Consensus Statement for the Prevention and Management of Pain in the Newborn

K. J. S. Anand, MBBS, DPhil; and the International Evidence-Based Group for Neonatal Pain

Objective: To develop evidence-based guidelines for preventing or treating neonatal pain and its adverse consequences. Compared with older children and adults, neonates are more sensitive to pain and vulnerable to its long-term effects. Despite the clinical importance of neonatal pain, current medical practices continue to expose infants to repetitive, acute, or prolonged pain.

Design: Experts representing several different countries, professional disciplines, and practice settings used systematic reviews, data synthesis, and open discussion to develop a consensus on clinical practices that were supported by published evidence or were commonly used, the latter based on extrapolation of evidence from older age groups. A practical format was used to describe the analgesic management for specific invasive procedures and for ongoing pain in neonates.

Results: Recognition of the sources of pain and routine assessments of neonatal pain should dictate the avoidance of recurrent painful stimuli and the use of specific environmental, behavioral, and pharmacological interventions. Individualized care plans and analgesic protocols for specific clinical situations, patients, and health care settings can be developed from these guidelines. By clearly outlining areas where evidence is not available, these guidelines may also stimulate further research. To use the recommended therapeutic approaches, clinicians must be familiar with their adverse effects and the potential for drug interactions.

Conclusion: Management of pain must be considered an important component of the health care provided to all neonates, regardless of their gestational age or severity of illness.


Newborns routinely experience pain associated with invasive procedures such as blood sampling, immunization, vitamin K injection, or circumcision. The sick or preterm infant may experience repetitive or prolonged pain resulting from many diagnostic, surgical, or therapeutic procedures.1-4

Multiple lines of evidence suggest an increased sensitivity to pain in neonates compared with older age groups.5,6 This pain sensitivity is further accentuated in preterm neonates, and may not be clinically evident.7,8 Critically ill and preterm neonates do not mount vigorous behavioral responses to pain, and therefore require particularly detailed assessment.6,8,9 The pain modulation systems that operate in older children and adults do not appear to be fully functional in newborns10,11 or may function only during maternal contact in healthy newborns.12 Even the most immature preterm neonates mount increasing responses to the pain caused by mild, moderate, or highly invasive procedures, and the magnitude of their responses increase with postnatal age.5,7,11 Compared with older children, neonates exhibit greater hormonal, metabolic, and cardiovascular responses to surgical operations, and may require relatively higher doses of anesthetics and analgesics for adequate pain control.5,14-17 The metabolism and clearance rates of most analgesic agents in preterm neonates are slower than in term neonates, but increase rapidly with age.5,8,10

Management of pain in the newborn is hampered by the lack of awareness among health care professionals that the neonate is capable of experiencing pain, and by fears about the adverse effects associated with analgesic use. Current evidence supports the general principles listed in Table 1 for the routine management of neonates using safe and effective environmental, behavioral, and pharmacological interventions for relieving pain and for preventing its adverse consequences.20

From the International Evidence-Based Group for Neonatal Pain, whose members are listed in the acknowledgments at the end of this article.
METHODS

These guidelines were developed from 2 consensus development meetings (in April 1998 and August 1999). A detailed search of the published literature on neonatal pain was conducted to identify the experts who were invited to these meetings. Databases searched were MEDLINE, Embase, and PubMed using the following terms: pain, nociception, stress, infant-newborn, and infant-premature. Faculty members were selected by the chairman (K.J.S.A.) based on their expertise in specific topics related to neonatal pain, coupled with a concerted effort to include professionals trained in different disciplines and representing different countries and distinct practice settings (eg, children’s hospitals, general hospitals, office practices). The disciplines represented were pediatrics, neonatology, child psychology, anesthesia, neuroscience, endocrinology, neonatal nursing, pharmacy/pharmacology, rehabilitation medicine, critical care medicine, rheumatology/immunology, and others. At the time of these meetings, faculty members were affiliated to academic institutions in Australia, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Poland, Sweden, Switzerland, the Netherlands, United Kingdom, and the United States.

Faculty members performed a systematic review of the published literature on their specific topic, critically evaluated the quality of published data, and synthesized these findings. Data from all relevant studies were presented at these meetings and were discussed by the experts present. Other faculty members were encouraged to present additional data and ample time was allowed for detailed discussion. Guidelines were developed after reaching a consensus on the clinical practices that were prevalent in most countries. As such, these guidelines were based on a combination of published evidence (from randomized controlled trials, systematic reviews, or meta-analyses of trials) and its critical evaluation by the faculty members. Between September 1999 and April 2000, 3 separate draft versions of this statement were circulated and modified by all members of the participating faculty. Approval of all faculty members was obtained for the final version of the consensus statement, which is organized around broad general principles (Table 1) and evidence-based guidelines for neonatal pain management. The pharmacological interventions recommended in these guidelines are not the exclusive products of the pharmaceutical company that funded these meetings, and the representatives of this company have had no input in the format or content of these guidelines.

