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Pediatric pain treatment and prevention for hospitalized children

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Abstract

Introduction: Prevention and treatment of pain in pediatric patients compared with adults is often not only inadequate but also less often implemented the younger the children are. Children 0 to 17 years are a vulnerable population.

Objectives: To address the prevention and treatment of acute and chronic pain in children, including pain caused by needles, with recommended analgesic starting doses.

Methods: This Clinical Update elaborates on the 2019 IASP Global Year Against Pain in the Vulnerable "Factsheet Pain in Children: Management" and reviews best evidence and practice.

Results: Multimodal analgesia may include pharmacology (eg, basic analgesics, opioids, and adjuvant analgesia), regional anesthesia, rehabilitation, psychological approaches, spirituality, and integrative modalities, which act synergistically for more effective acute pediatric pain control with fewer side effects than any single analgesic or modality. For chronic pain, an interdisciplinary rehabilitative approach, including physical therapy, psychological treatment, integrative mind–body techniques, and normalizing life, has been shown most effective. For elective needle procedures, such as blood draws, intravenous access, injections, or vaccination, overwhelming evidence now mandates that a bundle of 4 modalities to eliminate or decrease pain should be offered to every child every time: (1) topical anesthesia, eg, lidocaine 4% cream, (2) comfort positioning, eg, skin-to-skin contact for infants, not restraining children, (3) sucrose or breastfeeding for infants, and (4) age-appropriate distraction. A deferral process (Plan B) may include nitrous gas analgesia and sedation.

Conclusion: Failure to implement evidence-based pain prevention and treatment for children in medical facilities is now considered inadmissible and poor standard of care.

Keywords: Pediatric pain, Pain treatment, Pain prevention, Multimodal analgesia, Topical anesthesia, Comfort positioning, Sucrose, Breastfeeding, Distraction

1. Introduction

Data from children's hospitals around the world reveal that pain in pediatric patients from infancy to adolescence is common, under-recognized and undertreated.[6,48,144,148,162,170,179] Compared with adult patients, pediatric patients with the same diagnoses receive less analgesic doses, and the younger the children are, the less likely it is that they receive adequate analgesia in the medical setting.[5,9,117,137]

The pain experienced by children in a hospital, medical facility, or doctor's office can be disease- and/or treatment-related and may be based on one, several, or all of the following pathophysiologies:

(1) Acute somatic pain (eg, tissue injury), which arises from the activation of peripheral nerve endings (nociceptors) that respond to noxious stimulation [and may be described as localized, sharp, squeezing, stabbing, or throbbing].
(2) Neuropathic pain, resulting from injury to, or dysfunction of, the somatosensory system [burning, shooting, electric, or tingling]. Central pain would be caused by a lesion or disease of the central somatosensory nervous system.
(3) Visceral pain results from the activation of nociceptors of the thoracic, pelvic, or abdominal viscera [poorly localized, dull, crampy, or achy].
(4) Total pain: suffering that encompasses all of a child's physical, psychological, social, spiritual, and practical struggles[134]
(5) Chronic (or persistent) pain: pain beyond expected time of healing

A particularly vulnerable group of patients are infants and neonates. A recent systematic review showed that neonates admitted to intensive care units frequently suffer through an average of 7 to 17 painful procedures per day, with the most frequent procedures being venipuncture, heel lance, and insertion of a peripheral venous catheter.[2] In most infants no analgesic strategies are used.[135] In addition, children with serious medical conditions are

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Key Points

1. According to the 2010 Declaration of Montreal, access to pain management is a fundamental human right and it is a human rights violation not to treat pain
2. Evidence-based pain prevention and treatment must become a priority for all medical facilities providing pediatric care
3. Effective multimodal analgesia for acute pain act synergistically for more effective pediatric pain control with fewer side effects than single analgesic or modality and includes pharmacology (eg, basic analgesia, opioids, and adjuvant analgesia), regional anesthesia, rehabilitation, psychology, spirituality, and integrative ("nonpharmacological") modalities.
4. For chronic persistent pediatric pain, an interdisciplinary rehabilitative approach including (1) physical therapy, (2) psychological interventions, (3) active integrative mind–body techniques, and (4) normalizing life (eg, school, sleep, social, and sports) has been shown most effective.
5. Opioids are usually not indicated in chronic pain in the absence of new tissue injury.
6. For elective needle procedures, evidence now mandates to consistently offer 4 strategies to every child every time: (1) topical anesthetics, (2) sucrose or breastfeeding for infants 0 to 12 months, (3) comfort positioning (including swaddling, skin-to-skin contact, or facilitated tucking for infants, sitting upright for children), and (4) age-appropriate distraction.

exposed to frequent painful diagnostic and therapeutic procedures (eg, bone marrow aspirations, lumbar punctures, and wound dressing changes). Furthermore, even healthy children have to undergo significant amounts of painful medical procedures throughout childhood: Vaccinations are the most commonly performed needle procedure in childhood, and pain is a common reason for vaccine hesitancy.[32,90,156]

Exposure to severe pain in infants without adequate pain management has negative long-term consequences, including increased morbidity (eg, intraventricular hemorrhage) and mortality.[2,152] Exposure to pain in premature infants is associated with higher pain self-ratings during venipuncture by school age[172] and poorer cognition and motor function.[66] Research has also shown that exposure to pain early in life even heightens the risk for developing problems in adulthood (chronic pain, anxiety, and depressive disorders), implying that adequate management of infant and child pain is imperative.[8,74,177]

This Clinical Update, building on the *Factsheet Pain in Children: Management. 2019 Global Year against Pain in the Vulnerable of the International Association for the Study of Pain [IASP]*,[59] which have been translated into 18 languages so far, will address the prevention and treatment of the 3 most common pain entities in pediatric medicine: acute pain, chronic pain, and needle pain.

