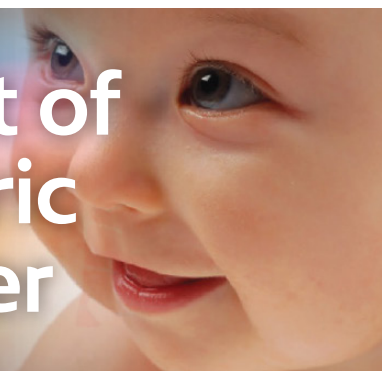




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# Management of mild paediatric pain and fever



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## About the Expert



### Dr Ross Drake

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Ross Drake is a Paediatrician who specialises in Pain Medicine and Palliative Care for children having gained fellowships in Paediatrics (2000), Palliative Medicine (2003) and Pain Medicine (2011) after he completed specialist training at Great Ormond Street in London and The Children's Hospital at Westmead in Sydney.

Ross is currently the Clinical Lead of the Paediatric Palliative Care and Complex Pain Services at Starship Children's Hospital; both being the only services of their type in New Zealand. Dr Drake also regularly presents and teaches on various topics in children's pain medicine and palliative care. More recently, he has been involved with establishing an international pharmacovigilance research collaborative looking at the effectiveness and adverse effects of medications and other interventions commonly used in palliative care and pain management.

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This publication is intended as an educational guide for primary healthcare providers. It reviews the management of short-term, mild paediatric pain and fever in the primary care setting, focusing on the comparative efficacy and safety of ibuprofen and paracetamol. This review is sponsored by Reckitt Benckiser Ltd.

## Introduction

Management of pain in children is often suboptimal, as a result of misconceptions that children do not feel pain in the same way as adults do, and for fear of adverse events to analgesic medication.<sup>1-3</sup> However, in most acute childhood presentations associated with pain, analgesia should be used to provide short-term symptomatic relief while the cause of the pain is being investigated and managed.<sup>4</sup> Pain experiences in childhood may shape future pain experiences in adulthood.<sup>5</sup> Paracetamol and ibuprofen are the most appropriate agents for children with mild pain.<sup>4,6,7</sup>

Paracetamol and ibuprofen are also commonly used as antipyretic agents in children with fever, and are often administered by parents/caregivers in an effort to maintain a "normal" body temperature.<sup>8</sup> However, fever is not an illness but a normal physiologic mechanism which aids in fighting infection.<sup>9,10</sup> Antipyretics are indicated only in cases of discomfort associated with fever and not with the sole aim of reducing body temperature.<sup>11</sup> Healthcare professionals must be responsible for counselling parents and caregivers on the appropriate use of antipyretics in children with fever.<sup>8</sup>

## Assessment of pain

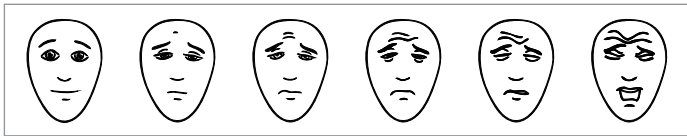
Identifying pain in children involves observing verbal and non-verbal cues, and listening to the parent/caregiver's judgement of pain.<sup>4</sup> Mild pain associated with general illness and injury in childhood can usually be managed in the primary care setting.<sup>4</sup> Referral should be considered if the source of the child's pain cannot be identified, particularly in those under 6 weeks of age.<sup>4</sup>

Self-reporting of pain by the child is the preferred method of assessing the level of pain.<sup>4,12</sup> From the age of 3-4 years, children may be able to provide information on the location of pain and describe characteristics of their pain.<sup>4,12</sup> Pain assessment tools can be considered, but it should be noted these are subjective and may under- or over-estimate pain.<sup>4</sup>

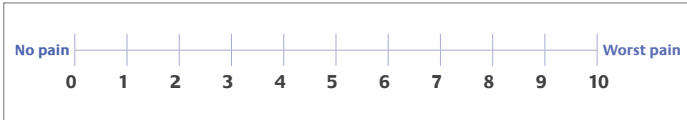
Assessment tools recommended by New Zealand's Starship Hospital Pain Services<sup>13</sup> are the FLACC pain rating scale for children under 3 years of age (see **Figure 1**),<sup>14</sup> The Faces Pain Scale - Revised for children aged 3 years and above (see **Figure 2**),<sup>15</sup> and the Visual Analogue/Numerical Rating scale for children aged 5 years and over (see **Figure 3**).<sup>13</sup> The Revised FLACC scale can be used for children with a developmental disability.<sup>16</sup>

	0	1	2
<b>Face</b>	No expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
<b>Legs</b>	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
<b>Activity</b>	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arches, rigid, or jerking
<b>Cry</b>	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
<b>Consolability</b>	Content, relaxed	Reassured by occasional touching, hugging, or "talking to", can be distracted	Difficult to console or comfort

**Figure 1.** The FLACC pain rating scale.<sup>14</sup> The child should be observed for 1-2 minutes and a score allocated for each category, with an overall score between 0-10.