RESULTS

EVIDENCE-BASED GUIDELINES FOR THE MANAGEMENT OF NEONATAL PAIN

Recognition of the Sources of Pain

Some of the painful procedures commonly performed on neonates in the neonatal intensive care unit (NICU) include heel lancing, venipuncture, venous or arterial catheter insertion, chest tube placement, tracheal intubation or suctioning, lumbar puncture, and subcutaneous or intramuscular injections (see Table 2 for additional procedures). Additional sources of pain may include areas of inflammation and hyperalgesia around previous tissue injury, postoperative pain, localized infection or inflammation, and skin burns or abrasions caused by transcutaneous probes, monitoring leads, or topical agents.

Table 1. General Principles for the Prevention and Management of Pain in Newborns

<table>
<thead>
<tr>
<th>Principle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pain in newborns is often unrecognized and undertreated. Neonates do feel pain, and analgesia should be prescribed when indicated during their medical care.</td>
</tr>
<tr>
<td>2. If a procedure is painful in adults, it should be considered painful in newborns, even if they are preterm.</td>
</tr>
<tr>
<td>3. Compared with older age groups, newborns may experience a greater sensitivity to pain and are more susceptible to the long-term effects of painful stimulation.</td>
</tr>
<tr>
<td>4. Adequate treatment of pain may be associated with decreased clinical complications and decreased mortality.</td>
</tr>
<tr>
<td>5. The appropriate use of environmental, behavioral, and pharmacological interventions can prevent, reduce, or eliminate neonatal pain in many clinical situations.</td>
</tr>
<tr>
<td>6. Sedation does not provide pain relief and may mask the neonate’s response to pain.</td>
</tr>
<tr>
<td>7. Health care professionals have the responsibility for assessment, prevention, and management of pain in neonates.</td>
</tr>
<tr>
<td>8. Clinical units providing health care to newborns should develop written guidelines and protocols for the management of neonatal pain.</td>
</tr>
</tbody>
</table>

Table 2. Painful Procedures Commonly Performed in the Neonatal Intensive Care Unit

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
</tr>
<tr>
<td>Arterial puncture</td>
</tr>
<tr>
<td>Bronchoscopy</td>
</tr>
<tr>
<td>Endoscopy</td>
</tr>
<tr>
<td>Heel lancing</td>
</tr>
<tr>
<td>Lumbar puncture</td>
</tr>
<tr>
<td>Retinopathy of prematurity examination</td>
</tr>
<tr>
<td>Suprapubic bladder tap</td>
</tr>
<tr>
<td>Venipuncture</td>
</tr>
<tr>
<td>Therapeutic</td>
</tr>
<tr>
<td>Bladder catheterization</td>
</tr>
<tr>
<td>Central line insertion/removal</td>
</tr>
<tr>
<td>Chest tube insertion/removal</td>
</tr>
<tr>
<td>Chest physiotherapy</td>
</tr>
<tr>
<td>Dressing change</td>
</tr>
<tr>
<td>Gavage tube insertion</td>
</tr>
<tr>
<td>Intramuscular injection</td>
</tr>
<tr>
<td>Peripheral venous catheterization</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Postural drainage</td>
</tr>
<tr>
<td>Removal of adhesive tape</td>
</tr>
<tr>
<td>Suture removal</td>
</tr>
<tr>
<td>Tracheal intubation/extubation</td>
</tr>
<tr>
<td>Tracheal suctioning</td>
</tr>
<tr>
<td>Ventricular tap</td>
</tr>
<tr>
<td>Surgical</td>
</tr>
<tr>
<td>Circumcision</td>
</tr>
<tr>
<td>Other surgical procedures</td>
</tr>
</tbody>
</table>
Assessment of Pain

• Concomitantly with the vital signs, assessment of neonatal pain must be undertaken and documented every 4 to 6 hours or as indicated by the pain scores or clinical condition of the neonate.21-24

• Standardized pain assessment methods with evidence of validity, reliability, and clinical utility should be used25-32 (Table 3).

