Analgesia and Sedation in pediatric intensive care unit

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ABSTRACT

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Treating children in an intensive care unit aims at the reversal of physiologic derangement of their organism while caring for comfortable physical and psychological environment. Any correctable environmental and physical factors causing discomfort should be addressed before the introduction of effective analgesia and sedation by pharmacological means; a normal schedule for sleep is desirable, and attention should be paid to the provision of feeding and hydration, lighting, environmental noise and the temporal orientation of the patients. All critically ill children have the right to adequate pain relief. Once adequate analgesia has been achieved, additional sedation may be required by some children. The aims of sedation are to reduce anxiety and distress of the child, and to allow for better tolerance of therapeutic and diagnostic procedures. Monitoring the level of analgesia and sedation will help to avoid both over and under treatment. There is no ideal method that will evaluate analgesia and sedation in all critically ill children. Pain scales according to child age should be used routinely, whereas the COMFORT scale is considered to be the most suitable clinical sedation scale for use in critically ill children requiring mechanical ventilation. Rather than seeking an ideal drug, strategies of drug administration that focus attention on principles of sedative pharmacology in critical illness should be utilized, and all sedation techniques must be patient-focused and individualized to patient needs through the utilization of Analgo-Sedation algorithms.

INTRODUCTION

Intensive Care Unit (ICU) is an unpleasant environment and while pain is often the root cause of distress experienced by the patient, anxiety, dyspnoea, delirium and sleep deprivation may be additive or synergistic. Factors that provoke these components of distress include underlying medical conditions, acute

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medical/surgical illness, and "routine" critical care practices like mechanical ventilation, the presence of indwelling catheters and tubes, iatrogenic illness, medication side effects, turning and suctioning, and excessive light and noise [1].

Important goals in the management of the critically ill patients include prevention and relief of suffering and distress and the provision of safe and effective care that leads to optimal outcome. Administration of sedatives and analgesics is a cornerstone for optimizing patient comfort and minimizing distress, particularly for patients on mechanical ventilation, yet it may lead to unintended consequences including adverse drug effects and delayed recovery from critical illness [2].

Effective analgesia and sedation in critically ill children includes caring for both their physiccal and psychological comfort. Any correctable environmental and physical factors causing discomfort should be addressed before the introduction of pharmacological agents; a normal sleep schedule should be attained, and attention should be paid to the provision of feeding and hydration, lighting, environmental noise, and the temporal orientation of the patients.

All critically ill children have the right to adequate pain relief. Once adequate analgesia has been achieved, additional sedative agents may be required by some children. The aims of sedation are to reduce anxiety and distress of the child, and to allow for better tolerance of therapeutic and diagnostic procedures. Facilitation of mechanical ventilation is particularly important when less physiological ventilator modes as controlled ventilation or high frequency oscillatory ventilation are applied. Further benefits of sedation may include reduced metabolic rate and oxygen demand, enhance analgesia, a less disrupted sleep pattern, and reduced patient recall of unpleasant interventions. It is also well recognized that insufficient sedation is a risk factor for inadvertent self-extubation [3].

A variety of pharmacologic factors "conspire" to increase the likelihood of excessive and/or prolonged sedative effect in a patient who is critically ill, which include altered pharmacokinetic and pharmacodynamic characteristics with prolonged administration, altered protein binding and volume status, and end-organ dysfunction. Therefore, all sedation techniques must be patient-focused and individualized to patient needs. This goal directed approach improves patient outcome and reduces the use of sedative drugs. With pain being central to ICU discomfort, current sedation strategies for critically ill adults are based on "analgo-sedation" providing analgesia first and adding sedation as required. Deep sedation with or without muscle relaxants is rarely indicated, and it is associated with a hi-

gher incidence of delirium and death [2, 4]. On the ground of better patient outcome by using lighter sedation in ICU, it is worth trying to explore whether an analogous practice could be used safely in pediatric intensive care patients as well. The objective of this article is to present a review of published data regarding analgesia and sedation in the pediatric intensive care unit (PICU).

CURRENT PRACTICE

There is considerable variation in the provision of analgesia and sedation for critically ill children. In a prospective observational study of 338 critically ill children in 20 UK PICUs, a total of 24 different sedative and analgesic agents were administered, the most commonly used drugs being midazolam and morphine. Written clinical sedation guidelines were available in 45% of the units and sedation was formally assessed in 40% of the units. One third (31%) of critically ill children were likely to receive Neuromuscular Blocking Agents (NMBA), with the depth of neuromuscular blockade routinely assessed in 16% of patients [5, 6]. An analogous study of 145 USA PICUs reported that midazolam and fentanyl predominate. Only 13.4% of the units reported using written protocols for sedatives and 26.1% for NMBA. Decisions regarding the choice of agent were usually based on clinician preference and experience and the duration of action of the agent. The depth or adequacy of sedation was monitored using clinical assessment (57%) or the Glasgow Coma Scale (47.3%) whereas NMBA activity was monitored by a peripheral nerve stimulator in 80% of units [7]. Better adherence to written sedation policy up to 66%, and use of a scoring system -COMFORT score in the majority- to assess agitation and pain in 87.7% of children, are mentioned in a relevant survey in pediatric intensive care units with fellowship training programs [8]. In a recent Spanish study of 36 PICUs it is reported that a written protocol for sedation and analgesia was used in 64% of them and diagnosis and clinical status adapted schemes in 30% of the units. Midazolam was the most widely used drug for sedation, followed by ketamine and propofol. Fentanyl was the most widely used drug for analgesia, followed by paracetamol and metamizole. The combination of midazolam and fentanyl in continuous infusion was used most frequently in patients on mechanical ventilation (MV), followed by propofol. Scales to monitor sedation and analgesia were employed in 45% of PICUs, with the Ramsay scale being the most frequently used. The bispectral index was used in 50% of PICUs. Muscle relaxants were administered to 26% of patients on MV; the most common indications for MV were head injury and severe respiratory disease. The principal methods implemented

to avoid withdrawal syndrome were a progresssive withdrawal of the drugs and morphine chloride [9]. Systematic review of published data regarding efficacy of sedation to facilitate mechanical ventilation in PICU patients showed that 39 studies evaluated 39 different sedation regimens, with 21 different scoring systems, in a total of 901 PICU/cardiac intensive care patients ranging in age from 3 days to 19 years old. The study concluded that despite the widespread use of sedatives to facilitate mechanical ventilation in the PICU, high-quality evidence to guide the clinical practice is still limited [10].

In critically ill adults, continuous infusions of sedative agents have been associated with prolonged periods of mechanical ventilation and a routine daily discontinuation of intravenous sedative agents is now recommended. This practice has been associated with a reduction in duration of mechanical ventilation and duration of intensive care unit stay, without any apparent adverse psychological effects. This approach has not yet been evaluated adequately in critically ill children where the potential adverse effects of discontinuing sedative agents include inadvertent self extubation, adverse cardiovascular effects, and possible negative psychological outcomes. However, the results of a recent randomized controlled trial of interrupted versus continuous sedative infusions in ventilated children are promising [11]. Length of mechanical ventilation, duration of intensive care unit stay, total dose of midazolam, and average calculated cost of therapy were significantly reduced in the interrupted as compared to the continuous group of sedation. Moreover, it has already been demonstrated that increased sedative use in the first 24h of weaning from mechanical ventilation is associated with failure of extubation in infants and children [12].

