



EDITORIAL

Antipyretic use in children: more than just temperature^{☆,☆☆}

Uso de antipiréticos em crianças: mais do que apenas temperatura

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One of the most remarkable facts about the treatment of febrile illness in children is that, despite its ubiquity and the plethora of guidelines, recommendations, and other publications, the exaggerated fear of fever (sometimes referred to as “fever phobia”) remains common around the world, and has remained so for many years.¹ The result of this fear is that parents and professionals worry unduly about fever, and many over-treat febrile children. Some of these interventions at least reduce fever, such as antipyretic drugs; others don’t even achieve this, such as physical cooling. Another manifestation of this fear is the over-use or combination of antipyretic drugs, which is the focus of the study by Pereira et al.²

From a historical context, the fear of fever makes sense, as in the past, and even today in many parts of the world, infectious diseases are a cause not just of morbidity, but also of significant mortality, and even in countries with highly developed health systems children continue to die from undiagnosed serious infections. The important issue for caregivers and professionals alike is to separate the symptom of fever, which is a normal physiological response that poses no danger, from the underlying condition, which in a relatively small number of cases may be a serious illness.

The question of what role fever plays in the recovery from illness is complex. Fever results from the release and conversion of arachidonic acid from cellular lipid membranes into prostaglandin E₂, through the action of

the cyclooxygenase enzymes COX-1 and COX-2. The former, which is constitutively expressed, is thought to be primarily responsible for maintaining homeostasis. The latter, which is induced by a range of cytokines including IL-1 and TNF- α ,³ is mainly responsible for fever and inflammation, a syndrome sometimes referred to as “acute phase response”. It is possible to construct both evolutionary and immunological arguments for the benefit of fever, based on its ubiquity throughout the animal kingdom and the important role of cytokines in the immune response. However, clinical studies have proved to be more difficult to conduct; even when performed, the results were not conclusive, and it is impossible to separate the possible beneficial effect of fever from the other parts of the acute phase response.^{4,5} One study that demonstrated a reduced antibody response to some vaccine antigens in children given prophylactic paracetamol has led many countries to advise against the routine prophylactic use of antipyretics, but such evidence is rare.⁶

Although the benefits of fever are hard to define, what is known is that the symptom and the underlying illness are separate issues, and their clear separation may make the fear of fever itself easier to manage. We can be unequivocal: fever will not harm an otherwise well child, and the highly exaggerated concerns regarding brain damage and death as a result of fever are not warranted. However, as this and other studies show, we are some length from achieving this. One manifestation of this phobia is the co-administration or

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alternation of antipyretic medicines such as paracetamol/acetaminophen and NSAIDs such as ibuprofen/dipyrene, a practice that this study found to be common in Southern Brazil.² As with fever phobia, this practice appears to be widespread throughout the world: a study in the United States showed that 67% of parents reported that they alternated antipyretics, and of these 81% reported being advised to do this by a healthcare professional,⁷ despite the American Academy of Pediatrics stating that there is insufficient evidence to support or refute this practice. The objections to this practice revolve around its unknown safety; a lack of evidence that it improves comfort, which is the primary goal of treatment; the possibility of confusion and consequent inaccurate or overdosing by parents; and the reinforcement of fever phobia.⁸

Although the primary objection may be one of safety, the reality is that despite this being a common practice, there has not been large numbers of reports of side-effects or toxicities resulting from it. While there have been cases reported in the literature of toxicity associated with the combined use of these drugs,⁹ these remain rare. Furthermore, there are also case reports and case-studies of toxicities associated with each drug individually.^{10,11} Meta-analyses and narrative reviews have failed to demonstrate any difference in safety between ibuprofen and paracetamol,^{12,13} or between either drug and combined or alternating treatments,¹⁴ although the studies reviewed were probably underpowered to identify such rare events, and lacked sensitivity due to short follow-up and passive reporting of side-effects.