**Figure 2.** The Faces Pain Scale – Revised.<sup>15</sup> The child is asked to point to the face showing how much they hurt. The face can then be scored as 0, 2, 4, 6, 8, 10, counting left to right.



**Figure 3.** Visual analogue/numerical rating scale.<sup>13</sup> The child is asked to rate their pain, from 0 being no pain to 10 being the worst pain imaginable.

## Management of pain

Multi-modal therapy that includes non-pharmacological techniques should be included in the management of children with pain.<sup>4</sup> These strategies include distraction and comfort by the parents/caregivers, education about the illness/injury, and cognitive behavioural strategies.<sup>4</sup> Rest, ice, compression and elevation (RICE), and techniques to stabilise an injury, will also reduce pain.<sup>4</sup>

Analgesics should be used to provide short-term symptomatic relief of pain, while the cause is being investigated and managed.<sup>4</sup> There are no specific international guidelines on short-term management of pain in children with over-the-counter analgesics, however there are several guidelines for pain management in a hospital setting, as well as indication-specific guidelines.<sup>17</sup> Paracetamol and ibuprofen are the medicines of choice in children with mild pain.<sup>4,6,7</sup> Diclofenac sodium 12.5 mg and 25 mg preparations are approved for use in children aged over 1 year, but are rarely used for analgesia in the primary care setting.<sup>4,18</sup> Furthermore, aspirin is contraindicated in children aged less than 16 years.<sup>19</sup>

Healthcare providers should discuss ongoing pain management with the child and their parents.<sup>4</sup> This should include instruction on ongoing assessment of pain, advice on when to stop pain relief, and when to seek further help.<sup>4</sup> If paracetamol or ibuprofen are insufficient to control pain, referral to secondary care is appropriate.<sup>4</sup>

If pain is constantly present, analgesics should be administered on a regular schedule, as this results in more predictable and consistent levels of analgesia.<sup>4,20</sup> In children with intermittent or unpredictable pain, for example due to otitis media, giving analgesia on an as-required basis is more appropriate.<sup>4,20</sup>

Combining or alternating paracetamol and ibuprofen is not routinely recommended for the treatment of pain in children.<sup>4,21</sup> However, short-term use of alternating doses of paracetamol and ibuprofen may be considered if the child has unmanaged pain despite optimal monotherapy.<sup>4,21</sup>

The relative analgesic efficacy of paracetamol and ibuprofen depends on the underlying cause of the pain. Ibuprofen is considered more effective for the treatment of inflammatory pain.<sup>3,22,23</sup> Comparative studies assessing the use of ibuprofen and paracetamol in common pain conditions are discussed below.

## Musculoskeletal pain

*In primary care, ibuprofen should be the first-line treatment for management of acute musculoskeletal pain.<sup>3,24</sup> Evidence suggests it provides more effective relief than paracetamol or codeine in this setting.<sup>25,26</sup>*

A randomised controlled trial compared the efficacy of a single oral dose of paracetamol 15 mg/kg, ibuprofen 10 mg/kg and codeine 1 mg/kg, in 336 children aged 6-17 years presenting to the emergency department for acute musculoskeletal injury which had occurred in the preceding 48 hours.<sup>25</sup> Children who received ibuprofen had a significantly greater improvement in pain score at 60 minutes compared with those who received paracetamol or codeine (mean decrease 24 mm vs 12 mm and 11 mm, respectively).<sup>25</sup>

Another randomised trial of 336 children discharged from the emergency department after acute arm fracture showed that the proportion of treatment failures was nonsignificantly lower with ibuprofen 10 mg/kg compared with paracetamol + codeine 1 mg/kg (20.3% vs 31.0%, respectively).<sup>26</sup> However, the proportion of children who had any function affected by pain (play, sleep, eating, school) was significantly lower in the ibuprofen group.<sup>26</sup>