• Pain assessment instruments should be sensitive and specific for infants of different gestational ages and/or with acute, recurrent, or continuous pain.13,32,33 Examples of ongoing, continuous pain may include postoperative pain or inflammatory conditions.1,3,33

• Pain assessment should be comprehensive and multidimensional, including contextual, behavioral, and physiological indicators.8,13,21-23

• Pain assessment must be performed after each potentially painful clinical intervention and to evaluate the efficacy of behavioral, environmental, and pharmacological agents.21,23,33,34

Management of Pain in the Newborn

• Strategies for prevention, particularly by avoiding recurrent painful stimuli.20,33

• Use of environmental interventions to reduce stress in the NICU.33,35,36

• Behavioral methods, including sucrose and nonnutritive sucking.12,20,37-56

• Pharmacological agents for preemptive analgesia20,57-76 (Table 4).

• Pharmacological therapy for ongoing pain17,19,34,58,71-80 (Table 4).

### Table 3. Commonly Used Methods for Assessment of Pain in Newborns

<table>
<thead>
<tr>
<th>Variables assessed</th>
<th>Premature Infant Pain Profile (PIPP)27,31</th>
<th>Neonatal Facial Coding Scale (NFCS)28,32</th>
<th>Neonatal Infant Pain Scale (NIPS)29</th>
<th>CRIES Score25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>Brow bulge</td>
<td>Facial expression</td>
<td>Crying</td>
<td></td>
</tr>
<tr>
<td>Behavioral state</td>
<td>Eye squeeze</td>
<td>Cry</td>
<td>Requires increased oxygen</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>Nasalabial furrow</td>
<td>Breathing patterns</td>
<td>administration</td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>Open lips</td>
<td>Arms</td>
<td>Increased vital signs</td>
<td></td>
</tr>
<tr>
<td>Brow bulge</td>
<td>Stretch mouth</td>
<td>Legs</td>
<td>Expression</td>
<td></td>
</tr>
<tr>
<td>Eye squeeze</td>
<td>Taut tongue</td>
<td>State of arousal</td>
<td>Sleeplessness</td>
<td></td>
</tr>
<tr>
<td>Nasalabial furrow</td>
<td>Chin quiver</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reliability data</th>
<th>Interrater and intrarater reliability &gt;0.93</th>
<th>Interrater reliability &gt;0.92</th>
<th>Interrater reliability &gt;0.72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forms of validity established</td>
<td>Face, content, construct (in preterm and term neonates)</td>
<td>Face, construct, and concurrent (r = 0.89)</td>
<td>Face, content, discriminant, and concurrent (r = 0.49-0.73)</td>
</tr>
</tbody>
</table>

| Clinical utility   | Feasibility and utility established at bedside | Feasibility established at bedside | Not established | Nurses preferred CRIES over another scale |

### Table 4. Recommended Analgesic Doses for Neonates*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Intermittent Dose</th>
<th>Infusion Dose</th>
<th>Local/Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid analgesics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>0.05-0.1 mg/kg intravenously (IV)</td>
<td>0.01-0.03 mg/kg per hour</td>
<td>...</td>
</tr>
<tr>
<td>Fentanyl citrate</td>
<td>0.5-3 µg/kg IV</td>
<td>0.5-2 µg/kg per hour</td>
<td>...</td>
</tr>
<tr>
<td>Anesthetic agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine (local/topical)</td>
<td>...</td>
<td>...</td>
<td>2-5 mg/kg subcutaneously; 0.5-1 mg/kg endotracheally</td>
</tr>
<tr>
<td>EMLA† (local/topical)</td>
<td>...</td>
<td>...</td>
<td>0.5-2 g under occlusive dressing 1 h before the procedure</td>
</tr>
<tr>
<td>Ketamine hydrochloride (systemic)</td>
<td>0.5-2 mg/kg IV</td>
<td>0.5-1 mg/kg per hour</td>
<td>...</td>
</tr>
<tr>
<td>Thiopental sodium (systemic)</td>
<td>2-5 mg/kg IV</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Other agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>10-15 mg/kg orally; 20-30 mg/kg rectally†</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>12%-24% solution given orally 2 min before the procedure, 2 mL for term neonates and 0.1-0.4 mL for preterm neonates</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

* It is advised that neonatal intensive care units use only 1 opioid analgesic agent to ensure familiarity with its use. The opioid doses noted are only applicable for opioid-naive patients. All patients receiving analgesic or anesthetic agents should be monitored and carefully observed, particularly if they are breathing spontaneously.

†EMLA indicates eutectic mixture of local anesthetics (lidocaine and prilocaine hydrochloride in an emulsion base).

‡Maximum daily dose: preterm infants (28-32 wk) = 40 mg/kg; preterm infants (32-36 wk) and term infants (<10 d) = 60 mg/kg; term infants (≥10 d) = 90 mg/kg.
SUGGESTED MANAGEMENT APPROACHES FOR NEONATAL PAIN

In the following sections, an asterisk indicates that evidence from studies in neonates is available to support the proposed intervention. The combined use of multiple interventions may have additive or synergistic clinical effects.

