Clinical recommendations for pain, sedation, withdrawal, and delirium assessment in critically ill infants and children: An ESPNIC Position Statement for healthcare professionals.

ESPNIC Position Statement Endorsed by ESPNIC (Medical & Nursing); Nursing Science section (Pain & Sedation study group) and Pharmacology section of ESPNIC.

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Abstract

Background: This position statement provides clinical recommendations for the assessment of pain, level of sedation, iatrogenic withdrawal syndrome and delirium in critically ill infants and children. Admission to a neonatal or paediatric intensive care unit (NICU, PICU) exposes a child to a series of painful and stressful events. Accurate assessment of the presence of pain and non-pain related distress (adequacy of sedation, iatrogenic withdrawal syndrome, and delirium) is essential to good clinical management and to monitoring the effectiveness of interventions to relieve or prevent pain and distress in the individual patient.

Methods: A multidisciplinary group of experts was recruited from the members of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). The group formulated clinical questions regarding assessment of pain and non-pain related distress in critically ill and non-verbal children, and searched the PubMed/Medline, Cinahl, and Embase databases for studies describing the psychometric properties of assessment instruments. Further, level of evidence of selected studies was assigned and recommendations were formulated, and grade or recommendations were added based on the level of evidence.

Results: An ESPNIC Position Statement was drafted which provides clinical recommendations on assessment of pain (n=5), distress and/or level of sedation (n=4), iatrogenic withdrawal syndrome (n=3), and delirium (n=3). These recommendations were based on the available evidence and consensus amongst the experts and other members of the ESPNIC society.

Conclusions: This multidisciplinary ESPNIC Position Statement guides professionals in the assessment and re-assessment of the effectiveness of treatment interventions for pain, distress, inadequate sedation, withdrawal syndrome and delirium.

Introduction

This position statement provides clinical recommendations for the assessment of pain, level of sedation, iatrogenic withdrawal syndrome and delirium in critically ill infants and children. Admission to a neonatal or paediatric intensive care unit (NICU, PICU) exposes a child to a series of painful and stressful events. The effects of these events are commonly resolved by the administration of analgesics (e.g. morphine, fentanyl) and/or sedatives (e.g. benzodiazepines, α2 selective adrenergic agonists) [1]. However, sedation with benzodiazepines in neonates is advised against in view of the unfavourable patient outcomes [2]. A recent survey showed wide variety in both the dosages and choices of drugs administered to neonates [3]. While adequate analgesia and sedation help reduce the stress response and improve the clinical and psychological outcomes [4] inadequate analgesia and sedation will lead to pain, pain-induced agitation or under-sedation and possibly to accidental extubation or removal of vascular access devices. Overuse of analgesic and sedative agents, on the other hand, can lead to over-sedation, prolonged ICU stay, longer ventilation times, drug tolerance and dependence. Furthermore, iatrogenic withdrawal syndrome and delirium could be identified as side effects of prolonged analgesia and sedation [5, 6]. Both are considered as concepts of non-pain related distress in critically ill children. The current clinical guidelines on analgesic and sedative drugs use in adult and paediatric ICU populations [7, 8] are based on evidence of highly variable level. Accurate and regular measurement of pain and non-pain related distress is essential, not only to establish their presence but also to monitor the effectiveness of interventions. Accurate and regular measurement of pain and non-pain related distress is essential to establish their presence [9]. Furthermore, the effectiveness of pharmacological interventions should be monitored because this may be affected by the specific pharmacokinetics and pharmacodynamics in the individual critically ill child [10]. The gold standard of assessing patient comfort is self-reporting. Self-report is impossible, however, in pre-verbal and non-verbal children who are often sedated or when a tracheal tube is in place. In these cases, healthcare professionals must resort to observing the child's physiological and behavioural responses. Still, healthcare professionals' observations and assessments of pain and non-

pain related distress will depend on their ideas and beliefs on discomfort, pain, best drugs and treatment, and on their knowledge. On the other hand, as we know from adults [11], it may be difficult to discriminate between pain, distress, IWS and delirium in critically ill children, because the behavioral cues will overlap in part (Figure 1). Therefore, standardized assessment tools have been proposed and validated so as to limit avoidable variability in assessment [12]. In practice, a patient's individual analgesia and sedation requirements will be assessed by different nurses, with varying degrees of expertise, which may lead to inconsistent dosing of sedatives and analgesics [13]. Use of a standard tool may counteract this effect and promote continuity of care [14].

This position paper specifically provides clinical recommendations for NICU and PICU healthcare clinicians on the assessment of pain, sedation, withdrawal and delirium in their patients.

Methods

A multidisciplinary group of expert clinicians and researchers in the fields of pain, sedation, withdrawal syndrome and delirium were recruited from the membership of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) to develop the position statement. The process of formulating the clinical recommendation comprised the following steps. First, questions were formulated regarding the clinical practice of assessment of pain related and non-pain related distress (e.g. adequacy of sedation, iatrogenic withdrawal syndrome, and delirium) in critically ill and non-verbal children. Second, an extensive search of the literature on assessment tools was performed to find evidence for recommendations. For this reason, the PubMed/Medline, Cinahl, and Embase databases were searched using the following MeSH and all fields search terms: (pain measurement, distress, sedation, substance withdrawal syndrome, delirium) AND (paediatric critical care OR neonatal intensive care) (See Appendix for search strategy). The search scope was limited to studies in the English or French language published between August 2005 and August 2015, so as to provided the most up to date relevant research, that included paediatric or neonatal critical care