## Otitis media, tonsillitis and pharyngitis

*Overall, studies indicate the efficacies of ibuprofen and paracetamol for the treatment of pain associated with otitis media, tonsillitis and pharyngitis are similar.<sup>27-29</sup>*

In a randomised controlled trial, children aged 1-6 years with otoscopically proven acute otitis media received ibuprofen 10 mg/kg, paracetamol or placebo three times daily for 48 hours.<sup>27</sup> At treatment end, 7%, 10% and 25% of children treated with ibuprofen, paracetamol and placebo, respectively, still had pain.<sup>27</sup> Relief of pain was significantly better with ibuprofen vs placebo, but not with paracetamol vs placebo.<sup>27</sup>

A recent Cochrane systematic review of randomised controlled trials comparing ibuprofen and paracetamol for short-term pain relief in children with acute otitis media concluded that both agents were effective, and that there was insufficient evidence for a difference between the two agents.<sup>28</sup>

Likewise, ibuprofen and paracetamol were found to be equally effective for the treatment of symptoms of tonsillitis and pharyngitis, in a randomised controlled trial in children.<sup>29</sup> In cases with a greater inflammatory component, such as exudative pharyngotonsillitis or when there is associated lymphadenitis, ibuprofen should be preferred due to its anti-inflammatory properties.<sup>3</sup>

## Migraine

*Practice guidelines from the American Academy of Neurology and the American Headache Society state that clinicians should prescribe ibuprofen 10 mg/kg as an initial treatment option to reduce pain in children and adolescents with migraine.<sup>30</sup>*

The practice guidelines also note that acute migraine treatments are more likely to be effective when used earlier in the migraine attack, when pain is still mild.<sup>30</sup> Paracetamol has not been shown to be effective for acute migraine in children.<sup>31</sup>

In a randomised, crossover study of 88 children aged 4-16 years with migraine, three attacks per child were treated with single doses of ibuprofen 10 mg/kg, paracetamol 15 mg/kg and placebo.<sup>32</sup> Ibuprofen was twice as likely as paracetamol to abort migraine within 2 hours.<sup>32</sup>

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## Dental procedures

*Studies indicate the ibuprofen may provide more effective relief of pain associated with dental procedures than paracetamol.<sup>33,34</sup>*

In a randomised controlled noninferiority trial of 159 children aged 12-16 years undergoing orthodontic separator placement, ibuprofen 400mg or paracetamol 1g was given 1 hour before and 6 hours after separator placement.<sup>33</sup> Mean pain score from 2 hours after separation until bedtime was higher in the paracetamol group, with 95% confidence intervals suggesting superiority of ibuprofen.<sup>33</sup> From day 1 onwards, children who received ibuprofen experienced less pain at most time intervals compared with those who received paracetamol.<sup>33</sup>

An earlier randomised controlled trial compared the effectiveness of a single dose of ibuprofen 200mg, paracetamol 240 or 360mg, and paracetamol + codeine 240mg/24mg, administered at home after dental extraction.<sup>34</sup> Ibuprofen, but not paracetamol, provided significant pain relief in 30 minutes compared with placebo.<sup>34</sup> Both agents were effective at 2 hours. The global rating of drug efficacy was statistically superior for ibuprofen.<sup>34</sup>

### EXPERT COMMENTARY

The effective management of procedural and acute pain should **always** be multi-modal and involve more than just medication; the majority of these techniques are simple to apply, do not require specialist training and are low in cost.

The medications of choice, when required, are paracetamol or ibuprofen. Ibuprofen has some evidence to suggest superiority over paracetamol when an inflammatory process is the primary cause of pain and should be the first option early in migraine management.

