Evidence on the use of paracetamol in febrile children

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Abstract Antipyretics, including acetaminophen (paracetamol), are prescribed commonly in children with pyrexia, despite minimal evidence of a clinical benefit. A literature review was performed by searching Medline and the Cochrane databases for research papers on the efficacy of paracetamol in febrile illnesses in children and adverse outcomes related to the use of paracetamol. No studies showed any clear benefit for the use of paracetamol in therapeutic doses in febrile children with viral or bacterial infections or with malaria. Some studies suggested that fever may have a beneficial role in infection, although no definitive prospective studies in children have been done to prove this. The use of paracetamol in therapeutic doses generally is safe, although hepatotoxicity has occurred with recommended dosages in children. In developing countries where malnutrition is common, data on the safety of paracetamol are lacking. The cost of paracetamol for poor families is substantial. No evidence shows that it is beneficial to treat febrile children with paracetamol. Treatment should be given only to children who are in obvious discomfort and those with conditions known to be painful. The role of paracetamol in children with severe malaria or sepsis and in malnourished, febrile children needs to be clarified.

Keywords Acetaminophen/pharmacology; Fever/drug therapy; Child; Virus diseases/drug therapy; Bacterial infections/drug therapy; Malaria, Falciparum/drug therapy; Febrile seizures/drug therapy; Treatment outcome; Review literature; Meta-analysis (*source: MeSH, NLM*).

Mots clés Paracétamol/pharmacologie; Fièvre/chimiothérapie; Enfant; Viroses/chimiothérapie; Infections bactériennes/chimiothérapie; Paludisme plasmodium falciparum/chimiothérapie; Crises convulsives fébriles/chimiothérapie; Evaluation résultats traitement; Revue de la littérature; Méta-analyse (*source: MeSH, INSERM*).

Palabras clave Acetaminofeno/farmacología; Fiebre/quimioterapia; Niño; Virosis/quimioterapia; Infecciones bacterianas/quimioterapia; Paludismo falciparum/quimioterapia; Ataques febriles/quimioterapia; Resultado del tratamiento; Literatura de revisión; Meta-análisis (*fuente: DeCS, BIREME*).

الكلمات المفتاحية: الأسيتأمينوفين، الخصائص الفارماكولوجية للأسيتأمينوفين، الحمى، المعالجة الدوائية للحمى، طفل، مرض فيروسي، المعالجة الدوائية للأمراض الفيروسية، عدوى جرثومية، المعالجة الدوائية للعدوى الجرثومية، الملاريا، المعالجة الدوائية للملاريا المنجلية، اختلاج حراري، المعالجة الدوائية للاختلاج الحراري، نتيجة المعالجة، مراجعة النشريات الطبية، التحليل التلوي (*المصدر: رؤوس الموضوعات الطبية، المكتب الإقليمي لشرق المتوسط*).

Bulletin of the World Health Organization 2003;81:367-372.

Voir page 370 le résumé en français. En la página 371 figura un resumen en español. يمكن الاطلاع على الملخص بالعربية على الصفحة ٣٧١.

Introduction

Fever is a common symptom of childhood illness in both developed and developing countries, and much time and effort is spent on attempts to reduce high temperatures in young children. Although the disease process that leads to fever may be harmful, no convincing evidence shows that fever itself is harmful. Temperatures that exceed the maximum of the normal febrile range (41 °C) are usually caused by heat stroke or brain injury (*1*) and so do not respond to antipyretics (*2*). Some evidence in fact shows that fever may be beneficial in enhancing the host response to infection (*3*). Despite this, many parents and physicians believe that antipyretic treatment improves febrile children's comfort and behaviour. Antipyretics are prescribed commonly, therefore, despite minimal data on their clinical benefit.

Few prospective human studies have documented whether antipyretics have any clinically relevant adverse effects. Some animal studies have shown that fever helps survival during infection, and that antipyresis increases mortality (*4–7*). Growing evidence shows the potential for hepatotoxicity in children given multiple therapeutic or subtherapeutic doses of acetaminophen (paracetamol) (*8–10*). Product information recommends a maximum daily dose of 60 mg/kg, but it is not uncommon for children to receive 90 mg/kg/day in hospital (*11*).

