-ICU) and Cornell Assessment of Pediatric Delirium (CAPD) tools use for determining pediatric delirium screening eligibility.90-92  Specifics of each scoring tool are found below in **SDC** **TABLES 19 and 20.**

#### C1a. SDC TABLE 6: Characteristics and Interpretation of Validated Sedation Scales in Critically Ill Children

|  |  |  |  |
| --- | --- | --- | --- |
| **SCALE** | **CHARACTERISTICS** | **SCORING** | **INTERPRETATION** |
| **COMFORT**83 | Heart Rate  Blood Pressure  Alertness  Calmness  Movement  Facial Tension  Muscle Tone  Respiratory response/crying | 1-5  1-5  1-5  1-5  1-5  1-5  1-5  1-5 | **Score ≥ 22:** Inadequate sedation  **Score 11-22:** Adequate sedation  **Score ≤ 11:** Excessive sedation |
| **COMFORT-B**85 | Alertness  Calmness  Movement  Facial Tension  Muscle Tone  Respiratory response/crying | 1-5  1-5  1-5  1-5  1-5  1-5 | **Score ≥ 22:** Inadequate sedation  **Score 11-22:** Adequate sedation  **Score ≤ 11:** Excessive sedation |
| **State Behavior Scale**  **(SBS)**87 | Respiratory Drive  Response to Ventilation  Coughing  Response to stimulation  Attentiveness to provider  Tolerance to care  Consolability  Movement after consolation | Aggregate used after pre-and post-stimulation periods of observation | **-3** Unresponsive  **-2** Responsive to noxious stimulus  **-1** Responsive to gentle touch or voice  **0** Awake and calm  **+1** Restless and difficult to calm  **+2** Agitated |
| **Richmond Agitation - Sedation Scale**  **(RASS)**89 | Activity  Aggression  Alertness  Purposefulness  Verbal responsiveness  Ventilator dysynchrony | See Interpretation | **-5** Unarousable  **-4** Deep sedation  **-3** Moderate sedation  **-2** Light sedation  **-1** Drowsy  **0** Alert and calm  **+1** Restless  **+2** Agitated  **+3** Very agitated  **+4** Combative |

### C2. PROTOCOLIZED SEDATION

#### C2a. SDC TABLE 7: Summary of Studies Assessing Impact of Protocolized Sedation†

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Design** | **Population** | **Intervention** | **Control** | **Summary implementation-based outcomes** | **Limitations** | **Risk of bias** |
| Curley  (2015)93 | **cRCT** | MED/SURG  PICU/CICU | Nurse-driven  PROT SED/ANALG  (n=1225) | Non-PROT (n=1224) | Inadequate ANALG: 16 vs 14% (p=0.65)  Inadequate SED: 25 vs 20% (p=0.93)  No difference in opioid/benzo exposure  LOMV: 6.5 vs 6.5d (p=0.61)  PICU LOS: 9.6 vs 9.6d (p=0.61)  IWS: 12 vs 9% (p=0.56) | Non-PROT cohort higher DEX/adjunct use. Unclear if sedation depths differed. | **L** |
| Kongkiattikul  (2019)94 | **RS** | MED/SURG  PICU/CICU | Nurse-driven  PROT SED/ANALG  IWS assessment (n=45) | Historical cohort  (n=45) | >60% SBS documentation compliance in PROT group  Midazolam use: 2.7 vs 3.7 **mg**/kg/d (p=0.009)  Morphine use: 2.6 vs 3.5 **mg**/kg/d (p=0.06)  Similar IWS development: 65 vs 64% | PROT compliance not discussed in detail.  MD-driven drug changes.  PROT assessments only. | **H** |
| Saelim  (2019)95 | **RS** | MED/SURG  PICU/CICU | Physician-driven PROT SED/ANALG  (n=50) | Historical cohort  (n=50) | Median COMFORT-B: 11.6 vs 11.7 (p=0.93)  Midazolam use: 0.3 vs 0.2 **mg**/kg/d (p=0.23)  Fentanyl use: 5.3 vs 3.4 **mcg**/kg/d (p=0.42)  LOMV: 4.5 vs 5.0d (p=0.83)  PICU LOS: 7 vs 7d (p=0.59) | Younger age in post-PROT group.  No data on compliance post-implementation. | **M/H** |
| Larson  (2018)96 | **RS** | MED/SURG  PICU/CICU | Nurse-driven  PROT SED/ANALG  (n=50) | Historical cohort  (n=50) | Midazolam use:  <50 kg: 24.5 vs 57.6 **mcg**/kg/d (p=0.02)  >50 kg: 8.3 vs 21.0 **mcg**/kg/d (p=0.22)  Morphine use:  <50 kg: 18.4 vs 23.9 **mcg**/kg/d (p=0.006)  >50 kg: 15 vs 20 **mcg**/kg/d (p=0.12)  LOMV: 19.0 vs 11.5h (p=0.008) | Younger age in post-PROT group.  No data on compliance post-implementation.  Small sample size for subgroup analyses. | **M/H** |
| Gaillard-Le Roux  (2017)97 | **RS** | MED/SURG  PICU/CICU | Nurse-driven  PROT SED/ANALG  (n=97) | Historical cohort  (n=107) | No group difference in adequacy of SED  Midazolam use: 1 vs 1.2 **mg**/kg/d (p=0.02)  Midazolam duration: 3 vs 4d (p=0.26)  Morphine use: 0.34 vs 0.34 **mg**/kg/d (p=0.73)  Morphine duration: 5 vs 4d (p=0.86)  LOMV: 5 vs 4d (p=0.44)  PICU LOS: 7 vs 7d (p=0.42)  No difference in AE’s (VAP, UE, IWS) | No data on compliance post-implementation | **M** |
| Neunhoeffer  (2017)98 | **RS** | Non-cardiac post-surg PICU | Nurse-driven  PROT SED/ANALG  (n=110) | Historical cohort  (n=116) | Target sedation score 83% of the time post  Midazolam use: 2.9 vs 4.4 **mg**/kg/d (p=0.04)  Morphine use (0.7 vs 0.8 **mg**/kg/d (p=0.35)  LOMV: 0.9 vs 1.0d (p=0.81)  PICU LOS: 3.3 vs 3.0d (p=0.59)  IWS: 20.0 vs 35.3% (p=0.01) | No formal sedation score pre-implementation.  No data on compliance post-implementation  Absence of target COMFORT range | **M** |
|  |  |  |  |  |  |  |  |
| Dreyfus  (2017)99 | **RS** | MED/SURG  PICU | Nurse-driven  PROT SED/ANALG  (n=104) | Historical cohort  (n=93) | Median COMFORT-B: 9.5 vs 8 (p=0.002)  Excess sedation: 60.7 vs 73.3% (p<0.0001)  Midazolam use: 2.9 vs 3.2 **mg**/kg/d (p=0.22)  Sufentanil use: 6.3 vs 5.6 **mcg**/kg/d (p=0.19)  LOMV: 6.6 vs 8.3d (p=0.09)  PICU LOS: 9.8 vs 9.0d (p=0.77)  IWS: 23 vs 14% (p=0.10)  VAP rate: 10 vs 14% (p=0.31) | No data on compliance post-implementation  Significantly more surgical in post implementation (38 vs 24%) | **M** |
| Neunhoeffer  (2015)100 | **RS** | MED/SURG  PICU/CICU | Nurse-driven  PROT SED/ANALG  (n=172) | Historical cohort  (n=165) | PROT – sedation adequate in 70%, inadequate in 18% and excess in 12%  Midazolam use: 4.2 vs 5.9 **mg**/kg/d (p=0.009)  Morphine use: 3.1 vs 3.9 **mg**/kg/d (p=NS)  LOMV: 1.7 vs 2.0d (p=NS)  PICU LOS: 5.0 vs 5.8d (p=NS)  UE: 0.64 vs 0.56/100d (p=NS)  IWS: 12.8 vs 23.6% (p=0.005) | No formal sedation score pre-implementation.  Time not at target relatively high | **M** |
| Deeter  (2011)101 | **RS** | MED/SURG  PICU/CICU | Nurse-driven  PROT SED/ANALG  (n=153) | Historical cohort  (n=166) | Lorazepam drip: 1.6 vs 6.6d (p<0.01)  Morphine drip: 7.0 vs 9.9d (p=0.15)  Total SED: 11.6 vs 15.9d (p=0.26)  LOMV: 6.3 vs 8.1d (p=0.16)  PICU LOS: 8.2 vs 9.5d (p=0.30)  UE: 0.22 vs 0.23/100d | No formal sedation score pre-implementation  No data on compliance with PROT post-implementation  No data on time within target sedation | **M/H** |
| Jin  (2007)102 | **RS** | Non-surgical PICU  >48h MV | MD/Pharmacist-driven  PROT SED  (n=26) | Historical cohort  (n=27) | Midazolam use: 37.5 vs 55 **mg**/d (p<0.01)  Fentanyl use: 204 vs 496 **mcg**/d (p=0.02)  LOMV: 11 vs 12.5d (p=0.04)  PICU LOS: 15.0 vs 19.5d (p=0.04)  IWS: 1.8 vs 35% (p=0.02) | No formal sedation score pre-implementation  No data on compliance with PROT post-implementation  Relatively infrequent sedation assessment (Q12h) | **H** |

**†Abbreviations**: (**AE**) adverse event, (**ANALG**) analgesia, (**BENZO**) benzodiazepine, (**CICU**) cardiac intensive care unit, (**d**) day(s), (**DEX**) dexmedetomidine, (**H**) high, (**h**) hour(s), (**IWS**) iatrogenic withdrawal syndrome, (**kg**) kilogram, (**L**) low, (**LOMV**) length of mechanical ventilation, (**LOS**) length of stay, (**M**) moderate, (**mcg**) microgram(s), (**med/surg**) medical/surgical, (**mg**) milligram(s), (**MV**) mechanical ventilation, (**PCS**) prospective cohort study, (**PICU**) pediatric intensive care unit, (**Q**) every, (**cRCT**) clustered randomized controlled trial, (**RS**) retrospective, (**SBS**) state behavioral scale, (**SED**) sedation, (**UE**) unplanned extubation, (**VAP**) ventilator associated pneumonia

### C3. Daily Sedation Interruptions or Drug Holidays

#### C3a. SDC TABLE 8: Summary of Studies Discussing Daily Sedation Interruptions (DSI):

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Design** | **Population** | **Intervention** | **Control** | **Summary implementation-based outcomes** | **Limitations** | **Risk of bias** |
| Vet  (2016)103 | **Multi-C**  **RCT** | MED/SURG  PICU  >24h MV | DSI if pass screen  (n=66) | No planned DSI  (n=63) | Ventilator-free days: 24 vs 24 (p=0.98)  LOMV: 5.1 vs 5.2d (p=0.71)  PICU LOS: 6.9 vs 7.4d (p=0.47)  30-day MR: 9.1 vs 0% (p=0.03)  Cumulative midazolam: 17 vs 14.1 **mg**/kg (p=0.11)  Cumulative morphine: 0.92 vs 1.16 **mg**/kg (p=0.17)  Median COMFORT-B: 12 vs 12 (p=0.048)  Oversedation: 24.1 vs 25.4% (p=0.27)  Undersedation: 3.2 vs 2.4% (p=0.04) | Definition of resumption of sedatives unclear.  Unclear who determined timing/amount SED titration.  Safety screen failed in 34%.  Trial prematurely stopped for slow enrollment. | **M** |
| Verlaat  (2013)104 | **RCT (open label)** | MED/SURG  PICU  >24h MV | DSI if pass screen  (n=15) | No planned DSI  (n=15) | LOMV: 4 vs 9d (p=0.03)  PICU LOS: 6 vs 10d (p=0.02)  Greater decrease in midazolam and morphine infusions during 1st 3 study days  (p=0.007 and 0.02 respectively)  Median “rescue” boluses: 1 vs 1 (p=0.98) | Exclusion of pts with “contraindication” to DSI  Small sample size  Median COMFORT-B scores low in control | **H** |
| Gupta  (2012)105 | **RCT (open label)** | MED/SURG  PICU  >48h MV | DSI  (n=46) | No planned DSI  (n=56) | LOMV: 7.1 vs 10.3d (p=0.02)  LOMV not significant after regression (p=0.07)  Median PICU LOS: 11 vs 14d (p=0.02)  % Days awake: 79 vs 61% (p=0.005)  Midazolam exposure: 7.1 vs 11 **mg**/kg/day (p=0.002)  Adverse events: 6 vs 8% (p=0.86) | Skewed population as >70% neurologic disease  High mortality rate in both groups (26.1 vs 26.8%)  Sedation not protocolized in control group | **H** |
| De Cristofano  (2016)106 | **PCS** | MED/SURG  PICU/CICU | DSI  VAP prevention bundle | N/A | Decrease in VAP from 6.3 to 2.4 episodes/1000 ventilator days over 2 years | Unclear impact of DSI on decrease in VAP | **H** |
| Cocoros  (2017)107 | **RS**  **CCS** | MED/SURG  PICU/CICU/  NICU | Patients with VACs | Controls without VACs | Multivariate analysis of factors associated with adverse ventilator-associated conditions (VAC)  In NICU patients, DSI protective from VACs  (OR 0.07; CI [0.01-0.79])  In PICU/CICU patients, no benefit from VACs  (OR 0.44; CI [0.18-1.44]) | Did not protocolize DSI or sedation provision | **H** |

**†Abbreviations**: (**CCS**) case-control study, (**CICU**) cardiac intensive care unit, (**d**) day(s), (**DSI**) daily sedation interruption, (**H**) high, (**h**) hour(s), (**kg**) kilogram, (**L**) low, (**LOMV**) length of mechanical ventilation, (**LOS**) length of stay, (**M**) moderate, (**mcg**) microgram(s), (**MED/SURG**) medical/surgical, (**mg**) milligram(s), (**MR**) mortality rate, (**Multi-C**) multi-center, (**MV**) mechanical ventilation, (**PCS**) prospective cohort study, (**PICU**) pediatric intensive care unit, (**Q**) every, (**RCT**) randomized controlled trial, (**SED**) sedation, (**VAC**) ventilator associated conditions, (**VAP**) ventilator associated pneumonia

### C4. Peri-Extubation Strategies

#### C4a. SDC TABLE 9: Summary of Studies Discussing Peri-Extubation Strategies and Outcomes†

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Design** | **Population** | **Intervention** | **Control** | **Summary implementation-based outcomes** | **Limitations** | **Risk of bias** |
| Curley  (2015)93 | **cRCT** | MED/SURG PICU/CICU | Nurse-driven PROT SED/ANALG (n=1225) | Non-PROT (n=1224) | No difference in AEs  No difference in UEs | Limited data on SED depth-related outcomes | **L** |
| Vet  (2016)103 | **Multi-C RCT** | MED/SURG PICU  >24h MV | DSI if pass screen (n=66) | No DSI  (n=63) | Undersedation: 3.2 vs 2.4% (p=0.04)  AEs: UE 1 vs 4 (p=0.20) | SED after DSI unclear  Trial cessation; slow enrollment  Failed safety DSI screen in 34% | **M** |
| Gupta  (2012)105 | **RCT (open label)** | MED/SURG PICU  >48h MV | DSI  (n=46) | No DSI (n=56) | AEs: 6 vs 8% (p=0.86)  Mortality rate: high both groups (26 vs 27%) | 70% neurologic diagnosis | **H** |
| Fitzgerald  (2015)108 | **PCS** | MED/SURG PICU/CICU | Observational  Factors for UE  (n=285) | 1- 4 controls per case (n=654) | Risk factors for UE:  Inadequate sedation (OR 9.1)  Age <6: 0.8 vs 0.5/100 vent days (p=0.001)  Loose ETT (OR 10.4)  Planned extubation w/n 12h (OR 2.3) | Did not look at other adverse sedation-depth-related events | **M** |
| Marcin  (2005)109 | **CC** | MED/SURG PICU | Pts with UE (n=55) | 3:1 matched controls (n=165) | Risk factors for UE:  Continuous sedation: 78 vs 71% (p=0.29)  Agitation w/n 12h of UE: 56 vs 35% (p<0.01) | Focused on nursing ratio  No data on sedation goals or depth at time of UE | **H** |
| Little  (1990)110 | **CC** | NICU/PICU | Pts with UE (n=153) | Cohort without UEs (n=2047) | Risk factors for UE:  No sedation w/in 2h of event  Lack of restraints being in place  Bedside procedure being performed | Lack of detail on SED practices  Concern over relevance (1990) | **H** |
| Da Silva  (2008)111 | **QI** | MED/SURG PICU | QI initiative  - SED PROT | N/A | Rate of UE  2.8 to 0.5/100 vent days |  | **H** |
| Tripathi  (2015)112 | **QI** | MED/SURG PICU | UE bundle  - SED PROT | N/A | UE rate  3.6 to 2.6/100 vent days | Multiple interventions  Unclear role of SED | **H** |
| Kaufman  (2012)113 | **QI** | PICU/CICU | QI initiative  - Daily assessment  - SED target | N/A | UE rates pre, during, and post-implementation  CICU: 0.7 to 0.4 to 0/100 vent days  PICU: 0.8 to 0.5 to 0.3/100 vent days | Multiple interventions  Unclear role of SED  No data on SED practice changes | **H** |
| Rachman  (2010)114 | **QI** | PICU | QI initiative  -SED education | N/A | UE rate  6.4 to 1.0/100 vent days  UE deemed related to inadequate sedation | No details on SED education or PROT vs usual practice | **H** |
| Popernack  (2004)115 | **QI** | MED/SURG PICU | SED PROT | N/A | UE rate  0.6 to 0.2/100 vent days  (5 years pre, 4 years post) | Unclear goal for sedation depth | **M/H** |
| Sadowski  (2004)116 | **QI** | MED/SURG PICU | QI initiative  -SED weaning protocol | N/A | UE rate  1.5 to 0.8/100 vent days  over 4 years  SED present in only 51% of UE | Multiple interventions so unclear what role sedation played | **H** |

**†Abbreviations:** (**AE**) adverse event, (**ANALG**) analgesia, (**CICU**) cardiac intensive care unit, (**d**) day(s), (**DSI**) daily sedation interruption, (**ETT**) endotracheal tube, (**H**) high, (**h**) hour(s), (**L**) low, (**M**) moderate, (**med/surg**) medical/surgical, (**Multi-C**) multi-center, (**MV**) mechanical ventilation, (**PCS**) prospective cohort study, (**PICU**) pediatric intensive care unit, (**QI**) quality improvement, (**RCT**) randomized controlled trial, (**SED**) sedation, (**UE**) unplanned extubation, (**VENT**) ventilator

### C5. PHARMACOLOGIC PROVISION OF SEDATION

Numerous sedative options exist for the pediatric critical care provider. Worldwide, survey-based studies have found benzodiazepines to be the most commonly prescribed agents19-21,117 although in more recent years, use of alpha2-agonists is increasing28,86 due to concerns about neurotoxicity of other agents in developing brains118 and growing evidence that benzodiazepine exposure is a risk factor for delirium development.119,120 Other agents described in reports include propofol, ketamine, and barbiturates.

*Benzodiazepines****:*** Benzodiazepines act via potentiation of the brain’s major neuroinhibitory neurotransmitter, -aminobutyric acid (GABA), specifically by binding to the GABAAreceptor.121,122 Their primary clinical effects include dose-dependent anxiolysis, sedation, and anterograde amnesia121 in addition to potent anticonvulsant effects.123,124 Midazolam and lorazepam are the most commonly used IV benzodiazepines, either intermittently or as continuous infusions, during the acute phase of illness with safe and efficacious conversion to enteral sedation with lorazepam has also been described.125 Due to concerns for accumulation of, and toxicity from, propylene glycol with lorazepam use,126-128 midazolam has become the preferred agent for continuous infusion use. However, as midazolam has active metabolites, caution should be used in patients with renal dysfunction.20,21,117 For enteral use, lorazepam tends to be preferred.125,129,130 Both agents demonstrate similar developmental pharmacokinetics and adverse effect profiles, with younger infants having decreased clearance and greater sensitivity to respiratory depressing effects.121,131,132 Cardiorespiratory depression may be exacerbated with concomitant administration of opioids.121,133-136 Prolonged exposure of critically ill pediatric patients to either midazolam or lorazepam is associated with the development of iatrogenic withdrawal syndrome.125,137-139

*Alpha2 adrenergic receptor agonists (Alpha2-agonists):* Alpha2-agonists confer sedation via central alpha2-agonism in addition to mild analgesia mediated via substance P at the spinal cord level.140 Peripheral alpha2-agonism may also occur early, resulting in hypertension while, later, centrally mediated sympatholysis predominates and dose/duration-dependent bradycardia and/or hypotension may occur.141-143 Dexmedetomidine is the most commonly used alpha2-agonist for PICU sedation and demonstrates fewer cardiovascular effects compared to its precursor, clonidine.144 Whereas dexmedetomidine is used almost exclusively as an IV infusion, clonidine use has been described via continuous infusion, intermittent IV, enteral, or transdermal administration.145-147 The sedation achieved with alpha2-agonists is unique compared with other agents in that, based on electroencephalographic (EEG) data, they more closely simulate natural sleep than any other available sedative.148,149 This effect is appealing as disruption of sleep has been increasingly recognized as a factor contributing to post-ICU stress responses,150 increased pain perception,151,152 and delirium development.150,153 Intra-sedation arousal and return to sleep also appear to be smoother, facilitating easier serial neurologic assessments154,155 and early mobilization.21,156,157 Alpha2-agonists have no clinically significant respiratory suppressing effects,158,159 allowing patients to remain sedated through extubation,160-162 or to facilitate cooperation with non-invasive respiratory supports.163-165 There is no suppression of epileptiform activity. Dose adjustments should be made in patients with liver disease while renal dose adjustments are not required.140 Prolonged use has been associated with the development of tolerance and IWS.166,167

*Propofol:* Propofol is an intravenous anesthetic which exerts its sedative/anesthetic effects primarily via GABA activation168 although glycine, nicotinic and M-muscarinic receptors also play a role.169 It has no analgesic properties but does possess anticonvulsant170,171 and anti-emetic172 effects. As the native drug is insoluble in water, it is commercially available in a lipid emulsion which is responsible for pain on injection173,174 which may be mitigated by pre/comedication with lidocaine, ketamine, opioids, dexmedetomidine, or dexamethasone.174-176 Rapid onset and offset of action make it attractive for use in children requiring frequent neurologic assessments while sedated. Major adverse effects include dose dependent respiratory depression or apnea,177,178 loss of airway protective reflexes,179 hypotension as a result of myocardial depression180 and/or vasodilation,181,182 and the development of Propofol-Related Infusion Syndrome (PRIS). While formal diagnostic criteria for PRIS have not been developed, the syndrome is characterized by a combination of acute onset lactic acidosis, hypertriglyceridemia, rhabdomyolysis, refractory cardiac dysrhythmias, and rapidly progressing myocardial failure without evidence of structural heart disease or myocarditis. The etiology of PRIS is likely multifactorial, but a propofol-induced interference with β-oxidation of free fatty acids,183-188 especially in children with underlying mitochondrial disorders,189,190 appears to be central. High lipophilicity may result in significant adipose accumulation, especially in obese patients, or after prolonged infusions.191-193 Tolerance and IWS to propofol have not been described.

*Ketamine:* Ketamine is a “dissociative anesthetic” chemically related to phencyclidine and exerts its effects primarily via N-methyl-D-aspartate receptor (NMDA) antagonism.194 It confers potent analgesic, anxiolytic/sedative, and anterograde amnestic properties.195 Additional attractive effects derive from its sympathomimetic properties196 which reliably result in preservation of cardiovascular function197,198 although this may be lost in patients with significant myocardial disease and/or catecholamine-depleted states.199,200 Respiratory drive is typically preserved201 including with high dose administration.133,198 In PICU patients, these properties make ketamine a popular choice for analgesia and sedation during performance of painful procedures in non-intubated patients.195 Its bronchodilating effects have made it attractive for use as a continuous infusion in patients with lower airway obstruction either prior to202,203 or during204 invasive MV. It may be used in patients experiencing adverse cardiovascular effects to other sedatives and/or analgesics.205 The most significant adverse effects include hypersalivation which may trigger laryngospasm206 and emergence delirium which occurs in up to 30% of recipients and may be severe.198 Caution is advised by some when administering to patients at risk of pulmonary hypertension207 or with suspected raised intraocular pressure.208-211

*Barbiturates:* Barbiturates are sedative/hypnotic agents with a long history of use in anesthesia but with fewer applications for overt PICU sedation. Their actions are exerted via GABA receptor agonism.212 Clinical effects include sedation, potent anticonvulsant activity213-215 and reductions in intracranial pressure via reductions in cerebral metabolism and cerebral blood flow.216-218 Two barbiturates have been primarily used in the PICU. Phenobarbital has the longest duration of action but use is predominantly as an anticonvulsant, especially in neonates.214,219 Sodium pentobarbital has a shorter duration of action and tends to be preferred for sedation,133 typically in the sedation of patients refractory to other agents, and/or to facilitate reductions in opioid and benzodiazepine infusion rates.220,221 Major adverse effects include myocardial depression and vasodilation, both leading to hypotension.221,222 Propylene glycol toxicity may occur with high dose and/or with prolonged infusions.223 While respiratory depression is common, in most PICU settings, barbiturates are used in mechanically ventilated patients, making this less of a clinical concern. Limited data suggest that tolerance and IWS may develop following prolonged exposure.221,224

#### C5a. SDC TABLE 10: Pharmacology of Sedative Medications†

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Class/Agent** | **Onset (IV)** | **Elimination Half-life** | **Metabolism** | **Active Metabolites** | **Loading Dose (IV)** | **Initial IV Infusion\*** | **Adverse effects** |
| **Midazolam**121,133,225  (Benzodiazepine) | 2-3 min | **Preterm**: 6.3h  **Neonates**: 4-12h  **Children**: 2.9-4.5h  **Adolescent/adult**: 3h | **Hepatic**:  CYP3A4  (**G**) | alpha-1 hydroxy midazolam  (10% native drug activity) | 0.05-0.1 **mg**/kg  Max 2-5**mg** | **<50 kg**:  0.05 **mg**/kg/h  **≥50 kg**:  2 **mg**/h | (3)(4)(28) |
| **Lorazepam**132,133,226  (Benzodiazepine) | 2-3 min | **Neonates**: 40h  **Children**: 15.8h  **Pre-adolescent**: 16.9h  **Adolescent**: 17.8h | **Hepatic**:  CYP3A4  (**G**) | None | 0.05-0.1 **mg**/kg  Max 2-4**mg** | **< 50 kg:**  0.03 **mg**/kg/h  **≥50 kg**:  2 **mg**/h | (3)(4)(29) |
| **Diazepam**  (Benzodiazepine) | 2-5 min | **Premature**: 54h  **Infants**: 30h  **Children**: 18h  **Adults**: 60-72h | **Hepatic**:  CYP3A4/2C19  (**DM**)(**G**)(**HyD**) | N-desmethyldiazepam  temazepam | 0.05-0.1 **mg**/kg  Max 5**mg** | N/A | (3)(4)(30) |
| **Propofol**178,180,192,193 | 1-2 min | **ST infusion**: 4-7h  **LT infusion**: 1-3d  **▲** in obesity | **Hepatic**:  CYP2B6, CYP3A4  (**G**) | None | 0.5-1 **mg**/kg MAX 50**mg** | 1-4 **mg**/kg/h  OR  16-66 **mcg**/kg/min | (3)(4)(31)(32)(33)(34) |
| **Dexmetomidine**160,227-229  (Alpha2-agonist)  **Clonidine**145,227,230,231 (Alpha2-agonist)  PO  IV  Transdermal patch | 5-10 min  45-60 min  5-10 min  12-24 h | **Preterm**: 7.6h  **Neonate**: 3.2h  **Infant/toddler**: 2.3h  **Children**: 1.6h  **Adults**:1.8-3.1h  **Neonate**: 44-72h  **Infant-adult**: 12-24h | **Hepatic**:  CYP450  (**G**)  **Hepatic**:  CYP450  (**HyD**)  **Renal**:  50% excreted unchanged in urine | None  None | 0.5-1 **mcg**/kg  2-3 **mcg**/kg  1-2 **mcg**/kg  0.1 **mg**/d Avoid <1yo Avoid <10kg | 0.2-2.5 **mcg**/kg/h  1-3 **mcg**/kg/h | (4)(35)  (4)(35) |
| **Ketamine**198,204,206,232-235 | 1-2 min | **Infants/child**: 1-2h  **Older child**: 2-3h  **Adult**: 2.5-5h | **Hepatic**:  CYP450  (**DM**) | Yes – norketamine  (less potent) | 0.5-1 **mg**/kg | 0.5-2 **mg**/kg/h | (3)(7)(36)(37) |
| Pentobarbital133,212,221-223 | 1-5 min | **Bolus**: 6-12h  **ST Infusion**: 12-24h  **LT infusion**: up to 72h | **Hepatic**:  CYP450  (**G**)(**HyD**) | None | 1-2 **mg**/kg | 1-5 **mg**/kg/h | (3)(4)(29) |

**†Abbreviations:** (**d**) day(s), (**h**) hour(s), (**IV**) intravenous, (**kg**) kilogram, (**LT**) long-term, (**mcg**) microgram(s), (**mg**) milligram(s), (**min**) minute(s), (**PO**) enteral/oral, (**ST**) short-term, (**yo**) years old

**‡Metabolism:** (**DM**) N-demethylation, (**G**) glucuronidation, (**HyD**) hydroxylation

**¥Adverse Events** may include the following**:** (**3**) respiratory depression, (**4**) hypotension, (**7**) nausea/vomiting, (**28**) myocardial depression, (**29**) propylene glycol toxicity, (**30**) phlebitis, (**31**) pain on injection, (**32**) hypertriglyceridemia, (**33**) pancreatitis, (**34**) propofol related infusion syndrome, (**35**) bradycardia, (**36**) hypersalivation, (**37**) hypertension

#### C5b. SDC TABLE 11: Summary of Studies Comparing Alpha-2 Agonists with Benzodiazepines†

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Design** | **Population** | **Intervention** | **Control** | **Summary implementation-based outcomes** | **Limitations** | **Risk of bias** |
| Garisto  (2018)236 | **RCT** | 1-24 mo with CHD | DEX +  opioid/benzo SED  (n=22) | Opioid/benzo SED alone (n=26) | **LOMV**: 41.5 vs 33.5h (p=0.51)  No impact on COMFORT, FLACC scores  Lower SOS scores: 11 vs 14 (p=0.001) | Small sample size  Limited population  No data on impact of drug exposure | **H** |
| Wolf  (2014)237  “SLEEPS” | **Multi-C**  **RET** | 1mo-15yo  On MV  PICU | CLON inf. SED  (n=65) | MIDAZ inf. (n=64) | Adequate SED >80% of time: 34 vs 33% (p=0.1)  Time adequately SED: 73.8 vs 72.8% (p=0.81)  Treatment failure: 18.8 vs 11.5% (p=0.26) | Inadequate enrollment  (goal 1000 – actual 129) | **M** |
| Hunseler  (2014)238 | **RCT** | MED/SURG  0-2yo  On MV  PICU/NICU | CLON inf. + FENT/MIDAZ (n=100) | Placebo + FENT/MIDAZ (n=112) | **↓** FENT use: - 0.86 **mcg**/kg/h (p=0.01)  Similar MIDAZ use: - 25.7 **mcg**/kg/h (p=0.117)  COMFORT score: 14.6 vs 15.8 (p=0.0006)  **<29 days old**: **↓** FENT - 1.1 **mcg**/kg/h (p=0.03)  **↓** MIDAZ - 67 **mcg**/kg/h (p=0.03)  **29 days-2 yo**: No difference in FENT or MIDAZ use | Only infants and neonates.  Some NICU enrollment.  Only 212 total enrolled across 21 ICU’s (bias). | **M** |
| Aydogan  (2013)239 | **RCT** | Postop scoliosis  12-18 yo | DEX SED (n=16) | MIDAZ SED (n=15) | **FENT use**: 124.1 vs 165.8 **mcg**/24h (p=0.002)  **Pain scores**: 1.2 vs 1.5/10 (p=0.004)  **RASS score**: 1.1 vs 1.8 (p<0.05)  **Delirium**: 12.5 vs 31.3% (p<0.05)  **Bradycardia**: 6.3 vs 25% (p=0.33) | Limited population.  Short mean LOMV (4 hrs).  Limited generalizability to broader PICU population.  Only hyperactive delirium. | **H** |
| Tobias  (2004)154 | **RCT (open label)** | MED/SURG PICU | DEX SED  (n=10) | MIDAZ SED (n=10) | **↓** MSO4 in high DEX dose: 20 vs 36 (p=0.02)  **↓** cum MSO4 in high DEX group: 0.28 vs 0.74 **mg**/kg (p=0.01)  No difference in mean SED score  No difference in BP | Non-blinded.  Relatively small sample size. | **H** |
| Hasegawa  (2015)240 | **RS**  **CCS** | Infants  24h postop from VSD repair | DEX + MIDAZ SED  (n=20) | MIDAZ SED (n=20) | MIDAZ use: 0.12 vs 0.2 **mg**/kg/h (p<0.05)  FENT use: 0.4 vs 0.36 **mcg**/kg/h (p=NS)  Lower mean heart rate (p=0.02)  Similar mean blood pressure (p=NS) | No discussion of SED efficacy.  Limited patient population (generalizability). | **H** |
| Jiang  (2015)241 | **RS**  **CCS** | < 36 mo post-op CHD with PHTN  on MV | DEX + FENT SED  (n=82) | MIDAZ/FENTSED  (n=105) | Adjunct MIDAZ: 0.3 vs 0.5 **mg**/kg (p=0.007)  Adjunct MSO4: 0.1 vs 0.2 **mg**/kg (p<0.001)  PAED score: 5.2 vs 7.1 (p=0.02)  Delirium: 18.2 vs 32.0% (p=0.04)  LOMV: 30 vs 38h (p=0.07) | Only indirect assess of SED efficacy.  Limited patient population (generalizability). | **M/H** |
| Fagin  (2012)242 | **RS**  **CCS** | PICU burns | DEX SED (n=21) | MIDAZ SED (n-21) | Similar time at RASS goal: - 0.91 vs - 1.33 (p=0.07)  LOMV: 32.9 vs 45.5 (p=0.3)  PICU LOS: 40.9 vs 55.4 (p=0.73)  Similar bradycardia, hypotension, IWS | 38% DEX pts on MIDAZ prior to SED assignment.  Small sample size. | **H** |

**†Abbreviations:** (**BENZO**) benzodiazepine, (**CCS**) case-control study, (**CHD**) congenital heart disease, (**CLON**) clonidine, (**cum**) cumulative, (**d**) day(s), (**DEX**) dexmedetomidine, (**FENT**) fentanyl, (**FLACC**) Face, Legs, Activity, Cry, Consolability scale; (**H**) high, (**h**) hour(s), (**inf**) infusion, (**IWS**) iatrogenic withdrawal syndrome, (**kg**) kilogram, (**L**) low, (**LOMV**) length of mechanical ventilation, (**LOS**) length of stay, (**M**) moderate, (**mcg**) microgram(s), (**med/surg**) medical/surgical, (**mg**) milligram(s), (**MIDAZ**) midazolam, (**min**) minute(s), (**mo**) months, (**MSO4**) morphine sulfate, (**Multi-C**) multi-center, (**MV**) mechanical ventilation, (**PAED**) Pediatric Anesthesia Emergence Delirium score, (**PHTN**) pulmonary hypertension, (**PICU**) pediatric intensive care unit, (**postop**) postoperative, (**RASS**) Richmond Agitation and Sedation Scale, (**RCT**) randomized controlled trial, (**RET**) randomized equivalence trial, (**RS**) retrospective, (**SBS**) state behavioral scale, (**SED**) sedation, (**SOS**) Sophia Observation Scale, (**ST**) short-term, (**yo**) years old

#### C5c. SDC TABLE 12: Summary of Studies Discussing Alpha-2 Agonists and Cardiovascular (CV) Surgery†

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Design** | **Population** | **Intervention** | **Control** | **Summary implementation-based outcomes** | **Limitations** | **Risk of bias** |
| Ghimire  (2018)243 | **SR** | Postop CV surgery and JET risk | DEX SED  7 studies  1616 subjects | No DEX SED | 5 RCT, 2 retrospective series  JET incidence: 5.1 vs 8.1% (p<0.001)  LOMV  h (p=0.007, 4 studies)  CICU LOS  1.5d (p=0.08; 4 studies)  Similar bradycardia or hypotension | Studies included pre-, intra-, and postop DEX SED  LOMV not clinically significant | **L** |
| Li  (2018)244 | **SR** | Postop CV surgery | DEX SED  9 studies  847 subjects | Placebo  7 studies  FENT SED  2 studies | LOMV  2.2d (p=0.001; 9 studies)  CICU LOS  0.5d (p=0.03; 7 studies)  Hospital LOS  1.8d (p=0.02; 5 studies)  JET: 7 vs 19% (p=0.0001) | No discussion of sedation quality or hemodynamic impact of DEX | **L** |
| Garisto  (2018)236 | **RCT** | 1-24 mo CHD | DEX SED + opioid/benzo (n=22) | Opioid/benzo  SED  (n=26) | LOMV: 41.5 vs 33.5h (p=0.51)  No impact on COMFORT, FLACC scores  SOS scores: 11 vs 14 (p=0.001) | Small sample size  Limited population  No data on drug dose impact | **H** |
| Prasad  (2012)245 | **RCT** | Postop CV surgery | DEX SED  (n=30) | FENT SED (n=30) | Rescue sedation: 3.3 vs 2.8 doses (p=0.61)  Sedation duration: 13.4 vs 13.1h (p=0.57)  Time to extubation after infusion cessation: 131 vs 373 min (p< 0.001) | Small sample size  Limited types of surgery | **H** |
| Shuplock  (2015)246 | **PCS** | Post-op CV surgery | DEX SED  CICU admit  (n=468) | No DEX  CICU admit (n=1125) | After propensity matching:  Tachyarrhythmias (29 vs 31%; p=0.66)  Bradyarrhythmias (12 vs 9%; p=0.17)  Dose dependent  in bradycardia (OR 2.18) - excluded controls receiving DEX | Lower surgical complexity  in DEX group  Controls may have received DEX later in course  No criteria for choosing DEX | **M/H** |
| Su  (2013)162 | **PCS**  **DE** | Post op CV surgery | DEX SED  up to 24h postop | 12h following DEX SED | Adequate sedation as no patients received adjunct benzo/opioid infusions  Less adjunct SED post DEX cessation:  0.07 vs 0.15 units/h (p=0.005) | Primarily PK study  Underpowered to assess efficacy and safety variables | **H** |
| Hasegawa  (2015)240 | **RS**  **CS** | Initial 24h post VSD repair | DEX SED + MIDAZ  (n=20) | MIDAZ SED (n=20) | Adjunct MIDAZ: 0.12 vs 0.2 **mg**/kg/h (p<0.05)  Adjunct FENT: 0.4 vs 0.36 **mcg**/kg/h (p=NS)  Lower mean heart rate (p=0.03)  Similar mean blood pressure (p=NS) | Limited population | **M/H** |
| Jiang  (2015)241 | **RS**  **CS** | < 36 mo postop CHD with PHTN | DEX/FENT SED  (n=82) | MIDAZ/FENT  SED  (n=105) | Adjunct MIDAZ: 0.3 vs 0.5 **mg**/kg (p=0.007)  Adjunct MSO4: 0.1 vs 0.2 **mg**/kg (p<0.001)  PAED score: 5.2 vs 7.1 (p=0.02)  Delirium: 18.2 vs 32.0% (p=0.04)  LOMV: 30 vs 38h (p=0.07) | Only indirect eval of sedation efficacy (adjunct medication)  Very specific and limited population (Low generalizability) | **M/H** |
| Gupta  (2012)247 | **RS**  **CS** | DEX  >96h postop  CV surg | DEX SED ± adjuncts (n=52) | Opioid/benzo SED  (n=42) | Adjunct MIDAZ: 33 vs 176 **mg**/kg/d (p<0.01)  Adjunct MSO4: 0 vs 0 **mg**/kg/d (p=0.03)  LOMV: 18.5 vs 11d (p=0.77)  CICU LOS: 30 vs 26d (p=0.29)  New arrhythmias: 5 vs 1% (p=0.045)  No difference in mean HR or BP | No data re sedation quality  Long mean LOMV and ICU LOS  (Low generalizability) | **H** |
| Le  (2011)248 | **RS** | Postop CV surgery | Peri/postop DEX SED (n=89) | Opioid/benzo SED  (n=180) | OR extubation: 42 vs 42% (p=1.0)  Early (<24 hr) extubation: 76 vs 75% (p=0.88)  Overall LOMV: 29 vs 35h (p=0.17) | Unclear effect of intraop intervention early extubation potential | **M/H** |
| Chrysostomou  (2009)249 | **RS** | Postop CV surgery | DEX SED ± benzo/opioid  (n=80) | None | 94% with adequate sedation  90% with no or mild pain   SBP post DEX addition: 89-85 (p=0.006)   HR post DEX addition: 149 vs 129 (p<0.001)  AE: bradycardia (3%) and hypotension (3%) | CS only with other agents – hard to determine DEX-specific effects  Proof of concept only  (tolerability and safety) | **H** |
| Chrysostomou  (2008)250 | **RS** | Postop CV surgery | DEX inf. for treatment of JET or atrial dysrhythmias (n=14) | None | 2 of 3 with Atrial flutter converted to NSR  5/6 with JET converted to NSR – mean 39h  4 of 5 with AET converted to NSR with bolus   mean HR in JET: 197 to 165 (p=0.01)  FENT use  0.86 **mcg**/kg/h (p=0.01)  AE: hypotension (n=3) and 3 block (n=1) | CS with no control  Unclear if selection bias  Some not treated with DEX | **H** |

**†Abbreviations:** (**AE**) adverse event, (**AET**) atrial ectopic tachycardia, (**BENZO**) benzodiazepine, (**CCS**) case-control study, (**CHD**) congenital heart disease, (**CS**) case series, (**CV**) cardiovascular, (**d**) day(s), (**DEX**) dexmedetomidine, (**DE**) dose escalation, (**FLACC**) Face, Legs, Activity, Cry, Consolability scale; (**H**) high, (**h**) hour(s), (**HR**) heart rate, (**inf**) infusion, (**intraop**) intraoperatively, (**IV**) intravenous, (**JET**) junctional ectopic tachycardia, (**kg**) kilogram, (**L**) low, (**LOMV**) length of mechanical ventilation, (**LOS**) length of stay, (**M**) moderate, (**mcg**) microgram(s), (**med/surg**) medical/surgical, (**mg**) milligram(s), (**min**) minute(s), (**mo**) months, (**MSO4**) morphine sulfate, (**Multi-C**) multi-center, (**MV**) mechanical ventilation, (**NSAIDs**) non-steroidal anti-inflammatory drugs, (**NSR**) normal sinus rhythm, (**PAED**) Pediatric Anesthesia Emergence Delirium score, (**PCS**) prospective cohort study, (**PHTN**) pulmonary hypertension, (**PK**) pharmacokinetic, (**PO**) enteral/oral, (**POD**) post-op day, (**postop**) postoperative, (**RCT**) randomized controlled trial, (**RS**) retrospective, (**SBP**) systolic blood pressure, (**SED**) sedation, (**SOS**) Sophia Observation Scale, (**SR**) systemic review, (**VSD**) ventricular septal defect

#### C5d. ADJUNCT SEDATION

##### C5d1. PROPOFOL

###### C5d1- SDC TABLE 13: Summary of Studies Discussing Propofol Sedation in Critically Ill Children

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Design** | **Population** | **Intervention** | **Control** | **Summary implementation-based outcomes** | **Limitations** | **Risk of bias** |
| Svensson  (2012)251 | **PCS** | MED/SURG PICU | Propofol SED (n=174) | None | Median dose: 2.9 **mg**/kg/h (0.3-6.5)  Median duration: 13h (1.3-179)  80% <24h and 4% > 48h  No indication of PRIS | Descriptive experience of low dose/duration only  Only 3 received propofol  > 3 **mg**/kg/h for >48h | **H** |
| Rigby-Jones  (2002)192 | **PCS** | General PICU  0-12 yo | Propofol 4 **mg**/kg/h + MSO4 up to 28h (n=21) | None | Propofol infusion rate: 3.1-6.0 **mg**/kg/h  Propofol infusion duration: 4.5-28h  Target sedation in 17/20 pts scored  Hypotension requiring dose reduction in 2  No metabolic complications | Short-term propofol use  Very small sample size  Limited dose/duration  Powered as PK study | **H** |
| Knibbe  (2002)252 | **PCS** | Postop CV surgery  1-5 yo | Propofol 2-3 **mg**/kg/h Up to 6h postop (n=6) | None | Adequate sedation in 50% | Powered as PK study  Adjunct MIDAZ in some patients | **H** |
| Cray  (2001)253 | **PCS**  **RS**  **CS** | Postop CV surgery | Propofol + intraop/postop SED  (n=103) | Historical controls without propofol (n=135) | 91% extubated within 15h  Median 5h to extubation  Mean PICU LOS: 1.7 vs 2.6d (p=0.005)  LOMV: 41.5 vs 33.5h (p=0.51)  No impact on COMFORT, FLACC scores  SOS scores: 11 vs 14 (p=0.001) | Included alterations in anesthetic techniques  Lack of data regarding some control outcomes | **H** |
| Martin  (1997)254 | **PCS** | General PICU | Propofol 1-4 **mcg**/kg/h + FENT inf. for 48h | None | Adequate sedation in all  No hemodynamic or biochemical abnormalities (acidosis, lipemia) | Short-term propofol use  Very small sample size  Limited dose/duration | **H** |
| Koriyama  (2014)255 | **RS**  **CS** | MED/SURG PICU | Propofol SED  (n=210)  (223 encounters) | None | Median propofol rate: 2.4 **mg**/kg/h  Number exceeding 4 **mg**/kg/h = 30  Mean duration: 10.3h (max 41h)  No incidences of PRIS | Descriptive experience of low dose/duration only | **H** |
| Teng  (2011)256 | **RS**  **CS** | Postop CV surgery | Transition from “traditional” SED to propofol  peri-extubation | None | 11 patients, 12 extubations  Propofol 0.4-5.6 **mg**/kg/h for 3-36h  All patients successfully extubated | Case series only  No control group | **H** |
| Sheridan  (2003)257 | **RS**  **CS** | Burn Unit | Propofol for 8h  peri-extubation  (n=11) | None | Mean 13d intubated pre-transition  Mean propofol dose 3.6 **mg**/kg/h  9/11 extubated; 2 reintubated for stridor | Case series only  No control group | **H** |
| Cornfield  (2002)258 | **RS**  **CS** | MED/SURG PICU | Propofol <3 **mg**/kg/h (n=142) | None | <50 **mcg**/kg/min in “vast majority”  Adequate sedation in all patients  Median propofol duration 16.5h  Infusion >4 days in 11%  62% also received opioids and/or benzos | No control group  Dose/duration safety unclear Sedation adequacy not formally assessed | **H** |
| Bray  (1998)259 | **RS**  **CS** | PICU  On MV | Propofol SED  (n=18; PRIS cohort) (n=128; risk cohort) | None | 18 patients with PRIS – all received doses >4 **mg**/kg/h for >24h  No PRIS if <48h and/or <4 **mg**/kg/h | Case series only  No control group | **H** |

**†Abbreviations:** (**BENZO**) benzodiazepine, (**CS**) case series, (**d**) day(s), (**FLACC**) Face, Legs, Activity, Cry, Consolability scale; (**H**) high, (**h**) hour(s), (**inf**) infusion, (**intraop**) intraoperatively, (**kg**) kilogram, (**L**) low, (**LOMV**) length of mechanical ventilation, (**LOS**) length of stay, (**M**) moderate, (**mcg**) microgram(s), (**med/surg**) medical/surgical, (**mg**) milligram(s), (**min**) minute(s), (**MSO4**) morphine sulfate, (**MV**) mechanical ventilation, (**PCS**) prospective cohort study, (**PICU**) pediatric intensive care unit, (**PK**) pharmacokinetic, (**postop**) postoperative, (**PRIS**) propofol related infusion syndrome, (**RS**) retrospective, (**SED**) sedation, (**SOS**) Sophia Observation Scale, (**yo**) years old

## D. NEUROMUSCULAR BLOCKADE

### D1. Neuromuscular Blocking Agent (NMBA) Pharmacology

NMBAs are largely hydrophilic drugs divided into two general classes, depolarizing or non-depolarizing, based on their mechanism of action at the neuromuscular junction.260 Succinylcholine is the only depolarizing NMBA used in clinical practice and simulates the action of acetylcholine within the neuromuscular junction. Non-depolarizing NMBAs act via reversible competitive antagonism of acetylcholine, blocking membrane depolarization and muscle contraction. Two major groups of non-depolarizing agents are available including aminosteroids (pancuronium, vecuronium, and rocuronium) and tetrahydroisoquinoline derivatives (atracurium. cisatracurium).260,261 Relevant pharmacology and dosing of different NMBAs is found in **SDC TABLE 14.** In the setting of renal and/or hepatic dysfunction, avoidance of aminosteroid-based NMBAs appears prudent.The prolonged use of NMBAs stimulates increased expression of acetylcholine receptors within the neuromuscular junction, requiring higher dosing to maintain stable clinical neuromuscular blockade.262 The depth of neuromuscular blockade may be impacted by various physiologic factors. Hyponatremia, hypokalemia, and hypocalcemia can potentiate NMBA effects, whereas hypermagnesemia can reduce their efficacy.263,264 Potentiation or antagonism of neuromuscular blockade may also occur in the setting of concomitant drug therapy or certain medical disease-states or conditions **(SDC TABLE 15)**.261,265,266 The impact of obesity on dosing is discussed separately below.

