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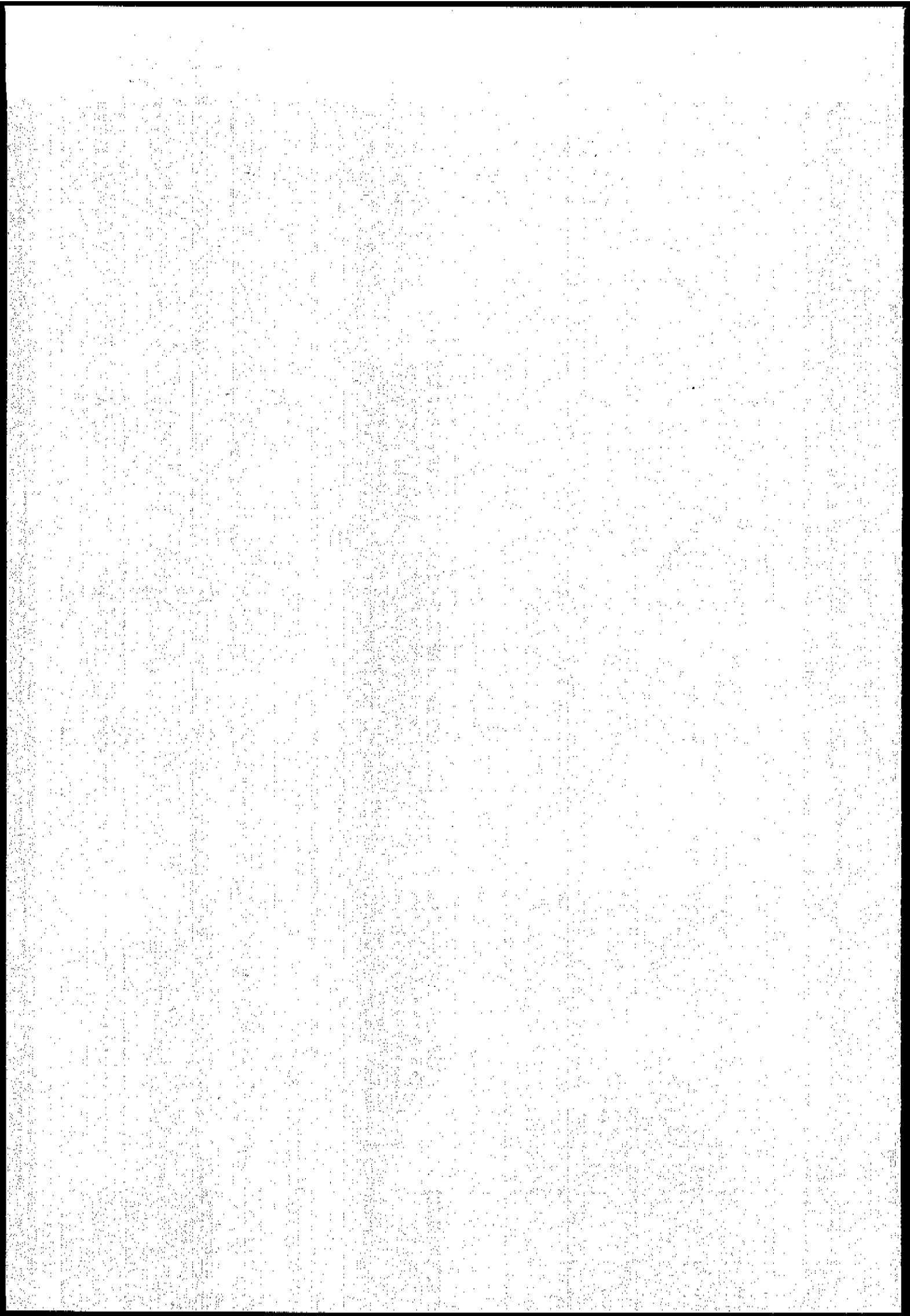
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**The management of
fever in young
children with acute
respiratory infections
in developing
countries**

**Programme for the Control of
Acute Respiratory Infections**

World Health Organization
Geneva





THE MANAGEMENT OF FEVER IN YOUNG CHILDREN WITH ACUTE RESPIRATORY INFECTIONS IN DEVELOPING COUNTRIES

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SUMMARY

It is important that all febrile children are carefully assessed to find the cause of fever. Fever alone in a child with ARI is not a specific sign of pneumonia and is not an indication for antibiotic treatment. However, fever in the first two months of life is a sign of possible serious bacterial infection and referral to hospital is indicated for further investigation and treatment. In malarious areas, children with fever should, in addition, be treated according to the recommendations of the national malaria programme.