2. Prevention and treatment of acute pain in children

Acute nociceptive pain might be due to tissue injury caused by disease, trauma, surgery, interventions, and/or disease-directed therapy. Untreated acute pain may lead to fear and even avoidance of future medical procedures.

Multimodal analgesia (**Fig. 1**) is the current recommended approach to address acute pain in hospitalized children. Pharmacology (including basic analgesia, opioids, and adjuvant analgesia) alone might not be sufficient to treat children with acute pain. The addition and integration of modalities such as regional anesthesia, rehabilitation, effective psychosocial interventions, spirituality, and integrative ("nonpharmacological") modalities acts synergistically for more effective (opioid-sparing) pediatric pain control with fewer side effects than single analgesic or modality.[55]

2.1. Treat underlying disease process

Pain is foremost a symptom and might be a warning sign. After a detailed medical history, clinical examination, and potentially further workup (including imagery or laboratory investigations), an underlying disease process (such as tissue injury including infection, and trauma) needs to be addressed as appropriate in the specific clinical scenario to avoid further harm. As an example, in a child with increasing foot pain after orthopedic surgery, the primary intervention would be to rule out and address a potential compartment syndrome, and not simply to increase the analgesic dose.

2.2. Basic analgesia

Basic (or "simple") analgesia usually includes acetaminophen (paracetamol) and nonsteroidal anti-inflammatory drugs (NSAIDs). Data have shown that ibuprofen-sodium (available over-the-counter in the United States and other countries) compared with standard ibuprofen has a faster analgesic onset (within 10 minutes), only requires 50% of the dose, and has a longer duration of action.[116] If NSAIDs are contraindicated due to their side-effect profile (which includes bleeding risk and gastrointestinal side effects), one may consider a COX-2 inhibitor (eg, celecoxib).[163] The renal toxicity profile may be somewhat better compared with classic NSAIDs.[118] For starting doses, see **Table 1**. Although in some countries dipyrone (metamizole) is commonly used as a basic analgesic, it is not available in many countries, including the United States.

2.3. Opioids

Opioids are often indicated for medium to severe acute pain due to tissue injury. The World Health Organization (WHO) step 2 suggests opioid use in children with persisting medium–severe pain due to medical illness in addition to basic analgesia (and not waiting for the effect of acetaminophen or an NSAID).[180] Morphine remains the "gold standard," but other "strong" opioids, such as fentanyl, oxycodone, hydromorphone, diamorphine (in the United Kingdom only), and methadone are equally effective in their respective analgesic effects. For opioid starting doses, see **Table 2**; for neonates, **Table 3**; and for usual patient-controlled analgesia (PCA) pump starting doses, see **Table 4**.

"Weak" opioids, with an analgesic ceiling effect, include codeine, which cannot be recommended anymore due to pediatric deaths, especially in cytochrome P450 2D6 ultrarapid metabolizers.[22,24,38,47,49,88,94] Tramadol, a multimechanistic analgesic, however, seems to continue playing a key role not only in outpatient surgery (eg, more than 6,000 pediatric tramadol scripts were filled at Children's Minnesota in 2018 in part due to its relative respiratory safety profile), but also in treating episodes of inconsolability in children with progressive neurologic, metabolic, or chromosomally based conditions with impairment of the central nervous system. Surprisingly, and not well based on scientific evidence, the US Food and Drug Administration (FDA) issued a warning against pediatric