Heel Lance
- Consider use of venipuncture instead of heel lance in full-term neonates and more mature preterm neonates* (because it is less painful, more efficient and requires less resampling).62,81-87 This approach may not apply to the care of extremely preterm infants.
- Use a pacifier* with sucrose* (concentration 12%-24%) given 2 minutes before the procedure.39-48,51-55
- Use swaddling, containment,* or facilitated tucking.37,38
- Consider skin-to-skin contact with the mother.*12
- Use a mechanical spring-loaded lance, eg, Autolance.*62,85,86
  EMLA (a eutectic mixture of local anesthetics: lidocaine and prilocaine hydrochloride in an emulsion base), acetaminophen, and warming the heel are ineffective for heel lancing*; squeezing for blood collection is the most painful part of the procedure.70,81-85,87

Percutaneous Venous Catheter Insertion
- Use a pacifier* with sucrose.39,41,70,81-84
- Use swaddling, containment, or facilitated tucking37,38
- Apply EMLA* to the proposed site (when non-urgent).60,82,88,89
- Consider opioid dose(s),* if intravenous access is available.58,73
- Consider a similar approach for venipuncture.88,89

Percutaneous Arterial Catheter Insertion
- Use a pacifier* with sucrose.39,41
- Use swaddling, containment, or facilitated tucking37,38
- Apply EMLA to the proposed site.50,70
- Consider subcutaneous infiltration of lidocaine.58,70
- Consider a similar approach for arterial puncture.

Peripheral Arterial or Venous Cutdown
- Use a pacifier with sucrose.39,41
- Use swaddling, containment, or facilitated tucking37,38
- Apply EMLA to the proposed site.38,60,70
- Consider subcutaneous infiltration of lidocaine; avoid intravascular injection.58,70
- Consider opioid dose(s), if intravenous access is available.15,58,76

Central Venous Line Placement
- Use a pacifier* with sucrose.39,41
- Use swaddling, containment, or facilitated tucking.37,38
- Apply EMLA to the proposed site, if nonurgent.60,90
- Consider subcutaneous infiltration of lidocaine.58,70
- Consider slow intravenous opioid infusion (morphine sulfate* or fentanyl citrate*)73,76
- Consider using general anesthesia for the procedure.15,70,76,91

Umbilical Catheter Insertion (Umbilical Arterial/Umbilical Venous)
- Consider the use of a pacifier with sucrose.39,41
- Use swaddling, containment, or facilitated tucking.37,38
- Avoid the placement of sutures or hemostat clamps on the skin around the umbilicus.

Peripherally Inserted Central Catheter Placement
- Use a pacifier with sucrose.39,41
- Use swaddling, containment, or facilitated tucking37,38
- Apply EMLA* to the proposed site (when non-urgent).58,60,90
- Consider opioid dose(s), if intravenous access is available.58,76,91

Lumbar Puncture
- Use a pacifier with sucrose.39,41
- Apply EMLA to the proposed site.60
- Consider subcutaneous infiltration of lidocaine.58,70
- Because containment is not possible, careful physical handling is advised.

Subcutaneous or Intramuscular Injection
- Avoid subcutaneous and intramuscular injections; give drugs intravenously whenever possible.
  If necessary:
- Use a pacifier with sucrose.39,41
- Use swaddling, containment, or facilitated tucking.37,38
- Apply EMLA to the proposed site (evidence for this approach is available from studies in children, but not from studies in neonates).92-94

Endotracheal Intubation
Many variations in clinical approach have been noted; the superior efficacy of any one technique is not supported by current evidence33,58,70,95-97:
- Use combination of atropine sulfate and ketamine hydrochloride*.95
- Use combination of atropine, thiopental sodium,* and succinylcholine chloride.97
- Use combination of atropine, thiopental sodium,* and succinylcholine chloride.97
- Use combination of atropine, morphine, or fentanyl, and nondepolarizing muscle relaxant (pancuronium, vecuronium, rocuronium).15,38
- Consider using a topical lidocaine spray, if available.98,99
- Other drug combinations are frequently used.58,70
Tracheal intubation without the use of analgesia or sedation should be performed only for resuscitation in the delivery room or for other life-threatening situations associated with the unavailability of intravenous access.

