# Nonpharmacologic Management of Pain During Common Needle Puncture Procedures in Infants



## **Current Research Evidence and Practical Considerations: An Update**

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#### **KEYWORDS**

- Pain
   Needle puncture
   Neonates
   Nonpharmacologic management
   Pain relief
- Effectiveness

#### **KEY POINTS**

- Medical procedures involving needle puncture are ubiquitous in contemporary health care; they are used to diagnose, treat and monitor medical conditions.
- Cumulatively, infants can be exposed to hundreds of needle procedures over the entire duration of a hospitalization.
- There is sufficient evidence to support the use of nonpharmacologic interventions, particularly breastfeeding, sweet tasting solutions, and skin-to skin care, as primary strategies for pain management during common needle puncture procedures.

#### INTRODUCTION

Medical procedures involving needle puncture are ubiquitous in contemporary health care; they are used to diagnose, treat, and monitor medical conditions. Healthy infants

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undergo about a dozen punctures in their first year of life alone. These procedures routinely include (1) intramuscular injection of vitamin K to prevent hemorrhagic disease, (2) intramuscular and subcutaneous injections of immunizations for vaccine-preventable diseases, and (3) heel lance and/or venipuncture for screening of conditions such as phenylketonuria, hyperbilirubinemia, hypoglycemia, and hypothyroidism. In approximately 10% to 15% of infants hospitalized for medical conditions such as prematurity, congenital anomalies, jaundice, and infection, additional needle puncture procedures are undertaken, such as venous cannulation, to enable administration of nutrition and medication. A list of common needle procedures undertaken in hospitalized infants is displayed in **Box 1**.

Numerous studies have quantified the burden of pain from needle puncture procedures undertaken in hospitalized infants (**Table 1**). Although estimates vary from study to study, research findings continue to demonstrate that sick infants or those delivered preterm routinely experience dozens of procedures per week. <sup>1–3</sup> A recent systematic review demonstrates infants with lower gestational age, lowest birth weights and need for ventilation have the highest number of needle procedures. <sup>3</sup> Cumulatively, infants can be exposed to hundreds of needle procedures over the entire duration of hospitalization.

It is important to treat needle pain in infants, not only to reduce acute distress and suffering, but to also reduce any potential long-term negative impact on brain development and functioning. <sup>11,12</sup> Despite evidence that pain experienced in infancy can have long-standing consequences, pain from needle punctures undertaken in infants remains undertreated. <sup>7,8,13</sup> Nonpharmacologic interventions represent a much more rational approach to minor needle procedures than pharmacologic approaches for managing needle pain in infants.

The past 3 decades witnessed a surge of research investigating the effectiveness of nonpharmacologic methods of pain relief. Recent audits of analgesic practices in hospitalized infants demonstrate that the use of nonpharmacologic interventions surpasses analgesic drugs. In 1 study, the use rate for nonpharmacologic interventions was 18% compared with 2% for pharmacologic interventions. In another study, procedures were more commonly treated with sucrose (14.3%) or other nonpharmacologic interventions (33%) compared with pharmacologic interventions (16%). Studies even more recently conducted in developing countries demonstrated that most infants still underwent painful procedures without any analgesic intervention. <sup>7,8</sup>

### Box 1 Needle puncture procedures undertaken in hospitalized infants

Intramuscular injection

Subcutaneous injection

Heel lance

Venipuncture

Venous cannulation

Central line insertion

Arterial puncture

Arterial cannulation

Lumbar puncture

Suprapubic aspiration

Table 1 Epidemiology of procedural pain in infants in intensive care											
No. of Painful Procedures	Period of Time	Total Percentage that Were Needle Punctures									
60.8 per patient	Total stay	70%	Barker & Rutter, 4 1995								
2–10 per day	First 7 d	90%	Johnston et al, <sup>5</sup> 1997								
14 per day	First 14 d	15.6%	Simons et al, <sup>6</sup> 2003								
12–16 per day	First 14 d	25.6%	Carbajal et al, <sup>2</sup> 2008								
0.8 per day	7 d	94%	Johnston et al, <sup>1</sup> 2011								
4.3 per day	Total stay	66%	Kyololo et al, <sup>7</sup> 2014								
7.5 per patient per day	First 14 d	19.8%	Jeong et al, <sup>8</sup> 2014								
11.4 per patient per day	First 14 d	14%	Roofthooft et al, <sup>9</sup> 2014								
6.6 per patient per day	Total stay	52.3%	Sposito et al, <sup>10</sup> 2017								

In a very recent study examining pain management over the entire hospital stay of 242 preterm infants, although improvements in provision of pain treatment from 68% to 84% related to heel lance and intravenous therapy, only 37% of infants undergoing intramuscular injection received any form of pain relief. Audits also demonstrate that organizations with strong pain guidelines for infants can improve the use of non-pharmacologic interventions. 9,15

This article is an overview of current evidence from systematic reviews for the effectiveness of nonpharmacologic interventions for the management of pain in infants undergoing needle procedures, including swaddling or containment, pacifier or non-nutritive sucking, rocking or holding, breastfeeding and breastmilk, skin-to-skin care, sweet tasting solutions, music therapy, sensorial saturation, and parental presence. In addition, implementation considerations and areas for future research are reviewed.

#### SWADDLING AND CONTAINMENT

Swaddling and containment are interventions that aim to limit the infant's boundaries, promote self-regulation, and attenuate physiologic and behavioral stress caused by acute pain. 16,17 These interventions are normally differentiated in that swaddling involves wrapping of the infant in a sheet or blanket; limbs flexed; head, shoulders, and hips neutral, without rotation; and hands accessible for exploration 18; whereas containment refers to restricting the infant's motions by holding or using an arm to place the infant's arms and legs near the trunk to maintain a flexed in utero posture, with limbs placed in body midline. 14 Containment can be achieved using accessories such as rolled blankets or commercially sold neonatal boundaries. Containment provided by a care provider or parent in which they use their hands to a hold the infant in a side lying, flexed fetal-type position is referred to as facilitated tucking. 19 In nonpain conditions, facilitated tucking has been associated with improved duration of sleep, neuromuscular development, and motor organization and reduction in physiologic distress. 20

#### Evidence Summary

The effects of swaddling and containment have been examined in both preterm and full-term infants undergoing commonly performed tissue-breaking procedures in the neonatal intensive care unit (NICU). Collectively, 9 studies including infants born at

less than 37 weeks and 1 study examining the response of term infants up to 1 month, were reported in a recent systematic review examining the effect of swaddling or tucking on pain-related distress pain reactivity and pain regulation. Additionally, a small meta-analysis of 4 studies conducted in Thailand reports a larger effect of swaddling compared with no intervention on pain scores during heel stick in term infants than in preterm infants. Although swaddling and containment may decrease biobehavioral pain response when compared with no treatment, its effect when compared with other interventions is considerably less and as such should be considered an adjuvant treatment used in combination with one of the more optimal treatments to be discussed elsewhere in this article.

#### Implementation Considerations

Both containment and swaddling keep the infant in a flexed position and restrain the infant's limbs, decreasing the stress caused by motor disorganization, which is triggered by strong stimuli. It is a simple and feasible intervention that should be provided to infants as an intervention for puncture-related procedural pain. The most limiting factors impacting the clinical usefulness of swaddling relate to (1) the inability to adequately visualize an acutely ill infant, (2) interference with control of body temperature overhead heating units, and (3) possible dislodgment of indwelling catheters or tubing. Conversely, the use of containment either with positional supports or by touch is a feasible option in these circumstances. There have been some issues raised regarding the cost-benefit ratio for the use of facilitated touch provided by neonatal care providers.<sup>23</sup> Swaddling or containment is also generally contraindicated for infants with conditions associated with poor skin integrity, such as extreme prematurity or epidermolysis bullosa.