non-verbal inpatients, with the age limits set from birth to 18 years. Neonates were included, as they can be admitted to PICUs in some European settings. In the past decades more than 40 neonatal pain assessment tools have been developed and validated. From two recent systematic reviews we derived the most recent evidence of the psychometric properties of neonatal pain (e.g. acute, prolonged pain) assessment instruments [15, 16]. Based on this, we described the psychometric properties of the most commonly used neonatal instruments. Additional search terms, such as pain questionnaires, pain scales, pain tools, pain instruments and search of authors known in the field served to verify completeness of the search results. Cross-referencing of key articles and recently published systematic reviews describing psychometric properties of assessment instruments [17, 18] served as a final check. Prior to full-text retrieval, studies describing the psychometric properties of instruments to assess physiological and behavioural cues of pain related and/or non-pain related distress were selected based on the title and abstract. Studies that did not report on psychometric properties of the tools and those that only reported on neonatal abstinence syndrome were excluded.

In the third phase, each of the articles selected was subjected to an independent Grade of Evidence Review by at least two of the authors and differences in grading were resolved through discussion. The level of the evidence was assigned a grade using the definitions is provided in a supplementary Table and based on reference test, specific research design, and methodology [19]. Subsequently, recommendations for assessment of pain related and non-pain related distress in children were formulated and discussed by the group during a meeting. The Recommendations were assigned according to the level of evidence. Lastly, to achieve consensus the draft Position Statement was reviewed by independent members of the ESPNIC Nursing Science section (Pain & Sedation study group) and the Pharmacology section; they graded the importance of the statements related to the topic area. This process did not lead to any fundamental changes. The final version was endorsed by the Executive Board of ESPNIC.

This position statement puts a focus on the assessment of 1) pain-related distress, and 2) non-pain related distress (level of sedation, withdrawal, and delirium) in the NICU/PICU as a first essential step in the management of pain and distress in these vulnerable populations.

RESULTS

Evidence from a total of 32 full-text articles describing the psychometric properties of assessment tools for pain related and non-pain related distress in children was used to underpin the recommendations in this position statement (see supplementary file).

Assessment of pain related distress

Pain assessment in hospitalised infants and children is notoriously difficult due to the different emotional and cognitive development stages of this patient group. Moreover, they are often ventilated and sedated, which complicates assessment of behaviours, and interpreting pain related behaviours is often subjective, relying on the clinicians' interpretation.

For intensive care settings, we can distinguish two relevant types of pain: 1) acute pain, including procedural and postoperative pain (e.g. pain caused heelstick, suctioning, venepuncture, thoracic drainage) and postoperative pain; and 2) prolonged pain (see Table 1 for definitions). For clinical reasons it is important to explore the underlying pathogenesis and the context of pain (Figure 2). However, different types of pain, e.g. neurogenic pain, visceral pain and somatic pain, can not be distinguished with the use of observational assessment tools.

Children and neonates in the intensive care setting undergo numerous procedures which potentially cause pain, e.g. intravenous cannulation, chest drain insertion, intubation, or discomfort, e.g. from invasive monitoring lines. Nurses and physicians should be aware, however, that daily care (e.g.

turning) can be painful as well, and that what is considered painful in older children and adults [20] should also be considered painful for children and neonates. Neonates are particularly at risk of pain exposure with a reported mean of 10.0 to 22.9 procedures per day [21, 22]. Prolonged pain is poorly understood, but is characterised by a lack of clear stimulus, a variable duration and slow recovery [23].Furthermore it is present after several days of hospitalisation and when no obvious cause for pain is present [24].

Recommendation:

- *Identify potential sources of pain and to take appropriate actions (grade of recommendation = D)*

The use of pain assessment instruments has been widely recommended as a means to provide consistency between clinicians, to provide an indication that pain/discomfort is present and to assess the effect of a pharmacological or non-pharmacological interventions.

There is limited literature on pain assessment in the PICU; the available studies concern the validation of instruments such as the COMFORT scale [25, 26], the COMFORT-B scale[1] [27-33], the FLACC scale [32, 34, 35] and the Multidimensional Assessment Pain Scale (MAPS) [36, 37]. The COMFORT-B scale has also been validated for patients with burns [38]. In contrast, more than 40 pain assessment instruments for neonates have been developed in the last few decades, but not all meet the minimum psychometric requirements for application in clinical practice [16]. The well-established, validated COMFORT-B scale and the FLACC scale (for infants and children [39] and the promising PIPP-R (for neonates) [40, 41] are recommended (See, Table 2, Table 3 and supplementary file for their psychometric properties).

Recommendation:

[1] The COMFORT scale was originally developed for assessing the level of distress in ventilated children. In combination with the use of the NRS pain the COMFORT-B scale is suitable to determine the need for analgesia or sedation.

- *Use an age-appropriate tool to assess acute, and prolonged pain, that is the PIPP(-revised) in neonates and the COMFORT behavior scale, (FLACC) or MAPS in critically ill children (grade of recommendation = A)*

The vital signs heart rate and mean arterial pressure have been moderately correlated with behaviour items [28, 42]. In children, these vital signs are probably less reliable indicators of pain than behavioural indicators. In heavily sedated or muscle relaxed children, however, increases in heart rate and mean arterial pressure may indicate that the body is under some stress – in the absence of behavioural signs pain must be one of the considerations in this scenario, the more so as there is no other method to assess these children.

It must be remembered that in the case of pain or discomfort in the non-verbal child, reflected by a high score, the practitioner should acknowledge possibly contributing environmental factors (temperature, noise) or other factors such as the need for a change of position, infant teething, or the need for nappy care. It is assumed that the nurse will check and modify these environmental factors first before making a treatment plan and re-assess once an intervention has taken place.

