Guideline Statement:
Management of Procedure-related Pain in Neonates
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1. Executive Summary
(See attachment)
2. Consequences of newborn pain

Newborn pain, which itself is generally a consequence of intervention, has both immediate, short term and long term consequences. The latter is an emerging field of research and particularly important as the possible impact of multiple neonatal pain exposure in the Neonatal Intensive Care Unit (NICU) on neurodevelopment, potentially contributes to later problems with attention, learning and behaviour.

- Newborn infants subjected to a variety of noxious stimuli have immediate hormonal, physiological and behavioural responses.\(^7\)
- Term and preterm infants behave differently in their short-term response to pain. Prior pain experience in healthy, term babies appears to increase subsequent behavioural response to pain. By contrast, in preterm infants, prior pain experience may diminish subsequent behavioural response to pain but not, necessarily, the experience of pain.\(^8\)
- Painful neonatal experiences do have long-term consequences and even if not expressed as conscious memory,\(^8-10\) memories of pain maybe recorded biologically and alter brain development and subsequent behaviour.\(^10\) This is consistent with laboratory studies in animal models where early injury can induce long-term behavioural and CNS effects which persist into adulthood.\(^2\) Taddio et al reported that circumcised boys had higher pain and cry scores during routine immunisation at 4-6 months of age than uncircumcised boys and scores were again higher if circumcision was unaccompanied by analgesia compared with those receiving topical anaesthesia.\(^11\) Extremely Low Birth Weight (ELBW) infants demonstrate lower pain sensitivity at 18 months of age compared with controls and significantly higher scores for non-specific physical complaints with no known medical cause at 4.5 years of age, as reported by parents.\(^8\)
### 3. Responses of infants to pain

(Reference\(^\text{12}\))

<table>
<thead>
<tr>
<th>Physiological changes</th>
<th>Behavioural changes</th>
<th>Hormonal changes</th>
<th>Autonomic changes</th>
<th>Body movements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in:</td>
<td>Change in facial expression:</td>
<td>Increased release of:</td>
<td>Mydriasis</td>
<td>Finger clenching</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Grimacing</td>
<td>Cortisol</td>
<td>Sweating</td>
<td>Thrashing of limbs</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Screwing up of eyes</td>
<td>Catecholamines</td>
<td>Flushing</td>
<td>Writhe</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Nasal flaring</td>
<td>Glucagon</td>
<td>Pallor</td>
<td>Arching of back</td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>Deep nasolabial groove</td>
<td>Growth hormone</td>
<td></td>
<td>Head hanging</td>
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<tr>
<td>Mean airway pressure</td>
<td>Curving of the tongue</td>
<td>Renin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Quivering of the chin</td>
<td>Aldosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial pressure</td>
<td></td>
<td>Antidiuretic hormone</td>
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</tbody>
</table>

- Decreased secretion of:
  - Insulin
4. General principles for the prevention and management of pain in newborns

Adapted from Anand 2001, Bell 1994 and the American Academy of Pediatrics 2000.4-6

1. Neuroanatomical components and neuroendocrine systems are sufficiently developed to allow transmission of painful stimuli in the both very preterm and term neonates.3
2. Pain in newborns is often unrecognised and undertreated. Neonates do feel pain, and analgesia should be prescribed when indicated during medical care.
3. If a procedure is painful in adults it should be considered painful in newborns, even if they are preterm.
4. 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.
5. Adequate treatment of pain may be associated with decreased clinical complications and decreased mortality.
6. The appropriate use of environmental, behavioural and pharmacological interventions can prevent, reduce or eliminate neonatal pain in many clinical situations.
7. Sedation does not provide pain relief and may mask the neonate's response to pain.
8. Health care professionals have the responsibility for assessment, prevention and management of pain in neonates. Severity of pain and effects of analgesia can be assessed in the neonate.
9. Clinical units providing health care to newborns should develop written guidelines and protocols for the management of neonatal pain.
10. A lack of behavioural responses (including crying and movement) does not necessarily indicate a lack of pain.
11. Systematic approach to pain management includes:
   - Prevention, limiting, avoiding noxious stimuli.
   - Assessment of neonatal pain by standardised methods with demonstrable validity, reliability and clinical utility.
   - Treatment including non-pharmacological (behavioural) and pharmacological.
12. Environment should be as conducive as possible to the well being of the neonate and family:
   - Avoiding unnecessary noxious stimuli (acoustic, visual, tactile, vestibular).
   - Minimising painful or stressful procedures (placement peripheral, central, arterial lines to reduce repeated IV punctures).
   - Non-invasive measurement where possible e.g. oximeter
   - Behavioural measures: sucrose, swaddling, non-nutritive sucking (dummy), multisensory stimulation, and skin to skin contact.
   - Pharmacological therapy when indicated with appropriate safe dosage by using computer generated medication doses if available.
5. Definitions