#### Research Considerations

The relative effectiveness of the swaddling and containment in infants of different gestational ages requires additional investigation given the lack of studies conducted in full-term infants and older infants. There is some evidence that the effect of swaddling may be very beneficial for infants with a higher gestational age. Swaddled infants with a postconceptional age 31 to 36 weeks seemed to recover physiologic parameters, specifically elevation in arterial oxygen saturation and reduction in heart rate, faster than infants with a postconceptional age of 27 to 31 weeks. To date, no studies have examined the effect of this intervention in older infants up to a year, or the sustained effectiveness of swaddling or containment over ongoing, or across varied procedures. Future research is recommended to fill these knowledge gaps.

## PACIFIER AND NON-NUTRITIVE SUCKING Evidence Summary

In the absence of breastmilk or supplemental infant formula, non-nutritive sucking, generally referred to as the placement of a pacifier or a gloved finger in the infant's mouth to stimulate a sucking response, has been well-studied and reviewed in a recent meta-analysis.<sup>17</sup> The systematic review consisted of the combined effect of 6 studies conducted in preterm infants, 7 in full-term infants, and 1 in infants older than 1 month of age. The authors concluded that there is sufficient evidence that sucking is efficacious when compared with no treatment in reducing pain-related distress reactivity in preterm infants and improving immediate pain-related regulation in preterm and term infants up to 1 month of age.<sup>17</sup>

The mechanism underlying the calming effect of the orotactile stimulation of non-nutritive sucking is unknown. Given the immediate onset of the action and rapid decrease in effect that seems to be associated solely with the action of sucking, it is unlikely to be opioid mediated. <sup>25,26</sup> It may simply be that sensory stimulation derived from sucking blocks the perception of pain or provides distraction. The most likely hypothesis is that sucking enhances the infants' ability to self-regulate their behavioral pain response. <sup>27</sup> Other investigators have found that lower heart rate is associated with non-nutritive sucking <sup>28</sup> and that in nonpain conditions less parasympathetic withdrawal occurs after nipple feeding. <sup>27,29</sup>

#### Implementation Considerations

For the most part, non-nutritive sucking is a feasible strategy best used as an adjuvant therapy. However, limitations to its use do exist, primarily related to infection risk, most notably in low- to middle-income countries and concerns regarding potential conflict with increasing movement in the Baby Friendly<sup>30</sup> and Neo Baby Friendly Hospital Initiatives.<sup>31</sup> There has however, been recent inclusion of non-nutritive sucking for pain relief as a medical indication that has lessened this concern.<sup>30</sup> Another consideration with non-nutritive sucking is the need for additional care provider support to ensure that the pacifier stays in place in the infant's mouth. This is of primary concern in sick and younger infants. However, given the trend toward family-integrated care, parents are the logical choice to provide this support.<sup>32,33</sup>

#### Research Considerations

Despite the high quality of studies examining the effectiveness of non-nutritive sucking and pain relief, many questions regarding its use remain unanswered. Although some evidence exists to suggest that longer sucking times (ie, >3 minutes), may be more advantageous, there are insufficient data to confirm or refute this hypothesis. <sup>17</sup> Additionally, as with many nonpharmacologic measures, there is a paucity of literature regarding the effectiveness of non-nutritive sucking in older infants, or the sustained effect across repeated and various tissue breaking and procedures. Sucking-related benefits may be particularly beneficial in older infants during routine immunization injections. Last, very little is known regarding the impact of using non-nutritive sucking for repeated procedural pain on breastfeeding success or the development of oral aversion. Further research is recommended to examine these issues.

## ROCKING AND HOLDING Evidence Summary

Rocking is considered a gentle back and forth motion that stimulates a vestibular response. This movement can be accomplished via simulated means, but in the case of pain relief effectiveness is greater if provided by another person. Holding is defined as the holding of a clothed infant by either a parent or care provider. The research evidence for rocking and holding demonstrates some support for the effectiveness of this intervention as a pain-relieving strategy. In a recent meta-analysis, <sup>17</sup> 2 studies investigated the effect of holding on the pain-related distress pain reactivity of infants after a painful procedure. <sup>34,35</sup> Although rocking or holding without skin contact was not pain relieving, there did seem to be sufficient evidence to recommend its use to enhance pain related regulation when compared with no treatment. <sup>35–37</sup> Separately, in a meta-analysis including infants undergoing immunization, there was some evidence for the effectiveness of holding on decrease injection-related pain and distress, but the mean difference was small and, as such, similar to the treatments described

elsewhere in this article, should be considered as adjuvant therapies used in combination with other more effective treatments rather than in isolation.<sup>36</sup>

#### Research and Implementation Considerations

Given the small number of studies evaluating rocking and holding and the high heterogeneity among them, further investigation is warranted across all age groups. Future studies should attempt to determine the mechanisms underlying the effects of this intervention, specifically with respect to skin contact and familiar presence during holding, which seem to be the salient pain-relieving factors. Also, the extreme importance of understanding better ways to enhance parental involvement as active participants in pain management for their infants cannot be overstated.

## BREASTFEEDING AND BREASTMILK Evidence Summary

There is clear evidence that breastfeeding, when compared with placebo or a no intervention control, effectively decreased pain associated with common needle puncture procedures in infants. 38-41 Results from a recent systematic review conducted by Benoit and colleagues<sup>41</sup> that included 21 studies; 15 evaluated breastfeeding or breastmilk in term infants, and 6 studies in preterm infants showed that direct breastfeeding was more effective than holding, skin-to-skin, and sweet tasting solutions in full-term infants. Breastmilk alone was not as effective.41 A previous systematic review that included 20 studies (10 pertaining to breastfeeding and 10 investigating supplemental breastmilk) demonstrated that pain scores derived from unidimensional and composite pain assessment tools were generally lower in breastfeeding groups compared with placebo.<sup>38</sup> This review also supported that supplemental breastmilk alone does not seem to be as beneficial as breastfeeding.<sup>38</sup> There seems to be some benefit on heart rate, cry duration, behavioral facial response, and some validated pain assessment tool scores when compared with placebo; however, the cumulative pooled results regarding its pain-relieving effect are inconsistent.<sup>38</sup> A similar systematic review evaluated 10 studies that found breastfeeding was also beneficial in decreasing the pain of vaccinations beyond the neonatal period.<sup>40</sup>

Although the exact mechanism of its pain-relieving effect is unknown, it is most likely related to the combined effects of close proximity of the mother, <sup>25</sup> full ventral skin contact (which may mediate of the release of beta endorphins and oxytocin), <sup>42</sup> sucking, and the effects of other chemicals in milk. The act of breastfeeding may also divert the infant's attention from the painful stimulus. <sup>43</sup>

#### Implementation Considerations

If a mother is breastfeeding, breastfeeding offers a feasible intervention for pain management that also promotes mother infant bonding and interaction. Limitations to its clinical use include (1) the delayed maturation of the sucking reflex of preterm infants, (2) impaired sucking ability of very sick or critically ill newborns, (3) acceptability of the staff to perform procedures during breastfeeding including, that is, dynamic considerations, availability of the mother, and flexibility of neonatal team to reschedule nonurgent procedures, (4) limitation of use to nursing women, and (5) possible adverse effects.

Little has been reported regarding adverse effects associated with breastmilk administration in younger or sick infants. One study demonstrated sucking in combination with breastmilk in preterm infants was effective in decreasing pain during heel lance.<sup>44</sup> Similarly to sweet tasting agents, the provision of small amounts of breastmilk

to a sick or very preterm infant can be associated with episodes of desaturation or choking that are transient and without long-term effect. There are no reports, however, of choking in infants who were breastfed during painful procedures. Practice uptake considerations previously described with respect to implementation of skin-to-skin contact are also applicable to the usefulness of breastfeeding, because there is strong evidence that breastfeeding is effective for needle pain in term infants and infants.

#### Research Considerations

There is strong evidence that breastfeeding is effective for decreasing needle pain in term infants and infants. There is limited knowledge regarding the sustained effect of breastfeeding across time or in combination with other interventions but there are currently 5 studies comparing these interventions. As with pacifier use, there are some concerns that infants may learn to anticipate breastfeeding with an impending painful procedure. Given that breastfeeding is so frequent and painful procedures uncommon or rare, it is unlikely that infants will learn to associate breastfeeding with pain. Nevertheless, this factor has not been evaluated to date and is worthy of future study. In addition, breastmilk is a naturally occurring agent and future research should investigate potential ways to optimize the use of expressed breastmilk for ill or preterm infants unable to breastfeed and undergoing painful procedures.