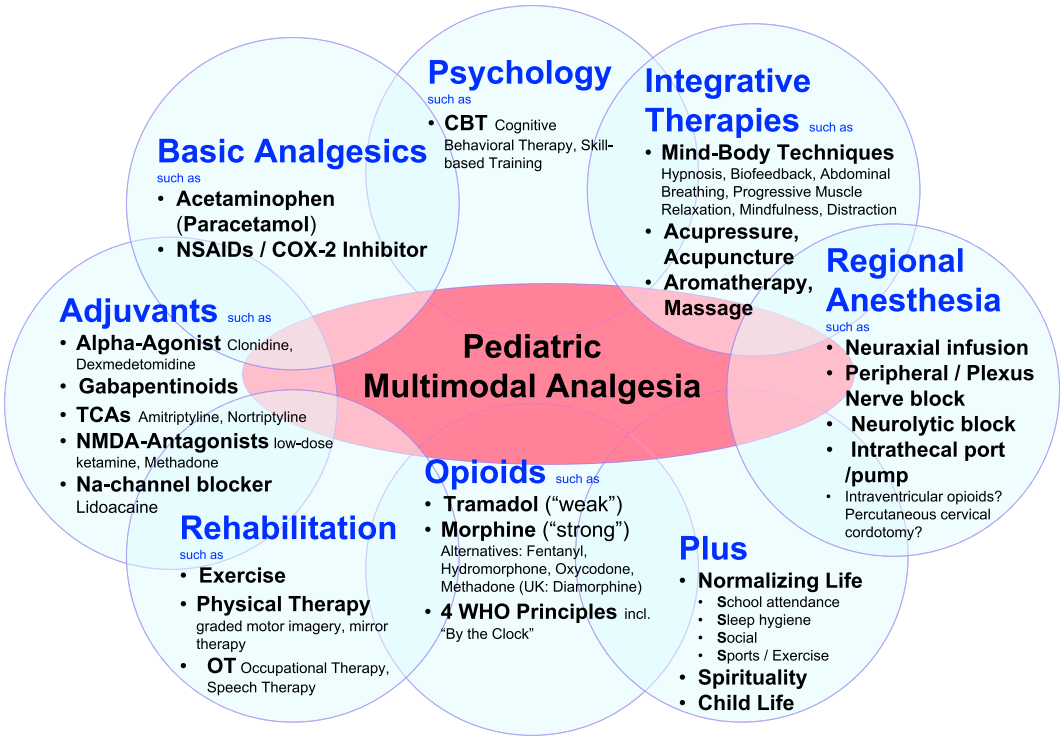

Figure 1. Pediatric Multimodal Analgesia: Implementing some or, depending on the clinical scenario, all modalities in the treatment of acute pain acts synergistically for more effective (opioid-sparing) pediatric pain control with fewer side effects than single analgesic or modality.

use of tramadol and cited the data of 3 children who have died worldwide in the previous 49 years, therefore actually making it far safer than any other opioid. Unfortunately, this warning may place children at greater risk for unrelieved pain and other distressing symptoms by encouraging clinicians to either use strong opioids in the outpatient setting with a higher risk of respiratory depression or not use opioids at all.[54]

"By the clock": when pain is constantly present, both administration of basic analgesia and opioid should usually be scheduled "around the clock" (eg, acetaminophen every 6 hours scheduled and/or morphine every 4 hours scheduled). As-needed prescriptions only (without scheduled analgesia) often do not reach the patient, and "PRN" ("pro re nata" or "as-needed") is often translated into "patient receives nothing", with 69 percent of hospitalized pediatric patients for whom analgesics had been ordered "PRN" did not receive a single dose in one study.[79]

2.4. Adjuvant analgesia

Adjuvant analgesics may improve pain control either in addition to basic analgesia and/or opioids, or they may also act as primary analgesics, especially in neuropathic and visceral pain treatment.[41,45]

Table 1

Basic analgesia for children.

Drug	Route	Age	Pediatric dose	Maximal dose	Dosing interval
Ibuprofen	PO	>3–6 months*	5–10 mg/kg	400–600 mg/dose	6–8 hours
Ibuprofen-sodium† 256-mg tablet = 200-mg ibuprofen	PO	>6 months	5–(10) mg/kg	200–(400) mg/dose	6–8 hours
Acetaminophen (paracetamol)	PO, PR	Neonates 0–30 days	5–10 mg/kg	20–40 mg/kg/day	4–6 hours (maximum 4 doses/day)
	PO, PR	Infants 1–3 months	10 mg/kg	40 mg/kg/day	4–6 hours (maximum 4 doses/day)
	PO, PR	4 months—2 years	10–15 mg/kg	40–60 mg/kg/day	4–6 hours (maximum 4 doses/day)
	PO, PR	>2 years	10–15 mg/kg	90 mg/kg/day or 650 mg Q6h	4–6 hours
	IV‡	<1 year	<10 kg = 7.5 mg/kg	30 mg/kg/day	6 hours
	IV‡	1–2 years	15 mg/kg	60 mg/kg/day	6 hours
	IV‡	>2 years (<50 kg)	15 mg/kg	75 mg/kg/day	6 hours
	IV‡	>13 years (>50 kg)	1000 mg	4000 mg/day	6 hours
Ketorolac§	IV	6 months–2 years*	0.25 mg/kg	30 mg/dose	6–8 hours
	IV	>2 years	0.5 mg/kg	30 mg/dose	6–8 hours
Celecoxib‖	PO	>6 months	1–2 mg/kg	100 mg/dose	12–24 hours

* For NSAIDs in infants <3 to 6 months, consult Pediatric Pain Service.
† Fast-acting, compared with standard ibuprofen: onset of analgesia after 10 minutes, last longer, and only half the dose required.
‡ Due to high cost, only if rectal or oral administration contraindicated, re-evaluate daily.
§ Recommend dosing no longer than 5 days
‖ If classical NSAIDs contraindicated, safety and efficacy have been established in children 2 years of age or older for a maximum of 6 months of treatment in JRA.
NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2

Opioid analgesics: usual starting doses for children with acute pain (>6 months).*,†

Medication (route of administration)	Starting dose IV	IV:PO ratio	Starting dose PO (or transdermal)
Morphine (PO, SL, IV, SC, and PR)‡	Bolus dose: 0.05–0.1 mg/kg (max. 5 mg) every 2–4 hours Continuous infusion: 0.01–0.02 mg/kg/h (max. 0.5–1 mg/h)	1:3 (ie, 1 mg IV = 3 mg PO)	0.15–0.3 mg/kg (max. 7.5—15 mg) every 4 hours
Fentanyl (IV, SC, SL, transdermal, and buccal)	Bolus dose: 0.5–1 mcg/kg (max. 25–50 mcg) (slowly over 3–5 minutes—fast bolus of high doses, especially >5–10 mcg/kg may cause thorax rigidity) Continuous infusion: 0.5–1 mcg/kg/h (max. 25–50 mcg/h)	1:1 (IV to transdermal)	12 mcg/h patch (must be on the equivalent of at least 30-mg oral morphine/24 hours, before switching to patch)
Hydromorphone (PO, SL, IV, SC, and PR)‡	Bolus dose: 15–20 mcg/kg (max. 1 mg) every 4 hours Continuous infusion: 2–5 mcg/kg/h (max. 100–250 mcg/h)	1:5 (ie, 1 mg IV = 5 mg PO)	60 mcg/kg (max. 2000–3000 mcg or 2–3 mg) every 3–4 hours
Oxycodone (PO, SL, and PR)‡	IV not available in the United States (Bolus dose: 0.05–0.1 mg/kg [max 2.5–5 mg] every 4 hours)	1:2 (ie, 1 mg IV = 2 mg PO) IV not available in the United States	0.1–0.2 mg/kg (max. 5–10 mg) every 4 hours or 0.15–0.3 mg/kg (max. 7.5–15 mg) every 6 hours
Tramadol (PO and PR)	IV not available in the United States (Bolus dose: 1 mg/kg every 3–4 hours) Continuous infusion: 0.25 mg/kg/h	1:1	1–2 mg/kg every 3–4 hours, max. Of 8 mg/kg/day (>50 kg: max. of 400 mg/day)
Methadone (PO, PR, SL, and IV)§	0.04–0.08-mg/kg (max. 2–4 mg) IV Q8h	1:1–1:2 (in adults usually IV usually 50% of PO dose, in pediatrics consider IV = 80% of PO dose)	0.05–0.1-mg/kg (max. 2.2–5 mg) PO Q8h