To forward knowledge in the field, the United Kingdom Paediatric Intensive Care Society Sedation, Analgesia and Neuromuscular Blockade Working Group produced consensus guidelines in sedation and analgesia in critically ill children, proposing grades of recommendations according to the strength and quality of levels of scientific evidence [13]. In summary, the recommendations of the working group are presented in the following areas:

1. Non-pharmacological interventions: environmental factors, relaxation, distraction, promotion of sleep and day-night orientation

Sympathetic nursing of critically ill children and careful attention to simple environmental factors enhances comfort and can reduce the need for pharmacological analgesic and sedative agents. Massage and relaxation are techniques frequently employed in the PICU and

have been shown to be beneficial. The viewing of videos has also been shown to reduce the sedation requirements of children undergoing echocardiography. The benefits of music therapy in critically ill adults have been well documented. It decreases anxiety and promotes relaxation. The play specialist has an important role in the PICU, assessing children and introducing individualized distraction therapy using music, relaxation techniques, bubble tubes and fiber-optic lights. Communication, continual reorientation, reassurance and the presence of relatives at the bedside can allay anxiety, whilst environmental factors such as special mattresses, noise reduction, and attention to fluids and feeding may all improve comfort, as these factors are frequently raised by PICU survivors as negative recollections [14]. It is important to maintain patient dignity and respect any cultural differences that may exist. Maintaining a daily schedule is helpful in reducing patient disorientation, together with the use of clocks, calendars and lighting changes to maintain day-night orientation.

Noise is one of the most common environmental complaints of both children and adults who can remember details of critical care admissions and is one of the major contributors to sleep disruption in the critically ill. Increasing evidence demonstrates the importance of normalizing the pattern of sleep in the critically ill. Even modest periods of sleep deprivation can have a significant effect on pulmonary function, and may also be detrimental to protein synthesis, healing and the function of the immune system.

Normal sleep do occur in critically ill patients independently of the level of sedation but PICU patients have disturbed sleep while in the pediatric intensive care unit related both to the illness itself and to light, noise, and caregiver activities disrupting an environment conducive to sleep. Medications administered in the pediatric intensive care unit can also disrupt sleep. In a sleep polysomnography study of 11 mechanically ventilated PICU patients sedated with midazolam and morphine severe alterations to sleep architecture were found throughout the 24 hrs, with no diurnal variations. Active sleep was severely reduced to a mean of 3% of total sleep time. There was severe sleep fragmentation as reflected by the high number of arousal episodes [15]. In another study assessing sleep patterns in two ventilated PICU patients under sedation and neuromuscular blockade found that the proportion of time in each stage was markedly differrent from developmental norms, and a greater proportion of sleep occurred during the day. Furthermore, there was substantial day-night and day-to-day variability. Interestingly, neither bolus sedation administration nor

endotracheal suctioning appeared to affect sleep [16].

APPENDIX I: Summary of recommendations

1. All critically ill children have the right to adequate relief of their pain
2. Any correctable environmental and physical factors causing discomfort should be addressed alongside the introduction of pharmacological agents.
3. A normal pattern of sleep should be encouraged. Attention should be paid to lighting, environmental noise and temporal orientation of patients.
4. Pain assessment should be performed regularly by using a scale appropriate to the age of the patient and routinely documented. The level of pain reported by the patient must be considered the current standard of analgesia.
5. Patients who cannot communicate should be assessed for the presence of pain-related behaviors and physiological indicators of pain.
6. A therapeutic plan for analgesia should be established for each patient and regularly reviewed.
7. Continuous intravenous infusions of morphine or fentanyl are recommended for relief of severe pain.
8. Non-steroidal anti-inflammatory drugs or paracetamol may be used as adjuncts to opioids in certain patients.
9. Local and regional anaesthetic techniques should be considered.
10. A patient controlled analgesia (PCA) device may be useful in older children.
11. Adequate analgesia should be provided to all critically ill children regardless of the need for sedation.
12. The level of sedation should be regularly assessed and documented using a sedation assessment scale, wherever possible using a validated scoring system such as the COMFORT scale.
13. The desired level of sedation should be identified for each patient and should be regularly reassessed.
14. Doses of sedative agents should be titrated to produce the desired level of sedation.
15. Midazolam is the recommended agent for the majority of critically ill children requiring intravenous sedation. It should be given by continuous infusion.
16. Clonidine given by continuous intravenous infusion may be used as an alternative sedative agent to midazolam.
17. Propofol should not be used to provide continuous sedation in critically ill children.
18. Early use of enteral sedative agents is recommended.
19. The use of clinical guidelines for sedation is recommended.
20. The potential for opioid and benzodiazepine withdrawal syndrome should be considered after 7 days of continuous therapy. When subsequently discontinued, the doses of these agents may need to be routinely tapered.

2. Pain assessment and analgesic management

Pain is a subjective experience, and in the absence of a clear reason to doubt them, the patient's report is the single most reliable indicator of pain and must be considered the standard to guide analgesic therapy. Whilst pain-related behaviors and physiological indicators of pain are neither sensitive nor specific to pain, their presence should be routinely documented, especially in those unable to communicate effectively.

In neonates, infants and children under 3 years of age, and patients unable to communicate, behavioral observational scales are the primary tools available for pain assessment. Such scales frequently utilize facial expres-

sion, motor responses and physiological indices to assess pain. Pain assessment in these age groups is a major challenge to health care professionals and, as in all cases where communication is impaired, one should be mindful of pathophysiological states and therapeutic interventions that are known to be painful, and integrate reports of pain from the patient's family and other care-givers. The Faces, Legs, Activity, Cry and Consolability (FLACC) Behavioral Pain Assessment Tool was developed to provide a simple and consistent method to identify, document, and evaluate pain in children who have difficulty verbalizing the presence or intensity of pain [17].

This tool includes five categories of pain behaviors, including facial expression, leg movement, activity, cry, and consolability. The acronym FLACC facilitates recall of these categories, each of which is scored from 0-2 to provide a total pain score ranging from 0-10.

In patients between 3 and 8 years of age, self reporting techniques such as "FACES scales" using either photographs or drawings of faces, may be used, although their application in the critical care environment is often difficult [18]. The Faces Pain Scale-Revised (FPS-R) was adapted from the Faces Pain Scale in order to make it possible to score on the widely accepted 0-10 metric [19]. It shows a close linear relationship with visual analog pain scales across the age range of 4 to 16 years. It is easy to administer and requires no additional equipment except for the photocopied faces.

APPENDIX II: Behavioral observational pain scale - FLACC scale

CATEGORY	SCORING		
	0	**1**	**2**
FACE	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
LEGS	Normal position or relaxe	Uneasy, restless, tense	Kicking, or legs drawn up
ACTIVITY	Lying quietly, normal position, mo-ves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
CRY	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
CONSOLABILITY	Content, relaxed	Reassured by occasionnal touching, hugging or being talked to, distractible	Difficult to consol or comfort

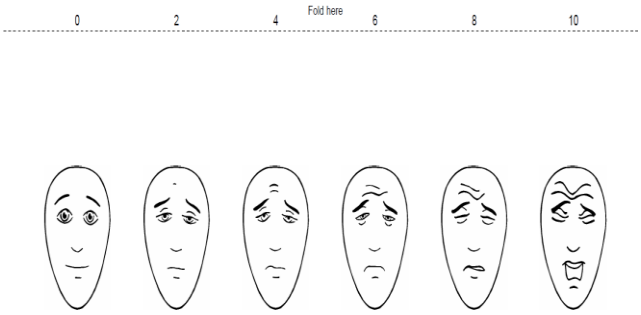
Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.

The absence of smiles and tears in this faces scale may be advantageous. The FPS-R could be used in parallel with numerical self rating scales for older children, and behavioral pain scales for younger children and those unable to provide self-report.

Willis et al. tested the validity of FLACC scale against a self report of pain using the FACES scale in 30 children aged 3-7 years and found that there were significant and positive

correlations between the FLACC and FACES scores for the entire sample and for the scores of children 5-7 years of age, but not for children < age 5. These findings provide additional support for the validity of the FLACC Pain Assessment Tool despite the disparities in the younger age group, highlighting the ongoing difficulties in pain assessment in this population [20].