#### SKIN-TO-SKIN CARE Evidence Summary

Ventral skin-to-skin contact between a baby and its mother is commonly referred to as Kangaroo Mother Care owing to its similarity to marsupial mother–infant behavior. Because there may be times in which caregivers other than the mother are holding the infant, it is simply known as kangaroo care or skin-to-skin care. In this paradigm, the infant wearing only a diaper and cap is placed on the mother's bare chest between her breasts and the two are wrapped together with a small blanket, sheet, or a shawl. Typically the mother sits at about a 60° angle.

Although this practice of holding the infant skin-to-skin exists in many cultures, it was specifically used as a facsimile of an incubator in Colombia where there was a shortage of incubators for preterm infants. <sup>46,47</sup> Because it provided warmth from the mother's body and nutrition from her breasts, it was successful as an incubator replacement for some preterm infants. Serendipitously, it was noted that infants in skin-to-skin care were more stable physiologically, <sup>48–50</sup> were in quiet sleep for longer periods of time, and had improved breastfeeding outcomes. <sup>51–53</sup> Since the first study to test this intervention for pain in 2000, <sup>54</sup> altogether 25 studies have been included in a recent systematic review of skin-to-skin care for heel lance, venipuncture, or intramuscular injection in preterm and full-term neonates. <sup>55</sup>

The systematic review demonstrated a reduction on composite pain scores including physiologic and behavioral indicators (eg, Premature Infant Pain Profile, Neonatal Infant Pain Scale). No clear pattern of effects on physiologic (eg, heart rate) and behavioral (eg, facial action) indicators of pain during painful procedures were reported. After painful procedures, skin-to-skin care was associated with more stable regulation.

Given the decrease in pain response, and that skin-to-skin care is a cost-neutral intervention, and that it also facilitates infant regulation and provides warmth and comfort via skin-to-skin contact, it has a clear role in neonatal pain management. At present, skin-to-skin care should be recommended as a nonpharmacologic pain

management intervention for common needle procedures in preterm infants and may be considered for full-term infants if breastfeeding is unavailable.

#### Implementation Considerations

The implementation of skin-to-skin care for procedural pain includes challenges over and above the introduction of change of any kind. 56,57 Some barriers to its implementation are pragmatic; for instance, the dynamics of taking blood from the heel while the infant is in skin-to-skin care and the availability of the mother. The stability of the infant, how it is determined, and the comfort of the staff with putting infants, especially intubated infants with many lines, into skin-to-skin care, as well as the comfort of the staff in doing a procedure in the presence of the parent are issues that involve educational efforts. 56,58 Unit guidelines that are clear and unambiguous are required to determine which infants are eligible for skin-to-skin care during painful procedures and strategies for educating staff and parents regarding how to carry out skin-to-skin care. There are a variety of resources available (eg., educational videos, skin-to-skin care equipment) to facilitate successful skin-to-skin care. 59 For example, a low padded stool, such as an ottoman, can be used for staff to sit on to perform a heel lance. The infant's foot can be gently pulled out from under the wrap around the mother. A more expensive stool with variable height settings will allow for different heights of staff or for different procedures, for example, starting an intravenous line on the scalp. Staff members can participate in choice of a seat and test its settings before actually using it. 56,59

Regarding issues of feasibility of skin-to-skin care, for nonurgent needle procedures, scheduling can often be done to accommodate the mother's availability. Other caregivers or providers may substitute if mothers are unavailable. 60-62

#### Research Considerations

The unanswered questions that remain regarding the use of skin-to-skin care for procedural pain management are numerous. Thus far, all studies have been performed for a single painful event. Studies examining the efficacy of skin-to-skin care over time and over multiple procedures are required to determine if it remains effective or becomes more or less effective over time. The optimal duration of skin-to-skin care before the painful procedure also warrants further examination. How little is needed and if there is a lower and an upper limit to age of effectiveness remain unanswered questions. Although there was a wide range of durations reported in studies included in the review, from 1 to 80 minutes, no direct comparisons were made. The dose may depend on age, and there have been no studies directly comparing infants of different gestational age groups, for example, less than or over 32 weeks.

## SWEET TASTING SOLUTION Evidence Summary

Oral sweet tasting solutions (eg, sucrose in water) are the most widely studied nonpharmacologic intervention for pain management in infants and have been consistently demonstrated to have analgesic effects in infants. Multiple systematic reviews demonstrate a decrease in behavioral pain behaviors in infants given sweet solutions during common needle procedures when compared with placebo water or no intervention, <sup>39,64–66</sup> and sweet tasting solutions are recommended in consensus statements and clinical practice guidelines. <sup>67,68</sup>

#### Implementation Considerations

Although a variety of sweet tasting chemicals have been evaluated, including natural and artificial, the most widely studied and used in clinical practice is sucrose.<sup>64</sup>

Sucrose is a disaccharide composed of glucose and fructose. Sweet tasting solutions are administered on the infant's tongue with a pacifier, syringe, or cup. Administration with a pacifier stimulates continuous non-nutritive sucking, which may improve effectiveness. Although this systematic review evaluated a variety of doses, a recent randomized controlled trial determined that 0.1 mL of sucrose may be the minimally effective dose across preterm infants.

Previously, as per the systematic review,<sup>64</sup> the usual single dose of sucrose was 0.5 to 2.0 mL of 12% to 24% strength (weight/volume); however, lower doses are typically used in preterm infants (as little as 0.05 mL of 24%) and larger doses in older infants (as much as 10 mL of 25%).<sup>64–66</sup> The onset of action is quick (within seconds), the peak effect occurs at 2 minutes, and the duration of action is up to 10 minutes.<sup>70</sup> Calming effects may last considerably longer than the analgesic effects, as demonstrated by a study of reduced behavioral distress responses during a subsequent handling procedure carried out up to 1 hour afterward.<sup>71</sup>

The mechanism of action by which sweet tasting solution blunts pain responses in infants has not been fully elucidated  $^{70,72}$ ; however, it has been speculated to involve several pathways. One proposed theory is based on the taste-induced release of endogenous opioids; however, other investigators include dopamine and acetylcholine pathways. In addition, sweet tasting solution may induce calming and analgesic effects through non-nutritive sucking and distraction. Of note, a study failed to demonstrate an effect on pain-specific brain activity, <sup>73</sup> questioning whether sucrose is a true analgesic. Behavioral indicators of pain, however, were decreased and, at present, the clinical significance of that study is not known.

Sweet tasting solution is generally well tolerated by infants; adverse effects are rare and transient, and include choking, bradycardia, and oxygen desaturation. <sup>64,74</sup> Data are sparse, however, regarding long-term effects. In 2 multiple dose studies that examined sucrose use over the first 7 and 28 days of life in preterm infants, no differences were reported in neurologic outcomes during the neonatal period. <sup>75,76</sup> However, 1 study suggested that increasing sucrose consumption was associated with worse neurobehavioral development scores. <sup>75,77</sup> A secondary analysis revealed that the cut off of 10 doses over 24 hours differentiated those with decreased neurobehavioral scores. <sup>75</sup> That, however, is the only report of cumulative dose effects and the significance of this result is unknown.

Investigation of the possible adverse effects of repeated exposure to sweet tasting solution in early life is ongoing. Two recent preclinical studies using a mouse model in which they randomly assigned 106 mice to receive sterile water or 24% oral sucrose across 1 of 3 exposures (10 times daily handling, touch, or needle prick) aimed to mimic the NICU context reported that, irrespective of the type of exposure, mice who received repeated doses of 24% oral sucrose had smaller brain volumes<sup>78</sup> and that mice who received repeated 24% oral sucrose during handling in the neonatal period had poorer short-term memory in adulthood compared with mice who received water during handling.<sup>79</sup>

Key issues to be considered when implementing sweet tasting solution analgesia include (1) guidelines for use (including dosing regimen and administration techniques), (2) procedures for ordering, dispensing and documentation, and (3) methods of evaluation. Increased use success may be observed in the presence of the following: a unit guideline, nurse-led ordering, and inclusion of sucrose as part of admission orders. Osme centers use commercially available unit-dose products (eg, Tootsweet, SweetEase) and others use pharmacy-compounded bulk preparations. Prepackaged products are more convenient, but individual units need to consider their storage capacities and frequency of use as considerations to which product they choose.

