DKK Ng 吳國強
JCY Lam 林青儒
KW Chow 周健華

Childhood fever revisited

再論兒童發燒

The academic study of body temperature began in 1868. Since then, a variety of thermometers have been developed for clinical use. A working knowledge of these different thermometers, the various sites for taking temperature, and the normal range of body temperatures, is essential. As the pathogenesis of fever is being elucidated, and the cytokines involved identified, the risks and benefits of fever to the organism are becoming better understood. The importance of recognising diagnostic fever patterns should be stressed. Acetaminophen (paracetamol) and ibuprofen are accepted as the standard medical treatments for fever.

體溫的學術研究始於1868年。自那時起已經開發研製出多種用於臨床的體溫計。我們除了需要知道人類體溫的正常範圍外，更需對不同種類的體溫計，其不同的探測體溫的位置有深入的理解。隨著發燒機理被闡明，有關的細胞活素被鑒別，發燒對人體的危險和益處已得到更全面的理解。應該強調識別診斷發燒模式的重要性。對乙酰氨基酚和布洛芬已被公認為標準的發燒治療藥。

Introduction

Carl Reinhold August Wunderlich[1] was the first to conduct extensive study on body temperature, and published his opus magnus in 1868. In this book, The Course of Temperature in Diseases, Wunderlich identified 98.6°F (37°C) as normal body temperature. He also established 100.4°F (38°C) as the upper limit of the normal range. His database was enormous, and is estimated to have included several million observations obtained from some 25 000 subjects. Wunderlich also concluded that fever, which had previously been viewed as a disease process in itself, was, rather, a sign of disease. Since his time, there have been a number of significant developments in this area including the development of a variety of thermometers, different sites of temperature measurement, different normal ranges of body temperature, and understanding of the mechanisms, effects, and treatment of fever. This review aims to summarise these developments in relation to children.

Thermometers

The term 'thermometer' refers to any device used to measure temperature. Clinical thermometers should possess sensitivity and accuracy meeting the requirements of the American Standards of Testing and Materials: maximum error allowed is 0.1°C for a temperature range from 37.0°C to 39.0°C, 0.2°C for a temperature range from 39.0°C to 41.0°C, and 0.3°C for temperature greater than 41.0°C.[1] Practical tests of the sensitivity and accuracy of thermometers include either simultaneous tests of a few thermometers or repeated tests of the same thermometer.

Types of thermometers

(1) Liquid-in-glass thermometers (mercury or spirit): Clinical thermometers differ from laboratory thermometers by virtue of a small constriction just below the scale, which prevents the indicator liquid from flowing back into the bulb as the thermometer cools. Its advantages include low cost and good accuracy. Its disadvantages include long dwell time (up to 8 minutes) for accurate readings, proneness to reading errors, and the potential hazard when broken.
(2) Thermistor-based electronic clinical thermometers: The principle of this

Key words:
Body temperature;
Child;
Fever/diagnosis;
Thermography/instrumentation;
Thermometers

關鍵詞：
體溫；
兒童；
發燒 / 診斷；
熱記錄法 / 儀器；
體溫計

HKMJ 2002;8:39-43

Kwong Wah Hospital, 25 Waterloo Road, Kowloon, Hong Kong:
Department of Paediatrics
DKK Ng, M Med Sc, FRCP (Edin)
Accident and Emergency Department
KW Chow, MB, ChB
The University of Hong Kong
JCY Lam

Correspondence to: Dr DKK Ng

kind of thermometer is that the change in thermal energy alters the resistance of the thermistor. Its advantages include an easily read digital display, and a shorter dwell time than mercury-in-glass thermometers. Its main disadvantage is the lack of indication of malfunction or calibration drift.

(3) Liquid crystal indicators: Cholesteric liquid crystals are twisted stacks of long molecules that wind and unwind in response to changes in temperature. Light at wavelengths commensurate with the spacing of these crystals is reflected preferentially, so that the colour of the liquid crystal is determined by its temperature, giving it the property of a thermometric sensor. In a related application, a small disc is applied to the forehead to monitor body temperature in the neonate. The accuracy and reliability of these instruments have generally been poor.