An understanding of the effects of fever alone can be gathered from a number of areas of research. Data from laboratory immunological studies and a limited number of animal studies suggest that a moderate rise in body temperature may improve immune defence against infection and may therefore be desirable. There are currently very few clinical studies which have looked at the clinical consequences of fever and antipyretic treatment in children; available evidence presents no clear picture at present.

Harmful effects of fever alone are rare and are found mainly in very ill and compromised children (with very severe pneumonia, for example) or in children with very high fever (above 42°C). High fevers or rapid rise in temperature in young children are associated with febrile convulsions but these generally resolve spontaneously and are not associated with long-term neurological complications. In addition there is no evidence that they can be prevented with antipyretic treatment. High fevers may also be associated with listlessness and reduced appetite in children.

The safest and most effective treatment for fever in young children is paracetamol in a dose of 10-15 mg/kg 6 hourly. As mentioned above, there is in most circumstances no indication to give antipyretic treatment for fever below 39°C (rectal). Such treatment will not normally improve the child's condition and will consume precious health services and family resources. Each child should be assessed individually, however, and it is reasonable to offer antipyretic treatment to any child who appears to be in discomfort as a consequence of fever.

The World Health Organization (WHO) recommends, in the guidelines for standard ARI case management, that treatment with paracetamol in children 2 months up to 5 years of age be limited to those with high fever (39°C rectal or above). Supportive care with additional fluids, appropriate clothing and environmental conditions should be emphasized. Tepid sponging is not effective and should be discouraged. It is important that health workers explain to parents the causes of fever and the reasons for treatment, and attempt to allay their fears over the child's fever.

1. INTRODUCTION

Fever has been recognized as an important sign of disease since the beginning of recorded history. Opinions have changed substantially, however, as to whether ill patients are better off with or without it. For Hippocrates and other ancients, fever was the body's defence mechanism for "cooking off" an excess of one of the four bodily humours: blood, phlegm, yellow bile, and black bile.¹ In fact, the view that fever is beneficial persisted well into the 19th century as eloquently enunciated by Thomas Sydenham, the noted English physician: "Fever is Nature's engine which she brings into the field to remove her enemy."² A change in this view occurred in the wake of experiments by the great French physiologist, Claude Bernard, who demonstrated that animals died when their body temperature was raised to 5-6°C above normal.³ These findings, combined with the beginning of thermometer use in medical practice (pioneered by Wunderlich)⁴ resulted in a dramatic shift in opinion, and fever became generally regarded as a threat to health.

Most parents are frightened when their child develops a fever. It has been demonstrated that undue fear of fever among - even highly educated - parents of infants and young children is common and has led to overly aggressive treatment: this has included treating children with temperatures below 38°C, waking sleeping children to administer antipyretics, and using physical methods that are both ineffective and uncomfortable.^{5,6} Whether such "fever phobia" stems from attitudes of doctors, nurses, and other health professionals, from widespread advertising by pharmaceutical companies, or from society's belief in "a pill for all ills", a careful review of the available scientific evidence may be helpful in developing a more rational approach to the management of children with fever.