Continual monitoring of clinical response is important to document effectiveness and safety and to allow for individualization of dosing (ie, dose titration to response). Finally, ongoing communication, support, and reinforcement of practices with staff are also critical to ensure continued implementation success. The use of sweet tasting solutions as a soothing technique in nonpain scenarios needs to be discouraged and staff may need reminders to ensure it is not overused.

#### Research Considerations

Despite the plethora of research with sweet tasting solution, audits of pain management practices demonstrate that sweet tasting solution use varies widely among different practice settings.<sup>64</sup> The variability in use of sweet tasting solution may be due to important knowledge gaps in its pharmacology, including the exact mechanism(s) of action, the relationship between dose and response for infants of different ages and for different procedures, and the long-term effects with repeated use, including potential effects on feeding behaviors. In addition, few trials have evaluated the added benefit of sucrose when coadministered with other nonpharmacologic and pharmacologic analgesics, particularly opioids, as well as contextual factors (eg, unit culture, staffing levels).<sup>81</sup> All of these factors may be contributing to suboptimal use of sweet tasting solution in the clinical setting. Further study of these issues is recommended to optimize its use in infants undergoing needle procedures.

Although there remains little evidence linking sucrose to adverse outcome in human infants, recent reports, despite some limitations in the model, of possible concern in preterm mice, 64,78 warrants further investigation.

#### MUSIC THERAPY Evidence Summary

There is some evidence that music therapy may be beneficial in relieving procedural pain in both full-term and preterm infant. Results from a recent review that included 9 randomized trials examining the efficacy of music for pain associated with circumcision and heel lance indicated that newborns exposed to music therapy seem to have greater physiologic stability and diminished pain response.<sup>82</sup>

#### Research and Implementation Considerations

Owing to the poor quality of some of the studies, a large variation in reported outcomes, and inconsistent findings across procedures, more rigorous trials are needed to confirm or refute the benefits of for pain relief associated with needle puncture. Additionally, although neonatal general recommendations report maintaining a range of 45 to 60 dB, 83 little is known regarding the optimal type or decibel level of the music or potential differences among various gestational age groups.

## SENSORIAL SATURATION Evidence Summary

Sensorial saturation is defined as a multisensorial stimulation consisting of delicate tactile, gustative, auditory, and visual stimuli<sup>84,85</sup> whereby, during the procedure, the infant's attention is attracted by massaging the face, speaking to the infant gently, and instilling a sweet solution on the infant's tongue. Results from systematic review of 8 studies examining the effect of sensorial saturation for pain relief during heel lance, intramuscular injection, and endotracheal suctioning demonstrated that pain scores were lower in the group receiving this intervention.<sup>85</sup>

#### Implementation Considerations

Sensorial interventions are straightforward and easy to implement. From a costeffectiveness perspective, one may argue whether the known benefits outweigh added costs of associated with the need for a second care provider. As with many nonpharmacologic interventions, the most logical solution to this concern would be to increase parental involvement.

One hypothesis addressing the beneficial effect of sensorial stimulation, is derived from the Gate Control Theory proposed by Melzack and Wall. Setimuli traveling ascending pathways inhibit the nociceptive signals from painful stimuli through various endogenous mechanisms located along the spino-thalamic tract. The stronger these competing stimuli are, including multiple modalities, the more effective they are in blocking the perception of pain. This finding is in keeping with evidence supporting modalities encompassing multiple stimuli and may help to explain why interventions such as kangaroo care, breastfeeding, or sensorial saturation, which involve tactile, auditory, and olfactory mechanisms are generally more effective than single modalities.

#### Research Considerations

Many unanswered questions remain related to mechanism of action regarding these interventions and what is the optimal dose—that is, finding the balance between too much and too little stimulation—and potential differences among various gestational age groups. Additionally, future research should focus on ways to educate and enhance parent participation so that parents can lead these interventions.

#### PARENTAL PRESENCE Evidence Summary

Researchers began evaluating the impact of parental presence and involvement in their children's care during painful medical procedures and resuscitation using mostly observational studies. Researchers developed a body of evidence for the pediatric emergency department and recent systemic reviews demonstrated that almost 90% of parents want the option of participating in their child's procedures and involving parents has no negative effect on emergency staff performing the procedures. Researchers are careful to the pediatric intensive care unit in a variety of observational studies where both parents and clinicians reported that parental presence during invasive procedures helps the child significantly. The this literature, the child's perceptions have not been assessed, although in related studies about immunization pain, children have reported a preference for parents to be present.

Overall, parental participation in their infant's general care has shown that, even in the absence of formal parental training about pain, parents can impact the use of pain treatment strategies given to their infants. In 2 separate audits of pain management practices in the NICU, investigators observed greater use of pain treatments if parents were present when procedures were being undertaken. Johnston and colleagues found that the presence of parents was associated with an increased use of physical pain treatment strategies or sweet tasting solutions. Similarly, Carbajal and colleagues found parental presence to be one of the factors associated with improved use of specific procedural analgesia. It should be noted, however, that these were observational designs and a causal link cannot be assumed.

In addition to parental presence, parental education may lead to increased use of pain treatment strategies via different mechanisms. Parents may participate in the provision of care, either by providing comfort measures themselves or by advocating for their use with health care providers, who then administer pain treatment interventions. This has been shown across studies whereby parents led use of skin-to-skin contact, facilitated tucking, and breastfeeding. 19,38,55,93

In 2 subsequent studies,  $^{94,95}$  including a qualitative study and a randomized controlled trial, parents expressed a desire to be involved in pain management. Eight-five percent of parents (n = 257) in the qualitative study wished to be involved.  $^{94}$ 

These studies clearly demonstrate parents' desire for knowledge about infant pain. When parents have more information, they are more likely to want to participate in comforting their infant. In addition, when parents are educated either verbally or with demonstrations about specific interventions, they have shown they will effectively use the intervention during subsequent painful procedures in their infants. He infants. He infants has been demonstrated for facilitated tucking and skin-to-skin care.

Separately, randomized controlled trials of parent education about pain interventions for infant vaccination have shown that parent-directed education using a video<sup>99,100</sup> and other electronic resources<sup>59,101</sup> increased the use of strategies to reduce pain during infant immunizations and needle-related procedures. <sup>102–104</sup> Giving parents options of various strategies allows parents to choose the strategy they are most comfortable with. Studies that review various parental education strategies support using a wide variety of educational approaches to enhance parental learning. <sup>105–107</sup>

Parents with infants in the NICU have expressed a preference to be present during invasive medical procedures carried out on their infants.  $^{88,94,108-111}$  In 1 qualitative study, Smith and colleagues  $^{112}$  showed that parental participation in their infant's care was a critical coping strategy for parents in the NICU. In an randomized controlled trial by Franck and colleagues,  $^{95}$  parents who received pain specific education were more satisfied than parents in the control group (P<.01) and parents who received the booklet expressed interest in being actively involved or present for painful procedures (90% vs 75%; P<.01).