Studies have shown that parents themselves wish to be more involved in the process of assessing pain in their child and urge for more consistent pain assessment and management practices by staff. Parents' knowledge of their own child and how they may display pain or distress may enhance clinician's assessment and management practices. Further research is needed with regard to pain assessment involving families.

Recommendation:

- *Parent and family assessment of pain should be considered to pain assessment (grade of recommendation = D)*

There are no clear-cut recommendations in the literature on the frequency of pain assessment; this position statement merely provides the clinician with a consensus on the frequency. Furthermore, the frequency of assessment will depend on the goal of therapeutic treatment (e.g. weaning of ventilation, transfer to pediatric ward).

Recommendation:

- *Pain assessment should take place routinely, depending on therapeutic goals, but at greater frequency (1-2 hourly) if the patient is receiving any analgesic infusion (grade of recommendation = D).*

Audits of pain assessment should take place regularly (e.g. every 12 months) to evaluate the quality of patient care and patient outcomes [43].

Recommendation:

- *Pain assessment audits should take place regularly (grade of recommendation = C).*

Non-pain related distress

Sedation assessment

Patients admitted to an intensive care unit are likely to develop physical and psychological distress. Non-pain related distress in ventilated children is treated with sedatives. Optimal sedation has been described as a state in which the patient is somnolent, responsive to the environment but untroubled by it, and without excessive movements [13] (Table 1). In practice this means that a child is conscious, breathes in synergy with the ventilator, and is tolerant or compliant with other therapeutic procedures. Still it can be challenging to reach this level of sedation. A recent systematic review revealed that across all studies of paediatric patients (n=25), patients were optimally sedated in 58%, undersedated in 10% and oversedated in 32% of the observations [44]. Optimal level of sedation varies for each patient and careful consideration should be given to the underlying diagnosis and severity of illness [1, 13]. Oversedation may lead to longer duration of mechanical

ventilation for a longer period and increased health care costs. On the other hand, undersedation can lead to increased distress, self- or accidental extubation, accidental displacements of catheters, tubes and vascular access. In clinical practice it can be challenging to reach the optimal level of sedation in infants and children. The majority of children in the PICU are below 4 years of age and in view of their development not yet able to understand or make sense of their situation, and will easier become anxious and scared. For this reason they often need greater amounts of sedatives to ensure lines and tubes remain in situ.

The sedation goal may vary considerably from patient to patient and depends on severity of illness, type of disease and treatment as well as environmental factors, such as noise. When a child shows signs of agitation and fighting against the ventilator, the child should be sedated after confirmation that the ventilator settings are well adjusted to the child's respiratory needs.

Recommendation:

- *Search for potential causes of non-pain related distress/discomfort to take appropriate actions (grade of recommendation = D).*

Although clinical judgement of trained ICU professionals is important, the use of a sedation assessment tool is needed to determine the efficacy of sedatives and related interventions, to facilitate inter-institutional comparisons, and to facilitate targeted sedation. Several behavioural sedation scoring scales (e.g. COMFORT scale [25, 45], COMFORT behaviour scale [14, 42], State Behaviour Scale [46]) have been described and validated for children (Table 2 and 4, supplementary file). Also, these tools are the most common used instruments in daily practice [47]. No single instrument has been shown to be superior for use in this population, and it is advisable to select a scale that has been validated for this patient population. The frequency of assessment reported in the included studies (n=25) varied considerably; i.e. from once daily to hourly [44]. Although the frequency of assessment will depend on whether symptoms have been controlled or nor and on the

goal of therapeutic treatment (e.g. weaning of ventilation), we recommend regular assessment at least once per shift and accurate documentation of the sedation score, we recommend regular assessment at least once per shift and accurate documentation of the sedation score.

Recommendation:

- *Use standardized sedation assessment tools with proven validity, reliability, and clinical utility; The COMFORT Behavior scale (grade of recommendation = A).*
- *Together with the vital signs, the level of sedation must be assessed and documented every 4 to 8 hours or as indicated by the sedation score or the child's clinical condition (grade of recommendation = D).*

Iatrogenic withdrawal syndrome assessment in infants and children

Prolonged administration of opioids and/or benzodiazepines in infants and children may induce drug tolerance and physiological dependency. Abrupt discontinuation or (too rapid) weaning of these drugs in physically dependent infants and children may result in iatrogenic withdrawal syndrome (IWS) (Table 1) [6, 48].

Tolerance and withdrawal symptoms may occur after 5 or more days of continuous infusion of opioids or benzodiazepines in infants as well as children. The onset of withdrawal can occur after 1 up to 48 hours after tapering off or discontinuation [6, 48]. An estimated 10% to 34% of all PICU patients are at risk for IWS [49, 50]. Fentanyl and morphine are the most frequently used analgesic drugs in the NICU and PICU that underlie opiate IWS, with prevalence rates of 9% to 57% [51, 52]. The reported prevalence rates of IWS in PICU patients who had received benzodiazepines and/or opioids for 5 or more days range from 35% to 57% [53, 54].

Recommendation:

- *The potential risk of opioid and/or benzodiazepine iatrogenic withdrawal syndrome should be considered after 5 days of continuous administration of these drugs (grade of recommendation = C).*

Diagnosing withdrawal symptoms in NICU and PICU patients is complicated by the fact that these symptoms may overlap with clinical signs of pain or distress, respiratory distress, delirium and noise-induced stress [6, 55, 56]. These other factors must be excluded before the diagnosis can be confirmed. Regarding the fact that IWS may occur after 5 days, we recommend to continue assessment of withdrawal symptoms after the child has been discharge from the PICU.