#### D1a. SDC TABLE 14: Pharmacology of neuromuscular blocking agents† 267,268

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Class/Agent** | **Onset** | **Duration of Action** | **Metabolism** | **Active Metabolites** | **Intermittent Dose** | **Initial IV**  **infusion rate\*** | **Renal/Hepatic Dose Adjustment?** |
| **Atracurium**  **(Benzyliso-quinolinium)** | 3-5 min | 20-35 min | **Ester Hydrolysis**  Hoffman elimination  5-10% renal | None | 0.5 **mg**/kg | 0.4-2.5 **mg**/kg/h | NO |
| **Cisatracurium**  **(Benzyliso-quinolinium)** | 2-3 min | 30-60 min | **Ester Hydrolysis** Hoffman elimination  5-10% renal | None | 0.1-0.2 **mg**/kg | 0.1-1 **mg**/kg/h | NO |
| **Pancuronium (Aminosteroid)** | 2-3 min | 60-100 min | 80% renal  10-20% hepatic | 3-OH pancuronium  17-OH pancuronium  (33-50%) | 0.1 **mg**/kg | 0.03-0.2 **mg**/kg/h | YES |
| **Rocuronium (Aminosteroid)** | 1-2 min | 20-35 min | 33% renal  75% hepatic | 17-desacetyl-rocuronium  (5-10%) | 0.6 **mg**/kg | 0.3-1 **mg**/kg/h | YES |
| **Vecuronium (Aminosteroid)** | 3-4 min | 20-35 min | 10-50% renal  35-50% hepatic | 3-desacetyl Vecuronium  (50-70%) | 0.1 **mg**/kg | 0.02-0.6 **mg**/kg/h | YES |
| **Succinylcholine\*\* (Depolarizing Agent)** | <1 min | 5-10 min | **Plasma cholinesterase** | None | 2-3 **mg**/kg | N/A | NO |

**†Abbreviations**: (**h**) hour(s), (**IV**) intravenous, (**kg**) kilogram, (**min**) minute(s), (**mg**) milligram(s)

#### D1b. SDC TABLE 15: Clinical Variables Affecting Pharmacodynamics

#### of Non-depolarizing Neuromuscular Blocking Agents (NMBAs)261,265,266

|  |  |
| --- | --- |
| **Potentiation of Blockade**  **Lower NMBA Drug Dose** | **Antagonization of Blockade**  **Increase NMBA Drug Dose** |
| **Electrolyte Abnormalities** | |
| * Hypokalemia * Hyponatremia * Hypocalcemia * Hypermagnesemia * Hypophosphatemia | * Hypercalcemia * Hyperkalemia |
| **Disease-states or Conditions** | |
| * Metabolic acidosis * Respiratory acidosis * Hypothermia * Myasthenia gravis * Muscular dystrophy * Neurofibromatosis * Poliomyelitis * Eaton-Lambert Syndrome * Multiple sclerosis * Acute intermittent porphyria * Amyotrophic lateral sclerosis | * Metabolic alkalosis~~.~~ * Hepatic failure with ascites * Hemiparesis * Demyelinating lesions * Peripheral neuropathies * Diabetes Mellitus |
| **Increased Drug Clearance** |
| * Pregnancy * Burns |
| **Drug Interactions** | |
| **Antimicrobial****Agents** | **Anticonvulsants** |
| * Aminoglycosides * Clindamycin * Colistimethatae * Metronidazole * Minocycline * Polymyxin B * tetracycline * Vancomycin | * Phenytoin/Fosphenytoin * Carbamazepine * Barbiturates |
| **Other Medications** |
| * Aminophylline * Theophylline * Azathiaprine * Mercaptopurine * Furosemide (high dose) |
| **Other Medications** |
| * α-blocking drugs * Procainamide * Quinidine * Quinine * Calcium channel blockers * Lithium * Cyclosporine * Cyclophosphamide * Dantrolene * Magnesium sulfate * Furosemide * Inhalational anesthetic agents |
|  |

#### D1c. DOSING NMBAs IN OBESE PEDIATRIC PATIENTS

**Unanswered Question:**

**How does body mass index impact dosing of NMBA, and what is the role of dosing based on actual body weight versus ideal body weight in the morbidly obese pediatric patient?**

**Discussion:** About 20% of pediatric patients are obese.269,270 Obese patients have increased total fat and lean body mass, a larger volume of distribution for lipophilic medications, and a higher drug elimination clearance as a result of increased glomerular filtration and total body clearance.271 Studies in obese adults report a prolonged duration of action of NMBA when dosing based on total body weight (TBW), and recommend dosing based on ideal body weight (IBW) or adjusted body weight (ABW) instead.272,273 Extrapolating from these findings in adults, some authors have recommended calculating pediatric dosing based on ABW for succinylcholine,274 cisatricurium,275 and rocuronium.272,276,277 For vecuronium, other sources have recommended calculation of doses based on IBW.273 However, pediatric studies evaluating NMBA dosing and obesity are limited. Rose and colleagues reported on the pharmacokinetics and pharmacodynamics of succinylcholine in obese children.274 In 30 obese children aged 9-15 years, effective dose (ED), needed to suppress 50% and 95% of muscle twitching, was similar to that reported in non-obese children and dosing based on TBW was recommended. Until future studies are conducted, to assure full effect of administered dose, NMBAs should be dosed initially based on TBW, and subsequent dosing titrated based on train-of-four (TOF) monitoring and/or clinical effect. Pediatric doses should not exceed the maximum dose for adults.269

### D2. NMBAs and CLINICAL OUTCOMES

#### D2a. OXYGEN DELIVERY

**Unanswered Question:**

**Does the use of neuromuscular blockade improve clinical outcomes in critically ill pediatric patients suffering from decreased oxygen delivery?**

**Discussion:** In clinical situations when oxygen delivery or utilization may be limited, the addition of neuromuscular blockade is thought to improve oxygen delivery and reduce oxygen consumption until the underlying pathophysiology resolves. Pediatric studies investigating the effect of neuromuscular blockade on oxygen consumption have reported variable results. In a small case series of general PICU patients, addition of a NMBA to midazolam and/or fentanyl sedation resulted in a modest (9%) decrease in oxygen consumption.278 Conversely, in cohorts of cardiac surgical patients, the addition of a NMBA did not alter oxygen consumption,279,280 except in patients exhibiting spontaneous muscle movement at the time of NMB initiation.281 While limited, these data suggest that addition of neuromuscular blockade may modestly reduce oxygen consumption in patients with exhibiting skeletal muscle activity. It is also possible that depth of sedation, rather than NMBA addition, has a larger effect on oxygen consumption.280 There were no data found to address the more important question of whether reductions in oxygen consumption with NMBAs improves clinical outcomes.

#### D2b. RESPIRATORY FAILURE

**Unanswered Question:**

**Does the use of NMBAs improve outcomes in critically ill pediatric patients with pediatric Acute Respiratory Distress Syndrome (pARDS) or severe status asthmaticus?**

**Discussion:** Benefits of NMBA use in patients with pARDS or status asthmaticus are thought to include improved chest wall compliance, elimination of patient-ventilator dysynchrony, facilitation of lung recruitment, reduction of inflammatory mediator release, decreased lung hyperinflation, and reduced oxygen consumption.282-284 A meta-analysis of 431 adults with acute lung injury/ARDS found that the use of cisatricurium was associated with reduced mortality but not duration of MV or ICU days.285 Pediatric data are limited to one single-center study which reported that addition of rocuronium to 22 children with acute hypoxemic respiratory failure was associated with reductions in mean airway pressure and oxygenation index but no difference in lung mechanics or hemodynamic status.286 Adult studies have demonstrated negative outcomes associated with NMBA use in severe asthma including longer duration of MV, longer ICU stay, and greater prevalence of pneumonia or ICU acquired weakness.287-289 No pediatric data were found specifically addressing the impact of NMBA use on these outcomes or mortality. In life threatening situations, when the use of deep sedation has failed to adequately impact respiratory support requirements or ameliorate risks, the potential benefits of NMBA use on respiratory compliance may outweigh the potential adverse effects.287-291 Due to the current lack of evidence, clinicians remain reliant on best clinical judgement.

#### D2c. TRAUMATIC BRAIN INJURY

**Unanswered Question:**

**Does the use of neuromuscular blockade improve survival or clinical outcomes for critically ill pediatric patients with acute brain injury or increased intracranial pressure?**

**Discussion:** Secondary analysis of a multicenter RCT of therapeutic hypothermia in pediatric patients with traumatic brain injury (TBI) indicated that NMBAs were associated with intracranial hypertension in children, although the authors considered this association was primarily a function of increased injury severity rather than NMBA use.292 Patients receiving NMBAs for TBI management had no increase in mortality, or development of ventilator-associated pneumonia, although ICU LOS was increased. Despite some suggestion that NMBAs may be used to aid in control of sustained ICP elevations,293 clinicians are referred to the SCCM guidelines for the management of pediatric traumatic brain injury, which found no data to support NMBA use other than during endotracheal intubation.294

### D3. NMBA ROTATION AND DRUG HOLDAYS

#### D3a. UNANSWERED QUESTIONS

**Unanswered Question:**

**Does rotation of NMBAs and/or class reduce the development of tolerance?**

**Discussion:** While the long-term use of neuromuscular blockade is increasingly discouraged, use during the acute phase of critical illness may be necessary.295 No studies were found evaluating the impact of NMBA agent rotation on prolonged neuromuscular blockage, residual paralysis, or the development of tolerance. However, when tolerance is suggested based on the need to continue escalating doses to maintain adequate blockade, transition to a different NMBA, particularly one in a different NMBA class, may be reasonable.

**Unanswered Question:**

**Does the use of routine “drug holidays” reduce prolonged neuromuscular blockade or other NMBA-associated complications in critically ill pediatric patients?**

**Discussion*:*** There is limited data evaluating whether NMBA “drug holidays” impact potential adverse events such as prolonged paresis, development of pneumonia, or increased duration of mechanical ventilation. As the median recovery time from most NMBA drug infusions in children is 30-60 minutes, some have recommended a daily infusion holiday for 30-60 minutes in stable patients.267 In patients without movement after 60 minutes, clinicians should consider decreasing the infusion dose by 50% and titrate to effect by clinical exam in conjunction with train-of-four (TOF) monitoring. While neither current pediatric cardiac or adult consensus guidelines for NMBAs have a recommendation for the practice of drug holidays,263,264 intermittent discontinuation to assess the level of sedation/analgesia, facilitate neurological examination, and reduce the total NMBA drug exposure has been supported.267,296,297

### D4. NUTRITION DURING NMBA USE

**D4a. UNANSWERED QUESTIONS**

**Unanswered Question:**

**In critically ill children receiving NMBA, how are caloric goals altered and what modalities are best to meet these goals?**

**Discussion*:*** Gastric emptying is not affected by NMBA use. In a small prospective cohort study of 20 sedated children requiring MV, with or without a NMBA, gastric emptying was assessed using the acetaminophen absorption technique. No difference was found in peak acetaminophen level (Tmax), time to reach peak concentration (Cmax), or the acetaminophen concentration time curve when cisatricurium was added to opiate sedation versus opiate sedation alone.298 While impaired gastric emptying develop during critical illness, other factors including the patient’s underlying illness, prolonged immobility, opioid use, and/or fluid/electrolyte abnormalities are responsible.263 The additive role of NMBAs on metabolism remains somewhat ill-defined in the pediatric population, however data has most consistently demonstrated that the use of a NMBA has a minimal to moderate impact on overall metabolism.278,299-301 Indirect calorimetry is commonly used to assess caloric requirements of critically ill pediatric patients, and is recommended by the American Society of Parenteral and Enteral Nutrition (ASPEN).302,303 When indirect calorimetry is not available, estimating caloric needs using the Schofield or World Health Organization formulas can be used.302

### D5. NMBA ADVERSE EFFECTS AND COMPLICATIONS

#### D5a. UNANSWERED QUESETIONS

**Unanswered Question:**

**Does use of NMBAs increase the risk of ventilator-associated events (VAE)?**

**Discussion:** Use of sustained neuromuscular blockade may lead to development of dependent atelectasis, decreased clearance of respiratory secretions, and increase in aspirated oropharyngeal secretions.304 In 2 retrospective, single center studies prior to 2018, ventilator associated pneumonia (VAP) was up to three times more likely to have occurred in patients received NMBAs.304,305 A large multicenter prospective study in 1997 reported that NMBA use in a cohort of 831 PICU patients was an independent risk factor for VAP development.306 Whereas a small prospective study of 58 PICU and NICU patients found no association between NMBA exposure and VAP, distinction was not made between isolated bolus versus continuous infusion NMBA use.307 While NMBA use may not always be avoidable, clinicians should consider this potential risk when making decisions regarding NMBA initiation and duration of use.

**Unanswered Question*:***

**Does concurrent use of corticosteroids affect the risk of myopathy/neuropathy/weakness in pediatric patients receiving NMBAs?**

**Discussion:**There are conflicting results when literature in adults is reviewed related to the use of NMBAs and corticosteroids and the development of ICU-acquired weakness.308-310 While an association has been suggested with the concomitant use of corticosteroids and NMBAs, causation in critically ill children remains unclear.311-313 There are no studies that demonstrate a direct additive effect between NMBA and corticosteroid use and the development of muscle weakness. Consistent with a lack of recommendation regarding this association in other adult or pediatric-based guidelines,263,264,296 the need for concomitant use and/or duration of use should be determined using best clinical judgement but represents an area requiring further study.

**Unanswered Question:**

**In critically ill pediatric patients with myasthenia gravis (MG), how should NMBAs be dosed, and clinical effect monitored?**

**Discussion:** Patients with MG have unpredictable reactions to NMBA exposure and may experience more variable degrees of blockade duration.314 As these patients are resistant to depolarizing agents, succinylcholine is not recommended. Rather, non-depolarizing agents are recommended, specifically aminosteroids such as rocuronium and vecuronium. Sugammadex is a novel NMBA reversal agent and has been used successfully and safely in both pediatric and adult patients with MG during anesthesia.315-317 In 117 patients with MG undergoing general anesthesia with rocuronium, time to reversal and extubation readiness after sugammadex reversal were rapid (117 and 276 seconds respectively) with no adverse effects or need for reintubation up to 120 hours post extubation.318 If NMBAs are needed in patients with myasthenia gravis, they should be used in lowest possible dose and reversed with sugammadex.315,319

## E. ICU DELIRIUM

### E1. DELIRIUM EPIDEMIOLOGY, RISK FACTORS AND OUTCOMES

#### E1a. PREVALENCE

The true prevalence of ICU-delirium among infants and children has become more accurately quantifiable since the validation of pediatric-specific delirium screening tools. Fifteen prospective observational studies with patient cohorts of at least 50 children have been published since 2011, with reported PICU-delirium prevalence ranging from 5 – 66%.90-92,320-333 An international point prevalence study using the Cornell Assessment of Pediatric Delirium (CAPD) reported a single day delirium prevalence of 25% in 994 critically ill children,330 and demonstrated feasibility of using a bedside screening tool within multiple different PICU environments. Much higher prevalence rates have been reported in single-site prospective studies that monitored for delirium over a longer period or assessed more than once daily. In a mixed medical/surgical PICU, 300 pediatric patients under 5 years of age were screened using the Preschool Confusion Assessment Method for the ICU (psCAM-ICU) and delirium prevalence was reported to be 47%.328 Even higher rates were reported among infants (56%) and those on MV (58%). Over two-thirds of delirium cases were the hypoactive subtype. In a recent study of 77 children over 5 years of age admitted to a mixed medical/surgical PICU, screening with the pCAM-ICU for delirium revealed a delirium prevalence of 20%, with rates as high as 80% in those requiring MV, and most cases being of the hypoactive subtype (53%).321

#### E1b. RISK FACTORS

Risk factors for delirium in children can be categorized as follows: predisposing/pre-existing factors, or precipitating factors (critical illness-related, iatrogenic or treatment-related). It is important for the clinician to be aware of these associations so that vigilance in assessing for delirium development in high-risk children is maintained. Precipitating factors related to treatment or the environment may be modifiable and deserve close attention. A summary of the studies discussing risk factors for delirium development is found in **SDC TABLE 16.** Eight prospective observational studies, and one large retrospective study, have demonstrated consistent associations between *younger age* and higher risk for delirium.320,324,325,328-330,334-336 Baseline *neurodevelopmental delay* has been shown to more than triple the risk for delirium compared to children with normal development.325,329,334,336 In addition to globally impacting clinical recovery, 2 studies have reported that baseline *poor nutritional status* (serum albumin <3mg/dL on admission) is associated with an increased risk for delirium.325,335 Similar to the potential long term effects of malnutrition, *cyanotic heart disease* (CHD) remains a key factor of concern for patient growth, development, and recovery following medical or surgical disease states. In two recent cohort studies, patients with cyanotic congenital heart disease (CHD) at baseline and another cohort who required longer cardiopulmonary bypass (CPB) times were both shown to have also have a greater risk of postoperative delirium.320,325 While data are limited, the need for *extracorporeal membrane oxygenation* (ECMO) has been linked to high delirium risk.337 Recent United States Food and Drug Administration (FDA) reports warn against the possible role of anesthetics, including benzodiazepines, on cognitive delay in children. Multiple prospective cohort studies report higher delirium rates in post-operative patients (47-66%),320,324,328,335 compared to the general PICU population (17-25%).327,329,330,334 In 6 prospective observational studies, children who requireinvasive MV are at increased risk for delirium development.320,325,329,330,334 This is relevant as most mechanically ventilated pediatric patients receive sedative and analgesic agents. Evidence continues to grow demonstrating that *benzodiazepine-based sedation* independently increases pediatric delirium risk.120,239,325,329,330,335 In a large single center study, the adjusted odds for delirium diagnosis were more than five times greater in children receiving any benzodiazepines.279 Two studies have also reported a dose-response component to benzodiazepine exposure risk.89,294 The relationship between opioids and delirium is less clear with 2 large prospective observational studies demonstrating a positive correlation329,330,335278,279,293 while a 3rd did not. Conversely, in a small RCT in 32 adolescents following scoliosis surgery, delirium rates were significantly lower in children sedated with dexmedetomidine (12.5%) compared to benzodiazepines (31.3%), suggesting a possible protective role for dexmedetomidine sedation.239 Despite the independent associations between many ICU-related interventions and delirium, the significance of severity of illness remains unclear. In 2 large prospective observational studies (n=877338 and n=1547329), a strong and independent association between higher Pediatric Index of Mortality (PIM) score and delirium development were found. However, in 5 other studies this association was not present. 320,321,324,327 Extensive literature describes environmental risk factors for delirium in adults, including immobility, sleep deprivation, lack of cognitive stimulation, and absence of family involvement in patient care.339-343 Similar studies have not yet been published in pediatrics. Indirect evidence that the PICU environment contributes to delirium development in pediatric patients can be found in an international point prevalence study, where delirium rates increased with length of time in the PICU (38% for PICU Day >5 vs. 20% for PICU day <5, p<0.001),330 and a single-center study demonstrating that delirium rates decreased with implementation of an early mobility program.327 Researchers have hypothesized that sleep disruption and noise pollution contribute to delirium development in children344,345 but further research is needed to better characterize the impact of these environmental factors.

##### E1b1. SDC TABLE 16: Summary of Studies Discussing ICU Delirium Risk Factors in Pediatric Patients†

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Design** | **Population** | **Intervention** | **Control** | **Summary implementation-based outcomes** | **Limitations** | **Risk of bias** |
| Traube (2017)330 | **Multi-C**  **PCS** | Admissions to 25 International PICUs | PD screening: CAPD  2-day point prevalence  PD prevalence and risk factors  (n=994) | N/A | Coma 13%, PD 25%, No PD 62%  **Risks (multivariate model):**  Age < 2 yo  Physical restraints (OR 4.0)  MV (OR 1.7)  Opioids (OR 2.3)  Benzodiazepines (OR 2.2)  Use of AED’s (OR 2.9)  Vasopressor use (OR 2.4)  **LESS delirium in:**  Postop <24h  ICU LOS <6 d (20 vs 38%) | Short observation period  (4 h vs end of shift)  Only performed during daytime – may have missed nighttime delirium | **L** |
| Traube (2017)329 | **PCS** | All PICU admissions | PD screening: CAPD  Twice daily screening  (n=1547 pts, 7591 observation days) | N/A | Any PD in 17.3%  **Risks (Multivariate model):**  Age <2 yo  Developmental delay (OR 3.3)  Mortality risk >1.4% (OR 1.5)  MV (OR 1.6)  Coma during admission (OR 4.2)  Benzodiazepines (OR 5.3)  Anticholinergics (OR 2.2)  Opioids fell out multivariate | Pre-existing modifications to decrease PD may nullify risks focusing on mitigating them | **L** |
| Traube (2017)335 | **RS** | Oncology inpatients  0-21 yo | PD screening: CAPD  Twice daily screening  (n=319 pts, 2731 observation days) | N/A | Any PD in 18.8%  **Risks (multivariate model):**  Age <5 yo (OR 2.6)  Brain tumor (OR 4.7)  Postoperative (OR 3.3)  Benzodiazepines (OR 3.7)  Opioids fell out in multivariate | Not a critical care population | **L/M** |
| Alvarez (2018)320 | **PCS** | CICU  0-21 yo | PD screening: CAPD  Twice daily PD screening  (n=99) | N/A | Any PD in 57%  **Risks (multivariate model):**  Age (OR  0.35/mo increase)  MV (OR 4.1)  Benzodiazepines (OR 3.8)  **Univariate only:**  Cyanotic Dx (50 vs 28%, p=0.048)  CPB time (126 vs 61 min, p<0.001) | 85% compliance with screening  Limited population (CVICU) | **L/M** |
| Smith (2016)328 | **PCS** | PICU/CICU 6 mo-5 yo | PD screening: psCAM-ICU and psychiatry  (n=300, 530 paired assessments) | N/A | Any PD in 44%  **Risks:**  Age <2 yo (53 s 33%) | Primary aim = validation study  No assessment of other risks | **L/M** |
| Silver (2015)334 | **PCS** | All PICU admissions | PD screening:  Psychiatry  (n=99, 252 assessments) | N/A | Any PD in 21%  **Risks (multivariate model):**  Age 2-5 yo (OR 2.6)  Developmental Delay (OR 3.5)  MV (OR 3.9) | Psychiatry assessment only – generalizability  Did not assess specific sedation agents | **L/M** |
| Meyburg (2017)324 | **PCS** | PICU admission post elective surgery | PD screening: CAPD  German translation (n=93) | N/A | Any PD in 65.6%  **Risks:**  Age (2.0 vs 6.4 yo; p<0.001)  NO PD association with type of surgery, CPB exposure, PIM2 score | Primarily aimed to assess natural Hx of PD | **L/M** |
| Patel (2017)325 | **PCS** | CICU  0-21 yo  Postop | PD screening: CAPD  (n=194; 1394 days) | N/A | Any PD in 49%  **Risks (multivariate model):**  Younger age  Developmental delay (OR 3.4)  Cyanotic (OR 2.4)  RACHS-1 or 3 or 4 (OR 2.9)  **Univariate (not part of multivariate):**  Opioids (p<0.0001)  Benzodiazepines (p<0.0001)  Physical restraints (p<0.0001)  Vasopressors (p<0.0001)  Higher PELOD (3 vs 2; p<0.0001)  DEX exposure (p<0.0001) | Limited population  (CPB exposure only)  No inclusion of medication exposure in MV analysis  Only once daily screening | **L/M** |
| Dervan (2020)336 | **RS** | All PICU admissions | PD screening: CAPD  (n=2446)  (n=908; LOS ≥48h for sub-analysis) | N/A | Any PD in 81% if LOS ≥48 h  **Risks (multivariate model):**  Age <2  Dev delay  Medical admission  Status epilepticus  MV  Benzodiazepines (dose response)  Low-mod dexmedetomidine  Inadequate pain control | Retrospective  Good compliance with scoring opportunities (92.3%) | **L/M** |
| Simone (2017)327 | **PCS**  **QI** | All PICU admissions | QI Initiative  -Delirium screening -SED PROT  -Early mobilization (n= 1875) | N/A | Progressive  in delirium (19.3 to 11.8%)  **Risks:**  Female gender (p=0.03)  PICU LOS (7.7 vs 5.7 d; p<0.001)  LOMV (5 vs 3 d; p<0.001)  **NOT associated:**  Age  Illness severity (PIM) | Multi-step process so unclear which impacted results most  Not designed for risk factors  Reported only on PD >48h | **L/M** |
| Aydogan (2013)239 | **RCT** | Postop scoliosis surgery  12-18 yo | DEX SED  (n=22) | MIDAZ SED (n=22) | Delirium increased in controls  (31.3 vs 12.5%; p<0.05) | Study designed to assess FENT SED  Limited population (scoliosis)  Small sample size | **M** |
| Smith (2017)120 | **PCS** | 6 mo-5 yo PICU/CICU | PD screening: psCAM-ICU validation  (n=300) | N/A | **Increased delirium associated with:**  Higher benzo exposure (p<0.005)  Younger age (p<0.005)  Higher illness severity (p=0.007) |  | **L/M** |
| Schieveld (2008)338 | **PCS** | All PICU admissions | PD screening:  Psychiatry  Patients with confusion, agitation (n=61 of 877 pts) | N/A | PD in 4.5% (65.5% of referrals)  **Risks:**  Older age (7.7 vs 5.8 yrs, p<0.001)  PIM (5.8 vs 1.6; p<0.001)  PRISM (11.3 vs 2.8; p<0.001)  MV (85 vs 40%; p<0.0005) | No formal screening – high possibility of missing PD  Only assessed illness severity as risk – no confounders | **M/H** |

**†Abbreviations:** (**BENZO**) benzodiazepine, (**CAPD**) Cornell Assessment of Pediatric Delirium tool, (**CICU**) cardiac intensive care unit, (**CPB**) cardiopulmonary bypass, (**d**) day(s), (**DEX**) dexmedetomidine, (**H**) high, (**h**) hour(s), (**L**) low, (**LOC**) level of consciousness, (**LOMV**) length of mechanical ventilation, (**LOS**) length of stay, (**M**) moderate, (**min**) minute(s), (**mo**) months, (**Multi-C**) multi-center, (**MV**) mechanical ventilation, (**OR**) odds ratio, (**PCS**) prospective cohort study, (**PD**) pediatric delirium, (**PICU**) pediatric intensive care unit, (**PIM**) Pediatric Index of Mortality score, (**postop**) postoperative, (**PRISM**) Pediatric Risk of Mortality score, (**pCAM-ICU**) pediatric Confusion Assessment Method for the ICU, (**psCAM-ICU**) preschool Confusion Assessment Method for the ICU, (**QI**) quality improvement, (**RACHS**) Risk Adjustment for Congenital Heart Surgery score, (**RASS**) Richmond Agitation and Sedation Scale, (**RCT**) randomized controlled trial, (**RS**) retrospective, (**SED**) sedation, (**SOS**) Sophia Observation Scale, (**SR**) systemic review, (**yo**) years old

#### E1c. OUTCOMES

Nine single-center prospective observational studies and 1 large retrospective study consistently reported that children diagnosed with delirium are at risk for increased PICU or hospital LOS.120,320,324,325,327,329,334-336,346 Duration of delirium further impacts these outcomes as children with delirium of at least 48 hours duration had an increased PICU LOS (7.7 vs. 5.7 days) and hospital LOS (14.2 vs. 5.7 days) compared to those both those with shorter duration of delirium (< 48 hours) and those who did not develop delirium.327 Five prospective observational studies have shown a strong association between delirium and prolonged duration of MV.320,324,325,327,329 The true relationship between invasive MV being a risk factor for delirium versus delirium causing prolonged MV remains a consideration for carefully controlled future studies. In a single high-quality observational study of 464 consecutive PICU admissions, the median costs were 85% higher in children who were ever delirious, with an incremental increase in costs for each day spent delirious.347 The association between delirium and mortality remains unclear. Whereas in one high-quality prospective longitudinal study (n=1547) a strong and independent association between delirium and mortality (DDS ratio 4.4) was found,329 a large retrospective study (N = 2,446) reported no association between either delirium presence or duration and mortality. The possible relationship between delirium and mortality remains extremely concerning and, until more evidence is available, the authors stress the importance to remain vigilant for delirium, as it may be a sensitive way to identify those patients at highest risk for poor outcome. Long-term cognitive impairment and psychological distress has been well-described in adult ICU survivors following delirium.339,348-351 Similar high-quality studies have not yet been performed in the pediatric population with inconclusive reports of delirium outcomes.324 In a cohort study of 102 children assessed at 3 months post-PICU discharge, children who reported delusional memories of their PICU stay were more likely to have received benzodiazepines and have higher post-traumatic stress symptoms (PTSS).352 The alteration of the perceived PICU experience may be impacted by the presence of delirium and exposure to choice of sedative. The true associations with psychological morbidity after discharge in both child-survivors and their caregivers requires further investigation.353-355

### E2. DELIRIUM MONITORING

#### E2a. FEASIBILITY OF DELIRIUM MONITORING

The realization of delirium phenomenology in pediatric patients and the improved understanding of patient assessment skills in younger children provided the foundation for development of the above-described delirium screening tools. Numerous prospective observational pediatric cohort studies have been successfully completed using pediatric specific screening tools to advance our understanding of delirium epidemiology,90,92,320-322,327,328,330 including a large international, multicenter point prevalence study. This international collaboration demonstrated the feasibility of delirium monitoring using a bedside screening tool within multiple difference PICU environments. In a single-site institution report of implementation of an ICU bundle consisting of delirium, sedation, and early mobility clinical protocols using the Plan-Do-Study-Act cycles for quality improvement, monthly compliance for delirium screening using the CAPD was 95% for the entire 22 month study period.327 Although there are success stories of tool implementation, both compliance and accuracy of delirium monitoring may be improved considering use of an electronic medical record, routine reminders during charting, ongoing education modules, and development of a delirium treatment protocol.356

#### E2b. TOOLS FOR DELIRIUM ASSESSMENT

The Child & Adolescent Psychiatrist is the reference standard for diagnosing delirium using criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM). However, reliance on psychiatry consultation services for routine delirium monitoring is not feasible in most ICU settings due to the time-consuming nature of a full patient evaluation, faculty availability, and the necessity for frequent and timely evaluations to rapidly diagnose and optimize management.354,357 Therefore, the ability to efficiently and accurately screen for delirium at the bedside is paramount. To date there have been five pediatric-specific instruments reported in the literature to screen for delirium in the PICU-setting for use by non-psychiatric trained staff.

**The pediatric CAM-ICU (pCAM-ICU)** is an adaptation of the adult CAM-ICU that has undergone validation of critically ill cohorts at various institutions.90,331 The preschool and pediatric CAM-ICU series assess for: (1) acute change or fluctuating course of mental status, (2) inattention, (3) altered level of consciousness, and (4) presence of disorganized thinking or dysregulated systems.90,120,358,359 For delirium presence, both features 1 and 2 are required (key DSM features for delirium) and then either feature 3 or 4. In a comparison of the PAED and pCAM-ICU with psychiatry assessment in a general PICU population, the PAED performed with lower sensitivity but similarly high sensitivity compared to the pCAM-ICU.323,360 A severity scale adapted from the pCAM-ICU (ss pCAM-ICU) was created using a score from 0 (no delirium) to 19 (severe delirium), and was found to have a high sensitivity (85%) and specificity (98%) respectively, compared to reference psychiatry assessment. **The preschool CAM-ICU (psCAM-ICU)** is an adaptation of the pCAM-ICU with specific adaptations including the development of a consistent 10-second evaluation for inattention in preverbal infants, and the dysregulation of systems determined using 1) sleep wake cycle disturbance, 2) inconsolability, and 3) unawareness of surroundings.328,361 (**SDC TABLE 17**)

**The Pediatric Anesthesia Emergence Delirium (PAED) Scale** is an observational instrument created to identify symptoms consistent with “agitated” behavior often referred to as “emergence delirium” in children following general anesthesia and surgery.362 Five items are observed by the caregiver, including eye contact, purposeful actions, awareness of surroundings, restlessness, and inconsolability, with each item scored based on severity using a 4-point Likert scale. The PAED was not validated against a reference standard. However, in postoperative patients diagnosed with delirium based on receiving dimenhydrinate for agitation, the tool performed with a sensitivity of 64% and good inter-rater reliability (kappa of 0.84). Because it is based on agitation treatment, however, this tool has been found to be much less sensitive when screening for all delirium subtypes, especially for more commonly observed hypoactive and mixed delirium in PICU patients.91 *Therefore, the validity, reliability, and generalizability of the PAED for the diagnosis of all delirium subtypes in the PICU-setting appears to be very low.* **The Cornell Assessment for Pediatric Delirium (CAPD)** is an observational delirium instrument, adapted from the Pediatric Anesthesia Emergence Delirium scale, designed to improve the ability to detect all delirium subtypes.92 The CAPD added 3 areas for assessment to the PAED including: 1) communication of needs, 2) underactivity while awake, and 3) prolonged response to interactions. Each assessment is scored using a Likert scale (never, rarely, sometimes, often, always), and a total score ≥ 10 is indicative of delirium presence. (**SDC TABLE 18**)

**The Sophia Observation Withdrawal Symptoms-Pediatric Delirium Scale (SOS-PD)** is a pediatric withdrawal tool that additionally assesses for 19 “delirium” symptoms, of which 5 correspond to DSM-based delirium symptomatology and others that overlap with “withdrawal” symptoms.363 Two prospective cohort studies were performed to validate the SOS-PD scale for delirium screening but utilized psychiatry assessment only in patients who screened positive for delirium.364,365 While sensitivity and specificity were high in both studies, significant limitations in study design including use of a convenience sample, selection bias, unblinding, and low prevalence of delirium (10%) and necessitate downgrading the quality of evidence in support of this tool at this time. Further testing is warranted in a larger cohort of patients and addressing study design limitations to fully assess the usefulness of this tool for delirium screening.

##### E2b1. SDC TABLE 17: Pediatric and Preschool Confusion Assessment Methods for the ICU 90,328,361

|  |  |  |  |
| --- | --- | --- | --- |
|  | | | |
| **FEATURES** | **TOOL** | **PATIENT ASSESSMENT** | **OUTCOME** |
| **Feature 1:**  Mental Status | **ps/pCAM-ICU** | **Ask 2 Questions:**   1. Is there an ***acute change*** from baseline mental status? 2. Has the patient’s mental status ***fluctuated*** during the past 24 hours? | **Feature 1** is **PRESENT** if **‘YES’** to ***either***  Question 1 or 2 |
| If Feature 1 is **NOT present,** then **STOP 🡪 DELIRIUM ABSENT**  If Feature 1 is **PRESENT 🡪** move onto **Feature 2** | | | |
| **Feature 2:**  Inattention**†** | **psCAM-ICU** | Attention exam showing 10 pictures/mirrors/toys  (~ 10 seconds) and assessing for eye contact | **Feature 2** is **PRESENT** if **≥3 errors**  (No eye contact or incorrect response) |
| **pCAM-ICU** | Vigilance A test (ABADBADAAY) or Attention Screening Exam |
| If Feature 2 is **NOT present,** then **STOP 🡪 DELIRIUM ABSENT**  If Feature 2 is **PRESENT 🡪** move onto **Feature 3** | | | |
| **Feature 3:**  Acute altered LOC | **ps/pCAM-ICU** | Is the patient currently alert and calm (RASS or SBS = 0)? 🡪 **YES/NO** | **Feature 3** is **PRESENT** if **‘NO’**  Not alert and calm |
| If Feature 3 is **PRESENT, then STOP 🡪 PATIENT HAS DELIRIUM**  If Feature 3 is **NOT present** **🡪** move onto **Feature 4** | | | |
| **Feature 4:**  Dysregulated Systems | **psCAM-ICU** | **Ask 2 Questions:**   1. Are symptoms of a ***sleep wake cycle (SWC) disturbance*** present? 2. Is the patient ***inconsolable*** AND ***unaware of surroundings***? | **Feature 4** is **PRESENT** if **‘YES’** to ***either***  Question 1 or 2 |
| **pCAM-ICU** | 1. Ask 4 simple YES/NO questions (4 possible points) 2. Give a 2-step command (1 possible point) | **Feature 4** is **PRESENT** if **≥ 2 errors** |
| If Feature 4 is **PRESENT 🡪 PATIENT HAS DELIRIUM**  If Feature 4 is **NOT present** **🡪 DELIRIUM ABSENT** | | | |
| **DELIRIUM = Features 1 AND 2 + *either* Feature 3 or 4** | | | |

***†***Infant or child should maintain spontaneous eye-opening during at least half of the assessment period, if unable to do so then inattention is present even if eye contact to pictures/mirror.