Throughout the world, parents and health professionals routinely treat fever in young children. The current guidelines of WHO on the management of fever recommend the use of paracetamol for children with a fever $\geqslant 39$ °C (*12*). This article aims to summarize existing evidence on the rational use of paracetamol in febrile children, highlight the deficiencies in current knowledge, and make recommendations for further research.

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Ref. No. **02-0166**

Methods

We searched Medline and the Cochrane databases from 1966–2002 with the search term paracetamol in combination with: fever, children, and trial; sepsis; malaria; fever and hospital discharge; febrile convulsion and trial; hepatotoxicity; adverse events and review; fever and parental anxiety; or comfort and trial. The same search was performed with the search term "acetaminophen" exchanged with "paracetamol". The search was limited to those articles that involved children and were in the English language only. As few randomized control trials were identified, other references from these articles were reviewed and other experimental study designs included. A total of 17 studies were identified.

Results

Paracetamol and viral infections

Few reports exist on the potential risks and benefits of giving paracetamol to children with viral infections. A randomized trial of paracetamol (10–15 mg/kg/dose every four hours) versus placebo in 225 febrile children with non-bacterial infections showed there was no significant difference between treated and placebo groups in mean duration of fever or other symptoms (*13*). Parents of children treated with paracetamol rated their children as being slightly more active and alert than those treated with placebo. No significant differences existed, however, in mood, comfort, appetite, or fluid intake. Another randomized trial that compared paracetamol (10 mg/kg/dose four times per day for four days) with placebo in 72 children with varicella infection showed no significant differences in durations of symptoms (itching, activity, or appetite) but a longer time to total crusting of lesions in children who received paracetamol than in those who received placebo (*14*).

Paracetamol and bacterial infections

Limited data exist on the use of paracetamol in sepsis in humans, particularly children. Despite this, antipyretic therapy commonly is administered to patients with bacterial sepsis (*15*). A mixed retrospective and prospective study of 180 hospitalized children (ages not stated) with uncomplicated proven bacterial infections were assessed for the effect of paracetamol treatment on duration of hospital stay (*16*). Patients were divided into six groups of 30 children. Children with pneumococcal pneumonia, staphylococcal cellulitis, or *Haemophilus influenzae* meningitis who received at least two doses of paracetamol were compared with counterparts who received one or no doses of paracetamol. Three of the children received both aspirin and paracetamol, however, and three received only aspirin. No statistically significant difference was seen in duration of hospital stay between any of the clinical groups who received paracetamol and those who did not after adjustments were made for age, temperature on admission, and the number of doses received (*16*). This study, however, only described the number of doses of paracetamol received rather than the actual dose received.

Two retrospective (and therefore non-randomized) studies have been published. Administration of paracetamol (dose not stated) at the time of blood culture was an independent predictor of survival in patients with *Escherichia coli* bacteraemia (*17*) and *Pseudomonas aeruginosa* sepsis (*18*). The use of paracetamol and improvement in survival did not correlate, however, with reductions in core temperature. It should be noted that as these studies are not randomized the effect of paracetamol on survival might only represent a proxy for the ability of the individual to mount an effective response to infection.

Many studies suggest that fever is a beneficial response to bacterial infection. Fever has been reported to be associated with increased survival in patients with spontaneous bacterial peritonitis (*19, 20*) and polymicrobial sepsis (*21*). A prospective study of 748 children with severe pneumonia in Papua New Guinea found mortality rates of 29% in afebrile malnourished children and 12% in febrile malnourished children; no such difference was found in well-nourished children with severe pneumonia (*22*). In three other prospective studies of sepsis, hypothermia was present in about 10% of adults surveyed and was associated with a greater than two-fold higher mortality than the presence of fever (*23, 24*). Several retrospective studies confirmed that human survival after serious infection is reduced in patients with hypothermia or in those who fail to generate a fever (*23–26*).