Two instruments for assessing IWS in children have been sufficiently validated, namely: the Withdrawal Assessment Tool version 1 (WAT-1) [57, 58] and the Sophia Observation withdrawal Symptoms-scale (SOS) [59, 60]. The WAT-1 is an 11-item scale and scores of three or higher (on a scale of 0–12) indicate that the child is suspected for withdrawal. The SOS consists of 15 items and is based on the underlying empirical structure of co-occurrences of withdrawal symptoms that experts considered relevant. A SOS score of 4 or higher reflects a high probability of withdrawal. Table 5 and supplementary file provide details on symptoms and the psychometric properties of these instruments, which are used in practice and in research.

Recommendation:

- *Use standardized IWS assessment instruments with proven clinical utility, validity, and reliability in infants and children; WAT-1 or the SOS (grade of recommendation = A)*

Delirium

Delirium is a neuro-cognitive disorder due to a somatic illness or its treatment. According to DSM-5 the core diagnostic criteria for delirium are (Table 1): a) a disturbance of attention or awareness; b) this disturbance is accompanied by changes in cognition that cannot be better accounted for by another pre-existing neurocognitive disorder (e.g., mental retardation, dementia); c) the condition develops within hours or days, and often fluctuates during the day, typically worsening in the evening ('sundowning'); and d) there are indications from the patient's history, examination or

laboratory results that the disturbance is probably the result of a medical condition or its treatment. [61]. The pathogenesis of delirium is largely unknown. The sufferers may be hyperactive, hypoactive or show signs of both states. Typical for the hypoactive delirium are slowed or sparse speech, hypoactive or slowed motor activity as well as lethargy, also described as reduced awareness or apathy. Adults and children largely show the same symptoms although hallucinations and hypoactive delirium are hard to observe in the very young children [62]. However, delirium has been described in infants below 1 year of age [63]. Delirium has not been described in neonates to date. Increasing evidence suggests there is a positive association between illness severity and paediatric delirium [64]. Many risk factors for delirium have been identified. These can be classified as patient-related, iatrogenic, and environmental. Patient factors (e.g. infections, metabolic disorders, withdrawal from medications, restraints, and sleep disturbance) and environmental factors may contribute to developing delirium [56].

The reported prevalence of paediatric delirium (PD) in PICU patients is 4% to 29% [56, 65, 66]. Colville et al. found that three months after discharge one third of PICU patients reported memories of psychotic features, including delusions and disturbing hallucinations, suggestive of delirium during PICU admission [67]. Adult delirium has been associated with higher mortality and morbidity and longer length of hospital stay [68]. PD, too, is associated with longer length of stay [69] and – as we suspect – increased morbidity. Thus, early recognition of this serious neuropsychiatric disorder is essential, and PICU nurses could facilitate this task.

Recommendation:

- *Search for potential sources of paediatric delirium and to take appropriate actions (grade of recommendation = D)*

Delirium assessment

According to the literature, PD is under-diagnosed especially in young critically ill children [56]. A likely reason is that nurses and ICU-physicians do not specifically focus on the symptoms of PD; and

moreover, it is difficult to assess the symptoms in preverbal patients. Looking at behaviours has been suggested as an alternative [56, 63]. Taking into account the child's developmental stages makes it possible to reliably and accurately interpret alterations in behaviour, communication, and emotion in the critically ill child of any age [70]. A number of delirium symptoms overlap with those observed in other conditions, such as pain, distress and withdrawal syndrome [6]. Thus it would seem essential to use a reliable, validated and clinical useful bedside tool to screen delirium and guide treatment. This is an area of development but assessment instruments are already available. These are: 1) the pediatric Confusion Assessment Method for ICU (pCAM-ICU) for children of 5 years or older [66]; 2) the Cornwell Assessment Pediatric Delirium tool (CAP-D) for children of 0 up to 18 years of age [65, 71]; and 3) the Sophia Observation withdrawal Symptoms-Pediatric Delirium scale [72, 73] (Table 5 and supplementary file). In the lack of evidence, we recommend assessment of delirium at least once per shift or as indicated by the clinical condition of the child.

Recommendation:

- *Use CAP-D as an instrument to assess paediatric delirium (grade of recommendation=A).*
- *Together with the vital signs, delirium must be assessed and documented every 8 to 12 hours (at least once per shift) 24-48 hours after admission, or as indicated by the delirium score of clinical condition of the child (grade of recommendation = D).*

Pain and non-pain related distress management protocols in relation to assessment

Effective pain and sedation management depends on the effectiveness of analgesics and sedatives, and the use of assessment instruments to measure the effects and target of the administered drugs. A number of randomized controlled trials have provided evidence for the use of individual drugs such as morphine, midazolam, paracetamol, clonidine and dexmedetomidine [74-77]. The combined use of drugs in infants has also been evaluated, like fentanyl versus remifentanil combined with midazolam [78] or remifentanil versus midazolam [79]. The use of fentanyl or morphine is common