(4) Radiometers for the ear canal: The tympanic membrane (TM) is an ideal site for measuring core temperature, because it is perfused by a tributary of the carotid artery which supplies the body's thermoregulatory centre.[2] The infrared TM thermometer works like a camera: it detects infrared energy emitted from the TM and portions of the ear canal, processes the information, and displays a value representing either the tissue temperature in the ear canal, or an adjusted estimate of the temperature in other sites, eg oral, rectal, or core. Its advantages include being a non-contact instrument and the short dwell time (less than a few seconds). Its disadvantages include the need for expensive probe covers, and conflicting reports of accuracy as compared with other thermometers. Unfavourable results were reported by Erickson and Kirklin,[3] Freed and Fraley,[4] and Stewart and Webster,[5] whereas favourable results were described by Ng et al[6] and Chamberlain et al.[7]

Site of temperature measurement

Body temperature is actually an ill-defined term, as different body parts have different temperatures. Within the body, there are two basic thermal compartments worthy of special consideration—the core and the shell.

The shell, which consists of skin and subcutaneous fat, insulates the core from the external environment. The core, of which the viscera are major components, also has temperature gradients of its own, resulting from the unique metabolic rate and blood flow of each organ contained therein. Although such differences are normally small, at times of vigorous exercise, muscle temperatures rise markedly in comparison with less metabolically active organs. During shock and under extreme environmental conditions, regional anatomical variations in temperature may also be exaggerated.

1. Mouth

This is the most easily accessible site. The temperature of the sublingual pocket is relevant clinically because its main artery is a branch of the external carotid artery and, like its parent artery, it responds promptly to changes in core temperature. Oral temperature measurements, however, require the cooperation of patients being examined, and not all patients (eg young children, uncooperative adults, and intubated individuals) are amenable to such measurements. In addition, oral temperature is subject to the influence of ingestion of hot or cold food, as well as smoking before measurement. Although a pacifier containing temperature-sensitive crystals has been marketed as a novel and convenient way of measuring oral temperature in infants, clinical tests revealed that only 10% of febrile infants were identified correctly as febrile with the device, and seven of eight infants with rectal temperatures ≥102°F (≥38.9°C) were incorrectly labelled as afebrile.[8]

2. Rectum (3 minutes for mercury)

The rectum is the site of the highest temperature measurement in the body. Rectal temperature is a reliable approximation of core temperature only if the patient is in thermal balance. Although generally safe, such measurements are associated with a small risk of rectal perforation, especially in neonates and very young infants. In a study by Robinson et al[9] of the most reliable sites for temperature measurement, in 15 children aged between 6 months and 6 years, rectal temperature responded slowly to changes in blood temperature. This finding was probably related to the heat sink effect of stool in rectum. Even at steady state, rectal temperature has been shown to differ significantly from pulmonary artery temperature. It was concluded that the accuracy of rectal temperature measurement is poor at extremes of temperature, because it is slow to measure change.

3. Axilla (9 minutes for mercury)

The main problem with axillary temperature measurement is the long dwell time to reach equilibrium, with only 18% of axillary readings reaching maximum at 5 minutes.[10] The axillary temperature provides, at best, a reasonable approximation of body temperature in the neonate, but not in the older child or adult. Axillary temperature measurement may be unreliable, and should not be attempted in the outpatient setting. Furthermore, Robinson et al[9] concluded that the axillary readings exhibited a wide deviation from rectal, tympanic, oesophageal, and pulmonary arterial readings, even with careful positioning of the thermometer.

4. Tympanic membrane

In theory, the TM is an ideal site for measuring core temperature because it is perfused by a tributary of the artery that supplies the body's thermoregulatory centre. The infrared TM thermometer is convenient. In a study by Robinson et al,[9] tympanic readings with Genius (Sherwood Medical, St Louis, US) and IVAC (IVAC, San Diego, US) tympanic thermometers were found to be less accurate than oesophageal readings, but more accurate than rectal, axillary, or bladder readings over a wide range of temperatures, with rapid cooling and rewarming. The two tympanic thermometers performed remarkably similarly throughout the study.

