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Physiology of fever

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Summary

Knowing how the body reacts to the presence of pathogens allows healthcare professionals to make informed decisions about what action to take in caring for the child with fever. A raised body temperature raises the metabolic rate and makes the immune response more efficient. It also stimulates naturally occurring anti-pyretics but can also have harmful effects. Careful monitoring based on risk of serious illness is recommended in new guidelines on the management of feverish illness in young children provide (National Institute of Health and Clinical Excellence (NICE 2007), which also provide an opportunity for standardising fever management.

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A raised temperature is one of the most common clinical features observed by nurses caring for children (Walsh 2005). The publication of *Feverish Illness: Assessment and management in children younger than five years of age* (National Institute of Health and Clinical Excellence (NICE 2007) is an ideal opportunity for nurses and others to standardise fever management. The guideline provides a clinical framework to assist healthcare professionals with this diagnostic and management challenge. This article supplements the NICE guideline by exploring the pathophysiology of fever. It does not address assessment of body temperature, identification of serious illness or the pharmacological and non-pharmacological management of fever as these are comprehensively addressed in the new guideline. With these two resources you will be able to satisfy K11 and K13 of the Level 4 Emergency Care Competence Framework Unit EC11L: Investigate and diagnose an individual presenting for emergency assistance with fever (Skills for Health 2004).

Aims and intended learning outcomes

After reading this article you should be able to:

- Describe the physiology underpinning fever
- Relate the physiological mechanisms to the presenting clinical features associated with fever
- Apply the physiological principles of fever to the NICE guideline *Feverish Illness: Assessment and management in children younger than five years of age*
- Identify the benefits and threats posed by fever in a child.

An understanding of normal temperature regulation is assumed. If needed, the Continuing Professional Development article by Casey (2000) Fever management. *Paediatric Nursing.* 12, 3, 38-42 would act as a good revision aid.

Defining fever

Fever is a normal adaptive systematic response to an immune stimulus (Thompson 2005). It is the body's natural response to illness and has been shown, in animal studies, to improve survival rates and shorten the duration of the disease (Jiang 2000). There are a number of differing definitions for fever; all are dependent on age and possibly more importantly the site or type of thermometer used (Kayman 2003). Fever can be simply defined as: 'an elevation of body temperature above the normal daily variation' (NICE 2007).

Now do Time Out 1.

Despite overwhelming evidence over the last 30 years of the beneficial effects of a mild fever, there remains a general fear of the fever process. Fever is generally seen as an indicator of disease severity and is treated aggressively by many healthcare professionals. This intervention is not always borne out in the literature as most fevers are generally self limiting and children appear to tolerate mild to moderate fevers with relative ease. Walsh and Edwards (2006) found that parents were equally concerned about fever, considering it as harmful and a disease in itself. In the main, this fever phobia stems from a limited appreciation of the physiological process which results in a fever.

Now do Time Out 2.

When experiencing a fever the child will often feel tired, have a general malaise, look pale and feel anorexic. There will be an increase in pulse and respiratory rate and the extremities will feel cold in contrast to the child's trunk that is likely to feel warm. It is not unusual for the child to feel physically cold and may shiver. Having considered the presenting features of a fever, what actually happens in the body to cause this rise in temperature?

Physiology of fever

Fever is a clinical indicator of a host response, usually to a microbial infection. It is one of a number of mechanisms the immune system utilises to rid the body of the invading pathogens (Tatro 2000). Substances that induce fever are termed pyrogens and these can be exogenous (from the outside), for example, pathogens, bacterial toxins, antigen/antibody complexes or endogenous (internally produced), for example, interleukin, interferon.

In this article we will concentrate on the most common exemplar seen in children, fever resulting from an infection. A microbial infection, if left unchecked, will result in localised tissue death or injury as the invading organisms multiply. Inflammatory mediators such as histamine, kinins, prostaglandins, leukotrienes and interleukins are released at the site of the infected area from these damaged cells. These inflammatory mediators help attract white blood cells (leukocytes) in a process called chemotaxis.

The first white blood cells to respond to the infective organisms are macrophages which engulf the pathogen (a process called phagocytosis) and initiate the release of a variety of cytokines and associated substances to continue and enhance the immune response. These small proteins assist immune communication and initiate many of the features of fever and inflammation associated with the infective process. These various macrophages are collectively termed monocytes and make up 10 to 15 per cent of all the cells in any organ in the body (Thibodeau and Patton 2007).

Endogenous pyrogens

There are many substances released as a result of the inflammatory process, but it is the cytokines that are most closely associated with the fever response. Cytokines include interleukins, interferon and tumour necrosis factor – α(TNF-α).

Cytokines have both a local and systematic action, interleukins, for example, assist cellular communication between leucocytes and because of their hormone-like action have the ability to influence the intensity and duration of the immune response.