APPENDIX III: The Faces Pain Scale - Revised



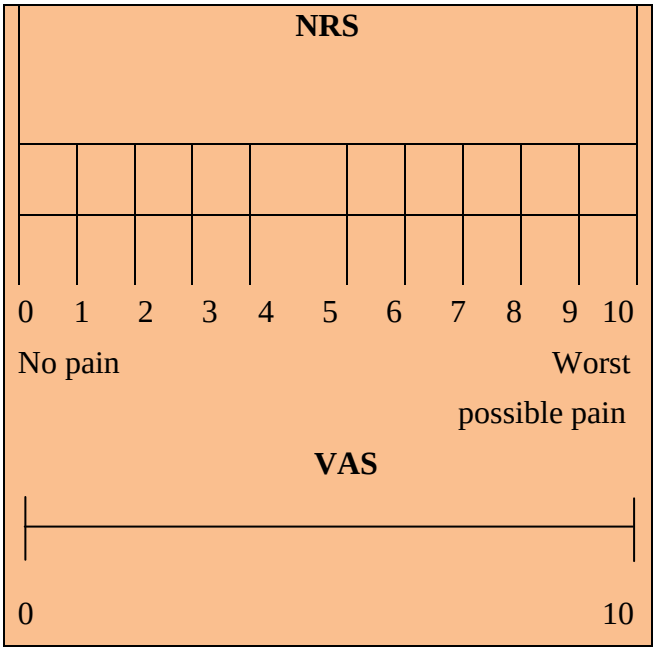
In the following instructions, say "hurt"or "pain", whichever seems right for a particular child

"These faces show how much something can hurt.This face (point-to left-most face) shows no pain. The faces show more and more pain (point to each from left to right) up to this one (point to right-most face)-it shows very much pain. Point to the face that shows how much you hurt (right now).

Score the choosen face 0,2,4,6,8,or 10, counting left to right, so 0=no pain and 10=very much pain. Do not use words like happy and sad.This scale is intended to measure how children feel inside, not how their face looks.

Above the age of 8 years, competent children can use one-dimensional tools, such as the verbal rating scale, visual analogue scale (VAS) and numeric rating scale (NRS) in the same way as adult patients. The NRS is a 0 to 10 scale where the patient chooses a number that describes their pain, with 10 representing the worst possible pain.

APPENDIX IV: Visual Analogue Pain Scale and Numeric Rating Pain Scale



The NRS has been validated against VAS and, because it can be completed by either writing or speaking, has potential advantages in critically ill patients. A therapeutic plan for analgesia should routinely be established for each patient and regularly reviewed as their clinical condition changes.

Recommended analgesic agents

The pharmacokinetics and pharmacodynamics of analgesic agents alter with age: Whilst neonates may have reduced clearance of many agents because of hepatic enzyme system immaturity, children between 2 and 6 years of age may have greater weight-indexed clearance of many agents than adults due to their higher relative liver mass.

Table 1. Recommended analgesic and sedative agents

Drug	Dosing information	Notes
Morphine	Intravenous bolus <60 kg; 100-200 μg/kg/dose >60 kg; 5-10 mg/dose Intravenous infusion <60 kg; 10-60 μg/kg/h >60 kg; 0.8-3 mg/h	Consider reduced dose in renal, hepatic impairment.Use with caution in asthmatic patients due to potential histamine release
Fentanyl	Intravenous bolus <60 kg; 1-2 μg/kg/dose >60 kg; 50-100 μg/dose Intravenous infusion <60 kg; 4-10 μg/kg/h >60 kg; 25-100 μg/h	Rapid onset Relatively long elimination half life
Remifentanil	0.02-0.15μg/kg/min (1.2-9 μg/kg/h)	Short contextsensitive half-time Relatively high cost
Paracetamol	<60kg; 10-15 mg/kg/ /dose/4 hourly >60kg; 650mg-1g/Kg/ /dose/4 hourly Max daily dose: <3 mo; 60mg/kg/day 3 mo-12y; 90mg/kg, >12y; 4g/day	
Ibuprofen	<60 kg; 6-10 mg/kg/ /dose/6 hourly >60 kg; 400-600 mg/ /dose/6 hourly Max daily dose: <60 kg; 40mg/kg/day >60 kg; 2.4 g/day	Use with caution in renal failure.Potential for gastrointestinal bleeding with platelet inhibition
Midazolam	Intravenous bolus <60 kg; 0.1-0.2 mg/kg /dose >60 kg; 5 mg/dose Intravenous infusion <60 kg;2-10 μg/kg/min (0.12-0.6 mg/kg/h) >60 kg; 5-15 mg/h	Tolerance and withdrawal.Prolonged sedation.Hypotension with bolus dosing. Consider reduced dose in renal, hepatic impairment. Reduced efficacy in infants
Lorazepam	Nasogastric tube (NG): 0.03-0.1 mg/kg/dose/6-12 h	Liver glucuronidation to inactive metabolites
Clonidine	Intravenous infusion 0.1-0.2 μg/kg/h	Avoid sudden discontinuation
Dexmedeto-midine	Intravenous infusion 0.1-0.7 μg/kg/h	Usual dose in addition to other agents, dosing up to 2 μg/kg/h
Chloral hydrate Triclofos	NG: 25-50mg/kg/d/4-6h Max 2g per dose Max daily dose: 200 mg/kg/day	Avoid in severe renal and hepatic failure.Paradoxical excitement may occur
Promethazine	NG: 1-2 mg/kg/dose/6h Max 50 mg per dose	Use with caution in neonates
Alimemazine trimeprazine	NG: 2-4 mg/kg/dose/6h Max 90 mg per dose	Avoid in renal and hepatic failure

Recommended pharmacological agents for analgesia include opioids for the relief of severe pain, nonsteroidal anti-inflammatory drugs (NSAIDs) for moderately severe pain, and paracetamol for mild to moderate pain.

Opioids

Opioids mediate analgesia by interacting at a variety of central and peripheral opioid receptorrs, most importantly μ- and κ-receptors. It is thought that interaction with other receptors may contribute to the generation of adverse effects. Morphine and fentanyl are the two most commonly used opioids in PICUs worldwide for both maintenance and breakthrough analgesia. Remifentanil is also discussed here as a newer potent opioid with unique properties.

Morphine

Morphine has a relatively long duration of action of around 2h when administered as a single dose of 0.1mg/Kg, and administration by either continuous infusion or repeated intermittent doses may therefore be considered in the PICU. Morphine has the lowest lipid solubility of all the opioids, which accounts for its slow entry into the brain and subsequent delayed onset of clinical effect. It is also the most widely used of the opioids and relieves visceral, somatic and neuropathic pain with peak analgesic effect occurring 20 min after intravenous administration. Morphine undergoes extensive hepatic and extra-hepatic glucuronidation, and metabolites are excreted primarily in the urine. Metabolism of morphine produces an active metabolite, morphine-6-

glucuronide, which may delay drug elimination in renal disease, and the analgesically inactive metabolite morphine-3-glucuronide, which fails to bind to opioid receptor and is considered to be antianalgesic. Morphine removal from the body is slow and quantitatively different in newborns (who preferentially form more morphine-3-glucuronide) but adjusts toward adult values within the first months of life. Morphine stimulates the release of significant amounts of histamine and inhibits compensatory sympathetic responses. The vasodilation produced by morphine may result in hypotension, particularly with bolus administration. Discontinuation of morphine infusions has been associated with withdrawal phenomena. The signs and symptoms include pupillary dilatation, lacrimation, sweating, goose pimples on the skin, hypertension, pyrexia, vomiting, abdominal pain, diarrhoea, muscle and joint pains and behavioural changes.

Fentanyl

Fentanyl is a synthetic opioid phenylpiperidine with approximately 100 times the analgesic potency of morphine. It is highly lipid soluble, which accounts for its rapid onset of action. Fentanyl causes less histamine release than morphine, and as such is associated with a reduced incidence of hypotension. However, fentanyl can reduce cardiac output by decreesing heart rate which is an advantage in cardiovascular conditions where ablation of the stress and/or pressor response is desirable. When given intravenously fentanyl has a relatively short half-life of 30–60 min because of rapid redistribution to peripheral compartments. With prolonged administration there is accumulation in these peripheral compartments, which increases the context sensitive half time and tolerance may rapidly develop. Metabolism occurs almost exclusively in the liver, with very little unchanged drug excreted in the urine. Clearance is therefore profoundly affected by hepatic blood flow. Fentanyl has no active metabolites and does not cross-react in patients with morphine allergy.