Correlation between temperatures at different body sites

On average, in a resting healthy adult, core temperature (pulmonary artery) is 0.4°C (0.7°F) higher than oral temperature, and 0.2°C (0.4°F) lower than rectal temperature.[11] Rabinowitz et al[12] studied the relationship between temperature measurements at different sites. Unadjusted ear temperature, as measured by IVAC Core-Check TM (IVAC, San Diego, US), was lower than rectal temperature by 0.8°C (1.6°F), while oral temperature was lower than rectal temperature by 0.4°C (0.8°F). In a study performed by Loveys et al,[13] 1175 paired observations of ear and rectal temperature measurements were prospectively obtained from 140 infants and toddlers from December 1995 to February 1996. Mean rectal temperature was 37.50°C (standard deviation [SD], 0.68°C) and mean ear temperature was 37.60°C (SD, 0.85°C). At the low end of the rectal temperature scale, however, ear temperatures tended to be higher, and at the high end of the rectal temperature scale, ear temperatures tended to be lower. There was clearly considerable interindividual variability in this correlation, and extreme caution must be employed in converting a temperature reading from one site to another.

Normal range of body temperature

Body temperature, like most physiological functions, varies in a circadian pattern. It reaches its peak in the late afternoon/early evening and its nadir in the early morning. In general, body temperature is highest at 4 to 6 pm and lowest at 6 am. The variation is up to 1°C. Thus, it is important to consider the time of the measurement, as well as the site at which the body temperature was taken. It is not practical, however, to define fever differently for different times of the day.

An interesting study by Wailoo et al[14] showed that the range of rectal temperatures of 74 3- to 4-month-old infants generally fell by 0.8°C to 1.0°C within an hour of their being placed in the cot. Before bedtime, 90% of rectal temperatures were around 36.9°C to 37.9°C. Two hours after bedtime, rectal temperatures were around 35.9°C to 36.9°C. Tuffnell et al[15] performed a study on factors affecting rectal temperature in infancy, recording 1197 overnight rectal temperatures from infants aged ≤24 weeks. Multivariable regression analysis was used to determine whether parental smoking, bottle feeding, sleeping position, or birth weight would affect overnight rectal temperature. The results showed that increased age and birth weight, and supine sleeping position all decreased the night-time rectal temperatures. An increase in night-time room temperature, body weight, and the combination of bottle feeding and parental smoking, however, produced an increase in rectal temperature. The individual effects of bottle feeding and parental smoking were not significant.

In a study by North et al,[16] it was found that supine-sleeping infants attained significantly lower rectal temperatures than those sleeping prone or laterally. The results were based on night-time rectal temperature recordings of 103 infants sleeping in their own homes in different sleeping positions. This finding may have implications for the lower vulnerability to sudden infant death syndrome among supine sleepers.

The definition of fever has been somewhat confused, with different sources using different definitions. Some textbooks do not even provide a definition, such as that authored by Campbell and McIntosh.[17] Ideally, the definition of fever should take account of the time of day, age, and sex of a resting subject who is suspected to have a disease. However, this would be unworkable in daily clinical practice, and a practical definition with reasonable predictive values for diseases should be adopted. For rectal temperature, a reading above 38°C is generally accepted as signifying fever in most medical textbooks. For oral temperature, a reading in excess of 37.5°C is accepted as indicating fever.[18] For axillary temperature, above 37.0°C appears to be a reasonable cut-off point. For tympanic temperature, a reading above 37.9°C for children younger than 11 years, and above 37.6°C for individuals aged 11 years or older, can be taken as a sign of fever.[19,20] It is important to note that a mild elevation of 1.0°C to 1.5°C can be caused by exercise, bottle or breast feeding, excessive clothing, or hot baths. In the event of doubt, temperature should be rechecked 30 minutes after eliminating possible environmental causes.