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## Assessment of fever

Guidelines from the UK National Institute for Health and Care Excellence (NICE) include a “traffic light” system for identifying risk of serious illness in children with fever (see **Figure 4**).<sup>35</sup>

	Green - low risk	Amber - intermediate risk	Red - high risk
<b>Colour (of skin, lips or tongue)</b>	<ul style="list-style-type: none"> <li>Normal colour</li> </ul>	<ul style="list-style-type: none"> <li>Pallor reported by parent/carer</li> </ul>	<ul style="list-style-type: none"> <li>Pale/mottled/ashen/ blue</li> </ul>
<b>Activity</b>	<ul style="list-style-type: none"> <li>Responds normally to social cues</li> <li>Content/smiles</li> <li>Stays awake or awakens quickly</li> <li>Strong normal cry/not crying</li> </ul>	<ul style="list-style-type: none"> <li>Not responding normally to social cues</li> <li>No smile</li> <li>Wakes only with prolonged stimulation</li> <li>Decreased activity</li> </ul>	<ul style="list-style-type: none"> <li>No response to social cues</li> <li>Appears ill to a healthcare professional</li> <li>Does not wake or if roused does not stay awake</li> <li>Weak, high-pitched or continuous cry</li> </ul>
<b>Respiratory</b>		<ul style="list-style-type: none"> <li>Nasal flaring</li> <li>Tachypnoea:                             <ul style="list-style-type: none"> <li>RR &gt;50 breaths/ minute, age 6–12 months</li> <li>RR &gt;40 breaths/ minute, age &gt;12 months</li> </ul> </li> <li>Oxygen saturation ≤95% in air</li> <li>Crackles in the chest</li> </ul>	<ul style="list-style-type: none"> <li>Grunting</li> <li>Tachypnoea: RR &gt;60 breaths/minute</li> <li>Moderate or severe chest indrawing</li> </ul>
<b>Circulation and hydration</b>	<ul style="list-style-type: none"> <li>Normal skin and eyes</li> <li>Moist mucous membranes</li> </ul>	<ul style="list-style-type: none"> <li>Tachycardia:                             <ul style="list-style-type: none"> <li>&gt;160 beats/minute, age &lt;12 months</li> <li>&gt;150 beats/minute, age 12–24 months</li> <li>&gt;140 beats/minute, age 2–5 years</li> </ul> </li> <li>CRT ≥3 seconds</li> <li>Dry mucous membranes</li> <li>Poor feeding in infants</li> <li>Reduced urine output</li> </ul>	<ul style="list-style-type: none"> <li>Reduced skin turgor</li> </ul>
<b>Other</b>	<ul style="list-style-type: none"> <li>None of the amber or red symptoms or signs</li> </ul>	<ul style="list-style-type: none"> <li>Age 3–6 months, temperature ≥39°C</li> <li>Fever for ≥5 days</li> <li>Rigors</li> <li>Swelling of a limb or joint</li> <li>Non-weight bearing limb/not using an extremity</li> </ul>	<ul style="list-style-type: none"> <li>Age &lt;3 months, temperature ≥38°C*</li> <li>Non-blanching rash</li> <li>Bulging fontanelle</li> <li>Neck stiffness</li> <li>Status epilepticus</li> <li>Focal neurological signs</li> <li>Focal seizures</li> </ul>

CRT: capillary refill time; PR: respiratory rate  
\* Some vaccinations have been found to induce fever in children aged under 3 months

**Figure 4.** Traffic light system for identifying risk of serious illness in children with fever.<sup>35</sup>

Children whose symptoms or combination of symptoms suggest an immediate life-threatening illness should be referred immediately for emergency medical care, usually by ambulance.<sup>35</sup>

Children with any “red” features but who are not considered to have an immediately life-threatening illness should be referred urgently to the care of the paediatric specialist.<sup>35</sup>

For children with “amber” features in whom no diagnosis has been reached, parents or caregivers should be provided with a “safety net”, or referred to specialist paediatric care for further assessment.<sup>35</sup> The safety net should include one or more of the following:

- Verbal and/or written information on warning systems and how further healthcare can be accessed
- Arranging further follow-up at a specified time and place
- Liaising with other healthcare professionals, including out-of-hours providers, to ensure direct access for the child if further assessment is required.<sup>35</sup>

Children with “green” features only can be cared for at home with appropriate advice for parents and caregivers, including advice on when to seek further attention from healthcare services.<sup>35</sup>



## Management of fever

A review of international clinical practice guidelines for management of fever in children found the following messages were common to all guidelines:<sup>11</sup>

- Antipyretics are indicated only in cases of discomfort associated with fever and not with the sole aim of reducing body temperature
- Recommended antipyretic agents are ibuprofen and paracetamol
- The use of antipyretics does not prevent either febrile convulsions or reactions to vaccines
- Tepid sponging and alcoholic baths are not recommended for the treatment of fever
- The use of cough and cold medicine is discouraged because of the risk of overdoses and interactions.<sup>11</sup>