There are also data available that have shown that how mothers' respond to their infants' pain experience is linked with how their infant responds to pain in the future. 113–115 Racine and colleagues 115 recently found that a mother's emotional availability can predict an infant's pain-related distress later in infancy. Their longitudinal observational study also showed mothers who had more secure attachment with their infant had infants with lower levels of pain-related distress. 115 These data suggest that engaging parents in the earliest days of their infants' pain management may create this sense of secure attachment and give parents skills to impact their infant's response to pain in later childhood. Moreover, there is some suggestion that a mother's memories of her preterm infant's pain may be associated with later post-traumatic stress symptoms, further emphasizing the importance of optimal pain control to enhance maternal well-being after hospitalization. 116

#### Implementation Considerations

All of the pain management interventions discussed in this review are simple and easy to use, yet despite evidence and a variety of practice guidelines, <sup>15,117</sup> studies show that many infants still undergo needle procedures without pain management. <sup>3,7,8</sup> Parents could easily be present and provide all of these interventions to ensure their infant receives appropriate pain management. <sup>14</sup>

Involving parents in providing various nonpharmacologic pain strategies at any age, but especially in infancy, is not a difficult task, yet research shows that many health care providers still do not ask parents to participate or even discuss pain management options with them. 14,92,102,104

#### Research Considerations

Further studies evaluating parents' provision of various nonpharmacologic pain management strategies can be a focus of future research. The majority of evidence currently available is with parents using facilitated tucking in NICU, skin-to-skin care, or breastfeeding. Studies with skin-to-skin care are also mostly in the NICU environment, but there are some studies in infants undergoing immunization. Further research with parents' presence or providing pain management in a variety of settings is needed. In addition, ongoing research regarding parental learning is also needed.

## COMPARISONS AND COMBINATIONS OF NONPHARMACOLOGIC PAIN MANAGEMENT INTERVENTIONS

There has been increasing research comparing individual nonpharmacologic pain management interventions as well as their combined effects. When compared with a sweet tasting solution (oral sucrose), facilitated tucking alone is not as effective in relieving pain reactivity after a heel lance in very preterm infants.<sup>23,118</sup> However, its use as an adjuvant therapy, in combination with oral sucrose and non-nutritive sucking, seems to be beneficial.<sup>23,119</sup> Similarly, non-nutritive sucking alone when combined with sucrose, 64 30% glucose, 120 or facilitated tucking 119 seems to be synergistic with respect to lower pain scores, less crying, more stable sleep patterns, and greater physiologic stability. Breastfeeding significantly decreased heart rate elevation and diminished the proportion of crying time, duration of first cry, and total crying time compared with positioning (swaddled and placed in a cot), maternal holding, placebo, pacifier use, no intervention, or oral sucrose group, or both. 38 Pain scores derived from unidimensional and composite pain assessment tools were generally lower in breastfeeding groups compared with positioning, placebo, or oral sucrose group, or both. There is some evidence that, when compared with sweet taste, breastfeeding is at least as effective, may be synergistic, and is potentially superior to sweet taste.39

In contrast, although supplemental expressed breastmilk provided in the absence of the mother seems to be of some benefit on heart rate, cry duration, behavioral facial response, and some validated pain assessment tool scores when compared with placebo, this was not the case when compared with sucrose 12.5%, 20%, or 25%. Increases in the heart rate, percentage of time crying, and pain scores were significantly higher in the breastmilk group. Skin-to-skin care has also been studied in combination of other therapies. There were 5 studies that used other treatment controls with skin-to-skin care. One compared enhanced skin-to-skin care that added rocking, singing, and sucking to skin-to-skin care and found no differences in the Premature Infant Pain Profile or time for heart rate to recover. Two studies compared sweet taste and holding (clothed) by female research assistant in full-term infants during heel lance. Duration of crying was decreased by both, with an additive effect in the combination, but facial actions were only decreased with holding.

#### **SUMMARY**

There is sufficient evidence to support the use of nonpharmacologic interventions, particularly breastfeeding, sweet tasting solutions, and skin-to skin care as primary strategies for pain management during common needle puncture procedures. They are recommended for managing acute pain and distress in infants during common needle procedures (Table 2). Music therapy, sensorial saturation, rocking and holding, swaddling and containment pacifier, and non-nutritive sucking would be considered adjunct

Table 2 Recommended use of non pharmacologic measures for selected needle puncture procedures in infants												
Procedure	Sweet Tasting Solution	Breastfeeding	Skin -to- Skin Care	Breastmilk	Swaddling or Containment	Pacifier and non-nutritive sucking	Music Therapy	Sensorial Saturation	Parental Presence	Rocking and Holding		
Intramuscular injection	Х	Х	X	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct		
Subcutaneous injection	Х	X	X	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct		
Heel lance	Х	Х	Х	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct		
Venipuncture, venous cannulation	Х	Х	Х	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct	As adjunct		

therapies based on current evidence and should be used in combination with breast-feeding, sweet tasting solutions or kangaroo care to ensure adequate management of needle pain. Despite our limited understanding of the underlying mechanisms of actions of nonpharmacologic interventions, there seem to be few documented short-term harms from their use. Similar to pediatric pain management, where distraction techniques are effective in managing painful procedures, <sup>123</sup> the soothing or calming effects of other nonpharmacologic interventions may only be beneficial in this manner.

Some nonpharmacologic interventions are easily implemented (pacifier or non-nutritive sucking, swaddling or containment), whereas others need a collaborative effort (skin-to-skin care, sweet tasting solution). Parents are an untapped resource and should be encouraged to be involved in providing these measures for their infant during painful procedures. 93 It is clear parents want to be involved and, with proper knowledge and support, they can. 82,95,108

Support from administration and leadership, both formal and informal, are crucial for the implementation of any of these strategies for procedures.<sup>57</sup> Informal leadership is part of the complex concept of unit culture. The culture of the unit must be accepting of any implementation.<sup>81,124</sup>

In summary, needle-related pain is a common experience for infants and as health care professionals; it behooves us to use all possible strategies to mitigate or prevent that pain and its negative consequences. Current research evidence suggests that nonpharmacologic interventions may be used to reduce needle pain.

#### **Best Practices**

What is the current practice for managing needle pain for infants?

Best practice, guideline or care path objective

- Provide effective pain management during common needle procedures in infants
- Improve long-term neurologic outcomes by minimizing pain exposures during a key stage of brain development

What changes in current practice are likely to improve outcomes?

Use effective non pharmacologic strategies to manage pain during needle procedures

Major recommendations

- Sweet tasting solutions, skin-to-skin care, or breastfeeding can be used as primary strategies to manage needle pain in infants
- Swaddling and containment, non-nutritive sucking or pacifier, music therapy, breastmilk, rocking and holding, and sensorial saturation can be used as adjunct treatments with primary strategies to further decrease pain, as appropriate
- Parental presence may also have some adjunct benefit, via direct and indirect promotion of pain mitigation strategy use

#### Summary

Commonly performed needle procedures in infants (heel lance, immunizations, venous cannulation, venous sampling) should always be undertaken in conjunction with proven nonpharmacologic strategies to minimize pain

Bibliographic Sources: Ref. 17,36,40,51,66

#### **REFERENCES**

1. Johnston C, Barrington K, Taddio A, et al. Pain in Canadian NICUs: have we improved over the past 12 years? Clin J Pain 2011;27:225–32.