*Above doses represent starting doses, which then need to be titrated to effect and may be significantly higher.
†Maximum per kg dose capped at 50-kg body weight.
‡Calculated rescue (breakthrough) dose: 10% to 16% of 24-hour opioid dose to be given every 2 hours as needed. (Depending on the clinical scenario a breakthrough dose may given every 1-4 hours as needed.) Inform prescribing clinician, if requiring more than 3 breakthrough doses in less than 24 hours.
§Methadone should not be prescribed without proper training about dosing and potential side effects. Prescribing clinicians should closely observe the child for potential side effects from the time he or she receives the first dosed and following medication changes such as tapering, titration, or adding other potentially sedating medications.
IV, intravenous; n/a, not applicable; PO, by mouth; PR, rectal; SL, sublingual; SC, subcutaneous.

This heterogenic group includes gabapentinoids[33,68] (such as gabapentin and pregabalin), alpha-2-adrenergic agonists[10,23,78] (such as clonidine or dexmedetomidine), low-dose tricyclic antidepressants (such as amitriptyline or nortriptyline), *N*-methyl-D-aspartate (NMDA) channel blockers (such as low-dose ketamine[40,86]), and sodium-channel blockers (such as lidocaine[39,109,127,139,178]). See **Table 5** for dosing recommendations.

Cannabis and medical marijuana (including cannabidiol [CBD] and tetrahydrocannabinol [THC]) lack any evidence to support its use for treatment of acute or chronic pain.[29,76] The updated American Academy of Pediatrics policy opposes marijuana use,[126] citing lack of research and potential harms including correlation with mental illness,[19] testicular cancer,[28,97,167] decline in IQ,[113,115] and increased risk of addiction.[114] In our clinical practice, we do not support the use of marijuana (or medical cannabis) for a child with a primary pain disorder and a normal life expectancy. However, in children with life-limiting conditions, the administration of medical cannabis might be requested by patients and their parents and certainly may be considered on a case-by-case basis. It is important to watch carefully for side effects (including pancreatitis and psychosis).

2.5. Integrative medicine

Many integrative medicine (other terms used may include "non-pharmacologic," "complementary," or "alternative medicine")

Table 3

Opioid analgesia for neonates and infants 0–6 months of age.*

Opioids			
Morphine	PO/PR/SL	0.075–0.15 mg (neonates 0–30 days) 0.08–0.2 mg (infants 1–6 months)	6 hours 4–6 hours
Morphine†	IV/SC‡	0.025–0.05 mg/kg (neonates 0–30 days) 0.1 mg/kg (infants 1–6 months) Infusion (with PCA bolus of same dose): 0.005–0.01 mg/kg/h (neonates 0–30 days) 0.01–0.03 mg/kg/h (infants 1–6 months)	6 hours 6 hours
Fentanyl†	IV/SC‡	1–2 mcg/kg (neonates and infants 0–12 months) Infusion (with PCA bolus of same dose): 0.5–1 mcg/kg/h (neonates and infants 0–6 months)	2–4 hours
Oxycodone	PO/PR/SL	0.05–0.125 mg/kg (infants 1–6 months)	4 hours

* World_Health_Organization. WHO—Principles of Acute Pain Management for Children http://whqlibdoc.who.int/publications/2012/9789241548120_Guidelines.pdf. 2012.
† The intravenous doses for neonates are based on acute pain management and sedation dosing information. Lower doses are required for nonventilated neonates.
‡ Administer IV slowly over at least 5 minutes.
PCA, patient-controlled analgesia.

Table 4

Usual starting doses for patient (or nurse)-controlled analgesia (PCA) pumps for children in acute pain (>6 months).