**‡Abbreviations:** (**LOC**) level of consciousness. (**pCAM-ICU**) pediatric confusion assessment method for the intensive care unit, (**psCAM-ICU**) preschool confusion assessment method for the intensive care unit

##### E2b2. SDC TABLE 18: Cornell Assessment of Pediatric Delirium (CAPD)92

|  |
| --- |
| **Cornell Assessment of Pediatric Delirium** |
| **Questions 1-4 scored:** Never **(4),** Rarely **(3),** Sometimes **(2),** Often **(1),** Always **(0)** |
| 1. Does the child make eye contact with the caregiver? |
| 1. Are the child’s actions purposeful? |
| 1. Is the child aware of his/her surroundings? |
| 1. Does the child communicate needs and wants? |
| **Questions 5-8 scored in reverse order:** Never **(0),** Rarely **(1),** Sometimes **(2),** Often **(3),** Always **(4)** |
| 1. Is the child restless? |
| 1. Is the child inconsolable? |
| 1. Is the child underactive – very little movement while awake? |
| 1. Does it take the child a long time to respond to interactions? |
| **DELIRIUM PRESENT when score ≥ 10** |

### E3. DELIRIUM PREVENTION AND MANAGEMENT IN THE PICU

#### E3a. SDC TABLE 19: Consideration for possible causes of Delirium (BRAIN MAPS)

**BRAIN MAPS**357 **is an acronym providing a differential for possible causes of ICU delirium†**

**B – BRING OXYGEN** [i.e., hypoxemia, decreased cardiac output, anemia, increased work of breathing]

**R – REMOVE OR REDUCE DELIRIOGENIC DRUGS** [i.e., anticholinergics, benzodiazepines]

**A** **– PATIENT ATMOSPHERE** [i.e., bright lights, incessant noise, lack of family presence, non-mobility]

**I – IMMOBILIZATION, INFLAMMATION, INFECTION**

**N – NEW ORGAN DYSFUNCTION/FAILURE** [i.e., renal insufficiency in the setting of shock]

**M – METABOLIC DISTURBANCES** [i.e., ↑↓Na+, ↑↓K+, ↓ glucose, ↓ Ca++, alkalosis, acidosis]

**A – AWAKE** [i.e., sleep-wake cycle disturbance]

**P – PAIN** [i.e., not enough analgesia OR excessive drug administration]

**S – SEDATION** [i.e., residual anesthesia, choice of sedative, over sedation]

**†Abbreviations:** (**Na+**) sodium, (**K+**) potassium, (**Ca++**) calcium

#### E3b. SDC TABLE 20: Summary of Studies Discussing Pharmacologic Management of Delirium in Pediatric Patients

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author** | **Design** | **Participants** | **Intervention** | **Outcome** | **Limitations** |
| Sloof VD  (2018)366 | **PCS** PK study | Patients with delirium  (n = 13)  Age: 0.4 – 13.8 yo | Haloperidol dosing: Median dose (range) 0.027 **mg**/kg/d  (0.005-0.085 **mg**/kg/d) | All patients were reported to have resolution of delirium.  ADEs reported in 5/13 patients. Biperiden given with resolution in 2 patients. Haloperidol discontinued or decreased in 6.  Plasma concentrations lower than expected therapeutic range 3-12 mcg/L. | Focus was on PK data. |
| Schieveld  (2007)326 | **DCS** | PICU  (n = 40)  Diagnosed with delirium by psychiatry  - 38 received antipsychotic therapy. Age: Mean 7.6 yo | Haloperidol dosing: load 0.15 - 0.25 **mg** then 0.05 - 0.5 **mg**/kg/d. Risperidone dosing: load 0.1 - 0.2 **mg** then 0.2 - 2 **mg**/d | Of the 38 patients requiring therapy, 27 received haloperidol, 10 received risperidone, and 1 patient received both.  In most cases, the beneficial results were observed rapidly.  Two patients experienced acute dystonia, associated with haloperidol, responded well to biperiden. | Assessment of "improvement" in delirium not well described though the assumption is psychiatry re-assessment. |
| Turkel  (2012)367 | **RS** | Hospitalized patients  (n = 110)  PD diagnosed by DRS-98 and assessed pre and post therapy. Age (Olanzapine): Median 12 yo Age (Risperidone): Median 8 yo Age (Quetiapine): Median 11 yo | Olanzapine dosing (n=78): 3 - 10 mg/d Risperidone dosing (n=13): 0.5 - 1 mg/d Quetiapine dosing (n=19): 25 - 75 mg/d | Final DRS-R98 scores were significantly lower than scores at diagnosis  (paired t-tests, p<0.001). Final scores were not significantly different between medication groups.  One patient treated with olanzapine developed mild dystonia, resolved when the dose was decreased. No other significant adverse side effects.  No arrhythmias | Decent sized cohort. Not powered as safety study and not randomized to assess for drug effect and control for bias. |
| Turkel (2013)368 | **RS** | Hospitalized with  delirium diagnosed by psychiatry.  (n = 19) Age: 7 - 30 mo | Starting doses:  Olanzapine: 0.625 or 1.25 **mg** QHS or BID Risperidone: 0.05 - 0.1 **mg** QHS or BID Maintenance dosing: Olanzapine dosing: 1.4 - 7.6 **mg**/d Risperidone dosing: 0.2 - 0.28 **mg**/d | Significant improvement in DRS scores without adverse events. Post-treatment DRS scores were significantly lower ( p < 0.0001) compared to baseline scores at time of delirium diagnosis. | Drug doses titrated to control insomnia and agitation.  Average duration of antipsychotic use was similar. |
| Sassano-Higgins (2013)369 | **RS** | PICU  (n = 59) Control group: 28  PD not treated  Intervention group: 31 PD treated with olanzapine | Starting doses:  Olanzapine: 0.625 – 5**mg** QHS or BID based on age. Titration not described. | Baseline DRS scores were higher in the olanzapine group. Despite this had a more drastic decrease in DRS scores compared to those without treatment. No adverse events noted in this cohort. | DRS scoring completed retrospectively - scorers blinded to patient treatment and time course of exam. |
| Slooff (2014)370 | **RS** | PICU  (n = 52) Age not reported. | No specific dosing protocol used for haloperidol. | Five patients (9.6%) suffered an ADE, all were female and no correlation to age or PRISM scores. Dose factor was not significant | ADEs: extrapyramidal symptoms, hyperpyrexia, decreased LOC, ECG changes, prolonged QTc interval |
| Joyce  (2015)371 | **RS** | PICU  (n = 50)  Age: 2 mo - 20 yo  >2400 doses of quetiapine administered | No specific dosing protocol used for quetiapine. Median dose 0.43 **mg**/kg TID. | No cases of NMS or EPS. 3 cases of prolonged QTc with 2/3 resolving without intervention and 1/3 with reduction of dose.  No clinically significant arrhythmias. | Decent sized cohort. Safety profile versus efficacy. |
| Campbell (2019)372 | **RS** | (n = 17) patients administered at least 1 dose of risperidone Age: Less than 2 yo | Risperidone dosing: Daily 0.1 - 0.25 **mg** QD or BID | Median daily doses of MSO4, FENT, ketamine and MIDAZ decreased after initiation of risperidone treatment. No ADEs reported. | No specific safety outcomes were followed prospectively. |
| Kishk (2019)373 | **RS**  **Matched cohort** | N = 188 with PD  (n = 15) treated with antipsychotics Age: 0.5 - 2.3 yo | Haloperidol dosing: 0.005 - 0.15 **mg**/kg/d  Haloperidol 9 patients. Risperidone 6 patients. Quetiapine 2 patients. | Intervention group (n = 15) were younger, had more delirium days (6 vs. 3, p=0.022), longer MV days (14 vs. 7, p=0.017), and longer PICU LOS (34 vs. 16 d, p=0.029). Clinical improvement in 10/15 patients. No ADEs reported. | Low delirium prevalence cohort. |
| Ratcliff (2004)374 | **RS** | Burn patients/PICU  (n = 26) Age: Mean 11.7 +/- 3.9 yo | Haloperidol dosing: 0.01 - 0.28 **mg**/kg | Clinical improvement of delirium severity by subjective clinical assessment.  Multiple ADEs reported:  Dystonia in 4 patients. Hyperpyrexia in 1 patient. Resolved with dose reduction/discontinuation or treatment with anticholinergic. | Clinical delirium assessment, non-specific |
| Harrison (2002)375 | **CS** | PICU  (n = 5) Age: Median 12 yo | Haloperidol dosing:  0.015 - 0.15 **mg**/kg Q6-8h | All 5 patients had decrease in agitation by clinical assessment, requiring less sedation/paralytic.  One child had dystonic reaction (eye reaction) requiring discontinuation of haloperidol. | No unbiased delirium screen. All improvement noted in clinical notes and based on sedation boluses. |
| Schieveld (2005)376 | **CR** | PICU  (n = 2) Age: 28 and 42 mo | Single dose of haloperidol administered | DRS assessments for delirium. One patient improved 30 minutes post haloperidol.  Second patient fell asleep and woke up the following morning back to baseline. | No quantitative measure of improvement |
| Karnik (2007)377 | **CS** | Adolescents with delirium  (n = 2)  Age: 14 and 16 yo | Risperidone dosing (hypoactive delirium): 0.5 **mg** QHS, increased to 0.5 **mg** BID. Risperidone dosing (hyperactive delirium): 0.5 - 1.5 **mg** BID x 5d, then transitioned to haloperidol of 0.5 **mg** BID | Both patients had resolution of delirium measured by DRS with clinical improvement. Hypoactive/mixed delirium effectively treatment with risperidone alone. Hyperactive delirium required transition to haloperidol. No major adverse reactions. |  |
| Traube (2013)378 | **CS** | PICU  (n = 4) 8 mo - 14 yo  PD screen w/ CAPD Verified by psychiatry | Quetiapine dosing:  2 - 8 **mg**/kg/d | Improvement in hyperactive symptoms based on the CAPD within 24h of initiation of treatment with no reported ADE |  |
| Traube (2014)379 | **CS** | PICU  (n = 4) Age: 0.6 - 3 yo with neuroblastoma and PD | Interventions: BENZO stopped in all 4. Anticholinergics stopped in 2. Opiates  in 3. DEX added in 2. Care clustered in 4. Quetiapine added in 4. | Delirium symptoms based on CAPD assessment improved in 2 patients within 24 hours without reported ADEs. | Multiple interventions not controlled for given CS. No conclusion to be drawn for efficacy. |
| Brahmbhatt (2016)380 | **CR** | (n = 1) Infant aged 7.5 mo Trisomy 21, CHD s/p surgical repair, with PD | Risperidone titrated up to 0.3 **mg** QHS | Clinical improvement  without ADEs | Vague description |
| Groves (2016)381 | **CS** | Infants in NICU  with PD  (n = 3) Age: Corrected GA of 4, 11, and 17 weeks | No specific PROT. Quetiapine dosing: 0.5 **mg**/kg TID BENZO use  in all 3. | Improvement in CAPD scores and clinical symptoms in all infants. No ADEs. | Authors highlight ability to wean other medications with quetiapine treatment. |

**†Abbreviations:** (**ADE**) adverse drug effect, (**BENZO**) benzodiazepine, (**BID**) twice daily, (**CAPD**) Cornell Assessment of Pediatric Delirium tool, (**CHD**) congenital heart disease, (**CICU**) cardiac intensive care unit, (**CPB**) cardiopulmonary bypass, (**CR**) case report, (**CS**) case series, (**d**) day(s), (**DCS**) descriptive cohort study, (**DEX**) dexmedetomidine, (**DRS**) Delirium Rating Scale, (**DRS-R98**) DRS-Revised, (**EPS**) Extrapyramidal Symptoms, (**FENT**) fentanyl, (**GA**) gestational age, (**h**) hour(s), (**LOC**) level of consciousness, (**LOMV**) length of mechanical ventilation, (**LOS**) length of stay, (**MIDAZ**) midazolam, (**min**) minute(s), (**mo**) months, (**MSO4**) morphine, (**Multi-C**) multi-center, (**MV**) mechanical ventilation, (**NMS**) Neuroleptic Malignant Syndrome, (**OR**) odds ratio, (**PCS**) prospective cohort study, (**PD**) pediatric delirium, (**PICU**) pediatric intensive care unit, (**PIM**) Pediatric Index of Mortality score, (**postop**) postoperative, (**PRISM**) Pediatric Risk of Mortality score, (**pCAM-ICU**) pediatric Confusion Assessment Method for the ICU, (**PROT**) protocol, (**psCAM-ICU**) preschool Confusion Assessment Method for the ICU, (**Q**) every, (**QD**) daily, (**QHS**) at nighttime, (**QI**) quality improvement, (**RACHS**) Risk Adjustment for Congenital Heart Surgery score, (**RASS**) Richmond Agitation and Sedation Scale, (**RCT**) randomized controlled trial, (**RS**) retrospective, (**SED**) sedation, (**SOS-PD**) Sophia Observation Scale-Pediatric Delirium, (**SR**) systemic review, (**TID**) three times a day, (**yo**) years old

## F. SEDATIVE and ANALGESIC TOLERANCE

Tolerance is broadly defined as a decrease in the pharmacologic effect of a drug with its repeated administration, necessitating incremental increases in dose to achieve the desired clinical effect.31,382,383 Most often this is due to post-receptor alterations, a process referred to as pharmacodynamic tolerance.384 While recognized as a common occurrence in critically ill pediatric patients, research into the epidemiology of, risk factors for, and strategies to mitigate its development, have been seriously hampered by the lack of a formal definition for tolerance. While some have operationally defined tolerance as occurring when the required dose of the agent of interest has doubled,385 this definition has not been universally adopted. Despite these limitations, tolerance remains highly relevant to the critical care provider as it impacts sedative and analgesic exposure which in turn may impact ability to wean mechanical ventilation, contribute to the development of iatrogenic withdrawal syndrome, and adversely affect PICU and hospital lengths of stay.386,387

### F1. UNANSWERED QUESTIONS

**Unanswered Question:**

**What is the prevalence of, and risk factors for, the development of tolerance to opioids, benzodiazepines, or alpha2-agonists in critically ill pediatric patients?**

**Discussion:** Due to the absence of an accepted definition, the prevalence of tolerance to specific analgesic and/or sedative agents is unclear. Simultaneous administration of analgesics and sedative agent classes, further complicate determination of tolerance prevalence rates as practices vary widely regarding which agent(s) are titrated in response to increases in apparent pain and/or agitation.

Longer duration of drug exposure increases the risk for development of tolerance.385 *In vitro* and animal studies suggest that tolerance is more common with synthetic and shorter-duration opioids and that it may be reduced with methadone use due to its additional NMDA-receptor antagonism although clinical corroboration studies are minimal.31,387 103,388 A single small prospective RCT found no differences in tolerance, defined as the number of drug dose escalations required, between fentanyl or remifentanil infusions in mechanically ventilated infants.389 Primary use of morphine versus fentanyl appeared to be protective for tolerance development in postoperative NICU patients but not in those with medical diagnoses.382 While adult data suggest a possible benefit for low-dose naloxone infusions to reduce opioid tolerance,387 this finding was not replicated in 2 small pediatric studies.34,35 In 3 RCT’s, daily and total drug exposure was decreased in patients receiving intermittent versus continuous opioids and/or sedatives.247,390,391 While none of these studies specifically aimed to address tolerance, it is plausible that decreasing the total cumulative daily drug exposure may decrease the development of tolerance. No data were found evaluating the impact of early addition of long-acting enteral benzodiazepines or alpha2-agonists on the development of tolerance.

**Unanswered Question:**

**Does goal-directed (targeted) sedation reduce sedation tolerance among critically ill pediatric patients receiving MV?**

**Discussion*:*** Tolerance to sedative and analgesic agents, defined as a decrease in their pharmacologic effect with repeated or prolonged administration, has long been observed in mechanically ventilated pediatric patients. Multiple assorted studies including case series and RCT’s have discussed risk factors for the development of tolerance. The most commonly reported risk factors include prolonged use of continuous infusions of agents385-387,392 and, by inference, cumulative dose of agents. Others have found tolerance to develop more rapidly with use of shorter duration agents,393 when infusions were delivered together in the same syringe versus as separate infusions,264 and during co-administration of opioid and benzodiazepine infusions.387 While most reports have focused on tolerance to opioids and benzodiazepines, other authors have pointed out that tolerance can develop after exposure to any sedative agent including barbiturates, alpha2-agonists, and ketamine.394 Consequently, efforts have shifted to consider targeted sedation and sedation protocols to reduce tolerance.392 To date, no studies have specifically addressed the impact of protocolized sedation on tolerance development although decreases in drug exposure described above indirectly suggest a possible positive impact.

**Unanswered Questions*:***

**Does the addition of adjunct enteral alpha2-agonists reduce requirements for other sedative or opioid agents in critically ill pediatric patients?**

**Discussion*:*** In a small prospective cohort, addition of enteral clonidine (3-5 mcg/kg every 8 hours) to mechanically ventilated children resulted in significant decreases in both lorazepam and morphine requirements without reported adverse events.395 Two RCT’s evaluated the effect of scheduled enteral clonidine (5 mcg/kg every 6 hours) compared to placebo in a total of 150 critically ill pediatric patients on MV and both reported significant reductions in opioid exposure and 1 reported reductions in benzodiazepine exposure.396,397 While limited, these data suggest that use of enteral clonidine to reduce IV sedative and analgesic exposure is feasible and efficacious.

## G. IATROGENIC WITHDRAWAL SYNDROME (IWS)

Iatrogenic Withdrawal Syndrome (IWS) is a clinical syndrome that manifests after a drug is either stopped, rapidly weaned, or chemically reversed after prolonged exposure. IWS is a common complication among critically ill pediatric patients who receive prolonged sedation and analgesia. While some agent and/or drug class specific withdrawal syndromes have been described, IWS symptoms are often non-specific and may be related to sympathetic activation and autonomic dysfunction (tachypnea, tachycardia, hyper-pyrexia, and diaphoresis),387,398 gastrointestinal dysfunction (vomiting and diarrhea), and central nervous system alterations (agitation, jitteriness, seizures, hallucinations, delirium).364,387,399-401 The onset of IWS symptoms may be delayed following weaning or discontinuation of drugs with active drug metabolites (e.g. morphine, diazepam, midazolam), or in the setting of renal and/or hepatic dysfunction.

### G1. OPIOID AND BENZODIAZEPINE IWS: PREVALENCE AND RISK FACTORS

#### G1a. SDC TABLE 21: Summary of Studies Discussing Prevalence and Risk Factors for Opioid/Benzodiazepine Withdrawal

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Design** | **Population** | **Outcome** | **Control** | **Summary implementation-based outcomes** | **Limitations** | **Risk of bias** |
| Best  (2015)137 | **SR** | General PICU | IWS prevalence  Risk factors | N/A | IWS prevalence: 5-87%  **Risk factors IWS from opioids:**  -Increased incidence in younger age  -Increased with longer duration of therapy -No specific duration though often correlations with >5d  -Strong dose correlation – no specific cutoff but high sensitivity and specificity with >32-166 **mg**/kg cumulative MSO4  **Risk factors IWS from** **Benzodiazepines**:  >5d – 83% sensitivity/92% specificity to predict IWS  Positive dose correlation but variable cumulative MIDAZ dose: 20-60 **mg**/kg | Small sample size  Did not report other potential symptoms | **M** |
| Best  (2017)400 | **Multi-C**  **RCT** | MED/SURG  PICU  >5 days opioid exposure  (n=1157) | IWS prevalence  Risk factors  Assessment:  WAT-1 | “Standard” SED practices | IWS prevalence: 47% (WAT >3 x2 scores)  **Risk factors IWS from opioids/benzos:**  -Age: 1.1 vs 1.6 yrs (p=0.01)  -Baseline cognitive impairment: 25 vs 18% (p=0.003)  -Baseline functional impairment: 29 vs 22% (p=0.01)  **Opioids (morphine equivalents):**  -Morphine (46%) vs fentanyl (48%): p=0.68  -Daily dose: 2.9 vs 2.6 mg/kg/d (p<0.0001)  -Cumulative dose: 19.1 vs 15.7 mg/kg (p<0.0001)  **Benzodiazepines (midazolam equivalents):**  -Midazolam (48%) vs lorazepam (39%): p=0.29  -Daily dose: 2.5 vs 2.1 mg/kg (p=0.001)  -Cumulative dose: 16.0 vs 12.3 mg/kg (p<0.0001)  -Number of classes: <3 (43%) vs ≥3 (50%): p=0.01 | Did not account for alpha-agonists | **M** |
| Amigoni (2017)402 | **PCS** | General PICU/CICU >5 days opioid/benzo exposure  (n=113) | IWS prevalence  8 PICUs  Risk factors  Assessment:  WAT-1 | N/A | IWS prevalence: 65%  **Opioids (morphine equivalents):**  Morphine < fentanyl (OR 0.17; p=0.003)  Duration: 12.3 vs 7.9 d (p=0.01)  Cumulative dose: 10.8 vs 5.8 mg/kg (p=0.001)  **Benzodiazepines:**  Duration: 10.8 d 6.0 d (p=0.001)  Cumulative dose: 65.3 vs 28.0 mg/kg (p=0.02)  Sedative duration: 7.9 vs 12.3 days (p=0.01) | Focus on opioid withdrawal  Only 19/113 patients received MSO4 – unclear if adequate power to assess IWS differences | **M/H** |
| Ista  (2013)364 | **PCS** | General PICU  >5 days continuous opioid/benzo  exposure  (n=154) | IWS prevalence IWS risks  Assessment:  SOS | N/A | IWS prevalence: 46.5%  **IWS risks/characteristics:**  -Age: median 7 vs 1 mo (p=0.012)  -LOMV: median 15 vs 10 days (p=0.001)  **Benzodiazepines (midazolam equivalent):**  Median duration: 17 vs 9 d (p<0.001)  Wean duration: 8 vs 5 d (p<0.0001)  Cumulative dose: 77.9 vs 34.8 **mg**/kg (p<0.0001)  **Opioids (morphine equivalent)**  Median duration, wean duration, median infusion rate and peak dose NOT significant | Majority (95%) received both opioids/benzos  Adjunct clonidine, ketamine, propofol in 27-40%  SOS cutoff score and psychometric validation study – not specifically designed to assess risks | **M/H** |
| Fisher (2013)403 | **PCS** | General PICU  >5-day continuous opioid exposure  (n=25) | IIWS prevalence  Risk Factors  Assessment:  WAT-1 | N/A | IWS prevalence: 44%  Risks:  Cumulative MSO4 >2.5 **mg**/kg | Non-standard taper  Enrolled only high risk  Small sample size | **H** |
| Ista  (2008)404 | **PCS** | General PICU/CICU >5-day continuous opioid/benzo  exposure  (n=79) | Sophia Opioid and Benzodiazepine Withdrawal Score (OBWS) | N/A | IWS prevalence: 30%  **Benzodiazepines (midazolam equivalent):**  Median dose: 176 (25-297) **mcg**/kg/h  Cumulative dose: 33 (2-595) **mg**/kg  Median duration: 10 (3-108) days  **Opioids (morphine equivalents):**  Median dose: 14 (5-559) **mcg**/kg/h  Cumulative dose: 3.8 (0-682) **mg**/kg  Median duration: 8 (1-41) days | OBWS validation study – not designed to assess risks  Only discusses prevalence  Cannot distinguish opioid vs benzodiazepine contributions | **H** |
| Katz  (1994)401 | **PCS** | General PICU  < 22 mo. on continuous FENT (n=23) | IWS prevalence  Risk factors  Assessment:  NAS scale | N/A | IWS prevalence: 57%  Total dose: 2.9 vs 0.5 **mg**/kg (p<0.05)  Fentanyl duration: 13.1.vs 3.8 d (p<0.001)  100% predictive if:  Cumulative >2.5 **mg**/kg or duration >9 d | Small sample size  Nice to only address opioids  Limited age (<22 mos)  Unclear if weaning protocols in place | **H** |
| Fernandez-Carrion (2013)399 | **RS** | General PICU/CICU >48h continuous opioid/benzo  exposure | IWS prevalence  Risk factors | N/A | IWS prevalence: 50%  **Opioid (fentanyl equivalent):**  Cumulative dose > 0.5 **mg**/kg  Infusion duration > 5.8 days  **Benzodiazepine (midazolam equivalent):**  Cumulative dose 40 **mg**/kg  Infusion duration >5.8 days | No description of weaning practices | **H** |
| Fonsmark (1999)138 | **RS** | General PICU (n=40) | IWS prevalence  Risk factors | N/A | IWS prevalence: 35%  Risks:  Midazolam: >60 **mg**/kg  Pentobarbital: >25 **mg**/kg  Taper in only 1/14 with IWS | No detail of MSO4 exposure  Withdrawal by symptoms only – no validated tool | **H** |

**†Abbreviations:** (**BENZO**) benzodiazepine, (**CICU**) cardiac intensive care unit, (**d**) day(s), (**H**) high, (**h**) hour(s), (**IWS**) iatrogenic withdrawal syndrome, (**kg**) kilogram, (**L**) low, (**M**) moderate, (**mcg**) microgram(s), (**med/surg**) medical/surgical, (**mg**) milligram(s), (**min**) minute(s), (**mo**) months, (**MSO4**) morphine sulfate, (**Multi-C**) multi-center, (**MV**) mechanical ventilation, (**NAS**) neonatal abstinence syndrome, (**PCS**) prospective cohort study, (**PICU**) pediatric intensive care unit, (**RCT**) randomized controlled trial, (**RS**) retrospective, (**SED**) sedation, (**SOS**) Sophia Observation Scale, (**SR**) systemic review, (**WAT-1**) withdrawal assessment tool

#### G1b. UNANSWERED QUESTIONS

**Unanswered Question:**

**What is the prevalence of IWS following exposure to opioids and/or benzodiazepines in critically ill pediatric patients?**

**Discussion:** The reported prevalence of IWS following administration of opioid and/or benzodiazepines ranges between 5 – 87% in the pediatric literature.21,137,139,364,401,404,405 **(SDC TABLE 21)** More recent data from 2 multicenter studies report rates of 35-68%.93,402 Due to the almost universal coadministration of these 2 drug classes, IWS specifically attributable to opioids or benzodiazepines as individual drug classes is difficult to determine. In studies of IWS in the setting of opioid administration alone, prevalence rates of 29 - 57% have been reported.137,138,382,386,401,403,406 Only 2 studies have assessed IWS to benzodiazepines alone, reporting prevalence rates of 17 and 24% but diagnosis was based on either clinician judgement or use of a non-validated scoring tool.407,408

**Unanswered Question:**

**What is the prevalence of IWS following exposure to alpha2-agonists in critically ill pediatric patients?**

**Discussion*:*** Screening for IWS due to alpha2-agonists remains challenging as a validated alpha2-agonist specific withdrawal assessment tool has not been developed. A wide spectrum of potential IWS-related symptoms has been reported following alpha2-agonist discontinuation. The most consistently reported symptoms include rebound tachycardia or hypertension, agitation, sleeplessness, neurologic disturbances including tremors and increased tone, emesis, and diarrhea.166,167,409-411 However, the common use of other sedatives and a degree of overlap with opioid and benzodiazepine withdrawal makes the relative attributability to alpha2-agonists unclear. Five retrospective studies (496 patients) reported withdrawal prevalence rates of 27-83% following weaning and/or abrupt cessation of alpha2-agonists.166,167,409-411 **(SDC** **TABLE 22)** Confounding factors in these studies included variable duration of infusion rates and weaning protocols, and variable withdrawal assessment mechanisms including clinical symptom presence and/or use of non-validated scoring tools. While IWS to alpha2-agonists is almost certainly a real entity, further study to delineate risks, symptoms, and to develop an alpha2-agonist-specific IWS screening tool are needed.

**Unanswered Question:**

**What are the risk factors for development of IWS to opioids and/or benzodiazepines in critically ill pediatric patients?**

**Discussion:** Longer duration of drug exposure increases the risk for development of IWS.385 Multiple prospective studies have demonstrated that patients with more than 5 days of opioid and/or benzodiazepine exposure are at significant risk for IWS.137,399,401,402,404,405 **(SDC TABLE 21)** Likely related to duration, cumulative opioid and benzodiazepine doses are also correlated with increased risk of IWS development although significant variability exists regarding reported cumulative dose thresholds. More recent larger multicenter RCT’s have reported that relatively lower cumulative opioid (11-19 mg/kg morphine equivalents) and benzodiazepine (16 mg/kg midazolam equivalents) exposures are associated with IWS development,361,365 suggesting that liberal thresholds for IWS screening would be prudent. Risks associated with specific opioids are less clear. In one multicenter study of patients receiving opioid and benzodiazepine infusions for >5 days (n=113), patients receiving morphine had less IWS than those receiving fentanyl (OR 0.17) although only 17% of patients studied received morphine.402 In a larger multicenter study (n=1157), no difference in IWS rates between recipients of fentanyl versus morphine was found.400 Limited literature suggests that the risk of opioid or benzodiazepine-related IWS may be decreased with coadministration of dexmedetomidine or long-acting alpha2-agonists although whether this is due to decreased cumulative opioid/benzodiazepine exposure or a direct alpha2-agonist effect is unclear.398 In apparent contrast, a large multicenter RCT reported that use of 3 or more classes of analgesics and/or sedatives was significantly and independently associated with an increased risk of IWS development.400 The multicenter RESTORE (spell out) trial is the largest pediatric study to assess non-pharmacologic risk factors for IWS among critically ill infants and children.93 Patient specific factors include age less than 6 years, and especially less than 6 months, which is postulated to be due to immature metabolic pathways and developmental pharmacokinetics. Additional patient-specific factors include baseline cognitive and/or functional impairment.400 Environmental factors verify that abrupt cessation of opioids and benzodiazepines is significantly associated with an increase of IWS.137,387,405 Inconsistent sedation practices within individual units are also associated with an increased risk. Nursing workload was moderately associated with higher risk of IWS; units with more 1:1 patient: staff pairs demonstrated lower cumulative opioid exposure compared to units with fewer 1:1 staffing.400 The authors postulated that this allowed for improved patient assessment and easier implementation of non-pharmacologic comfort interventions which could decrease analgesic and sedative exposure, and lead to earlier recognition of and intervention for IWS.

**Unanswered Question:**

**What are the risk factors for development of IWS to alpha2-agonists?**

**Discussion:** Recent small retrospective and prospective studies report a constellation of cardiovascular and neuropsychiatric symptoms observed in pediatric patients following high dose dexmedetomidine sedation for a greater than 5-day duration.167,247,410 A cumulative dose of 107 mcg/kg (equivalent to roughly 1 mcg/kg/hr infusion for 4 days) was reported in one study to be associated with IWS from dexmedetomidine.166 However, rebound hypertension and tachycardia have also been reported following abrupt cessation of shorter duration alpha2-agonist infusions. Patient- and environment-specific risk factors for alpha2-agonist withdrawal have not been specifically evaluated.

### G2. ALPHA-2 AGONIST IWS

#### G2a. SDC TABLE 22: Summary of Studies Discussing Prevalence and Symptoms of Apha-2 Agonist Withdrawal†

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Design** | **Population** | **Outcome** | **Control** | **Summary implementation-based outcomes** | **Limitations** | **Risk of bias** |
| Bannasch (2018)410 | **RS** | General  PICU  (n=219) | Withdrawal assessment:  WAT-1  Symptoms | N/A | Median infusion duration: 27h  **IWS incidence: 80%**  **Most common symptoms:**  Hypertension: 53%  Tachycardia: 53%  WAT-1 score >3: 38% | WAT-1 not validated for α2-agonists.  Multiple SED in 52%  - unclear if all IWS symptoms were from α2-agonist withdrawal | **H** |
| Haenecour (2017)166 | **RS** | General PICU/CICU  DEX >48h  (n= 52) | Withdrawal assessment:  WAT-1  Symptoms | N/A | Median infusion duration: 124h  **IWS: 35%**  **Most common symptoms:**  Agitation: 100%  Fever: 68%  Vomiting: 45.8%  Jitteriness: 33.3%  Diaphoresis: 33.3%  Abnormal movements: 33.3%  Decreased sleep: 29.2%  Median WAT-1: 4  Association with cumulative dose >107 **mcg**/kg | 54% received enteral clonidine to transition off DEX  No inclusion of hypertension or tachycardia as possible symptoms  Common additional use of opioids (100%) and benzos (72%) | **H** |
| Whalen (2014)167 | **RS** | General PICU/CICU DEX >72h (n=87) | Withdrawal assessment:  OBWS  Symptoms | N/A | Median infusion duration: 141h  **IWS: 30%**  **Most common symptoms:**  Agitation: 65%  Decreased sleep: 54%  Tremors: 38%  Secretions: 27%  Diarrhea: 19%  Emesis: 12%  Median OBWS: 11 | OBWS not validated for α2-agonist  Most received opioids and/or benzos  No report of hypertension, tachycardia | **M** |
| Burbano (2013)409 | **RS** | Postop cardiac  (n=62) | Withdrawal assessment:  Symptoms | N/A | Median infusion duration: 5-6 d  IWS incidence: not overtly reported  **Most common symptoms:**  Tachycardia: 27%  Transient hypertension: 35%  Agitation: 27% | Relatively small sample size  Did not report other potential symptoms | **M** |
| Carney (2013)411 | **RS** | General PICU/CICU  DEX >24h (n=60) | Withdrawal assessment:  WAT-1  Symptoms | N/A | Median infusion duration: 20.5h  **IWS: 83% (1 symptom), 50% (≥ 2 symptoms)**  **Most common symptoms:**  Agitation: 62%  Hypertension: 33%  Emesis: 24%  Diarrhea: 24%  Anxiety: 11%  WAT-1 >3 in only 2% | WAT-1 not validated for α2-agonists  Reviewer-estimated WAT-1 if missing in chart  Other sedatives in 78% while assessing IWS | **M/H** |
| Gupta (2012)247 | **RS** | CICU  Age: <18 yo DEX >96h | Safety, withdrawal symptoms  (n=52) | No DEX (n=42) | **Possible IWS symptoms:**  Rebound hypertension (12%)  Rebound tachycardia (8%)  31% received clonidine to transition off DEX | No validated IWS score  No IWS scoring in controls  No data on symptoms in patients with shorter duration infusions | **H** |

**†Abbreviations:** (**BENZO**) benzodiazepine, (**CICU**) cardiac intensive care unit, (**d**) day(s), (**DEX**) dexmedetomidine, (**H**) high, (**h**) hour(s), (**IWS**) iatrogenic withdrawal syndrome, (**kg**) kilogram, (**L**) low, (**M**) moderate, (**mcg**) microgram(s), (**NAS**) neonatal abstinence syndrome, (**OBSW**) Opioid and Benzodiazepine Withdrawal Score, (**PICU**) pediatric intensive care unit, (**postop**) postoperative, (**PPD**) pretest posttest design, (**RS**) retrospective, (**SED**) sedation, (**WAT-1**) withdrawal assessment tool

### G3. IWS Prevention and Management

#### G3b. SDC TABLE 23: Summary of Studies Discussing Sedation Weaning Protocols†

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Design** | **Population** | **Intervention** | **Control** | **Summary implementation-based outcomes** | **Limitations** | **Risk of bias** |
| Solodiuk (2019)416 | **PPD** | SED >5 d  On MV  4 PICUs | Risk-stratified opioid and benzo PROT wean  (n=233) | Non-PROT wean  (n=219) | Discharged on taper: 11 vs 7% (p=0.03)  Hospital LOS: 39 vs 42 d (p=0.35)  Moderate IWS: 21 vs 11% (p=0.002)  Severe IWS: 1 vs 0.6% (p=0.11) | Collected data for 5 years  Only 2 quarters of data presented | **H** |
| Vipond (2018)415 | **PPD** | MED/SURG PICU | Pharmacist-driven methadone and lorazepam taper (n=17) | Non-PROT taper (n=24) | Reduced taper time  Methadone: 6 vs 9.5 d (p=0.01)  Lorazepam: 6 vs 13 d (p=0.0006)  No difference in breakthrough doses for IWS, PICU LOS, or hospital LOS | Younger age in control group  Small sample size and even smaller groups with risk stratification | **H** |
| Sanchez-Pinto (2018)413 | **PPD** | MED/SURG PICU | Opioid PROT wean  IWS assessment  (n=39) | Non-PROT wean  (n=68) | Faster opioid wean: 21 vs 18 d (p=0.01)  Shorter post-extubation time: 7 vs 11 d (p=0.02)  No difference in IWS: 2.6 vs 4% (p=0.29) | No SED PROT.  Primarily opioid-based.  No SED wean PROT.  Lack of risk-stratified data. | **H** |
| Amirnovin (2018)414 | **PPD** | CICU | Opioid and benzo PROT wean  IWS assessment  (n=55) | Non-PROT wean  (n=64) | Similar exposure to opioids/benzos prior to wean  Faster opioid wean: 12 vs 23 d (p<0.001)  Faster benzo wean: 2 vs 15 d (p<0.001)  Shorter hospital LOS: 34 vs 42 d (p<0.01)   IWS: 4.9 vs 14.1% (p<0.01) | Pre-wean without PROT SED | **M** |
| Abdouni  (2016)412 | **PPD** | General PICU | Opioid PROT wean  IWS assessment  (n=134) | Non-PROT wean  (n=42) | More rapid opioid wean: 9.5 vs 15.3 d (p=0.0002)   cumulative FENT dose: 1 vs 2.8 mg/kg (p=0.017)  rescue FENT: 5.5 vs 1.8 doses (p=0.0001) | Geared to opioids alone.  No data on IWS prevalence.  Only 2/3 compliance with all aspects of the protocol | **M** |
| Jin  (2007)102 | **PPD** | MED/SURG PICU  On MV >48h | MD-Pharmacist Protocolized SED Use of SED target (n=26) | Non-PROT SED (n=27) |  SED days: 8.0 vs 11.5 (p=0.05)  Reduced IWS: 4.8 vs 35% (p=0.02) | Could not evaluate relative contributions target vs de-escalation components of the protocol | **H** |

**†Abbreviations:** (**BENZO**) benzodiazepine, (**CICU**) cardiac intensive care unit, (**d**) day(s), (**DEX**) dexmedetomidine, (**FENT**) fentanyl, (**H**) high, (**h**) hour(s), (**IWS**) iatrogenic withdrawal syndrome, (**kg**) kilogram, (**L**) low, (**LOS**) length of stay, (**M**) moderate, (**med/surg**) medical/surgical, (**MV**) mechanical ventilation, (**PICU**) pediatric intensive care unit, (**PPD**) pretest posttest design, (**PROT**) protocol, (**SED**) sedation

#### G3a. UNANSWERED QUESTIONS

**Unanswered Question:**

**Should protocolized analgesic/sedative versus non-protocolized analgesic/sedative weaning be used to reduce the duration of agent tapering and prevent or reduce IWS development in critically ill pediatric patients?**

**Discussion*:***Protocolized sedation has been evaluated primarily using outcome metrics of PICU and hospital LOS, duration of mechanical ventilation, and total drug exposure. However, these study protocols have been insufficiently powered, lack comparable interventions, and do not control the use or weaning of other sedatives. Whereas protocolized sedation typically encompasses titration of agents to meet sedation targets during mechanical ventilation, IWS most often occurs during ventilator weaning or following extubation, when sedatives are being more aggressively weaned. Six studies were found more specifically addressing protocolization of opioid and benzodiazepine weaning (IV and/or enteral agents) and their impact on weaning process duration, cumulative drug exposure, and development of IWS symptoms **(SDC TABLE 23)**. Of studies reporting duration of sedative wean, all 5 reported more rapid weaning with protocolization.102,412-415 More importantly, the same studies also reported a decrease in102,414 or no difference in413,415 IWS development. A single study found no difference in hospital or PICU LOS or IWS rates with protocolized versus non-protocolized weaning although more protocolized patients were totally weaned off sedatives prior to hospital discharge.416 Despite being small studies, the consistency of results showing benefits with none showing negative or possibly harmful results, support this strategy.

**Unanswered Question:**

**Does use of an “analgesia with sedative” compared to “single-class” sedation strategy decrease IWS development and associated outcomes in critically ill pediatric patients?**

**Discussion*:*** To date, data regarding the impact of type of sedative and/or analgesic regimen on the development of IWS and/or associated outcomes in critically ill pediatric patients remains limited and insufficient upon which to base a recommendation. Since concomitant use of opioids and benzodiazepines is widespread, the equipoise necessary to rigorously study use of analgesics or sedatives alone versus in combination may be difficult to achieve. In a secondary analysis of a large multicenter RCT of protocolized versus usual sedation practices, patients who received combination therapy with 3 classes of agents (opioid, benzodiazepine and alpha2-agonist) were at greatest risk for IWS development.400361 Other strategies to prevent the development of IWS have been proposed, including cycling of analgesics or benzodiazepines, intermittent versus continuous drug delivery, daily sedative interruptions, and adjunct use of regional analgesia although few data formally studying these techniques exist. Two small retrospective reviews of ketamine addition to sedation rotation regimens describe modest decreases in opioid and benzodiazepine exposure but did not specifically comment on the impact on IWS development.417,418 A single RCT was found evaluating the incidence of IWS before and after the implementation of a drug rotation protocol which included both cycling between opioids and cycling between sedative classes (midazolam, dexmedetomidine, and propofol) at 4-day intervals. While compliance with the protocol was low at only 35%, rates of IWS were much lower in patients where the rotation was adhered to.419 Use of intermittent drug dosing appears to decrease opioid and benzodiazepine exposure but the impact on IWS has not been specifically studied.

**Unanswered Question:**

**Are alpha2-agonists effective in preventing or treating symptoms in critically ill pediatric patients with opioid and/or benzodiazepine-related IWS?**

**Discussion:**Available data discussing the role of alpha2-agonists for mitigation or management of IWS from opioids or benzodiazepines are largely limited to case reports and small retrospective studies which are further confounded by variable sedation regimens, inconsistent IWS screening, and non-protocolized alpha2-agonist administration.146,392,398,420 In 10 patients receiving opioid and benzodiazepine sedation following laryngotracheal reconstruction, no IWS was described with placement of a transdermal clonidine patch prior to discontinuation of sedation infusions.420 In a small prospective RCT of children sedated with opioid/benzodiazepines alone or with low dose dexmedetomidine following congenital cardiac surgery, withdrawal scores were reduced with dexmedetomidine addition although the short duration of MV limits conclusions from these data.236

**Unanswered Question:**

**In patients with IWS from prolonged alpha2-agonist sedation, what is the optimal replacement strategy for reducing development of or treating alpha2-agonist** **related IWS?**

**Discussion*:***As alpha2-agonist use continues to increase in pediatric critical care, associated IWS has become more clinically relevant. However, studies evaluating the optimal weaning strategies and/or the benefits of conversion from IV to enteral or transdermal agents have not been rigorously performed. A retrospective study found that weaning of dexmedetomidine was more common than conversion to enteral clonidine but that presumptive withdrawal symptoms (tachycardia, hypertension) still developed in almost half of the cohort.410 Others have reported that symptoms, specifically tachycardia and hypertension, are reduced with adjunct use of enteral clonidine prior to dexmedetomidine infusion discontinuation.421 In a small (n=19) retrospective study in patients receiving prolonged dexmedetomidine, transition off of dexmedetomidine via a clonidine taper versus abrupt discontinuation was associated with a trend to lower WAT-1 scores and significantly lower post-transition heart rates422 although another retrospective study did not find that addition of clonidine reduced withdrawal-associated symptoms.166 Transition from IV agents to transdermal clonidine patches has received some interest and may provide more stable drug administration, particularly in patients unable to tolerate enteral clonidine. However, transdermal use remains challenging due to the prolonged time required to achieve steady state serum levels and a lack of evaluated and accepted protocols.146,422 Additional challenges in defining best practices regarding prevention and management of alpha2-agonist IWS include the lack of a formal definition for alpha2-agonist IWS and lack of a validated IWS screening tool.

## H. OPTIMIZING THE ICU ENVIRONMENT

### H1. FAMILY PRESENCE

#### H1a. UNANSWERED QUESTIONS

**Unanswered Question:**

**Should a parent or caregiver be present during interventional procedures in critically ill infants and children?**

**Discussion:** Despite the increasing emphasis on family centered care in recent years, there remains a dearth of data regarding the full impact of parent/caregiver presence on anxiety and pain during interventional procedures in critically ill infants and children. However, there are promising studies such as the PICU sooth protocol that includes parental comforting performed once daily followed by a quiet time. Despite incomplete occurrence, most parents (70%) and all nurses in the intervention group reported that they felt the intervention had positive patient impact.392 Although specifically targeted at NICU patients, an RCT of kangaroo care compared to controls during blooding sampling from a heel stick reported reductions in heart rate, pain scores, and duration of crying post procedure.423 While concern has been raised that parental or caregiver presence during procedures would increase the stress levels and contribute to increased procedure failures, a description of family presence during tracheal intubation reported no adverse impact on first attempt success, adverse events, or team stress level.424 While not directly patient focused, remaining data regarding caregiver presence during interventional procedures show that presence actually leads to less stress and anxiety and increased satisfaction of care. This remains an area in which additional research is much needed.

### H2. SLEEP HYGIENE AND THE ICU ATMOSPHERE

The impact of sleep disruption on outcomes in PICU patients is of increasing interest. Studies utilizing clinical observational tools such as the Patient Sleep Observation Tool (PSBOT) have demonstrated that PICU admission is associated with decreases in total sleep time, duration of sleep425 and frequent sleep disruptions.426 Polysomnographic (PSG) studies have added that clinical assessments significantly overestimate the amount of time patients are truly asleep427 and that sleep interruptions are frequent.428,429 These disruptions are associated with decreases in time spent in Stage 3 and 4 sleep, the stages associated with restoration and healing.430,431 In fact, PICU patients only spend 4-20% of total sleep time in restorative stages, compared to 40-50% in healthy children.428,429,432 Use of sedative and analgesic medications also affect sleep quality with opioid and/or benzodiazepine infusions being associated with primarily stages 1 and 2 sleep.429,432,433

Ambient noise is ubiquitous within the ICU environment, with sources including monitor and equipment alarms, expressions of patient discomfort, and conversations between ICU caregivers and parents. While the World Health Organization has recommended that hospital noise levels not exceed 30 dB during the daytime with peak levels not exceeding 40 dB, measured mean daytime noise levels in PICUs range from 55-79 dB.434 Nighttime decreases are only minimal but levels still exceed recommendations. Much of this evidence involves melatonin, which regulates circadian rhythm and sleep in addition to immune function.435-437 Critically ill children show abnormal melatonin levels and disruption of the normal melatonin secretion pattern.438,439 This merits further study. Potential interventions to improve sleep in the PICU include efforts to reduce ambient noise, decrease nighttime lighting, or bundling care assessments and treatments to decrease interruptions. Medications, in particular melatonin, are increasingly utilized to promote sleep. Additional research should also evaluate the impact of environmental interventions and of commonly used pharmacological sleep aids.

#### H2a. UNANSWERED QUESTIONS

**Unanswered Question:**

**Do environmental interventions to improve day-night cycling positively impact sleep hygiene in critically ill pediatric patients?**

**Discussion*:*** In the adult ICU setting, cycled lighting (manipulating light to resemble natural patterns) compared with non-controlled lighting was qualitatively reported as pleasing, and possibly beneficial for day-night orientation and sleep facilitation.440 In a mixed study incorporating scheduled periods of reduced ambient lighting and noise in neuro-intensive care patients, “quiet time” implementation was feasible and patients were more likely to appear asleep compared to non-quiet times.441 A single study evaluating cycled lighting on circadian rhythm development and sleep behaviors found no impact.442 None of these studies reported the use of sedating medications during study intervention. Four adult ICU trials found in utilizing a combination of eye masks and ear plugs443-445 with one also adding “sleep conducive music” prior to mask/plug placement at night,446 improved perception of sleep in all of the intervention groups and decreased night awakenings in two studies. To date, no published data have evaluated the impact of a cycled lighting intervention in a pediatric critical care setting.