The alternate use of two antipyretic agents is discouraged by most of the guidelines, while NICE guidelines permit alternate use only if the discomfort persists after the administration of one antipyretic.<sup>11,35</sup> Combination use of ibuprofen and paracetamol is generally not recommended.<sup>11</sup>

NICE guidelines state that antipyretic agents should be continued for only as long as the child appears distressed.<sup>35</sup>

## Choice of antipyretic agent

*Studies show that ibuprofen appears to have both a more rapid onset and a longer duration of action compared with paracetamol, and that it provides more effective relief of fever-associated discomfort, particularly in the first 24 hours of the child's illness.*<sup>36,37</sup>

In the randomised, double-blind PITCH study involving 156 children receiving treatment at home for fever, ibuprofen was associated with faster fever clearance and longer time without fever in the first 24 hours compared with paracetamol.<sup>38</sup> Furthermore, a greater number of children treated with ibuprofen vs paracetamol had no discomfort at 24 hours (69% vs 44%, respectively).<sup>38</sup> The PITCH study findings are consistent with an earlier study, which also reported higher comfort (assessed using scores of general behaviour and degree of relief) in patients treated with ibuprofen vs paracetamol.<sup>39</sup>

Reduction in fever with ibuprofen starts to take effect from 15 minutes after dosing, with a single dose lasting for up to 8 hours, significantly longer than paracetamol.<sup>40,41</sup> Several meta-analyses have confirmed the overall superiority of ibuprofen compared with paracetamol for controlling temperature in children.<sup>42-44</sup>

Rapid symptom relief is an important consideration in children; those who are comfortable are more likely to maintain adequate hydration and nutrition.<sup>36</sup> Furthermore, the longer duration of action with ibuprofen compared with paracetamol may improve sleep patterns.<sup>45</sup>

## EXPERT COMMENTARY

Fever is a sign requiring wider assessment for the cause in children. This is particularly important in the infant <6 weeks of age where a temperature >38°C carries a 15% risk of bacterial infection and the possibility of rapidly progressive disease, and in the child 6 weeks to 3 months of age where a temperature >38.9°C carries a 6% risk. The use of an antipyretic should be limited to children experiencing fever-related distress and, regardless of agent, should only be used for a short duration. The choice of agent, paracetamol or ibuprofen, is generally one of personal preference when effectiveness and the potential for adverse effects are taken into account.

## Safety of ibuprofen and paracetamol

Meta-analyses have confirmed that the risks of adverse events with both ibuprofen and paracetamol are low, when used in children for the short-term relief of pain and/or discomfort associated with fever.<sup>46-48</sup> Adverse events of specific interest, including gastrointestinal (GI) events, asthma, renal injury, hepatotoxicity, and immune response to vaccination, are immune response to vaccination, are discussed in more detail below.

### Gastrointestinal events

*Large clinical trials have indicated that the GI safety profile of ibuprofen and paracetamol in children is similar.<sup>49,50</sup> However, ibuprofen should be avoided in children with active GI ulceration or bleeding, and in children with a history of these disorders.<sup>51</sup>*

In the Boston University Fever Study, a randomised controlled trial involving 84,192 children with fever, the risk of GI bleeding with ibuprofen 5 or 10 mg/kg was not significantly different from the risk with paracetamol 12 mg/kg.<sup>49</sup> The four cases of GI bleeding with ibuprofen reported in this study all occurred in patients who had received previous treatment with ibuprofen, and all were managed conservatively with no endoscopy required.<sup>49</sup>

In the observational Children's Analgesic Medicine Project, 30,144 children with fever and/or pain were assigned to receive ibuprofen or paracetamol.<sup>50</sup> The incidence of any GI adverse event with ibuprofen was similar to the incidence with paracetamol in those aged <2 years, but higher in those aged ≥2 to <12 years.<sup>50</sup> Differences were not considered clinically relevant, and the authors noted that a disproportionate use of ibuprofen in sicker children may have led to a higher incidence of GI adverse events in the ibuprofen group.<sup>50</sup>

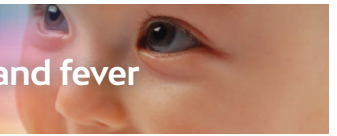
A retrospective cohort study of 180,333 infants who received a prescription for an antipyretic within the first 6 months of life found a higher risk of any GI adverse event and a moderate or severe GI adverse event in those prescribed ibuprofen with or without paracetamol, compared with those prescribed paracetamol alone.<sup>52</sup> However, it is important to note that only a small proportion of infants (n=1724) received a prescription for ibuprofen but never paracetamol during the study period.<sup>52</sup>