Mechanisms of fever

Fever is basically the elevation of the regulated set-point temperature by the effect of pyrogens. Temperature set-point is regulated by the thermoregulatory area, which is located in the rostral hypothalamus, part of the preoptic region. Within this area, there are warm-sensitive and cold-sensitive neurons. The preoptic thermosensitive neurons are able to integrate central and peripheral thermal information. Some preoptic neurons not only sense local temperature, but also receive synaptic output from afferent pathways of thermoreceptors in the skin, spinal cord, and other locations throughout the body. As their names imply, the warm-sensitive neurons increase their firing with increased warmth or decreased cold information from the afferent pathways, whereas the cold-sensitive neurons increase their firing with decreased warmth or increased cold information from the afferent pathways. The balance in the firing rate of cold- and warm-sensitive neurons produces the ultimate set-point temperature.

There are two types of pyrogens: exogenous and endogenous. Exogenous pyrogens include: micro-organisms (primarily cell wall components), microbial toxins (usually Gram-positive organisms), antigen-antibody complexes, drugs, and polynucleic acids. They can induce the host cells (primarily macrophages) to produce endogenous pyrogens. Some endogenous molecules can also induce endogenous pyrogens; these include antigen-antibody complexes, certain androgenic steroid metabolites, inflammatory bile acids, complement components, and some lymphocyte products. Endogenous pyrogens include: interleukins (ILs)-1, 2, 6, and

8, tumour necrosis factor (TNF)–α, and prostaglandin E, which is a component of the final common pathway of action on the thermoregulatory centre. Endogenous pyrogens decrease the firing rate of preoptic warm-sensitive neurons, and increase the firing rate of the preoptic cold-sensitive neurons. The inhibition of warm-sensitive neurons causes a decrease in heat loss responses. Similarly, excitation of cold-sensitive neurons increases heat production, such as shivering, and heat retention responses, such as vaso-constriction. Pyrogen inhibition of warm-sensitive neurons raises the regulated set-point temperature of the anterior hypothalamus. In short, pyrogens disturb the balance in firing of warm- and cold-sensitive neurons in the hypothalamus, leading to elevation of the set-point temperature.

Effects of fever—benefits versus risks

Benefits

With few exceptions, both vertebrates and invertebrates manifest fever in response to challenge with micro-organisms or other known pyrogens. This has been viewed as one of the strongest pieces of evidence that fever is an adaptive response: it is held that the metabolically expensive increase in body temperature that accompanies the febrile response would not have evolved, and been so faithfully preserved within the animal kingdom, unless fever had some net benefit to the host. Fever has been shown to enhance monocytic elimination of *Leishmania* and neutrophilic elimination of pneumococci, *Candida*, *Escherichia coli*, *Salmonella typhimurium*, *Listeria monocytogenes*, and *Staphylococcus aureus*. Fever also has been shown to decrease bacterial and viral growth rates.[21]

Risks of fever

The potential of fever for harm is reflected by reports suggesting that IL-1, TNF-α, and interferon mediate the physiological abnormalities of certain infections. Interleukin-1 causes fever, hypoglycaemia, shock, and death. Tumour necrosis factor–α antagonists were found to protect against hypotension. Proof of an adverse influence of fever on the clinical outcome of infection has yet to be established. However, the potential implication is that if pyrogenic cytokines contribute to the pathophysiological burden of infection, not only these cytokines but also the febrile response are potentially deleterious.

Fever pattern

Febrile pattern is often helpful to clinicians in establishing a specific diagnosis, particularly in infectious disease. In considering the febrile pattern, observation over a considerable time interval is important, in the absence of any effect of antipyretics, in order that the pattern observed is clinically significant.

Definitions of febrile pattern

(1) Continuous (sustained) fever with slight remissions not exceeding 2.0°F. Within this group fall fevers caused by lobar and Gram-negative types of pneumonia, rickettsial diseases, typhoid fever, central nervous system disorders, tularemia, and *Plasmodium falciparum* (malignant tertian) malaria.

(2) Intermittent fever with wide fluctuations, usually normal or low in the morning with a peak at 4 to 8 pm. This group includes fevers caused by localised pyrogenic infections and bacterial endocarditis. Malaria presents as quotidian (daily spike), tertian (spike every third day), or quartian (spike every fourth day) types, depending on type of organisms and host defence. In acute brucellosis, fever is often intermittent, with sweating associated with leukopenia or a normal leukocyte count.