### H3. EARLY MOBILITY

#### H3a. UNANSWERED QUESTIONS

**Unanswered Question:**

**Is early mobility safe and feasible in critically ill pediatric patients?**

**Discussion:** Two pilot RCTs have examined feasibility and safety of EM in critically ill children. The use of in-bed cycling or standard physiotherapy has been evaluated in 30 PICU patients aged 3-17 years of age.447 Sixty-five percent of the in-bed cycling arm were mechanically ventilated and had a median time to EM of 1.5 days and no increased adverse events were reported. Implementation of an EM protocol vs usual care (consultation to rehabilitation per team discretion) was associated with a significant increase in physical therapy consults and more patient mobility sessions than in the usual care arm with no reported adverse events.448 Prospective cohort studies examining the impact of an EM protocol have also demonstrated feasibility and safety of EM for critically ill children.449-452 Interventions included passive and active mobilization activities and unique modalities such as in-bed cycling and virtual reality exercises. Safety and tolerance criteria for interrupting or discontinuing mobilization therapy included cardiorespiratory instability or significant vital sign changes, increases in intracranial pressure, and agitation or discomfort. Adverse events were primarily defined as unplanned extubations, hemodynamic instability, device disconnections or dislodgements, falls, and patient discomfort. EM has also been shown to be safe and feasible in a variety of pediatric critically ill populations, including medical, cardiac, neurologic, and post-surgical.453,454 Three systematic reviews have been published describing current EM evidence including safety and feasibility of EM protocols in critically ill children under 18 years of age.455-457

**Unanswered Question:**

**What factors promote success of EM among critically ill pediatric patients?**

**Discussion:** Bundled strategies such as the ABCDEF bundle introduced by the SCCM ICU Liberation initiative to shorten duration of MV and reduce the adverse effects of excessive sedation, prolonged immobilization, sleep disturbance and delirium have demonstrated significant positive impact on adult ICU clinical outcomes.458 Although pediatric data is limited, quality improvement data demonstrate the interconnectedness of these care strategies such that optimizing mobility requires modifying other aspects of care such as preventing over-sedation and delirium to promote EM readiness, and engaging family members in patient mobility activities.327,450,459 Recent consensus clinical practice guidelines for EM in critically ill children support this bundled care approach to promote the effectiveness of EM strategies and improve clinical outcomes.431

Multidisciplinary personnel resources (e.g. rehabilitation services) and equipment (e.g. cycle ergometers) to operationalize EM of critically ill children has been shown to be a primary limitation.447,459-461 Although physical therapists serve an important role in the functional recovery of PICU patients, many of the mobilization activities can be implemented by nurses, respiratory therapists, and family members. Several of the aforementioned quality improvement EM programs were able to effectively train ICU personnel to safely mobilize critically ill children despite limited rehabilitation resources.327,462,463 Preliminary single center pediatric EM interventional studies suggest that the use of standardized guidelines or protocols, the support of interdisciplinary team education, and resources increase the proportion of patients who receive EM, time to mobilization and frequency of mobilizations. As significant variation in EM pediatric practices exist, much research is needed to determine optimal timing, duration, frequency, and mobilization techniques for various pediatric critical care populations, chronological and developmental ages and cognitive and functional abilities, as well as strategies to overcome perceived barriers.

## I. Search Strategy: Appendix 1

*Downloaded sets are indicated with highlighting*

Pain – Monitoring and Management

2019 Dec 30

| Search | Query | Items found |
| --- | --- | --- |
| [#96](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #94 AND #95 | [165](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=96) |
| [#95](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search "2012"[Date - Publication] : "2020"[Date - Publication] | [8858461](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=95) |
| [#94](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #82 AND #93 | [230](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=94) |
| [#93](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search systematic review[pt] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy\*[tw] OR metanaly\*[tw] OR metaanaly\*[tw] OR met analy\*[tw] OR integrative research[tw] OR integrative review\*[tw] OR integrative overview\*[tiab] OR research integration\*[tw] OR research overview\*[tw] OR collaborative review\*[tw] OR collaborative overview\*[tw] OR systematic review\*[tw] OR systematic overview\*[tw] OR evidence-based review\*[tw] OR evidence-based overview\*[tw] OR meta-review\*[tw] OR meta-overview\*[tw] OR meta-synthes\*[tw] OR rapid review\*[tw] OR "review of reviews"[tw] OR "Technology Assessment, Biomedical"[mh] OR technology assessment\*[tw] OR HTA[tw] OR HTAs[tw] OR "Cochrane Database Syst Rev"[Journal:\_\_jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] OR Network MA[tw] OR Network MAs[tw] OR indirect comparison\*[tw] OR indirect treatment comparison\*[tw] OR indirect treatments comparison[tw] OR multiple treatment comparison\*[tw] OR multiple treatments comparison\*[tw] OR mixed treatment comparison\*[tw] OR mixed treatments comparison[tw] OR multi-treatment comparison\*[tw] OR multi-treatments comparison\*[tw] OR simultaneous comparison\*[tw] OR mixed comparison\*[tw] | [309561](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=93) |
| [#92](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #91 NOT (#86 OR #88) | [761](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=92) |
| [#91](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #84 AND #90 | [1040](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=91) |
| [#90](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Cohort Studies[mh] OR cohort[tw] OR cohorts[tw] OR Retrospective Studies[mh] OR longitudinal[tw] OR prospective[tw] OR retrospective[tw] OR follow-up study[tw] OR followup study[tw] OR Observational Study[pt] OR observational study[tw] OR population study[tw] OR population analys\*[tw] OR population-based study[tw] OR population-based analys\*[tw] OR multidimensional study[tw] OR multi-dimensional study[tw] OR Comparative Study[pt] OR comparative study[tw] OR comparison study[tw] OR Case-Control Studies[mh] OR case-control study[tw] OR case-controlled study[tw] OR case-based comparison\*[tw] OR case-comparison study[tw] OR Cross-Sectional Studies[mesh] OR cross-sectional study[tw] OR crosssectional study[tw] | [4572519](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=90) |
| [#89](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #88 NOT #86 | [69](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=89) |
| [#88](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #84 AND #87 | [445](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=88) |
| [#87](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Controlled Clinical Trial[mh] OR Controlled Clinical Trials as Topic[mh] OR controlled trial\*[tw] OR controlled clinical trial\*[tw] OR Non-Randomized Controlled Trials as Topic[mh] OR nonrandom\*[tw] OR non-random\*[tw] OR quasi-random\*[tw] OR quasi-experiment\*[tw] OR nRCT[tw] OR non-RCT[tw] OR Controlled Before-After Studies[mh] OR (control\*[tw] AND (“before and after”[tw] OR “before after”[tw])) OR Interrupted Time Series Analysis[mh] OR time series[tw] OR (pretest[tw] AND posttest[tw]) OR (pre-test[tw] AND post-test[tw]) OR Historically Controlled Study[mh] OR control study[tw] OR controlled study[tw] OR Control Groups[mh] OR control group\*[tw] OR controlled groups[tw] | [1371264](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=87) |
| [#86](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #84 AND #85 | [455](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=86) |
| [#85](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Controlled Clinical Trial[pt] OR Randomized Controlled Trial[pt] OR Pragmatic Clinical Trial[pt] OR Equivalence Trial[pt] OR Randomized Controlled Trials as Topic[mh] OR Clinical Trials as Topic [mesh:noexp] OR randomised[tw] OR randomized[tw] OR randomisation\*[tw] OR randomization\*[tw] OR randomly[tw] OR RCT[tw] OR placebo\*[tw] OR ((singl\*[tw] OR doubl\*[tw] OR trebl\*[tw] OR tripl\*[tw]) AND (mask\*[tw] OR blind\*[tw] OR dumm\*[tw])) or trial[ti] | [1397438](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=85) |
| [#84](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #82 AND #83 | [2135](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=84) |
| [#83](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search ("2015"[Date - Publication] : "2020"[Date - Publication]) | [5879967](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=83) |
| [#82](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search (#80 NOT #81) | [8462](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=82) |
| [#81](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search (editorial[pt] OR news[pt] OR newspaper article[pt]) | [725933](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=81) |
| [#80](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search (#78 NOT #79) | [8535](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=80) |
| [#79](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search (Animals[mesh] NOT Humans[mesh]) | [4653747](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=79) |
| [#78](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #45 AND #77 | [8678](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=78) |
| [#77](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 | [1181059](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=77) |
| [#76](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search "Cold Temperature/therapeutic use"[MeSH Terms] | [4721](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=76) |
| [#75](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search "Hot Temperature/therapeutic use"[MeSH Terms] | [10199](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=75) |
| [#74](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search acupunctur\*[tw] OR pharmacopuncture\*[tw] OR pharmaco-puncture\*[tw] OR acupressure\*[tw] OR magnet[tw] OR magnets[tw] OR electric nerve stimulation\*[tw] OR electrical nerve stimulation\*[tw] OR electroanalgesia\*[tw] OR electro-analgesia\*[tw] OR electrical neuromodulat\*[tw] OR electrical neuro-modulat\*[tw] OR transdermal electrostimulation\*[tw] OR trans-dermal electrostimulation\*[tw] OR transcutaneous nerve stimulation\*[tw] OR TENS[tw] OR moxibustion[tw] | [64932](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=74) |
| [#73](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Acupuncture[mesh] | [24414](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=73) |
| [#72](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search music therapy[tw] OR musical therapy[tw] OR music therapies[tw] OR musical therapies[tw] OR music therapeutic\*[tw] OR musical therapeutic\*[tw] | [4222](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=72) |
| [#71](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Music Therapy[mesh] | [3413](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=71) |
| [#70](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search (anaesthe\*[tw] OR anesthe\*[tw]) AND (conduction[tw] OR regional\*[tw] OR caudal[tw] OR epidural\*[tw] OR extradural\*[tw] OR peridural\*[tw] OR spinal\*[tw] OR supraspinal\*[tw] OR supra-spinal\*[tw] OR neuraxial\*[tw] OR neur-axial\*[tw]) | [80825](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=70) |
| [#69](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Anesthesia, Conduction[mesh] | [63877](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=69) |
| [#68](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search ketorolac[tw] OR acular[tw] OR toradol[tw] | [3092](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=68) |
| [#67](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Ketorolac[mesh] | [1438](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=67) |
| [#66](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search tramadol[tw] OR adolonta[tw] OR amadol[tw] OR biodalgic[tw] OR biokanol[tw] OR contramal[tw] OR jutadol[tw] OR "k-315"[tw] OR nobligan[tw] OR prontofort[tw] OR takadol[tw] OR theradol[tw] OR tiral[tw] OR topalgic[tw] OR tradol[tw] OR tradonal[tw] OR tralgiol[tw] OR tramabeta[tw] OR tramadin[tw] OR tramadoc[tw] OR tramadolor[tw] OR tramadura[tw] OR tramagetic[tw] OR tramagit[tw] OR tramake[tw] OR tramal[tw] OR tramex[tw] OR tramundin[tw] OR trasedal[tw] OR ultram[tw] OR xymel[tw] OR zamudol[tw] OR zumalgic[tw] OR zydol[tw] OR zytram[tw] | [5308](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=66) |
| [#65](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Tramadol[mesh] | [3032](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=65) |
| [#64](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search hydromorphone[tw] OR dihydromorphinone[tw] OR di-hydromorphinone[tw] OR dilaudid[tw] OR hydromorphon[tw] OR laudacon[tw] OR palladone[tw] | [2124](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=64) |
| [#63](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search hydromorphone[mesh] | [1263](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=63) |
| [#62](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search remifentanil[tw] OR "GI 87084B"[tw] OR GI87084B[tw] OR Ultiva[tw] | [5083](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=62) |
| [#61](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Remifentanil [mesh] | [3256](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=61) |
| [#60](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search morphine[tw] OR duramorph[tw] OR "MS Contin"[tw] OR morphia[tw] OR oramorph[tw] OR "SDZ 202-250"[tw] OR "SDZ202-250"[tw] | [57678](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=60) |
| [#59](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Morphine[mesh] | [37764](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=59) |
| [#58](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search fentanyl[tw] OR duragesic[tw] OR durogesic[tw] OR fentanest[tw] OR fentora[tw] OR phentanyl[tw] OR "R-4263"[tw] OR Sublimaze[tw] | [22182](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=58) |
| [#57](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Fentanyl[mesh] | [15513](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=57) |
| [#56](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search nonopioid\*[tw] OR non-opioid\*[tw] | [3828](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=56) |
| [#55](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search opioid[tw] OR opioids[tw] | [114885](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=55) |
| [#54](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search "COMFORT-B" or Hartwig[tw] OR Cardiac Analgesia Assessment Scale[tw] OR CAAS[tw] OR Visual Analogue Scale[tw] OR Visual Analog Scale[tw] OR Numeric Rating Scale[tw] OR Oucher[tw] OR Wong-Baker Faces[tw] | [52234](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=54) |
| [#53](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search "Faces Legs Activity Cry Consolability"[tw] OR FLACC[tw] | [280](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=53) |
| [#52](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search analgosedat\*[tw] or analgo-sedat\*[tw] | [349](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=52) |
| [#51](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search pain[tw] OR pains[tw] OR painful\*[tw] | [722582](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=51) |
| [#50](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Pain[mesh] | [385530](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=50) |
| [#49](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search anodyne[tw] OR anodynes[tw] OR antinociceptive\*[tw] OR anti-nociceptive\*[tw] | [13362](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=49) |
| [#48](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search analgesi\*[tw] | [187027](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=48) |
| [#47](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Analgesics[mesh] | [186830](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=47) |
| [#46](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Pain Management[mesh] | [32249](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=46) |
| [#45](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #37 AND #44 | [123486](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=45) |
| [#44](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #38 OR #39 OR #40 OR #41 OR #42 OR #43 | [4207003](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=44) |
| [#43](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search newborn\*[tw] OR neonat\*[tw] OR premie[tw] OR premies[tw] OR VLBW[tw] OR SGA[tw] | [832913](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=43) |
| [#42](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search pediatric\*[tw] OR paediatric\*[tw] | [386994](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=42) |
| [#41](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Pediatric Emergency Medicine[mesh] | [223](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=41) |
| [#40](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Pediatrics[mesh] | [56725](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=40) |
| [#39](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search infant[tw] OR infants[tw] OR infanc\*[tw] OR baby[tw] OR babies[tw] OR child\*[tw] OR toddler\*[tw] OR preschool\*[tw] OR pre-school\*[tw] OR school-age[tw] OR school-aged[tw] OR adolescen\*[tw] OR teen[tw] OR teens[tw] OR teenager\*[tw] OR youth[tw] OR youths[tw] OR highschool\*[tw] OR high-school\*[tw] | [3967380](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=39) |
| [#38](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Infant[mesh] OR Child[mesh] OR Adolescent[mesh] | [3481479](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=38) |
| [#37](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #17 OR #36 | [408342](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=37) |
| [#36](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 | [198381](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=36) |
| [#35](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search IPPB[tw] | [286](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=35) |
| [#34](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search APRV[tw] | [165](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=34) |
| [#33](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search airway pressure release[tw] AND ventilat\*[tw] | [269](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=33) |
| [#32](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search controlled ventilat\*[tw] | [2330](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=32) |
| [#31](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search high-frequency ventilat\*[tw] | [2552](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=31) |
| [#30](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search artificial airway[tw] OR artificial airways[tw] | [440](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=30) |
| [#29](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search intubat\*[tw] OR extubat\*[tw] OR detubat\*[tw] | [89948](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=29) |
| [#28](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Intubation, Intratracheal[mesh] | [38010](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=28) |
| [#27](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Airway Extubation[mesh] | [1374](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=27) |
| [#26](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search ventilat\*[tw] AND (wean\*[tw] OR liberat\*[tw]) | [7924](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=26) |
| [#25](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search endotrachea\*[tw] AND (tube[tw] OR tubes[tw] OR tubat\*[tw] OR ventilat\*[tw]) | [13339](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=25) |
| [#24](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search tracheotom\*[tw] OR tracheostom\*[tw] | [25320](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=24) |
| [#23](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Tracheostomy[mesh] | [7185](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=23) |
| [#22](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search invasive ventilat\*[tw] | [3213](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=22) |
| [#21](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search high-frequency ventilation[tw] | [2526](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=21) |
| [#20](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search artificial respiration[tw] OR artificial ventilation\*[tw] OR mechanical respiration[tw] OR mechanical ventilation\*[tw] | [73567](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=20) |
| [#19](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Ventilators, Mechanical[mesh] | [8946](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=19) |
| [#18](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Respiration, Artificial[mesh] | [74795](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=18) |
| [#17](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 | [251692](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=17) |
| [#16](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search specialized weaning unit[tw] OR specialized weaning units[tw] OR specialized weaning centre\*[tw] OR specialized weaning center\*[tw] | [23](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=16) |
| [#15](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search specialised weaning unit[tw] OR specialised weaning units[tw] OR specialised weaning centre\*[tw] OR specialised weaning center\*[tw] | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=15) |
| [#14](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search HDU[tw] OR HDUs[tw] OR SDU[tw] OR SDUs[tw] OR EDSDU[tw] OR EDSDU[tw] | [515](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=14) |
| [#13](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search high dependency unit[tw] OR high dependency units[tw] OR high dependency centre\*[tw] OR high dependency center\*[tw] | [650](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=13) |
| [#12](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search critically ill[tw] OR critical illness\*[tw] | [56284](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=12) |
| [#11](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Critical Illness[mesh] | [27391](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=11) |
| [#10](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search respiratory unit[tw] OR respiratory units[tw] OR respiratory centre\*[tw] OR respiratory center\*[tw] | [3468](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=10) |
| [#9](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search burn unit[tw] OR burn units[tw] OR burn centre\*[tw] OR burn center\*[tw] | [4856](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=9) |
| [#8](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search ICU[tw] OR ICUs[tw] OR PICU[tw] OR PICUs[tw] OR SICU[tw] OR SICUs[tw] OR CCU[tw] OR CCUs[tw] | [61261](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=8) |
| [#7](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search critical care [tw] OR intensive care[tw] | [203396](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=7) |
| [#6](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Critical Care [mesh] | [56086](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=6) |
| [#5](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Intensive Care Units, Pediatric [mesh:noexp] | [7336](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=5) |
| [#4](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Respiratory Care Units [mesh] | [589](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=4) |
| [#3](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Coronary Care Units [mesh] | [4321](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=3) |
| [#2](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Burn Units [mesh] | [2502](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=2) |
| [#1](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Intensive Care Units [mesh:noexp] | [52243](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=1) |

Neuromuscular Blockade

2020 Jan 9

| Search | Add to builder | Query | Items found | Time |
| --- | --- | --- | --- | --- |
| [#74](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | #68 AND #73 | 276 | 08:01:44 |
| [#73](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search "2015"[Date - Publication] : "2020"[Date - Publication] | 5910244 | 08:01:35 |
| [#72](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #70 AND #71 | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=69) | 07:57:38 |
| [#71](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search "2012"[Date - Publication] : "2020"[Date - Publication] | [8888767](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=68) | 07:57:26 |
| [#70](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #68 AND #69 | [28](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=67) | 07:57:14 |
| [#69](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search systematic review[pt] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy\*[tw] OR metanaly\*[tw] OR metaanaly\*[tw] OR met analy\*[tw] OR integrative research[tw] OR integrative review\*[tw] OR integrative overview\*[tiab] OR research integration\*[tw] OR research overview\*[tw] OR collaborative review\*[tw] OR collaborative overview\*[tw] OR systematic review\*[tw] OR systematic overview\*[tw] OR evidence-based review\*[tw] OR evidence-based overview\*[tw] OR meta-review\*[tw] OR meta-overview\*[tw] OR meta-synthes\*[tw] OR rapid review\*[tw] OR "review of reviews"[tw] OR "Technology Assessment, Biomedical"[mh] OR technology assessment\*[tw] OR HTA[tw] OR HTAs[tw] OR "Cochrane Database Syst Rev"[Journal:\_\_jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] OR Network MA[tw] OR Network MAs[tw] OR indirect comparison\*[tw] OR indirect treatment comparison\*[tw] OR indirect treatments comparison[tw] OR multiple treatment comparison\*[tw] OR multiple treatments comparison\*[tw] OR mixed treatment comparison\*[tw] OR mixed treatments comparison[tw] OR multi-treatment comparison\*[tw] OR multi-treatments comparison\*[tw] OR simultaneous comparison\*[tw] OR mixed comparison\*[tw] | [310599](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=66) | 07:57:04 |
| [#68](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #66 NOT #67 | [2118](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=65) | 07:56:47 |
| [#67](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search editorial[pt] OR news[pt] OR newspaper article[pt] | [726802](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=64) | 07:56:34 |
| [#66](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #64 NOT #65 | [2129](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=63) | 07:56:16 |
| [#65](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Animals[mesh] NOT Humans[mesh] | [4657481](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=62) | 07:56:05 |
| [#64](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #45 AND #63 | [2149](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=61) | 16:49:16 |
| #63 | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 | 54670 | 16:48:42 |
| #62 | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search paralytic[tw] OR paralytics[tw] | 7176 | 16:48:31 |
| #61 | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search depolarizing[tw] or depolarising[tw] | 17287 | 16:47:55 |
| [#60](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search non-depolarizing[tw] or non-depolarising[tw] or nondepolarizing[tw] or nondepolarising[tw] | 5943 | 16:43:17 |
| [#59](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search NMBD[tw] OR NMBDs[tw] | [73](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=59) | 07:54:49 |
| [#58](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search skelet\*[tw] AND (muscle\*[tw] OR muscular\*[tw]) AND relax\*[tw] | [5841](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=58) | 07:49:17 |
| [#57](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search succinylcholine[tw] OR anectine[tw] OR celocurine[tw] OR dicholine succinate[tw] OR ditilin[tw] OR listenon[tw] OR lysthenon[tw] OR myorelaxin[tw] OR quelicin[tw] OR succicuran[tw] OR succinyldicholine[tw] OR suxamethonium[tw] | [8380](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=57) | 07:48:27 |
| [#56](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Succinylcholine[mesh] | [6377](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=56) | 07:44:04 |
| [#55](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search atracurium[tw] OR "33 A 74"[tw] OR "BW-33A"[tw] OR relatrac[tw] OR tracrium[tw] | [2611](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=55) | 07:43:11 |
| [#54](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Atracurium[mesh] | [1863](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=54) | 07:41:59 |
| [#53](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search cisatracurium[tw] OR 51W89[tw] OR nimbex[tw] | [729](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=53) | 07:41:05 |
| [#52](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Cisatracurium[Supplementary Concept] | [378](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=52) | 07:40:02 |
| [#51](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search rocuronium[tw] OR esmeron[tw] OR esmerone[tw] OR "ORG 9426"[tw] OR zemuron[tw] | [2906](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=51) | 07:39:13 |
| [#50](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Rocuronium[mesh] | [1790](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=50) | 07:38:03 |
| [#49](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search NMB[tw] OR NMBs[tw] OR NMBA[tw] OR NMBAs[tw] | [1544](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=49) | 07:37:35 |
| [#48](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (neuro-muscular[tw] OR neuromuscular\*[tw]) AND block\*[tw] | [16048](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=48) | 07:37:29 |
| [#47](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Neuromuscular Blocking Agents[mesh] | [10178](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=47) | 07:32:21 |
| [#46](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Neuromuscular Blockade[mesh] | [2238](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=46) | 07:31:11 |
| [#45](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #37 AND #44 | [123709](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=45) | 07:30:56 |
| [#44](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #38 OR #39 OR #40 OR #41 OR #42 OR #43 | [4211478](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=44) | 07:30:50 |
| [#43](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search newborn\*[tw] OR neonat\*[tw] OR premie[tw] OR premies[tw] OR VLBW[tw] OR SGA[tw] | [833724](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=43) | 07:30:36 |
| [#42](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search pediatric\*[tw] OR paediatric\*[tw] | [387705](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=42) | 07:30:28 |
| [#41](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatric Emergency Medicine[mesh] | [226](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=41) | 07:30:18 |
| [#40](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatrics[mesh] | [56781](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=40) | 07:30:08 |
| [#39](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search infant[tw] OR infants[tw] OR infanc\*[tw] OR baby[tw] OR babies[tw] OR child\*[tw] OR toddler\*[tw] OR preschool\*[tw] OR pre-school\*[tw] OR school-age[tw] OR school-aged[tw] OR adolescen\*[tw] OR teen[tw] OR teens[tw] OR teenager\*[tw] OR youth[tw] OR youths[tw] OR highschool\*[tw] OR high-school\*[tw] | [3971608](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=39) | 07:30:02 |
| [#38](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Infant[mesh] OR Child[mesh] OR Adolescent[mesh] | [3485246](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=38) | 07:29:54 |
| [#37](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #17 OR #36 | [408974](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=37) | 07:29:44 |
| [#36](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 | [198619](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=36) | 07:29:37 |
| [#35](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search IPPB[tw] | [286](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=35) | 07:29:31 |
| [#34](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search APRV[tw] | [167](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=34) | 07:29:18 |
| [#33](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search airway pressure release[tw] AND ventilat\*[tw] | [271](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=33) | 07:29:10 |
| [#32](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search controlled ventilat\*[tw] | [2331](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=32) | 07:29:04 |
| [#31](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilat\*[tw] | [2555](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=31) | 07:28:57 |
| [#30](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial airway[tw] OR artificial airways[tw] | [441](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=30) | 07:28:49 |
| [#29](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search intubat\*[tw] OR extubat\*[tw] OR detubat\*[tw] | [90056](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=29) | 07:28:41 |
| [#28](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intubation, Intratracheal[mesh] | [38051](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=28) | 07:28:33 |
| [#27](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Airway Extubation[mesh] | [1383](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=27) | 07:28:26 |
| [#26](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search ventilat\*[tw] AND (wean\*[tw] OR liberat\*[tw]) | [7935](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=26) | 07:28:17 |
| [#25](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search endotrachea\*[tw] AND (tube[tw] OR tubes[tw] OR tubat\*[tw] OR ventilat\*[tw]) | [13352](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=25) | 07:28:10 |
| [#24](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search tracheotom\*[tw] OR tracheostom\*[tw] | [25345](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=24) | 07:28:00 |
| [#23](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Tracheostomy[mesh] | [7194](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=23) | 07:27:54 |
| [#22](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search invasive ventilat\*[tw] | [3223](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=22) | 07:27:48 |
| [#21](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilation[tw] | [2529](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=21) | 07:27:40 |
| [#20](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial respiration[tw] OR artificial ventilation\*[tw] OR mechanical respiration[tw] OR mechanical ventilation\*[tw] | [73658](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=20) | 07:27:31 |
| [#19](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Ventilators, Mechanical[mesh] | [8950](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=19) | 07:27:24 |
| [#18](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiration, Artificial[mesh] | [74883](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=18) | 07:27:16 |
| [#17](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 | [252157](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=17) | 07:27:10 |
| [#16](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialized weaning unit[tw] OR specialized weaning units[tw] OR specialized weaning centre\*[tw] OR specialized weaning center\*[tw] | [23](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=16) | 07:27:04 |
| [#15](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialised weaning unit[tw] OR specialised weaning units[tw] OR specialised weaning centre\*[tw] OR specialised weaning center\*[tw] | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=15) | 07:26:56 |
| [#14](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search HDU[tw] OR HDUs[tw] OR SDU[tw] OR SDUs[tw] OR EDSDU[tw] OR EDSDU[tw] | [517](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=14) | 07:26:46 |
| [#13](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search high dependency unit[tw] OR high dependency units[tw] OR high dependency centre\*[tw] OR high dependency center\*[tw] | [652](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=13) | 07:26:32 |
| [#12](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search critically ill[tw] OR critical illness\*[tw] | [56416](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=12) | 07:26:25 |
| [#11](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Illness[mesh] | [27460](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=11) | 07:26:17 |
| [#10](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search respiratory unit[tw] OR respiratory units[tw] OR respiratory centre\*[tw] OR respiratory center\*[tw] | [3470](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=10) | 07:26:10 |
| [#9](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search burn unit[tw] OR burn units[tw] OR burn centre\*[tw] OR burn center\*[tw] | [4862](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=9) | 07:26:03 |
| [#8](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search ICU[tw] OR ICUs[tw] OR PICU[tw] OR PICUs[tw] OR SICU[tw] OR SICUs[tw] OR CCU[tw] OR CCUs[tw] | [61427](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=8) | 07:25:54 |
| [#7](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search critical care [tw] OR intensive care[tw] | [203773](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=7) | 07:25:47 |
| [#6](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Care [mesh] | [56157](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=6) | 07:25:40 |
| [#5](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units, Pediatric [mesh:noexp] | [7349](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=5) | 07:25:34 |
| [#4](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiratory Care Units [mesh] | [589](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=4) | 07:25:26 |
| [#3](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Coronary Care Units [mesh] | [4321](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=3) | 07:25:18 |
| [#2](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Burn Units [mesh] | [2505](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=2) | 07:25:11 |
| [#1](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units [mesh:noexp] | [52339](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=1) | 07:25:04 |

Drug Tolerance/Iatrogenic Withdrawal Syndrome

2020 Jan 12

| Search | Add to builder | Query | Items found | Time |
| --- | --- | --- | --- | --- |
| [#81](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #75 AND #80 | [335](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=81) | 12:17:59 |
| [#80](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search ("2015"[Date - Publication] : "2020"[Date - Publication]) | [5921982](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=80) | 12:17:35 |
| [#79](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #77 AND #78 | [27](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=79) | 12:16:09 |
| [#78](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search "2012"[Date - Publication] : "2020"[Date - Publication] | [8900516](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=78) | 12:16:00 |
| [#77](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #75 AND #76 | [45](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=77) | 12:15:53 |
| [#76](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search systematic review[pt] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy\*[tw] OR metanaly\*[tw] OR metaanaly\*[tw] OR met analy\*[tw] OR integrative research[tw] OR integrative review\*[tw] OR integrative overview\*[tiab] OR research integration\*[tw] OR research overview\*[tw] OR collaborative review\*[tw] OR collaborative overview\*[tw] OR systematic review\*[tw] OR systematic overview\*[tw] OR evidence-based review\*[tw] OR evidence-based overview\*[tw] OR meta-review\*[tw] OR meta-overview\*[tw] OR meta-synthes\*[tw] OR rapid review\*[tw] OR "review of reviews"[tw] OR "Technology Assessment, Biomedical"[mh] OR technology assessment\*[tw] OR HTA[tw] OR HTAs[tw] OR "Cochrane Database Syst Rev"[Journal:\_\_jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] OR Network MA[tw] OR Network MAs[tw] OR indirect comparison\*[tw] OR indirect treatment comparison\*[tw] OR indirect treatments comparison[tw] OR multiple treatment comparison\*[tw] OR multiple treatments comparison\*[tw] OR mixed treatment comparison\*[tw] OR mixed treatments comparison[tw] OR multi-treatment comparison\*[tw] OR multi-treatments comparison\*[tw] OR simultaneous comparison\*[tw] OR mixed comparison\*[tw] | [310964](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=76) | 12:15:41 |
| [#75](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #73 NOT #74 | [1333](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=75) | 12:15:33 |
| [#74](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (editorial[pt] OR news[pt] OR newspaper article[pt]) | [727186](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=74) | 12:15:23 |
| [#73](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #71 NOT #72 | [1350](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=73) | 12:15:11 |
| [#72](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Animals[mesh] NOT Humans[mesh] | [4658273](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=72) | 12:14:53 |
| [#71](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #45 AND #70 | [1389](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=71) | 12:14:44 |
| [#70](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 | [92455](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=70) | 12:14:18 |
| [#69](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search drug tolerance\*[tw] | [21660](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=69) | 12:14:04 |
| [#68](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (tolerat\*[tw] OR toleranc\*[tw]) AND (Adrenergic alpha-2 Receptor Agonists[mesh] OR alpha-2 agonist\*[tw] OR Clonidine[mesh] OR catapres[tw] OR catapresan[tw] OR catapressan[tw] OR chlophazolin[tw] OR clofelin[tw] OR clofenil[tw] OR clonidine dihydrochloride[tw] OR clonidine hydrochloride[tw] OR clonidine monohydrobromide[tw] OR clonidine monohydrochloride[tw] OR clopheline[tw] OR dixarit[tw] OR gemiton[tw] OR hemiton[tw] OR isoglaucon[tw] OR klofelin[tw] OR klofenil[tw] OR m-5041t[tw] OR st-155[tw] OR Dexmedetomidine[mesh] OR dexmedetomidine[tw] OR "mpv-1440"[tw] OR precedex[tw]) | [698](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=68) | 12:12:30 |
| [#67](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (tolerat\*[tw] OR toleranc\*[tw]) AND (Benzodiazepines[mesh] OR benzodiazepine\*[tw] OR Diazepam[mesh] OR diazepam\*[tw] OR alboral[tw] OR aliseum[tw] OR amiprol[tw] OR "an-ding"[tw] OR ansilive[tw] OR ansiolin[tw] OR ansiolisina[tw] OR antenex[tw] OR anxicalm[tw] OR anxionil[tw] OR apaurin[tw] OR apo-diazepam[tw] OR apozepam[tw] OR armonil[tw] OR arzepam[tw] OR assival[tw] OR atensine[tw] OR atilen[tw] OR azedipamin[tw] OR baogin[tw] OR bensedin[tw] OR benzopin[tw] OR betapam[tw] OR bialzepam[tw] OR britazepam[tw] OR "BRN 0754371"[tw] OR calmaven[tw] OR calmocitene[tw] OR calmociteno[tw] OR calmod[tw] OR calmpose[tw] OR caudel[tw] OR "CB 4261"[tw] OR centrazepam[tw] OR cercine[tw] OR ceregulart[tw] OR chuansuan[tw] OR Midazolam[[mesh] OR midazolam[tw] OR dormicum[tw] OR "Ro 21-3981"[tw] OR versed[tw] OR Lorazepam[mesh] OR Lorazepam\*[tw] OR almazine[tw] OR anxiedin[tw] OR anxira[tw] OR anzepam[tw] OR aplacasse[tw] OR aplacassee[tw] OR apo-lorazepam[tw] OR aripax[tw] OR ativan[tw] OR azurogen[tw] OR bonatranquan[tw] OR bonton[tw] OR "BRN 0759084" [tw] OR delormetazepam[tw] OR demethyllormetazepam[tw] OR donix[tw] OR duralozam[tw] OR efasedan[tw] OR "EINECS 212-687-6"[tw] OR emotival[tw] OR equitam[tw] OR idalprem[tw] OR kalmalin[tw]) | [1035](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=67) | 12:12:08 |
| [#66](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (tolerat\*[tw] OR toleranc\*[tw]) AND ("Hypnotics and Sedatives"[mesh] OR sedat\*[tw]) | [4465](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=66) | 12:11:48 |
| [#65](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (tolerat\*[tw] OR toleranc\*[tw]) AND (Analgesics, Opioid[mesh] OR opioid[tw] OR opioids[tw] OR Morphine[mesh] OR morphine[tw] OR duramorph[tw] OR "MS Contin"[tw] OR morphia[tw] OR oramorph[tw] OR "SDZ 202-250"[tw] OR "SDZ202-250"[tw] OR Hydromorphone[mesh] OR hydromorphone[tw] OR dihydromorphinone[tw] OR di-hydromorphinone[tw] OR dilaudid[tw] OR hydromorphon[tw] OR laudacon[tw] OR palladone[tw] OR Fentanyl[mesh] OR fentanyl[tw] OR duragesic[tw] OR durogesic[tw] OR fentanest[tw] OR fentora[tw] OR phentanyl[tw] OR "R-4263"[tw] OR Sublimaze[tw] OR Sufentanil[mesh] OR sufentanil[tw] OR sufenta[tw] OR sulfentanyl[tw] OR "R-30730"[tw] OR Remifentanil [mesh] OR remifentanil[tw] OR "GI 87084B"[tw] OR GI87084B[tw] OR Ultiva[tw]) | [10301](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=65) | 12:11:22 |
| [#64](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (tolerat\*[tw] OR toleranc\*[tw]) AND (Pain Management[mesh] OR Analgesics[mesh] OR analgesi\*[tw] OR anodyne[tw] OR anodynes[tw] OR antinociceptive\*[tw] OR anti-nociceptive\*[tw] OR analgosedat\*[tw] or analgo-sedat\*[tw]) | [13781](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=64) | 12:10:41 |
| [#63](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search iatrogenic\*[tw] AND (tolerat\*[tw] OR toleranc\*[tw]) | [462](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=63) | 12:09:22 |
| [#62](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Iatrogenic Disease[mesh] AND (tolerat\*[tw] OR toleranc\*[tw]) | [567](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=62) | 12:09:00 |
| [#61](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Drug Tolerance[mesh] | [22118](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=61) | 12:07:41 |
| [#60](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (withdraw\*[tw] OR wean\*[tw]) AND (Adrenergic alpha-2 Receptor Agonists[mesh] OR alpha-2 agonist\*[tw] OR Clonidine[mesh] OR catapres[tw] OR catapresan[tw] OR catapressan[tw] OR chlophazolin[tw] OR clofelin[tw] OR clofenil[tw] OR clonidine dihydrochloride[tw] OR clonidine hydrochloride[tw] OR clonidine monohydrobromide[tw] OR clonidine monohydrochloride[tw] OR clopheline[tw] OR dixarit[tw] OR gemiton[tw] OR hemiton[tw] OR isoglaucon[tw] OR klofelin[tw] OR klofenil[tw] OR m-5041t[tw] OR st-155[tw] OR Dexmedetomidine[mesh] OR dexmedetomidine[tw] OR "mpv-1440"[tw] OR precedex[tw]) | [1561](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=60) | 12:06:29 |
| [#59](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (Iatrogenic Disease[mesh] OR iatrogenic\*[tw]) AND (Adrenergic alpha-2 Receptor Agonists[mesh] OR alpha-2 agonist\*[tw] OR Clonidine[mesh] OR catapres[tw] OR catapresan[tw] OR catapressan[tw] OR chlophazolin[tw] OR clofelin[tw] OR clofenil[tw] OR clonidine dihydrochloride[tw] OR clonidine hydrochloride[tw] OR clonidine monohydrobromide[tw] OR clonidine monohydrochloride[tw] OR clopheline[tw] OR dixarit[tw] OR gemiton[tw] OR hemiton[tw] OR isoglaucon[tw] OR klofelin[tw] OR klofenil[tw] OR m-5041t[tw] OR st-155[tw] OR Dexmedetomidine[mesh] OR dexmedetomidine[tw] OR "mpv-1440"[tw] OR precedex[tw]) | [24](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=59) | 12:06:13 |
| [#58](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (withdraw\*[tw] OR wean\*[tw]) AND (Benzodiazepines[mesh] OR benzodiazepine\*[tw] OR Diazepam[mesh] OR diazepam\*[tw] OR alboral[tw] OR aliseum[tw] OR amiprol[tw] OR "an-ding"[tw] OR ansilive[tw] OR ansiolin[tw] OR ansiolisina[tw] OR antenex[tw] OR anxicalm[tw] OR anxionil[tw] OR apaurin[tw] OR apo-diazepam[tw] OR apozepam[tw] OR armonil[tw] OR arzepam[tw] OR assival[tw] OR atensine[tw] OR atilen[tw] OR azedipamin[tw] OR baogin[tw] OR bensedin[tw] OR benzopin[tw] OR betapam[tw] OR bialzepam[tw] OR britazepam[tw] OR "BRN 0754371"[tw] OR calmaven[tw] OR calmocitene[tw] OR calmociteno[tw] OR calmod[tw] OR calmpose[tw] OR caudel[tw] OR "CB 4261"[tw] OR centrazepam[tw] OR cercine[tw] OR ceregulart[tw] OR chuansuan[tw] OR Midazolam[[mesh] OR midazolam[tw] OR dormicum[tw] OR "Ro 21-3981"[tw] OR versed[tw] OR Lorazepam[mesh] OR Lorazepam\*[tw] OR almazine[tw] OR anxiedin[tw] OR anxira[tw] OR anzepam[tw] OR aplacasse[tw] OR aplacassee[tw] OR apo-lorazepam[tw] OR aripax[tw] OR ativan[tw] OR azurogen[tw] OR bonatranquan[tw] OR bonton[tw] OR "BRN 0759084" [tw] OR delormetazepam[tw] OR demethyllormetazepam[tw] OR donix[tw] OR duralozam[tw] OR efasedan[tw] OR "EINECS 212-687-6"[tw] OR emotival[tw] OR equitam[tw] OR idalprem[tw] OR kalmalin[tw]) | [1022](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=58) | 12:06:06 |
| [#57](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (Iatrogenic Disease[mesh] OR iatrogenic\*[tw]) AND (Benzodiazepines[mesh] OR benzodiazepine\*[tw] OR Diazepam[mesh] OR diazepam\*[tw] OR alboral[tw] OR aliseum[tw] OR amiprol[tw] OR "an-ding"[tw] OR ansilive[tw] OR ansiolin[tw] OR ansiolisina[tw] OR antenex[tw] OR anxicalm[tw] OR anxionil[tw] OR apaurin[tw] OR apo-diazepam[tw] OR apozepam[tw] OR armonil[tw] OR arzepam[tw] OR assival[tw] OR atensine[tw] OR atilen[tw] OR azedipamin[tw] OR baogin[tw] OR bensedin[tw] OR benzopin[tw] OR betapam[tw] OR bialzepam[tw] OR britazepam[tw] OR "BRN 0754371"[tw] OR calmaven[tw] OR calmocitene[tw] OR calmociteno[tw] OR calmod[tw] OR calmpose[tw] OR caudel[tw] OR "CB 4261"[tw] OR centrazepam[tw] OR cercine[tw] OR ceregulart[tw] OR chuansuan[tw] OR Midazolam[[mesh] OR midazolam[tw] OR dormicum[tw] OR "Ro 21-3981"[tw] OR versed[tw] OR Lorazepam[mesh] OR Lorazepam\*[tw] OR almazine[tw] OR anxiedin[tw] OR anxira[tw] OR anzepam[tw] OR aplacasse[tw] OR aplacassee[tw] OR apo-lorazepam[tw] OR aripax[tw] OR ativan[tw] OR azurogen[tw] OR bonatranquan[tw] OR bonton[tw] OR "BRN 0759084" [tw] OR delormetazepam[tw] OR demethyllormetazepam[tw] OR donix[tw] OR duralozam[tw] OR efasedan[tw] OR "EINECS 212-687-6"[tw] OR emotival[tw] OR equitam[tw] OR idalprem[tw] OR kalmalin[tw]) | [73](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=57) | 12:05:36 |
| [#56](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (withdraw\*[tw] OR wean\*[tw]) AND ("Hypnotics and Sedatives"[mesh] OR sedat\*[tw]) | [3808](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=56) | 12:05:08 |
| [#55](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (Iatrogenic Disease[mesh] OR iatrogenic\*[tw]) AND ("Hypnotics and Sedatives"[mesh] OR sedat\*[tw]) | [446](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=55) | 12:05:03 |
| [#54](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (withdraw\*[tw] OR wean\*[tw]) AND (Analgesics, Opioid[mesh] OR opioid[tw] OR opioids[tw] OR Morphine[mesh] OR morphine[tw] OR duramorph[tw] OR "MS Contin"[tw] OR morphia[tw] OR oramorph[tw] OR "SDZ 202-250"[tw] OR "SDZ202-250"[tw] OR Hydromorphone[mesh] OR hydromorphone[tw] OR dihydromorphinone[tw] OR di-hydromorphinone[tw] OR dilaudid[tw] OR hydromorphon[tw] OR laudacon[tw] OR palladone[tw] OR Fentanyl[mesh] OR fentanyl[tw] OR duragesic[tw] OR durogesic[tw] OR fentanest[tw] OR fentora[tw] OR phentanyl[tw] OR "R-4263"[tw] OR Sublimaze[tw] OR Sufentanil[mesh] OR sufentanil[tw] OR sufenta[tw] OR sulfentanyl[tw] OR "R-30730"[tw] OR Remifentanil [mesh] OR remifentanil[tw] OR "GI 87084B"[tw] OR GI87084B[tw] OR Ultiva[tw]) | [11067](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=54) | 12:04:57 |
| [#53](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (Iatrogenic Disease[mesh] OR iatrogenic\*[tw]) AND (Analgesics, Opioid[mesh] OR opioid[tw] OR opioids[tw] OR Morphine[mesh] OR morphine[tw] OR duramorph[tw] OR "MS Contin"[tw] OR morphia[tw] OR oramorph[tw] OR "SDZ 202-250"[tw] OR "SDZ202-250"[tw] OR Hydromorphone[mesh] OR hydromorphone[tw] OR dihydromorphinone[tw] OR di-hydromorphinone[tw] OR dilaudid[tw] OR hydromorphon[tw] OR laudacon[tw] OR palladone[tw] OR Fentanyl[mesh] OR fentanyl[tw] OR duragesic[tw] OR durogesic[tw] OR fentanest[tw] OR fentora[tw] OR phentanyl[tw] OR "R-4263"[tw] OR Sublimaze[tw] OR Sufentanil[mesh] OR sufentanil[tw] OR sufenta[tw] OR sulfentanyl[tw] OR "R-30730"[tw] OR Remifentanil [mesh] OR remifentanil[tw] OR "GI 87084B"[tw] OR GI87084B[tw] OR Ultiva[tw]) | [361](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=53) | 12:04:49 |
| [#52](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (withdraw\*[tw] OR wean\*[tw]) AND (Pain Management[mesh] OR Analgesics[mesh] OR analgesi\*[tw] OR anodyne[tw] OR anodynes[tw] OR antinociceptive\*[tw] OR anti-nociceptive\*[tw] OR analgosedat\*[tw] or analgo-sedat\*[tw]) | [10018](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=52) | 12:04:40 |
| [#51](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (Iatrogenic Disease[mesh] OR iatrogenic\*[tw]) AND (Pain Management[mesh] OR Analgesics[mesh] OR analgesi\*[tw] OR anodyne[tw] OR anodynes[tw] OR antinociceptive\*[tw] OR anti-nociceptive\*[tw] OR analgosedat\*[tw] or analgo-sedat\*[tw]) | [759](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=51) | 12:04:33 |
| [#50](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search (drug[tw] OR drugs[tw] OR substance\*[tw]) AND (withdraw\*[tw] OR wean\*[tw]) AND (syndrome\*[tw] OR disease\*[tw]) | [44018](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=50) | 12:04:27 |
| [#49](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search withdrawal syndrome\*[tw] | [22800](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=49) | 12:04:19 |
| [#48](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search iatrogenic\*[tw] AND (withdraw\*[tw] OR wean\*[tw]) | [522](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=48) | 12:04:13 |
| [#47](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Iatrogenic Disease[mesh] AND (withdraw\*[tw] OR wean\*[tw]) | [461](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=47) | 12:04:07 |
| [#46](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Substance Withdrawal Syndrome[mesh] | [22884](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=46) | 12:03:37 |
| [#45](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #37 AND #44 | [123765](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=45) | 12:03:30 |
| [#44](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #38 OR #39 OR #40 OR #41 OR #42 OR #43 | [4212921](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=44) | 12:03:20 |
| [#43](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search newborn\*[tw] OR neonat\*[tw] OR premie[tw] OR premies[tw] OR VLBW[tw] OR SGA[tw] | [833964](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=43) | 12:03:12 |
| [#42](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search pediatric\*[tw] OR paediatric\*[tw] | [387975](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=42) | 12:03:05 |
| [#41](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatric Emergency Medicine[mesh] | [226](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=41) | 12:03:00 |
| [#40](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatrics[mesh] | [56790](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=40) | 12:02:54 |
| [#39](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search infant[tw] OR infants[tw] OR infanc\*[tw] OR baby[tw] OR babies[tw] OR child\*[tw] OR toddler\*[tw] OR preschool\*[tw] OR pre-school\*[tw] OR school-age[tw] OR school-aged[tw] OR adolescen\*[tw] OR teen[tw] OR teens[tw] OR teenager\*[tw] OR youth[tw] OR youths[tw] OR highschool\*[tw] OR high-school\*[tw] | [3972931](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=39) | 12:02:46 |
| [#38](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Infant[mesh] OR Child[mesh] OR Adolescent[mesh] | [3486033](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=38) | 12:02:34 |
| [#37](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #17 OR #36 | [409177](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=37) | 12:02:27 |
| [#36](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 | [198703](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=36) | 12:02:22 |
| [#35](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search IPPB[tw] | [286](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=35) | 12:02:14 |
| [#34](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search APRV[tw] | [167](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=34) | 12:02:09 |
| [#33](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search airway pressure release[tw] AND ventilat\*[tw] | [271](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=33) | 12:02:04 |
| [#32](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search controlled ventilat\*[tw] | [2332](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=32) | 12:01:58 |
| [#31](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilat\*[tw] | [2555](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=31) | 12:01:52 |
| [#30](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial airway[tw] OR artificial airways[tw] | [441](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=30) | 12:01:46 |
| [#29](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search intubat\*[tw] OR extubat\*[tw] OR detubat\*[tw] | [90099](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=29) | 12:01:38 |
| [#28](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intubation, Intratracheal[mesh] | [38056](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=28) | 12:01:29 |
| [#27](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Airway Extubation[mesh] | [1385](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=27) | 12:01:21 |
| [#26](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search ventilat\*[tw] AND (wean\*[tw] OR liberat\*[tw]) | [7938](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=26) | 12:01:15 |
| [#25](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search endotrachea\*[tw] AND (tube[tw] OR tubes[tw] OR tubat\*[tw] OR ventilat\*[tw]) | [13362](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=25) | 12:01:09 |
| [#24](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search tracheotom\*[tw] OR tracheostom\*[tw] | [25352](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=24) | 12:01:04 |
| [#23](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Tracheostomy[mesh] | [7200](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=23) | 12:00:57 |
| [#22](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search invasive ventilat\*[tw] | [3223](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=22) | 12:00:51 |
| [#21](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilation[tw] | [2529](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=21) | 12:00:47 |
| [#20](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial respiration[tw] OR artificial ventilation\*[tw] OR mechanical respiration[tw] OR mechanical ventilation\*[tw] | [73695](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=20) | 12:00:42 |
| [#19](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Ventilators, Mechanical[mesh] | [8951](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=19) | 12:00:36 |
| [#18](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiration, Artificial[mesh] | [74906](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=18) | 12:00:30 |
| [#17](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 | [252304](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=17) | 12:00:25 |
| [#16](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialized weaning unit[tw] OR specialized weaning units[tw] OR specialized weaning centre\*[tw] OR specialized weaning center\*[tw] | [23](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=16) | 12:00:19 |
| [#15](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialised weaning unit[tw] OR specialised weaning units[tw] OR specialised weaning centre\*[tw] OR specialised weaning center\*[tw] | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=15) | 12:00:13 |
| [#14](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search HDU[tw] OR HDUs[tw] OR SDU[tw] OR SDUs[tw] OR EDSDU[tw] OR EDSDU[tw] | [517](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=14) | 12:00:05 |
| [#13](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search high dependency unit[tw] OR high dependency units[tw] OR high dependency centre\*[tw] OR high dependency center\*[tw] | [653](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=13) | 11:59:57 |
| [#12](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search critically ill[tw] OR critical illness\*[tw] | [56456](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=12) | 11:59:52 |
| [#11](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Illness[mesh] | [27476](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=11) | 11:59:46 |
| [#10](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search respiratory unit[tw] OR respiratory units[tw] OR respiratory centre\*[tw] OR respiratory center\*[tw] | [3471](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=10) | 11:59:39 |
| [#9](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search burn unit[tw] OR burn units[tw] OR burn centre\*[tw] OR burn center\*[tw] | [4863](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=9) | 11:59:34 |
| [#8](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search ICU[tw] OR ICUs[tw] OR PICU[tw] OR PICUs[tw] OR SICU[tw] OR SICUs[tw] OR CCU[tw] OR CCUs[tw] | [61488](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=8) | 11:59:23 |
| [#7](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search critical care [tw] OR intensive care[tw] | [203888](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=7) | 11:59:03 |
| [#6](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Care [mesh] | [56187](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=6) | 11:58:57 |
| [#5](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units, Pediatric [mesh:noexp] | [7353](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=5) | 11:58:50 |
| [#4](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiratory Care Units [mesh] | [589](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=4) | 11:58:43 |
| [#3](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Coronary Care Units [mesh] | [4323](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=3) | 11:58:37 |
| [#2](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Burn Units [mesh] | [2505](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=2) | 11:58:32 |
| [#1](https://www.ncbi.nlm.nih.gov/pubmed) | [Add](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units [mesh:noexp] | [52363](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=1) | 11:58:26 |