A common rationale for reducing fever is to prevent tissue injury caused by elevated core temperatures. No published reports, however, show cytotoxicity from temperatures within the febrile range that are associated with infections (*15*). Another rationale for reducing fever is to decrease the metabolic demands associated with the febrile response, which may be important in patients with cardiac or respiratory failure. In one study, 12 critically ill patients with sepsis were treated with paracetamol. Oxygen consumption, carbon dioxide production, and cardiac output were reduced by 18%, 20%, and 23%, respectively (*27*).

Paracetamol and malaria

Fever is a striking clinical feature of malaria. The biological role of fever in malaria is unclear, although some recent evidence shows that it may be beneficial (*28*). Tumour necrosis factor is an important mediator of malarial fever (*29, 30*), and experimental data suggest that both tumour necrosis factor and fever have antiparasitic properties (*31, 32*). Fifty children from Gabon with non-severe *Plasmodium falciparum* malaria were randomized to receive mechanical antipyresis either alone or in combination with paracetamol (10–15 mg/kg/dose per rectum, every four hours while febrile) (*33*). Time to parasitic clearance was significantly longer in the paracetamol group. As no difference was found in the course of fever between the two groups, however, the difference in parasite clearance may not be attributable to fever per se. Levels of tumour necrosis factor (TNF) were reduced in the paracetamol group, whereas concentrations of interleukin (IL-6) were not affected. This suggests that paracetamol has more of an immunomodulatory effect on TNF than on IL-6. As TNF has an important antiparasitic role in malaria, the longer time to parasite clearance in the paracetamol group was postulated to be due to the significantly decreased production of TNF and oxygen radicals in the paracetamol group (*33*).

Vomiting is a major problem in children with malaria, as it interferes with the absorption of antimalarials. Previous studies suggested that febrile patients are more likely to vomit mefloquine, so antipyresis might improve the management of malaria (*34*). A randomized controlled trial on the western border of Thailand in 321 children with non-severe *P. falciparum* malaria assessed the effect of early antipyresis on the proportion of children who vomited (*35*). Children were randomized to receive acetaminophen (15 mg/kg/dose) and

tepid sponging either before or at the same time as mefloquine. Reduction of fever with acetaminophen and tepid sponging before mefloquine was given did not reduce the incidence of early vomiting, which was the same for both groups (*35*).

Paracetamol and febrile convulsions

Many clinicians treat fever with paracetamol to prevent febrile convulsions in susceptible children. Febrile convulsions occur in 4% of children, however, and they are usually self-limiting. Moreover, no evidence shows that antipyretic treatment reduces the risk of febrile convulsions. In a randomized controlled trial, 157 children enrolled after their first febrile convulsion were followed for two years (*36*). Children were assigned to receive either one dose of rectally administered diazepam followed by oral doses three times daily for the first two days if the temperature was >38.5 °C or a placebo. In addition, each subsequent febrile episode was assigned randomly to receive paracetamol or placebo. Neither paracetamol nor diazepam made a difference to the recurrence of convulsions (*36*). This study had 80% power to detect a statistically significant result with the given sample size (*36*). Another controlled trial studied the antipyretic effect of paracetamol in 104 children: one group received regular paracetamol and the other sporadic paracetamol. Prophylactic paracetamol was no more effective than sporadic paracetamol in preventing fever or early recurrence of febrile convulsions (*37*).