(3) Saddleback (biphasic) fever, with several days of fever, a gap of reduced fever of about 1 day, and then several additional days of fever. Characteristic of this type are dengue and yellow fever, Colorado tick fever, Rift Valley fever, and viral infections such as influenza, poliomyelitis, and lymphocytic choriomeningitis.

(4) Pel-Ebstein fever, characterised by weekly or longer periods of fever, and equally long afebrile periods with repetition of the cycle. It occurs in Hodgkin's disease, brucellosis of the *Brucella melitensis* type, and relapsing fever. Occasionally in tuberculosis the febrile course may be similarly intermittent.

(5) The Jarisch-Herxheimer reaction refers to the sharp elevation of temperature and exacerbation of clinical manifestations several hours after beginning penicillin treatment of primary or secondary syphilis.

Treatment of fever

Physical treatment of fever includes rest in a well-ventilated room, adequate fluid intake, 12% increase in fluid requirement for every 1°C rise in temperature, and body sponging with a lukewarm water–soaked towel. Fluid requirements can be met by either enteral or parenteral routes, as dictated by the clinical situation. Alcohol sponging is not recommended because of the risk of systemic absorption.

Aspirin (acetylsalicylic acid) was an acceptable treatment of fever in children before 1980, when Starko et al[22] published a case-control study that implicated aspirin as the cause of Reye's syndrome. Further epidemiological study confirmed this association.[23] After a warning about the use of aspirin was issued in the US in 1980, there was a sharp decline in the incidence of Reye's syndrome in that country.[24] Now, acetaminophen (paracetamol) is the standard agent for treating fever in children because of its effectiveness, low cost, and minimal side-effects. Unlike aspirin, it is not a gastric irritant, nor an antiplatelet agent, and has not been associated with Reye's syndrome. It is rarely associated with the hypersensitivity phenomena, such as bronchoconstriction, that are sometimes seen with aspirin. The recommended maximum dosage of acetaminophen for children is 15 mg/kg every 4 hours, not to exceed 4 g/day. Caution is required in patients with

liver insufficiency. At excessive dosages (higher than 150 mg/kg), acetaminophen overwhelms the detoxification capacity of hepatocytes, and forms toxic aryl intermediates that interact with cellular proteins. Although hepatotoxicity is less common in children younger than 24 months than in adults, acetaminophen should be kept safely stored and out of the reach of all children.

Ibuprofen (5 mg/kg four times daily, as required) is increasingly being used to treat fevers that do not respond to acetaminophen. Any additional benefit derived from ibuprofen in these situations is probably small, and must be weighed against ibuprofen's potential toxicity, which includes an antiplatelet effect, potential hypersensitivity, and gastrointestinal irritation. With regard to its small incremental benefit, Autret et al[25] found, in a trial comparing acetaminophen with ibuprofen, no statistically significant difference in mean reduction in temperature after 4 hours: 1.02°C versus 1.32°C, respectively. Ibuprofen was slightly superior to acetaminophen in children with a temperature above 39°C, in terms of mean reduction of fever at 4 hours (1.84°C versus 1.24°C in the ibuprofen and acetaminophen groups, respectively).

Conclusion

Fever is the most common reason for children's presenting to a medical practitioner. It cannot be emphasised too strongly that the individual medical practitioner must answer the basic question: "What is the cause of fever in this patient?" Sometimes, identifying diagnostic patterns of fever will assist in answering this question. The practitioner should have a basic understanding of the mechanisms of fever and the effects of fever on the body. A working knowledge of the various commercially available thermometers is important in answering possible questions from parents. Finally, it is of paramount importance that medical practitioners be able to prescribe safe symptomatic treatments, both physical and pharmaceutical, while avoiding overdose and the use of unsafe medications such as aspirin.