practice around the world for postoperative analgesia in term newborns, infants and children, with recommended continuous infusions and dosages between 1-5 mcg/kg/h (fentanyl) and 10-40 mcg/kg/h (morphine), respectively [8]. Opioids and/or benzodiazepines are often given during artificial ventilation. The use of morphine as the drug of first choice for postoperative analgesia has been debated given the equipotency of intravenous paracetamol as the drug of first choice. With regards to sedation, Curley et al. failed to show beneficial effects of protocolized sedation versus usual care on length of artificial ventilation in a multicenter cluster randomised study of 31 PICUs in the US [80]. Still, daily interruption of sedatives significantly improved short- and long-term outcomes in adults. All evidence indicates that the use of sedatives should be reduced. In children, daily interruption of sedation seems feasible and safe [81, 82]. However, the effectiveness needs to be demonstrated in large trials [83]. Following the evaluation of the level of evidence of analgesic and sedative drugs by Playfor (2006) [8], increased attention is being paid to optimal dosing of many of the drugs used routinely in the PICUs around the world. Studies have demonstrated that re-assessment after an intervention is often neglected, although it is crucial in evaluating whether an intervention is effective or not [84, 85]. In summary, the overall aim of assessment of pain and non-pain related distress in relation to treatment is to find the most appropriate dose for the individual patient to eliminate or reduce pain and discomfort to an acceptable level without side effects of therapy. Therefore, we recommend that the effect of a drug (e.g. increasing or decreasing of a pump, bolus) is re-evaluated depending on the drug's half-life. One value outside the normal range of the score should not immediately result into a change in drug dosages. Strategies to reduce the incidence of iatrogenic withdrawal syndrome should begin by making efforts to reduce doses of benzodiazepines and/or opioids, and thereby preventing oversedation [44, 86].

Recommendation:

- *The effect (e.g. increasing or decreasing of a pump, bolus) of a drug should be re-evaluated depending on the drug's half-life (grade of recommendation = D).*

A weaning strategy for gradual decreasing of opioid and/or benzodiazepine dosages is essential to prevent IWS. Strategy options include slowly tapering off the intravenous infusion rate or using an alternative route, like the enteral or subcutaneous route. However, the evidence of different strategies is scarce. At each step in the weaning process, possible withdrawal symptoms should be carefully monitored with the help of the WAT-1 or SOS.

Recommendation:

- *Re-assess for symptoms of withdrawal after treatment interventions (grade of recommendation = D).*

Delirium in PICU patients has been treated with haloperidol and risperidone and both drugs demonstrated beneficial effects without significant side effects [56]. There remains a need for well-designed, randomized, placebo-controlled trials assessing the efficacy and safety of delirium drug therapy. Clinical pharmacological principles should go hand in hand with the daily use of validated assessment instruments with good psychometric properties. In this way optimal dosing and evaluation of specific behaviours of the individual critically ill patient will result in optimal synergy between care and cure.

Recommendation:

- *Validated assessment tools for pain, sedation, withdrawal syndrome and delirium should be integrated in pain and non-pain related treatment protocols (grade of recommendation = C).*

Discussion and conclusion

Providing comfort and minimizing anxiety, fear and distress in critically ill infants and children is an important part of the daily activities of intensive care nurses. These patients, who are unable to communicate their pain, discomfort, anxiety and fear, are at great risk for inadequate analgesia, sedation or delayed recognition of withdrawal syndrome and/or delirium. Just like all infants and

children, this special population deserves consistent, on-going assessment and re-assessment of interventions to confirm the best possible treatment for pain, distress, inadequate sedation, withdrawal syndrome and delirium. This position paper offers recommendations to this aim. To achieve the best possible outcome, interdisciplinary collaboration of nurses, physicians, and hospital pharmacists/clinical pharmacologists is therefore warranted. Distress can be reduced by creating an optimal environment with little noise (<45dB), favourable conditions for day-night (sleep) rhythm in combination with day-light, and family presence [87]. However, more research is needed to establish the effectiveness of non-pharmacological interventions in critically ill children. Furthermore, the nursing role includes providing information to parents, asking them about the nature and intensity of pain and distress of their infant or child, and consequently listening to parents. This requires a particular awareness, knowledge of and insight into these phenomena. It may be difficult to discriminate between pain, distress, IWS and delirium in critically ill children, because the behavioral cues will overlap in part (Figure 1). Pain frequently results in distress, but distress may have other causes than pain. Despite their close association, distinguishing between these concepts is clinically important as they are treated differently. A behavioral tool that is able to discriminate pain, sedation, iatrogenic withdrawal syndrome, and delirium in all circumstances is not available. It could be challenging for clinicians to deal with all these different instruments. The decision to apply a particular instrument should always be driven by interpreting factors related to the context of the patient (e.g. use of sedatives, postoperative, prolonged administration of sedatives/opioids as a risk for IWS), environment, and response to therapies (See Figure 2). Combining this with the different scores then allows to decide on the necessary action.

As the evidence for several recommendations is poor (e.g. grade D recommendations) further research is needed to strengthen these recommendations. Clinicians are recommended to select a validated and reliable assessment instrument and could be guided in the choice by the grade of recommendation. Furthermore, other factors should be considered like the ease of use, complexity of the tool, and the time it takes to complete the assessment. All staff working on the NICU or PICU

(physicians, nurses and nursing support staff) should be trained in the application of these instruments. Further, assessment outcomes should be integrated in treatment decision trees with recommended dosages based on RCTs in paediatric patients. In addition to pain as the 5th vital sign, it may be time to also endorse non-pain related distress in critically ill infants and children as the composite 6th vital sign [88].

