

Supplementary Table 5. Summary of clinical settings and implemented sedation protocols of the included studies

Study	Setting	Intervention	Sedation protocol			
			Assessment	Modification	Sedatives	Major analgesics
Blackwood <sup>3)</sup>	Medical and surgical ICU	Protocolized sedation	COMFORT Original or COMFORT B score every 6 hours, SBT readiness twice daily if patient is eligible, initiation of SBT when screening criteria are satisfied, daily multiprofessional round Target level: acute phase: 13-17/10-12, weaning: 18-25/12-17	During ward round, ICU team reviews patients' sedation management including COMFORT scores, sedative regimen and setting sedation targets, bedside nurse modifies sedation settings to reach target level	Data on sedatives, analgesics, and sedation levels were not collected; it was recommended that ICU teams consider the sedation needs of the infant or child based on COMFORT scores and SBT readiness screenings	
Chomat <sup>4)</sup>	CICU	Protocolized sedation	SBS, CAPD documented twice daily when SBS $\geq -1$ , WAT-1 score is used to identify withdrawal, initiation, and weaning of intermittent sedative medications	Modified according to attending physician	Primary: midazolam, dexmedetomidine Weaning: lorazepam for benzodiazepine habituation, and clonidine for dexmedetomidine habituation	Primary: fentanyl Weaning: morphine or methadone for opioid habituation
Curley <sup>5)</sup>	Mixed (medical, surgical)	Protocolized sedation	SBS daily, modified arousal assessment if SBS $\leq -2$ , ERT daily when screening criteria are satisfied, WAT-1 during weaning	Nurses used the algorithm with a standardized order set to manage sedation per phase of illness and prescribed SBS score.	Primary: midazolam Secondary: propofol, dexmedetomidine, clonidine, pentobarbital, ketamine	Primary: morphine Secondary: fentanyl

Deeter <sup>6)</sup>	Mixed (medical, surgical, cardiac)	Protocolized sedation	SCCP: COMFORT score every 4 hours after intubation/admission, reassess every 12 hours	Boluses prn by nurse, continuous infusion dose, weaning ordered by attending physician	lorazepam	morphine
Gaillard-Le Roux <sup>7)</sup>	Mixed (medical, surgical, cardiac)	Protocolized sedation	COMFORT-B scale every 3 hours, target set by attending physician, withdrawal suspicion: SOS	Continuous dose and bolus prescribed daily by attending physician, nurses adjusted dose per protocol to reach target level of sedation	Primary: midazolam Secondary: ketamine, clonidine	Morphine, sufentanil
Hanser <sup>8)</sup>	CICU	Protocolized sedation	COMFORT-B every 8 hours, target 12-18, NISS: target 2	Continuous infusion rate and additional boluses administered by nurse according to protocol to reach target level of sedation, during weaning medications were reduced according to protocol	Midazolam, clonidine Secondary: chloral hydrate,	Morphine
Jin <sup>9)</sup>	Medical PICU	Protocolized sedation	COMFORT twice daily, target 17-26, weaning: modified Finnegan score for withdrawal	Continuous infusion rate and additional boluses administered by nurse according to protocol to reach target level of sedation, weaning according to protocol	Midazolam, lorazepam, chloral hydrate	fentanyl
Keogh <sup>10)</sup>	Mixed (medical, surgical)	Protocolized sedation	SBS, MAPS, Opioid Benzodiazepine WAS	Phases: acute, plateau, weaning Prescribed by attending physician, implemented by nurses	Primary: midazolam Secondary: clonidine Weaning: diazepam	Primary: morphine Secondary: fentanyl Weaning: methadone
Kleiber <sup>11)</sup>	CICU	Protocolized sedation	COMFORT-B every 4 hours, target 10-20	Titrated by bedside nurse within boundary of protocol	Primary: clonidine Secondary: midazolam	Morphine
Kozin <sup>12)</sup>	Surgical PICU (LTR surgery)	Protocolized sedation weaning	Clinical assessment, withdrawal assessment every 6 hours	Decrease doses according to protocol, rescue therapy when necessary	Midazolam, propofol, dexmedetomidine, lorazepam	Morphine, fentanyl