Overdosing is a possible problem, and one that increases with the more drugs that caregivers provide. Interestingly, in this study, most doses that were given were below the recommended level, which may be one explanation as to why so many parents felt the need to give alternative drugs. Another clue as to the reason for alternating drugs may be the temperature at which caregivers defined fever. The mean temperature considered to be fever by caregivers in this study was only 37.4 °C, which is actually within the normal range for most children,¹⁵ suggesting that at least some healthy children are treated for fever.² As a treatment for fever, if required, there is some scientific rationale for combining these drugs, as they have different modes of action: ibuprofen is a non-selective cyclooxygenase inhibitor, and while the mode of action of paracetamol is not known with certainty, it is thought to act centrally, in a different manner than ibuprofen.¹⁶ However, guidelines emphasize the importance of not using these drugs with the sole aim of reducing temperature, but rather to use them to improve overall comfort.⁸ The problem with interpreting such recommendations is to know exactly what is meant by comfort, especially considering that fever is usually just one part of a complex acute phase response that includes immunological, physiological, and behavioral responses. Indeed, any apparent improvement from the treatment of fever with drugs that have a broad range of effects, including anti-inflammatory and analgesic actions, may be the result of these rather than, or in addition to, their effect on temperature.

However, use of antipyretics, either alone or in combination may have other benefits. Parents of sick

children often feel that they have a responsibility to protect their children from being harmed by the illness, a need that has two aspects: the first is the threat posed by the illness; and the second is their sense of personal control in a situation where realistically they often have no control.¹⁷ By enabling parents to give medicines which they perceive as providing benefit, this might give them a sense of control, reducing their anxiety, and so perhaps also reducing anxiety in their children and their use of healthcare facilities.¹⁸ This may be linked to real improvements, but there may also be benefit in just administering something, whether this benefit is the result of a pharmacological effect caused by an active ingredient; some other property of the medicine, such as its taste; the psychological effect of doing something (the true placebo effect); or indeed just that it coincides with recovery.¹⁹

Although the focus of this study is the use of alternating antipyretics, there is another important detail that should be of concern, which is that 73% of respondents answered that their first action when their child had a temperature was to medicate them.² Illness, with or without fever, does impose a metabolic burden on the child, and so maintaining fluid and nutrition is important. Even more important is ensuring that caregivers and non-pediatric specialists can differentiate between children at low, intermediate, and high risk of serious illness. While there is little evidence that the use of antipyretics either alone or in combination masks these signs and symptoms, the rush to use them as a first action might distract from their identification. It was for this reason that the United Kingdom National Institute for Health and Clinical Excellence (NICE) devised the “traffic light” system of signs and symptoms that are indicative of each category.²⁰ This system, which is in the process of being updated in the light of new research, can be adapted for local use to encourage caregivers to concentrate on those most indicative of serious illness in each case.

Alongside the “traffic light” is the idea of safety net advice. Although not a new idea, the NICE guidelines included specific recommendations that the safety net should include one or more of the following: information on warning symptoms and how further healthcare can be accessed; further follow-up at a specific time and place; and liaison with other healthcare providers to ensure direct access if necessary. The way in which this is provided will differ from place to place, but in many circumstances it would include verbal and written information. The “traffic light” alongside with the safety net advice can be used to encourage caregivers to concentrate upon the important part of febrile illness, which is not the fever itself but what the fever is indicating, and providing appropriate supportive care.

Despite being one of the most common symptoms of illness in childhood, resulting in many consultations with healthcare providers, fever remains surprisingly misunderstood by professionals and caregivers alike. While there are some things about it that are known, there is much that is still to be understood. However, what can be stated quite clearly is that the most important action is the differentiation of those children with serious illness from those without. Following this should be

the issue of supportive care, ensuring that children are receiving sufficient fluids and calories, and that they are comfortable. If it is decided to give antipyretic medication, although not usually necessary, there are at least two safe and effective drugs available in most countries. Even in the absence of evidence of harm, it is never a good idea to encourage polypharmacy, which increases the risk of confusion, interactions with other drugs, and maintains the fear of fever itself.

Conflicts of interest

The author has spoken at educational meetings sponsored by Berlin-Chemie and Abbott on the subject of fever in children. He also co-wrote the NICE Guidelines referred to in the text.

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