- Interleukin 1 (IL-1) activates the vascular epithelium and increases vascular access to the infective site while promoting and stimulating the action of lymphocytes.
- Interleukin 6 (IL-6) has a similar action on lymphocytes but also stimulates the production of antibodies.
- TNF-α increases the permeability of capillaries and promotes drainage of excess fluids to the lymph nodes. Interestingly, TNF-α has both a cytolitic – the ability to destroy cells – and a cytostatic – the ability to inhibit or suppress cell growth – effect. These actions have a role in the inflammatory process. TNF-α has been associated with cancer cell destruction, and its over production connected with cases of rheumatoid arthritis.
- Interferon is present when the immune system has been compromised by a viral attack and is related to a group of proteins that have a role in directly destroying the virus. It assists cell communication to enhance cell resistance to viral attack.

Increase in 'set-point' of body temperature

Interleukins, interferon and TNF-α in combination have an endogenous pyrogenic action producing prostaglandin E_2 (PGE_2). Prostaglandins are produced from essential fatty acids and are easily transported across the cell walls and into the circulation. They are found in virtually all organs and tissues of the body and exhibit a hormone-like action on the cell, regulating the production of adenyl cyclase; this has the end effect of influencing the metabolic rate of the cell. In the hypothalamus, PGE_2 plays a key role in establishing a specific thermoregulatory change (DiMicco and Zaretsky 2005). It has been noted that there is a high concentration of PGE_2 receptors in the pre-optic area of the hypothalamus responsible for the genesis of the fever (Biddle 2006). The hypothalamus is in close contact with the general circulation by a cluster of neurons termed the circumventricular organ system. This structure extends beyond the blood brain barrier and allows direct contact with both exogenous and endogenous pyrogens in the circulation as well as the PGE_2 found in the cerebral circulation (see Figure 1).

The consequence of this direct action on the hypothalamus is an increase in the body temperature 'set point'. The change in the temperature set by the hypothalamus is now deemed to be physiologically normal. The

Time out 1

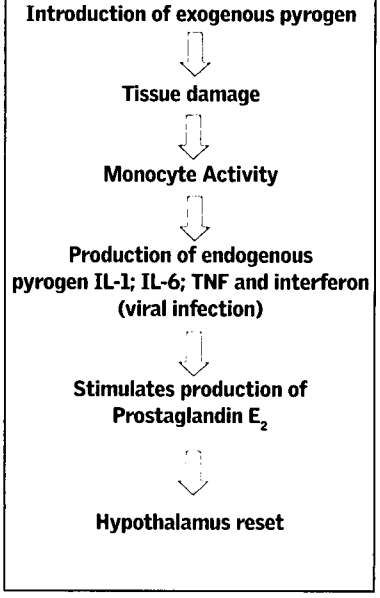
Describe your reactions when faced with a child with a fever. Do you see fever as an expression of disease or illness or as part of the child's physiological response?

Time out 2

Take a sheet of paper and create a list that describes the clinical features produced during a febrile episode. Do not worry too much about terminology at this stage, get your ideas down and compare these with a colleague.

FIGURE 1

Physiology of fever



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temperature will remain at this new preset level as long as there is a production of endogenous pyrogens. A practical analogy of how this process works, before we cover the more complex physiology, would be your central heating system. If your central heating thermostat is set at 21°C then your boiler will heat the system until it reaches that temperature. The boiler automatically switches off when the temperature drifts above 21°C and fires up when the temperature falls below the preset level. If you increase the thermostat temperature to 30°C, the boiler will continue to heat the system until that new temperature is reached and then maintain that temperature at the new set point.

Effect of increased temperature

An increasing body temperature requires a complex and interacting behavioural, endocrine and autonomic nervous system response. There is an increase in the production of the hormone adrenaline by the adrenal medulla. This has the effect of increasing heart rate, metabolic rate and muscle tone. Adrenaline stimulates glycolysis – the conversion of glucose to energy – which speeds up the chemical reactions within the cell and as a by-product produces heat (Huether and McCance 2000). Adrenaline is also a powerful peripheral vasoconstrictor; this has an important role in heat conservation. The decreased lumen of the arterioles increases peripheral vascular resistance shunting blood away from the capillary beds in the skin allowing blood to remain in the deep tissues close to the core, thereby maintaining heat and reducing heat loss through convection, conduction, radiation and evaporation. There is a reduction in the production of anti-diuretic hormone; produced and stored in the posterior segment of the pituitary. Normally, this has the effect of concentrating urine by reducing water loss from the collection ducts of the nephron. However, in a child with a fever this reduction increases fluid loss resulting in a reduction in the vascular and extracellular fluid compartments, as a result less energy is required to maintain the core temperature. These physiological processes also have behavioural consequences. The child will feel cold and as a result will wish to wrap up warm, curl up to reduce the amount of surface area exposed to the environment, or maybe retire to bed.

Now do Time Out 3.

Time out 3

With the information gained from the text above how do you think a febrile child's body will react to any external cooling measures?