Neunhoeffter 2015 <sup>13)</sup>	Mixed (medical, surgical, cardiac)	Protocolized sedation	COMFORT-B target 12-18, NISS target 2, weaning: SOS every 8 hours	Titrate by bedside nurse within boundary of protocol	Primary: midazolam Secondary: clonidine, chloral hydrate	Morphine
Neunhoeffter 2016 <sup>14)</sup>	Surgical PICU	Protocolized sedation	COMFORT-B target 12-18, NISS target 2, weaning: SOS every 8 hours	Titrate by bedside nurse within boundary of protocol	Primary: midazolam Secondary: clonidine, chloral hydrate	Primary: morphine Secondary: fentanyl
Saelim <sup>15)</sup>	Mixed (medical, surgical)	Protocolized sedation	COMFORT-B target 11-22 twice daily	Titrate by bedside nurse within boundary of protocol	Primary: midazolam Secondary: lorazepam, chloral hydrate	Primary: morphine Secondary: fentanyl
Sanchez-Pinto <sup>16)</sup>	Mixed (medical, surgical)	Protocolized sedation weaning	Opioid weaning protocol, withdrawal assessed with WAT-1 every 6 hours	Risk stratification before weaning, decrease dose and convert medication to according to protocol, rescue therapy determined by bedside team		Primary: fentanyl, hydromorphone Weaning: hydromorphone, methadone
Solodiuk <sup>17)</sup>	Mixed (medical, surgical, cardiac)	Protocolized sedation weaning	Sedative and opiate weaning, WAT-1 > 3 indicate withdrawal	Implemented by bedside nurse according to weaning protocol to reach weaning duration goal	Midazolam, lorazepam, diazepam, clonidine, dexmedetomidine, pentobarbital	Morphine, methadone, hydromorphone, fentanyl
Tiacharoen <sup>18)</sup>	Mixed (medical, surgical)	Protocolized sedation weaning	Sedative and opioid weaning, WAT-1 > 3 indicate withdrawal, every 4 hours, sedation was assessed using SBS, target 0 to -1	Iv midazolam and fentanyl converted to oral lorazepam and methadone according to protocol	Primary: midazolam Secondary: lorazepam, dexmedetomidine	Primary: fentanyl Secondary: methadone
Verlaet <sup>19)</sup>	Mixed (medical, surgical)	Daily sedation interruption	COMFORT-B every 2 hours, target ≤ 17, daily sedation interruption	Sedatives stopped at 1 pm, restarted when COMFORT-B ≥ 17	midazolam	morphine

Wilson <sup>20)</sup>	Mixed (medical, trauma, surgical, cardiac)	Protocolized sedation weaning	Low-/high risk for withdrawal, convert iv fentanyl and morphine to enteral methadone, iv midazolam to enteral lorazepam, WAT-1 every 12 hours and after rescue dose, $\geq 3$ indicates withdrawal	Medications converted doses modified according to written protocol, withdrawal symptoms indicate rescue therapy according to protocol	Primary: midazolam Secondary: lorazepam	Primary: morphine, fentanyl Secondary: methadone
Achuff <sup>21)</sup>	Cardiac ICU	Protocolized sedation weaning	WAT-1 scores on 1 <sup>st</sup> day of weaning and continued for 72 hr, threshold is a score of 4, Sedation is protocolized in both cohorts with SBS assessment every 4 hr	IV opioids are given if WAT-1 greater or equal to 4, once dose thresholds are met, conversion to enteral opioids	Primary: none Secondary: Dexmedetomidine, benzodiazepines (midazolam, diazepam, lorazepam, clonazepam)	Primary: fentanyl Weaning: Methadone or morphine
Alfraij <sup>22)</sup>	Mixed (medical, surgical)	Protocolized sedation	Bloomsbury score (BBS), target 0 to +1 (arousal/awake sedation target), daily revision of target	Four level algorithm applied, use according to protocol to reach target sedation  Level 1: as needed doses of intermittent opioids with restricted use of benzodiazepines  Level 2: intermittent doses of opioids with/without benzodiazepines  Level 3: continuous infusions of opioids and sedatives  Level 4: opioids, sedatives and a paralytic agent	Not specified	Not specified