The International Association for the Study of Pain (IASP) has developed a standard definition of pain, noting that **pain** is always subjective: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (www.iasp-pain.org). Furthermore, Zempsky and Schechter emphasise that this experience occurs from an early age and define pain as "an inherent quality of life that appears early in development and serves as a signal for tissue damage".\(^{13}\)

**Multisensory stimulation** may include the use of massage, speaking with a soothing voice and providing eye contact, even providing a mother's perfume to smell.
6. Methods

There have been several recent consensus statements concerning neonatal pain.\textsuperscript{4-6, 14} This policy draws extensively from these references, in particular the most recent two, evidence-based statements.\textsuperscript{5, 14} The same general outline has been used as that employed by Anand and colleagues. Their statement summarises the literature up to 2001. A literature review, using key words of pain and pain measurement, was used to update the suggested management approaches for neonatal pain (evidence-based consensus statements). The Cochrane Library was searched for systematic reviews and randomised control trials and then MEDLINE, CINAHL and EMBASE databases. The search strategy was limited to “infant newborn or newborn” and to human and English language and systematically explored guidelines, systematic reviews, randomised control trials, consensus statements, from 2001 to 2004. Cross-references were obtained from the bibliography of identified papers.
7. Assessment of pain in neonates

Assessment of pain in the neonate is complicated by the inability of neonates to verbalise pain. Thus, while self-reporting is the single most reliable indicator of the existence and intensity of acute pain, indirect measurements including hormonal, behavioural, physiological measures have been used to validate pain in the neonate. There are a variety of tools available for the assessment of neonatal pain which rely on contextual indicators (gestational age, sleep/wake state), behavioural responses, physiological responses or a combination of the three. Four assessment tools which have been evaluated to varying levels are listed below. These are included because they are multi-dimensional and demonstrate evidence of reliability, validity and utility.

7.1 Commonly used methods for assessment of pain in newborns

(Reference)

<table>
<thead>
<tr>
<th></th>
<th>Premature Infant Pain Profile (PIPP)</th>
<th>Neonatal Facial Coding Scale (NFCS)</th>
<th>Neonatal Infant Pain Scale (NIPS)</th>
<th>CRIES Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables assessed</td>
<td>Gestational age</td>
<td>Brow bulge</td>
<td>Facial expression</td>
<td>Crying</td>
</tr>
<tr>
<td></td>
<td>Behavioural state</td>
<td>Eye squeeze</td>
<td>Cry</td>
<td>Requires increase</td>
</tr>
<tr>
<td></td>
<td>Heart Rate</td>
<td>Nasolabial furrow</td>
<td>Breathing patterns</td>
<td>Oxygen administration</td>
</tr>
<tr>
<td></td>
<td>Oxygen saturation</td>
<td>Open lips</td>
<td>Arms</td>
<td>Increased vital signs</td>
</tr>
<tr>
<td></td>
<td>Brow bulge</td>
<td>Stretch mouth</td>
<td>Legs</td>
<td>Expression</td>
</tr>
<tr>
<td></td>
<td>Eye squeeze</td>
<td>Lip purse</td>
<td>State of arousal</td>
<td>Sleeplessness</td>
</tr>
<tr>
<td></td>
<td>Nasolabial furrow</td>
<td>Taut tongue</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Chin quiver</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Tongue protrusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reliability data</td>
<td>Interrater and intrarater reliability&gt;0.93</td>
<td>Interrater and intrarater Reliability&gt;0.85</td>
<td>Interrater reliability &gt;0.92</td>
<td></td>
</tr>
<tr>
<td>Forms of validity</td>
<td>Face, content, construct</td>
<td>Face, content, construct, and convergent (r = 0.89)</td>
<td>Face, content, and Concurrent (r = 0.53-0.84)</td>
<td>Face, content, Discrimination, and Concurrent (r = 0.49-0.73)</td>
</tr>
<tr>
<td>Established</td>
<td>(in preterm and term neonates)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Clinical utility</td>
<td>Feasibility and utility established at bedside</td>
<td>Feasibility established at Bedside</td>
<td>Not established</td>
<td>Nurses preferred CRIES over another Scale</td>
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</table>
8. Painful procedures performed in Neonatal Intensive Care Units