- 2. Carbajal R, Rousset A, Danan C, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. JAMA 2008;300:60–70. Journal Article. Multicenter Study Research Support, Non-U.S. Gov't.
- 3. Cruz MD, Fernandes AM, Oliveira CR. Epidemiology of painful procedures performed in neonates: a systematic review of observational studies. Eur J Pain 2016;20:489–98.
- 4. Barker DP, Rutter N. Exposure to invasive procedures in neonatal intensive care unit admissions. Arch Dis Child Fetal Neonatal Ed 1995;72:F47–8.
- Johnston CC, Collinge JM, Henderson SJ, et al. A cross-sectional survey of pain and pharmacological analgesia in Canadian neonatal intensive care units. Clin J Pain 1997;13:308–12.
- Simons SHP, van Dijk M, Anand KS, et al. Do we still hurt newborn babies? Arch Pediatr Adolesc Med 2003;157:1058–964.
- 7. Kyololo OBM, Stevens B, Gastaldo D, et al. Procedural pain in neonatal units in Kenya. Arch Dis Child Fetal Neonatal Ed 2014;99:F464–7.
- Jeong IS, Park SM, Lee JM, et al. Perceptions on pain management among Korean nurses in neonatal intensive care units. Asian Nurs Res (Korean Soc Nurs Sci) 2014;8:261–6. Multicenter Study. Research Support, Non-U.S. Gov't.
- 9. Roofthooft DWE, Simons SHP, Anand KJS, et al. Eight years later, are we still hurting newborn infants? Neonatology 2014;105:218–26.
- Sposito NPB, Rossato LM, Bueno M, et al. Assessment and management of pain in newborns hospitalized in a neonatal intensive care unit: a crosssectional study. Rev Lat Am Enfermagem 2017;25:e2931.
- 11. Brummelte S, Gurnau RE, Chau V, et al. Procedural pain and brain development in premature newborns. Ann Neurol 2012;71:385–96.
- 12. Walker SM, Franck LS, Fitzgerald M, et al. Long-term impact of neonatal intensive care and surgery on somatosensory perception in children born extremely preterm. Pain 2009;141:79–87.
- Cong X, Wu J, Vittner D, et al. The impact of cumulative pain/stress on neurobehavioral development of preterm infants in the NICU. Early Hum Dev 2017; 108:9–16.
- Orovec A, Disher T, Caddell K, et al. Assessment and management of procedural pain during the entire neonatal intensive care unit hospitalization. Pain Manag Nurs 2019. https://doi.org/10.1016/j.pmn.2018.11.061.
- 15. Lago P, Frigo AC, Baraldi E, et al. Sedation and analgesia practices at Italian neonatal intensive care units: results from the EUROPAIN study. Ital J Pediatr 2017;43:26. Multicenter Study. Observational Study.
- Huang CM, Tung WS, Kuo LL, et al. Comparison of pain responses of premature infants to the heelstick between containment and swaddling. J Nurs Res 2004; 12:31–40.
- Pillai Riddell R, Racine N, Turcotte K, et al. Nonpharmacological management of procedural pain in infants and young children: an abridged Cochrane review. Pain Res Manag 2011;16:321–30. Journal Article Research Support, Non-U.S. Gov't Review.
- 18. Aucott S, Donohue PK, Atkins E, et al. Neurodevelopmental care in the NICU. Ment Retard Dev Disabil Res Rev 2002;8:298–308.
- Axelin A, Salantera S, Lehtonen L. Facilitated tucking by parents' in pain management of preterm infants-a randomized crossover trial. Early Hum Dev 2006;82:241–7. Randomized Controlled Trial Research Support, Non-U.S. Gov't.
- 20. van Sleuwen BE, Engelberts AC, Boere-Boonekamp MM, et al. Swaddling: a systematic review. Pediatrics 2007;120:e1097–106.

- Prasopkittikun T, Tilokskulchai F. Management of pain from heel stick in neonates: an analysis of research conducted in Thailand. J Perinat Neonatal Nurs 2003;17:304–12.
- 22. Pillai Riddell RR, Racine NM, Turcotte K, et al. Non-pharmacological management of infant and young child procedural pain. Cochrane Database Syst Rev 2011;(10):CD006275. Journal Article. Meta-Analysis. Review.
- 23. Cignacco E, Axelin A, Stoffel L, et al. Facilitated tucking as a non-pharmacological intervention for neonatal pain relief: is it clinically feasible? ACTA Paediatr 2010;99:1763–5.
- 24. Fearon I, Kisilevsky BS, Hains SM, et al. Swaddling after heel lance: age-specific effects on behavioral recovery in preterm infants. J Dev Behav Pediatr 1997;18:222–32. Clinical Trial Research Support, Non-U.S. Gov't.
- 25. Blass EM. Behavioral and physiological consequences of suckling in rat and human newborns. Acta Paediatr Suppl 1994;397:71–6. Review.
- 26. Blass EM, Watt L. Sucking-and sucrose-induced analgesia in human newborns. Pain 1999:83:611–23.
- 27. Carbajal R, Chauvet X, Couderc S, et al. Randomized trial of analgesic effects of sucrose, glucose and pacifiers in term neonates. Br Med J 1999;319:1393–7.
- 28. Blass E, Ciaramitraro V. A new look at some old mechanisms in human newborns: taste and tactile determinants of state, affect, and action. Monogr Soc Res Child Dev 1994;59:1–81.
- 29. McCain G, Knupp A, Loucas Fontaine J, et al. Heart rate variability responses to nipple feeding for preterm infants with bronchopulmonary dysplasia: three case studies. J Pediatr Nurs 2010;25:215–20.
- 30. Semenic S, Childerhose JE, Lauriere J, et al. Barriers, facilitators and recommendations related to implementing the Baby-Friendly Initiative (BFI): an integrative review. J Hum Lact 2012;28:317–34.
- 31. Nyqvist KH, Haggkvist AP, Hansen MN, et al. Expansion of the baby-friendly hospital initiative ten steps to successful breastfeeding into neonatal intensive care: expert group recommendations. J Hum Lact 2013;29:300–9. Practice Guideline.
- 32. O'Brien K, Robson K, Bracht M, et al. Effectiveness of Family Integrated Care in neonatal intensive care units on infant and parent outcomes: a multicentre, multinational, cluster-randomised controlled trial. Lancet Child Adolesc Health 2018;4:245–54.
- **33.** Gale C. Family integrated care for very preterm infants: evidence for a practice that seems self-evident. Lancet Child Adolesc Health 2018;4:230–1.
- 34. Carbajal R, Veerapen S, Couderc S, et al. Analgesic effect of breast feeding in term neonates: randomised controlled trial. BMJ 2003;326:13. Clinical Trial Journal Article Randomized Controlled Trial Research Support, Non-U.S. Gov't.
- **35.** Gormally S, Barr RG, Wertheim L, et al. Contact and nutrient caregiving effects on newborn infant pain responses. Dev Med Child Neurol 2001;43:28–38.
- 36. Taddio A, Ilersich AL, Ipp M, et al. Physical interventions and injection techniques for reducing injection pain during routine childhood immunizations: systematic review of randomized controlled trials and quasi-randomized controlled trials. Clin Ther 2009;31(Suppl 2):S48–76. Journal Article Meta-Analysis Research Support, Non-U.S. Gov't Review.
- 37. Campos R. Soothing pain-elicited distress in infants with swaddling and pacifiers. Child Development 1989;60:781–92.
- 38. Shah PS, Herbozo C, Aliwalas LL, et al. Breastfeeding or breast milk for procedural pain in neonates. Cochrane Database Syst Rev 2012;(12):CD004950.