2. UNDERSTANDING FEVER

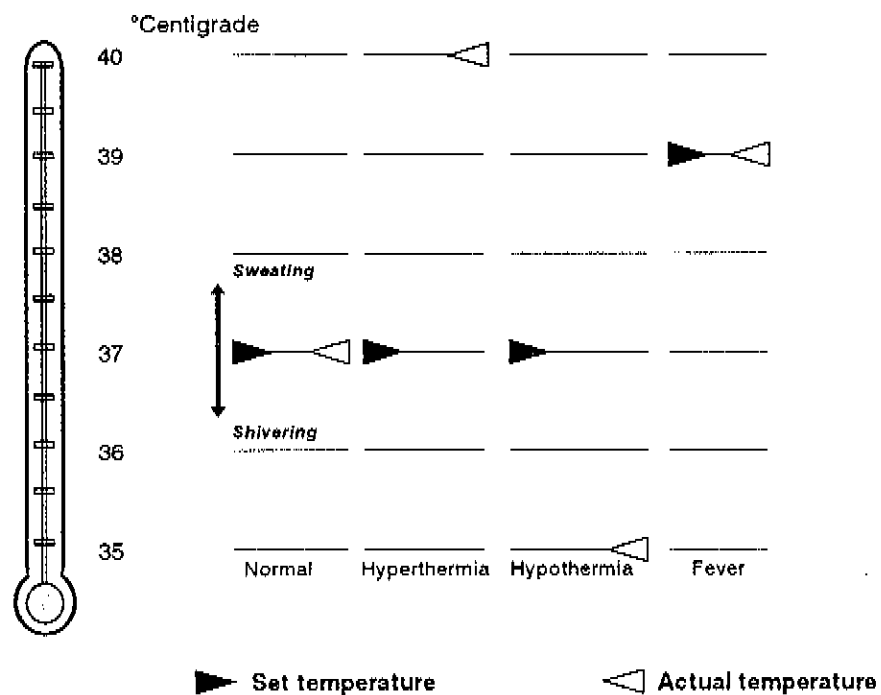
2.1 Temperature measurement

The rectal temperature provides a close approximation to core body temperature, with rectal temperatures of 38.0°C and above generally regarded as indicating an "abnormality" (e.g., fever or hyperthermia). Oral and axillary temperatures are generally lower than rectal temperatures (approximately 0.5 and 0.8°C, respectively, provided that thermometers are left in place for at least one minute).⁷⁻⁹ Where the ambient temperature exceeds 37°C, it is important to place the thermometer in the rectum, mouth, or armpit immediately after shaking it down and to read it promptly after removal (D. Ross, personal communication). Despite prevailing wisdom to the contrary, most mothers are able to subjectively determine the absence of fever in their children.¹⁰ Moreover, the mothers' subjective assessments are quite sensitive for detection of high fevers (rectal temperature 39.0°C and above).

2.2 The difference between fever and hyperthermia

In order to understand fever and the correct response to fever in young children it is first necessary to appreciate the important distinction between fever and hyperthermia (Figure 1). The anterior hypothalamus in the human brain normally regulates the set-point for central ("core") body temperature at $37 \pm 1^\circ\text{C}$ and responds to an increase or decrease in environmental temperature by sending nerve signals that lead respectively to heat loss or conservation. Heat loss is achieved principally by the dilation of small blood vessels in the skin (which enhances heat exchange from the blood to the surrounding air) and by sweating (cooling through evaporation). If these mechanisms are insufficient to compensate for a heat gain from the environment, the core temperature rises above the set-point, a condition called hyperthermia. Hyperthermia almost never occurs in response to infection (including ARI); it typically arises during heavy physical activity or overdressing in a hot, humid environment. Fever, on the other hand, is an upward adjustment of the set-point. Unlike hyperthermia, therefore, fever does not represent a failure of temperature control, but rather an upward shift of the regulated temperature.

Figure 1
Set and actual temperature in the normal child
and in the child with hyperthermia, hypothermia and fever



2.3 Physiology of fever

Fever usually occurs as a result of the body's exposure to infecting micro-organisms, immune complexes, or other sources of inflammation. In children with ARI, fever can be seen with either viral or bacterial infection. In response to invading viruses or bacteria, circulating monocytes and lymphocytes and fixed-tissue macrophages release chemicals called cytokines that function as "endogenous pyrogens", including interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor (TNF), and interferon.¹¹ These mediators, in turn, stimulate prostaglandin E₂ production in the anterior hypothalamus, which then brings about a rise in the temperature set-point by a variety of physiological mechanisms.