(Reference 5)

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Therapeutic</th>
<th>Surgical</th>
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<tbody>
<tr>
<td>Arterial puncture</td>
<td>Bladder catheterization</td>
<td>Other surgical procedures</td>
</tr>
<tr>
<td>Heel lancing</td>
<td>Central line insertion/removal</td>
<td>e.g. peritoneal drain, cut-down</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>Chest tube insertion/removal</td>
<td></td>
</tr>
<tr>
<td>Retinopathy of prematurity examination</td>
<td>Chest physiotherapy</td>
<td></td>
</tr>
<tr>
<td>Suprapubic bladder tap</td>
<td>Dressing change</td>
<td></td>
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<tr>
<td>Venipuncture</td>
<td>Gavage tube insertion</td>
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<tr>
<td>Eye examination</td>
<td>Intramuscular injection</td>
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<td></td>
<td>Laser therapy for retinopathy</td>
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<td></td>
<td>Peripheral venous catheterization</td>
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<td></td>
<td>Mechanical ventilation</td>
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<td></td>
<td>Postural drainage</td>
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<td></td>
<td>Removal of adhesive tape</td>
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<tr>
<td></td>
<td>Suture removal</td>
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<tr>
<td></td>
<td>Tracheal intubation/extubation</td>
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<tr>
<td></td>
<td>Ventricular tap</td>
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</tbody>
</table>
9. Principles of management of pain in neonates

- **Prevention** - consider whether each test / intervention is necessary or can be reduced
- **Environment** - reduce stress from noxious stimuli (acoustic, visual, tactile, vestibular)
- **Behavioural methods** - breast feeding, glucose/sucrose, non nutritive sucking, swaddling, multisensory stimulation
- **Pharmacological agents** for pre-emptive analgesia
- **Pharmacological therapy** for ongoing pain
10. Suggested management approaches for neonatal pain

In 2005, there are high levels of evidence (systematic reviews and randomised control trials) to indicate which behavioural and pharmacological interventions are effective in reducing neonatal pain. The combined use of multiple interventions may have additive or synergistic clinical effects, for example multisensory stimulation and oral sucrose are more effective than either alone in reducing pain due to heel lancing. Multisensory stimulation may involve massage, eye contact, use of a soothing/familiar voice or familiar smells.

10.1 Blood sampling

1. Venepuncture is the preferred method for blood sampling in term newborns as it is less painful, more efficient and requires less resampling. This approach may not apply to the care of extremely preterm infants.
   - Apply EMLA (0.5-1g) 60-90 minutes prior to venepuncture when time allows.
   - Use oral sucrose (concentration 12% - 24%). Systematic reviews of the literature suggest doses in the order of 0.5–1.0mls of 24% sucrose in 0.25ml aliquots, commencing 2 minutes before the procedure. Concomitant use of a pacifier may further reduce behavioural responses to painful stimuli. A pacifier should only be used in accordance with parental wishes and its one-off use is not intended to promote or encourage regular pacifier use in infants.
   - Encourage the mother to breast-feed or if the baby is taking artificial milk then bottle-feed during the procedure.
   - Ensure the parent or carer holds the infant during the procedure and employs multisensory stimulation (± skin contact).
   - Use swaddling, containment by flexing and holding the infant and employ multisensory stimulation.

2. If heel lancing is used:
   - Do not warm the heel prior to lancing as this does not reduce pain or aid blood collection during lancing.
   - Consider use of oral sucrose as above.
   - Encourage the mother to breast-feed or if the baby is taking artificial milk then bottle-feed during the procedure.
   - Ensure the parent or carer holds the infant during the procedure and employs multisensory stimulation (± skin contact).
   - Use an automated lancet, preferably fully retractable.

NOTE: Topical anaesthesia, such as EMLA cream (a Eutectic Mixture of Local Anaesthetics: lidocaine and prilocaine hydrochloride in an emulsion base) or amethocaine gel, paracetamol, and warming the heel are ineffective for heel lancing, as heel squeezing is the most painful part of the procedure.
10.2 Intramuscular injections

- Avoid subcutaneous and intramuscular injections; give drugs intravenously whenever possible.
- Consider use of oral sucrose as above.\textsuperscript{18 19}
- Use holding, swaddling or containment by flexing and holding the infant and employ multisensory stimulation.
- Application of EMLA cream (0.5-1g) 60-90 minutes prior to injection.