	Continuous infusion (mcg/kg/h)	PCA bolus (mcg)	Lock-out time (minutes)	Maximum number of boluses/hour
Morphine	10–20 (max. 500–1000)	10–20 (max. 500–1000)	5–10	4–6
Hydromorphone	2–5 (max. 100–250)	2–5 (max. 100–250)	5–10	4–6
Fentanyl	0.5–1 (max. 25–50)	0.5–1 (max. 25–50)	5	4–6

Dose escalation usually in 50% increments both for continuous and PCA bolus dose (Department of Pain Medicine, Palliative Care & Integrative Medicine, Children's Hospitals and Clinics of Minnesota, USA). Doses for children >6 months of age and are capped at 50-kg body weight.

modalities seem very effective in treating and preventing pediatric acute pain. In infants, these modalities include breastfeeding, non-nutritive sucking with sucrose 24%, and skin-to-skin contact.[21,56,141,149] In toddlers, school children's and young adults' age-appropriate effective integrative modalities include distraction, deep breathing, biofeedback, self-hypnosis, yoga, acupuncture, transcutaneous electrical nerve stimulation and massage.[12,35–37,44,46,81,96,133,171,173,175,181] Many active mind-body techniques, such as guided imagery, hypnosis, biofeedback, yoga, and distraction may result in pain reduction through involvement of several mechanisms simultaneously within the analgesic neuraxis.[3,36,93,95,151]

2.6. Psychological interventions

Anxiety, depression, catastrophizing thoughts about pain, and behavioral disorders represent risk factors for the evolvement of acute to chronic pain in children and adolescents.[103,164] A recent meta-analysis of clinical trials involving adolescents and adults undergoing orthopedic surgery[166] demonstrated that preoperative psychological interventions, such as cognitive-behavioral therapy (CBT), hypnosis, relaxation, emotional counselling, and mixed psychotherapies, are effective to reduce acute post-operative anxiety and to improve longer term quality of life, with no effects found on postoperative pain.

2.7. Physical therapy, exercise, and rehabilitation

Physical therapy and exercise are key modalities in the treatment of children with acute and other pain conditions, including pediatric patients with serious illness.[30,101,105,108,110,119,120,143] Independent from pain treatment, increasing physical activity levels has also shown to decrease levels of depression.[84] Graded Motor Imagery, including mirror therapy, is the process of thinking about moving without actually moving and has been shown especially effective in children when moving the injured body part is too painful.[131]

2.8. Spirituality

A correlation between spiritual coping and the quality of life in pediatric patients with chronic illness has been described.[65,132]

Table 5

Adjuvant analgesics used in pediatric pain management.*

Class	Medication	Dose	Route of administration	Comments/side effects (see text for further details)
Tricyclic antidepressants (TCA)	Amitriptyline	Starting dose 0.1 mg/kg QHS, usually slowly titrated up to 0.5 mg/kg (max. 20–25 mg)	PO	Tertiary amine TCA; stronger anticholinergic side effects (including sedation) than nortriptyline
	Nortriptyline	Starting dose 0.1 mg/kg QHS, usually titrated up to 0.5 mg/kg (max. 20–25 mg)	PO	Secondary amine TCA; anticholinergic side effects
Gabapentinoids	Gabapentin	Starting dose 2 mg/kg QHS, usually slowly titrated up to initial target dose of 6 mg/kg/dose TID (max. 300 mg/dose TID). Max. dose escalation to 24 mg/kg/dose TID (max. 1200 mg/dose TID) Infants <1 year; 4.5 mg/kg/dose Q6h, titrated to max. 18 mg/kg/dose Q6h	PO	Slow dose increase required; side effects: Ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, and peripheral edema
	Pregabalin	Starting dose 0.3 mg/kg QHS, usually slowly titrated up to initial target dose of 1.5 mg/kg/dose BID (max. 75 mg/dose BID). Max. dose escalation to 6 mg/kg/dose BID (max. 300 mg/dose BID)	PO	Switch from gabapentin, if distressing side effects or inadequate analgesia. Side effects: Ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, and peripheral edema, associated with weight gain
Sodium channel blocker/local anesthetic	Lidocaine 5%	Max. of 4 patches (in patients >50 kg) 12 hours on/12 hours off	Transdermal patch	Not for severe hepatic dysfunction
Alpha agonist	Clonidine Dexmedetomidine	1–3 mcg/kg (max 150 mcg) QHS to Q6h Infusion: 0.3 mcg/kg/h; titrate to max. 2 mcg/kg/h	PO/transdermal IV	
Hormone	Melatonin	0.06–0.2 mg/kg (max. 3–10 mg) QHS	PO	For sleep induction; use extended-release, if interrupted sleep, possible analgesic effect

* Friedrichsdorf SJ. Prevention and treatment of pain in hospitalized infants, children, and teenagers: from myths and morphine to multimodal analgesia. In: *Pain 2016: Refresher Courses. 16th World Congress on Pain.* Washington, DC: International Association for the Study of Pain, IASP Press; 2016:309–319.

BID, bis in die, twice a day; IV, intravenous administration; PO, per os, oral administration; Q6h, every 6 hours; QHS, every night at bedtime; TID, ter in die, 3 times a day.

Parents of children with serious illness described religion, spirituality, and/or life philosophy playing an important role in their life and of the affected child.[75] Most children's hospitals encourage the inclusion of spiritual aspects of life into health care, for instance, by making hospital chaplains available.

2.9. Regional anesthesia

One of the most effective analgesic modalities in children with tissue injury represents regional or neuraxial anesthesia.[13,26,27,73,140,142] Nociceptive pathways may be blocked using central neuraxial infusions, peripheral nerve, and plexus blocks or infusions, or neurolytic blocks.[136] Benefits of regional anesthesia include reduced (or no) need for opioid analgesics, absence of systemic side effects such as sedation or nausea, improved gastrointestinal motility, reduced incidence of delirium, and the opportunity for the patient to be awake and able to remember conversations with clinicians and family.[11] In addition to motor weakness, less common potential side effects with epidural include pruritus, urinary retention, and hypotension.

