Does the Use of Antipyretics in Children Who Have Acute Infections Prolong Febrile Illness? A Systematic Review and Meta-Analysis

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Objective To review the literature and test the hypothesis that the use of antipyretic drugs in children with acute infections slows recovery.

Study design A systematic review and meta-analysis of the literature was undertaken to investigate the effect of antipyretic drugs upon recovery from infectious diseases in children. A search of Medline (1946 until November 2012) and EMBASE (1980 until November 1, 2012) was undertaken to identify studies in which the authors compared the use of antipyretic medications with nonpharmacologic treatments for fever.

Results Six papers were identified, 5 of which were included in the meta-analysis. Three studies focused on children with malaria and the other 3 considered general viral and respiratory infections and varicella. The pooled mean difference in time to fever clearance was 4.16 hours and was faster in those receiving antipyretics compared with those not (95% CI −6.35 to −1.96 hours; P = .0002). There was little evidence of statistical heterogeneity (χ^2 4.84; 4 df; P = .3; I^2 17%).

Conclusion There is no evidence from these studies that the use of antipyretics slows the resolution of fever in children. *(J Pediatr 2013;163:822-7)*.

Fever is an important part of the inflammatory response to infection and a number of other bodily insults arising from the action of prostaglandin E_2 (PGE_2) on cells of the anterior hypothalamus leading to physiological and behavioral changes that result in increased temperature. This process begins with the release of arachidonic acid from cellular lipid membranes by phospholipase A_2 and its subsequent conversion first to prostaglandin G_2, and prostaglandin H_2, by the cyclooxygenase (COX) enzymescy COX-1 and COX-2, and then finally to a range of prostaglandins, including PGE_2 by prostaglandin E synthase.[1]

In endothelial cells COX-2 is induced by a number of cytokines, including interleukin (IL)-1α, IL-1β, IL-6, IL-8, tumor necrosis factor-α, interferon-γ, and lipopolysaccharide,[2] and both COX-2 and prostaglandin E synthase expression are induced by IL-1β, suggesting possible coregulation[1] and a possible role for fever in the immune response. The possibility of a beneficial role for fever also is suggested by data from animal studies showing that fever is associated with an increase in survival,[3,4] potentiates some immunologic responses in vivo,[5] and is an evolutionarily conserved trait.[6] However, there may be circumstances under which it is less beneficial, for example, if the resultant increased energy requirements are unable to be met,[6] and it is not clear if all the observed benefits were the result of increased temperature per se or some other correlated factor, such as antibody response or cytokine expression.

Despite these possible benefits, there is substantial evidence that both parents and professionals worry about fever in children,[7,8] leading to the widespread use of antipyretic drugs, in particular paracetamol (acetaminophen) and ibuprofen. These drugs work by blocking the action of the COX enzymes: ibuprofen is a nonselective COX inhibitor that inhibits COX-1 and COX-2, and even though the action of paracetamol is not so clearly understood, it is thought to have a tissue-specific peripheral and central action, primarily inhibiting COX-2.[9] Nonsteroidal anti-inflammatory drugs (NSAIDs) have been categorized in a number of different ways, mainly according to their COX specificity and kinetics[10]; however, with the exception of aspirin, which is not recommended for use in children, such differences probably are too small to be of clinical significance.

The popularity of antipyretic drugs is not problematic as long as they do not cause morbidity such as toxicity or slowed recovery. Indeed, in the absence of these negative outcomes, they may be helpful in reducing parental anxiety that may in turn be transmitted to the child.[11] In this meta-analysis, we examined the effect of antipyretic use by testing the hypothesis that the use of antipyretic drugs in children with acute infections slows their recovery.

COX	Cyclooxygenase
IL	Interleukin
NSAID	Nonsteroidal anti-inflammatory drug
PGE_2	Prostaglandin E_2
RCT	Randomized controlled trial

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E.P. has spoken at educational and scientific meetings sponsored by Abbott and Berlin-Chemi. A.W. declares no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2013.03.069