*The intramuscular route is the preferred route of administration for Vitamin K. Vitamin K should be given as soon as possible after birth. The birth process produces high levels of endogenous endorphins\textsuperscript{29} and most centres would not use oral sucrose or EMLA in this setting.*

10.3 Nasogastric or orogastric tube insertion

- Consider use of oral sucrose as above.\textsuperscript{18 19}
- Use holding, swaddling or containment by flexing and holding the infant.\textsuperscript{30 31}
- Use a gentle technique with appropriate lubrication ensuring the head is in the neutral or “sniffing” position and inserting the tube in a vertical direction at right angles to the face.\textsuperscript{32}

10.4 Umbilical catheter insertion (umbilical arterial/umbilical venous)

If a newborn seems distressed during the procedure employ the following:
- Consider use of oral sucrose as above.\textsuperscript{18 19}
- Use containment by holding the infant.\textsuperscript{30 31}
- Secure catheter as soon as possible to prevent displacement.
- Avoid the placement of sutures or hemostat clamps on the skin around the umbilicus.

10.5 Arterial puncture, percutaneous venous catheter insertion, percutaneous arterial catheter insertion, peripheral arterial or venous cut down, peripherally inserted central catheter placement

- Apply EMLA (0.5-1g) to the proposed site 60-90 minutes prior to insertion (when non-urgent and NICU organisational safety makes this option possible).\textsuperscript{17 33-38}
- Consider use of oral sucrose as above.\textsuperscript{18 19}
- Use swaddling or containment by holding the infant.\textsuperscript{30 31}
- Consider opioid dose(s), if intravenous access is available.\textsuperscript{37 39}
- Consider subcutaneous infiltration of lignocaine for arterial catheter insertion or cutdowns.\textsuperscript{34 35 37}

10.6 Lumbar puncture

- Apply EMLA (0.5-1g) the proposed site 60-90 minutes beforehand.\textsuperscript{17 40}
- Consider use of oral sucrose as above.\textsuperscript{18 19}
- Consider subcutaneous infiltration of lignocaine.\textsuperscript{34 35 37}
10.7 Endotracheal intubation

Many variations in clinical approach have been noted, each usually consists of a combination of atropine, an opioid and a muscle relaxant. The superior efficacy of any one technique is not supported by current evidence.\(^\text{34-35,37,41-44}\)

Combinations for which evidence of efficacy exists include:
- Atropine and ketamine hydrochloride.\(^\text{42}\)
- Atropine, morphine and succinylcholine chloride.\(^\text{45}\)
- Atropine, thiopental sodium, and succinylcholine chloride.\(^\text{44}\)
- Atropine, morphine, or fentanyl, and nondepolarizing muscle relaxant (pancuronium, vercuronium, rorcuronium).\(^\text{37,39}\)

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.\(^\text{42-44}\)

10.8 Endotracheal suction

This is considered a stressful procedure and may be associated with the same physiological responses that accompany other painful procedures.\(^\text{46-51}\)
- Consider use of oral sucrose as above.\(^\text{18,19}\)
- Use swaddling or containment by holding the infant.\(^\text{30,31}\)
- Consider continuous intravenous infusion of opioids (morphine)\(^\text{46}\) or slow injection of intermittent opioid doses (morphine)

10.9 Chest tube insertion

- Anticipate the need for intubation and ventilation in neonates breathing spontaneously.\(^\text{37}\)
- Consider use of oral sucrose as above.\(^\text{18,19}\)
- Consider subcutaneous infiltration of lignocaine.\(^\text{34,35,37}\)
- Consider slow intravenous opioid infusion (morphine).\(^\text{37,39}\) Intravenous midazolam is not recommended.\(^\text{52,53}\)
- Other approaches may include the use of short acting anaesthetic agents).\(^\text{37,39}\)

10.10 Laser therapy for retinopathy of prematurity

- Intubate and ventilate in neonates breathing spontaneously.
- Consider use of oral sucrose as above.\(^\text{18,19}\)
- Consider slow intravenous opioid infusion (morphine).\(^\text{37,39}\) Intravenous midazolam is not recommended.\(^\text{52,53}\)
- Other approaches may include the use of short acting anaesthetic agents.\(^\text{37,39}\)
- Consider oral paracetamol after extubation (although evidence of benefit or harm not available and data limited in neonates).\(^\text{54}\)
10.11 Circumcision