3. Management of chronic pediatric pain

Pediatric chronic pain is a significant problem with conservative estimates that posit 20% to 35% of children and adolescents affected by it worldwide.[58,91,147] Pain experienced by patients in children's hospitals is known to be common, with more than 10% of hospitalized children showing features of chronic pain.[48,148,162,182] Although the majority of children reporting chronic pain are not greatly disabled by it,[80,176] about 3% of pediatric chronic pain patients require intensive rehabilitation.[71]

The 2012 American Pain Society Position Statement, "Assessment and Management of Children with Chronic Pain," indicates that chronic pain in children is the result of a dynamic integration of biological processes, psychological factors, and sociocultural variables, considered within a developmental trajectory.[43] Unlike in adult medicine, chronic pain in children is not necessarily defined by using arbitrary temporal parameters (eg, 3 months) but rather uses a more functional definition such as "pain that extends beyond the expected period of healing" and "hence lacks the acute warning function of physiological nociception."[168,169]

3.1. Interdisciplinary management of chronic pediatric pain

An interdisciplinary approach combining (1) rehabilitation, (2) integrative medicine/active mind–body techniques, (3) psychology interventions, and (4) normalizing daily school attendance, sports, social life, and sleep seem to be most effective. As a result of restored function, pain improves and commonly resolves. Opioids are not indicated for primary pain disorders (including centrally mediated abdominal pain syndrome, primary headaches [tension headaches/migraines], and widespread musculoskeletal pain) and other medications, with few exceptions, are usually not first-line therapy.

A recent Cochrane review concluded that face-to-face psychological treatments might be effective in reducing pain outcomes for children and adolescents with headache and other types of chronic pain.[42] Psychological treatments have also been found to be effective for reducing pain-related disability in children and adolescents with mixed chronic pain conditions at post-treatment and follow-up and for children with headache at follow-up.[31] The most commonly used psychological therapy, CBT,[31,121] has been shown to reduce pain severity in children and adolescents with widespread musculoskeletal/joint pain, headaches, abdominal pain, and headaches.[31,121]

As proposed by Palermo's conceptual framework for understanding chronic pain in children and adolescents[122,124] and the Interpersonal Fear-Avoidance Model,[60,62] a child's social environment and especially parents play a key role in understanding childhood chronic pain. Increasing evidence suggests that it is important to target parental catastrophizing thoughts, parental distress, and parental behaviors with regard to child pain (eg, protective behaviors), which has led to recommendations to incorporate parents within the multidisciplinary treatment.[62] A recent Cochrane review[100] indeed indicated a beneficial effect of psychological therapies for parents of children with chronic pain conditions on parenting behavior (eg, reduction of protective behaviors) at post-treatment and follow-up. Furthermore, this review also showed that psychological therapies can improve parent mental health in this population. When considering children's treatment outcomes, a small beneficial effect was found on children's behavior and disability at post-treatment and follow-up. Furthermore, a moderate beneficial effect was found on children's pain at post-treatment, but no effects on child mental health at post-treatment or follow-up.

With regard to the specific effects of CBT, the available evidence shows that CBT is effective in decreasing parents' protective responses in children with chronic (or persistent) abdominal pain.[102] Furthermore, a recent randomized controlled trial examining the effects of family-based CBT delivered through the internet[99,123] demonstrated greater reductions in activity limitations from baseline to 6-month follow-up for internet-delivered CBT compared with an educational intervention. Additional beneficial effects of CBT were found on sleep quality, reduction of parents' protective behaviors, and treatment satisfaction.[123] Secondary longitudinal analyses further showed that child disability, parent protective behavior, and parent distress improved over the 12-month study period.[99] Indeed, a recent systematic review on the effects of internet-delivered CBT in youth with chronic pain and their parents[161] showed that, compared with pretreatment, internet-delivered CBT had medium to large benefits on child pain intensity, activity limitations, and parental protective behaviors immediately after treatment. Furthermore, small to medium positive effects were found for child depressive symptoms, anxiety, and sleep quality. However, still limited evidence is available, and more trials are needed (Box 1).[161]

3.2. Early screening of children's risk profile to tailor clinical care

To ensure optimal clinical care and treatment for children and adolescents who present with chronic pain complaints at the hospital, early identification of risk factors for adverse outcomes may be warranted. Recently, a 9-item Pediatric Pain Screening Tool (PPST)[70,145] has been developed, to rapidly assess risk factors associated with adverse outcomes, such as sleep problems, catastrophizing thoughts, pain-related fear, and depression. Early identification of risk factors that may maintain chronic pain allows optimal stratified care and may improve recovery rates. Importantly, evidence supports the generalizability of the PPST across pain complaints.[70,145] Based on this brief scale, a risk profile of the child can be calculated, which provides indications for the type of care needed, ie, conservative treatment including education/advice, for instance, regarding sleep hygiene (low-risk profile), referral to physiotherapy (medium-risk profile), or

Box 1. Treatment of chronic pain and primary pain disorders.[50]

(1) Rehabilitation (eg, physical therapy, graded motor imagery,[131] and occupational therapy)
(2) Integrative ("nonpharmacological") modalities (eg, mind–body techniques such as diaphragmatic breathing, bubble blowing, self-hypnosis, progressive muscle relaxation, and biofeedback plus modalities such as massage, aromatherapy, acupressure, and acupuncture)
(4) Psychology (eg, cognitive-behavioral therapy, acceptance and commitment therapy)
(4) Normalizing life (usually life gets back to normal first, then pain goes down—not the other way around)
- Sports/exercise
- Sleep hygiene
- Social life
- School attendance

(5) Medications (may or may not be required)
- Basic analgesia (eg, paracetamol/acetaminophen, NSAIDs, and COX-2 inhibitor)
- Adjuvant analgesics (eg, gabapentin, clonidine, and/or amitriptyline)
- Of note: Opioids in the absence of new tissue injury, eg, epidermolysis bullosa and osteogenesis imperfecta, are usually not indicated

referral for multidisciplinary treatment, for instance, including psychological treatment and physical therapy for elevated pain-related fear (high-risk profile).[70,145]

Given the major role of parents in influencing a child's pain experience and functioning,[60,62] Simons et al. also developed a brief 12-item self-report screening tool (Parent Risk and Impact Screening Measure [PRISM][146]) to assess parents' psychosocial functioning (ie, parents' distress and health), behavioral responses to their child's pain, and the impact of the child's pain on the family. Similar to the PPST, risk profiles of parents can be calculated, identifying parents at low, medium, or high risk and informing the clinician, which parents would benefit from a referral for parent-focused treatment or targeted pain-related interventions for parents (eg, to reduce protective behaviors).

