Antipyretic therapy for children with fever

A Cochrane review finds that giving paracetamol and ibuprofen together or one agent after the other is more effective at eliminating fever in febrile children than either therapy alone.

Overview: Feverish illness is very common in young children, with between 20% and 40% of parents reporting such an illness each year. A child with a temperature of around 38°C or higher is considered to have a fever. In most cases fever is caused by a self-limiting viral infection, but, very rarely, it may also be the presenting feature of serious bacterial infections such as meningitis.

Parents and doctors may use antipyretic drugs – most commonly paracetamol and ibuprofen – to minimise distress in children with fever. Using treatment to reduce distress and improve comfort means the child is more likely to eat and drink, avoiding complications of dehydration and the effects of poor nutrition.

Paracetamol and ibuprofen have different mechanisms of action, which means that they may be more effective when used together than when used alone. One approach is to give both paracetamol and ibuprofen simultaneously (combined therapy); an alternative is to start with one antipyretic and then administer the second medication if the fever does not subside (alternating therapy).

See the NICE Evidence Services topic page on fever in children for a general overview of this condition.

Current advice: The NICE guideline on feverish illness in children recommends using either paracetamol or ibuprofen alone to reduce body temperature in children with fever who appear distressed. Antipyretic agents should not be used with the sole aim of reducing body temperature in children with fever and should be continued only as long as the child appears distressed.

When using paracetamol or ibuprofen in children with fever, consider alternating these agents if the child’s distress is not alleviated or recurs before the next dose is due. The guideline recommends that paracetamol and ibuprofen should not be given simultaneously.

The NICE Pathway on feverish illness in children brings together all related NICE guideline and associated products on the condition in a set of interactive topic-based diagrams.

New evidence: A Cochrane systematic review by Wong et al. (2013) assessed whether combining paracetamol and ibuprofen or alternating the two drugs reduced child discomfort (for example, stress scores, number of doses of medications given and absences from daycare or school) and fever compared with either drug alone in febrile children. The analysis comprised 6 randomised controlled trials (n=915) in children aged 6 months to 14 years with new fever (≥37.8°C) of presumed infectious origin.

Combined paracetamol and ibuprofen reduced mean temperature by more than either single agent at 1 hour (mean difference [MD]=–0.27°C, 95% confidence interval [CI] –0.45 to –0.08°C, p=0.0043; 2
studies, n=163), 4 hours (MD=–0.70°C, 95% CI –1.05 to –0.35°C, p=0.00008; 2 studies, n=173) and 6 hours (MD=–1.30°C, 95% CI –2.01 to –0.59°C, p=0.00032; 1 study, n=40). The proportion of children remaining febrile was significantly lower with combined treatment at 4 hours (risk ratio [RR]=0.08, 95% CI 0.02 to 0.42; 2 studies, n=196) and 6 hours (RR=0.10, 95% CI 0.01 to 0.71; 1 study, n=40). The 1 study (n=156) that assessed child discomfort showed no benefit of combined therapy over a single agent for fever-associated symptoms.

Giving 1 drug followed by another 3–4 hours later had a significantly greater effect on temperature than a single agent at 4 hours (MD=–0.60°C, 95% CI –0.94 to –0.26°C, 0.00046; 2 studies, n=78) and 6 hours (MD=–1.60°C, 95% CI –2.27 to –0.93°C, p<0.00001; 1 study, n=40). The proportion of children still febrile at 6 hours was lower among children given ibuprofen followed by paracetamol than in children given ibuprofen alone (RR=0.25, 95% CI 0.11 to 0.55; 2 trials, n=109). A single study found that child discomfort was lower in children receiving alternating therapy than in those receiving either of the single agents (MD versus paracetamol alone=–2.51, 95% CI –3.08 to –1.94, n=309 participants; MD versus ibuprofen alone=–2.22, 95% CI –2.78 to 1.66, n=310).

One study (n=40) compared giving combined ibuprofen and paracetamol with giving ibuprofen followed by paracetamol 3 hours later. The proportion of infants who were febrile at 1, 4 and 6 hours was very low in both groups and not significantly different.

The authors concluded that both alternating and combined antipyretic therapy may be more effective at reducing temperatures than monotherapy, but that the evidence for how these approaches affect child discomfort is inconclusive. The systematic review was limited by the variation among the included trials in medication dosage, regimens of administration, and frequency and type of assessment and by the small number of patients in the analyses.

**Commentary:** “This is the first published systematic review comparing combined and alternating paracetamol and ibuprofen with single antipyretic treatment to report useful treatment effects (based on 6 trials). Of the 3 previous systematic reviews, Purssell (2011) included a seventh trial and concluded that combined or alternating treatment should not be used because there was no evidence of benefit or harm. Similar conclusions were reached by Nabulsi (2009), who analysed 5 studies, and Pereira et al. (2012), who looked at 4 studies. The NICE guideline on feverish illness in children used the same evidence to conclude that if a child has not responded to a single antipyretic agent, alternating agents can be given, but not simultaneously.

“This evidence is unlikely to change UK clinical practice, because many clinicians are already advising, and many parents already using, alternating antipyretics. Theoretical safety concerns have not manifested, so it is appropriate that parents are encouraged to give sufficient antipyretics to relieve distress. The most likely problem is that a parent may inadvertently give too much medicine as a result of confusing which medicine was given and when – especially if he or she is caring for more than one unwell child. This risk can be mitigated by advising parents to record the medicine dosing times (and to which child medicine was given).

“There could be potential cost savings from using combined or alternating antipyretics, largely through enabling parents to improve the relief of distressing symptoms for unwell children at home. The economic evaluation of paracetamol plus ibuprofen for the treatment of fever in children (PITCH) randomised controlled trial (Hollinghurst et al. 2008) showed that the use of 2 medicines was no more expensive to the NHS or families, because the additional medicine costs were offset by reduced need to consult GPs.” – **Professor Alastair D Hay, GP, NIHR Research Professor and Professor of Primary Care, University of Bristol**

**Study sponsorship:** Alberta Children’s Hospital Foundation, Canada.
About this article: This article appeared in the July 2014 issue of the Eyes on Evidence e-bulletin. This free monthly e-bulletin from NICE Evidence outlines interesting new evidence and what it means for current practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

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