Early Mobilization

2020 Jan 13

| Search | Query | Items found |
| --- | --- | --- |
| [#66](https://www.ncbi.nlm.nih.gov/pubmed) | Search #60 AND #65 | [213](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=66) |
| [#65](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search "2015"[Date - Publication] : "2020"[Date - Publication] | [5922034](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=65) |
| [#64](https://www.ncbi.nlm.nih.gov/pubmed) | Search #62 AND #63 | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=64) |
| [#63](https://www.ncbi.nlm.nih.gov/pubmed) | Search "2012"[Date - Publication] : "2020"[Date - Publication] | [8900568](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=63) |
| [#62](https://www.ncbi.nlm.nih.gov/pubmed) | Search #60 AND #61 | [18](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=62) |
| [#61](https://www.ncbi.nlm.nih.gov/pubmed) | Search systematic review[pt] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy\*[tw] OR metanaly\*[tw] OR metaanaly\*[tw] OR met analy\*[tw] OR integrative research[tw] OR integrative review\*[tw] OR integrative overview\*[tiab] OR research integration\*[tw] OR research overview\*[tw] OR collaborative review\*[tw] OR collaborative overview\*[tw] OR systematic review\*[tw] OR systematic overview\*[tw] OR evidence-based review\*[tw] OR evidence-based overview\*[tw] OR meta-review\*[tw] OR meta-overview\*[tw] OR meta-synthes\*[tw] OR rapid review\*[tw] OR "review of reviews"[tw] OR "Technology Assessment, Biomedical"[mh] OR technology assessment\*[tw] OR HTA[tw] OR HTAs[tw] OR "Cochrane Database Syst Rev"[Journal:\_\_jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] OR Network MA[tw] OR Network MAs[tw] OR indirect comparison\*[tw] OR indirect treatment comparison\*[tw] OR indirect treatments comparison[tw] OR multiple treatment comparison\*[tw] OR multiple treatments comparison\*[tw] OR mixed treatment comparison\*[tw] OR mixed treatments comparison[tw] OR multi-treatment comparison\*[tw] OR multi-treatments comparison\*[tw] OR simultaneous comparison\*[tw] OR mixed comparison\*[tw] | [310964](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=61) |
| [#60](https://www.ncbi.nlm.nih.gov/pubmed) | Search #58 NOT #59 | [720](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=60) |
| [#59](https://www.ncbi.nlm.nih.gov/pubmed) | Search editorial[pt] OR news[pt] OR newspaper article[pt] | [727185](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=59) |
| [#58](https://www.ncbi.nlm.nih.gov/pubmed) | Search #56 NOT #57 | [724](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=58) |
| [#57](https://www.ncbi.nlm.nih.gov/pubmed) | Search Animals[mesh] NOT Humans[mesh] | [4658273](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=57) |
| [#56](https://www.ncbi.nlm.nih.gov/pubmed) | Search #45 AND #55 | [726](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=56) |
| [#55](https://www.ncbi.nlm.nih.gov/pubmed) | Search #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 | [97478](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=55) |
| [#54](https://www.ncbi.nlm.nih.gov/pubmed) | Search walk\*[tw] AND (early\*[tw] OR earlier[tw] or earliest[tw] OR accelerat\*[tw] OR expeditious\*[tw] OR delay\*[tw] OR immediate\*[tw] OR prompt\*[tw] OR quick\*[tw] OR soon[tw] OR sooner[tw] OR timely[tw]) | [19844](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=54) |
| [#53](https://www.ncbi.nlm.nih.gov/pubmed) | Search (exercise rehabilitat\*[tw] OR exercise therap\*[tw] OR physical therap\*[tw] OR physiotherap\*[tw] OR physio-therap\*[tw] OR remedial exercis\*[tw]) AND (early\*[tw] OR earlier[tw] or earliest[tw] OR accelerat\*[tw] OR expeditious\*[tw] OR delay\*[tw] OR immediate\*[tw] OR prompt\*[tw] OR quick\*[tw] OR soon[tw] OR sooner[tw] OR timely[tw]) | [14809](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=53) |
| [#52](https://www.ncbi.nlm.nih.gov/pubmed) | Search (physical recovery[tw] OR physical rehabilitation[tw] OR physically rehabilitat\*[tw] OR rehabilitate physical\*[tw] OR rehabilitated physical\*[tw] OR rehabilitates physical\*[tw]OR rehabilitating physical\*[tw]) AND (early\*[tw] OR earlier[tw] or earliest[tw] OR accelerat\*[tw] OR expeditious\*[tw] OR delay\*[tw] OR immediate\*[tw] OR prompt\*[tw] OR quick\*[tw] OR soon[tw] OR sooner[tw] OR timely[tw]) | [921](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=52) |
| [#51](https://www.ncbi.nlm.nih.gov/pubmed) | Search (physical recovery[tw] OR physical rehabilitation[tw] OR physically rehabilitat\*[tw] OR rehabilitate physical\*[tw] OR rehabilitated physical\*[tw] OR rehabilitates physical\*[tw]OR rehabilitating physical\*[tw]) AND Time Factors[mesh] | [315](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=54) |
| [#50](https://www.ncbi.nlm.nih.gov/pubmed) | Search ("muscle weakness/rehabilitation"[mesh] OR "muscle weakness/therapy"[mesh]) AND Time Factors[mesh] | [86](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=50) |
| [#49](https://www.ncbi.nlm.nih.gov/pubmed) | Search ("muscular atrophy/rehabilitation"[mesh] OR "muscular atrophy/therapy"[mesh]) AND Time Factors[mesh] | [202](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=49) |
| [#48](https://www.ncbi.nlm.nih.gov/pubmed) | Search Physical Therapy Modalities[mesh] AND Time Factors[mesh] | [9946](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=48) |
| [#47](https://www.ncbi.nlm.nih.gov/pubmed) | Search (early\*[tw] OR earlier[tw] or earliest[tw] OR accelerat\*[tw] OR expeditious\*[tw] OR delay\*[tw] OR immediate\*[tw] OR prompt\*[tw] OR quick\*[tw] OR soon[tw] OR sooner[tw] OR timely[tw]) AND (ambulat\*[tw] OR mobility[tw] OR mobiliz\*[tw] OR mobilis\*[tw]) | [60381](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=47) |
| [#46](https://www.ncbi.nlm.nih.gov/pubmed) | Search Early Ambulation[mesh] | [2799](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=46) |
| [#45](https://www.ncbi.nlm.nih.gov/pubmed) | Search #37 AND #44 | [123765](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=45) |
| [#44](https://www.ncbi.nlm.nih.gov/pubmed) | Search #38 OR #39 OR #40 OR #41 OR #42 OR #43 | [4212931](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=44) |
| [#43](https://www.ncbi.nlm.nih.gov/pubmed) | Search newborn\*[tw] OR neonat\*[tw] OR premie[tw] OR premies[tw] OR VLBW[tw] OR SGA[tw] | [833965](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=43) |
| [#42](https://www.ncbi.nlm.nih.gov/pubmed) | Search pediatric\*[tw] OR paediatric\*[tw] | [387976](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=42) |
| [#41](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatric Emergency Medicine[mesh] | [226](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=41) |
| [#40](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatrics[mesh] | [56790](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=40) |
| [#39](https://www.ncbi.nlm.nih.gov/pubmed) | Search infant[tw] OR infants[tw] OR infanc\*[tw] OR baby[tw] OR babies[tw] OR child\*[tw] OR toddler\*[tw] OR preschool\*[tw] OR pre-school\*[tw] OR school-age[tw] OR school-aged[tw] OR adolescen\*[tw] OR teen[tw] OR teens[tw] OR teenager\*[tw] OR youth[tw] OR youths[tw] OR highschool\*[tw] OR high-school\*[tw] | [3972940](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=39) |
| [#38](https://www.ncbi.nlm.nih.gov/pubmed) | Search Infant[mesh] OR Child[mesh] OR Adolescent[mesh] | [3486033](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=38) |
| [#37](https://www.ncbi.nlm.nih.gov/pubmed) | Search #17 OR #36 | [409179](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=37) |
| [#36](https://www.ncbi.nlm.nih.gov/pubmed) | Search #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 | [198704](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=36) |
| [#35](https://www.ncbi.nlm.nih.gov/pubmed) | Search IPPB[tw] | [286](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=35) |
| [#34](https://www.ncbi.nlm.nih.gov/pubmed) | Search APRV[tw] | [167](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=34) |
| [#33](https://www.ncbi.nlm.nih.gov/pubmed) | Search airway pressure release[tw] AND ventilat\*[tw] | [271](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=33) |
| [#32](https://www.ncbi.nlm.nih.gov/pubmed) | Search controlled ventilat\*[tw] | [2332](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=32) |
| [#31](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilat\*[tw] | [2555](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=31) |
| [#30](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial airway[tw] OR artificial airways[tw] | [441](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=30) |
| [#29](https://www.ncbi.nlm.nih.gov/pubmed) | Search intubat\*[tw] OR extubat\*[tw] OR detubat\*[tw] | [90100](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=29) |
| [#28](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intubation, Intratracheal[mesh] | [38056](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=28) |
| [#27](https://www.ncbi.nlm.nih.gov/pubmed) | Search Airway Extubation[mesh] | [1385](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=27) |
| [#26](https://www.ncbi.nlm.nih.gov/pubmed) | Search ventilat\*[tw] AND (wean\*[tw] OR liberat\*[tw]) | [7938](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=26) |
| [#25](https://www.ncbi.nlm.nih.gov/pubmed) | Search endotrachea\*[tw] AND (tube[tw] OR tubes[tw] OR tubat\*[tw] OR ventilat\*[tw]) | [13362](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=25) |
| [#24](https://www.ncbi.nlm.nih.gov/pubmed) | Search tracheotom\*[tw] OR tracheostom\*[tw] | [25352](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=24) |
| [#23](https://www.ncbi.nlm.nih.gov/pubmed) | Search Tracheostomy[mesh] | [7200](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=23) |
| [#22](https://www.ncbi.nlm.nih.gov/pubmed) | Search invasive ventilat\*[tw] | [3223](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=22) |
| [#21](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilation[tw] | [2529](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=21) |
| [#20](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial respiration[tw] OR artificial ventilation\*[tw] OR mechanical respiration[tw] OR mechanical ventilation\*[tw] | [73695](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=20) |
| [#19](https://www.ncbi.nlm.nih.gov/pubmed) | Search Ventilators, Mechanical[mesh] | [8951](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=19) |
| [#18](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiration, Artificial[mesh] | [74906](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=18) |
| [#17](https://www.ncbi.nlm.nih.gov/pubmed) | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 | [252305](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=17) |
| [#16](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialized weaning unit[tw] OR specialized weaning units[tw] OR specialized weaning centre\*[tw] OR specialized weaning center\*[tw] | [23](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=16) |
| [#15](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialised weaning unit[tw] OR specialised weaning units[tw] OR specialised weaning centre\*[tw] OR specialised weaning center\*[tw] | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=15) |
| [#14](https://www.ncbi.nlm.nih.gov/pubmed) | Search HDU[tw] OR HDUs[tw] OR SDU[tw] OR SDUs[tw] OR EDSDU[tw] OR EDSDU[tw] | [517](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=14) |
| [#13](https://www.ncbi.nlm.nih.gov/pubmed) | Search high dependency unit[tw] OR high dependency units[tw] OR high dependency centre\*[tw] OR high dependency center\*[tw] | [653](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=13) |
| [#12](https://www.ncbi.nlm.nih.gov/pubmed) | Search critically ill[tw] OR critical illness\*[tw] | [56456](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=12) |
| [#11](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Illness[mesh] | [27476](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=11) |
| [#10](https://www.ncbi.nlm.nih.gov/pubmed) | Search respiratory unit[tw] OR respiratory units[tw] OR respiratory centre\*[tw] OR respiratory center\*[tw] | [3471](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=10) |
| [#9](https://www.ncbi.nlm.nih.gov/pubmed) | Search burn unit[tw] OR burn units[tw] OR burn centre\*[tw] OR burn center\*[tw] | [4863](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=9) |
| [#8](https://www.ncbi.nlm.nih.gov/pubmed) | Search ICU[tw] OR ICUs[tw] OR PICU[tw] OR PICUs[tw] OR SICU[tw] OR SICUs[tw] OR CCU[tw] OR CCUs[tw] | [61489](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=8) |
| [#7](https://www.ncbi.nlm.nih.gov/pubmed) | Search critical care [tw] OR intensive care[tw] | [203889](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=7) |
| [#6](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Care [mesh] | [56187](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=6) |
| [#5](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units, Pediatric [mesh:noexp] | [7353](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=5) |
| [#4](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiratory Care Units [mesh] | [589](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=4) |
| [#3](https://www.ncbi.nlm.nih.gov/pubmed) | Search Coronary Care Units [mesh] | [4323](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=3) |
| [#2](https://www.ncbi.nlm.nih.gov/pubmed) | Search Burn Units [mesh] | [2505](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=2) |
| [#1](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units [mesh:noexp] | [52363](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=1) |

Delirium

2020 Jan 13

| Search | Query | Items found |
| --- | --- | --- |
| [#75](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #69 AND #74 | [468](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=75) |
| [#74](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search "2015"[Date - Publication] : "2020"[Date - Publication] | [5922034](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=74) |
| [#73](https://www.ncbi.nlm.nih.gov/pubmed) | Search #71 AND #72 | [34](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=73) |
| [#72](https://www.ncbi.nlm.nih.gov/pubmed) | Search "2012"[Date - Publication] : "2020"[Date - Publication] | [8900568](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=72) |
| [#71](https://www.ncbi.nlm.nih.gov/pubmed) | Search #69 AND #70 | [42](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=71) |
| [#70](https://www.ncbi.nlm.nih.gov/pubmed) | Search systematic review[pt] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy\*[tw] OR metanaly\*[tw] OR metaanaly\*[tw] OR met analy\*[tw] OR integrative research[tw] OR integrative review\*[tw] OR integrative overview\*[tiab] OR research integration\*[tw] OR research overview\*[tw] OR collaborative review\*[tw] OR collaborative overview\*[tw] OR systematic review\*[tw] OR systematic overview\*[tw] OR evidence-based review\*[tw] OR evidence-based overview\*[tw] OR meta-review\*[tw] OR meta-overview\*[tw] OR meta-synthes\*[tw] OR rapid review\*[tw] OR "review of reviews"[tw] OR "Technology Assessment, Biomedical"[mh] OR technology assessment\*[tw] OR HTA[tw] OR HTAs[tw] OR "Cochrane Database Syst Rev"[Journal:\_\_jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] OR Network MA[tw] OR Network MAs[tw] OR indirect comparison\*[tw] OR indirect treatment comparison\*[tw] OR indirect treatments comparison[tw] OR multiple treatment comparison\*[tw] OR multiple treatments comparison\*[tw] OR mixed treatment comparison\*[tw] OR mixed treatments comparison[tw] OR multi-treatment comparison\*[tw] OR multi-treatments comparison\*[tw] OR simultaneous comparison\*[tw] OR mixed comparison\*[tw] | [310964](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=70) |
| [#69](https://www.ncbi.nlm.nih.gov/pubmed) | Search #67 NOT #68 | [1458](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=69) |
| [#68](https://www.ncbi.nlm.nih.gov/pubmed) | Search editorial[pt] OR news[pt] OR newspaper article[pt] | [727185](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=68) |
| [#67](https://www.ncbi.nlm.nih.gov/pubmed) | Search #65 NOT #66 | [1474](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=67) |
| [#66](https://www.ncbi.nlm.nih.gov/pubmed) | Search Animals[mesh] NOT Humans[mesh] | [4658273](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=66) |
| [#65](https://www.ncbi.nlm.nih.gov/pubmed) | Search #45 AND #64 | [1479](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=65) |
| [#64](https://www.ncbi.nlm.nih.gov/pubmed) | Search #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 | [109055](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=64) |
| [#63](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatric Anesthesia Emergence Delirium scale[tw] OR PAED[tw] | [182](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=63) |
| [#62](https://www.ncbi.nlm.nih.gov/pubmed) | Search PreSchool Confusion Assessment Method[tw] OR "psCAM-ICU"[tw] OR "psCAMICU"[tw] OR "ps-CAM-ICU"[tw] OR "ps-CAMICU"[tw] | [5](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=62) |
| [#61](https://www.ncbi.nlm.nih.gov/pubmed) | Search Cornell Assessment for Pediatric Delirium[tw] OR CAPD[tw] | [6621](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=61) |
| [#60](https://www.ncbi.nlm.nih.gov/pubmed) | Search clouded state[tw] OR clouded states[tw] | [104](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=60) |
| [#59](https://www.ncbi.nlm.nih.gov/pubmed) | Search Anesthesia Recovery Period[mesh] AND (brain[tw] OR cogniti\*[tw]) AND (dysfunction\*[tw] OR function\*[tw] OR confus\*[tw]) | [148](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=59) |
| [#58](https://www.ncbi.nlm.nih.gov/pubmed) | Search Anesthesia Recovery Period[mesh] AND (agitat\*[tw] OR distress\*[tw] OR excitation\*[tw] OR excitement[tw] OR tumultuous\*[tw] OR turbulen\*[tw] OR turmoil\*[tw]) | [332](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=58) |
| [#57](https://www.ncbi.nlm.nih.gov/pubmed) | Search (emergent\*[tw] OR emergence[tw] OR postanesthe\*[tw] OR post-anesthe\*[tw] OR postanaesthe\*[tw] OR post-anaesthe\*[tw] or postoperati\*[tw] OR post-operati\*[tw]) AND (brain[tw] OR cogniti\*[tw]) AND (dysfunction\*[tw] OR function\*[tw] or confus\*[tw]) | [14626](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=57) |
| [#56](https://www.ncbi.nlm.nih.gov/pubmed) | Search (emergent\*[tw] OR emergence[tw] OR postanesthe\*[tw] OR post-anesthe\*[tw] OR postanaesthe\*[tw] OR post-anaesthe\*[tw] or postoperati\*[tw] OR post-operati\*[tw]) AND (agitat\*[tw] OR distress\*[tw] OR excitation\*[tw] OR excitement[tw] OR tumultuous\*[tw] OR turbulen\*[tw] OR turmoil\*[tw]) | [9194](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=56) |
| [#55](https://www.ncbi.nlm.nih.gov/pubmed) | Search psychos\*[tw] AND (toxic\*[tw] OR exogenous\*[tw] OR chemical\*[tw] OR drug[tw] OR drugs[tw] OR medication\*[tw] OR substance\*[tw]) | [46138](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=55) |
| [#54](https://www.ncbi.nlm.nih.gov/pubmed) | Search Psychoses, Substance-Induced/ | [7548](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=54) |
| [#53](https://www.ncbi.nlm.nih.gov/pubmed) | Search hallucinat\*[tw] | [18370](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=53) |
| [#52](https://www.ncbi.nlm.nih.gov/pubmed) | Search Hallucinations[mesh] | [10677](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=52) |
| [#51](https://www.ncbi.nlm.nih.gov/pubmed) | Search "confusion/chemically induced"[MeSH Terms] | [1904](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=51) |
| [#50](https://www.ncbi.nlm.nih.gov/pubmed) | Search (psycho-organic syndrome\*[tw] OR psychoorganic syndrome\*[tw] OR organic psychosyndrome\*[tw] OR organic psycho-syndrome\*[tw]) AND acute[tw] | [39](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=50) |
| [#49](https://www.ncbi.nlm.nih.gov/pubmed) | Search cloud\*[tw] AND consciousness\*[tw] | [283](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=49) |
| [#48](https://www.ncbi.nlm.nih.gov/pubmed) | Search acute brain dysfunction\*[tw] OR acute brain failure\*[tw] OR acute brain dysfunction\*[tw] | [119](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=48) |
| [#47](https://www.ncbi.nlm.nih.gov/pubmed) | Search deliri\*[tw] | [17755](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=47) |
| [#46](https://www.ncbi.nlm.nih.gov/pubmed) | Search Delirium[mesh] | [9049](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=46) |
| [#45](https://www.ncbi.nlm.nih.gov/pubmed) | Search #37 AND #44 | [123765](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=45) |
| [#44](https://www.ncbi.nlm.nih.gov/pubmed) | Search #38 OR #39 OR #40 OR #41 OR #42 OR #43 | [4212931](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=44) |
| [#43](https://www.ncbi.nlm.nih.gov/pubmed) | Search newborn\*[tw] OR neonat\*[tw] OR premie[tw] OR premies[tw] OR VLBW[tw] OR SGA[tw] | [833965](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=43) |
| [#42](https://www.ncbi.nlm.nih.gov/pubmed) | Search pediatric\*[tw] OR paediatric\*[tw] | [387976](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=42) |
| [#41](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatric Emergency Medicine[mesh] | [226](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=41) |
| [#40](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatrics[mesh] | [56790](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=40) |
| [#39](https://www.ncbi.nlm.nih.gov/pubmed) | Search infant[tw] OR infants[tw] OR infanc\*[tw] OR baby[tw] OR babies[tw] OR child\*[tw] OR toddler\*[tw] OR preschool\*[tw] OR pre-school\*[tw] OR school-age[tw] OR school-aged[tw] OR adolescen\*[tw] OR teen[tw] OR teens[tw] OR teenager\*[tw] OR youth[tw] OR youths[tw] OR highschool\*[tw] OR high-school\*[tw] | [3972940](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=39) |
| [#38](https://www.ncbi.nlm.nih.gov/pubmed) | Search Infant[mesh] OR Child[mesh] OR Adolescent[mesh] | [3486033](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=38) |
| [#37](https://www.ncbi.nlm.nih.gov/pubmed) | Search #17 OR #36 | [409179](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=37) |
| [#36](https://www.ncbi.nlm.nih.gov/pubmed) | Search #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 | [198704](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=36) |
| [#35](https://www.ncbi.nlm.nih.gov/pubmed) | Search IPPB[tw] | [286](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=35) |
| [#34](https://www.ncbi.nlm.nih.gov/pubmed) | Search APRV[tw] | [167](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=34) |
| [#33](https://www.ncbi.nlm.nih.gov/pubmed) | Search airway pressure release[tw] AND ventilat\*[tw] | [271](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=33) |
| [#32](https://www.ncbi.nlm.nih.gov/pubmed) | Search controlled ventilat\*[tw] | [2332](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=32) |
| [#31](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilat\*[tw] | [2555](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=31) |
| [#30](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial airway[tw] OR artificial airways[tw] | [441](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=30) |
| [#29](https://www.ncbi.nlm.nih.gov/pubmed) | Search intubat\*[tw] OR extubat\*[tw] OR detubat\*[tw] | [90100](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=29) |
| [#28](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intubation, Intratracheal[mesh] | [38056](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=28) |
| [#27](https://www.ncbi.nlm.nih.gov/pubmed) | Search Airway Extubation[mesh] | [1385](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=27) |
| [#26](https://www.ncbi.nlm.nih.gov/pubmed) | Search ventilat\*[tw] AND (wean\*[tw] OR liberat\*[tw]) | [7938](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=26) |
| [#25](https://www.ncbi.nlm.nih.gov/pubmed) | Search endotrachea\*[tw] AND (tube[tw] OR tubes[tw] OR tubat\*[tw] OR ventilat\*[tw]) | [13362](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=25) |
| [#24](https://www.ncbi.nlm.nih.gov/pubmed) | Search tracheotom\*[tw] OR tracheostom\*[tw] | [25352](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=24) |
| [#23](https://www.ncbi.nlm.nih.gov/pubmed) | Search Tracheostomy[mesh] | [7200](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=23) |
| [#22](https://www.ncbi.nlm.nih.gov/pubmed) | Search invasive ventilat\*[tw] | [3223](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=22) |
| [#21](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilation[tw] | [2529](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=21) |
| [#20](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial respiration[tw] OR artificial ventilation\*[tw] OR mechanical respiration[tw] OR mechanical ventilation\*[tw] | [73695](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=20) |
| [#19](https://www.ncbi.nlm.nih.gov/pubmed) | Search Ventilators, Mechanical[mesh] | [8951](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=19) |
| [#18](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiration, Artificial[mesh] | [74906](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=18) |
| [#17](https://www.ncbi.nlm.nih.gov/pubmed) | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 | [252305](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=17) |
| [#16](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialized weaning unit[tw] OR specialized weaning units[tw] OR specialized weaning centre\*[tw] OR specialized weaning center\*[tw] | [23](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=16) |
| [#15](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialised weaning unit[tw] OR specialised weaning units[tw] OR specialised weaning centre\*[tw] OR specialised weaning center\*[tw] | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=15) |
| [#14](https://www.ncbi.nlm.nih.gov/pubmed) | Search HDU[tw] OR HDUs[tw] OR SDU[tw] OR SDUs[tw] OR EDSDU[tw] OR EDSDU[tw] | [517](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=14) |
| [#13](https://www.ncbi.nlm.nih.gov/pubmed) | Search high dependency unit[tw] OR high dependency units[tw] OR high dependency centre\*[tw] OR high dependency center\*[tw] | [653](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=13) |
| [#12](https://www.ncbi.nlm.nih.gov/pubmed) | Search critically ill[tw] OR critical illness\*[tw] | [56456](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=12) |
| [#11](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Illness[mesh] | [27476](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=11) |
| [#10](https://www.ncbi.nlm.nih.gov/pubmed) | Search respiratory unit[tw] OR respiratory units[tw] OR respiratory centre\*[tw] OR respiratory center\*[tw] | [3471](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=10) |
| [#9](https://www.ncbi.nlm.nih.gov/pubmed) | Search burn unit[tw] OR burn units[tw] OR burn centre\*[tw] OR burn center\*[tw] | [4863](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=9) |
| [#8](https://www.ncbi.nlm.nih.gov/pubmed) | Search ICU[tw] OR ICUs[tw] OR PICU[tw] OR PICUs[tw] OR SICU[tw] OR SICUs[tw] OR CCU[tw] OR CCUs[tw] | [61489](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=8) |
| [#7](https://www.ncbi.nlm.nih.gov/pubmed) | Search critical care [tw] OR intensive care[tw] | [203889](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=7) |
| [#6](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Care [mesh] | [56187](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=6) |
| [#5](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units, Pediatric [mesh:noexp] | [7353](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=5) |
| [#4](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiratory Care Units [mesh] | [589](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=4) |
| [#3](https://www.ncbi.nlm.nih.gov/pubmed) | Search Coronary Care Units [mesh] | [4323](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=3) |
| [#2](https://www.ncbi.nlm.nih.gov/pubmed) | Search Burn Units [mesh] | [2505](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=2) |
| [#1](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units [mesh:noexp] | [52363](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=1) |

Early Mobilization

2020 Jan 13

| Search | Query | Items found |
| --- | --- | --- |
| [#66](https://www.ncbi.nlm.nih.gov/pubmed) | Search #60 AND #65 | [213](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=66) |
| [#65](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search "2015"[Date - Publication] : "2020"[Date - Publication] | [5922034](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=65) |
| [#64](https://www.ncbi.nlm.nih.gov/pubmed) | Search #62 AND #63 | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=64) |
| [#63](https://www.ncbi.nlm.nih.gov/pubmed) | Search "2012"[Date - Publication] : "2020"[Date - Publication] | [8900568](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=63) |
| [#62](https://www.ncbi.nlm.nih.gov/pubmed) | Search #60 AND #61 | [18](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=62) |
| [#61](https://www.ncbi.nlm.nih.gov/pubmed) | Search systematic review[pt] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy\*[tw] OR metanaly\*[tw] OR metaanaly\*[tw] OR met analy\*[tw] OR integrative research[tw] OR integrative review\*[tw] OR integrative overview\*[tiab] OR research integration\*[tw] OR research overview\*[tw] OR collaborative review\*[tw] OR collaborative overview\*[tw] OR systematic review\*[tw] OR systematic overview\*[tw] OR evidence-based review\*[tw] OR evidence-based overview\*[tw] OR meta-review\*[tw] OR meta-overview\*[tw] OR meta-synthes\*[tw] OR rapid review\*[tw] OR "review of reviews"[tw] OR "Technology Assessment, Biomedical"[mh] OR technology assessment\*[tw] OR HTA[tw] OR HTAs[tw] OR "Cochrane Database Syst Rev"[Journal:\_\_jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] OR Network MA[tw] OR Network MAs[tw] OR indirect comparison\*[tw] OR indirect treatment comparison\*[tw] OR indirect treatments comparison[tw] OR multiple treatment comparison\*[tw] OR multiple treatments comparison\*[tw] OR mixed treatment comparison\*[tw] OR mixed treatments comparison[tw] OR multi-treatment comparison\*[tw] OR multi-treatments comparison\*[tw] OR simultaneous comparison\*[tw] OR mixed comparison\*[tw] | [310964](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=61) |
| [#60](https://www.ncbi.nlm.nih.gov/pubmed) | Search #58 NOT #59 | [720](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=60) |
| [#59](https://www.ncbi.nlm.nih.gov/pubmed) | Search editorial[pt] OR news[pt] OR newspaper article[pt] | [727185](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=59) |
| [#58](https://www.ncbi.nlm.nih.gov/pubmed) | Search #56 NOT #57 | [724](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=58) |
| [#57](https://www.ncbi.nlm.nih.gov/pubmed) | Search Animals[mesh] NOT Humans[mesh] | [4658273](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=57) |
| [#56](https://www.ncbi.nlm.nih.gov/pubmed) | Search #45 AND #55 | [726](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=56) |
| [#55](https://www.ncbi.nlm.nih.gov/pubmed) | Search #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 | [97478](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=55) |
| [#54](https://www.ncbi.nlm.nih.gov/pubmed) | Search walk\*[tw] AND (early\*[tw] OR earlier[tw] or earliest[tw] OR accelerat\*[tw] OR expeditious\*[tw] OR delay\*[tw] OR immediate\*[tw] OR prompt\*[tw] OR quick\*[tw] OR soon[tw] OR sooner[tw] OR timely[tw]) | [19844](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=54) |
| [#53](https://www.ncbi.nlm.nih.gov/pubmed) | Search (exercise rehabilitat\*[tw] OR exercise therap\*[tw] OR physical therap\*[tw] OR physiotherap\*[tw] OR physio-therap\*[tw] OR remedial exercis\*[tw]) AND (early\*[tw] OR earlier[tw] or earliest[tw] OR accelerat\*[tw] OR expeditious\*[tw] OR delay\*[tw] OR immediate\*[tw] OR prompt\*[tw] OR quick\*[tw] OR soon[tw] OR sooner[tw] OR timely[tw]) | [14809](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=53) |
| [#52](https://www.ncbi.nlm.nih.gov/pubmed) | Search (physical recovery[tw] OR physical rehabilitation[tw] OR physically rehabilitat\*[tw] OR rehabilitate physical\*[tw] OR rehabilitated physical\*[tw] OR rehabilitates physical\*[tw]OR rehabilitating physical\*[tw]) AND (early\*[tw] OR earlier[tw] or earliest[tw] OR accelerat\*[tw] OR expeditious\*[tw] OR delay\*[tw] OR immediate\*[tw] OR prompt\*[tw] OR quick\*[tw] OR soon[tw] OR sooner[tw] OR timely[tw]) | [921](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=52) |
| [#51](https://www.ncbi.nlm.nih.gov/pubmed) | Search (physical recovery[tw] OR physical rehabilitation[tw] OR physically rehabilitat\*[tw] OR rehabilitate physical\*[tw] OR rehabilitated physical\*[tw] OR rehabilitates physical\*[tw]OR rehabilitating physical\*[tw]) AND Time Factors[mesh] | [315](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=54) |
| [#50](https://www.ncbi.nlm.nih.gov/pubmed) | Search ("muscle weakness/rehabilitation"[mesh] OR "muscle weakness/therapy"[mesh]) AND Time Factors[mesh] | [86](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=50) |
| [#49](https://www.ncbi.nlm.nih.gov/pubmed) | Search ("muscular atrophy/rehabilitation"[mesh] OR "muscular atrophy/therapy"[mesh]) AND Time Factors[mesh] | [202](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=49) |
| [#48](https://www.ncbi.nlm.nih.gov/pubmed) | Search Physical Therapy Modalities[mesh] AND Time Factors[mesh] | [9946](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=48) |
| [#47](https://www.ncbi.nlm.nih.gov/pubmed) | Search (early\*[tw] OR earlier[tw] or earliest[tw] OR accelerat\*[tw] OR expeditious\*[tw] OR delay\*[tw] OR immediate\*[tw] OR prompt\*[tw] OR quick\*[tw] OR soon[tw] OR sooner[tw] OR timely[tw]) AND (ambulat\*[tw] OR mobility[tw] OR mobiliz\*[tw] OR mobilis\*[tw]) | [60381](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=47) |
| [#46](https://www.ncbi.nlm.nih.gov/pubmed) | Search Early Ambulation[mesh] | [2799](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=46) |
| [#45](https://www.ncbi.nlm.nih.gov/pubmed) | Search #37 AND #44 | [123765](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=45) |
| [#44](https://www.ncbi.nlm.nih.gov/pubmed) | Search #38 OR #39 OR #40 OR #41 OR #42 OR #43 | [4212931](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=44) |
| [#43](https://www.ncbi.nlm.nih.gov/pubmed) | Search newborn\*[tw] OR neonat\*[tw] OR premie[tw] OR premies[tw] OR VLBW[tw] OR SGA[tw] | [833965](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=43) |
| [#42](https://www.ncbi.nlm.nih.gov/pubmed) | Search pediatric\*[tw] OR paediatric\*[tw] | [387976](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=42) |
| [#41](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatric Emergency Medicine[mesh] | [226](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=41) |
| [#40](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatrics[mesh] | [56790](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=40) |
| [#39](https://www.ncbi.nlm.nih.gov/pubmed) | Search infant[tw] OR infants[tw] OR infanc\*[tw] OR baby[tw] OR babies[tw] OR child\*[tw] OR toddler\*[tw] OR preschool\*[tw] OR pre-school\*[tw] OR school-age[tw] OR school-aged[tw] OR adolescen\*[tw] OR teen[tw] OR teens[tw] OR teenager\*[tw] OR youth[tw] OR youths[tw] OR highschool\*[tw] OR high-school\*[tw] | [3972940](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=39) |
| [#38](https://www.ncbi.nlm.nih.gov/pubmed) | Search Infant[mesh] OR Child[mesh] OR Adolescent[mesh] | [3486033](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=38) |
| [#37](https://www.ncbi.nlm.nih.gov/pubmed) | Search #17 OR #36 | [409179](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=37) |
| [#36](https://www.ncbi.nlm.nih.gov/pubmed) | Search #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 | [198704](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=36) |
| [#35](https://www.ncbi.nlm.nih.gov/pubmed) | Search IPPB[tw] | [286](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=35) |
| [#34](https://www.ncbi.nlm.nih.gov/pubmed) | Search APRV[tw] | [167](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=34) |
| [#33](https://www.ncbi.nlm.nih.gov/pubmed) | Search airway pressure release[tw] AND ventilat\*[tw] | [271](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=33) |
| [#32](https://www.ncbi.nlm.nih.gov/pubmed) | Search controlled ventilat\*[tw] | [2332](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=32) |
| [#31](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilat\*[tw] | [2555](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=31) |
| [#30](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial airway[tw] OR artificial airways[tw] | [441](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=30) |
| [#29](https://www.ncbi.nlm.nih.gov/pubmed) | Search intubat\*[tw] OR extubat\*[tw] OR detubat\*[tw] | [90100](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=29) |
| [#28](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intubation, Intratracheal[mesh] | [38056](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=28) |
| [#27](https://www.ncbi.nlm.nih.gov/pubmed) | Search Airway Extubation[mesh] | [1385](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=27) |
| [#26](https://www.ncbi.nlm.nih.gov/pubmed) | Search ventilat\*[tw] AND (wean\*[tw] OR liberat\*[tw]) | [7938](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=26) |
| [#25](https://www.ncbi.nlm.nih.gov/pubmed) | Search endotrachea\*[tw] AND (tube[tw] OR tubes[tw] OR tubat\*[tw] OR ventilat\*[tw]) | [13362](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=25) |
| [#24](https://www.ncbi.nlm.nih.gov/pubmed) | Search tracheotom\*[tw] OR tracheostom\*[tw] | [25352](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=24) |
| [#23](https://www.ncbi.nlm.nih.gov/pubmed) | Search Tracheostomy[mesh] | [7200](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=23) |
| [#22](https://www.ncbi.nlm.nih.gov/pubmed) | Search invasive ventilat\*[tw] | [3223](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=22) |
| [#21](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilation[tw] | [2529](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=21) |
| [#20](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial respiration[tw] OR artificial ventilation\*[tw] OR mechanical respiration[tw] OR mechanical ventilation\*[tw] | [73695](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=20) |
| [#19](https://www.ncbi.nlm.nih.gov/pubmed) | Search Ventilators, Mechanical[mesh] | [8951](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=19) |
| [#18](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiration, Artificial[mesh] | [74906](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=18) |
| [#17](https://www.ncbi.nlm.nih.gov/pubmed) | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 | [252305](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=17) |
| [#16](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialized weaning unit[tw] OR specialized weaning units[tw] OR specialized weaning centre\*[tw] OR specialized weaning center\*[tw] | [23](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=16) |
| [#15](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialised weaning unit[tw] OR specialised weaning units[tw] OR specialised weaning centre\*[tw] OR specialised weaning center\*[tw] | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=15) |
| [#14](https://www.ncbi.nlm.nih.gov/pubmed) | Search HDU[tw] OR HDUs[tw] OR SDU[tw] OR SDUs[tw] OR EDSDU[tw] OR EDSDU[tw] | [517](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=14) |
| [#13](https://www.ncbi.nlm.nih.gov/pubmed) | Search high dependency unit[tw] OR high dependency units[tw] OR high dependency centre\*[tw] OR high dependency center\*[tw] | [653](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=13) |
| [#12](https://www.ncbi.nlm.nih.gov/pubmed) | Search critically ill[tw] OR critical illness\*[tw] | [56456](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=12) |
| [#11](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Illness[mesh] | [27476](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=11) |
| [#10](https://www.ncbi.nlm.nih.gov/pubmed) | Search respiratory unit[tw] OR respiratory units[tw] OR respiratory centre\*[tw] OR respiratory center\*[tw] | [3471](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=10) |
| [#9](https://www.ncbi.nlm.nih.gov/pubmed) | Search burn unit[tw] OR burn units[tw] OR burn centre\*[tw] OR burn center\*[tw] | [4863](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=9) |
| [#8](https://www.ncbi.nlm.nih.gov/pubmed) | Search ICU[tw] OR ICUs[tw] OR PICU[tw] OR PICUs[tw] OR SICU[tw] OR SICUs[tw] OR CCU[tw] OR CCUs[tw] | [61489](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=8) |
| [#7](https://www.ncbi.nlm.nih.gov/pubmed) | Search critical care [tw] OR intensive care[tw] | [203889](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=7) |
| [#6](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Care [mesh] | [56187](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=6) |
| [#5](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units, Pediatric [mesh:noexp] | [7353](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=5) |
| [#4](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiratory Care Units [mesh] | [589](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=4) |
| [#3](https://www.ncbi.nlm.nih.gov/pubmed) | Search Coronary Care Units [mesh] | [4323](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=3) |
| [#2](https://www.ncbi.nlm.nih.gov/pubmed) | Search Burn Units [mesh] | [2505](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=2) |
| [#1](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units [mesh:noexp] | [52363](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=1) |