3.3. Strengthening resilience mechanisms

Next to identifying and targeting risk factors for adverse outcomes, it has increasingly been acknowledged that it is also important to identify and promote factors or strengths that can improve adaptive or resilient functioning.[25,61] Resilient functioning can be best defined as the ability to restore and sustain living a fulfilling life in the presence of pain[61] (eg, is the child able to engage in activities he/she finds important despite the pain; can he/she keep high levels of well-being despite the pain). When a child presents with pain complaints at the hospital, attention should not only be paid to malfunctioning but also to what goes well in the child's life, and how this resilient functioning can be further improved. This can be performed by strengthening resilience mechanisms such as positive affect, psychological flexibility, acceptance of pain, gratitude, and availability of family support over and above targeting/reducing risk factors such as pain-related fear.[61] Although empirical evidence is still in its infancy, studies in adults show promising results of resilience-based treatment approaches such as positive psychology interventions[128] and acceptance-based approaches.[174] Although more empirical research is needed which interventions are most effective for whom, interventions promoting resilience mechanisms may be particularly valuable in early stages of treatment, to support adaptive domains of functioning and to prevent adverse outcomes in the long run. In children with high-risk profiles, it may be an important component of a multimodal approach to treatment.

Research on Acceptance and Commitment Therapy (ACT),[69,129] a third generation behavior therapy that aims to promote resilient functioning by fostering psychological flexibility and acceptance of pain, is growing, and there is accumulating evidence that it can promote better functioning in adolescents with chronic pain, better pain acceptance, better school attendance, and reduced catastrophizing and anxiety and reduced use of health care facilities.[57,129] Furthermore, a recent nonrandomized clinical trial in adolescents with chronic pain and their parents[89] showed that acceptance and commitment therapy had positive effects not only on adolescents' functioning but also on parents. Specifically, it was found to lead to significant improvements in parents' depressive symptoms and psychological flexibility. Moreover, this study showed that improvements in parents' psychological flexibility were associated with better adolescent pain acceptance over time.

4. Management of needle pain in children

Untreated needle pain, caused by procedures such as vaccinations, blood draws, injections, and venous cannulation can have long-term consequences including needle phobia, preprocedural anxiety, hyperalgesia, and avoidance of health care, resulting in increased morbidity and mortality.[153,154] Current evidence,[154,158,159] supported by guidelines from the Canadian Paediatric Society,[18,82] HELPinKids,[72,111,112,157] and recently brought forward by science-to-social media campaigns ("Be Sweet to Baby"[21] and especially "It Doesn't Have to Hurt" by Chambers et al.[20]), strongly suggests that 4 bundled modalities

Box 2. Prevention and treatment of needle pain.

Offer a bundle of these 4 (or 3 for >12 months) evidence-based modalities to all children all the time:
(1) Topical anesthesia "Numb the skin" eg, 4% lidocaine cream (administered 30 minutes prior procedure), EMLA (lidocaine 2.5% and prilocaine 2.5%) cream (60 minutes prior), amethocaine [tetracaine] 4% gel (30–60 minutes prior) or needleless lidocaine application using pressurized gas to propel medication through the skin (1 minutes prior) eg J-Tip®
(2) Sucrose or breastfeeding for infants 0 to 12 months.
(3) Comfort positioning "Do not hold children down." For infants, consider parent-infant skin-to-skin (kangaroo care) contact. If not feasible, consider swaddling, warmth, facilitated tucking, and/or cobedding for twins. For children 6 months and older, offer sitting upright with parents holding them on their lap or sitting nearby.
(4) Age-appropriate distraction,[9,137,171] such as toys, books, blowing bubbles or pinwheels, stress balls, and using apps, videos, or games on electronic devices.

Of note: If above ineffective or not feasible, consider nitrous gas analgesia/sedation. For needle phobia, in addition, consider referral to pediatric psychologist.

should be offered for elective needle procedures to reduce or eliminate pain and anxiety experienced by children (Box 2).[52]

Failure to prevent or minimize treatable procedural pain in children is now considered both inappropriate and unethical.[51]

(1) Topical anesthesia needs to be offered (and unless verbal children decline for themselves), administered to all children 36 weeks' corrected gestational age and older for every elective needle procedure. Topical anesthetics include 4% liposomal lidocaine cream[160] (of note, currently, all 4% lidocaine cream available over-the-counter in the United States and Canada is liposomal), EMLA (lidocaine 2.5% and prilocaine 2.5%) cream, or needle-less lidocaine application through a J-tip (sterile, single-use, disposable injector that uses pressurized gas to propel medication through the skin).[106,107]