Remifentanil

Remifentanil is a synthetic opioid, a phenylpiperidine derivative that acts as a pure μ-receptor agonist, equipotent to fentanyl. It has cardiorespiratory effects similar to other opioids. Remifentanil's half-life is short in all age groups as it undergoes widespread extrahepatic hydrolysis by non-specific esterases in blood and tissue to form an inactive metabolite, and has a very small volume of distribution. Its clearance is not altered by pseudocholinesterase deficiency. The effects of remifentanil therefore dissipate rapidly even after prolonged infusion, giving it a short context-sensitive half-time (3-5 min) [21].

Remifentanil has been used to provide ongoing analgesia in the PICU although prolon-

ged use of this agent is associated with the rapid development of tolerance and relatively high cost. In the study of Rigby-Jones and coworkers, remifentanil/midazolam was used for sedation in 26 children 1 month–9 years old, receiving mechanical ventilation after cardiac surgery. Midazolam infusion 50 μg/kg/h at fixed rate was given with remifentanil 0.8 μg/kg/min for 60 min and decreased by 0.1 μg/kg/min every 20 min until awakening. They concluded that a combination of remifentanil and midazolam provided satisfactory sedation; younger children required higher remifentanil infusion rates than older children and adults to achieve equivalent blood concentrations [22]. In another randomized controlled trial of remifentanil versus fentanyl in 22 pediatric postoperative orthopedic patients, receiving either remifentanil 0.1 μg/kg/min or fentanyl 0.025 μg/kg/min titrated to predefined level of analgesia, with propofol added if sedation was unsatisfactory after analgesia has been achieved, it is reported that remifentanil provides clinically comparable analgesia to fentanyl and that these two drugs are suitable for short-term analgesia-based sedation in pediatric post-operative ICU patients [23].

Until more reports appeared on long-term suitability of remifentanil for PICU patients, it may have more potential for procedural analgesia in critical care, given its rapid onset and offset times, being vigilant for cardiovascular depressant effects. Moreover, it could be used at the final phase of the weaning process, replacing fentanyl and midazolam with remifentanil and propofol, as mentioned in a promising small one-center study [24].

NSAIDs and paracetamol

NSAIDs provide analgesia via the nonselective, competitive inhibition of cyclooxygenase (COX), a critical enzyme in the inflammatory cascade. Whilst the administration of NSAIDs may reduce opioid requirements for adult and pediatric post-surgical pain by 15–30%, the analgesic benefit of NSAIDs has not been systematically studied in critically ill children. Paracetamol is an analgesic used to treat mild to moderate pain. In combination with an opioid, paracetamol produces a greater analgesic effect than higher doses of the opioid alone and has an opioid sparing effect in adults.

3. Sedation assessment and sedative agents commonly used in the PICU

Surveys of UK and US PICU sedative and analgesic practice have demonstrated a wide range of clinical practice in terms of both the range of pharmacological agents employed and the ways in which they are administered. In adult critical care units, the introduction of clinical guidelines has been associated with better outcome and a significant drop in the sedative costs per bed - day [2, 4, 25].

Sedation assessment

The consequences of under sedation include inadequate treatment resulting in excessive pain and anxiety, agitation, hyperactivity and self-removal of tubes and catheters, violence towards caregivers, patient-ventilator asynchrony, hypoxemia, increased oxygen consumption, pain related immune suppression, minimal amnesia and perhaps delirium and post-traumatic stress disorder (PTSD). In contrast, over sedation can lead to hypo-activity, respiratory depression, and prolonged mechanical ventilation and associated problems such as ventilator-associated pneumonia (VAP) and increase in length of stay (LOS), inability to communicate with health care providers or the family, unnecessary testing for altered mental status, delirium and PTSD [2,4].

In order to avoid the potential complications of both excessive and inadequate sedation, it is necessary to regularly assess and document the level of sedation of critically ill children. Whilst PICU staff informally assess the depth of sedation of their patients at every point of contact, the level of sedation should be regularly assessed and documented using a formal sedation assessment scale, wherever possible using a validated scoring system such as the COMFORT scale [26].

APPENDIX V: The Comfort sedation scale

Alertness	
Deeply asleep	**(1)**
Lightly asleep	**(2)**
Drowsy	**(3)**
Fully awake and alert	**(4)**
Hyper-alert	**(5)**
Calmness or agitation	
Calm	**(1)**
Slightly anxious	**(2)**
Anxious	**(3)**
Very anxious	**(4)**
Panicky	**(5)**
Respiratory Response	
No coughing and no spontaneous respirations	**(1)**
Spontaneous respirations with little or no response to	**(2)**
ventilation	**(3)**
Occasional cough or resistance to ventilator	**(4)**
Actively breaths against ventilator or coughs regularly	**(5)**
Fights ventilator; coughing or chocking	
Respiratory Response	
No coughing and no spontaneous respirations	**(1)**
Spontaneous respirations with little or no response to	**(2)**
ventilation	**(3)**
Occasional cough or resistance to ventilator	**(4)**
Actively breaths against ventilator or coughs regularly	**(5)**
Fights ventilator; coughing or chocking	
Respiratory Response	
No coughing and no spontaneous respirations	**(1)**
Spontaneous respirations with little or no response to	**(2)**
ventilation	**(3)**
Occasional cough or resistance to ventilator	**(4)**
Actively breaths against ventilator or coughs regularly	**(5)**
Fights ventilator; coughing or chocking	
Physical Movement	
No movement	**(1)**
Occasional, slight movement	**(2)**
Frequent slight movement	**(3)**
Vigorous movement limited to extremities	**(4)**
Vigorous movement including torso and head	**(5)**
Blood Pressure	
BP bellow baseline	**(1)**
BP consistently at baseline	**(2)**
Infrequent elevations of 15% or more (1 to 3 episodes)	**(3)**
Frequent elevations of 15% or more (more than 3 episodes)	**(4)**
Sustained elevation >15%	**(5)**
Heart Rate	
HR below baseline	**(1)**
HR consistently at baseline	**(2)**
Infrequent elevations of 15% or more (1 to 3 episodes)	**(3)**
Frequent elevations of 15% or more (more than 3 episodes)	**(4)**
Sustained elevation >15%	**(5)**
Muscle Tone	
Muscles totally relaxed; no muscle tone	**(1)**
Reduced muscle tone	**(2)**
Normal muscle tone	**(3)**
Increased muscle tone and flexion of fingers/toes	**(4)**
Extreme muscle rigidity and flexion of fingers/toes	**(5)**
Facial Tension	
Facial muscles totally relaxed	**(1)**
Facial muscle tone normal; no facial muscle tension	**(2)**
Tension evident in some facial muscles	**(3)**
Tension evident throughout facial muscles	**(4)**
Facial muscle contorted and grimacing	**(5)**

The COMFORT Scale – Application

Introduction: The goal of using a sedation scale is to facilitate the early recognition of progression to over-sedation.
The **COMFORT** Scale was developed at the Medical College of Wisconsin for children 0-18 years of age in the pediatric intensive care unit, who were not muscle relaxed. Using both behavioral and physiological items the scale consists of eight dimensions, which allow for nonintrusive measurement of distress in PICU patients. Each of the eight dimensions has five response categories (1 to 5), allowing assessment of subtle changes. Ambuel et al, tested validity (1992) and found that interrater agreement and internal consistency were high.
Dimensions: Alertness, Calmness or agitation, Respiratory response, Physical movement, Blood pressure, Heart rate, Muscle tone, Facial tension.
Measurement: The COMFORT scale is composed of six behavioral dimensions (alertness, calmness, muscle tone, movement, facial tension and respiratory response) and two physiological dimensions (heart rate and mean arterial pressure). Each dimension is rated individually with a score from 1 to 5. The level of sedation is obtained by adding all eight-dimension scores together (see scoring sheet).
HR and BP measurements: Review the medical record for heart rate (HR) and blood pressure (BP) data recorded over the 24-hour period prior to initial Comfort Score determination. Using the following data and equations, calculate the Baseline range limits (e.g. Hi, Lo) and record where appropriate.
Heart Rate: Range of Normal Values