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Table 1 Definitions of pain, distress, withdrawal syndrome, and delirium

Definitions of pain, distress, iatrogenic withdrawal syndrome, and delirium
Pain "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. *Note:* The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment." (IASP, 2014) *Acute pain:* "Acute pain should be viewed as the initiation phase of an extensive, persistent nociceptive and behavioural cascade triggered by tissue injury. This cascade has the potential to span orders of magnitude of space and time, but generally subsides within weeks" [89] *Postoperative pain* acute pain experienced post-surgery *Prolonged pain*: The terms prolonged and recurrent are used interchangeably in the literature. Prolonged or persistent pain is primarily caused by disease e.g. peritonitis. Prolonged pain differs from chronic pain in that there is a clear stimulus caused by disease (e.g. peritonitis) or therapy (e.g. mechanical ventilation, insertion of tubes or drains), with a clear definable beginning and an expected endpoint. But less than 3 months and full recovery of tissue damage can be expected, which is not the case in chronic pain[23].
Non-pain related distress *Distress* is an organism's response to aversive internal and external stimuli and may include discomfort, anxiety, and fear" [25]. *Optimal sedation*: a state in which the patient is somnolent, responsive to the environment but untroubled by it, and with no excessive movements [13].
Iatrogenic withdrawal syndrome A clinical syndrome that manifests after stopping or reversing a drug after prolonged exposure to that drug [3, 4]. *Tolerance:* a decrease in a drug's effect or the need to increase the dose to achieve the same effect [3, 4]. *Physiological dependence:* the requirement for continued administration of a sedative or analgesic to prevent signs of withdrawal syndrome**.**
Delirium A neuro-cognitive disorder due to a somatic illness or its treatment [61] DSM-V criteria: A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment). B. The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day. C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception). D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma. E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Table 2: Panel of Behavioral instruments specific to paediatric critical care

COMFORT behavior scale	
Categories	**Score**
Alertness	**1-5**
Calmness/agitation	**1-5**
Respiratory response or crying*	**1-5**
Physical movement	**1-5**
Muscle tone	**1-5**
Facial tension	**1-5**
	Total score 6-30
Withdrawal Assessment Tool	
Information from patient record	
Loose /watery stools	No=0, yes=1
Vomiting/retching/gagging	No=0, yes=1
Temperature > 37.8°	No=0, yes=1
2 minute pre-stimulus observation	
State*	SBS≤0 = 0, SBS≥1 =1
Tremor	No=0, moderate/severe=1
Any sweating	No=0, yes=1
Uncoordinated/repetitive movement	No=0, moderate/severe=1
Yawning of sneezing	No=0, yes=1
1 minute stimulus observation	
Startle to touch	No=0, moderate/severe=1
Muscle tone	Normal=0, increased=1
Post-stimulus recovery	
Time to gain calm state (SBS ≤ 0)	0-2
	Total score 0-12
Sophia Observation withdrawal Symptoms-scale	
Items	**Score**
Autonomic dysfunction	
Tachycardia	No=0, yes=1 (for all items)
Tachypnea	
Fever (≥ 38.5°)	
Sweating	
CNS irritability	
Agitation	
Anxiety	
Tremors	
Increased muscle tension	
Inconsolable crying	
Grimacing	
Sleeplessness	
Motor disturbance	
Hallucinations	
Gastrointestinal dysfunction	
Vomiting	
Diarrhea	
	Total score 0-15

*Crying only in spontaneous breathing children

Table 3 Pain: Summary of recommended assessment tools for neonates and critically ill children

	NEONATES				INFANTS & CHILDREN		
	PIPP[90-92]	**PIPP-Revised [40, 41]**	**N-PASS [93, 94]**	**COMFORTneo [95]**	**COMFORT behavior scale [26, 29, 31, 33]**	**FLACC [35, 96]**	**Multidimensional Assessment of Pain Scale (MAPS)[36, 97]**
Age range	28-40 weeks	28-40 weeks	23-40 weeks	24-42 weeks	0-3 years	0-7 years	0-31 months
Type of pain	Procedural and postoperative pain	Procedural pain	Procedural and prolonged pain	Prolonged pain	Postoperative pain	Postoperative pain	Postoperative pain
Variables assessed	Heart rate*, Oxygen saturation *, Brow bulge, * Eye squeeze * Nasolabial furrow*, Behavioral state	Heart rate*, Oxygen saturation*, Brow bulge[ǂ], Eye squeeze[ǂ], Nasolabial furrow[ǂ], Behavioral state	Heart rate, Respiratory rate, Blood pressure, Oxygen saturation Crying, irritability, Facial expressions, Behavioral state, Extremities/tone	Alertness, Calmness/agitation, Respiratory response or crying, Body movement, Muscle tone, Facial tension	Alertness, Calmness/agitation, Respiratory response or crying, Physical movement, Muscle tone, Facial tension	Facial expression, Movement of limbs, Cry, Consolability	Vital signs HR and / or BP, Breathing pattern, Facial expression, Body movements, State of arousal
Score range (cut off point)	0-21 0-6 No to mild pain 7-12 moderate pain >12 severe pain	0-21 0-6 No to mild pain 7-12 moderate pain >12 severe pain	Pain: 0-10 >3	6-30 6-13 no to mild discomfort 14-21 moderate discomfort >22 severe discomfort	6-30 >17 pain	0-10 1-3 mild discomfort 4-6 moderate discomfort 6-10 Severe discomfort/ pain	
Adjustment for gestational age	Yes	Yes**	Yes	No	NA	NA	NA
Reliability data	+	-	+	+	+	+	+
Forms of validity established	Construct and concurrent	Construct and concurrent	Construct and convergent	Concurrent	Construct and concurrent		Construct and concurrent
Clinical utility	+	-	+	+	+		
GRADE	A	A	B	B	A	B	A

*Changes expressed in % (in PIPP used to look at heart rate increases only but the revised version also takes heart rate declines into account); [ǂ]changes expressed in seconds; ** only if the score on the other items >0

See supplemental file for detailed data regarding psychometric properties.