Adverse events

Although paracetamol generally is regarded as a very safe antipyretic drug, liver failure is a well-recognized consequence of paracetamol overdose (*9, 10, 38–40*). Recent case reports have suggested that liver failure can be caused by the administration of multiple doses of paracetamol that are only just greater than the recommended maximum dose (*8*). The largest paediatric series of hepatotoxicity secondary to paracetamol reviewed cases reported to the Food and Drug Administration and National Poisons Center in the US over a 15-year period (*9*). This review documented 47 children aged between five weeks and 10 years who developed hepatotoxicity after taking doses of paracetamol ranging between 60 and 420 mg/kg/day. The duration of treatment ranged from one day to six weeks. The mortality rate was high: half the children died (24 deaths), and three survived after they received liver transplants. Six children with hepatotoxicity had received doses of paracetamol within, or only slightly above, the approved dose (⩽100 mg/kg/day) (*9*). The total number of cases in this report was small compared with the total number of children who were treated with paracetamol; however, this study may under-represent the total number of cases of hepatotoxicity, as it is likely that many less severely affected were unreported.

In the same study, children who were febrile and acutely malnourished had an increased risk of paracetamol-induced hepatotoxicity (*41*). This is important, because paracetamol is used in the developing world. There are sound theoretical reasons why malnourished children may be at higher risk. Reductions in caloric or protein intake combined with multiple doses of paracetamol may have profound effects on sulfation, glucuronidation, and glutathione production (*41*). In particular, the presumed depletion of glutathione and impairment of the glucuronidation pathway caused by fasting may also apply to acutely ill children who are not eating. Repeated administration of paracetamol may lead to further reductions in hepatic glutathione, which may impair the biotransformation of paracetamol and cause hepatotoxicity (*9*). The risk of hepatotoxicity is increased if a child is aged under two years and has repeated vomiting, diarrhoea, or poor fluid intake for more that 24 hours, and if paracetamol has been given at a dose ⩾90 mg/kg/day (*9*).

In contrast, a large randomized controlled trial of over 27 000 febrile children compared the risk of serious adverse events between three groups randomized to receive acetaminophen (12 mg/kg/dose) or ibuprofen in one of two doses (5 or 10 mg/kg/dose) (*2*). A median of 6–10 doses was received over three days. The risk of hospitalization for any reason during the four-week follow up period was 1.4%. The risk of hospitalization for secondary study outcomes such as asthma, bronchiolitis, vomiting, or gastritis did not differ significantly between those who received paracetamol or ibuprofen. These data indicate little risk of serious adverse events that require hospitalization among febrile children treated with low doses of paracetamol or ibuprofen (*2*). No cases of hepatotoxicity were reported.

Costs

Fever is an extremely common symptom in children and a frequent reason for attendance at paediatric emergency departments. For poor families, the cost of a bottle of paracetamol is substantial. Repeated febrile episodes in a number of young children within a family may result in considerable expense for an unnecessary medication. Using United Nations Children's Fund (UNICEF) prices, the cost of a dose of paracetamol is US$ 0.50 for 100 ml for a 24 mg/ml preparation (*42*).

In developing countries, prescribing practices may be different. Infants and children may be given a quarter or half of a 100 mg or 500 mg tablet of paracetamol. The UNICEF cost of paracetamol tablets is less than that of syrup (US$ 0.0031 per 100 mg tablet and US$ 0.0061 per 500 mg tablet) (*42*), however over- or under-prescribing becomes a problem. In addition, little accuracy can be assured for a child of any weight when a dose per kilogram of paracetamol is prescribed but only 500-mg tablets of paracetamol are available.

Discussion

Fever is one of the most common symptoms of illness in childhood. The costs associated with the prescribing of paracetamol are not trivial for many families. No studies show any clear benefit for the use of paracetamol in therapeutic doses in febrile children. A Cochrane Review was unable to show a superior antipyretic effect with paracetamol compared with placebo (*43*). Many of the studies in the Cochrane Review used inadequate doses of paracetamol; this review therefore provides inadequate evidence to support the proposition that paracetamol is ineffective treatment for fever. Our literature search was limited to English language articles, and therefore it may have excluded some relevant articles in other languages.

Some studies suggest that fever may have a beneficial role, although no definitive prospective studies in children have been done to prove this. Hyperthermia is known to be harmful if temperatures exceed 41 °C. Temperatures above the usual febrile maximum (>41 °C) are usually caused by heat stroke or brain injury (*1*) and so do not respond to antipyretics (*2*). The paucity of data means it is difficult to make conclusive recommendations on the rational use of paracetamol in febrile

children, particularly those with comorbidities from developing countries.