Methods

The primary outcome measure was time to fever resolution as defined by study authors, and secondary outcomes were infection-specific indications of disease resolution. The primary outcome measure was chosen because it is a commonly measured metric across studies with different infections, it can be seen as a surrogate for infection, and it is a symptom of importance for parents. Studies eligible for inclusion were randomized or quasirandomized controlled trials in which the authors compared any commonly used antipyretic drug with no antipyretic drug, with a measureable outcome of time to recovery. Medline was searched from 1946 until week 1, November 2012 and EMBASE from 1980 until week 46, 2012 with the following search terms for the population, intervention, and outcome, respectively, each of which were searched as a freetext and MeSH term (ie, Medical Subject Headings; where applicable): child, children; temperature, fever, acetaminophen, antipyretic, ibuprofen, NSAID, paracetamol, antibodies; and behavioral symptoms or symptoms, fever clearance, healing, recovery. A randomized controlled trial (RCT) filter was applied. Reference lists of the papers identified and Google Scholar were subsequently searched by hand. Papers were screened and selected by the 2 authors independently.

Data comparing the summary measure (mean time to fever clearance in the antipyretic and placebo groups) were extracted and checked for reliability of extraction by both authors. Means and SDs were entered into RevMan 5.1 (The Cochrane Collaboration, Oxford, United Kingdom)[12] and were combined by the use of the random effects mode to provide the summary pooled effect and heterogeneity statistics. Study bias was assessed with the Cochrane Risk of Bias Tool contained within RevMan 5.1.

Results

The database search identified a total of 110 papers (**Figure 1**). The hand search resulted in one additional paper being identified, which was excluded because the authors used aspirin as the antipyretic intervention.[13] Both researchers identified the same 6 papers of interest from the search; one

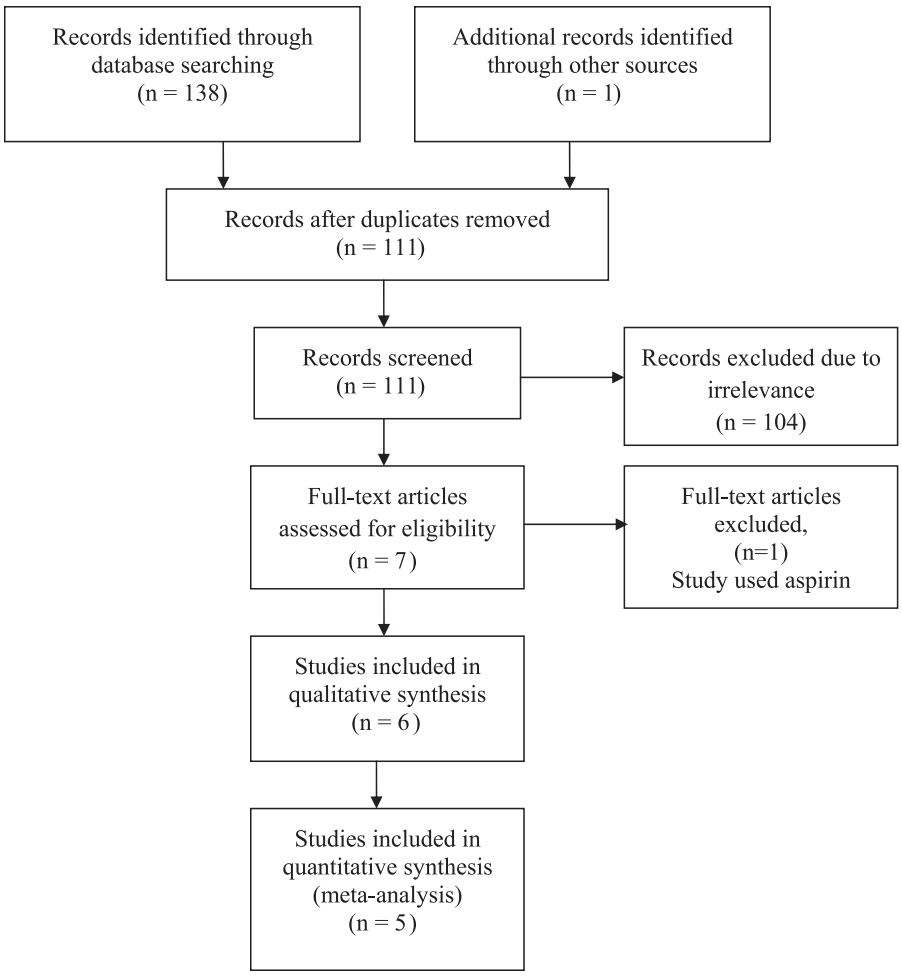

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) flowchart.