Age	***Heart rate (beats/minute)***
0-1	120-180
>1-2	100-130
>2-4	90-120
>4-8	80-110
>8	70-100

Study limits calculations: Observe baseline HR=lowest HR rate within normal range the previous 24h
Lo limit HR = Observed baseline – (observed baselinex15%) =
Hi limit HR = Observed baseline + (observed baselinex15%) =
Mean Arterial Blood pressure (MAP): Range of Normal Values

Age	***MAP (mmHg)***
0-1	47-82
>1-5	60-90
>5-7	60-93
>7-10	67-100
>10-12	68-102
>12-14	72-107

Study limits calculations: Observe baseline MAP=lowest MAP within normal range the previous 24h
Lo limit MAP = Observed baseline – (observed baselinex15%) =
Hi limit MAP = Observed baseline + (observed baselinex15%) =
The patient observation period is 2 minutes; all patients must have an arterial line in situ in order the measurements not to be disturbed by the inflation of the blood pressure cuff.
Non ventilating children: a crying version has developed with the following adaptations

1. Quiet breathing-no crying
2. Sobbing or gasping
3. Moaning
4. Crying
5. Screaming

Level of sedation: 8 to 16 points indicates deep sedation, 17 to 26 points indicates optimal sedation, 27 to 40 points indicates inadequate sedation
Documentation: Using the COMFORT scale, sedated patients will be assessed every four (4) hours for their level of sedation. The total COMFORT score will be documented in the sedation column on the flow sheet.

The COMFORT scale is a subjective physiological and behavioral scoring system that requires no disturbance of the patient. Eight variables–mean arterial blood pressure, heart rate, muscle tone, facial tension, alertness, calmness/agitation, respiratory behavior and physical movement–are scored after a 2-min period of observation. Clearly the COMFORT scale cannot be used during the administration of neuromuscular blocking agents. The desired level of sedation for an individual should be identified and frequently reassessed. This desired level will vary according to the underlying pathophysiological process and the need for certain therapeutic, invasive or investigative procedures. Administered doses of sedative agents should be titrated in light of these fluctuating requirements to ensure the desired level of sedation is being provided.

Adult sedation assessment tools such as the Ramsay Sedation Scale (RSS), the Sedation-Agitation Scale (SAS) and the Richmond Agitation Sedation Scale (RASS) have also been used in the PICU setting in numerous studies, perhaps such as more familiar and easier to apply tools compared to COMFORT scale which is a bit laborious and time consuming [27, 28, 29].

Use of a sedation scale is a key component of sedation algorithms and it can be used to establish a target level of sedation, for medication titration and to detect over sedation when the

target level is exceeded. The introduction of a sedation scale into clinical practice has been shown to result in fewer hours of over sedation, reduced sedation cost, a reduction in the amount of vasopressor therapy for hypotension, a shorter duration of mechanical ventilation and the incidence of nosocomial infections and /or shorter LOS [2].

Sedation algorithms can vary considerably in terms of complexity; however a common practice is to reduce the likelihood of over-sedation while treating pain and anxiety adequately, whether implementation concerns favor as simple an approach as is feasible [2]. In one of the first studies assessing the performance of a protocol-driven approach to sedation, Brook and colleagues noted a signifycant reduction in the duration of mechanical ventilation, ICU and hospital length of stay, and the need for tracheostomy among adult ICU patients with acute respiratory failure when sedatives were administered by nurses according to a written protocol [30].

Neurophysiological monitors that may assess sedation depth

Given the difficulties involved in the subjective assessment of sedation during deep sedation or during the administration of neuromuscular blocking agents there are clearly potential benefits in the objective measurement of sedation using neurophysiological techniques such as the bispectral index (BIS) or auditory evoked potentials. Considerable interest exists in the use of electroencephalogram (EEG) analysis tools such as BIS, which uses a digital scale from 100 (completely awake) to 0 (isoelectric EEG) [31]. BIS has been found to reliably differentiate between inadequate and adequate levels of sedation, but appears to be relatively insensitive for differrentiating between adequate and excessive sedation [32]. However, comparisons of BIS and COMFORT scale measurements at isolated moments during a prolonged PICU admission are less well correlated. BIS has a technical limitation in the critical care environment, where the impact of polypharmacy, electrical interference and variability of physiological parameters is poorly defined [33]. BIS scores may vary between patients at the same subjective level of sedation, particularly at the deeper levels of sedation as defined by the COMFORT scale. It has been suggested that subjective sedation scoring systems may be more reproducible during light sedation, where electrical interference due to muscle activity may artificially elevate BIS scores.

Although there are numerous studies on the efficacy of BIS for monitoring depth of sedation in children, its use is questionable in neonates and infants because of the differences between immature infant EEG patterns and the adult EEG patterns that the BIS algorithm

utilizes. Moreover, it is worth noting that the BIS values recorded in deep sleep are comparable with those observed under deep sedation, a finding that confirms the nonspecificity of the BIS. This tool does not enable a distinction between the cause of the change in level of consciousness and the ability to wake up again. It is consequently impossible to use BIS values to distinguish "natural or endogenous" from "exogenous or pharmacological" sedation; such discrimination has to be based on known clinical variables (reaction to touch or voice, eye movement, e.t.c.) to avoid the risk of misinterpreting the subject's actual condition [34]. Therefore, there is insufficient evidence to support the routine use of the BIS monitor in the PICU [35]. Its use could be particularly useful for achieving the correct level of sedation in paralyzed or deeply sedated patients, as the clinical scales are not applicable in these patients.

Recommended and commonly used sedative agents in PICU

Benzodiazepines

Benzodiazepines have for many years been used to provide sedation in the PICU. They have specific activity at γ-aminobutyric acid (GABA) receptors, which form part of the major inhibitory system of the central nervous system. The benzodiazepines most commonly used for sedation in the PICU are midazolam, lorazepam and diazepam. Midazolam is an excellent agent for inducing antegrade amnesia without impairing the ability to retrieve previously learned information; an effect which can be achieved even when sedation is minimally evident. The amnesic effects of midazolam probably play an important role in the low levels of unpleasant experiences recalled by survivors of PICU treated with this agent. Midazolam is a water-based acidic preparation; at plasma pH, it converts into an un-ionised form that crosses the blood–brain barrier rapidly. It has the shortest elimination half-life of the benzodiazepine group. Following a single bolus intravenous injection in healthy adult patients, the time to peak sedation is 5–10 min and the duration of action is 30–120 min. When given by continuous intravenous infusion the duration of action is significantly longer, and if midazolam is given for more than a week, sedation may last for 48 h following discontinuation. Midazolam is metabolised by hydroxylation to 1- hydroxymidazolam and 1,4-dihydroxymidazolam by cytochrome P450 isoenzyme 3A4, and is then glucuronidated. In patients with renal insufficiency prolonged sedative effects may be caused by the accumulation of the active metabolite, α-hydroxymidazolam, whilst a reduction in cytochrome P450 isoenzyme 3A4 availability as the result of inflammatory response, drugs or hypoxia may account for the failure of some

critically ill patients to metabolise midazolam. Substrate competition may also occur leading to prolonged sedation following the co-administration of certain pharmacological agents, including erythromycin. Midazolam is by no means an ideal sedative agent and the main adverse events associated with its use are tolerance, dependence and withdrawal following subsequent discontinuation. Hypotension may occur and is most likely with bolus administration, particularly in the setting of hypovolaemia. There is also evidence of reduced sedative efficacy in younger children [36].

Clonidine

Clonidine is being used with increasing frequency as a first-line agent to provide sedation in UK PICUs. The α2-adrenoreceptor agonists produce sedation without causing respiratory depression, and exert anxiolytic effects that are comparable with those of benzodiazepines. They reduce the requirement for other sedative agents and improve haemodynamic and sympathoadrenal stability. They also have analgesic properties, which are probably mediated through the prevention of substance P release. Adverse effects associated with the use of clonidine include bradycardia and hypotension. Withdrawal of clonidine after prolonged administration has been associated with hypertension and seizures, and abrupt discontinuation should be avoided.