Table 4 Sedation: summary of recommended assessment tools for critically ill children

	COMFORT scale [25, 45, 98]	COMFORT behavior scale [14, 31, 32, 42, 99]	State Behavioral Scale (SBS) [46]
Age range	0-16 years	0-16 years	6 weeks-6 years
Variables assessed	Distress Heart rate, Mean arterial pressure, Alertness, Calmness, Respiratory response, Movement, Muscle tone, Facial expression	Distress Alertness, Calmness/agitation Respiratory response or crying Physical movement, Muscle tone, Facial tension	Respiratory drive, Coughing, Best response to stimuli, Attentiveness to care provider, Tolerance to care, Consolability, Movement after consoled
Score range (cut off point)	8-40 <17 oversedation 17-26 optimal sedation >26 undersedation	6-30 <11 oversedation 11-22 adequate sedation >22 undersedation	6-point scale; state behavior on a scale of -3 to +2 0 = Awake and calm
Reliability data	+	+	+
Forms of validity established	Face, construct and concurrent	Face, construct and concurrent, responsiveness	Face, construct
Clinical utility		Feasibility and utility established bedside	Feasibility and utility established bedside
Grade	A	A	B

See supplemental file for detailed data regarding psychometric properties.

Table 5 IWS and Delirium: summary of recommended assessment tools for critically ill children

	Withdrawal Assessment Tool version-1 (WAT-1) [57, 58]	**Sophia Observation withdrawal Symptoms-scale (SOS) [59, 60]**	**Pediatric Confusion Assessment Method-Intensive Care Unit (pCAM-ICU) [66]**	**Cornell Assessment Pediatric-Delirium (CAP-D) [65, 71]**	**Sophia Observation withdrawal Symptoms-Pediatric Delirium scale (SOS-PD) [72, 73]**
Age range	Children 0-16 years	Children 0-16 years	5-16 years	0-21 years	0-16 years
Variables assessed	Loose /watery stools Vomiting/retching/gagging Temperature > 37.8° State* Tremor Sweating Uncoordinated/repetitive movement Yawning of sneezing Startle to touch Muscle tone Time to gain calm state (SBS ≤ 0)	Tachycardia Tachypnea Fever (≥ 38.5°) Sweating Agitation Anxiety Tremors Increased muscle tension Inconsolable crying Grimacing Sleeplessness Motor disturbance Hallucinations Vomiting Diarrhea	Four features: Acute change or fluctuation course of mental status, Inattention, Altered level of consciousness, Disorganized Thinking.	Eye contact with caregiver, Purposeful actions, Awareness of surrounding, Communicate needs, Restless, Inconsolable, Underactive, Response to interaction.	Agitation (restless), Anxiety, eye contact, grimacing, impaired attention, Speech, Tremors, Muscle tone, Purposeful actions, Sleeplessness, Hallucinations, Disorientation, Sweating, Acute change / fluctuation, Parents.
Score range (cut off point)	0-12 points ≥3	0-15 points ≥4	Features 1, 2 and 3 or 4 positive = delirium; or feature 1 and negative = no delirium*	0-40 (9)	0-15 (4)
Reliability data	+	+	+	+	+/-
Forms of validity established	Content, construct, responsiveness	Face, construct	Criterion	Criterion	Face (Criterion pilot)
Clinical utility	Feasibility and utility established bedside	Feasibility and utility established bedside	Feasibility	Utility established bedside	Feasibility
GRADE	A	A	B	A	C

See supplemental file for detailed data regarding psychometric properties.

Figure 1: Overlap behavioural cues in pain, sedation, withdrawal syndrome and delirium.