Reports about the role of cytokines and the possible beneficial or detrimental effects on clinical outcomes are conflicting. Fever is due to the production of endogenous pyrogens, including the cytokines IL-1, IL-6, TNF, interferon-β, interferon-γ, and prostaglandin E2. Exogenous pyrogens, such as microbial products, stimulate macrophages to produce endogenous pyrogens, which results in fever. In vitro and in vivo experiments have raised the possibility of a protective effect of the cytokines IL-1, IL-6, TNF-α, and interferon and therefore the possibility that they enhance resistance to infection. This has been shown in animal models for *Plasmodia* species (*44–46*), *Toxoplasma gondii* (*47*), *Leishmania major* (*48*), *Trypanosoma cruzi* (*49*), and *Cryptosporidium* species (*50*). These studies suggest, therefore, that suppression of fever might be counterproductive. Other reports suggest, however, that for at least some infections, these mediators may have a detrimental effect on clinical outcomes. Emerging evidence from studies on Gram-negative bacterial sepsis shows that these cytokines are mediators of the clinical and humoral manifestations of Gram-negative sepsis (*51–52*) and that detectable levels of IL-1, IL-6, and TNF-α correlated inversely with survival (*53*).

From the limited data available, paracetamol in therapeutic doses seems to offer little benefit for children with viral infections. A prospective, placebo-controlled trial of antipyretic therapy in bacterial sepsis is needed to develop a rational approach to treating fever in these patients. On the basis of available data, we recommend that antipyretics be withheld — at least during the early stages of sepsis. If febrile children have cardiac or respiratory failure, paracetamol may reduce oxygen consumption, carbon dioxide production, and cardiac output (*1*). Recent but limited research suggests the time to parasite clearance in non-severe malaria is longer in children given paracetamol (*33*). Further studies are required, however, to define the role of paracetamol in severe malaria. For otherwise healthy children, the use of paracetamol in therapeutic doses generally is safe, although hepatotoxicity has occurred with recommended dosages in children — often those with comorbidities. Data on the safety of paracetamol is lacking for developing countries in which malnutrition is common. Further research is recommended to determine the safety of paracetamol in this population of sick, malnourished children.

Paracetamol is often given to febrile children to improve patient comfort. There is, however, a lack of well-designed studies to quantify this. In a randomized trial of paracetamol versus placebo in 225 febrile children with non-bacterial infections, children treated with paracetamol were more likely to be rated by their parents as having at least a one-category improvement in activity (38% vs 11%; $P = 0.005$) and alertness (33 vs 12%; $P = 0.036$), but no significant difference was noted in mood, comfort, appetite, or fluid intake (*13*). The lack of any significant improvement in behaviour and comfort with paracetamol was emphasized by the inaccuracy of the parents' "guesses" at the end of the trial as to which agent their child had received: 45% correctly guessed paracetamol and 52% placebo (*13*). Although clinicians have argued that administration of paracetamol can be justified because it improves patient comfort, no trials have adequately documented this benefit.

The relative costs of the benefits of symptomatic relief versus the adverse effect of toxicity or the impact on illness response have not been determined. Some evidence shows that paracetamol may prolong patient discomfort by prolonging the duration of illness. Children with varicella infection who were treated with paracetamol showed a longer time to total crusting of lesions compared with those who received placebo (*14*). This may prolong pruritis. In addition, patients with malaria who were treated with paracetamol had a longer time to parasitic clearance (*33*).

The current WHO recommendations for the management of fever in children include the use of paracetamol for children with fever of $\geqslant 39\ ^{\circ}C$ (*12*). Insufficient data, however, support this recommendation. We recommend that health professionals should not be encouraged to give antipyretics routinely to febrile children. Treatment should only be given to those children in obvious discomfort or those with known painful conditions. The role of paracetamol in children with severe malaria or sepsis and in sick, malnourished, febrile children needs to be clarified further. ■

Conflicts of interest: none declared.