Dexmetedomidine

Dexmedetomidine is a relatively selective α2-adrenergic agonist with sedative properties and a higher α2: α1 activity ratio compared to clonidine (1620:1 vs. 220:1). A2-adrenoreceptors are widely distributed throughout the peripheral and central nervous system and a variety of organs and have been located at presynaptic, postsynaptic, and extrasynaptic sites. Of these, the presynaptic and postsynaptic receptors may be the more clinically important in analgesia. In general, activation of α2-presynaptic receptors inhibits norepinephrine release and possibly substance P release, thereby inhibiting pain signal transmission. Postsynaptic activation in the central nervous system inhibits sympathetic activity, thus moderating heart rate and blood pressure. Together, these effects produce analgesia, sedation and anxiolysis [37].

Dexmedetomidine has been used for sedation in pediatric intensive care unit, in higher dosages compared to adults [38]. Three case reports describing the use of dexmedetomidine in addition to opioid and benzodiazepine achieved adequate sedation with infusions ranging from 0.25-1.4 μg/kg/h, whereas in a case series study of 65 burn patients even higher doses of 0.1-2 μg/kg/h are mentioned. Moreover, one cohort study of 17 PICU patients evaluated the additive effect of dexmedetomidine on prior sedation regiments and found

that infusions titrated between 0.1-0.7 μg/kg/h could achieve clinically adequate sedation and half of patients were able to wean off midazolam. Finally, in a randomized controlled trial comparing the efficacy of midazolam infusion (100 μg/kg/h), to both low (0.25 μg/kg/h) and high dose (0.5 μg/kg/h) of dexmedetomidine by three separate sedation and pain scores, high dexmedetomidine dose was found to be the most efficient scheme [10].

Enteral sedative agents

Where the enteral route is available, enteral sedatives such as the hypnotic agents chloral hydrate or triclofos sodium, and sedating antihistamines such as promethazine or alimemazine (trimeprazine), can be introduced. Chloral hydrate and promethazine have been shown to be more effective than intravenous midazolam in providing maintenance sedation in critically ill children [39]. Chloral hydrate is rapidly absorbed from the gastrointestinal tract and is converted to the active metabolite trichloroethanol. The drug starts to act within 15–60 min, being metabolised in the liver and other tissues and excreted in the urine and bile. Duration of action is 60–120 min but may be prolonged in renal or hepatic disease. Gastrointestinal irritation is the most commonly reported adverse effect. Triclofos sodium is converted to the same active metabolite as chloral hydrate but it is believed to cause fewer gastrointestinal disturbances.

Propofol

Propofol has never been licensed for the provision of sedation in critically ill children. The longer-term administration of propofol by continuous infusion has been associated with the recently identified propofol infusion syndrome, a rare but frequently fatal complication characterised by acidosis, bradyarrhythmia and rhabdomyolysis that has been reported in at least 21 children and 14 adults. It has recently been demonstrated that transient elevations in malonylcarnitine and C5-acylcarnitine occur during propofol infusion syndrome, suggesting that propofol impairs fatty acid oxidation and mitochondrial activity at the subcellular level. After early reports of adverse events, the manufacturers of propofol cautionned against the use of propofol in children in 1991. Parke and colleagues went on to report the deaths of five children aged 6 years and under who died as a result of increasing metabolic acidosis, bradycardia and progressive myocardial failure following the administration of infusions of propofol. Warnings were reinforced by Astra-Zeneca in March 2001 in a letter to healthcare providers detailing a prospective study apparently demonstrating an increased mortality in PICU patients sedated with propofol. The UK Commit-

tee on Safety of Medicines subsequently published a categorical statement that propofol was contraindicated for the sedation of children aged 16 years and below. Long-term sedation of children with propofol cannot be supported. Occasionally, it could be used during the weaning process for short periods, as a short lasting agent to facilitate the wean off other long lasting sedatives [24].

4. Withdrawal syndrome assessment, prevention and management

Withdrawal syndrome may occur following the discontinuation of sedative agents, particularly benzodiazepines and opioids, and is thought to be related to the total drug doses received. The incidence of midazolam withdrawal syndrome has been estimated at between 17% and 30%. Fonsmark and colleagues have suggested that a total dose of midazolam of >60 mg/kg is significantly associated with the occurrence of withdrawal syndrome, whilst Katz found that a total fentanyl dose of >1.5mg/kg was associated with a greater than 50% chance of the development of withdrawal syndrome [40, 41]. This study also found that the duration of fentanyl infusions was significantly greater in those infants with withdrawal syndrome than in those without; duration of infusion greater than 9 days was 100% predictive of withdrawal syndrome. Features of withdrawal syndrome usually occur within a few hours of stopping the drug in question and can include central nervous system manifestations (agitation, seizures, arterial oxygen desaturation, hallucinations and psychosis) and autonomic features (vomiting, tachycardia, hypertension and fever). Withdrawal syndrome is frequently under-recognised and under-treated as it can mimic other conditions, most commonly neurological, in the critically ill child. Recently, the **S**ophia **O**bservation withdrawal **S**ymptoms-scale (SOS) was developed for the assessment of withdrawal symptoms in critically ill children by the researchers of Sofia's Children Hospital, in Rotterdam, Netherlands. The most frequent symptoms mentioned were tachypnea, agitation, motor disturbances and hypertension followed by anxiety, inconsolable crying, increased muscle tension, tremors, tachycardia and sweating [42].

Although tolerance, physical dependence and subsequent withdrawal syndrome can be anticipated when patients have been administered high doses or prolonged infusions of opioids and sedative agents, the exact cellular mechanisms responsible for their development remain poorly defined. It has been suggested that the key mechanism may not be a decrease in agent-specific cell surface receptors or binding affinity, but rather alterations in the interactions between such receptors, regulatory G proteins, and intracellular enzyme systems

such as phospholipase and adenylate cyclase. There is evidence that the noradrenergic system is involved in the expression of the somatic symptoms of opiate withdrawal. There is little evidence upon which to make recommenddations regarding the prevention, assessment and management of withdrawal syndrome in critically ill children. Strategies to reduce the incidence of withdrawal syndrome are based on reducing the total doses of benzodiazepines and opioids administered by using sedation and pain-scoring systems and on the application of non-pharmacological intervenetions already described, such as noise control, relaxation, and promotion of sleep. Adult sedative and analgesic guidelines recommend the routine tapering of sedative agents and opioids in high-risk patients to minimise the risk of developing features of withdrawal syndrome. It is standard practice in many units to taper doses off by daily increments of 5–10% of the initial dose [25]. There is, however, little evidence to support this practice in the PICU. Other approaches include the planned substitution of one class of agent for another, "drug holidays", the introduction of long-acting preparations of parenteral agents such as lorazepam or clonidine, the introduction of enteral agents such as diazepam, clonidine, methadone or modified-release oral morphine preparations, and the use of novel delivery routes such as the subcutaneous and transdermal administration of fentanyl. It should also be remembered that less commonly used agents such as clonidine and barbiturates have also been associated with withdrawal syndrome.

5. Delirium

Delirium should be considered if there is regression to earlier stages of development, chaotic behavior, anxiety, and moaning in severely ill young children [43]. Because of the serious impact of delirium on prognosis as well as the disruptive nature of the delirium, it should be considered a pediatric psychiatric emergency and treated accordingly. Even if the condition is recognized, its seriousness is often underestimated and the condition is not treated. Formal psychiatric assessment, including the assessment of orientation in time and place, memory deficits, and language difficulties, may not be possible in young children, and for this reason, observed behavior and caretaker information are important. Delirium in children should be treated actively and not conservatively for several reasons. First, it is important to control psychomotor agitation to prevent the child from harming him-or herself, for example, by extubating him-or herself, disconnecting lines, and falling out of bed. Moreover, reducing the stress associated with delirium improves recovery from the somatic disorder. Last, because delirium is a di-

sturbing and frightening experience for both the child and his or her caretakers, treating delirium restores quality of life and may reduce the incidence of posttraumatic stress. The Pediatric Anesthesia Emergence Delirium scale (PADS) and the Pediatric Confusion Assessment Method for Intensive Care Unit (pCAM-ICU) could be used for diagnosing delirium in critically ill children [44, 45]. Treatment of delirium could start with a small intravenous dose of midazolam (0.1 mg/kg), and sporadically neuroleptic medication such as haloperidol could be used, based on adult's guidelines for delirium [25].