A considerable body of research has demonstrated that vertebrates (and many invertebrates) are capable of regulating their body temperature by intrinsic physiological or behavioural mechanisms, and of developing fever in response to infection.¹² In humans, shivering, constriction of blood vessels to the skin, and increased metabolic rate cause a rise in the core temperature to between 38°C and 41°C. During febrile illnesses, the hypothalamus carefully controls the rise in the set-point so that the body temperature rarely exceeds 41°C, even in children.^{13,14} By contrast, in hyperthermia temperatures often rise above 41°C, which can lead to heat stroke.

3. EFFECTS OF FEVER

As indicated above, opinions on the relative beneficial and harmful effects of fever have changed considerably over the ages. But it seems unlikely that the febrile response to infection found throughout the vertebrate line would have persisted for so long (some hundreds of millions of years) if it did not have some selective advantage. The available evidence from animal experiments, *in vitro* studies of human immune function, and clinical trials and observational studies is reviewed below.

3.1 Beneficial effects of fever

3.1.1 Animal studies

A number of animal studies have shown various beneficial effects of fever. The survival value of fever in the desert iguana has been convincingly demonstrated.¹⁵ Iguanas were infected with *Aeromonas hydrophila*, a natural gram-negative bacterium pathogenic for iguanas. Almost all animals kept at 40-42°C survived, whereas most of those kept at 34-38°C died. In a subsequent study, antipyretic treatment was also found to increase the mortality from *Aeromonas* infection.¹⁶ Similar results have

been reported in goldfish,¹⁷ salmon,¹⁸ and pigeons,¹⁹ although studies in rabbits have produced conflicting results.²⁰⁻²³

Fever also appears to be of adaptive value in viral infections. Newborn mice infected with coxsackie virus had considerably lower mortality when allowed to develop a fever than did controls which were kept afebrile.²⁴ Similar results have been obtained with herpes-infected newborn dog pups.²⁵ A study of influenza-infected ferrets demonstrated a highly significant negative correlation between the ferrets' rectal temperatures and the presence of live viruses in nasal washes.²⁶ In a follow-up study by the same research group, suppressing the fever (either by cooling the ferrets or by treating them with aspirin) increased the quantity and duration of viral shedding.²⁷

3.1.2 Effects on human immune function

Considerable *in vitro* evidence indicates that a variety of human immunological defences function better at febrile temperatures than at normal ones.¹¹ IL-1 and other endogenous pyrogens have a number of direct effects on the immune response, including enhancement of chemotaxis, oxidative (metabolic) activity, lactoferrin release in neutrophils (which leads to a decrease in serum iron, thereby inhibiting the growth of many micro-organisms), B-lymphocyte proliferation and antibody production, and T-lymphocyte activation. But the fever induced by endogenous pyrogens has additional immunological benefits, including helper T-lymphocyte proliferation, enhanced T-lymphocyte cell killing, and

interferon production and function. Moreover, the growth of some organisms (including the polio virus,²⁸ pneumococcus,²⁹ gonococcus,³⁰ and syphilis treponeme³¹) are inhibited at febrile temperatures. In fact, induction of fever by deliberate malarial infection was used to treat tertiary syphilis in the pre-antibiotic era.³¹

3.2 Harmful effects of fever

There are three circumstances in which high fever can be harmful in young children with ARI. First, children who are extremely debilitated or who have severe pulmonary or cardiovascular disease can be compromised by the increased oxygen consumption and cardiac output that occur at febrile temperatures. This might be particularly relevant in a child with very severe pneumonia, who may suffer from hypoxaemia.

Second, fever above 42°C can lead to neurological damage, but as mentioned above this is a very rare event. There is no evidence the fevers below 42°C cause neurological damage, even in young infants.

Finally, children under the age of 5 years, and especially those between 6 months and 3 years, are at risk of febrile convulsions, particularly at rectal

temperatures of 40°C or above. Many such convulsions, however, occur early in the course of the febrile illness, while the temperature is rising and in many cases before the parents are even aware of the presence of the fever.³² These febrile convulsions usually resolve spontaneously and are not associated with long-term neurological complications.