In a prospective, case-control study of 2416 children admitted to hospital via emergency departments, the risk of upper GI complications with ibuprofen was not significantly different from the risk with paracetamol.<sup>53</sup> However, a retrospective survey of 177 children hospitalised for upper GI bleeding found a higher risk with ibuprofen exposure compared with aspirin.<sup>54</sup> This study had several limitations, including a limited dataset and the possibility of recall bias.<sup>54</sup>

### Asthma

*Evidence suggests that the risk of developing wheezing or asthma following use of ibuprofen or paracetamol is low.<sup>55-57</sup> In infants and children with pre-existing asthma, ibuprofen carries a small risk of bronchospasm.<sup>59</sup> However, the risk of asthma exacerbations with ibuprofen is similar to, if not smaller than, the risk with paracetamol.<sup>60,61</sup>*

A retrospective cohort study of 1490 children found that higher intake of paracetamol or ibuprofen during the first year of life was associated with an increased risk of current asthma at 3-5 years of age in unadjusted models.<sup>55</sup> However, after adjustment for respiratory tract infections, the risk was null with paracetamol and attenuated with ibuprofen.<sup>55</sup> In children 7-10 years of age, some suggestion of increased risk with paracetamol exposure remained after adjustment for respiratory tract infections, but was null with ibuprofen.<sup>55</sup> This study highlights the importance of controlling for confounding factors in studies of antipyretics and asthma.<sup>55</sup>



A cross-sectional study of 347 children with fever aged 6 months to 6 years found that use of paracetamol was not associated with a higher rate of wheezing, and that ibuprofen was associated with a lower risk of wheezing.<sup>56</sup>

In the previously-mentioned Boston University Fever Study, the rate of physician visits for asthma was significantly lower in children who received ibuprofen vs paracetamol. There was no difference in the rate of hospital admissions for asthma between treatment groups.<sup>57</sup>

The ongoing Paracetamol or Ibuprofen in the Primary Prevention of Asthma in Tamariki trial is assessing the prevalence of asthma in New Zealand children given paracetamol or ibuprofen in the first year of life. The randomised trial aims to assign 3922 infants to paracetamol 15 mg/kg every 4 hours (every 6 hours for those aged <1 month) or ibuprofen 10 mg/kg (5 mg/kg for those aged ≤3 months) every 6 hours, on an as-required basis for fever and/or pain.<sup>58</sup>

A randomised controlled bronchoprovocation challenge study of 100 children with mild-to-moderate asthma found a small risk of bronchospasm after a single 10 mg/kg dose of ibuprofen, with two children meeting criteria for ibuprofen-sensitive asthma.<sup>59</sup> Neither patient was known to have had any exposure to ibuprofen before the study.<sup>59</sup>

A randomised controlled trial assigned 300 children with mild persistent asthma to receive paracetamol 15 mg/kg or ibuprofen 9.4 mg/kg, every 6 hours when needed for alleviation of fever or pain.<sup>60</sup> Over the 46-week follow-up period, there was no significant difference between groups in the number of asthma exacerbations.<sup>60</sup> There were also no significant differences between groups in the percentage of asthma-control days, use of rescue salbutamol or unscheduled healthcare utilisation for asthma.<sup>60</sup>

A sub-analysis of data from Boston University Fever Study, assessing only children receiving treatment for asthma (n=1879), found that the risks of hospitalisation due to asthma, and outpatient visits, were significantly lower in those who received ibuprofen vs paracetamol.<sup>61</sup>

## Renal injury

*Acute kidney injury is a rare but serious adverse event associated with ibuprofen use.<sup>23</sup> It is usually reversible following withdrawal of treatment.<sup>23</sup> Ibuprofen should not be given to children who are dehydrated or who have severe renal impairment.<sup>37,51</sup>*

The Boston University Fever Study and the Children's Analgesic Project, which included 55,785 and 20,111 children treated with ibuprofen, respectively, found no incidences of acute renal failure.<sup>49,50</sup> A randomised controlled trial of 285 children with fever treated with ibuprofen or paracetamol found that the risk of less severe renal impairment was small and was not different between treatment groups.<sup>62</sup>