6. Post Traumatic Stress Disorder and adverse long term sequelae

The numbers of children worldwide that require intensive care annually are increasing, because of advances in pediatric therapeutic techniques and a changing spectrum of pediatric disease. These children are especially vulnerable to a multitude of short and long-term negative emotional, behavioral, and academic outcomes, including a higher risk of PTSD and a greater need for psychiatric treatment, compared with matched hospitalized children who do not require intensive care. In addition, the parents of these children are also at risk for the development of PTSD, as well as other negative emotional outcomes (e.g., depression and anxiety disorders).

To evaluate the effects of a preventive educationnal-behavioral intervention program on the mental health/psychosocial outcome of critically ill young children and their mothers, a study was conducted in the USA, the Creating Opportunities for Parent Empowerment (COPE). Mothers in the experimental (COPE) group received a 3-phase educational-behavioral intervention program. Phase-1: 6 to 16 hours after PICU admission, phase2: 2 to 16 hours after transfer to the general pediatric unit, and phase3: 2 to 3 days after their children were discharged from the hospital. Control mothers received a structurally equivalent control program. The COPE intervention was based on self-regulation theory, control theory, and the emotional contagion hypothesis. The COPE program, which was delivered with audiotapes and matching written information, as well as a parent-child activity workbook that facilitated implementing the audiotaped information, focused on increasing 1) parent's knowledge and understanding of the range of behaviors and emotions that young children typically display during and after hospitalization and 2) direct parent participation in their children's emotional and physical care. The COPE workbook, which was provided to parents and children after transfer from the PICU to the general pediatric unit, contained 3 activities to be completed before discharge from the hospital, i.e. puppet play to

encourage expression of emotions in a non-threatening manner, therapeutic medical play to assist children in obtaining some sense of mastery and control over the hospital experience, and reading and discussing *Jenny's Wish*, a story about a young child who successfully copes with a stressful hospitalization.

One year after discharge, a significantly higher percentage of control group children (25.9%) exhibited clinically significant behavioral symptoms, compared with COPE children (2.3%). In addition, 6 and 12 months after discharge, significantly higher percentages of control group children exhibited clinically significant externalizing symptoms (6 months, 14.3%; 12 months, 22.2%), compared with COPE children (6 months, 1.8%; 12 months, 4.5%). The study concluded that with routine provision of the COPE program in PICUs, family burdens and costs associated with the mental health treatment of these problems might be substantially reduced [46].

STRATEGIES FOR ADMINISTERING ANALGESICS AND SEDATIVES IN THE PICU

Because no single drug can achieve all the indications for analgesia and sedation in the PICU, a combination strategy may allow lower doses of individual drugs and reduce problems of drug accumulation. Analgesics and sedatives can be administered either by intermittent bolus dosing or by continuous infusion. The former may result in periods of both oversedation and undersedation and increased demands on nursing time. Continuous drug administration on the other hand includes a more consistent level of sedation with greater levels of patient comfort, but might lead to undesirable drug accumulation and adverse side effects [47]. Recently, the advantages of intermittent sedation strategies are increasingly supported both in adult and pediatric ICU patients [2, 4, 11].

Apart from postoperative patients who are in obvious pain, **ALL** PICU patients experience varied pain intensity due to the presence of endotracheal tubes and catheters plus procedural pain related to other instantaneous interferences such as suctioning, needle paracentisis e.t.c., so a minimal baseline analgesic therapy is necessary. After the introduction of remifentanil into clinical practice this can be safely done with remifentanil titration, even for long term sedation, avoiding the side effects of the other long lasting opioids like morphine and fentanyl. Starting point is 0.02 μg/kg/min up to max dose of 0.15 μg/kg/min (0.12-9 μg/kg/h). Occasionally, larger doses up to 0.2 μg/kg/min are necessary, especially in cases with increased metabolic rate as it happens in patients with burns (personal observation, anecdotal data). Usual remifentanil dosing in our unit ranges from 0.02 to 0.18 μg/kg/min,

for 1-30 days and infrequently longer, without any apparent cardiovascular side effects.

If analgesic therapy alone is not sufficient to keep the patient calm, sedation is achieved with continuous infusion of midazolam. Although midazolam dose in literature ranges from 0.025-0.6 mg/kg/h [10,13], our personal observation is that in many instances higher doses are required, up to 1.6 mg/kg/h, especially in patients with intact cerebral function suffered from respiratory failure, as is the case in adult ICU patients with respiratory failure as well [47]. Initial midazolam infusion rate in our unit is 0.1 mg/kg/h and usual range 0.5 - 1 mg/kg/h.

On arrival, pain and sedation needs are estimated accordingly. If **Pain** is present it is treated with fentanyl bolus (1-2 μg/kg) and if **Agitation** is present it is treated with midazolam bolus (0.1-0.2 mg/kg). In case of mechanical ventilation and extreme agitation, in danger of endotracheal tube and other catheters removal, a simultaneous dose of a paralytic agent, usually cisatracurium, (0.2 mg/kg) is also indicated. Then, continuous Analgo-Sedation infusion starts with remifenanil at a rate of 0.02-0.04 μg/kg/min, and midazolam at 0.1-0.2 mg/kg/h. Due to their rapid metabolic rates, analgesia and sedation needs in children are high, especially in neurologic intact cases, so the child usually wakes up often. During such a spontaneous awakening period (open eyes, spontaneous limp movement, spontaneous respiration efforts, and cough) analgesic and sedation needs are assessed. The above described clinical situation corresponds to COMFORT score of 19 to 27, in other words approximates an ideal level of sedation. However, if left untreated it will develop rapidly to more rigorous awakening which is undesirable and will lead to agitation. Thus, each time that the child wakes up spontaneously, Analgo-Sedation is up titrated by 0.02 μg/kg/min remifentanil and 0.1 mg/kg/h midazolam, whereas in cases of extreme agitation during the waking up periods a concomitant bolus administration of midazolam (0.2 mg/kg) and cisatracurium (0.2 mg/kg) is necessary. For the majority of the patients, spontaneous awakening period is targeted to 1 to 2 hours, and Analgo-Sedation is titrated up or down accordingly (see algorithm). When a deeper level of sedation is indicated (e.g., Head trauma) then the spontaneous awakening period - the alternate to sedation goal - is set to longer time intervals (4-6h or even longer).

Drug titration could be extremely difficult and clinicians often face the dilemma of providing the desired level of sedation while preventing the inevitable drug accumulation. In the ICU, sedatives typically exhibit multicompartamental pharmacokinetics with a tendency to accumulate in the peripheral compartment thus

prolonging their clinical effect. For busy clinicians and PICUs, a state of drug-induced coma may be more safe and desirable than unmanageable agitation, and is often natural to "overshoot" when sedating agitating patients, especially early on the course of critical illness (e.g., initial stabilization on the ventilator). Furthermore, advantages of critical care (e.g., prone positioning, permissive hypercapnia, and inverse ratio pressure controlled ventilation) lead to clinical situations that are extremely stressful to the patients and on these occasions a deeper level of sedation is also required [47].

A protocol-driven approach to sedation may help navigate some of sedation dilemmas and allow optimization of sedative administration to meet the patient needs. Nurses at patient bedside are the fist to notice any change in sedation level and effective clinician-nurse communication is fundamental. Ideally, one would prefer a patient with all the targets of sedation met, which is being in comfort, free of pain and fully communicative. Such a state of sedation correlates with a Ramsay score of 2 to 3, SAS of 3 to 4, and COMFORT score of 17 to 26, with difficulties arising when a deeper level of sedation is clinically indicated, where the application of the sedation scales becomes more difficult.