There are no randomized controlled trials comparing antipyretics and placebo for prevention of initial or recurrent febrile convulsions; medical opinion is divided as to whether antipyretic treatment can prevent febrile convulsions from occurring. One controlled trial has shown that even aggressive antipyretic treatment of fevers was associated with very high recurrence rates of febrile convulsions and suggests that antipyretic treatment is unlikely to be of major preventive benefit.³³ Phenobarbital has been shown to be effective in preventing febrile convulsions,^{32,33} but its clinical use is limited by associated adverse cognitive side-effects.³⁴

Febrile illnesses are often accompanied by other symptoms, including headache, anorexia, malaise, fatigue, and muscle aches. However, the extent to which these symptoms are a consequence of fever *per se* is unclear, as many of them appear to be mediated by IL-1 and other endogenous pyrogens.¹¹ Symptoms mediated by endogenous pyrogens are unlikely to respond to antipyretic drugs (except for pain, as these drugs also have analgesic properties).

3.3 Effects of antipyretic treatment

One study reported that adult volunteers experimentally infected with rhinovirus and treated with therapeutic doses of aspirin were more likely to exhibit nasal viral shedding than those receiving placebo.³⁵ A similar (but non-significant) trend was recently reported with both aspirin and paracetamol; moreover, both drugs (and ibuprophen) increased nasal obstruction and suppressed the serum neutralizing antibody response.³⁶ Other studies, however, have not confirmed these findings.^{37,38}

In a survey of 147 children hospitalized with bacterial infections, no difference in length of stay was found between patients receiving two or more doses of antipyretics during their stay and those receiving no or one antipyretic dose.³⁹ A randomized trial in children with chicken-pox found no significant differences in duration of symptoms (itching, activity, or appetite) but a longer time to total crusting of lesions in paracetamol compared to placebo-treated subjects.⁴⁰

Finally, a recently published randomized trial of young children with fever of presumed viral origin showed no deleterious effect of paracetamol in terms of prolonging the duration of fever or other illness-associated symptoms, and a statistically significant but modest improvement in activity and alertness among those treated with paracetamol.⁴¹

Thus, despite the enhanced immune function that occurs at febrile temperatures, studies in humans have not convincingly demonstrated

clinically important risks with the use of antipyretic therapy in common viral and bacterial infections, including ARI in children.

4. RECOMMENDATIONS FOR THE MANAGEMENT OF FEVER

4.1 Indications for antipyretic treatment

4.1.1 Children 2 months up to 5 years of age

The main documented benefit of antipyretic treatment in the majority of febrile children appears to be a modest improvement in comfort and behaviour, whether that relief is achieved by the antipyretic or analgesic effect of the medication. In principle, therefore, children who appear to be in the greatest discomfort would perhaps gain most from antipyretic treatment.

Reported anorexia has been shown to be independently associated with fever, often related to acute respiratory infections, in infants (KH Brown, personal communication). However, there is currently no published evidence that antipyretic treatment significantly improves children's appetite. Anorexia appears to be mediated by IL-1 and other endogenous pyrogens,¹¹ and simply lowering the temperature may be unable to affect this symptom. In developing countries, where malnutrition is prevalent among young children, this issue is potentially of considerable importance and merits further investigation, given the well-recognized association between malnutrition and infection.

The decision to administer antipyretic therapy should be based on balancing the likely benefits (improved comfort and behaviour) and risks (medication side-effects, see below) of treatment. A child who appears alert and comfortable is unlikely to benefit from treatment of his or her fever. It is recognized, however, that the assessment of the child's comfort and behaviour can be difficult. The WHO ARI Programme recommends that antipyretic treatment should generally be restricted to young children with high fever (that is, rectal temperatures of 39°C or above).

If a febrile child remains alert, active and playful despite a high temperature, health workers should seek to relieve any excessive parental anxiety concerning the child's fever and attempt to play down the dangers of the fever itself. It has been demonstrated that interventions such as teaching parents about the definition of fever, measurement of a child's temperature, and appropriate antipyretic treatment can be effective in changing parents' knowledge and behaviour.⁴²

In developing countries, health workers dealing with a febrile child should first look for signs and symptoms indicating the presence of an underlying cause of fever and institute an adequate treatment. If an underlying cause

of fever is not found, health workers should act differently in malarious and non-malarious areas. In malarious areas, all children with fever or a history of fever should be given appropriate antimalarial treatment, according to national guidelines. Health workers should encourage parents to return with the child if fever persists for 2 days or reappears within 14 days. In non-malarious areas, health workers should advise parents to return if their child's fever persists for more than 2 days. These children should be reassessed and, if the cause of fever is not ascertained, referred to hospital for further investigation.