Sleep Hygiene

2020 Jan 13

| Search | Query | Items found |
| --- | --- | --- |
| [#61](https://www.ncbi.nlm.nih.gov/pubmed) | Search #55 AND #60 | [808](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=61) |
| [#60](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search "2015"[Date - Publication] : "2020"[Date - Publication] | [5922034](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=60) |
| [#59](https://www.ncbi.nlm.nih.gov/pubmed) | Search #57 AND #58 | [49](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=59) |
| [#58](https://www.ncbi.nlm.nih.gov/pubmed) | Search "2012"[Date - Publication] : "2020"[Date - Publication] | [8900568](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=58) |
| [#57](https://www.ncbi.nlm.nih.gov/pubmed) | Search #55 AND #56 | [67](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=57) |
| [#56](https://www.ncbi.nlm.nih.gov/pubmed) | Search systematic review[pt] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy\*[tw] OR metanaly\*[tw] OR metaanaly\*[tw] OR met analy\*[tw] OR integrative research[tw] OR integrative review\*[tw] OR integrative overview\*[tiab] OR research integration\*[tw] OR research overview\*[tw] OR collaborative review\*[tw] OR collaborative overview\*[tw] OR systematic review\*[tw] OR systematic overview\*[tw] OR evidence-based review\*[tw] OR evidence-based overview\*[tw] OR meta-review\*[tw] OR meta-overview\*[tw] OR meta-synthes\*[tw] OR rapid review\*[tw] OR "review of reviews"[tw] OR "Technology Assessment, Biomedical"[mh] OR technology assessment\*[tw] OR HTA[tw] OR HTAs[tw] OR "Cochrane Database Syst Rev"[Journal:\_\_jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] OR Network MA[tw] OR Network MAs[tw] OR indirect comparison\*[tw] OR indirect treatment comparison\*[tw] OR indirect treatments comparison[tw] OR multiple treatment comparison\*[tw] OR multiple treatments comparison\*[tw] OR mixed treatment comparison\*[tw] OR mixed treatments comparison[tw] OR multi-treatment comparison\*[tw] OR multi-treatments comparison\*[tw] OR simultaneous comparison\*[tw] OR mixed comparison\*[tw] | [310964](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=56) |
| [#55](https://www.ncbi.nlm.nih.gov/pubmed) | Search #53 NOT #54 | [3255](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=55) |
| [#54](https://www.ncbi.nlm.nih.gov/pubmed) | Search editorial[pt] OR news[pt] OR newspaper article[pt] | [727185](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=54) |
| [#53](https://www.ncbi.nlm.nih.gov/pubmed) | Search #51 NOT #52 | [3280](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=53) |
| [#52](https://www.ncbi.nlm.nih.gov/pubmed) | Search Animals[mesh] NOT Humans[mesh] | [4658273](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=52) |
| [#51](https://www.ncbi.nlm.nih.gov/pubmed) | Search #45 AND #50 | [3339](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=51) |
| [#50](https://www.ncbi.nlm.nih.gov/pubmed) | Search #46 OR #47 OR #48 OR #49 | [295650](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=50) |
| [#49](https://www.ncbi.nlm.nih.gov/pubmed) | Search circadium[tw] OR diurnal rhythm\*[tw] OR diurnal cycle\*[tw] OR nycthemeral rhythm\*[tw] OR nycthemeral cycle\*[tw] OR nyctohemeral rhythm\*[tw] OR nyctohemeral cycle\*[tw] OR ((twenty-four hour[tw] OR 24 hour[tw] OR twenty-four hours[tw] OR 24 hours[tw]) AND (clock\*[tw] OR cycle[tw] OR cycles[tw] OR cyclic\*[tw] OR rhythm\*[tw])) | [18405](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=49) |
| [#48](https://www.ncbi.nlm.nih.gov/pubmed) | Search sleep\*[tw] OR awak\*[tw] OR wakeful\*[tw] OR wakening\*[tw] | [22758](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=48) |
| [#47](https://www.ncbi.nlm.nih.gov/pubmed) | Search Circadian Rhythm[mesh] | [69772](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=47) |
| [#46](https://www.ncbi.nlm.nih.gov/pubmed) | Search Sleep[mesh] | [77406](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=46) |
| [#45](https://www.ncbi.nlm.nih.gov/pubmed) | Search #37 AND #44 | [123765](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=45) |
| [#44](https://www.ncbi.nlm.nih.gov/pubmed) | Search #38 OR #39 OR #40 OR #41 OR #42 OR #43 | [4212931](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=44) |
| [#43](https://www.ncbi.nlm.nih.gov/pubmed) | Search newborn\*[tw] OR neonat\*[tw] OR premie[tw] OR premies[tw] OR VLBW[tw] OR SGA[tw] | [833965](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=43) |
| [#42](https://www.ncbi.nlm.nih.gov/pubmed) | Search pediatric\*[tw] OR paediatric\*[tw] | [387976](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=42) |
| [#41](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatric Emergency Medicine[mesh] | [226](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=41) |
| [#40](https://www.ncbi.nlm.nih.gov/pubmed) | Search Pediatrics[mesh] | [56790](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=40) |
| [#39](https://www.ncbi.nlm.nih.gov/pubmed) | Search infant[tw] OR infants[tw] OR infanc\*[tw] OR baby[tw] OR babies[tw] OR child\*[tw] OR toddler\*[tw] OR preschool\*[tw] OR pre-school\*[tw] OR school-age[tw] OR school-aged[tw] OR adolescen\*[tw] OR teen[tw] OR teens[tw] OR teenager\*[tw] OR youth[tw] OR youths[tw] OR highschool\*[tw] OR high-school\*[tw] | [3972940](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=39) |
| [#38](https://www.ncbi.nlm.nih.gov/pubmed) | Search Infant[mesh] OR Child[mesh] OR Adolescent[mesh] | [3486033](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=38) |
| [#37](https://www.ncbi.nlm.nih.gov/pubmed) | Search #17 OR #36 | [409179](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=37) |
| [#36](https://www.ncbi.nlm.nih.gov/pubmed) | Search #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 | [198704](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=36) |
| [#35](https://www.ncbi.nlm.nih.gov/pubmed) | Search IPPB[tw] | [286](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=35) |
| [#34](https://www.ncbi.nlm.nih.gov/pubmed) | Search APRV[tw] | [167](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=34) |
| [#33](https://www.ncbi.nlm.nih.gov/pubmed) | Search airway pressure release[tw] AND ventilat\*[tw] | [271](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=33) |
| [#32](https://www.ncbi.nlm.nih.gov/pubmed) | Search controlled ventilat\*[tw] | [2332](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=32) |
| [#31](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilat\*[tw] | [2555](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=31) |
| [#30](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial airway[tw] OR artificial airways[tw] | [441](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=30) |
| [#29](https://www.ncbi.nlm.nih.gov/pubmed) | Search intubat\*[tw] OR extubat\*[tw] OR detubat\*[tw] | [90100](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=29) |
| [#28](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intubation, Intratracheal[mesh] | [38056](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=28) |
| [#27](https://www.ncbi.nlm.nih.gov/pubmed) | Search Airway Extubation[mesh] | [1385](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=27) |
| [#26](https://www.ncbi.nlm.nih.gov/pubmed) | Search ventilat\*[tw] AND (wean\*[tw] OR liberat\*[tw]) | [7938](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=26) |
| [#25](https://www.ncbi.nlm.nih.gov/pubmed) | Search endotrachea\*[tw] AND (tube[tw] OR tubes[tw] OR tubat\*[tw] OR ventilat\*[tw]) | [13362](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=25) |
| [#24](https://www.ncbi.nlm.nih.gov/pubmed) | Search tracheotom\*[tw] OR tracheostom\*[tw] | [25352](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=24) |
| [#23](https://www.ncbi.nlm.nih.gov/pubmed) | Search Tracheostomy[mesh] | [7200](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=23) |
| [#22](https://www.ncbi.nlm.nih.gov/pubmed) | Search invasive ventilat\*[tw] | [3223](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=22) |
| [#21](https://www.ncbi.nlm.nih.gov/pubmed) | Search high-frequency ventilation[tw] | [2529](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=21) |
| [#20](https://www.ncbi.nlm.nih.gov/pubmed) | Search artificial respiration[tw] OR artificial ventilation\*[tw] OR mechanical respiration[tw] OR mechanical ventilation\*[tw] | [73695](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=20) |
| [#19](https://www.ncbi.nlm.nih.gov/pubmed) | Search Ventilators, Mechanical[mesh] | [8951](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=19) |
| [#18](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiration, Artificial[mesh] | [74906](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=18) |
| [#17](https://www.ncbi.nlm.nih.gov/pubmed) | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 | [252305](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=17) |
| [#16](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialized weaning unit[tw] OR specialized weaning units[tw] OR specialized weaning centre\*[tw] OR specialized weaning center\*[tw] | [23](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=16) |
| [#15](https://www.ncbi.nlm.nih.gov/pubmed) | Search specialised weaning unit[tw] OR specialised weaning units[tw] OR specialised weaning centre\*[tw] OR specialised weaning center\*[tw] | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=15) |
| [#14](https://www.ncbi.nlm.nih.gov/pubmed) | Search HDU[tw] OR HDUs[tw] OR SDU[tw] OR SDUs[tw] OR EDSDU[tw] OR EDSDU[tw] | [517](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=14) |
| [#13](https://www.ncbi.nlm.nih.gov/pubmed) | Search high dependency unit[tw] OR high dependency units[tw] OR high dependency centre\*[tw] OR high dependency center\*[tw] | [653](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=13) |
| [#12](https://www.ncbi.nlm.nih.gov/pubmed) | Search critically ill[tw] OR critical illness\*[tw] | [56456](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=12) |
| [#11](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Illness[mesh] | [27476](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=11) |
| [#10](https://www.ncbi.nlm.nih.gov/pubmed) | Search respiratory unit[tw] OR respiratory units[tw] OR respiratory centre\*[tw] OR respiratory center\*[tw] | [3471](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=10) |
| [#9](https://www.ncbi.nlm.nih.gov/pubmed) | Search burn unit[tw] OR burn units[tw] OR burn centre\*[tw] OR burn center\*[tw] | [4863](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=9) |
| [#8](https://www.ncbi.nlm.nih.gov/pubmed) | Search ICU[tw] OR ICUs[tw] OR PICU[tw] OR PICUs[tw] OR SICU[tw] OR SICUs[tw] OR CCU[tw] OR CCUs[tw] | [61489](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=8) |
| [#7](https://www.ncbi.nlm.nih.gov/pubmed) | Search critical care [tw] OR intensive care[tw] | [203889](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=7) |
| [#6](https://www.ncbi.nlm.nih.gov/pubmed) | Search Critical Care [mesh] | [56187](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=6) |
| [#5](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units, Pediatric [mesh:noexp] | [7353](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=5) |
| [#4](https://www.ncbi.nlm.nih.gov/pubmed) | Search Respiratory Care Units [mesh] | [589](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=4) |
| [#3](https://www.ncbi.nlm.nih.gov/pubmed) | Search Coronary Care Units [mesh] | [4323](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=3) |
| [#2](https://www.ncbi.nlm.nih.gov/pubmed) | Search Burn Units [mesh] | [2505](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=2) |
| [#1](https://www.ncbi.nlm.nih.gov/pubmed) | Search Intensive Care Units [mesh:noexp] | [52363](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=1) |

Parental/Caregiver Presence

Search Strategy

2020 Jan 13

PubMed

| Search | Add to builder | Query | Items found | Time |
| --- | --- | --- | --- | --- |
| [#77](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #76 NOT (#71 OR #73) | [587](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=77) | 12:02:25 |
| [#76](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #69 AND #75 | [682](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=76) | 12:00:55 |
| [#75](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Cohort Studies[mh] OR cohort[tw] OR cohorts[tw] OR Retrospective Studies[mh] OR longitudinal[tw] OR prospective[tw] OR retrospective[tw] OR follow-up study[tw] OR followup study[tw] OR Observational Study[pt] OR observational study[tw] OR population study[tw] OR population analys\*[tw] OR population-based study[tw] OR population-based analys\*[tw] OR multidimensional study[tw] OR multi-dimensional study[tw] OR Comparative Study[pt] OR comparative study[tw] OR comparison study[tw] OR Case-Control Studies[mh] OR case-control study[tw] OR case-controlled study[tw] OR case-based comparison\*[tw] OR case-comparison study[tw] OR Cross-Sectional Studies[mesh] OR cross-sectional study[tw] OR crosssectional study[tw] | [4582476](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=75) | 11:59:57 |
| [#74](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #73 NOT #71 | [63](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=74) | 11:58:48 |
| [#73](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #69 AND #72 | [192](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=73) | 11:58:08 |
| [#72](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Controlled Clinical Trial[mh] OR Controlled Clinical Trials as Topic[mh] OR controlled trial\*[tw] OR controlled clinical trial\*[tw] OR Non-Randomized Controlled Trials as Topic[mh] OR nonrandom\*[tw] OR non-random\*[tw] OR quasi-random\*[tw] OR quasi-experiment\*[tw] OR nRCT[tw] OR non-RCT[tw] OR Controlled Before-After Studies[mh] OR (control\*[tw] AND (“before and after”[tw] OR “before after”[tw])) OR Interrupted Time Series Analysis[mh] OR time series[tw] OR (pretest[tw] AND posttest[tw]) OR (pre-test[tw] AND post-test[tw]) OR Historically Controlled Study[mh] OR control study[tw] OR controlled study[tw] OR Control Groups[mh] OR control group\*[tw] OR controlled groups[tw] | [1374554](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=72) | 11:57:50 |
| [#71](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #69 AND #70 | [167](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=71) | 11:56:19 |
| [#70](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Controlled Clinical Trial[pt] OR Randomized Controlled Trial[pt] OR Pragmatic Clinical Trial[pt] OR Equivalence Trial[pt] OR Randomized Controlled Trials as Topic[mh] OR Clinical Trials as Topic [mesh:noexp] OR randomised[tw] OR randomized[tw] OR randomisation\*[tw] OR randomization\*[tw] OR randomly[tw] OR RCT[tw] OR placebo\*[tw] OR ((singl\*[tw] OR doubl\*[tw] OR trebl\*[tw] OR tripl\*[tw]) AND (mask\*[tw] OR blind\*[tw] OR dumm\*[tw])) or trial[ti] | [1400512](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=70) | 11:55:29 |
| [#69](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #63 AND #68 | [1565](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=69) | 11:55:22 |
| [#68](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search "2015"[Date - Publication] : "2020"[Date - Publication] | [5926847](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=68) | 11:50:19 |
| [#67](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #65 AND #66 | [97](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=67) | 11:49:27 |
| [#66](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search "2012"[Date - Publication] : "2020"[Date - Publication] | [8905381](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=66) | 11:48:40 |
| [#65](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #63 AND #64 | [129](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=65) | 11:48:25 |
| [#64](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search systematic review[pt] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy\*[tw] OR metanaly\*[tw] OR metaanaly\*[tw] OR met analy\*[tw] OR integrative research[tw] OR integrative review\*[tw] OR integrative overview\*[tiab] OR research integration\*[tw] OR research overview\*[tw] OR collaborative review\*[tw] OR collaborative overview\*[tw] OR systematic review\*[tw] OR systematic overview\*[tw] OR evidence-based review\*[tw] OR evidence-based overview\*[tw] OR meta-review\*[tw] OR meta-overview\*[tw] OR meta-synthes\*[tw] OR rapid review\*[tw] OR "review of reviews"[tw] OR "Technology Assessment, Biomedical"[mh] OR technology assessment\*[tw] OR HTA[tw] OR HTAs[tw] OR "Cochrane Database Syst Rev"[Journal:\_\_jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] OR Network MA[tw] OR Network MAs[tw] OR indirect comparison\*[tw] OR indirect treatment comparison\*[tw] OR indirect treatments comparison[tw] OR multiple treatment comparison\*[tw] OR multiple treatments comparison\*[tw] OR mixed treatment comparison\*[tw] OR mixed treatments comparison[tw] OR multi-treatment comparison\*[tw] OR multi-treatments comparison\*[tw] OR simultaneous comparison\*[tw] OR mixed comparison\*[tw] | [311123](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=64) | 11:48:18 |
| [#63](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #61 NOT #62 | [4385](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=63) | 11:48:09 |
| [#62](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search editorial[pt] OR news[pt] OR newspaper article[pt] | [727385](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=62) | 11:48:02 |
| [#61](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #59 NOT #60 | [4406](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=61) | 11:47:41 |
| [#60](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Animals[mesh] NOT Humans[mesh] | [4658967](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=60) | 11:47:32 |
| [#59](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #45 AND #58 | [4443](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=59) | 11:47:04 |
| [#58](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #52 AND #57 | [436741](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=58) | 11:46:44 |
| [#57](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #53 OR #54 OR #55 OR #56 | [4731192](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=57) | 11:46:35 |
| [#56](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Patients' Rooms[mesh] | [2687](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=56) | 11:41:18 |
| [#55](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search bedside[tw] OR "take part"[tw] OR "takes part"[tw] OR "taking part"[tw] OR participat\*[tw] | [577690](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=55) | 11:38:24 |
| [#54](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search attend\*[tw] OR present[tw] OR presence[tw] OR visit\*[tw] | [4276275](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=54) | 11:37:21 |
| [#53](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Visitors to Patients[mesh] | [2052](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=53) | 11:37:15 |
| [#52](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #46 OR #47 OR #48 OR #49 OR #50 OR #51 | [1795718](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=52) | 11:37:05 |
| [#51](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search caregiver\*[tw] OR care giver\*[tw] OR carer[tw] OR carers[tw] OR parent[tw] OR parents[tw] OR parental[tw] OR parenting[tw] OR mother\*[tw] OR maternal\*[tw] OR father\*[tw] OR paternal\*[tw] OR family[tw] OR families[tw] | [1795718](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=51) | 11:36:56 |
| [#50](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Family[mesh:noexp] OR Nuclear Family[mesh:noexp] | [79525](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=50) | 11:36:30 |
| [#49](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Parenting[mesh] | [16042](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=49) | 11:36:20 |
| [#48](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Parent-Child Relations[mesh] | [55329](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=48) | 11:35:05 |
| [#47](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Parents[mesh] | [108696](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=47) | 11:34:55 |
| [#46](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Caregivers[mesh] | [34773](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=46) | 11:34:49 |
| [#45](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #37 AND #44 | [123796](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=45) | 11:34:43 |
| [#44](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #38 OR #39 OR #40 OR #41 OR #42 OR #43 | [4213715](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=44) | 11:34:36 |
| [#43](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search newborn\*[tw] OR neonat\*[tw] OR premie[tw] OR premies[tw] OR VLBW[tw] OR SGA[tw] | [834094](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=43) | 11:34:30 |
| [#42](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search pediatric\*[tw] OR paediatric\*[tw] | [388097](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=42) | 11:34:23 |
| [#41](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Pediatric Emergency Medicine[mesh] | [226](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=41) | 11:34:17 |
| [#40](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Pediatrics[mesh] | [56795](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=40) | 11:34:11 |
| [#39](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search infant[tw] OR infants[tw] OR infanc\*[tw] OR baby[tw] OR babies[tw] OR child\*[tw] OR toddler\*[tw] OR preschool\*[tw] OR pre-school\*[tw] OR school-age[tw] OR school-aged[tw] OR adolescen\*[tw] OR teen[tw] OR teens[tw] OR teenager\*[tw] OR youth[tw] OR youths[tw] OR highschool\*[tw] OR high-school\*[tw] | [3973704](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=39) | 11:34:05 |
| [#38](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Infant[mesh] OR Child[mesh] OR Adolescent[mesh] | [3486786](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=38) | 11:33:58 |
| [#37](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #17 OR #36 | [409272](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=37) | 11:33:49 |
| [#36](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 | [198745](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=36) | 11:33:43 |
| [#35](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search IPPB[tw] | [286](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=35) | 11:33:38 |
| [#34](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search APRV[tw] | [167](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=34) | 11:33:32 |
| [#33](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search airway pressure release[tw] AND ventilat\*[tw] | [271](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=33) | 11:33:28 |
| [#32](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search controlled ventilat\*[tw] | [2332](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=32) | 11:33:21 |
| [#31](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search high-frequency ventilat\*[tw] | [2556](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=31) | 11:33:16 |
| [#30](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search artificial airway[tw] OR artificial airways[tw] | [441](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=30) | 11:33:09 |
| [#29](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search intubat\*[tw] OR extubat\*[tw] OR detubat\*[tw] | [90118](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=29) | 11:33:01 |
| [#28](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Intubation, Intratracheal[mesh] | [38065](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=28) | 11:32:50 |
| [#27](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Airway Extubation[mesh] | [1386](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=27) | 11:32:40 |
| [#26](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search ventilat\*[tw] AND (wean\*[tw] OR liberat\*[tw]) | [7944](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=26) | 11:32:35 |
| [#25](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search endotrachea\*[tw] AND (tube[tw] OR tubes[tw] OR tubat\*[tw] OR ventilat\*[tw]) | [13362](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=25) | 11:32:29 |
| [#24](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search tracheotom\*[tw] OR tracheostom\*[tw] | [25359](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=24) | 11:32:23 |
| [#23](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Tracheostomy[mesh] | [7206](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=23) | 11:32:17 |
| [#22](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search invasive ventilat\*[tw] | [3225](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=22) | 11:32:11 |
| [#21](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search high-frequency ventilation[tw] | [2530](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=21) | 11:32:04 |
| [#20](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search artificial respiration[tw] OR artificial ventilation\*[tw] OR mechanical respiration[tw] OR mechanical ventilation\*[tw] | [73713](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=20) | 11:31:57 |
| [#19](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Ventilators, Mechanical[mesh] | [8951](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=19) | 11:31:52 |
| [#18](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Respiration, Artificial[mesh] | [74918](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=18) | 11:31:46 |
| [#17](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 | [252369](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=17) | 11:31:40 |
| [#16](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search specialized weaning unit[tw] OR specialized weaning units[tw] OR specialized weaning centre\*[tw] OR specialized weaning center\*[tw] | [23](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=16) | 11:31:34 |
| [#15](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search specialised weaning unit[tw] OR specialised weaning units[tw] OR specialised weaning centre\*[tw] OR specialised weaning center\*[tw] | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=15) | 11:31:27 |
| [#14](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search HDU[tw] OR HDUs[tw] OR SDU[tw] OR SDUs[tw] OR EDSDU[tw] OR EDSDU[tw] | [517](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=14) | 11:31:20 |
| [#13](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search high dependency unit[tw] OR high dependency units[tw] OR high dependency centre\*[tw] OR high dependency center\*[tw] | [653](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=13) | 11:31:14 |
| [#12](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search critically ill[tw] OR critical illness\*[tw] | [56466](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=12) | 11:31:08 |
| [#11](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Critical Illness[mesh] | [27487](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=11) | 11:31:00 |
| [#10](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search respiratory unit[tw] OR respiratory units[tw] OR respiratory centre\*[tw] OR respiratory center\*[tw] | [3471](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=10) | 11:30:55 |
| [#9](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search burn unit[tw] OR burn units[tw] OR burn centre\*[tw] OR burn center\*[tw] | [4864](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=9) | 11:30:48 |
| [#8](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search ICU[tw] OR ICUs[tw] OR PICU[tw] OR PICUs[tw] OR SICU[tw] OR SICUs[tw] OR CCU[tw] OR CCUs[tw] | [61511](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=8) | 11:30:42 |
| [#7](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search critical care [tw] OR intensive care[tw] | [203949](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=7) | 11:30:36 |
| [#6](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Critical Care [mesh] | [56203](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=6) | 11:30:30 |
| [#5](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Intensive Care Units, Pediatric [mesh:noexp] | [7358](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=5) | 11:30:24 |
| [#4](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Respiratory Care Units [mesh] | [589](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=4) | 11:30:14 |
| [#3](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Coronary Care Units [mesh] | [4323](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=3) | 11:30:08 |
| [#2](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Burn Units [mesh] | [2506](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=2) | 11:30:03 |
| [#1](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | [Add](https://www.ncbi.nlm.nih.gov/pubmed/advanced) | Search Intensive Care Units [mesh:noexp] | [52379](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=1) | 11:29:55 |

Sedation

2020 Jan 25

| Search | Query | Items found |
| --- | --- | --- |
| #91 | Search #90 NOT (#83 OR #86) | [684](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=91) |
| #90 | Search #89 AND #82 | [965](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=90) |
| #89 | Search #75 AND #88 | [3736](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=89) |
| #88 | Search Cohort Studies[mh] OR cohort[tw] OR cohorts[tw] OR Retrospective Studies[mh] OR longitudinal[tw] OR prospective[tw] OR retrospective[tw] OR follow-up study[tw] OR followup study[tw] OR Observational Study[pt] OR observational study[tw] OR population study[tw] OR population analys\*[tw] OR population-based study[tw] OR population-based analys\*[tw] OR multidimensional study[tw] OR multi-dimensional study[tw] OR Comparative Study[pt] OR comparative study[tw] OR comparison study[tw] OR Case-Control Studies[mh] OR case-control study[tw] OR case-controlled study[tw] OR case-based comparison\*[tw] OR case-comparison study[tw] OR Cross-Sectional Studies[mesh] OR cross-sectional study[tw] OR crosssectional study[tw] | [4590817](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=88) |
| #87 | Search #86 NOT #83 | [85](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=87) |
| #86 | Search #85 AND #82 | [444](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=86) |
| #85 | Search #75 AND #84 | [1855](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=85) |
| #84 | Search Controlled Clinical Trial[mh] OR Controlled Clinical Trials as Topic[mh] OR controlled trial\*[tw] OR controlled clinical trial\*[tw] OR Non-Randomized Controlled Trials as Topic[mh] OR nonrandom\*[tw] OR non-random\*[tw] OR quasi-random\*[tw] OR quasi-experiment\*[tw] OR nRCT[tw] OR non-RCT[tw] OR Controlled Before-After Studies[mh] OR (control\*[tw] AND (“before and after”[tw] OR “before after”[tw])) OR Interrupted Time Series Analysis[mh] OR time series[tw] OR (pretest[tw] AND posttest[tw]) OR (pre-test[tw] AND post-test[tw]) OR Historically Controlled Study[mh] OR control study[tw] OR controlled study[tw] OR Control Groups[mh] OR control group\*[tw] OR controlled groups[tw] | [1377231](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=84) |
| #83 | Search #81 AND #82 | [434](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=83) |
| #82 | Search ("2015"[Date - Publication] : "2020"[Date - Publication]) | [5971879](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=82) |
| #81 | Search #75 AND #80 | [1852](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=81) |
| #80 | Search Controlled Clinical Trial[pt] OR Randomized Controlled Trial[pt] OR Pragmatic Clinical Trial[pt] OR Equivalence Trial[pt] OR Randomized Controlled Trials as Topic[mh] OR Clinical Trials as Topic [mesh:noexp] OR randomised[tw] OR randomized[tw] OR randomisation\*[tw] OR randomization\*[tw] OR randomly[tw] OR RCT[tw] OR placebo\*[tw] OR ((singl\*[tw] OR doubl\*[tw] OR trebl\*[tw] OR tripl\*[tw]) AND (mask\*[tw] OR blind\*[tw] OR dumm\*[tw])) or trial[ti] | [1403011](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=80) |
| #79 | Search #77 AND #78 | [143](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=79) |
| #78 | Search "2012"[Date - Publication] : "2020"[Date - Publication] | [8950401](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=78) |
| #77 | Search #75 AND #76 | [206](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=77) |
| #76 | Search systematic review[pt] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy\*[tw] OR metanaly\*[tw] OR metaanaly\*[tw] OR met analy\*[tw] OR integrative research[tw] OR integrative review\*[tw] OR integrative overview\*[tiab] OR research integration\*[tw] OR research overview\*[tw] OR collaborative review\*[tw] OR collaborative overview\*[tw] OR systematic review\*[tw] OR systematic overview\*[tw] OR evidence-based review\*[tw] OR evidence-based overview\*[tw] OR meta-review\*[tw] OR meta-overview\*[tw] OR meta-synthes\*[tw] OR rapid review\*[tw] OR "review of reviews"[tw] OR "Technology Assessment, Biomedical"[mh] OR technology assessment\*[tw] OR HTA[tw] OR HTAs[tw] OR "Cochrane Database Syst Rev"[Journal:\_\_jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] OR Network MA[tw] OR Network MAs[tw] OR indirect comparison\*[tw] OR indirect treatment comparison\*[tw] OR indirect treatments comparison[tw] OR multiple treatment comparison\*[tw] OR multiple treatments comparison\*[tw] OR mixed treatment comparison\*[tw] OR mixed treatments comparison[tw] OR multi-treatment comparison\*[tw] OR multi-treatments comparison\*[tw] OR simultaneous comparison\*[tw] OR mixed comparison\*[tw] | [312415](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=76) |
| #75 | Search #73 NOT #74 | [8491](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=75) |
| #74 | Search editorial[pt] OR news[pt] OR newspaper article[pt] | [728561](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=74) |
| #73 | Search #71 NOT #72 | [8579](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=73) |
| #72 | Search Animals[mesh] NOT Humans[mesh] | [4662296](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=72) |
| #71 | Search #47 AND #70 | [8834](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=71) |
| #70 | Search #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 | [1020267](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=70) |
| #69 | Search mitten[tw] OR mittens[tw] | [555](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=69) |
| #68 | Search (belt\*[tw] OR strap\*[tw] OR tie[tw] OR tied[tw] OR ties[tw]) AND (bed[tw] OR beds[tw] OR down[tw]) | [1360](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=68) |
| #67 | Search vest jacket\*[tw] OR vestjacket\*tw] OR straight jacket\*[tw] OR straightjacket\*[tw] | [64](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=67) |
| #66 | Search (ankle[tw] OR ankles[tw] OR appendage\*[tw] OR arm[tw] OR arms[tw] OR body[tw] OR bodies[tw] OR foot[tw] OR feet[tw] OR hand[tw] OR hands[tw] OR leg[tw] OR legs[tw] OR limb[tw] OR limbs[tw] OR patient[tw] OR patients[tw] OR wrist[tw] OR wrists[tw]) AND (tie[tw] OR ties[tw] OR tied[tw]) | [6391](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=66) |
| #65 | Search (disallow\*[tw] or limit\*[tw] or restrict\*[tw] or stop\*[tw]) AND movement\*[tw] | [51879](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=65) |
| #64 | Search Restraint, Physical[tw] OR restrain\*[tw] OR immobiliz\*[tw] OR immobilis\*[tw] | [165456](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=64) |
| #63 | Search Massage[mesh] OR massag\*[tw] OR Kangaroo-Mother Care Method[mesh] OR Kangaroo\*[tw] OR swaddl\*[tw] | [17724](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=63) |
| #62 | Search parkotal[tw] OR pharmetten[tw] OR phen bar[tw] OR phenaemal[tw] OR phenemal[tw] OR phenethylbarbital sodium[tw] OR phenobal[tw] OR phenobarb[tw] OR phenobarbito\*[tw] OR phenobarbitural[tw] OR phenobarbyl[tw] OR phenonyl[tw] OR phenotal[tw] OR phenoturic[tw] OR phenoyl[tw] OR phenyl ethyl barbituric acid[tw] OR phenylethyl barbituric acid[tw] OR phenylethylbarbituric acid[tw] OR phenylethylmalonyl urea[tw] OR phenylethylmalonylurea[tw] OR phenyletten[tw] OR phenyral[tw] OR polcominal[tw] OR promptonal[tw] OR seda tablinen[tw] OR sedabar[tw] OR sedicat[tw] OR sedizorin[tw] OR sedlyn[tw] OR sedofen[tw] OR sedonal[tw] OR sedonettes[tw] OR seneval[tw] OR sevenal[tw] OR sombutol[tw] OR somnolens[tw] OR somnoletten[tw] OR somnosan[tw] OR somonal[tw] OR spasepilin[tw] OR starifen[tw] OR starilettae[tw] OR stental[tw] OR teolaxin[tw] OR theolaxin[tw] OR triabarb[tw] OR tridezibarbitur[tw] OR uni-feno[tw] OR versomnal[tw] OR wakobital[tw] OR zadoletten[tw] OR zadonal[tw] | [620847](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=62) |
| #61 | Search haplopan[tw] OR haplos[tw] OR helional[tw] OR hennoletten[tw] OR hypnaletten[tw] OR hypno tablinetten[tw] OR hypnogen fragner[tw] OR hypnolone[tw] OR hypnotal[tw] OR hypnotalon[tw] OR hysteps[tw] OR lefebar[tw] OR leonal[tw] OR lephebar[tw] OR lepinal[tw] OR lethyl[tw] OR linasen[tw] OR liquital[tw] OR lixophen[tw] OR lubergal[tw] OR lubrokal[tw] OR lumesettes[tw] OR lumesyn[tw] OR lumofridetten[tw] OR luphenil[tw] OR luramin[tw] OR menobarb[tw] OR molinal[tw] OR neurobarb[tw] OR nirvonal[tw] OR noptil[tw] OR nova pheno[tw] OR nunol[tw] | [31](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=61) |
| #60 | Search calmetten[tw] OR calminal[tw] OR carbronal[tw] OR cardenal[tw] OR cemalonal[tw] OR codibarbital[tw] OR coronaletta[tw] OR cratecil[tw] OR damoral[tw] OR dezibarbitur[tw] OR dormina[tw] OR dormiral[tw] OR dromural[tw] OR ensobarb[tw] OR ensodorm[tw] OR epanal[tw] OR epidorm[tw] OR epilol[tw] OR episedal[tw] OR epsylone[tw] OR eskabarb[tw] OR etilfen[tw] OR euneryl[tw] OR fenbital[tw] OR fenemal[tw] OR fenobarbital[tw] OR fenolbarbital[tw] OR fenosed[tw] OR fenylettae[tw] OR gardenal[tw] OR gardenale[tw] OR gardepapnyl[tw] OR glysoletten[tw] | [53](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=60) |
| #59 | Search adonal[tw] OR aephenal[tw] OR agrypnal[tw] OR alepsal[tw] OR amylofene[tw] OR andral[tw] OR aparoxal[tw] OR aphenylbarbit[tw] OR aphenyletten[tw] OR atrofen[tw] OR austrominal[tw] OR barbapil[tw] OR barbellen[tw] OR barbenyl[tw] OR barbilettae[tw] OR barbilixir[tw] OR barbinal[tw] OR barbiphen[tw] OR barbiphenyl[tw] OR barbivis[tw] OR barbonal[tw] OR barbonalett[tw] OR barbophen[tw] OR bardorm[tw] OR bartol[tw] OR bialminal[tw] | [23](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=59) |
| #58 | Search Phenobarbital[mesh] OR phenobarbital[tw] | [25296](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=58) |
| #57 | Search Barbiturates[mesh:noexp] OR barbiturate\*[tw] OR barbital derivative[tw] | [19422](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=57) |
| #56 | Search Chloral Hydrate[mesh] OR ansopal[tw] OR aquachloral[tw] OR chloral glycerolate[tw] OR chloraldurat[tw] OR chloral hydrate[tw] OR chloralhydrate[tw] OR chloralum hydratum[tw] OR escre[tw] OR hydral[tw] OR lorinal[tw] OR medianox[tw] OR neochloral[tw] OR noctec[tw] OR notec[tw] OR novochlorhydrate[tw] OR nycton[tw] OR phaldrone[tw] OR pocral[tw] OR rectules[tw] OR somnos[tw] OR somnote[tw] OR somnox[tw] OR sorosil[tw] | [4554](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=56) |
| #55 | Search Propofol[mesh] OR propofol[tw] OR anepol[tw] OR aquafol[tw] OR cryotol[tw] OR diprivan[tw] OR disoprivan[tw] OR disoprofol[tw] OR fresofol[tw] OR gobbifol[tw] OR "ICI-35 868"[tw] OR "ICI-35868"[tw] OR ivofol[tw] OR pofol[tw] OR propocam[tw] OR rapinovet[tw] OR recofol[tw] OR safol[tw] | [21957](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=55) |
| #54 | Search Ketamine[mesh] OR ketamine[tw] OR calipsol[tw] OR calypsol[tw] OR "CI-581"[tw] OR imalgene[tw] OR kalipsol[tw] OR katamine[tw] OR keta-hameln[tw] OR ketaject[tw] OR ketalar[tw] OR ketalin[tw] OR ketamax[tw] OR kalipsol[tw] OR ketalar[tw] OR ketaminol[tw] OR ketanest[tw] OR ketased[tw] OR ketaset[tw] OR ketaved[tw] OR ketavet[tw] OR ketmin[tw] OR ketoject[tw] OR ketolar[tw] OR narkamon[tw] OR narketan[tw] OR "soon-soon"[tw] OR tekam[tw] OR velonarcon[tw] OR vetalar[tw] | [19557](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=54) |
| #53 | Search Benzodiazepines[mesh] OR benzodiazepine\*[tw] OR Diazepam[mesh] OR diazepam\*[tw] OR alboral[tw] OR aliseum[tw] OR amiprol[tw] OR "an-ding"[tw] OR ansilive[tw] OR ansiolin[tw] OR ansiolisina[tw] OR antenex[tw] OR anxicalm[tw] OR anxionil[tw] OR apaurin[tw] OR apo-diazepam[tw] OR apozepam[tw] OR armonil[tw] OR arzepam[tw] OR assival[tw] OR atensine[tw] OR atilen[tw] OR azedipamin[tw] OR baogin[tw] OR bensedin[tw] OR benzopin[tw] OR betapam[tw] OR bialzepam[tw] OR britazepam[tw] OR "BRN 0754371"[tw] OR calmaven[tw] OR calmocitene[tw] OR calmociteno[tw] OR calmod[tw] OR calmpose[tw] OR caudel[tw] OR "CB 4261"[tw] OR centrazepam[tw] OR cercine[tw] OR ceregulart[tw] OR chuansuan[tw] OR Midazolam[[mesh] OR midazolam[tw] OR dormicum[tw] OR "Ro 21-3981"[tw] OR versed[tw] OR Lorazepam[mesh] OR Lorazepam\*[tw] OR almazine[tw] OR anxiedin[tw] OR anxira[tw] OR anzepam[tw] OR aplacasse[tw] OR aplacassee[tw] OR apo-lorazepam[tw] OR aripax[tw] OR ativan[tw] OR azurogen[tw] OR bonatranquan[tw] OR bonton[tw] OR "BRN 0759084" [tw] OR delormetazepam[tw] OR demethyllormetazepam[tw] OR donix[tw] OR duralozam[tw] OR efasedan[tw] OR "EINECS 212-687-6"[tw] OR emotival[tw] OR equitam[tw] OR idalprem[tw] OR kalmalin[tw] | [19289](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=53) |
| #52 | Search Adrenergic alpha-2 Receptor Agonists[mesh] OR alpha-2 agonist\*[tw] OR Clonidine[mesh] OR catapres[tw] OR catapresan[tw] OR catapressan[tw] OR chlophazolin[tw] OR clofelin[tw] OR clofenil[tw] OR clonidine dihydrochloride[tw] OR clonidine hydrochloride[tw] OR clonidine monohydrobromide[tw] OR clonidine monohydrochloride[tw] OR clopheline[tw] OR dixarit[tw] OR gemiton[tw] OR hemiton[tw] OR isoglaucon[tw] OR klofelin[tw] OR klofenil[tw] OR m-5041t[tw] OR st-155[tw] OR Dexmedetomidine[mesh] OR dexmedetomidine[tw] OR "mpv-1440"[tw] OR precedex[tw] | [20680](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=52) |
| #51 | Search "Hypnotics and Sedatives"[mesh] | [29167](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=51) |
| #50 | Search sedat\*[tw] | [76472](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=50) |
| #49 | Search Deep Sedation[mesh] | [1231](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=49) |
| #48 | Search Conscious Sedation[mesh] | [8721](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=48) |
| #47 | Search #39 AND #46 | [123980](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=47) |
| #46 | Search #40 OR #41 OR #42 OR #43 OR #44 OR #45 | [4219211](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=46) |
| #45 | Search newborn\*[tw] OR neonat\*[tw] OR premie[tw] OR premies[tw] OR VLBW[tw] OR SGA[tw] | [835006](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=45) |
| #44 | Search pediatric\*[tw] OR paediatric\*[tw] | [389007](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=44) |
| #43 | Search Pediatric Emergency Medicine[mesh] | [228](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=43) |
| #42 | Search Pediatrics[mesh] | [56855](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=42) |
| #41 | Search infant[tw] OR infants[tw] OR infanc\*[tw] OR baby[tw] OR babies[tw] OR child\*[tw] OR toddler\*[tw] OR preschool\*[tw] OR pre-school\*[tw] OR school-age[tw] OR school-aged[tw] OR adolescen\*[tw] OR teen[tw] OR teens[tw] OR teenager\*[tw] OR youth[tw] OR youths[tw] OR highschool\*[tw] OR high-school\*[tw] | [3978873](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=41) |
| #40 | Search Infant[mesh] OR Child[mesh] OR Adolescent[mesh] | [3490719](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=40) |
| #39 | Search #19 OR #38 | [409959](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=39) |
| #38 | Search #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 | [198983](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=38) |
| #37 | Search IPPB[tw] | [286](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=37) |
| #36 | Search APRV[tw] | [167](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=36) |
| #35 | Search airway pressure release[tw] AND ventilat\*[tw] | [272](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=35) |
| #34 | Search controlled ventilat\*[tw] | [2333](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=34) |
| #33 | Search high-frequency ventilat\*[tw] | [2557](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=33) |
| #32 | Search artificial airway[tw] OR artificial airways[tw] | [441](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=32) |
| #31 | Search intubat\*[tw] OR extubat\*[tw] OR detubat\*[tw] | [90206](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=31) |
| #30 | Search Intubation, Intratracheal[mesh] | [38112](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=30) |
| #29 | Search Airway Extubation[mesh] | [1393](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=29) |
| #28 | Search ventilat\*[tw] AND (wean\*[tw] OR liberat\*[tw]) | [7955](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=28) |
| #27 | Search endotrachea\*[tw] AND (tube[tw] OR tubes[tw] OR tubat\*[tw] OR ventilat\*[tw]) | [13377](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=27) |
| #26 | Search tracheotom\*[tw] OR tracheostom\*[tw] | [25384](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=26) |
| #25 | Search Tracheostomy[mesh] | [7215](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=25) |
| #24 | Search invasive ventilat\*[tw] | [3236](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=24) |
| #23 | Search high-frequency ventilation[tw] | [2530](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=23) |
| #22 | Search artificial respiration[tw] OR artificial ventilation\*[tw] OR mechanical respiration[tw] OR mechanical ventilation\*[tw] | [73825](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=22) |
| #21 | Search Ventilators, Mechanical[mesh] | [8956](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=21) |
| #20 | Search Respiration, Artificial[mesh] | [75009](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=20) |
| #19 | Search #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 | [252881](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=19) |
| #18 | Search specialized weaning unit[tw] OR specialized weaning units[tw] OR specialized weaning centre\*[tw] OR specialized weaning center\*[tw] | [23](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=18) |
| #17 | Search specialised weaning unit[tw] OR specialised weaning units[tw] OR specialised weaning centre\*[tw] OR specialised weaning center\*[tw] | [14](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=17) |
| #16 | Search HDU[tw] OR HDUs[tw] OR SDU[tw] OR SDUs[tw] OR EDSDU[tw] OR EDSDU[tw] | [517](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=16) |
| #15 | Search high dependency unit[tw] OR high dependency units[tw] OR high dependency centre\*[tw] OR high dependency center\*[tw] | [656](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=15) |
| #14 | Search critically ill[tw] OR critical illness\*[tw] | [56598](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=14) |
| #13 | Search Critical Illness[mesh] | [27558](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=13) |
| #12 | Search respiratory unit[tw] OR respiratory units[tw] OR respiratory centre\*[tw] OR respiratory center\*[tw] | [3473](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=12) |
| #11 | Search burn unit[tw] OR burn units[tw] OR burn centre\*[tw] OR burn center\*[tw] | [4867](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=11) |
| #10 | Search ICU[tw] OR ICUs[tw] OR PICU[tw] OR PICUs[tw] OR SICU[tw] OR SICUs[tw] OR CCU[tw] OR CCUs[tw] | [61677](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=10) |
| #9 | Search critical care [tw] OR intensive care[tw] | [204370](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=9) |
| #8 | Search Critical Care [mesh] | [56281](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=8) |
| #7 | Search Intensive Care Units, Pediatric [mesh:noexp] | [7370](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=7) |
| #6 | Search Respiratory Care Units [mesh] | [590](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=6) |
| #5 | Search Coronary Care Units [mesh] | [4324](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=5) |
| #4 | Search Burn Units [mesh] | [2508](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=4) |
| #3 | Search Intensive Care Units [mesh:noexp] | [52490](https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=3) |