Dokken <sup>23)</sup>	Mixed (medical, surgical)	Protocolized sedation	COMFORT-B every 4hr, target $\leq$ 17, during weaning WAT-1 every 12 hr	First 2 days sedation according to COMFORT-B 2-5 days perform WAT-1, protocolized starting dose and reduction rate of opioids and sedatives After 5 days perform WAT-1, reduction rate of opioids and sedatives according to protocol	Primary: Midazolam Secondary: Dexmedetomidine, Clonidine, Ketamine	Fentanyl Morphine
King <sup>24)</sup>	Cardiac ICU	Protocolized sedation weaning	SBS scores every 2 hr in both groups, risk stratification for withdrawal 48 hr prior to extubation, WAT-1 score every 12 hr	low/moderate/high risk for withdrawal, regular assessment of WAT-1, low risk discontinue, moderate/high risk: conversion to methadone/lorazepam/clonidine	Primary: Midazolam, Dexmedetomidine Weaning: Lorazepam, Clonidine	Primary: fentanyl Weaning: methadone Rescue: morphine
Leu <sup>25)</sup>	Surgical PICU	Protocolized sedation	Adequate sedation was defined to limit spontaneous movement or signs of pain (grimacing, tachycardia, tachypnea, etc) According to bedside physician	Sedatives and opioids were titrated every 2-4 hr according to protocol doses until sedation is adequate, if not reached, dexmedetomidine or neuromuscular blockade is added, sedatives were discontinued per protocol before planned extubation	Primary: midazolam	Primary: morphine
Loberger <sup>26)</sup>	Mixed (medical, surgical)	Protocolized sedation	SBS 4 hr, target -2 to 0, when eligible for extubation SBT every 6 hr	SBS every 4 hr, to reach target sedation, Individualized Number, Faces, and FLACC pain scales for pain assessment, if goal not achieved, protocolized titration of benzodiazepines and opioids, adjuvants and non-pharmacological	Midazolam, Lorazepam, Dexmedetomidine	Fentanyl, morphine, oxycodone, hydromorphone

				treatment, when eligible for ERT, SBT, if failed, repeat after 6 hr		
Shildt <sup>27)</sup>	Mixed (medical, surgical)	Protocolized sedation	Regular SBS target -2 to -1, early planned extubation (<48 hr) and over 48 hr until extubation groups	<48-hr group: dexmedetomidine with intermittent benzodiazepine, intermittent morphine Over 48-hr group: fentanyl infusion, additional morphine or hydromorphone as needed, dexmedetomidine infusion, additional benzodiazepine as needed	Midazolam, lorazepam, dexmedetomidine	Morphine, fentanyl, hydromorphone
Taffarel <sup>28)</sup>	Mixed (medical, surgical)	Protocolized sedation	Regular RASS, assess pain with FLACC, during weaning regular SOS	Regular sedation and pain assessment, titrate sedatives and opioids according to protocol, first line dexmedetomidine or clonidine, midazolam or lorazepam, chloral hydrate, use morphine or fentanyl, in refracter inadequate sedation ketamine, propofol, thiopental Weaning: regular SOS, in high-risk group conversion to methadone	Midazolam, lorazepam, dexmedetomidine, clonidine, chloral hydrate, ketamine, propofol, thiopental	Morphine, fentanyl, methadone

COMFORT original scale<sup>29)</sup>; COMFORT B, COMFORT behavioral scale<sup>30)</sup>; SBT, spontaneous breathing trial; SBS, State Behavioral Scale<sup>31)</sup>; CAPD, Cornell's Assessment of Pediatric Deirium<sup>32)</sup>; WAT-1, Withdrawal Assessment Tool 1<sup>33)</sup>; ERT, Extubation Readiness Test; SCCP, Seattle Children's Comfort Protocol<sup>6)</sup>; SOS, Sophia Observation withdrawal Symptoms-scale<sup>34)</sup>; NISS, Nurse Interpretation of Sedation Score; MAPS, Multidisciplinary Assessment of Pain Scale<sup>35-37)</sup>; WAS, Withdrawal Assessment Scale<sup>38,39)</sup>; BBS, Bloomsbury Sedation Score; RASS, Richmond Agitation Sedation Scale; FLACC, Face, Leg, Activity, Cry, Consolability.