In children with significant pulmonary or cardiovascular compromise (for example, children with severe or very severe pneumonia requiring oxygen), the use of antipyretics to lower the hypothalamic set-point should be beneficial in reducing oxygen consumption and cardiac output.

It also seems reasonable to treat fevers in children under 5 years with a history of febrile convulsions even in the absence of strong evidence that such treatment is effective.

4.1.2 Young infants under 2 months of age

There are no data to suggest that fever in young infants (under 2 months of age) is itself more harmful, and therefore should be treated more aggressively, than in older infants and children. However, fever is less common and high fevers are unusual in this age group, and any fever should be considered a danger sign of very severe disease. In developing countries, these young infants should be given the first dose of an antibiotic and referred to hospital for a careful search for the presence of a hidden bacterial infection of the blood, urine, lungs or meninges. Empiric parenteral antibiotic treatment is recommended if such a search is not feasible. As with older infants and children, the principal danger is the cause of the fever, not its effect.

Despite the absence of convincing evidence that antipyretic treatment can mask the signs and symptoms of a serious underlying infection, the potential for such a scenario urges caution in the treatment of fever when its causes are unknown, particularly in young infants. Moreover, the false sense of security that might result from successful reduction of fever could lead to delayed diagnosis and treatment of a serious infection. Antipyretic treatment is therefore not generally recommended in young infants.

4.2 Antipyretic treatment

4.2.1 Mechanism of action

Paracetamol, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs) are all effective antipyretic agents. They work by inhibiting production of prostaglandin E₂ in the anterior hypothalamus in response

to endogenous pyrogens, although stimulation of endogenous "cryogens" (antipyrogens such as vasopressin and melanocyte-stimulating hormone) may also play a role.¹¹

4.2.2 Paracetamol

Paracetamol is the drug of choice in young children. The dose of paracetamol is 10-15 mg/kg/dose. The table indicates paracetamol doses by age and weight (in kilograms). The weights corresponding to each age group are based on United States National Child Health Survey (NCHS) standards and may exceed those found in many developing countries. When age and weight categories do not coincide, dosage should be based on weight.

**Table: Recommended doses of paracetamol
in young children (every 6 hours)**

Age and weight	100 mg tablets	500 mg tablets
2 months - 3 years 6 kg - 14 kg	1	1/4
3-5 years 15 kg - 19 kg	1 1/2	1/2

In developing countries, the main available dosage forms (along with their 1992 UNICEF prices free on board, excluding freight and insurance) include:

- * 100 mg tablets (US \$0.86 per 100 and US \$3.02 per 1000)
- * 500 mg tablets (US \$2.50 per 200 and US \$12.48 per 1000)
- * 125 mg/5ml syrup (US \$0.31 per bottle of 60 ml).

Since other dosage forms exist, health workers should check the number of milligrams per tablet or per millilitre of liquid before drug prescription and administration.

Paracetamol is conjugated in the liver to form sulphate and glucuronide derivatives, with a small amount metabolized to toxic aryl intermediates. The latter metabolite is quite hepatotoxic when present in quantities greater than the capacity of the liver to conjugate it with glutathione or other sulfhydryl donors (more than 150 mg/kg). Ideally, the 500 mg tablets should not be given to young children (as few as three 500 mg tablets could be dangerous for an infant weighing less than 10 kg, for example) and, when prescribed to adults, packaged in child-proof containers and kept out of reach of children. The 100 mg tablets should be similarly packaged, and dispensed for young children in small quantities (no more than 15 per

prescription). The standard 60 ml bottle of syrup should not pose a serious threat.

4.2.3 Aspirin

Aspirin is an effective antipyretic, but its use in children is associated with adverse effects greater than those of paracetamol. It is a gastric irritant that increases the risk of gastric ulcer, haemorrhage, and perforation. Its inhibition of cyclo-oxygenase also interferes with platelet function and may augment the risk of bleeding (although this is unlikely to be an important consideration in the otherwise healthy child with an ARI). Aspirin has been associated (rarely in children) with a worsening of asthma symptoms and even serious anaphylactic reactions. Overdose (usually with the adult-strength tablets) leads to a syndrome called salicylism, which is characterized by hyperventilation, depressed level of consciousness, and severe metabolic acidosis.