References

1. Mackowiak PA. History of clinical thermometry. In: Mackowiak PA, editor. Fever: basic mechanisms and management. 2nd ed. Philadelphia: Lippincott-Raven; 1995:1-10.
2. Klein DG, Mitchell C, Petrinec A, et al. A comparison of pulmonary artery, rectal, and tympanic membrane temperature measurement in the ICU. Heart Lung 1993;22:435-41.
3. Erickson RS, Kirklin SK. Comparison of ear-based, bladder, oral, and axillary methods for core temperature measurement. Crit Care Med 1993;21:1528-34.
4. Freed GL, Fraley JK. Lack of agreement of tympanic membrane temperature assessments with conventional methods in a private setting. Pediatrics 1992;89:384-6.
5. Stewart JV, Webster D. Re-evaluation of the tympanic thermometer in the emergency department. Ann Emerg Med 1992;21:158-61.
6. Ng DK, Liu YS, Ho JC. Use of infrared emission detection thermometer in Chinese neonates. Chin Med J 1999;112:665-7.
7. Chamberlain JM, Terndrup TE, Alexander DT, et al. Determination of normal ear temperature with an infrared emission detection thermometer. Ann Emerg Med 1995;25:15-20.
8. Banco L, Jayashekaramurthy S, Graffam J. The inability of a temperature-sensitive pacifier to identify fevers in ill infants. Am J Dis Child 1988;142:171-2.
9. Robinson JL, Seal RF, Spady DW, Joffres MR. Comparison of esophageal, rectal, axillary, bladder, tympanic, and pulmonary artery temperatures in children. J Pediatr 1998;133:553-6.
10. Nicholas GA, Kulvi RL, Life HR, Christ NM. Measuring oral and rectal temperatures of febrile children. Nurs Res 1972;21:261-4.
11. Togawa T. Body temperature measurement. Clin Phys Physiol Meas 1985;6:83-108.
12. Rabinowitz RP, Cookson ST, Wasserman SS, Mackowiak PA. Effects of anatomic site, oral stimulation, and body position on estimates of body temperature. Arch Intern Med 1996;156:777-80.
13. Loveys AA, Dutko-Fioravanti I, Eberly SW, Powell KR. Comparison of ear to rectal temperature measurements in infants and toddlers. Clin Pediatr (Phila) 1999;38:463-6.
14. Wailoo MP, Petersen SA, Whittaker H, Goodenough P. Sleeping body temperatures in 3-4 month old infants. Arch Dis Child 1989;64:596-9.
15. Tuffnell CS, Petersen SA, Wailoo MP. Factors affecting rectal temperature in infancy. Arch Dis Child 1995;73:443-6.
16. North RG, Petersen SA, Wailoo MP. Lower body temperature in sleeping supine infants. Arch Dis Child 1995;72:340-2.
17. Campbell AG, McIntosh N, editors. Forfar and Arneil's textbook of paediatrics. 5th ed. New York: Churchill Livingstone; 1998.
18. Headley RM, Schmitt BD. Ambulatory pediatrics. In: Merenstein GB, Kaplan DW, Rosenbery AA, editors. Handbook of pediatrics. 18th ed. Connecticut: Appleton & Lange; 1997:31-49.
19. Chamberlain JM, Terndrup TE, Alexander DT, et al. Determination of normal ear temperature with an infrared emission detection thermometer. Ann Emerg Med 1995;25:15-20.
20. Ng KK, Liu YS, Ho JC. Use of infrared emission detection thermometer in Chinese neonates. Chin Med J (Engl) 1999;112:665-7.
21. Hasday JD. The influence of temperature on host defenses. In: Mackowiak PA, editor. Fever: basic mechanisms and management. 2nd ed. Philadelphia: Lippincott-Raven; 1995:177-97.
22. Starko KM, Ray CG, Dominguez LB, Stromberg WL, Woodall DF. Reye's syndrome and salicyclate use. Pediatrics 1980;66:859-64.
23. Forsyth BW, Horwitz RI, Acampora D, et al. New epidemiologic evidence confirming that bias does not explain aspirin/Reye's syndrome association. JAMA 1989;261:2517-24.
24. Belay ED, Bresee JS, Holman RC, Khan AS, Shahriari A, Schonberger LB. Reye's syndrome in the United States from 1981 through 1997. N Engl J Med 1999;340:1377-82.
25. Autret E, Breart G, Jonville AP, Courcier S, Lassale C, Goehrs JM. Comparative efficacy and tolerance of ibuprofen syrup and acetaminophen syrup in children with pyrexia associated with infectious diseases and treated with antibiotics. Eur J Clin Pharmacol 1994;46:197-201.