The Paediatrics & Child Health Division, the Royal Australasian College of Physicians (RACP), after extensive review of the literature reaffirms that **there is no medical indication for routine male circumcision.**

Refer to the Royal Australasian College of Physicians circumcision policy at [http://www.racp.edu.au/hpu/paed/circumcision/index.htm](http://www.racp.edu.au/hpu/paed/circumcision/index.htm) where there is advice on analgesia and also a parent information brochure and a summary of interventions to minimise the pain of circumcision.

Medical indications for circumcision usually occur well beyond the neonatal period and, in this setting, general anaesthesia is preferred.
11. Ongoing analgesia for routine nursery care and procedures

- Reduce acoustic, thermal, and other environmental stresses.\cite{41,55,56}
- Use swaddling or containment, by holding the infant ± multisensory stimulation.\cite{30,31}
- Use a pacifier and if possible and safe to do so give with sucrose.\cite{18,19}
- Consider low-dose continuous infusion of morphine if patient is ventilated.\cite{46,57,58}
- The use of midazolam is not recommended.\cite{52}
12. Summary of evidence

12.1 Interventions with evidence of benefit

**Level I:**
- Venipuncture is less painful than heel lancing for blood sampling in newborns. ²⁸
- Sucrose is safe and effective in reducing pain from heel lancing. ¹⁸

**Level II:**
- Sucrose is safe and effective in reducing pain from venepuncture and heel lancing in preterm infants. ⁵⁹-⁶¹
- Pacifiers (dummies), non-nutritive sucking, rocking are effective in reducing pain responses. ⁶²-⁶⁴
- Sucrose with pacifiers are effective in reducing pain responses in newborn infants. ¹⁹ ⁶⁵-⁶⁷
- Sucrose and holding are effective in reducing pain responses. ²⁴
- Multisensory stimulation (massage, voice, eye contact and perfume smelling) with oral glucose and sucking is most effective in reducing pain responses to heel lancing in term and preterm infants. ¹⁵
- Breast-feeding is effective in reducing pain responses during heel lancing in healthy newborns. ²¹
- Skin to skin contact is effective in reducing pain responses during heel lancing in newborns. ²²
- Automated lancets are superior to conventional lancets (less need for repeat punctures, shorter procedure time, increased volume of blood collected, reduction in haemolysed blood samples). ²⁸ ⁶⁸-⁷⁰
- A fully retractable automatic lancet is superior to a partially retractable automatic lancet (less pain, less time to perform, fewer punctures but more expensive). ²⁸

12.2 Interventions with no evidence of benefit or evidence of harm

**Level I:**
- Midazolam maybe associated with a higher incidence of adverse neurological event and longer NICU stay. ⁵²

**Level II:**
- EMLA cream, topical amethocaine, lignocaine ointment, oral paracetamol are not effective for heel lancing pain. ¹⁷ ⁷¹ ⁷²
- Warming the heel does not reduce pain or aid blood collection during heel lancing. ²⁶ ²⁷
- Routine repeated use of sucrose analgesia in preterm neonates <31 weeks post-conceptional age may result in poorer neuro behavioural development. ⁷³
- Routine morphine infusion in preterm ventilated newborns is currently controversial. Some studies suggest no measurable analgesic effect, no effect on adverse neurological outcome and adverse effects in preterm neonates. ⁷⁴ Adverse effects include a dose dependent respiratory depression leading to apnea, decreased gut motility, urinary
retention, hypotension and bradycardia (uncommonly reported in neonates\textsuperscript{5}). A systematic review does not recommend routine use and suggests use of opioids be selective based on clinical judgement and pain indicators.\textsuperscript{76} However a beneficial effect was found in a recent blinded, randomised placebo controlled trial where continuous morphine infusion significantly decreased stress levels (noradrenaline concentration) in ventilated newborns.\textsuperscript{77}

<table>
<thead>
<tr>
<th>NHMRC levels of evidence\textsuperscript{78}</th>
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<tbody>
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<td>I</td>
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<tr>
<td>II</td>
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<td>III-1</td>
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<td>III-2</td>
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<tr>
<td>III-3</td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
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13 References


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