Finally, unequivocal evidence has linked the administration of aspirin in children with viral infections, mainly influenza and varicella, to the subsequent development of Reye's syndrome,^{43,44} a rare disease (with an annual incidence of 1 to 2 per 100,000 children prior to 1980) manifested by liver and brain dysfunction. Aspirin has become a progressively less commonly used antipyretic in children in developed countries since the first reports of the association between aspirin and Reye's syndrome in the early 1980's; concurrently, the incidence of Reye's syndrome (which decreased 10-fold), and mortality from it, have fallen.^{45,46} Because influenza is often impossible to rule out in a child with an acute respiratory infection, the use of aspirin as an antipyretic should be discouraged. This is equally true in developing countries, as there is no reason to believe that children in developing countries are at lower risk of Reye's syndrome, despite the absence of reliable epidemiological data from such settings. Paracetamol, if it can be afforded, should be the antipyretic of choice.

When paracetamol is unavailable and aspirin must be given, the dosage (which should be carefully checked prior to prescription and administration) is identical to that of paracetamol as shown in the table. The cost of aspirin is only about 60% that of paracetamol, based on UNICEF, free on board, excluding freight and insurance, prices. Given the relative risks and benefits of these two drugs, however, it is difficult to defend the use of aspirin on economic grounds; economies may be better achieved by limiting the use of paracetamol to those children likely to benefit from it.

4.2.4 Non-steroidal anti-inflammatory agents (NSAIDs)

Other NSAIDs have also been used as antipyretic agents in children, the most common being ibuprofen. Current evidence indicates that in doses of 5-10 mg/kg ibuprofen is of comparable antipyretic efficacy to recommended doses of aspirin or paracetamol.^{47,48} In acute overdoses, ibuprofen appears to be much safer than paracetamol or aspirin. Like

aspirin and other NSAIDs, ibuprofen can lead to gastric ulceration, perforation, and haemorrhage (although these complications are rare in young children) and, like aspirin, could worsen asthma symptoms or lead to anaphylactic reactions.

Although there are no data linking ibuprofen to Reye's syndrome, the mechanism by which aspirin interacts with the viruses to produce Reye's syndrome is not understood, and to the extent that such a mechanism is shared by ibuprofen or other NSAIDs, one might suspect (at least on theoretical grounds) such a link with these medications. Because ibuprofen is also more expensive than aspirin or paracetamol, and because it does not appear to carry any unique therapeutic benefits, it is difficult to recommend it as a drug of first choice, particularly in developing countries.

4.2.5 Other agents

Many other drugs, including pyrazolon derivatives such as phenylbutazone and dipyron, are effective as antipyretics but far too toxic to justify their use for this purpose. Antispasmodics, such as atropine derivatives and antimuscarinic drugs, have also occasionally been used, particularly in developing countries, under the mistaken notion that fever has a gastrointestinal cause; such agents not only are ineffective but can also lead to considerable toxicity. The use of injectable solutions of these and other drugs for the treatment of fever in young children can never be justified.

4.3 Supportive care

4.3.1 Recommended supportive measures

Because fever is accompanied by an increased metabolic rate and insensible water losses, increased fluid intake should be encouraged. Correct hydration is considered to act as an expectorant by loosening respiratory secretions. Severe dehydration in the absence of concurrent diarrhoea and vomiting is rare.

Where possible the child should be lightly clothed in a warm but well-ventilated environment. A neutral thermal environment (with a room temperature of about 25°C) is particularly desirable for young infants.