Résumé

Observations concernant l'utilisation du paracétamol chez l'enfant fébrile

Les antipyrétiques, y compris le paracétamol, sont prescrits couramment chez l'enfant pyrétique, malgré le peu d'arguments qui sous-tendent son intérêt clinique. Une mise au point bibliographique a été effectuée en recherchant les articles de recherche dans les bases de données Cochrane et Medline sur l'efficacité du paracétamol dans les affections fébriles pédiatriques et les événements indésirables associés à son utilisation. Aucune étude ne montre d'avantage manifeste du paracétamol à dose thérapeutique chez l'enfant fébrile atteint d'infection virale ou bactérienne ou de paludisme. D'après certaines études, la fièvre semblerait même avoir un effet bénéfique sur l'infection, bien qu'aucune étude prospective définitive n'ait été réalisée chez l'enfant pour tester cette hypothèse. L'utilisation du paracétamol à dose thérapeutique est généralement sans danger ; des manifestations d'hépatoxicité ont toutefois été observées à la posologie pédiatrique recommandée. Dans les pays où la malnutrition est fréquente l'innocuité du paracétamol est mal connue. Pour les familles pauvres, le coût du paracétamol est considérable. Rien n'indique l'intérêt du traitement de l'enfant fébrile par le paracétamol. Ce traitement ne devrait donc être administré qu'à l'enfant manifestement incommodé ou dont l'affection est douloureuse. La place du paracétamol chez l'enfant atteint de paludisme grave ou d'infection ainsi que chez l'enfant mal nourri et fébrile demande à être clarifiée.

Resumen

Evidencia sobre los efectos del paracetamol en los niños febriles

La prescripción de antipiréticos, entre ellos el acetaminofeno (paracetamol), a los niños con pirexia es una práctica común, pese a los pocos datos demostrativos de un beneficio clínico. Se realizó una revisión de la literatura buscando en MEDLINE y en las bases de datos de Cochrane artículos de investigación sobre la eficacia del paracetamol en los niños con enfermedades febriles y sobre las reacciones adversas asociadas a su uso. Ninguno de los estudios revelaba que la administración de dosis terapéuticas de paracetamol a los niños febriles afectados por infecciones virales o bacterianas o con malaria tuviera efectos beneficiosos. Algunos estudios llevan a pensar que la fiebre podría tener una función beneficiosa en las infecciones, pero no se han hecho estudios prospectivos definitivos en niños para probar tal cosa. Las dosis terapéuticas de paracetamol son por lo general seguras, aunque se han dado casos de hepatotoxicidad en niños con las dosis recomendadas. En los países en desarrollo donde la malnutrición es común, faltan datos sobre la seguridad del paracetamol. El costo de este medicamento para las familias pobres es sustancial. No hay ningún dato que indique que el tratamiento de los niños febriles con paracetamol tenga efectos beneficiosos. El fármaco debe administrarse únicamente a los niños con claros síntomas de malestar o con enfermedades reconocidamente dolorosas. Es necesario esclarecer la acción del paracetamol en los niños febriles que padecen malaria grave o septicemia o que están malnutridos.