EMLA cream may be on the skin for up to 4 hours and provides maximum analgesia after at least 60 minutes compared with 4% lidocaine cream, which is already effective after 30 minutes and may be on skin up to 2 hours.[34,92] In comparison with EMLA cream, amethocaine (tetracaine) 4% gel is superior in preventing pain associated with needle procedures.[98]

Only topical anesthesia, such as lidocaine provided consistent analgesia within an additive pain intervention regimen during vaccinations in infants.[160] Dispelling a common myth, topical anesthetics do not constrict veins and do not decrease the chance of venous cannulation.[52,106,138] Not surprisingly, topical anesthesia even works for kids under general anesthesia and should therefore be considered.[67]

Other modalities, including vapocoolants, ice, cool/cold packs, and vibrating devices might be helpful but currently have insufficient evidence for or against their use to reduce pain at time of injection and therefore should be considered in addition to topical anesthetics, but not instead of numbing cream.[155]

(2) For term infants 0 to 12 months,[21] breastfeeding is effective in preventing or decreasing procedural pain in infants and equally effective to sucrose.[141] Sucrose reduces pain and cry during painful procedures, such as venipunctures, and seems to facilitate the release of endogenous opioids, as the mu-opioid antagonist naloxone blunts the effect.[56,149] The minimally effective dose of 24% sucrose for procedural pain relief in neonates in a recent randomized controlled trial (RCT) has been determined as "just a drop" (0.1 mL)[150] and therefore can be administered to infants who are "NPO" (nothing by mouth). It should be administered about 2 minutes before the painful procedure and may be repeated during the intervention.

(3) Comfort positioning: For elective needle procedures, children should not be held down (this might be different in a life-saving intervention). For infants, consider primarily skin-to-skin (kangaroo care) contact. If not feasible, consider swaddling, warmth, facilitated tucking, and/or cobedding for twins.[4,14–17,63,64,85] For children 6 months and older, offer sitting upright with parents holding them on their laps or sitting nearby.

Restraining children for procedures is never supportive, creates a negative experience, and increases their anxiety and pain. In fact, children with cancer who have been restrained for procedures report that it makes them feel ashamed, humiliated, powerless, and they report having lost their right to control their own body.[87]

Of note, a just-published RCT with 242 stable preterm infants by Campbell-Yeo et al.[17] seems not only to suggest that maternal-infant skin-to-skin contact, or kangaroo care (KC) is equally effective as 24% oral sucrose, but that the combination of maternal KC and sucrose did not seem to provide additional benefit. Further research on this topic would be required, and as the result of this, future RCTs may challenge current recommendations. The current recommendation of using sucrose as a standard of care will remain in place for the time being.

(4) Age-appropriate distraction includes the use of toys, books, blowing bubbles or pinwheels, stress balls, and using apps, videos, or games on electronic devices.[9,137,171] A recent Cochrane review identified sufficient evidence for the effectiveness of cognitive-behavioral therapy, breathing interventions, distraction, and hypnosis for reducing children's pain and/or fear due to needles.[7]

Offering these 4 simple modalities (or 3 to children older than 12 months) and not just some of them for all needle procedures for all children all the time has now be implemented systemwide in children's hospitals and pediatricians' offices on several continents.[52,130]

In addition to these 4 modalities, it is recommended that health care professionals and parents use neutral words and avoid language that can increase fear and may be falsely reassuring (eg, "it will be over soon"; "you will be ok").[153]

(5) Deferral process (or "plan B"): If adequate procedural analgesia and anxiolysis is not feasible with the above bundled modalities alone (eg, because the child has been held down in the past and has become too anxious, and/or it was difficult to draw blood in the past, etc.) consider involving a child-life specialist, referral to a child-psychologist to offer CBT to overcome needle phobia and/or consider nitrous gas.[53]

4.1. Nitrous gas analgesia and sedation

Data reveal that children receiving nitrous gas before and during painful procedures have lower levels of distress, lower pain scores, were more relaxed, and many have no recollection of the procedure afterwards.[77,125,165] Nitrous gas concentrations between 40% and 70% can be titrated to achieve minimal sedation only, avoiding moderate sedation.[104,183] Children receiving minimal sedation are able to respond to verbal commands, maintain, and protect their airway, spontaneous ventilation, and cardiovascular functions are unaffected.[1]

5. Conclusion

Access to pain management is a fundamental human right, and it is a human rights violation not to treat pain.[83] Yet, pain prevention and treatment in pediatric patients compared with adult medicine is often not only inadequate, but also even less often implemented the younger pediatric patients are. Effective multimodal analgesia for acute pain includes pharmacology, regional anesthesia, rehabilitation, psychology, spirituality and integrative ("nonpharmacological") modalities, which act synergistically for more effective pediatric pain control with fewer side effects than single analgesic or modality. For chronic pediatric pain, including primary headaches (migraines/tension headaches), centrally mediated abdominal pain, and widespread musculoskeletal pain, an interdisciplinary rehabilitative approach including physical therapy, psychological approaches (eg, CBT, ACT), integrative active mind-body techniques, and normalizing life (school, sleep, social, sports) has been shown most effective. Opioids are usually not indicated in chronic pain in the absence of new tissue injury. For elective needle procedures, such as blood draws, intravenous access, injections, or vaccination, overwhelming evidence now mandates that a bundle of 4 modalities to eliminate or decrease pain must be offered to every child every time: (1) topical anesthesia, eg, lidocaine 4% cream; (2) comfort positioning, eg,

skin-to-skin contact for infants or not restraining children; (3) sucrose or breastfeeding for infants; and (4) age-appropriate distraction. A deferral process for children where this bundle is ineffective may include nitrous gas analgesia and sedation.

Disclosures

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