However, case reports of reversible renal insufficiency in children with fever treated with ibuprofen have been reported, largely associated with dehydration.<sup>63-65</sup>

In a prospective study of 105 children with acute gastroenteritis, 46 children developed acute kidney injury, including 54% of those treated with ibuprofen.<sup>66</sup> After adjusting for the degree of dehydration, ibuprofen exposure was independently associated with acute renal injury.<sup>66</sup> A retrospective analysis of clinical records of 1015 children with acute renal injury found that 1.8% of cases were associated with ibuprofen use.<sup>67</sup> However, the majority of these children had dehydration upon presentation.<sup>67</sup>

## Hepatotoxicity

*Paracetamol overdose secondary to medication errors is the leading cause of paediatric acute liver failure in New Zealand.<sup>68,69</sup> Paracetamol should be avoided in children with severe liver impairment.<sup>70</sup>*

Adverse events with paracetamol are relatively uncommon when used at recommended doses.<sup>71</sup> However, cases of hepatotoxicity in children have been attributed to cumulative toxicity from multiple supratherapeutic doses of paracetamol or frequent administration of appropriate single doses at intervals less than 4 hours, resulting in doses of more than 90 mg/kg per day for several days.<sup>72,73</sup> Amongst 14 cases of paediatric acute liver failure attributed to paracetamol in New Zealand and Australia, the majority were the result of medication errors. Some of the reasons for paracetamol toxicity were coadministration of other medicines containing paracetamol, or administration of regular paracetamol for up to 24 days. Three children required a liver transplant and two died, one before transplant and one after transplant.<sup>69</sup>

Children susceptible to toxicity are more likely to be less than 2 years of age, have been taking at least 90 mg/kg/day for more than 1 day, and are acutely malnourished and dehydrated as a consequence of vomiting, diarrhoea or decreased fluid and nutrient intake.<sup>74</sup> Children with a family history of hepatic toxicity to paracetamol have an increased risk of developing a toxic reaction themselves.<sup>37</sup>

## Immune response to vaccination

*Paracetamol and ibuprofen may reduce immune response to routine paediatric vaccines, when administered around the time of immunisation.<sup>75,76</sup> They are therefore not recommended for the prophylactic management of fever, discomfort or pain associated with National Immunisation Schedule vaccines.<sup>77</sup>*

A randomised controlled trial of 459 infants found significantly lower antibody concentrations in those given 3 prophylactic paracetamol doses within 24 hours of administration of routine childhood vaccines, compared with those who received no paracetamol.<sup>75</sup> In a more recent study, 908 infants were randomised to receive paracetamol, ibuprofen or neither antipyretic, starting at the time of routine infant vaccination or 6-8 hours afterwards.<sup>76</sup> Vaccine immune response was affected by both paracetamol and ibuprofen, with effects varying depending on the type of vaccine, antipyretic agent and time of administration.<sup>76</sup> However, the clinical significance of reduced immune responses to vaccination remains unclear.<sup>78</sup>

While the Immunisation Advisory Centre does not recommend prophylactic antipyretic use for routine childhood vaccines, paracetamol is recommended where there is a clinical indication, such as discomfort associated with fever, or pain following immunisation.<sup>77</sup>

Prophylactic paracetamol does not affect immunogenicity of the meningococcal group B vaccine 4CMenB,<sup>79</sup> and prophylactic use in children aged <2 years is recommended by the Immunisation Advisory Centre to help manage post-4CMenB fever.<sup>80</sup>

Neither paracetamol nor ibuprofen significantly blunted immune response to inactivated influenza vaccine, when administered prophylactically in a randomised, placebo-controlled trial of 142 children.<sup>81</sup>

## EXPERT COMMENTARY

Ibuprofen and paracetamol are over-the-counter medications that enjoy wide use in the community often without primary care oversight. Fortunately, they are at low risk of causing adverse events but not without some risk. In well described populations of children that risk is increased. The prophylactic use of either agent should be actively discouraged for National Immunisation Schedule vaccinations; being relegated to managing distress from fever or pain which has not first responded to simple, non-pharmacological options.