**Endotracheal Suction**

This is considered a stressful procedure and may be associated with the same physiological responses that accompany other painful procedures. Anticipate the need for intubation and ventilation in company other painful procedures associated with the same physiological responses that accompany other painful procedures. Anticipate the need for intubation and ventilation in company other painful procedures. Use a pacifier; may consider giving sucrose. Use swaddling, containment, or facilitated tucking. Consider continuous intravenous infusion of opioids (morphine*) or slow injection of intermittent opioid doses (fentanyl, meperidine, alfentanil*). The use of midazolam is not recommended.

**Nasogastric or Orogastric Tube Insertion**

- Use a pacifier with sucrose.
- Use swaddling, containment, or facilitated tucking.
- Use a gentle technique and appropriate lubrication.

The use of intravenous midazolam is not recommended.

**Circumcision**

If deemed necessary, use an appropriate clamp (Mogen clamp preferred over Gomco®). Apply EMLA* to the proposed site. Place a dorsal penile nerve block. Use a pacifier with sucrose. Consider acetaminophen for postoperative pain.

Analgesics can be combined for maximum efficacy, although the addition of sodium bicarbonate to lidocaine does not alter the neonatal responses to lidocaine injection.

**Ongoing Analgesia for Routine NICU Care and Procedures**

- Use swaddling, containment, or facilitated tucking.* Use a pacifier; may consider giving sucrose. Low-dose continuous infusion of morphine* or fentanyl* if patient is ventilated.

There is no evidence to show that neonates can be safely sedated for several weeks or months, and the use of midazolam is not recommended.

### Table 5. Adverse Effects of Analgesic Agents in Neonates

<table>
<thead>
<tr>
<th>Analgesic Agents</th>
<th>Adverse Effects</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate</td>
<td>Respiratory depression Decreased gastrointestinal motility Hypotension† Urinary retention</td>
<td>129-134 135 136-138 139</td>
</tr>
<tr>
<td>Fentanyl citrate</td>
<td>Respiratory depression Hypotension Muscle rigidity Hypothermia</td>
<td>75, 140 141 142-146 147, 148</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Hematoma at injection site Recurrent seizures Heart block</td>
<td>64, 111 149 150</td>
</tr>
<tr>
<td>EMLA*</td>
<td>Redness, blistering, petechial rash Methemoglobinemia†</td>
<td>111, 151 61, 90, 152, 153</td>
</tr>
<tr>
<td>Ketamine hydrochloride</td>
<td>Respiratory depression or apnea Increased secretions†</td>
<td>154-156 157</td>
</tr>
<tr>
<td>Thiopental sodium</td>
<td>Hypotension</td>
<td>158</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>None reported‡</td>
<td>...</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Hyperglycemia†</td>
<td>39-41, 54</td>
</tr>
</tbody>
</table>

*EMLA indicates eutectic mixture of local anesthetics (lidocaine and prilocaine hydrochloride in an emulsion base).
†These adverse effects have not been reported or reported rarely or uncommonly in neonates.
‡No side effects are reported with therapeutic doses of acetaminophen, and neonates are relatively less susceptible to the hepatotoxicity resulting from acetaminophen overdose.

- Consider acetaminophen therapy.

The efficacy and safety of repeated acetaminophen doses is unknown, rectal absorption is variable, and intravenous propacetamol is not available in the United States.

- Reduce acoustic, thermal, and other environmental stresses.

**COMMENT**

Recognition of the clinical importance of neonatal pain and stress has been delayed by outdated professional attitudes (that newborns are less sensitive to pain), lack of education, need for accurate assessment methods, and lack of evidence for the safety and efficacy of management approaches that can be applied to the routine care of neonates. This is a preliminary attempt to present the available evidence so that it may be useful to the clinicians at the bedside. We hope to stimulate further research by clearly outlining the areas where current evidence is not available for defining the efficacy of specific therapeutic approaches. Although these management approaches are mainly applicable for established NICUs that provide advanced medical and nursing care for critically ill neonates, they can be adapted for management of neonatal pain in other clinical settings or geographical locations.

Adverse effects that may result from these therapies are listed in Table 5, and all clinicians using these guidelines must be familiar with the safe use of an-
algesic agents in healthy or critically ill, term and preterm neonates. Professionals working with neonates are expected to be knowledgeable about the current assessment and management approaches through participation in ongoing pain education, interaction with pain experts, attention to the most recent research evidence, and adherence to professional standards and clinical guidelines. We strongly support the initiative taken by national professional organizations for the prevention and management of neonatal pain and for the development of standards for health care professionals and institutions. This consensus statement provides evidence-based protocols for developing neonatal pain management guidelines that can be uniquely designed for various clinical situations and diverse practice settings. Adherence to such guidelines will not only improve the clinical care provided to all neonates, but may also have a positive impact on their subsequent health and behaviors during childhood and adolescence.

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REFERENCES