## REFERENCES

1. McGrath PA, Seifert CE, Speechley KN, et al:. A new analogue scale for assessing children's pain: An initial validation study. *Pain.* 1996;64:435-443

2. Szyfelbein SK, Osgood PF, Carr DB. The assessment of pain and plasma beta-endorphin immunoactivity in burned children. *Pain.* 1985;22:173-182

3. Beyer JE, Aradine CR. Content validity of an instrument to measure young children's perceptions of the intensity of their pain. *J Pediatr Nurs.* 1986;1:386-395

4. Bieri D, Reeve RA, Champion DG, et al:. The faces pain scale for the self-assessment of the severity of pain experienced by children: Development, initial validation, and preliminary investigation for ratio scale properties. *Pain.* 1990;41:139-150

5. Voepel-Lewis T, Zanotti J, Dammeyer JA, et al:. Reliability and validity of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients. *Am J Crit Care.* 2010;19:55-61; quiz 62

6. Johansson M, Kokinsky E. The comfort behavioural scale and the modified flacc scale in paediatric intensive care. *Nurs Crit Care.* 2009;14:122-130

7. Malviya S, Voepel-Lewis T, Burke C, et al:. The revised flacc observational pain tool: Improved reliability and validity for pain assessment in children with cognitive impairment. *Paediatr Anaesth.* 2006;16:258-265

8. van Dijk M, de Boer JB, Koot HM, et al:. The reliability and validity of the comfort scale as a postoperative pain instrument in 0 to 3-year-old infants. *Pain.* 2000;84:367-377

9. Ambuel B, Hamlett KW, Marx CM, et al:. Assessing distress in pediatric intensive care environments: The comfort scale. *J Pediatr Psychol.* 1992;17:95-109

10. Hunseler C, Merkt V, Gerloff M, et al:. Assessing pain in ventilated newborns and infants: Validation of the hartwig score. *Eur J Pediatr.* 2011;170:837-843

11. Brunow de Carvalho W, Lucas da Silva PS, Paulo CS, et al:. Comparison between the comfort and hartwig sedation scales in pediatric patients undergoing mechanical lung ventilation. *Sao Paulo medical journal = Revista paulista de medicina.* 1999;117:192-196

12. Suominen P, Caffin C, Linton S, et al:. The cardiac analgesic assessment scale (caas): A pain assessment tool for intubated and ventilated children after cardiac surgery. *Paediatr Anaesth.* 2004;14:336-343

13. World Health O. Cancer pain relief: With a guide to opioid availability. *World Health Organization.* 1996:15

14. World Health O. Who guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. *World Health Organization.* 2012;Annex 2:82-99

15. Olkkola KT, Hamunen K, Maunuksela EL. Clinical pharmacokinetics and pharmacodynamics of opioid analgesics in infants and children. *Clin Pharmacokinet.* 1995;28:385-404

16. Thigpen JC, Odle BL, Harirforoosh S. Opioids: A review of pharmacokinetics and pharmacodynamics in neonates, infants, and children. *Eur J Drug Metab Pharmacokinet.* 2019;44:591-609

17. German JW, Aneja R, Heard C, et al:. Continuous remifentanil for pediatric neurosurgery patients. *Pediatr Neurosurg.* 2000;33:227-229

18. Ward RM, Drover DR, Hammer GB, et al:. The pharmacokinetics of methadone and its metabolites in neonates, infants, and children. *Paediatr Anaesth.* 2014;24:591-601.PMC4016164

19. Twite MD, Rashid A, Zuk J, et al:. Sedation, analgesia, and neuromuscular blockade in the pediatric intensive care unit: Survey of fellowship training programs. *Pediatr Crit Care Med.* 2004;5:521-532

20. Jenkins IA, Playfor SD, Bevan C, et al:. Current united kingdom sedation practice in pediatric intensive care. *Paediatr Anaesth.* 2007;17:675-683

21. Garcia Guerra G, Joffe AR, Cave D, et al:. Survey of sedation and analgesia practice among canadian pediatric critical care physicians. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2016;17:823-830

22. Welzing L, Oberthuer A, Junghaenel S, et al:. Remifentanil/midazolam versus fentanyl/midazolam for analgesia and sedation of mechanically ventilated neonates and young infants: A randomized controlled trial. *Intensive Care Med.* 2012;38:1017-1024

23. Reiter PD, Ng J, Dobyns EL. Continuous hydromorphone for pain and sedation in mechanically ventilated infants and children. *J Opioid Manag.* 2012;8:99-104

24. Akinci SB, Kanbak M, Guler A, et al:. Remifentanil versus fentanyl for short-term analgesia-based sedation in mechanically ventilated postoperative children. *Paediatr Anaesth.* 2005;15:870-878

25. Chiaretti A, Pietrini D. Safety and efficacy of remifentanil infusion in craniosynostosis repair in infants. *Pediatr Neurosurg.* 2002;36:55-56

26. Alencar AJ, Sanudo A, Sampaio VM, et al:. Efficacy of tramadol versus fentanyl for postoperative analgesia in neonates. *Arch Dis Child Fetal Neonatal Ed.* 2012;97:F24-29

27. Hungerford JL, O'Brien N, Moore-Clingenpeel M, et al:. Remifentanil for sedation of children with traumatic brain injury. *J Intensive Care Med.* 2019;34:557-562

28. Goodarzi M. Comparison of epidural morphine, hydromorphone and fentanyl for postoperative pain control in children undergoing orthopaedic surgery. *Paediatr Anaesth.* 1999;9:419-422

29. Smith MT, Watt JA, Cramond T. Morphine-3-glucuronide--a potent antagonist of morphine analgesia. *Life Sciences.* 1990;47:579-585

30. Pasternak GW, Bodnar RJ, Clark JA, et al:. Morphine-6-glucuronide, a potent mu agonist. *Life Sci.* 1987;41:2845-2849

31. Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. *Crit Care Med.* 2000;28:2122-2132

32. Monitto CL, Kost-Byerly S, White E, et al:. The optimal dose of prophylactic intravenous naloxone in ameliorating opioid-induced side effects in children receiving intravenous patient-controlled analgesia morphine for moderate to severe pain: A dose finding study. *Anesth Analg.* 2011;113:834-842.PMC4461032

33. Maxwell LG, Kaufmann SC, Bitzer S, et al:. The effects of a small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-controlled analgesia: A double-blind, prospective, randomized, controlled study. *Anesth Analg.* 2005;100:953-958

34. Cheung CL, van Dijk M, Green JW, et al:. Effects of low-dose naloxone on opioid therapy in pediatric patients: A retrospective case-control study. *Intensive Care Med.* 2007;33:190-194

35. Darnell CM, Thompson J, Stromberg D, et al:. Effect of low-dose naloxone infusion on fentanyl requirements in critically ill children. *Pediatrics.* 2008;121:e1363-1371

36. Ross EL, Reiter PD, Murphy ME, et al:. Evaluation of prolonged epidural chloroprocaine for postoperative analgesia in infants. *J Clin Anesth.* 2015;27:463-469

37. Thammasitboon S, Rosen DA, Lutfi R, et al:. An institutional experience with epidural analgesia in children and young adults undergoing cardiac surgery. *Paediatr Anaesth.* 2010;20:720-726

38. Shenkman Z, Hoppenstein D, Erez I, et al:. Continuous lumbar/thoracic epidural analgesia in low-weight paediatric surgical patients: Practical aspects and pitfalls. *Pediatr Surg Int.* 2009;25:623-634

39. Graham RJ, Athiraman U, Laubach AE, et al:. Anesthesia and perioperative medical management of children with spinal muscular atrophy. *Paediatr Anaesth.* 2009;19:1054-1063

40. Westerlind A, Nilsson F, Ricksten SE. The use of continuous positive airway pressure by face mask and thoracic epidural analgesia after lung transplantation. Gothenburg lung transplant group. *Journal of cardiothoracic and vascular anesthesia.* 1999;13:249-252

41. Dohms K, Hein M, Rossaint R, et al:. Inguinal hernia repair in preterm neonates: Is there evidence that spinal or general anaesthesia is the better option regarding intraoperative and postoperative complications? A systematic review and meta-analysis. *BMJ Open.* 2019;9:e028728.PMC6797401

42. Kaushal B, Chauhan S, Magoon R, et al:. Efficacy of bilateral erector spinae plane block in management of acute postoperative surgical pain after pediatric cardiac surgeries through a midline sternotomy. *J Cardiothorac Vasc Anesth.* 2020;34:981-986

43. Singh AP, Lakshminrusimha S, Thompson ME. Regional analgesia in neonates undergoing thoracoabdominal surgeries: A pilot study. *J Neonatal Perinatal Med.* 2019;12:73-79

44. Monahan A, Guay J, Hajduk J, et al:. Regional analgesia added to general anesthesia compared with general anesthesia plus systemic analgesia for cardiac surgery in children: A systematic review and meta-analysis of randomized clinical trials. *Anesth Analg.* 2019;128:130-136

45. Maharramova M, Taylor K. A systematic review of caudal anesthesia and postoperative outcomes in pediatric cardiac surgery patients. *Semin Cardiothorac Vasc Anesth.* 2019;23:237-247

46. Mattila I, Patila T, Rautiainen P, et al:. The effect of continuous wound infusion of ropivacaine on postoperative pain after median sternotomy and mediastinal drain in children. *Paediatr Anaesth.* 2016;26:727-733

47. Kaushal B, Chauhan S, Saini K, et al:. Comparison of the efficacy of ultrasound-guided serratus anterior plane block, pectoral nerves ii block, and intercostal nerve block for the management of postoperative thoracotomy pain after pediatric cardiac surgery. *J Cardiothorac Vasc Anesth.* 2019;33:418-425

48. Huang JJ, Hirshberg G. Regional anaesthesia decreases the need for postoperative mechanical ventilation in very low birth weight infants undergoing herniorrhaphy. *Paediatric anaesthesia.* 2001;11:705-709

49. McNeely JK, Farber NE, Rusy LM, et al:. Epidural analgesia improves outcome following pediatric fundoplication. A retrospective analysis. *Reg Anesth.* 1997;22:16-23

50. Bairdain S, Dodson B, Zurakowski D, et al:. Paravertebral nerve block catheters using chloroprocaine in infants with prolonged mechanical ventilation for treatment of long-gap esophageal atresia. *Paediatric anaesthesia.* 2015;25:1151-1157

51. Di Pede A, Morini F, Lombardi MH, et al:. Comparison of regional vs. Systemic analgesia for post-thoracotomy care in infants. *Paediatr Anaesth.* 2014;24:569-573

52. Raghavan M, Montgomerie J. Anesthetic management of gastrochisis--a review of our practice over the past 5 years. *Paediatric anaesthesia.* 2008;18:1055-1059

53. Almenrader N, Patel D. Spinal fusion surgery in children with non-idiopathic scoliosis: Is there a need for routine postoperative ventilation? *British journal of anaesthesia.* 2006;97:851-857

54. Kendigelen P, Tutuncu C, Ashyralyyeva G, et al:. Transversus abdominis plane (tap) block for postoperative analgesia in neonates and young infants: Retrospective analysis of a case series. Tap blocks in neonates and young infants. *Minerva Anestesiol.* 2017;83:282 - 287

55. Beamer S, Ferns S, Edwards L, et al:. Early extubation in pediatric heart surgery across a spectrum of case complexity: Impact on hospital length of stay and chest tube days. *Prog Pediatr Cardiol.* 2017;45:63-68.PMC5509209

56. Garg R, Rao S, John C, et al:. Extubation in the operating room after cardiac surgery in children: A prospective observational study with multidisciplinary coordinated approach. *J Cardiothorac Vasc Anesth.* 2014;28:479-487

57. Warmann SW, Lang S, Fideler F, et al:. Perioperative epidural analgesia in children undergoing major abdominal tumor surgery--a single center experience. *J Pediatr Surg.* 2014;49:551-555

58. Bichel T, Rouge JC, Schlegel S, et al:. Epidural sufentanil during paediatric cardiac surgery: Effects on metabolic response and postoperative outcome. *Paediatr Anaesth.* 2000;10:609-617

59. Miller RP, Roberts RJ, Fischer LJ. Acetaminophen elimination kinetics in neonates, children, and adults. *Clin Pharmacol Ther.* 1976;19:284-294

60. Zuppa AF, Hammer GB, Barrett JS, et al:. Safety and population pharmacokinetic analysis of intravenous acetaminophen in neonates, infants, children, and adolescents with pain or fever. *J Pediatr Pharmacol Ther.* 2011;16:246-261.PMC3385039

61. Kauffman RE, Nelson MV. Effect of age on ibuprofen pharmacokinetics and antipyretic response. *J Pediatr.* 1992;121:969-973

62. Wells TG, Mortensen ME, Dietrich A, et al:. Comparison of the pharmacokinetics of naproxen tablets and suspension in children. *J Clin Pharmacol.* 1994;34:30-33

63. Cohen MN, Christians U, Henthorn T, et al:. Pharmacokinetics of single-dose intravenous ketorolac in infants aged 2-11 months. *Anesth Analg.* 2011;112:655-660

64. Mahmoodi AN, Kim PY. Ketorolac. In: *Statpearls.* Treasure Island (FL)2021.

65. Di Massa A, Scardigli M, Bruni L, et al:. Ketorolac for paediatric postoperative pain. A review. *Minerva Anestesiol.* 2000;66:749-756

66. Zhu A, Benzon HA, Anderson TA. Evidence for the efficacy of systemic opioid-sparing analgesics in pediatric surgical populations: A systematic review. *Anesth Analg.* 2017;125:1569-1587

67. Wong I, St John-Green C, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (nsaids) in children. *Paediatr Anaesth.* 2013;23:475-495.PMC4272569

68. Ceelie I, de Wildt SN, van Dijk M, et al:. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: A randomized controlled trial. *JAMA.* 2013;309:149-154

69. Munro HM, Walton SR, Malviya S, et al:. Low-dose ketorolac improves analgesia and reduces morphine requirements following posterior spinal fusion in adolescents. *Can J Anaesth.* 2002;49:461-466

70. Sutters KA, Shaw BA, Gerardi JA, et al:. Comparison of morphine patient-controlled analgesia with and without ketorolac for postoperative analgesia in pediatric orthopedic surgery. *American journal of orthopedics (Belle Mead, NJ).* 1999;28:351-358

71. Olbrecht VA, Ding L, Spruance K, et al:. Intravenous acetaminophen reduces length of stay via mediation of postoperative opioid consumption after posterior spinal fusion in a pediatric cohort. *Clin J Pain.* 2018;34:593-599.PMC5984111

72. Dawkins TN, Barclay CA, Gardiner RL, et al:. Safety of intravenous use of ketorolac in infants following cardiothoracic surgery. *Cardiology in the young.* 2009;19:105-108

73. Inoue M, Caldarone CA, Frndova H, et al:. Safety and efficacy of ketorolac in children after cardiac surgery. *Intensive Care Med.* 2009;35:1584-1592

74. Jindal V, Ge A, Mansky PJ. Safety and efficacy of acupuncture in children: A review of the evidence. *J Pediatr Hematol Oncol.* 2008;30:431-442.PMC2518962

75. Ni X, Xie Y, Wang Q, et al:. Cardioprotective effect of transcutaneous electric acupoint stimulation in the pediatric cardiac patients: A randomized controlled clinical trial. *Paediatr Anaesth.* 2012;22:805-811

76. Tsao GJ, Messner AH, Seybold J, et al:. Intraoperative acupuncture for posttonsillectomy pain: A randomized, double-blind, placebo-controlled trial. *Laryngoscope.* 2015;125:1972-1978

77. Lin YC, Tassone RF, Jahng S, et al:. Acupuncture management of pain and emergence agitation in children after bilateral myringotomy and tympanostomy tube insertion. *Paediatr Anaesth.* 2009;19:1096-1101

78. Tsai SL, Fox LM, Murakami M, et al:. Auricular acupuncture in emergency department treatment of acute pain. *Ann Emerg Med.* 2016;68:583-585

79. Chen KL, Lindrea KB, Quah-Smith I, et al:. Magnetic noninvasive acupuncture for infant comfort (magnific) - a single-blinded randomised controlled pilot trial. *Acta Paediatr.* 2017;106:1780-1786

80. Abbasoglu A, Cabioglu MT, Tugcu AU, et al:. Acupressure at bl60 and k3 points before heel lancing in preterm infants. *Explore (NY).* 2015;11:363-366

81. Cho YS, Choi YH. Comparison of three cooling methods for burn patients: A randomized clinical trial. *Burns.* 2017;43:502-508

82. Ragg PG, Cahoon G, Yeo A, et al:. A clinical audit to assess the efficacy of the coolsense(r) pain numbing applicator for intravenous cannulation in children. *Anaesth Intensive Care.* 2017;45:251-255

83. Carnevale FA, Razack S. An item analysis of the comfort scale in a pediatric intensive care unit. *Pediatr Crit Care Med.* 2002;3:177-180

84. Bear LA, Ward-Smith P. Interrater reliability of the comfort scale. *Pediatr Nurs.* 2006;32:427-434

85. Ista E, van Dijk M, Tibboel D, et al:. Assessment of sedation levels in pediatric intensive care patients can be improved by using the comfort "behavior" scale. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2005;6:58-63

86. van Dijk M, Peters JW, van Deventer P, et al:. The comfort behavior scale: A tool for assessing pain and sedation in infants. *Am J Nurs.* 2005;105:33-36

87. Curley MA, Harris SK, Fraser KA, et al:. State behavioral scale: A sedation assessment instrument for infants and young children supported on mechanical ventilation. *Pediatr Crit Care Med.* 2006;7:107-114.PMC1626525

88. Lebet R, Hayakawa J, Chamblee TB, et al:. Maintaining interrater agreement of core assessment instruments in a multisite randomized controlled clinical trial: The randomized evaluation of sedation titration for respiratory failure (restore) trial. *Nurs Res.* 2017;66:323-329.PMC5488692

89. Kerson AG, DeMaria R, Mauer E, et al:. Validity of the richmond agitation-sedation scale (rass) in critically ill children. *J Intensive Care.* 2016;4:65.PMC5080705

90. Smith HA, Boyd J, Fuchs DC, et al:. Diagnosing delirium in critically ill children: Validity and reliability of the pediatric confusion assessment method for the intensive care unit. *Crit Care Med.* 2011;39:150-157.PMC3776416

91. Silver G, Traube C, Kearney J, et al:. Detecting pediatric delirium: Development of a rapid observational assessment tool. *Intensive Care Med.* 2012;38:1025-1031

92. Traube C, Silver G, Kearney J, et al:. Cornell assessment of pediatric delirium: A valid, rapid, observational tool for screening delirium in the picu\*. *Crit Care Med.* 2014;42:656-663.PMC5527829

93. Curley MA, Wypij D, Watson RS, et al:. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: A randomized clinical trial. *JAMA.* 2015;313:379-389.PMC4955566

94. Kongkiattikul L, Dagenais M, Ruo N, et al:. The impact of a quality improvement project to standardize pain, agitation, and withdrawal assessments on the use of morphine and midazolam in the pediatric intensive care unit. *Paediatr Anaesth.* 2019;29:322-330

95. Saelim K, Chavananon S, Ruangnapa K, et al:. Effectiveness of protocolized sedation utilizing the comfort-b scale in mechanically ventilated children in a pediatric intensive care unit. *J Pediatr Intensive Care.* 2019;8:156-163.PMC6687447

96. Larson GE, McKeever S. Nurse titrated analgesia and sedation in intensive care increases the frequency of comfort assessment and reduces midazolam use in paediatric patients following cardiac surgery. *Aust Crit Care.* 2018;31:31-36

97. Gaillard-Le Roux B, Liet JM, Bourgoin P, et al:. Implementation of a nurse-driven sedation protocol in a picu decreases daily doses of midazolam. *Pediatr Crit Care Med.* 2017;18:e9-e17

98. Neunhoeffer F, Seitz G, Schmidt A, et al:. Analgesia and sedation protocol for mechanically ventilated postsurgical children reduces benzodiazepines and withdrawal symptoms-but not in all patients. *European journal of pediatric surgery : official journal of Austrian Association of Pediatric Surgery [et al] = Zeitschrift fur Kinderchirurgie.* 2017;27:255-262

99. Dreyfus L, Javouhey E, Denis A, et al:. Implementation and evaluation of a paediatric nurse-driven sedation protocol in a paediatric intensive care unit. *Ann Intensive Care.* 2017;7:36.PMC5366991

100. Neunhoeffer F, Kumpf M, Renk H, et al:. Nurse-driven pediatric analgesia and sedation protocol reduces withdrawal symptoms in critically ill medical pediatric patients. *Paediatr Anaesth.* 2015;25:786-794

101. Deeter KH, King MA, Ridling D, et al:. Successful implementation of a pediatric sedation protocol for mechanically ventilated patients. *Crit Care Med.* 2011;39:683-688

102. Jin HS, Yum MS, Kim SL, et al:. The efficacy of the comfort scale in assessing optimal sedation in critically ill children requiring mechanical ventilation. *J Korean Med Sci.* 2007;22:693-697.PMC2693822

103. Vet NJ, de Wildt SN, Verlaat CW, et al:. A randomized controlled trial of daily sedation interruption in critically ill children. *Intensive Care Med.* 2016;42:233-244.PMC4726735

104. Verlaat CW, Heesen GP, Vet NJ, et al:. Randomized controlled trial of daily interruption of sedatives in critically ill children. *Paediatr Anaesth.* 2014;24:151-156

105. Gupta K, Gupta VK, Jayashree M, et al:. Randomized controlled trial of interrupted versus continuous sedative infusions in ventilated children. *Pediatr Crit Care Med.* 2012;13:131-135

106. De Cristofano A, Peuchot V, Canepari A, et al:. Implementation of a ventilator-associated pneumonia prevention bundle in a single picu. *Pediatr Crit Care Med.* 2016;17:451-456

107. Cocoros NM, Priebe G, Gray JE, et al:. Factors associated with pediatric ventilator-associated conditions in six u.S. Hospitals: A nested case-control study. *Pediatr Crit Care Med.* 2017;18:e536-e545

108. Fitzgerald RK, Davis AT, Hanson SJ, et al:. Multicenter analysis of the factors associated with unplanned extubation in the picu. *Pediatr Crit Care Med.* 2015;16:e217-223

109. Marcin JP, Rutan E, Rapetti PM, et al:. Nurse staffing and unplanned extubation in the pediatric intensive care unit. *Pediatr Crit Care Med.* 2005;6:254-257

110. Little LA, Koenig JC, Jr., Newth CJ. Factors affecting accidental extubations in neonatal and pediatric intensive care patients. *Crit Care Med.* 1990;18:163-165

111. da Silva PS, de Aguiar VE, Neto HM, et al:. Unplanned extubation in a paediatric intensive care unit: Impact of a quality improvement programme. *Anaesthesia.* 2008;63:1209-1216

112. Tripathi S, Nunez DJ, Katyal C, et al:. Plan to have no unplanned: A collaborative, hospital-based quality-improvement project to reduce the rate of unplanned extubations in the pediatric icu. *Respiratory care.* 2015;60:1105-1112

113. Kaufman J, Rannie M, Kahn MG, et al:. An interdisciplinary initiative to reduce unplanned extubations in pediatric critical care units. *Pediatrics.* 2012;129:e1594-1600

114. Rachman BR, Watson R, Woods N, et al:. Reducing unplanned extubations in a pediatric intensive care unit: A systematic approach. *Int J Pediatr.* 2009;2009:820495.PMC2804049

115. Popernack ML, Thomas NJ, Lucking SE. Decreasing unplanned extubations: Utilization of the penn state children's hospital sedation algorithm. *Pediatr Crit Care Med.* 2004;5:58-62

116. Sadowski R, Dechert RE, Bandy KP, et al:. Continuous quality improvement: Reducing unplanned extubations in a pediatric intensive care unit. *Pediatrics.* 2004;114:628-632

117. Benini F, Farina M, Capretta A, et al:. Sedoanalgesia in paediatric intensive care: A survey of 19 italian units. *Acta Paediatr.* 2010;99:758-762

118. United States F, Drug A. Fda drug safety communication: Fda review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women. In*.* Vol 20192016.

119. Mody K, Kaur S, Mauer EA, et al:. Benzodiazepines and development of delirium in critically ill children: Estimating the causal effect. *Crit Care Med.* 2018;46:1486-1491.PMC6095819

120. Smith HAB, Gangopadhyay M, Goben CM, et al:. Delirium and benzodiazepines associated with prolonged icu stay in critically ill infants and young children. *Crit Care Med.* 2017;45:1427-1435

121. Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet.* 1998;35:37-47

122. Zorumski CF, Isenberg KE. Insights into the structure and function of gaba-benzodiazepine receptors: Ion channels and psychiatry. *The American Journal of Psychiatry.* 1991;148:162-173

123. McTague A, Martland T, Appleton R. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. *Cochrane Database Syst Rev.* 2018;1:CD001905.PMC6491279

124. Zhao ZY, Wang HY, Wen B, et al:. A comparison of midazolam, lorazepam, and diazepam for the treatment of status epilepticus in children: A network meta-analysis. *J Child Neurol.* 2016;31:1093-1107

125. Lugo RA, Chester EA, Cash J, et al:. A cost analysis of enterally administered lorazepam in the pediatric intensive care unit. *Crit Care Med.* 1999;27:417-421

126. "Inactive" ingredients in pharmaceutical products: Update (subject review). American academy of pediatrics committee on drugs. *Pediatrics.* 1997;99:268-278

127. Chicella M, Jansen P, Parthiban A, et al:. Propylene glycol accumulation associated with continuous infusion of lorazepam in pediatric intensive care patients. *Crit Care Med.* 2002;30:2752-2756

128. Hansen L, Lange R, Gupta S. Development and evaluation of a guideline for monitoring propylene glycol toxicity in pediatric intensive care unit patients receiving continuous infusion lorazepam. *J Pediatr Pharmacol Ther.* 2015;20:367-372.PMC4596122

129. van der Vossen AC, van Nuland M, Ista EG, et al:. Oral lorazepam can be substituted for intravenous midazolam when weaning paediatric intensive care patients off sedation. *Acta Paediatr.* 2018.PMC6120549

130. Warrington SE, Collier HK, Himebauch AS, et al:. Evaluation of iv to enteral benzodiazepine conversion calculations in a pediatric intensive care setting. *Pediatr Crit Care Med.* 2018;19:e569-e575

131. Hall RW, Shbarou RM. Drugs of choice for sedation and analgesia in the neonatal icu. *Clinics in perinatology.* 2009;36:15-26

132. McDermott CA, Kowalczyk AL, Schnitzler ER, et al:. Pharmacokinetics of lorazepam in critically ill neonates with seizures. *J Pediatr.* 1992;120:479-483

133. Tobias JD. Sedation and analgesia in paediatric intensive care units: A guide to drug selection and use. *Paediatric drugs.* 1999;1:109-126

134. Lloyd-Thomas AR, Booker PD. Infusion of midazolam in paediatric patients after cardiac surgery. *Br J Anaesth.* 1986;58:1109-1115

135. Silvasi DL, Rosen DA, Rosen KR. Continuous intravenous midazolam infusion for sedation in the pediatric intensive care unit. *Anesth Analg.* 1988;67:286-288

136. Macnab AJ, Levine M, Glick N, et al:. Midazolam following open heart surgery in children: Haemodynamic effects of a loading dose. *Paediatr Anaesth.* 1996;6:387-397

137. Best KM, Boullata JI, Curley MA. Risk factors associated with iatrogenic opioid and benzodiazepine withdrawal in critically ill pediatric patients: A systematic review and conceptual model. *Pediatr Crit Care Med.* 2015;16:175-183.PMC5304939

138. Fonsmark L, Rasmussen YH, Carl P. Occurrence of withdrawal in critically ill sedated children. *Crit Care Med.* 1999;27:196-199

139. Franck LS, Naughton I, Winter I. Opioid and benzodiazepine withdrawal symptoms in paediatric intensive care patients. *Intensive Crit Care Nurs.* 2004;20:344-351

140. Phan H, Nahata MC. Clinical uses of dexmedetomidine in pediatric patients. *Paediatr Drugs.* 2008;10:49-69

141. Su F, Hammer GB. Dexmedetomidine: Pediatric pharmacology, clinical uses and safety. *Expert Opin Drug Saf.* 2011;10:55-66

142. Mason KP, Zurakowski D, Zgleszewski S, et al:. Incidence and predictors of hypertension during high-dose dexmedetomidine sedation for pediatric mri. *Paediatr Anaesth.* 2010;20:516-523

143. Bloor BC, Ward DS, Belleville JP, et al:. Effects of intravenous dexmedetomidine in humans. Ii. Hemodynamic changes. *Anesthesiology.* 1992;77:1134-1142

144. Kamibayashi T, Maze M. Clinical uses of alpha2 -adrenergic agonists. *Anesthesiology.* 2000;93:1345-1349

145. Wang JG, Belley-Cote E, Burry L, et al:. Clonidine for sedation in the critically ill: A systematic review and meta-analysis. *Crit Care.* 2017;21:75.PMC5363026

146. Capino AC, Miller JL, Johnson PN. Clonidine for sedation and analgesia and withdrawal in critically ill infants and children. *Pharmacotherapy.* 2016;36:1290-1299

147. Ambrose C, Sale S, Howells R, et al:. Intravenous clonidine infusion in critically ill children: Dose-dependent sedative effects and cardiovascular stability. *Br J Anaesth.* 2000;84:794-796

148. Mason KP, O'Mahony E, Zurakowski D, et al:. Effects of dexmedetomidine sedation on the eeg in children. *Paediatr Anaesth.* 2009;19:1175-1183

149. Keidan I, Ben-Menachem E, Tzadok M, et al:. Electroencephalography for children with autistic spectrum disorder: A sedation protocol. *Paediatr Anaesth.* 2015;25:200-205

150. Chahraoui K, Laurent A, Bioy A, et al:. Psychological experience of patients 3 months after a stay in the intensive care unit: A descriptive and qualitative study. *J Crit Care.* 2015;30:599-605

151. Roehrs T, Hyde M, Blaisdell B, et al:. Sleep loss and rem sleep loss are hyperalgesic. *Sleep.* 2006;29:145-151

152. Christensen J, Noel M, Mychasiuk R. Neurobiological mechanisms underlying the sleep-pain relationship in adolescence: A review. *Neurosci Biobehav Rev.* 2019;96:401-413

153. Playfor S, Thomas D, Choonara I. Recollection of children following intensive care. *Arch Dis Child.* 2000;83:445-448.PMC1718553

154. Tobias JD, Berkenbosch JW. Sedation during mechanical ventilation in infants and children: Dexmedetomidine versus midazolam. *South Med J.* 2004;97:451-455

155. Buck ML, Willson DF. Use of dexmedetomidine in the pediatric intensive care unit. *Pharmacotherapy.* 2008;28:51-57

156. Benneyworth BD, Downs SM, Nitu M. Retrospective evaluation of the epidemiology and practice variation of dexmedetomidine use in invasively ventilated pediatric intensive care admissions, 2007-2013. *Frontiers in pediatrics.* 2015;3:109

157. Grant MJ, Schneider JB, Asaro LA, et al:. Dexmedetomidine use in critically ill children with acute respiratory failure. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2016;17:1131-1141

158. Najafi N, Veyckemans F, Van de Velde A, et al:. Usability of dexmedetomidine for deep sedation in infants and small children with respiratory morbidities. *Acta Anaesthesiol Scand.* 2016;60:865-873

159. Belleville JP, Ward DS, Bloor BC, et al:. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. *Anesthesiology.* 1992;77:1125-1133

160. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care.* 2000;4:302-308.PMC29047

161. Bejian S, Valasek C, Nigro JJ, et al:. Prolonged use of dexmedetomidine in the paediatric cardiothoracic intensive care unit. *Cardiology in the young.* 2009;19:98-104

162. Su F, Nicolson SC, Zuppa AF. A dose-response study of dexmedetomidine administered as the primary sedative in infants following open heart surgery. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2013;14:499-507

163. Venkatraman R, Hungerford JL, Hall MW, et al:. Dexmedetomidine for sedation during noninvasive ventilation in pediatric patients. *Pediatr Crit Care Med.* 2017;18:831-837

164. Piastra M, Pizza A, Gaddi S, et al:. Dexmedetomidine is effective and safe during niv in infants and young children with acute respiratory failure. *BMC pediatrics.* 2018;18:282-y

165. Shutes BL, Gee SW, Sargel CL, et al:. Dexmedetomidine as single continuous sedative during noninvasive ventilation: Typical usage, hemodynamic effects, and withdrawal. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2018;19:287-297

166. Haenecour AS, Seto W, Urbain CM, et al:. Prolonged dexmedetomidine infusion and drug withdrawal in critically ill children. *J Pediatr Pharmacol Ther.* 2017;22:453-460.PMC5736258

167. Whalen LD, Di Gennaro JL, Irby GA, et al:. Long-term dexmedetomidine use and safety profile among critically ill children and neonates. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2014;15:706-714

168. Sanna E, Mascia MP, Klein RL, et al:. Actions of the general anesthetic propofol on recombinant human gabaa receptors: Influence of receptor subunits. *J Pharmacol Exp Ther.* 1995;274:353-360

169. Trapani G, Altomare C, Liso G, et al:. Propofol in anesthesia. Mechanism of action, structure-activity relationships, and drug delivery. *Curr Med Chem.* 2000;7:249-271

170. van Gestel JP, Blusse van Oud-Alblas HJ, Malingre M, et al:. Propofol and thiopental for refractory status epilepticus in children. *Neurology.* 2005;65:591-592

171. Brown LA, Levin GM. Role of propofol in refractory status epilepticus. *Ann Pharmacother.* 1998;32:1053-1059

172. Gan TJ, Diemunsch P, Habib AS, et al:. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2014;118:85-113

173. Nathanson MH, Gajraj NM, Russell JA. Prevention of pain on injection of propofol: A comparison of lidocaine with alfentanil. *Anesth Analg.* 1996;82:469-471

174. Desousa KA. Pain on propofol injection: Causes and remedies. *Indian J Pharmacol.* 2016;48:617-623.PMC5155459

175. Jalota L, Kalira V, George E, et al:. Prevention of pain on injection of propofol: Systematic review and meta-analysis. *BMJ.* 2011;342:d1110

176. Picard P, Tramer MR. Prevention of pain on injection with propofol: A quantitative systematic review. *Anesth Analg.* 2000;90:963-969

177. Dahan A, Nieuwenhuijs DJ, Olofsen E. Influence of propofol on the control of breathing. *Adv Exp Med Biol.* 2003;523:81-92

178. Lee YS. Effects of propofol target-controlled infusion on haemodynamic and respiratory changes with regard to safety. *J Int Med Res.* 2004;32:19-24

179. Eastwood PR, Platt PR, Shepherd K, et al:. Collapsibility of the upper airway at different concentrations of propofol anesthesia. *Anesthesiology.* 2005;103:470-477

180. Robinson BJ, Ebert TJ, O'Brien TJ, et al:. Mechanisms whereby propofol mediates peripheral vasodilation in humans. Sympathoinhibition or direct vascular relaxation? *Anesthesiology.* 1997;86:64-72

181. Chidambaran V, Costandi A, D'Mello A. Propofol: A review of its role in pediatric anesthesia and sedation. *CNS Drugs.* 2015;29:543-563.PMC4554966

182. Williams GD, Jones TK, Hanson KA, et al:. The hemodynamic effects of propofol in children with congenital heart disease. *Anesth Analg.* 1999;89:1411-1416

183. Timpe EM, Eichner SF, Phelps SJ. Propofol-related infusion syndrome in critically ill pediatric patients: Coincidence, association, or causation? *J Pediatr Pharmacol Ther.* 2006;11:17-42.PMC3468086

184. Withington DE, Decell MK, Al Ayed T. A case of propofol toxicity: Further evidence for a causal mechanism. *Paediatric anaesthesia.* 2004;14:505-508

185. Wolf A, Weir P, Segar P, et al:. Impaired fatty acid oxidation in propofol infusion syndrome. *Lancet.* 2001;357:606-607

186. Cray SH, Robinson BH, Cox PN. Lactic acidemia and bradyarrhythmia in a child sedated with propofol. *Crit Care Med.* 1998;26:2087-2092

187. Wolf AR, Potter F. Propofol infusion in children: When does an anesthetic tool become an intensive care liability? *Paediatric anaesthesia.* 2004;14:435-438

188. Veldhoen ES, Hartman BJ, van Gestel JP. Monitoring biochemical parameters as an early sign of propofol infusion syndrome: False feeling of security. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2009;10:19

189. Farag E, Deboer G, Cohen BH, et al:. Metabolic acidosis due to propofol infusion. *Anesthesiology.* 2005;102:697-699

190. Vanlander AV, Jorens PG, Smet J, et al:. Inborn oxidative phosphorylation defect as risk factor for propofol infusion syndrome. *Acta Anaesthesiologica Scandinavica.* 2012;56:520-525

191. Schuttler J, Ihmsen H. Population pharmacokinetics of propofol: A multicenter study. *Anesthesiology.* 2000;92:727-738

192. Rigby-Jones AE, Nolan JA, Priston MJ, et al:. Pharmacokinetics of propofol infusions in critically ill neonates, infants, and children in an intensive care unit. *Anesthesiology.* 2002;97:1393-1400

193. Al-Jahdari WS, Yamamoto K, Hiraoka H, et al:. Prediction of total propofol clearance based on enzyme activities in microsomes from human kidney and liver. *Eur J Clin Pharmacol.* 2006;62:527-533

194. Corssen G, Domino EF. Dissociative anesthesia: Further pharmacologic studies and first clinical experience with the phencyclidine derivative ci-581. *Anesthesia and Analgesia.* 1966;45:29-40

195. Reich DL, Silvay G. Ketamine: An update on the first twenty-five years of clinical experience. *Can J Anaesth.* 1989;36:186-197

196. Chernow B, Lake CR, Cruess D, et al:. Plasma, urine, and csf catecholamine concentrations during and after ketamine anesthesia. *Crit Care Med.* 1982;10:600-603

197. Roberts DJ, Hall RI, Kramer AH, et al:. Sedation for critically ill adults with severe traumatic brain injury: A systematic review of randomized controlled trials. *Crit Care Med.* 2011;39:2743-2751

198. Aroni F, Iacovidou N, Dontas I, et al:. Pharmacological aspects and potential new clinical applications of ketamine: Reevaluation of an old drug. *J Clin Pharmacol.* 2009;49:957-964

199. Waxman K, Shoemaker WC, Lippmann M. Cardiovascular effects of anesthetic induction with ketamine. *Anesth Analg.* 1980;59:355-358

200. Spotoft H, Korshin JD, Sorensen MB, et al:. The cardiovascular effects of ketamine used for induction of anaesthesia in patients with valvular heart disease. *Canadian Anaesthetists' Society journal.* 1979;26:463-467

201. Mankikian B, Cantineau JP, Sartene R, et al:. Ventilatory pattern and chest wall mechanics during ketamine anesthesia in humans. *Anesthesiology.* 1986;65:492-499

202. Strube PJ, Hallam PL. Ketamine by continuous infusion in status asthmaticus. *Anaesthesia.* 1986;41:1017-1019

203. Denmark TK, Crane HA, Brown L. Ketamine to avoid mechanical ventilation in severe pediatric asthma. *J Emerg Med.* 2006;30:163-166

204. Youssef-Ahmed MZ, Silver P, Nimkoff L, et al:. Continuous infusion of ketamine in mechanically ventilated children with refractory bronchospasm. *Intensive Care Med.* 1996;22:972-976

205. Tobias JD, Martin LD, Wetzel RC. Ketamine by continuous infusion for sedation in the pediatric intensive care unit. *Crit Care Med.* 1990;18:819-821

206. Taylor PA, Towey RM. Depression of laryngeal reflexes during keatmine anaesthesia. *Br Med J.* 1971;2:688-689.PMC1796260

207. Gooding JM, Dimick AR, Tavakoli M, et al:. A physiologic analysis of cardiopulmonary responses to ketamine anesthesia in noncardiac patients. *Anesth Analg.* 1977;56:813-816

208. Drayna PC, Estrada C, Wang W, et al:. Ketamine sedation is not associated with clinically meaningful elevation of intraocular pressure. *Am J Emerg Med.* 2012;30:1215-1218.PMC3761376

209. Nagdeve NG, Yaddanapudi S, Pandav SS. The effect of different doses of ketamine on intraocular pressure in anesthetized children. *J Pediatr Ophthalmol Strabismus.* 2006;43:219-223

210. Halstead SM, Deakyne SJ, Bajaj L, et al:. The effect of ketamine on intraocular pressure in pediatric patients during procedural sedation. *Acad Emerg Med.* 2012;19:1145-1150

211. Wadia S, Bhola R, Lorenz D, et al:. Ketamine and intraocular pressure in children. *Ann Emerg Med.* 2014;64:385-388 e381

212. Coupey SM. Barbiturates. *Pediatr Rev.* 1997;18:260-264; quiz 265

213. Wilkes R, Tasker RC. Pediatric intensive care treatment of uncontrolled status epilepticus. *Crit Care Clin.* 2013;29:239-257

214. Holmes GL, Riviello JJ, Jr. Midazolam and pentobarbital for refractory status epilepticus. *Pediatr Neurol.* 1999;20:259-264

215. Tasker RC, Goodkin HP, Sanchez Fernandez I, et al:. Refractory status epilepticus in children: Intention to treat with continuous infusions of midazolam and pentobarbital. *Pediatr Crit Care Med.* 2016;17:968-975.PMC5052105

216. Pittman T, Bucholz R, Williams D. Efficacy of barbiturates in the treatment of resistant intracranial hypertension in severely head-injured children. *Pediatr Neurosci.* 1989;15:13-17

217. Bruce DA. Efficacy of barbiturates in the treatment of resistant intracranial hypertension in severely head-injured children. *Pediatr Neurosci.* 1989;15:216

218. Mellion SA, Bennett KS, Ellsworth GL, et al:. High-dose barbiturates for refractory intracranial hypertension in children with severe traumatic brain injury. *Pediatr Crit Care Med.* 2013;14:239-247

219. Ahmad KA, Desai SJ, Bennett MM, et al:. Changing antiepileptic drug use for seizures in us neonatal intensive care units from 2005 to 2014. *Journal of perinatology : official journal of the California Perinatal Association.* 2017;37:296-300

220. Tobias JD, Deshpande JK, Pietsch JB, et al:. Pentobarbital sedation for patients in the pediatric intensive care unit. *South Med J.* 1995;88:290-294

221. Yanay O, Brogan TV, Martin LD. Continuous pentobarbital infusion in children is associated with high rates of complications. *Journal of critical care.* 2004;19:174-178

222. Cote CJ, Karl HW, Notterman DA, et al:. Adverse sedation events in pediatrics: Analysis of medications used for sedation. *Pediatrics.* 2000;106:633-644

223. Chandler CJ, Cunnyngham C, Miller J, et al:. Propylene glycol-induced lactic acidosis in a child receiving a pentobarbital continuous infusion. *J Pediatr Intensive Care.* 2014;3:73-77.PMC6530744

224. Okamoto M. Barbiturate tolerance and physical dependence: Contribution of pharmacological factors. *NIDA Res Monogr.* 1984;54:333-347

225. Wandel C, Bocker R, Bohrer H, et al:. Midazolam is metabolized by at least three different cytochrome p450 enzymes. *British journal of anaesthesia.* 1994;73:658-661

226. Gonzalez D, Chamberlain JM, Guptill JT, et al:. Population pharmacokinetics and exploratory pharmacodynamics of lorazepam in pediatric status epilepticus. *Clin Pharmacokinet.* 2017;56:941-951.PMC5466505

227. Nguyen V, Tiemann D, Park E, et al:. Alpha-2 agonists. *Anesthesiol Clin.* 2017;35:233-245

228. Karol MD, Maze M. Pharmacokinetics and interaction pharmacodynamics of dexmedetomidine in humans. *Best Practice & Research Clinical Anaesthesiology.* 2000;14:261-269

229. Carroll CL, Krieger D, Campbell M, et al:. Use of dexmedetomidine for sedation of children hospitalized in the intensive care unit. *J Hosp Med.* 2008;3:142-147.18438790

230. Lowenthal DT. Pharmacokinetics of clonidine. *J Cardiovasc Pharmacol.* 1980;2 Suppl 1:S29-37

231. Frisk-Holmberg M, Paalzow L, Edlund PO. Clonidine kinetics in man--evidence for dose dependency and changed pharmacokinetics during chronic therapy. *Br J Clin Pharmacol.* 1981;12:653-658.PMC1401969

232. Zanos P, Moaddel R, Morris PJ, et al:. Ketamine and ketamine metabolite pharmacology: Insights into therapeutic mechanisms. *Pharmacological reviews.* 2018;70:621-660

233. Hijazi Y, Boulieu R. Contribution of cyp3a4, cyp2b6, and cyp2c9 isoforms to n-demethylation of ketamine in human liver microsomes. *Drug Metab Dispos.* 2002;30:853-858

234. Golding CL, Miller JL, Gessouroun MR, et al:. Ketamine continuous infusions in critically ill infants and children. *Ann Pharmacother.* 2016;50:234-241

235. Hornik CP, Gonzalez D, van den Anker J, et al:. Population pharmacokinetics of intramuscular and intravenous ketamine in children. *J Clin Pharmacol.* 2018;58:1092-1104.PMC6195858

236. Garisto C, Ricci Z, Tofani L, et al:. Use of low-dose dexmedetomidine in combination with opioids and midazolam in pediatric cardiac surgical patients: Randomized controlled trial. *Minerva anestesiologica.* 2018;84:1053-1062

237. Wolf A, McKay A, Spowart C, et al:. Prospective multicentre randomised, double-blind, equivalence study comparing clonidine and midazolam as intravenous sedative agents in critically ill children: The sleeps (safety profile, efficacy and equivalence in paediatric intensive care sedation) study. *Health technology assessment (Winchester, England).* 2014;18:1-212

238. Hunseler C, Balling G, Rohlig C, et al:. Continuous infusion of clonidine in ventilated newborns and infants: A randomized controlled trial. *Pediatr Crit Care Med.* 2014;15:511-522

239. Aydogan MS, Korkmaz MF, Ozgul U, et al:. Pain, fentanyl consumption, and delirium in adolescents after scoliosis surgery: Dexmedetomidine vs midazolam. *Paediatr Anaesth.* 2013;23:446-452

240. Hasegawa T, Oshima Y, Maruo A, et al:. Dexmedetomidine in combination with midazolam after pediatric cardiac surgery. *Asian Cardiovasc Thorac Ann.* 2015;23:802-808

241. Jiang L, Ding S, Yan H, et al:. A retrospective comparison of dexmedetomidine versus midazolam for pediatric patients with congenital heart disease requiring postoperative sedation. *Pediatr Cardiol.* 2015;36:993-999

242. Fagin A, Palmieri T, Greenhalgh D, et al:. A comparison of dexmedetomidine and midazolam for sedation in severe pediatric burn injury. *J Burn Care Res.* 2012;33:759-763

243. Ghimire LV, Chou FS. Efficacy of prophylactic dexmedetomidine in preventing postoperative junctional ectopic tachycardia in pediatric cardiac surgery patients: A systematic review and meta-analysis. *Paediatr Anaesth.* 2018;28:597-606

244. Li X, Zhang C, Dai D, et al:. Efficacy of dexmedetomidine in prevention of junctional ectopic tachycardia and acute kidney injury after pediatric cardiac surgery: A meta-analysis. *Congenit Heart Dis.* 2018;13:799-807

245. Prasad SR, Simha PP, Jagadeesh AM. Comparative study between dexmedetomidine and fentanyl for sedation during mechanical ventilation in post-operative paediatric cardiac surgical patients. *Indian Journal of Anaesthesia.* 2012;56:547-552

246. Shuplock JM, Smith AH, Owen J, et al:. The association between peri-operative dexmedetomidine and arrhythmias after surgery for congenital heart disease. In*.* Vol 82015:643-650.