4.3.2 Measures not recommended

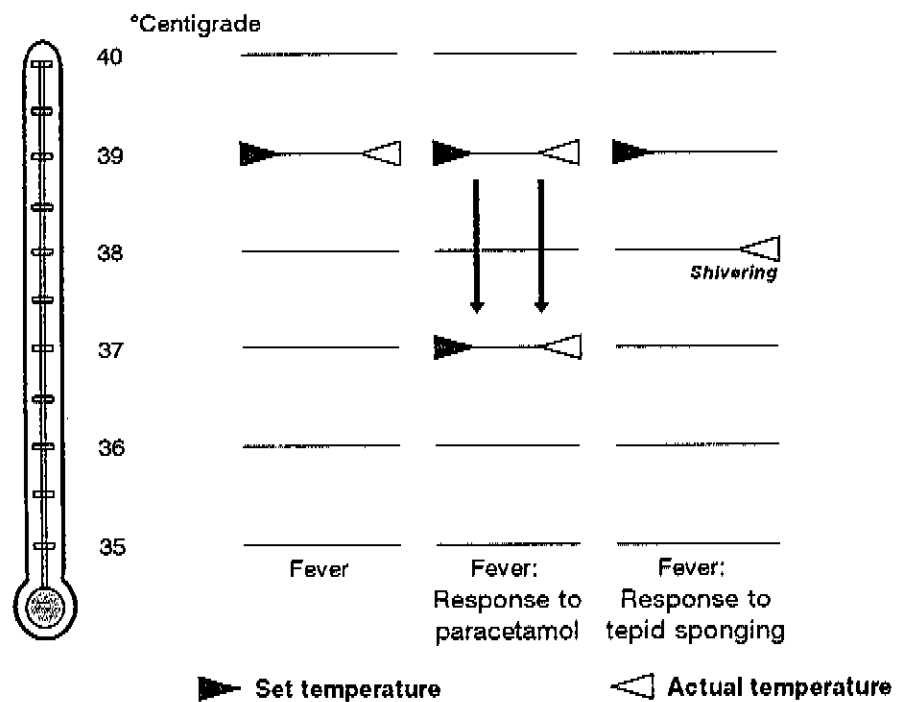
External cooling by removing clothing, bathing, sponging in cold or tepid water or applying of isopropyl alcohol is not very effective when used alone (unless the child has been overwrapped or otherwise overheated) and is of dubious value even when combined with antipyretic drug therapy.⁴⁹⁻⁵¹ Moreover, the use of physical methods alone runs counter to the

physiological mechanisms discussed earlier. Unless the hypothalamic set-point has first been lowered pharmacologically, underdressing or underwrapping a child or applying water or alcohol to the skin will only lead to shivering (and therefore discomfort) as the body attempts to maintain the core temperature at the regulated set-point (Figure 2).

The discomfort induced by cold water or alcohol bathing or sponging can be considerable. In addition, isopropyl alcohol can be absorbed through the skin, with appreciable blood levels and risk of systemic toxicity. Its use should therefore be discouraged.

In unusual circumstances (for example, in children whose temperature is above 41°C) when rapid lowering of the body temperature is desirable, tepid water sponging or bathing can be considered as an adjunct to antipyretic treatment.

Figure 2
Set and actual temperature in the child with fever
treated with paracetamol or with tepid sponging



5. CONCLUSIONS

Right up till a century ago, society's attitude towards fever was in complete contrast to the "modern" view: fever was considered a healthy response to disease and was deliberately encouraged. When one contrasts our current practice of aggressive treatment of even minor fevers with the available scientific evidence, one is left to conclude that the principal rationale for antipyretic therapy is to soothe worried parents and health care workers and to give them the sense that they are controlling the child's illness, rather than it controlling them.

When an otherwise healthy child presents with an acute febrile illness (including an acute respiratory infection not requiring oxygen therapy), treatment of the fever should not receive high priority. The major effort should be the timely identification and treatment of a bacterial infection (pneumonia, otitis media, streptococcal pharyngitis, meningitis or generalized sepsis) and the referral and admission to hospital of children requiring parenteral antibiotic therapy, oxygen or further investigation.

Parents and health care workers should not, as is often the case at present, automatically give antipyretic treatment to all children with fever. They should "treat the child, not the thermometer". Reduction of fever should be oriented towards relieving the child's discomfort (if significant) and this is generally best achieved by the oral administration of paracetamol to children with high fever only. This will promote an efficient use of health service (and family) resources targeted at children who are likely to benefit, will encourage emphasis on the cause rather than the effect of the fever, and, by discouraging needless polypharmacy, will promote better compliance with essential treatments such as oral antibiotic therapy.

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