ملخص

بيّنات حول استخدام الباراسيتامول لدى الأطفال المصابين بالحمى

يشيع وصف خافضات الحرارة والتي يعد الأسيتامينوفين (الباراسيتامول) واحداً منها لدى الأطفال المصابين بالحمى، رغم توافر القليل من المعطيات حول فائدتها السريرية. وقد أجري بحث في النشريات الطبية في قواعد المعطيات Medline وCochrane عن المقالات التي تتناول فعالية الباراسيتامول في الأمراض الحموية لدى الأطفال، والنتائج الضائرة الناجمة عن استخدام الباراسيتامول. ولم تظهر أي دراسة من هذه الدراسات فائدة واضحة لاستخدام الباراسيتامول بجرعات علاجية لدى الأطفال المصابين بالحمى الناجمة عن عدوى بالفيروسات أو بالجراثيم أو بالملاريا. وأشارت بعض الدراسات إلى أن الحمى قد يكون لها دور مفيد عند العدوى، دون أن تتوافر دراسات استباقية على الأطفال تثبت ذلك. إن استعمال الباراسيتامول بجرعات علاجية يتسم بالسلامة، رغم حدوث سمية كبدية قد تنتج عن الجرعات الموصى بها لدى الأطفال. وفي البلدان النامية التي يشيع فيها سوء التغذية، تفتقد المعطيات حول سلامة استخدام الباراسيتامول. وتعد تكاليف شراء الأسر الفقيرة للباراسيتامول باهظة، دون أن يكون هناك أية بينة على فائدته في معالجة الأطفال المصابين بالحمى، وعلى هذا فإن المعالجة ينبغي أن تقتصر على الأطفال الذين يعانون من ضائقة واضحة أو من حالة مؤلمة. إن دور الباراسيتامول في معالجة الأطفال المصابين بملاريا وخيمة أو إنتان وخيم مع سوء تغذية وحمى يحتاج للتوضيح.

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Commentary

Fever and antipyresis

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Whether fever represents a beneficial or harmful response to infection has been debated for hundreds of years. The issue is clouded by a common misunderstanding that fever is the reason an individual with infection feels ill: often once the elevated body temperature abates, the patient feels better. It is assumed therefore that reducing the fever would improve the patient's condition and shorten their illness. From there, it is only a short step to conceive of the fever as the illness itself.

Although this logical fallacy remains attractive to medical personnel and patients, what evidence exists that fever is harmful or beneficial to the course of an infectious illness? At first glance, studies to answer the question seem simple to perform. Unfortunately, however, to investigate the problem directly is virtually impossible, because every method available to reduce fever has secondary metabolic consequences: antipyretics affect the body in many ways, and even physical methods — such as sponging with cold water — result in a wide range of responses, including shivering and stimulation of the adrenal–cortical axis. We thus must seek other lines of evidence — ranging from teleology and comparative zoology through detailed clinical observation of defined cases to molecular biology.

Perhaps the most powerful arguments to support a beneficial effect of fever on infection come from teleology and genetics. Fever is established as a phylogenetically ancient host

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response that is conserved highly in all mammals (*1*). That fever, despite high metabolic and nutritional costs, is conserved so highly argues forcefully for its evolutionary value, as does the endogenous nature of its mechanism, which requires a complex series of steps and interactions. Recent work on the biology of cytokines has enabled the effects of individual components of this response — all of which are beneficial to the host — to be examined. It is reasonable to argue on the basis on the many similarities in the febrile response and its mechanism among different vertebral classes, that fever is an adaptive benefit to the host — despite the fact that it is an energy-expensive phenomenon. Our inability to demonstrate directly the beneficial effects of fever in the intact vertebral host because of the diverse metabolic effects of antipyresis means that this evolutionary evidence is probably the best we have.

Some support for fever comes from comparative biology. Cold-blooded animals such as lizards lack a mechanism to produce fever when they become infected. A "heat-seeking" instinct has been described in these creatures, however; this allows them to raise their body temperature by *external* means: the animals find the warmest spot in the environment and remain there while their body temperature increases in response to the external stimulus. The survival value of such behaviour has been shown clearly in the laboratory.

A question often raised about the evolutionary argument is why fever would be beneficial in mild to moderately severe infections but demonstrably deleterious in fulminant disease (*2*). Such a difference can be explained by the fact that evolution has no interest in the preservation of the individual, only in preserving the species: recovery of many individuals with mild to moderately severe infections is far more important than the survival of the occasional case of fulminant illness.