The pioneer study of Kress and co-workers on daily interruption of sedation in adult ICU patients, a milestone in sedation administration in modern intensive care unit, showed that in the interruption group the duration of mechanical ventilation was reduced by 2.5 days and ICU length of stay was reduced by 3.5 days. Furthermore, they noted a significant reduction in diagnostic studies to investigate unexplained alterations in mental status [48]. On the basis of this study, daily interruption of sedation is proposed as an approach to optimize patient's outcome. However, because this technique could result in abrupt awakening and extreme patient agitation (32% of patients in the previous study), this potential situation must be anticipated by the ICU team to avoid complications such as patient self-extubation. Certainly, excessive agitation should lead to cessation of the wake-up attempt. It is questionable if such an approach could be used in pediatric intensive care as well. Despite the encouraging results of an analogous study in pediatric critical care patients, we could not recommend yet this teqnique for widespread use in children [11].

In pediatric intensive care, the patients could seldom remain so deeply sedated as to require a daily interruption of sedation. As it is already mentioned, they experience frequent spontaneous awakening periods during which the clinician can estimate Analgo-Sedation needs. We could name it **"spontaneous awakening period assessment"** as a modified proposal to

daily interruption of sedation. During such a period we could follow a set of end points for assessment the level of sedation. Asking the patient to (1) open eyes to verbal command, (2) follow the bedside observer with eyes, (3) hand grasp on command, and (4) stick out tongue on command is a common simple and quick bedside practice, which was found to be objective and reproducible [47]. Nevertheless, if a spontaneous awakening period doesn't happen for more than 4 hours a down titration by 25% is necessary, to facilitate arousing so that patient assessment can be done.

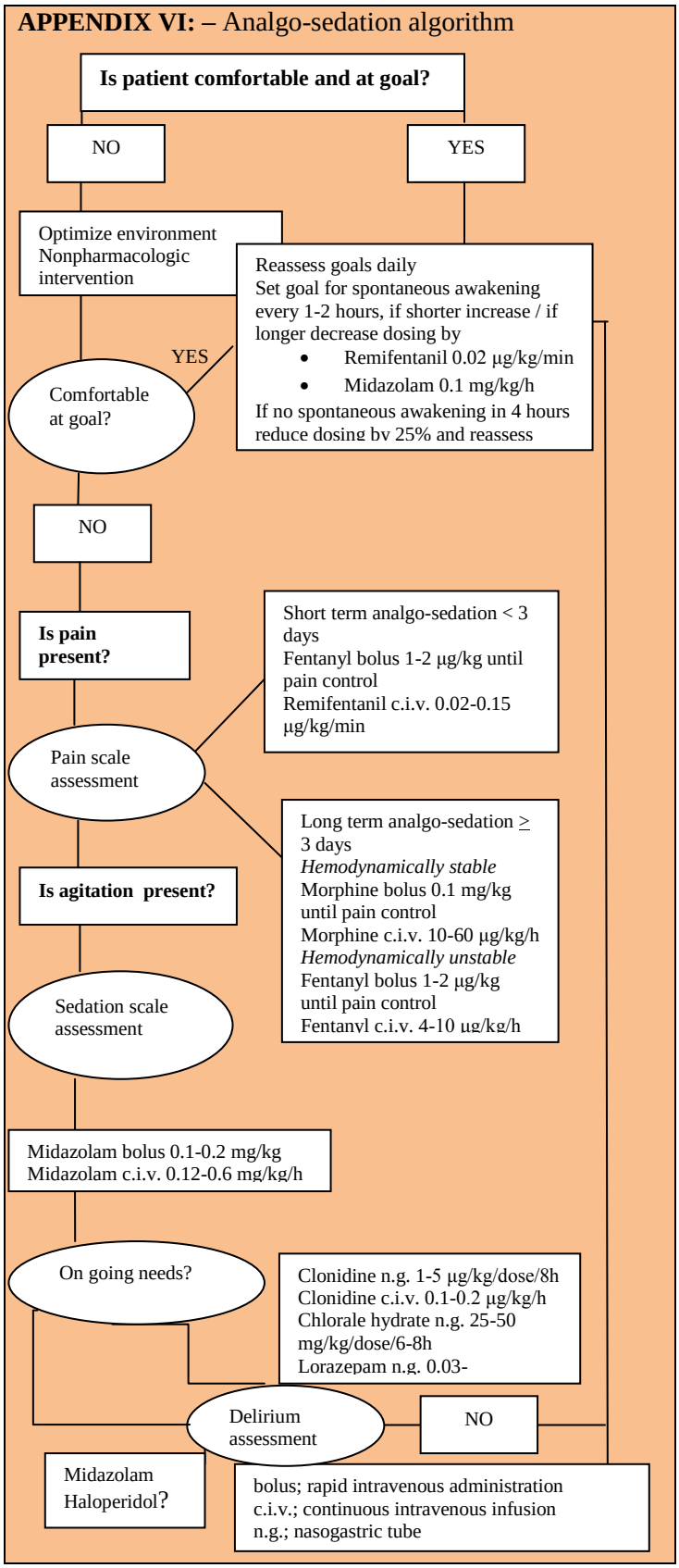
Systematic NMBA use is rarely needed except for special indications as to facilitate mechanical ventilation of severe ARDS and/or for the better control of intracranial hypertension after severe traumatic brain injury. The most common agent is cisatracurium in doses of 5-15 μg/kg/min [49]. Patients requiring muscle paralysis should never be awakened from sedation until the paralytic agent is worn off and the monitoring of the depth of neuromuscular blockade is desirable. Daily or even twice daily interruption of NMBA is advisable to assess the adequacy of analgesia and sedation and the ongoing need for neuromusscular blockade. Special sedative agents like sodium thiopental is indicated for barbiturate coma in patients with severe traumatic brain injury and intractable status epilepticus, according to protocols [50, 51].

When long term sedation is necessary and sedation challenges develop, oral sedatives are an option, given that gastrointestinal system is functional. One could use oral chloral hydrate, lorazepam and or clonidine as adjuncts to continuous regimens (Table 1). Continuous clonidine infusion at a dose 0.1-0.2 μg/kg/h is frequently used also during weaning process, mainly to dull the agitation and the adverse cardio-respiratory effects of drug withdrawal, especially after long term sedation. The above recommended dosing according to the literature seems insufficient in some patients, our experience indicate that even higher clonidine rates, up to 0.5-0.6 μg/kg/h are sometimes necessary and well tolerated.

FOLLOWING AN ALGORITHM

A typical starting place with patient assessment is to ask "is the patient comfortable?" The first decision point for the patient who is not comfortable addresses the following question, "is the patient in pain?" with management directed towards analgesic therapy if pain is present. Next question is typically "is the patient agitated?" with therapy focused on sedative medications if agitation is present, as proposed in the analgo-sedation algorithm (Appendix VI) [2, 25].

APPENDIX VI: – Analgo-sedation algorithm



CONCLUSIONS

Analgesia and Sedation are essential parts of the management of the critically ill child. There are currently a wide variety of phar-macological agents available for the diverse needs of this heterogeneous group of patients. Rather than seeking an ideal drug, strategies of drug administration that focus attention on principles of sedative pharmacology in critical illness should be utilized. It is not possible to establish an optimal level of comfort for all critically ill pediatric patients, as this depends on the clinical situation at every moment; continuous individualized monitoring of the level of analgesia and sedation is therefore necessary in order to adjust the dose of se-datives and analgesics. Analgo-Sedation prin-ciples seem that can be used safely in the pe-diatric intensive care as well. Monitoring the level of analgesia and sedation will help to a-void both over and under treatment. There is no ideal method that will evaluate analgesia and sedation in all critically ill children. Pain scales according to child age should be used routinely whereas the COMFORT scale is considered to be the most suitable clinical se-dation scale for use in critically ill children re-quiring mechanical ventilation. Directing treatment to specific and

individualized goals through Analgo-Sedation algorithms will assure that patient needs are met.

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