- Journal Article Meta-Analysis Research Support, N.I.H., Intramural Research Support, Non-U.S. Gov't. Review.
- 39. Shah V, Taddio A, Rieder MJ. Effectiveness and tolerability of pharmacologic and combined interventions for reducing injection pain during routine childhood immunizations: systematic review and meta-analyses. Clin Ther 2009;31: S104–51. Review.
- 40. Harrison D, Reszel J, Bueno M, et al. Breastfeeding for procedural pain in infants beyond the neonatal period. Cochrane Database Syst Rev 2016;(10):CD011248. Meta-Analysis Research Support, Non-U.S. Gov't Review Systematic Review.
- 41. Benoit B, Martin-Misener R, Latimer M, et al. Breast-feeding analgesia in infants: an update on the current state of evidence. J Perinat Neonatal Nurs 2017;31: 145–59. Meta-Analysis. Review.
- 42. Hofer M. Hidden regulators in attachment, separation, and loss. Monogr Soc Res Child Dev 1994;59:192–207.
- 43. Gunnar M. The effects of a pacifying stimulus on behavioural and adrenocortical responses to circumcision in the newborn. J Am Acad Child Psychiatry 1984; 23:34–8.
- 44. Peng HF, Yin T, Yang L, et al. Non-nutritive sucking, oral breast milk, and facilitated tucking relieve preterm infant pain during heel-stick procedures: a prospective, randomized controlled trial. Int J Nurs Stud 2018;77:162–70. Randomized Controlled Trial.
- 45. Fallah R, Naserzadeh N, Ferdosian F, et al. Comparison of effect of kangaroo mother care, breastfeeding and swaddling on Bacillus Calmette-Guerin vaccination pain score in healthy term neonates by a clinical trial. J Matern Fetal Neonatal Med 2017;30:1147–50. Randomized Controlled Trial.
- 46. Charpak N, Ruiz-Pelaez JG, Charpak Y. Rey-Martinez Kangaroo Mother Program: an alternative way of caring for low birth weight infants? One year mortality in a two cohort study. Pediatrics 1994;94:804–10. Comparative Study Research Support, Non-U.S. Gov't.
- 47. Whitelaw A, Sleath K. Myth of the marsupial mother: home care of very low birth weight babies in Bogota, Colombia. Lancet 1985;1:1206–8. Research Support, Non-U.S. Gov't.
- 48. Bosque E, Brady J, Afffonso D, et al. Physiological measures of kangaroo versus incubator in a tertiary nursery. J Obstet Gynecol Neonatal Nurs 1995;24:219–26.
- 49. Ludington-Hoe SM. Evidence-based review of physiologic effects of kangaroo care. Curr Womens Health Rev 2011;7:243–53. Review.
- 50. Ferber SG, Makhoul IR. Neurobehavioural assessment of skin-to-skin effects on reaction to pain in preterm infants: a randomized, controlled within-subject trial. Acta Paediatr 2008;97:171–6. Journal Article Randomized Controlled Trial.
- 51. Ferber S, Makhoul I. The effect of skin-to-skin contact (kangaroo care) shortly after birth on the neurobehavioral responses of the term newborn: a randomized, controlled trial. Pediatrics 2004;113:858–65.
- 52. Furman L, Kennell J. Breastmilk and skin to skin kangaroo care for premature infants. Avoiding bonding failure. Acta Paediatr 2000;89:1280–3.
- 53. Flacking R, Ewald U, Wallin L. Positive effect of kangaroo mother care on long-term breastfeeding in very preterm infants. J Obstet Gynecol Neonatal Nurs 2011:2011:2.
- 54. Gray L, Watt L, Blass EM. Skin-to-skin contact is analgesic in healthy newborns. Pediatrics 2000;105:e14. Clinical Trial Journal Article Randomized Controlled Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.

- 55. Johnston C, Campbell-Yeo M, Disher T, et al. Skin-to-skin care for procedural pain in neonates. Cochrane Database Syst Rev 2017. https://doi.org/10.1002/14651858.CD008435.pub3.
- 56. Benoit B, Campbell-Yeo M, Johnston C, et al. Staff nurse utilization of kangaroo care as an intervention for procedural pain in preterm infants. Adv Neonatal Care 2016;16:229–38. Clinical Trial Comparative Study.
- 57. Johnston A. Factors influencing implementation of kangaroo holding in a special care nursery. MCN Am J Matern Child Nurs 2007;32:25–9.
- 58. Chia P, Sellick K, Gan S. The attitudes and practices of neonatal nurses in the use of kangaroo care. Aust J Adv Nurs 2006;23:20–7.
- 59. Campbell-Yeo M, Dol J, Disher T, et al. The power of a parent's touch: evaluation of reach and impact of a targeted evidence-based YouTube video. J Perinat Neonatal Nurs 2017;31:341–9.
- 60. Johnston CC, Campbell-Yeo M, Filion F. Paternal vs maternal kangaroo care for procedural pain in preterm neonates: a randomized crossover trial. Arch Pediatr Adolesc Med 2011;165:792–6. Journal Article Randomized Controlled Trial Research Support, Non-U.S. Gov't.
- Johnston C, Byron J, Filion F, et al. Alternative female kangaroo care for procedural pain in preterm neonates: a pilot study. Acta Paediatr 2012;101:1147–50.
   Journal Article. Randomized Controlled Trial. Research Support, Non-U.S. Gov't.
- 62. Murmu J, Venkatnarayan K, Thapar R, et al. When alternative female Kangaroo care is provided by other immediate postpartum mothers, it reduces postprocedural pain in preterm babies more than swaddling. Acta Paediatr 2017;106: 411–5.
- 63. Campbell-Yeo M, Johnston C, Benoit B, et al. Trial of repeated analgesia with kangaroo mother care (TRAKC trial). BMC Pediatr 2013;13:182. Journal Article Randomized Controlled Trial. Research Support, Non-U.S. Gov't.
- 64. Stevens B, Yamada J, Ohlsson A, et al. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst Rev 2016;(7). CD001069. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858. CD001069.pub5/abstract.
- 65. Harrison D, Yamada J, Adams-Webber T. Sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years. Cochrane Database Syst Rev 2011;(10):CD008408.
- 66. Harrison D, Beggs S, Stevens B. Sucrose for procedural pain management in infants. Pediatrics 2012;130:918–25.
- 67. Lago P, Garetti E, Merazzi D, et al. Guidelines for procedural pain in the newborn. Acta Paediatr 2009;98:932–9.
- 68. Taddio A, Yiu A, Smith R, et al. Variability in clinical practice guidelines for sweetening agents in newborn infants undergoing painful procedures. Clin J Pain 2009;25:153–5.
- 69. Stevens B, Yamada J, Campbell-Yeo M, et al. The minimally effective dose of sucrose for procedural pain relief in neonates: a randomized controlled trial. BMC Pediatr 2018;18. https://doi.org/10.1186/s12887-018-1026-x.
- 70. Stevens B, Craig K, Johnston C, et al. Oral Sucrose for procedural pain in infants. Lancet 2011;377:25–6.
- 71. Taddio A, Shah V, Katz J. Reduced infant response to a routine care procedure after sucrose analgesia. Pediatrics 2009;123:e425–9. Journal Article Randomized Controlled Trial Research Support, Non-U.S. Gov't.
- 72. Holsti L, Grunau RE. Considerations for using sucrose to reduce procedural pain in preterm infants. Pediatrics 2010;124:1042–7.

- 73. Slater R, Cornelissen L, Fabrizi L, et al. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomized controlled trial. Lancet 2010;376:1225–32.
- Taddio A, Shah V, Hancock R, et al. Effectiveness of sucrose analgesia in newborns undergoing painful medical procedures. Can Med Assoc J 2008;179: 37–43.
- 75. Johnston C, Filion F, Snider L, et al. Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks' postconceptual age. Pediatrics 2002;110:523–8.
- 76. Stevens BRNP, Yamada JRNM, Beyene JP, et al. Consistent management of repeated procedural pain with sucrose in preterm neonates: is it effective and safe for repeated use over time? Clin J Pain 2005;21:543–8 [Article].
- 77. Johnston C, Filion F, Snider L, et al. How much sucrose is too much sucrose? Pediatrics 2007;119:226.
- 78. Tremblay S, Ranger M, Chau CMY, et al. Repeated exposure to sucrose for procedural pain in mouse pups leads to long-term widespread brain alterations. Pain 2017;158(8):1586–98.
- Ranger M, Tremblay S, Chau CMY, et al. Adverse behavioral changes in adult mice following neonatal repeated exposure to pain and sucrose. Front Psychol 2019;9:2394.
- 80. Lafrak L, Burch K, Caravantes R. Sucrose analgesia: identifying potentially better practices. Pediatrics 2006;119:S197–202.
- 81. Stevens B, Riahi S, Cardoso R, et al. The influence of context on pain practices in the NICU: perceptions of health care professionals. Qual Health Res 2011;21: 757–70. Research Support, Non-U.S. Gov't.
- 82. Hartling L, Shaik M, Tjosvold L, et al. Music for medical indications in the neonatal period: a systematic review of randomised controlled trials. Arch Dis Child Fetal Neonatal Ed 2009;94:F349–54.
- 83. Etzel R, Balk S, Bearer C, et al. Noise: a hazard for the fetus and newborn. Pediatrics 1997;100:724–7.
- 84. Bellieni CV, Cordelli DM, Marchi S, et al. Sensorial saturation for neonatal analgesia. Clin J Pain 2007;23:219–21. Clinical Trial Comparative Study Journal Article Randomized Controlled Trial.
- 85. Bellieni CV, Tei M, Coccina F, et al. Sensorial saturation for infants' pain. J Matern Fetal Neonatal Med 2012;25:79–81.
- 86. Melzack R, Wall P. Pain mechanisms: a new theory. Science 1965;150:971-9.
- 87. Quirion R. Pain, nociception, and spinal opioid receptors. Prog Neuropsychopharmacol Biol Psychiatry 1984;8:571–9.
- 88. Power N, Franck L. Parent participation in the care of hospitalized children: a systematic review. J Adv Nurs 2008;62:622–41.
- 89. Smith RW, Shah V, Goldman RD, et al. Caregiver's response to pain in their children in the emergency department. Arch Pediatr Adolesc Med 2007;161: 578–82.
- **90.** Dingeman S, Mitchell E, Meyer EC, et al. Parent presence during complex invasive procedures and cardiopulmonary resuscitation: a systematic review of the literature. Pediatrics 2007;120:842–54.
- 91. Curley MAQ, Meyer EC, Scoppettuolo LA, et al. Parent presence during invasive procedures and resuscitation: evaluating a clinical practice change. Am J Respir Crit Care Med 2012;186:1133–9.
- 92. Taddio A, Shah V, Leung E, et al. Knowledge translation of the HELPinKIDS clinical practice guideline for managing childhood vaccination pain: usability and