As Russell et al. point out, it has proved difficult to show an unequivocal effect from reducing fever as part of the treatment of infection. As mentioned, to undertake such studies is a daunting task — because a beneficial effect predictably would be found primarily in mild to moderately severe disease, end-points are impossible to select. Obviously the duration of fever cannot be one endpoint, but what other sign or symptom can be objectively and quantitatively measured in a reproducible manner? Hundreds and probably thousands of patients would have to be enrolled in double-blind, placebo-controlled studies and followed in exquisite detail. This is why so little clinical data are available, and it seems unlikely that more will be obtained. The information summarized by Russell et al., however, does seem to support the conclusion that reducing fever in mild infection can adversely influence the course of at least some illnesses.

On the other hand, good evidence supports the view that the high fevers encountered in septic states are deleterious to the host and that their suppression is helpful in assuring survival (*2*). As pointed out earlier, these instances are comparatively rare, and from an evolutionary perspective all of the affected individuals would have died.

In addition to the probability that antipyretics may prolong the course of mild to moderate infectious illnesses, what other deleterious effects might they have? Russell et al. point out that little is known about the pharmacokinetics of these drugs in poorly or malnourished children. Even in developed countries, all available methods of antipyresis must be treated with respect. Warning labels became required for paracetamol recently and for aspirin in the more distant past. In addition to acute poisoning, the former has been implicated in the development of chronic renal disease, and perhaps liver failure, when repeatedly administered over prolonged periods of time (*3*). Perhaps more important is the fact that antipyretics mask symptoms or signs; children with pneumonia, for example, may not receive a proper diagnosis because their respiratory rate decreases (*4*) or because, when the body temperature starts to fall, the child may be considered to be on the way to recovery and thus needing no further observation. Finally, of course, the costs may consume a significant amount of resources that, in developing countries, could be better devoted to specific diagnosis and therapy.

Other potential benefits of reducing fever are sometimes cited to justify the use of antipyresis. A common assumption is that these drugs make patients feel better, but no clear evidence shows that this is so. Parents and physicians consistently cannot distinguish between the effects of placebo and paracetamol in most circumstances (*5*). Perhaps the exceptions are conditions accompanied by pain, for which the analgesic effects of the medication provide the benefit. When fevers rise above 39.5 °C, a reduction in body temperature is sometimes accompanied by an improvement in subjective symptoms, but this is inconstant, with young children seeming to benefit more than older children (*6*).

The major problem when evaluating the subjective effects of antipyretics is that they have an enormous placebo value — as various studies have shown (*5, 6*). Despite the firm belief in the effects of antipyretics, children do not feel any better, eat better, or become more active after their use than they do after they receive placebo. The argument that the use of antipyretics reduces the occurrence of febrile seizures also is not based on evidence: no studies have shown this to be true. Even in children with previous febrile seizures, the use of antipyretics has not been helpful (*7*). Some physicians believe that the response to antipyretics can be used to differentiate between bacterial and viral infections, with the latter responding more completely and promptly. Numerous studies have shown this to be a fallacy (*8, 9*).

In summary, what does the evidence seem to indicate? Fever represents a universal, ancient, and usually beneficial response to infection, and its suppression under most circumstances has few, if any, demonstrable benefits. On the other hand, some harmful effects have been shown to occur as a result of suppressing fever: in most individuals, these are slight, but when translated to millions of people, they may result in an increase in morbidity and perhaps the occurrence of occasional mortality. It is clear, therefore, that widespread use of antipyretics should not be encouraged either in developing countries or in industrial societies. Unfortunately though, just as fever represents an ancient biological response, an emotional effect is embedded deeply. Through the ages, parents have seen that when fever begins to diminish and disappears, the child feels better and recovers from the illness — whatever it was. Thus, the fever has become synonymous with the illness. This flaw in logic has persisted in parents' and physicians' minds, and they are seduced by the thought that if they "make the fever go away, the patient will be well." No amount of scientific discourse will change this attitude, and antipyresis will continue to be used in children with low-grade fevers, or even no fevers, in the home as well as the hospital. A reasonable evidence-based approach is to discourage the use of antipyretics in fevers <39 °C, reserving them for patients with higher temperatures. ■

Conflicts of interest: none declared.

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