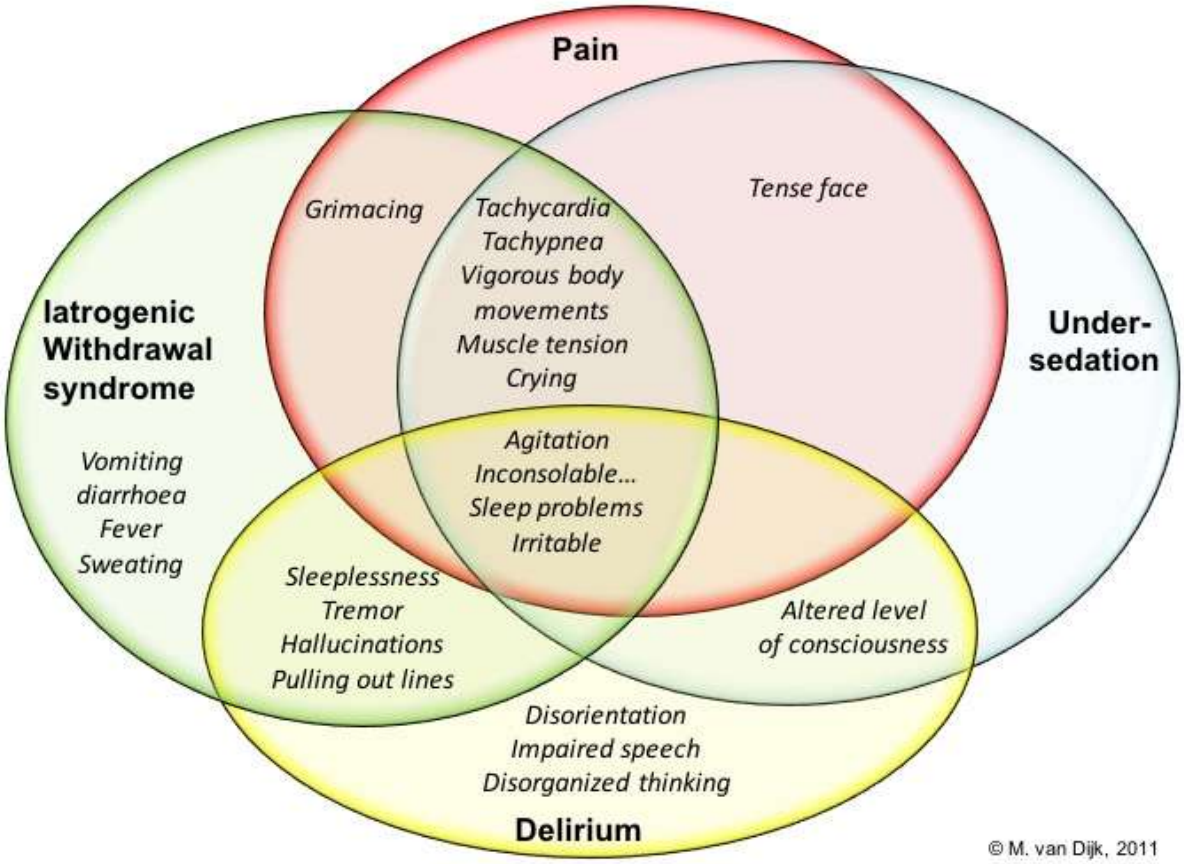
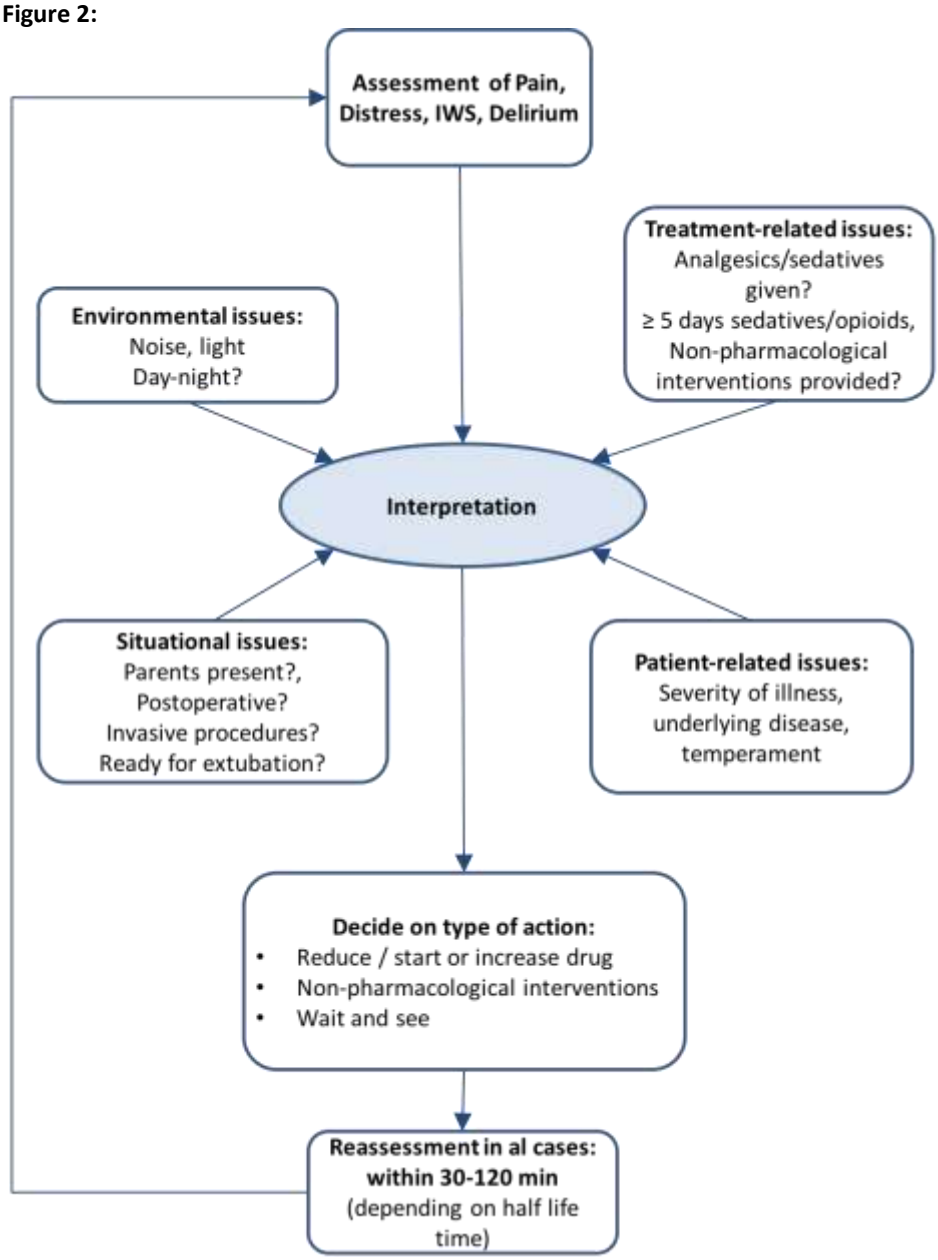


Figure 2:



Interpretation pain and non-pain related distress in critically ill children, based on van Dijk et al. 2012 [16]