247. Gupta P, Whiteside W, Sabati A, et al:. Safety and efficacy of prolonged dexmedetomidine use in critically ill children with heart disease\*. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2012;13:660-666

248. Le KN, Moffett BS, Ocampo EC, et al:. Impact of dexmedetomidine on early extubation in pediatric cardiac surgical patients. *Intensive Care Med.* 2011;37:686-690

249. Chrysostomou C, Sanchez De Toledo J, Avolio T, et al:. Dexmedetomidine use in a pediatric cardiac intensive care unit: Can we use it in infants after cardiac surgery? *Pediatr Crit Care Med.* 2009;10:654-660.19295456

250. Chrysostomou C, Beerman L, Shiderly D, et al:. Dexmedetomidine: A novel drug for the treatment of atrial and junctional tachyarrhythmias during the perioperative period for congenital cardiac surgery: A preliminary study. *Anesth Analg.* 2008;107:1514-1522

251. Svensson ML, Lindberg L. The use of propofol sedation in a paediatric intensive care unit. *Nursing in critical care.* 2012;17:198-203

252. Knibbe CA, Melenhorst-de Jong G, Mestrom M, et al:. Pharmacokinetics and effects of propofol 6% for short-term sedation in paediatric patients following cardiac surgery. *Br J Clin Pharmacol.* 2002;54:415-422.PMC1874439

253. Cray SH, Holtby HM, Kartha VM, et al:. Early tracheal extubation after paediatric cardiac surgery: The use of propofol to supplement low-dose opioid anaesthesia. *Paediatric anaesthesia.* 2001;11:465-471

254. Martin PH, Murthy BV, Petros AJ. Metabolic, biochemical and haemodynamic effects of infusion of propofol for long-term sedation of children undergoing intensive care. *Br J Anaesth.* 1997;79:276-279

255. Koriyama H, Duff JP, Guerra GG, et al:. Is propofol a friend or a foe of the pediatric intensivist? Description of propofol use in a picu\*. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2014;15:66

256. Teng SN, Kaufman J, Czaja AS, et al:. Propofol as a bridge to extubation for high-risk children with congenital cardiac disease. *Cardiology in the young.* 2011;21:46-51

257. Sheridan RL, Keaney T, Stoddard F, et al:. Short-term propofol infusion as an adjunct to extubation in burned children. *The Journal of burn care & rehabilitation.* 2003;24:356-360

258. Cornfield DN, Tegtmeyer K, Nelson MD, et al:. Continuous propofol infusion in 142 critically ill children. *Pediatrics.* 2002;110:1177-1181

259. Bray RJ. Propofol infusion syndrome in children. *Paediatr Anaesth.* 1998;8:491-499

260. Lien CA, Eikermann M. Neuromuscular blockers and reversal drugs. In: Hemmings HC, Egan TD, eds. *Pharmacology and physiology for anesthesia.* Second ed.: Elsevier; 2019:428-454.

261. Tobias JD. Neuromuscular blocking agents. In: Fuhrman BPZJJ, ed. *Pediatric critical care.* 4 ed. Philadelphia, PA: Elsevier-Saunders; 2011.

262. Tobias JD. The use of neuromuscular-blocking agents in children. *Pediatric annals.* 1997;26:482-489

263. Murray MJ, DeBlock H, Erstad B, et al:. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med.* 2016;44:2079-2103

264. Lucas SS, Nasr VG, Ng AJ, et al:. Pediatric cardiac intensive care society 2014 consensus statement: Pharmacotherapies in cardiac critical care: Sedation, analgesia and muscle relaxant. *Pediatr Crit Care Med.* 2016;17:S3-S15

265. Jacobi JFEA. Supportive care of the critically ill patient. In: Carter BLLKDRMA, ed. *Pharmacology self-assessment program, critical care, module 2.* Kansas City: American College of Clinical Pharmacy; 1998:129-159.

266. Jurado LATAGBFEA. Neuromuscular blocking agents. In: Cohen H, ed. *Casebook in clinical pharmacokinetics and drug dosing.* McGraw-Hill Publishing; 2015.

267. Johnson PN, Miller J, Gormley AK. Continuous-infusion neuromuscular blocking agents in critically ill neonates and children. *Pharmacotherapy.* 2011;31:609-620

268. Taketomo CK. *Pediatric & neonatal dosage handbook: Lexi-comp's drug reference handbooks.* 24 ed: Lexi-Comp, Incorporated; 2018.

269. Johnson PN, Miller JL, Hagemann TM, et al:. Assessment of inpatient admissions and top 25 medications for obese pediatric patients at two academic hospitals. *American Journal of Health-System Pharmacy : AJHP : Official Journal of the American Society of Health-System Pharmacists.* 2016;73:1243-1249

270. Woo JG, Zeller MH, Wilson K, et al:. Obesity identified by discharge icd-9 codes underestimates the true prevalence of obesity in hospitalized children. *J Pediatr.* 2009;154:327-331.PMC4664085

271. Vaughns JD, Conklin LS, Long Y, et al:. Obesity and pediatric drug development. *J Clin Pharmacol.* 2018;58:650-661.PMC7335432

272. Mann R, Blibner M, Probst R, et al:. Reduced clearance of rocuronium in the obese patient. *European Journal of Anaesthesiology.* 1997;14:17-18

273. Schwartz AE, Matteo RS, Ornstein E, et al:. Pharmacokinetics and pharmacodynamics of vecuronium in the obese surgical patient. *Anesth Analg.* 1992;74:515-518

274. Rose JB, Theroux MC, Katz MS. The potency of succinylcholine in obese adolescents. *Anesth Analg.* 2000;90:576-578

275. Leykin Y, Pellis T, Lucca M, et al:. The effects of cisatracurium on morbidly obese women. *Anesth Analg.* 2004;99:1090-1094

276. Meyhoff CS, Lund J, Jenstrup MT, et al:. Should dosing of rocuronium in obese patients be based on ideal or corrected body weight? *Anesthesia and Analgesia.* 2009;109:787-792

277. Leykin Y, Pellis T, Lucca M, et al:. The pharmacodynamic effects of rocuronium when dosed according to real body weight or ideal body weight in morbidly obese patients. *Anesthesia and Analgesia.* 2004;99:1086-1089, table of contents

278. Vernon DD, Witte MK. Effect of neuromuscular blockade on oxygen consumption and energy expenditure in sedated, mechanically ventilated children. *Crit Care Med.* 2000;28:1569-1571

279. Gebara BM, Gelmini M, Sarnaik A. Oxygen consumption, energy expenditure, and substrate utilization after cardiac surgery in children. *Crit Care Med.* 1992;20:1550-1554

280. Lemson J, Driessen JJ, van der Hoeven JG. The effect of neuromuscular blockade on oxygen consumption in sedated and mechanically ventilated pediatric patients after cardiac surgery. *Intensive Care Med.* 2008;34:2268-2272

281. Palmisano BW, Fisher DM, Willis M, et al:. The effect of paralysis on oxygen consumption in normoxic children after cardiac surgery. *Anesthesiology.* 1984;61:518-522

282. Forel JM, Roch A, Marin V, et al:. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. *Crit Care Med.* 2006;34:2749-2757

283. Grawe ES, Bennett S, Hurford WE. Early paralysis for the management of ards. *Respir Care.* 2016;61:830-838

284. Bourenne J, Hraiech S, Roch A, et al:. Sedation and neuromuscular blocking agents in acute respiratory distress syndrome. *Ann Transl Med.* 2017;5:291.PMC5537113

285. Alhazzani W, Alshahrani M, Jaeschke R, et al:. Neuromuscular blocking agents in acute respiratory distress syndrome: A systematic review and meta-analysis of randomized controlled trials. *Crit Care.* 2013;17:R43.PMC3672502

286. Wilsterman MEF, de Jager P, Blokpoel R, et al:. Short-term effects of neuromuscular blockade on global and regional lung mechanics, oxygenation and ventilation in pediatric acute hypoxemic respiratory failure. *Ann Intensive Care.* 2016;6:103.PMC5081313

287. Adnet F, Dhissi G, Borron SW, et al:. Complication profiles of adult asthmatics requiring paralysis during mechanical ventilation. *Intensive Care Med.* 2001;27:1729-1736

288. Kesler SM, Sprenkle MD, David WS, et al:. Severe weakness complicating status asthmaticus despite minimal duration of neuromuscular paralysis. *Intensive Care Med.* 2009;35:157-160

289. Behbehani NA, Al-Mane F, D'Yachkova Y, et al:. Myopathy following mechanical ventilation for acute severe asthma: The role of muscle relaxants and corticosteroids. *Chest.* 1999;115:1627-1631

290. Oddo M, Feihl F, Schaller MD, et al:. Management of mechanical ventilation in acute severe asthma: Practical aspects. *Intensive Care Med.* 2006;32:501-510

291. Goh AY, Chan PW. Acute myopathy after status asthmaticus: Steroids, myorelaxants or carbon dioxide? *Respirology.* 1999;4:97-99

292. Chin KH, Bell MJ, Wisniewski SR, et al:. Effect of administration of neuromuscular blocking agents in children with severe traumatic brain injury on acute complication rates and outcomes: A secondary analysis from a randomized, controlled trial of therapeutic hypothermia. *Pediatr Crit Care Med.* 2015;16:352-358.PMC4424136

293. Morrow SE, Pearson M. Management strategies for severe closed head injuries in children. *Semin Pediatr Surg.* 2010;19:279-285

294. Kochanek PM, Tasker RC, Carney N, et al:. Guidelines for the management of pediatric severe traumatic brain injury, third edition: Update of the brain trauma foundation guidelines. *Pediatr Crit Care Med.* 2019;20:S1-S82

295. Venkataraman ST. Mechanical ventilation and repiratory care. In: Fuhrman BP, Zimmerman J, eds. *Pediatric critical care.* Fourth ed.: Elsevier; 2011:657-688.

296. Playfor S, Jenkins I, Boyles C, et al:. Consensus guidelines for sustained neuromuscular blockade in critically ill children. *Paediatr Anaesth.* 2007;17:881-887

297. Zuppa AF, Curley MAQ. Sedation analgesia and neuromuscular blockade in pediatric critical care: Overview and current landscape. *Pediatr Clin North Am.* 2017;64:1103-1116

298. Tamion F, Hamelin K, Duflo A, et al:. Gastric emptying in mechanically ventilated critically ill patients: Effect of neuromuscular blocking agent. *Intensive Care Med.* 2003;29:1717-1722

299. Briassoulis G, Venkataraman S, Thompson AE. Energy expenditure in critically ill children. *Crit Care Med.* 2000;28:1166-1172

300. Taylor RM, Cheeseman P, Preedy V, et al:. Can energy expenditure be predicted in critically ill children? *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2003;4:176-180

301. McCall M, Jeejeebhoy K, Pencharz P, et al:. Effect of neuromuscular blockade on energy expenditure in patients with severe head injury. *JPEN J Parenter Enteral Nutr.* 2003;27:27-35

302. Mehta NM, Compher C, Directors ASPENBo. A.S.P.E.N. Clinical guidelines: Nutrition support of the critically ill child. *JPEN J Parenter Enteral Nutr.* 2009;33:260-276

303. Skillman HE, Mehta NM. Nutrition therapy in the critically ill child. *Curr Opin Crit Care.* 2012;18:192-198

304. Guess R, Vaewpanich J, Coss-Bu JA, et al:. Risk factors for ventilator-associated events in a picu. *Pediatr Crit Care Med.* 2018;19:e7-e13

305. Hamele M, Stockmann C, Cirulis M, et al:. Ventilator-associated pneumonia in pediatric traumatic brain injury. *J Neurotrauma.* 2016;33:832-839.PMC4939445

306. Fayon MJ, Tucci M, Lacroix J, et al:. Nosocomial pneumonia and tracheitis in a pediatric intensive care unit: A prospective study. *Am J Respir Crit Care Med.* 1997;155:162-169

307. Srinivasan R, Asselin J, Gildengorin G, et al:. A prospective study of ventilator-associated pneumonia in children. *Pediatrics.* 2009;123:1108-1115

308. Puthucheary Z, Rawal J, Ratnayake G, et al:. Neuromuscular blockade and skeletal muscle weakness in critically ill patients: Time to rethink the evidence? *Am J Respir Crit Care Med.* 2012;185:911-917

309. Greenberg SB, Vender J. The use of neuromuscular blocking agents in the icu: Where are we now? *Critical Care Medicine.* 2013;41:1332-1344

310. Hraiech S, Forel JM, Papazian L. The role of neuromuscular blockers in ards: Benefits and risks. *Curr Opin Crit Care.* 2012;18:495-502

311. Iodice F, Salzano M, Prosperi M, et al:. Acute quadriplegic myopathy in a 16-month-old child. *Paediatr Anaesth.* 2005;15:611-615

312. Banwell BL, Mildner RJ, Hassall AC, et al:. Muscle weakness in critically ill children. *Neurology.* 2003;61:1779-1782

313. Tabarki B, Coffinieres A, Van Den Bergh P, et al:. Critical illness neuromuscular disease: Clinical, electrophysiological, and prognostic aspects. *Arch Dis Child.* 2002;86:103-107.PMC1761057

314. Bagshaw O. A combination of total intravenous anesthesia and thoracic epidural for thymectomy in juvenile myasthenia gravis. *Paediatr Anaesth.* 2007;17:370-374

315. Rubin JE, Ramamurthi RJ. The role of sugammadex in symptomatic transient neonatal myasthenia gravis: A case report. *A A Case Rep.* 2017;9:271-273

316. Schaller SJ, Fink H. Sugammadex as a reversal agent for neuromuscular block: An evidence-based review. *Core evidence.* 2013;8:57-67

317. Sungur Z, Senturk M. Anaesthesia for thymectomy in adult and juvenile myasthenic patients. *Curr Opin Anaesthesiol.* 2016;29:14-19

318. Vymazal T, Krecmerova M, Bicek V, et al:. Feasibility of full and rapid neuromuscular blockade recovery with sugammadex in myasthenia gravis patients undergoing surgery - a series of 117 cases. *Ther Clin Risk Manag.* 2015;11:1593-1596.PMC4610805

319. Matthews HJ, Thambundit A, Allen BR. Anti-musk-positive myasthenic crisis in a 7-year-old female. *Case Rep Emerg Med.* 2017;2017:8762302.PMC5429919

320. Alvarez RV, Palmer C, Czaja AS, et al:. Delirium is a common and early finding in patients in the pediatric cardiac intensive care unit. *The Journal of pediatrics.* 2018;195:206-212

321. Cano Londono EM, Mejia Gil IC, Uribe Hernandez K, et al:. Delirium during the first evaluation of children aged five to 14years admitted to a paediatric critical care unit. *Intensive Crit Care Nurs.* 2018;45:37-43

322. Grover S, Kate N, Malhotra S, et al:. Symptom profile of delirium in children and adolescent--does it differ from adults and elderly? *General hospital psychiatry.* 2012;34:626-632

323. Luetz A, Gensel D, Muller J, et al:. Validity of different delirium assessment tools for critically ill children: Covariates matter. *Crit Care Med.* 2016;44:2060-2069

324. Meyburg J, Dill ML, Traube C, et al:. Patterns of postoperative delirium in children. *Pediatr Crit Care Med.* 2017;18:128-133

325. Patel AK, Biagas KV, Clarke EC, et al:. Delirium in children after cardiac bypass surgery. *Pediatr Crit Care Med.* 2017;18:165-171.PMC5658045

326. Schieveld JN, Leroy PL, van Os J, et al:. Pediatric delirium in critical illness: Phenomenology, clinical correlates and treatment response in 40 cases in the pediatric intensive care unit. *Intensive Care Med.* 2007;33:1033-1040.PMC1915613

327. Simone S, Edwards S, Lardieri A, et al:. Implementation of an icu bundle: An interprofessional quality improvement project to enhance delirium management and monitor delirium prevalence in a single picu. *Pediatr Crit Care Med.* 2017;18:531-540

328. Smith HA, Gangopadhyay M, Goben CM, et al:. The preschool confusion assessment method for the icu: Valid and reliable delirium monitoring for critically ill infants and children. *Crit Care Med.* 2016;44:592-600.PMC4764386

329. Traube C, Silver G, Gerber LM, et al:. Delirium and mortality in critically ill children: Epidemiology and outcomes of pediatric delirium. *Crit Care Med.* 2017;45:891-898.PMC5392157

330. Traube C, Silver G, Reeder RW, et al:. Delirium in critically ill children: An international point prevalence study. *Crit Care Med.* 2017;45:584-590.PMC5350030

331. de Castro REV, Prata-Barbosa A, de Magalhaes-Barbosa MC, et al:. Validity and reliability of the brazilian portuguese version of the pediatric confusion assessment method for the icu. *Pediatr Crit Care Med.* 2020;21:e39-e46

332. Ista E, van Beusekom B, van Rosmalen J, et al:. Validation of the sos-pd scale for assessment of pediatric delirium: A multicenter study. *Crit Care.* 2018;22:309.PMC6247513

333. Matsuishi Y, Hoshino H, Shimojo N, et al:. Verifying the japanese version of the preschool confusion assessment method for the icu (pscam-icu). *Acute Med Surg.* 2019;6:287-293.PMC6603317

334. Silver G, Traube C, Gerber LM, et al:. Pediatric delirium and associated risk factors: A single-center prospective observational study. *Pediatr Crit Care Med.* 2015;16:303-309.PMC5031497

335. Traube C, Ariagno S, Thau F, et al:. Delirium in hospitalized children with cancer: Incidence and associated risk factors. *J Pediatr.* 2017;191:212-217

336. Dervan LA, Di Gennaro JL, Farris RWD, et al:. Delirium in a tertiary picu: Risk factors and outcomes. *Pediatr Crit Care Med.* 2020;21:21-32

337. Patel AK, Biagas KV, Clark EC, et al:. Delirium in the pediatric cardiac extracorporeal membrane oxygenation patient population: A case series. *Pediatr Crit Care Med.* 2017;18:e621-e624

338. Schieveld JN, Lousberg R, Berghmans E, et al:. Pediatric illness severity measures predict delirium in a pediatric intensive care unit. *Crit Care Med.* 2008;36:1933-1936

339. Barr J, Fraser GL, Puntillo K, et al:. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical Care Medicine.* 2013;41:263-306

340. Hshieh TT, Yue J, Oh E, et al:. Effectiveness of multicomponent nonpharmacological delirium interventions: A meta-analysis. *JAMA Intern Med.* 2015;175:512-520.PMC4388802

341. Inouye SK, Bogardus ST, Jr., Charpentier PA, et al:. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med.* 1999;340:669-676

342. Litton E, Carnegie V, Elliott R, et al:. The efficacy of earplugs as a sleep hygiene strategy for reducing delirium in the icu: A systematic review and meta-analysis. *Critical Care Medicine.* 2016;44:992-999

343. Patel J, Baldwin J, Bunting P, et al:. The effect of a multicomponent multidisciplinary bundle of interventions on sleep and delirium in medical and surgical intensive care patients. *Anaesthesia.* 2014;69:540-549

344. Kudchadkar SR, Yaster M, Punjabi NM. Sedation, sleep promotion, and delirium screening practices in the care of mechanically ventilated children: A wake-up call for the pediatric critical care community\*. *Crit Care Med.* 2014;42:1592-1600.PMC4061156

345. Kawai Y, Weatherhead JR, Traube C, et al:. Quality improvement initiative to reduce pediatric intensive care unit noise pollution with the use of a pediatric delirium bundle. *J Intensive Care Med.* 2019;34:383-390

346. Smeets IA, Tan EY, Vossen HG, et al:. Prolonged stay at the paediatric intensive care unit associated with paediatric delirium. *European child & adolescent psychiatry.* 2010;19:389-393

347. Traube C, Mauer EA, Gerber LM, et al:. Cost associated with pediatric delirium in the icu. *Crit Care Med.* 2016;44:e1175-e1179.PMC5592112

348. Gunther ML, Morandi A, Krauskopf E, et al:. The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: The visions cohort magnetic resonance imaging study\*. *Critical Care Medicine.* 2012;40:2022-2032

349. Girard TD, Jackson JC, Pandharipande PP, et al:. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Critical Care Medicine.* 2010;38:1513-1520

350. Pandharipande PP, Girard TD, Jackson JC, et al:. Long-term cognitive impairment after critical illness. *N Engl J Med.* 2013;369:1306-1316.PMC3922401

351. Fann JR, Alfano CM, Roth-Roemer S, et al:. Impact of delirium on cognition, distress, and health-related quality of life after hematopoietic stem-cell transplantation. *J Clin Oncol.* 2007;25:1223-1231

352. Colville G, Kerry S, Pierce C. Children's factual and delusional memories of intensive care. *Am J Respir Crit Care Med.* 2008;177:976-982

353. Pandharipande PP, Ely EW, Arora RC, et al:. The intensive care delirium research agenda: A multinational, interprofessional perspective. *Intensive Care Med.* 2017;43:1329-1339.PMC5709210

354. Paterson RS, Kenardy JA, De Young AC, et al:. Delirium in the critically ill child: Assessment and sequelae. *Dev Neuropsychol.* 2017;42:387-403

355. Colville GA, Pierce CM. Children's self-reported quality of life after intensive care treatment. *Pediatr Crit Care Med.* 2013;14:e85-92

356. Rohlik GM, Fryer KR, Tripathi S, et al:. Overcoming barriers to delirium screening in the pediatric intensive care unit. *Crit Care Nurse.* 2018;38:57-67

357. Smith HA, Brink E, Fuchs DC, et al:. Pediatric delirium: Monitoring and management in the pediatric intensive care unit. *Pediatr Clin North Am.* 2013;60:741-760

358. Ely EW, Margolin R, Francis J, et al:. Evaluation of delirium in critically ill patients: Validation of the confusion assessment method for the intensive care unit (cam-icu). *Crit Care Med.* 2001;29:1370-1379

359. Ely EW, Inouye SK, Bernard GR, et al:. Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (cam-icu). *JAMA.* 2001;286:2703-2710

360. Tsuruta R, Yamase H. Investigation of delirium in critically ill children:Japanese version of the pediatric confusion assessment method for the intensive care unit（ pcam-icu）. *Journal of Japan Academy of Critical Care Nursing.* 2011;7:45-51

361. Canter MO, Tanguturi YC, Ellen Wilson J, et al:. Prospective validation of the preschool confusion assessment method for the icu to screen for delirium in infants less than 6 months old. *Crit Care Med.* 2021;49:e902-e909

362. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology.* 2004;100:1138-1145

363. van Dijk M, Knoester H, van Beusekom BS, et al:. Screening pediatric delirium with an adapted version of the sophia observation withdrawal symptoms scale (sos). *Intensive Care Med.* 2012;38:531-532.PMC3286512

364. Ista E, de Hoog M, Tibboel D, et al:. Psychometric evaluation of the sophia observation withdrawal symptoms scale in critically ill children. *Pediatr Crit Care Med.* 2013;14:761-769

365. Ista E, Te Beest H, van Rosmalen J, et al:. Sophia observation withdrawal symptoms-paediatric delirium scale: A tool for early screening of delirium in the picu. *Aust Crit Care.* 2018;31:266-273

366. Slooff VD, van den Dungen DK, van Beusekom BS, et al:. Monitoring haloperidol plasma concentration and associated adverse events in critically ill children with delirium: First results of a clinical protocol aimed to monitor efficacy and safety. *Pediatr Crit Care Med.* 2018;19:e112-e119

367. Turkel SB, Jacobson J, Munzig E, et al:. Atypical antipsychotic medications to control symptoms of delirium in children and adolescents. *J Child Adolesc Psychopharmacol.* 2012;22:126-130

368. Turkel SB, Jacobson JR, Tavare CJ. The diagnosis and management of delirium in infancy. *J Child Adolesc Psychopharmacol.* 2013;23:352-356

369. Sassano-Higgins S, Freudenberg N, Jacobson J, et al:. Olanzapine reduces delirium symptoms in the critically ill pediatric patient. *J Pediatr Intensive Care.* 2013;2:49-54.PMC6530712

370. Slooff VD, Spaans E, van Puijenbroek E, et al:. Adverse events of haloperidol for the treatment of delirium in critically ill children. *Intensive Care Med.* 2014;40:1602-1603

371. Joyce C, Witcher R, Herrup E, et al:. Evaluation of the safety of quetiapine in treating delirium in critically ill children: A retrospective review. *J Child Adolesc Psychopharmacol.* 2015;25:666-670.PMC4808274

372. Campbell CT, Grey E, Munoz-Pareja J, et al:. An evaluation of risperidone dosing for pediatric delirium in children less than or equal to 2 years of age. *Ann Pharmacother.* 2020;54:464-469

373. Kishk OA, Simone S, Lardieri AB, et al:. Antipsychotic treatment of delirium in critically ill children: A retrospective matched cohort study. *J Pediatr Pharmacol Ther.* 2019;24:204-213.PMC6510524

374. Ratcliff SL, Meyer WJ, 3rd, Cuervo LJ, et al:. The use of haloperidol and associated complications in the agitated, acutely ill pediatric burn patient. *J Burn Care Rehabil.* 2004;25:472-478

375. Harrison AM, Lugo RA, Lee WE, et al:. The use of haloperidol in agitated critically ill children. *Clinical pediatrics.* 2002;41:51-54

376. Schieveld JN, Leentjens AF. Delirium in severely ill young children in the pediatric intensive care unit (picu). *J Am Acad Child Adolesc Psychiatry.* 2005;44:392-394; discussion 395

377. Karnik NS, Joshi SV, Paterno C, et al:. Subtypes of pediatric delirium: A treatment algorithm. *Psychosomatics.* 2007;48:253-257

378. Traube C, Witcher R, Mendez-Rico E, et al:. Quetiapine as treatment for delirium in critically ill children: A case series. *Journal of pediatric intensive care.* 2013;2:121-126

379. Traube C, Augenstein J, Greenwald B, et al:. Neuroblastoma and pediatric delirium: A case series. *Pediatr Blood Cancer.* 2014;61:1121-1123

380. Brahmbhatt K, Whitgob E. Diagnosis and management of delirium in critically ill infants: Case report and review. *Pediatrics.* 2016;137:e20151940

381. Groves A, Traube C, Silver G. Detection and management of delirium in the neonatal unit: A case series. *Pediatrics.* 2016;137:e20153369

382. Anand KJ, Arnold JH. Opioid tolerance and dependence in infants and children. *Crit Care Med.* 1994;22:334-342

383. Sorce LR. Adverse responses: Sedation, analgesia and neuromuscular blocking agents in critically ill children. *Crit Care Nurs Clin North Am.* 2005;17:441-450, xi-xii

384. Bateson AN. Basic pharmacologic mechanisms involved in benzodiazepine tolerance and withdrawal. *Curr Pharm Des.* 2002;8:5-21

385. Anand KJ, Clark AE, Willson DF, et al:. Opioid analgesia in mechanically ventilated children: Results from the multicenter measuring opioid tolerance induced by fentanyl study. *Pediatr Crit Care Med.* 2013;14:27-36.PMC3581608

386. Arnold JH, Truog RD, Orav EJ, et al:. Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. *Anesthesiology.* 1990;73:1136-1140

387. Anand KJ, Willson DF, Berger J, et al:. Tolerance and withdrawal from prolonged opioid use in critically ill children. *Pediatrics.* 2010;125:1208

388. Suresh S, Anand KJ. Opioid tolerance in neonates: A state-of-the-art review. *Paediatr Anaesth.* 2001;11:511-521

389. Welzing L, Link F, Junghaenel S, et al:. Remifentanil-induced tolerance, withdrawal or hyperalgesia in infants: A randomized controlled trial. Rapip trial: Remifentanil-based analgesia and sedation of paediatric intensive care patients. *Neonatology.* 2013;104:34-41

390. Penk JS, Lefaiver CA, Brady CM, et al:. Intermittent versus continuous and intermittent medications for pain and sedation after pediatric cardiothoracic surgery; a randomized controlled trial. *Crit Care Med.* 2018;46:123-129

391. van Dijk M, Bouwmeester NJ, Duivenvoorden HJ, et al:. Efficacy of continuous versus intermittent morphine administration after major surgery in 0-3-year-old infants; a double-blind randomized controlled trial. *Pain.* 2002;98:305-313

392. Cho HH, O'Connell JP, Cooney MF, et al:. Minimizing tolerance and withdrawal to prolonged pediatric sedation: Case report and review of the literature. *J Intensive Care Med.* 2007;22:173-179

393. Hammer GB. Sedation and analgesia in the pediatric intensive care unit following laryngotracheal reconstruction. *Paediatr Anaesth.* 2009;19 Suppl 1:166-179

394. Grindstaff RJ, Tobias JD. Applications of bispectral index monitoring in the pediatric intensive care unit. *J Intensive Care Med.* 2004;19:111-116

395. Arenas-Lopez S, Riphagen S, Tibby SM, et al:. Use of oral clonidine for sedation in ventilated paediatric intensive care patients. *Intensive care medicine.* 2004;30:1625-1629

396. Duffett M, Choong K, Foster J, et al:. Clonidine in the sedation of mechanically ventilated children: A pilot randomized trial. *J Crit Care.* 2014;29:758-763

397. Salarian S, Khosravi R, Khanbabaei G, et al:. Impact of oral clonidine on duration of opioid and benzodiazepine use in mechanically ventilated children: A randomized, double-blind, placebo-controlled study. *Iran J Pharm Res.* 2019;18:2157-2162.PMC7059056

398. Oschman A, McCabe T, Kuhn RJ. Dexmedetomidine for opioid and benzodiazepine withdrawal in pediatric patients. *Am J Health Syst Pharm.* 2011;68:1233-1238

399. Fernandez-Carrion F, Gaboli M, Gonzalez-Celador R, et al:. Withdrawal syndrome in the pediatric intensive care unit. Incidence and risk factors. *Med Intensiva.* 2013;37:67-74

400. Best KM, Wypij D, Asaro LA, et al:. Patient, process, and system predictors of iatrogenic withdrawal syndrome in critically ill children. *Crit Care Med.* 2017;45:e7-e15

401. Katz R, Kelly HW, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. *Crit Care Med.* 1994;22:763-767

402. Amigoni A, Mondardini MC, Vittadello I, et al:. Withdrawal assessment tool-1 monitoring in picu: A multicenter study on iatrogenic withdrawal syndrome. *Pediatr Crit Care Med.* 2017;18:e86-e91

403. Fisher D, Grap MJ, Younger JB, et al:. Opioid withdrawal signs and symptoms in children: Frequency and determinants. *Heart Lung.* 2013;42:407-413

404. Ista E, van Dijk M, Gamel C, et al:. Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: A first evaluation. *Critical Care Medicine.* 2008;36:2427-2432

405. Franck LS, Harris SK, Soetenga DJ, et al:. The withdrawal assessment tool-1 (wat-1): An assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. *Pediatr Crit Care Med.* 2008;9:573-580.PMC2775493

406. Jeffries SA, McGloin R, Pitfield AF, et al:. Use of methadone for prevention of opioid withdrawal in critically ill children. *The Canadian journal of hospital pharmacy.* 2012;65:12-18

407. Hughes J, Gill A, Leach HJ, et al:. A prospective study of the adverse effects of midazolam on withdrawal in critically ill children. *Acta Paediatr.* 1994;83:1194-1199

408. Dominguez KD, Crowley MR, Coleman DM, et al:. Withdrawal from lorazepam in critically ill children. *Ann Pharmacother.* 2006;40:1035-1039

409. Burbano NH, Otero AV, Berry DE, et al:. Discontinuation of prolonged infusions of dexmedetomidine in critically ill children with heart disease. *Intensive Care Med.* 2012;38:300-307.PMC3741648

410. Banasch HL, Dersch-Mills DA, Boulter LL, et al:. Dexmedetomidine use in a pediatric intensive care unit: A retrospective cohort study. *The Annals of Pharmacotherapy.* 2018;52:133-139

411. Carney L, Kendrick J, Carr R. Safety and effectiveness of dexmedetomidine in the pediatric intensive care unit (sad-picu). *Can J Hosp Pharm.* 2013;66:21-27.PMC3583774

412. Abdouni R, Reyburn-Orne T, Youssef TH, et al:. Impact of a standardized treatment guideline for pediatric iatrogenic opioid dependence: A quality improvement initiative. *J Pediatr Pharmacol Ther.* 2016;21:54-65.PMC4778697

413. Sanchez-Pinto LN, Nelson LP, Lieu P, et al:. Implementation of a risk-stratified opioid weaning protocol in a pediatric intensive care unit. *J Crit Care.* 2018;43:214-219

414. Amirnovin R, Sanchez-Pinto LN, Okuhara C, et al:. Implementation of a risk-stratified opioid and benzodiazepine weaning protocol in a pediatric cardiac icu. *Pediatr Crit Care Med.* 2018;19:1024-1032

415. Vipond JM, Heiberger AL, Thompson PA, et al:. Shortened taper duration after implementation of a standardized protocol for iatrogenic benzodiazepine and opioid withdrawal in pediatric patients: Results of a cohort study. *Pediatr Qual Saf.* 2018;3:e079.PMC6132810

416. Solodiuk JC, Greco CD, O'Donnell KA, et al:. Effect of a sedation weaning protocol on safety and medication use among hospitalized children post critical illness. *J Pediatr Nurs.* 2019;49:18-23

417. Neunhoeffer F, Hanser A, Esslinger M, et al:. Ketamine infusion as a counter measure for opioid tolerance in mechanically ventilated children: A pilot study. *Paediatric drugs.* 2017;19:259-265

418. Heiberger AL, Ngorsuraches S, Olgun G, et al:. Safety and utility of continuous ketamine infusion for sedation in mechanically ventilated pediatric patients. *J Pediatr Pharmacol Ther.* 2018;23:447-454.PMC6336171

419. Sanavia E, Mencia S, Lafever SN, et al:. Sedative and analgesic drug rotation protocol in critically ill children with prolonged sedation: Evaluation of implementation and efficacy to reduce withdrawal syndrome. *Pediatr Crit Care Med.* 2019;20:1111-1117

420. Deutsch ES, Nadkarni VM. Clonidine prophylaxis for narcotic and sedative withdrawal syndrome following laryngotracheal reconstruction. *Arch Otolaryngol Head Neck Surg.* 1996;122:1234-1238

421. Ista E, van Dijk M, Gamel C, et al:. Withdrawal symptoms in children after long-term administration of sedatives and/or analgesics: A literature review. "Assessment remains troublesome". *Intensive care medicine.* 2007;33:1396-1406

422. Lardieri AB, Fusco NM, Simone S, et al:. Effects of clonidine on withdrawal from long-term dexmedetomidine in the pediatric patient. *J Pediatr Pharmacol Ther.* 2015;20:45-53.PMC4353200

423. Seo YS, Lee J, Ahn HY. Effects of kangaroo care on neonatal pain in south korea. *J Trop Pediatr.* 2016;62:246-249

424. Sanders RC, Jr., Nett ST, Davis KF, et al:. Family presence during pediatric tracheal intubations. *JAMA Pediatr.* 2016;170:e154627

425. Corser NC. Sleep of 1- and 2-year-old children in intensive care. *Issues Compr Pediatr Nurs.* 1996;19:17-31

426. Cureton-Lane RA, Fontaine DK. Sleep in the pediatric icu: An empirical investigation. *Am J Crit Care.* 1997;6:56-63

427. Armour AD, Khoury JC, Kagan RJ, et al:. Clinical assessment of sleep among pediatric burn patients does not correlate with polysomnography. *Journal of burn care & research : official publication of the American Burn Association.* 2011;32:529-534

428. Gottschlich MM, Jenkins ME, Mayes T, et al:. The 1994 clinical research award. A prospective clinical study of the polysomnographic stages of sleep after burn injury. *J Burn Care Rehabil.* 1994;15:486-492

429. Al-Samsam RH, Cullen P. Sleep and adverse environmental factors in sedated mechanically ventilated pediatric intensive care patients. *Pediatr Crit Care Med.* 2005;6:562-567

430. Goldie L, Van Velzer C. Innate sleep rhythms. *Brain.* 1965;88:1043-1056

431. Stern E, Parmelee AH, Akiyama Y, et al:. Sleep cycle characteristics in infants. *Pediatrics.* 1969;43:65-70

432. Carno MA, Hoffman LA, Henker R, et al:. Sleep monitoring in children during neuromuscular blockade in the pediatric intensive care unit: A pilot study. *Pediatr Crit Care Med.* 2004;5:224-229

433. Kudchadkar SR, Aljohani OA, Punjabi NM. Sleep of critically ill children in the pediatric intensive care unit: A systematic review. *Sleep Med Rev.* 2014;18:103-110.PMC3883975

434. Berglund B, Lindvall T, Schwela DH. *World health organization guidelines for community noise.* Geneva, Switzerland: World Health Organization;1999.

435. Maestroni GJ. The immunoneuroendocrine role of melatonin. *J Pineal Res.* 1993;14:1-10

436. Pandi-Perumal SR, Srinivasan V, Maestroni GJ, et al:. Melatonin: Nature's most versatile biological signal? *The FEBS journal.* 2006;273:2813-2838

437. Pandi-Perumal SR, Trakht I, Srinivasan V, et al:. Physiological effects of melatonin: Role of melatonin receptors and signal transduction pathways. *Prog Neurobiol.* 2008;85:335-353

438. Bagci S, Horoz OO, Yildizdas D, et al:. Melatonin status in pediatric intensive care patients with sepsis. *Pediatr Crit Care Med.* 2012;13:e120-123

439. Marseglia L, D'Angelo G, Manti S, et al:. Melatonin secretion is increased in children with severe traumatic brain injury. *International journal of molecular sciences.* 2017;18:10.3390/ijms18051053

440. Engwall M, Fridh I, Johansson L, et al:. Lighting, sleep and circadian rhythm: An intervention study in the intensive care unit. *Intensive Crit Care Nurs.* 2015;31:325-335

441. Dennis CM, Lee R, Woodard EK, et al:. Benefits of quiet time for neuro-intensive care patients. *J Neurosci Nurs.* 2010;42:217-224

442. Mirmiran M, Baldwin RB, Ariagno RL. Circadian and sleep development in preterm infants occurs independently from the influences of environmental lighting. *Pediatr Res.* 2003;53:933-938

443. Jones C, Dawson D. Eye masks and earplugs improve patient's perception of sleep. *Nurs Crit Care.* 2012;17:247-254

444. Richardson A, Allsop M, Coghill E, et al:. Earplugs and eye masks: Do they improve critical care patients' sleep? *Nursing in critical care.* 2007;12:278-286

445. Le Guen M, Nicolas-Robin A, Lebard C, et al:. Earplugs and eye masks vs routine care prevent sleep impairment in post-anaesthesia care unit: A randomized study. *Br J Anaesth.* 2014;112:89-95

446. Hu RF, Jiang XY, Hegadoren KM, et al:. Effects of earplugs and eye masks combined with relaxing music on sleep, melatonin and cortisol levels in icu patients: A randomized controlled trial. *Crit Care.* 2015;19:115.PMC4391192

447. Choong K, Awladthani S, Khawaji A, et al:. Early exercise in critically ill youth and children, a preliminary evaluation: The weecycle pilot trial. *Pediatr Crit Care Med.* 2017;18:e546-e554

448. Fink EL, Beers SR, Houtrow AJ, et al:. Early protocolized versus usual care rehabilitation for pediatric neurocritical care patients: A randomized controlled trial. *Pediatr Crit Care Med.* 2019;20:540-550.PMC7112470

449. Tsuboi N, Hiratsuka M, Kaneko S, et al:. Benefits of early mobilization after pediatric liver transplantation. *Pediatr Crit Care Med.* 2019;20:e91-e97

450. Wieczorek B, Ascenzi J, Kim Y, et al:. Picu up!: Impact of a quality improvement intervention to promote early mobilization in critically ill children. *Pediatr Crit Care Med.* 2016;17:e559-e566.PMC5138131

451. Abdulsatar F, Walker RG, Timmons BW, et al:. "Wii-hab" in critically ill children: A pilot trial. *J Pediatr Rehabil Med.* 2013;6:193-204

452. Choong K, Chacon MDP, Walker RG, et al:. In-bed mobilization in critically ill children: A safety and feasibility trial. *J Pediatr Intensive Care.* 2015;4:225-234.PMC6513137

453. Jacobs BR, Salman BA, Cotton RT, et al:. Postoperative management of children after single-stage laryngotracheal reconstruction. *Crit Care Med.* 2001;29:164-168

454. Melchers P, Maluck A, Suhr L, et al:. An early onset rehabilitation program for children and adolescents after traumatic brain injury (tbi): Methods and first results. *Restor Neurol Neurosci.* 1999;14:153-160

455. Wieczorek B, Burke C, Al-Harbi A, et al:. Early mobilization in the pediatric intensive care unit: A systematic review. *J Pediatr Intensive Care.* 2015;2015:129-170.PMC4568750

456. Cuello-Garcia CA, Mai SHC, Simpson R, et al:. Early mobilization in critically ill children: A systematic review. *J Pediatr.* 2018;203:25-33 e26

457. Piva TC, Ferrari RS, Schaan CW. Early mobilization protocols for critically ill pediatric patients: Systematic review. *Rev Bras Ter Intensiva.* 2019;31:248-257.PMC6649221

458. Ely EW. The abcdef bundle: Science and philosophy of how icu liberation serves patients and families. *Crit Care Med.* 2017;45:321-330.PMC5830123

459. Choong K, Foster G, Fraser DD, et al:. Acute rehabilitation practices in critically ill children: A multicenter study. *Pediatr Crit Care Med.* 2014;15:e270-279

460. Zheng K, Sarti A, Boles S, et al:. Impressions of early mobilization of critically ill children-clinician, patient, and family perspectives. *Pediatr Crit Care Med.* 2018;19:e350-e357

461. Joyce CL, Taipe C, Sobin B, et al:. Provider beliefs regarding early mobilization in the pediatric intensive care unit. *Journal of pediatric nursing.* 2018;38:15-19

462. Colwell BRL, Olufs E, Zuckerman K, et al:. Picu early mobilization and impact on parent stress. *Hosp Pediatr.* 2019;9:265-272

463. Betters KA, Hebbar KB, Farthing D, et al:. Development and implementation of an early mobility program for mechanically ventilated pediatric patients. *J Crit Care.* 2017;41:303-308