## Dosing and administration of ibuprofen and paracetamol

When administering paracetamol or ibuprofen, it is important to check the strength of the formulation being used.<sup>4</sup> Calculate the dose based on age and an up-to-date measurement of the child's body weight.<sup>4,7</sup> For paracetamol dosing in overweight or obese children, consider using ideal body weight for age to dose.<sup>7</sup>

Due to its narrow therapeutic index, dosing errors are of concern when prescribing paracetamol.<sup>68</sup> Check when paracetamol was last administered, and the cumulative dose over the previous 24 hours, before giving a repeat dose.<sup>70</sup> Ensure the child is not receiving any other medication containing paracetamol.<sup>70</sup> As noted in the section on safety, paracetamol is contraindicated in children with severe liver impairment.<sup>70</sup>

Before giving ibuprofen, check whether the child is receiving any other regular medication, particularly those containing nonsteroidal anti-inflammatories (NSAIDs).<sup>51</sup> Ibuprofen is contraindicated in children with hypersensitivity to aspirin or other NSAIDs, severe heart failure, ischaemic heart disease, active GI ulceration or bleeding or a history of GI ulceration or bleeding, and severe renal impairment.<sup>51</sup>

Starship Child Health Paediatric Analgesia guidelines recommend the following dosing regimens for paracetamol and ibuprofen (see **Table 1**).<sup>7</sup>

Dose calculators are also available online at Health Navigator New Zealand:

- Ibuprofen <https://www.healthnavigator.org.nz/tools/i/ibuprofen-paediatric-dose-calculator/>
- Paracetamol <https://www.healthnavigator.org.nz/tools/p/paracetamol-dose-calculator/>

It should be noted however, that consumer labelling for individual brands of ibuprofen and paracetamol products differ.

### EXPERT COMMENTARY

The dosing and administration of both paracetamol and ibuprofen, like all medications, should be individualised to the needs of the child. Age is a very important aspect in dosing considerations, especially for younger infants. A reasonable “rule of thumb” to highlight to parents is using the lowest dose for the shortest possible duration to get the desired effect, which will further minimise any potential for inadvertent harm.

Medication	Age	Dose	Maximum daily dose
Paracetamol	0-3 months	10 mg/kg, every 6 hours	Do not exceed 60 mg/kg per 24 hours
	Over 3 months	15 mg/kg, 4 times per day	Do not exceed 90 mg/kg per 24 hours or 4 g per 24 hours
Ibuprofen	1-3 months	5 mg/kg, every 6-8 hours	Do not exceed 40 mg/kg/day
	Over 3 months	5-10 mg/kg, every 6-8 hours	Do not exceed 40 mg/kg/day or 1.6 g per 24 hours

**Table 1.** Dosing regimens for paracetamol and ibuprofen recommended in Starship Child Health Paediatric Analgesia guidelines.<sup>7</sup>

## EXPERT CONCLUSIONS

Paracetamol and ibuprofen enjoy widespread use in the community for the management of mild acute pain and fever with the minimum, but not absence, of adverse effects. This commentary provides up-to-date information to enhance judicious and effective prescribing and, in doing so, minimise potential adverse effects. However, use of both medications in the management of mild pain could be reduced without compromising pain relief by the application of simple, non-pharmacological strategies.

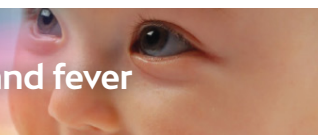
### TAKE-HOME MESSAGES

- Analgesics should be used to provide short-term symptomatic relief of pain in children, while the cause is being investigated and managed<sup>4</sup>
- Antipyretics are indicated only in cases of discomfort associated with fever and not with the sole aim of reducing body temperature<sup>11</sup>
- Paracetamol and ibuprofen are the medicines of choice in children with mild pain and discomfort associated with fever<sup>4,6,7</sup>
- Children should be referred for secondary care if paracetamol or ibuprofen are insufficient to control pain, or if symptoms associated with fever indicate the presence of serious illness<sup>4,35</sup>
- Ibuprofen is considered more effective than paracetamol for the treatment of inflammatory pain<sup>3,22,23</sup>
- Ibuprofen appears to have a more rapid onset of action and longer duration of effect, and provides more effective relief of fever-associated discomfort compared with paracetamol<sup>36,37</sup>
- The risks of adverse events with both ibuprofen and paracetamol are low, when used in children for the short-term relief of pain and/or discomfort associated with fever<sup>46-48</sup>
- Correct dosing of paracetamol and ibuprofen, and consideration of pre-existing conditions, is important to minimise the risk of adverse events with both medicines.<sup>4,68</sup>

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