- knowledge uptake of educational materials directed to new parents. BMC Pediatr 2013;13:23. Clinical Trial Research Support, Non-U.S. Gov't.
- 93. Campbell-Yeo M, Fernandes A, Johnston C. Procedural pain management for neonates using nonpharmacological strategies: part 2: mother-driven interventions. Adv Neonatal Care 2011;11:312–8 [quiz: 319–20]. Journal Article Review.
- 94. Franck LS, Allen A, Cox S, et al. Parents' views about infant pain in neonatal intensive care. Clin J Pain 2005;21:133–9.
- 95. Franck LS, Oulton K, Nderitu S, et al. Parent involvement in pain management for NICU infants: a randomized controlled trial. Pediatrics 2011;128:510–8. Journal Article Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't.
- **96.** Axelin A, Salantera S, Kirjavainen J, et al. Oral glucose and parental holding preferable to opioid in pain management in preterm infants. Clin J Pain 2009; 25:138–45. Randomized Controlled Trial Research Support, Non-U.S. Gov't.
- 97. Axelin A, Salanterä S, Lehtonen L. Facilitated tucking by parents in pain management of preterm infants- A randomized crossover trial. Early Hum Dev 2006;82:241–7.
- 98. Johnston C, Filion F, Campbell-Yeo M, et al. Kangaroo mother care diminishes pain from heel lance in very preterm neonates: a crossover trial. BMC Pediatr 2008;8. https://doi.org/10.1186/1471-2431-8-13.
- 99. Hillgrove-Stuart J, Pillai Riddell R, Flora DB, et al. Caregiver soothing behaviors after immunization and infant attachment: a longitudinal analysis. J Dev Behav Pediatr 2015;36:681–9. Research Support, Non-U.S. Gov't.
- 100. Harrison D, Sampson M, Reszel J, et al. Too many crying babies: a systematic review of pain management practices during immunizations on YouTube. BMC Pediatr 2014;14:134. Journal Article Research Support, Non-U.S. Gov't.
- 101. Stinson J, Gupta A, Dupuis F, et al. Usability testing of an online self-management program for adolescents with cancer. J Pediatr Oncol Nurs 2015;32:70–82.
- 102. Taddio A, MacDonald NE, Smart S, et al. Impact of a parent-directed pamphlet about pain management during infant vaccinations on maternal knowledge and behavior. Neonatal Netw 2014;33:74–82. Journal Article Research Support, Non-U.S. Gov't.
- 103. Taddio A, Shah V, Bucci L, et al. Effectiveness of a hospital-based postnatal parent education intervention about pain management during infant vaccination: a randomized control trial. CMAJ 2018;190:E1245–52.
- 104. Taddio A, Ipp M, Vyas C, et al. Teaching parents to manage pain during infant immunizations: laying the foundation for better pain management practices. Clin J Pain 2014;30:987–94. Journal Article.
- 105. Ranger M, Grunau RE. Early repetitive pain in preterm infants in relation to the developing brain. Pain Manag 2014;4(1):57–67.
- 106. Ranger M, Chau CM, Garg A, et al. Neonatal pain-related stress predicts cortical thickness at age 7 years in children born very preterm. PLoS One 2013;8:e76702. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't.
- 107. Richardson B, Falconer A, Shrestha J, et al. Parent-targeted education regarding infant pain management delivered during the perinatal period: a scoping review. Journal of Perinatal and Neonatal Nursing, in press.
- Franck LS, Oulton KB, Bruce ER. Parental involvement in neonatal pain management: an empirical and conceptual update. J Nurs Scholarsh 2012;44:45–54.

- Franck L, Cox S, Allen A, et al. Parental concerns and distress about infant pain. Arch Dis Child 2004;89:F71.
- 110. Franck LS, Scurr K, Couture S. Parent views of infant pain and pain management in the neonatal intensive care unit. Newborn Infant Nurs Rev 2001;1: 106–13.
- 111. Gale G, Franck LS, Kools S, et al. Parents' perceptions of their infant's pain experience in the NICU. Int J Nurs Stud 2004;41:51–8.
- 112. Smith VC, Steelfisher GK, Salhi C, et al. Coping with the neonatal intensive care unit experience: parents' strategies and views of staff support. J Perinat Neonatal Nurs 2012;26:343–52.
- 113. Din Osmun L, Pillai Riddell R, Flora DB. Infant pain-related negative affect at 12 months of age: early infant and caregiver predictors. J Pediatr Psychol 2014;39:23–34. Research Support, Non-U.S. Gov't.
- 114. Pillai Riddell R, Campbell L, Flora DB, et al. The relationship between caregiver sensitivity and infant pain behaviors across the first year of life. Pain 2011;152: 2819–26. Research Support, Non-U.S. Gov't.
- 115. Racine NM, Pillai Riddell RR, Flora D, et al. A longitudinal examination of verbal reassurance during infant immunization: occurrence and examination of emotional availability as a potential moderator. Journal of Pediatric Psychology 2012;37(8):935–44.
- 116. Vinall J, Noel M, Disher T, et al. Memories of infant pain in the neonatal intensive care unit influence posttraumatic stress symptoms in mothers of infants born preterm. Clin J Pain 2018;34:963.
- 117. Committee on Fetus and Newborn and Section On Anesthesiology and Pain Medicine. Prevention and management of procedural pain in the neonate: an update. Pediatrics 2016;137:e20154271.
- 118. Campbell-Yeo M. Combining facilitated tucking and non-nutritive sucking appears to promote greater regulation for preterm neonates following heel lance, but does not provide effective pain relief. Invited commentary. Evid Based Nurs 2019;22(1):19.
- Cignacco EL, Sellam G, Stoffel L, et al. Oral sucrose and facilitated tucking for repeated pain relief in preterms: a randomized controlled trial. Pediatrics 2012; 129:299–308.
- 120. Mekkaoui N, Issef I, Kabiri M, et al. Analgesic effect of 30% glucose, milk and non-nutritive sucking in neonates. J Pain Res 2012;5:573–7.
- 121. Johnston CC, Filion F, Campbell-Yeo M, et al. Enhanced kangaroo mother care for heel lance in preterm neonates: a crossover trial. J Perinatology 2009;29: 51–6. Journal Article Randomized Controlled Trial Research Support, Non-U.S. Gov't.
- 122. Gabriel MAM, de Mendoza BDH, Figueroa LJ, et al. Analgesia with breastfeeding in addition to skin-to-skin contact during heel prick. Arch Dis Child Fetal Neonatal Ed 2013;98:F499–503. Article.
- 123. Cohen LL. Behavioral approaches to anxiety and pain management for pediatric venous access. Pediatrics 2008;122(Suppl 3):S134–9. Journal Article Review.
- 124. Kitson A. Recognizing relationships: reflections on evidence-based practice. Nurs Inq 2002;9:179–86.