Any attempt to cool the periphery will result in an increase in metabolic rate and greater effort to conserve heat from the febrile body. Using the central heating example to explore this point further: the most efficient way to reduce the temperature in the house from 30°C to 21°C would not be opening the windows; this will only result in the boiler attempting to maintain the ambient temperature to 30°C, resulting in a great deal of energy usage. A similar effect can be seen in a febrile child. Any reduction in the peripheral temperature will result in the hypothalamus deeming this to be a threat to the core temperature and as a result initiating a raise in the metabolic rate, possibly excessive shivering or rigours and further heat conservation mechanisms.

Naturally occurring anti-pyretics

In most instances the body temperature during the febrile state rarely exceeds 40°C. The febrile process is self limiting and the body produces a variety of hormones that have an effect of ensuring the temperature does not spiral out of control (see Box 1). It is thought that these naturally occurring anti-pyretic agents effectively limit the destructive effect of the fever through a negative feedback mechanism. The negative feedback of these substances may also account for the fluctuation of temperature seen in the clinical environment. As the fever increases this acts as a stimulus for the production of the anti-pyretic agents that will in effect lower the temperature. As the temperature falls so the stimulus for the release of anti-pyretic agents decreases and as a result the temperature starts to increase to the preset level determined by the hypothalamus providing stimulus for the release of more naturally occurring antipyretic agents.

There is much debate about the actions of the endogenous anti-pyretics but there is evidence that they attenuate fever by acting on the thermoregulatory neurones in the pre-optic region of the anterior hypothalamus and the ventral septum of the limbic system (Roth 2006). There is some evidence to suggest that they may also enhance the role of non steroidal anti-inflammatory drugs by reducing the production of PGE_2 (Richmond 2003). What is clear is that their production provides a natural barrier to an uncontrolled fever.

Benefits of a fever

The evolutionary processes that have allowed the immune system to develop such complex mechanisms have also provided many beneficial actions. With a body temperature of between 37.5°C and 40°C there is an increase in metabolic rate (Thibodeau and Patton 2007). This alone provides many advantages and allows the immune response to become more efficient. With every 1°C increase in body temperature there is a corresponding 10 per cent increase in metabolic rate (Martini 2006). Using the central heating analogy this could be likened to employing additional appliances to boost heat generation, supplementing the output of the central heating system. Enzyme reactions occur at a quicker rate, mobilisation of the cellular immune system improves. The higher temperatures generated by the raised metabolic rate stimulate lymphocyte transformation, motility of polymorphonuclear neutrophils improves, phagocytosis becomes more effective and there is some evidence to suggest that interferon production is influenced (Montague *et al* 2005). Immune efficiency improves and with everything ticking over faster there is also accelerated tissue repair.

To make the circulatory environment hostile to the exogenous pathogens the body shifts from glucose metabolism to one based on lipolysis and proteolysis. Lipolysis is the hydrolysis of fats into free fatty acids available to the circulation; and proteolysis is the enzyme-mediated breakdown of proteins into polypeptides. Reducing the amount of free glucose available in the circulation that can be used by the invading microorganisms helps hinder the disease process. This immune response is further enhanced by the release of acute phase proteins by the liver. As TNF, IL-1 and IL-6 are released by monocytes into the circulation, this has the effect of stimulating the production of an array of proteins and other substances in response to these inflammatory mediators.

Acute phase proteins are used for energy and tissue repair and also have a beneficial effect of binding cations necessary for bacterial replication (McCance and Huether 2002). Cations are positively charged ions and are minerals such as iron, copper and zinc. The effect of binding these circulatory minerals reduces their circulatory concentration and ultimately limits their supply. These minerals are required for bacterial and viral reproduction; if they are not present in normal circulatory concentration the rate of pathogen replication is slowed down and so influencing the progression of the disease process (Montague *et al* 2005). As the fever continues, cellular auto-destruction is used as a method of controlling the spread of infection. Lysosomes, sac-like intracellular vessels containing digestive enzymes, are activated at a low pH created by the actions above. Breakdown of the lysosomes destroys the cells that have been infected by the invading organism.

An increasing body temperature directly affects the invading organisms. Most bacteria are heat sensitive and function most efficiently between 33°C to 41°C (Mackowiak 1981). As the temperature is elevated growth rate and mobility is decreased, self destruction of the bacteria (autolysis) increases and cell walls become damaged (Vertree *et al* 2002). Likewise, viruses are sensitive to environmental temperature and slow down their rate of replication. Stanley *et al* (1990) found that cells chronically infected with Human Immunodeficiency Virus (HIV) had a reduction in viral activity as the temperature increased, decreasing from eight- to 16-fold increase in viral production at 37.5°C to six-fold at temperatures between 41.6°C and 42.5°C. This study demonstrated that as the body temperature increases, viral replication decreases.

Harmful effects of fever

Now do Time Out 4.

Febrile convulsions are the likely reason child health nurses will respond aggressively to fevers. The aetiology of febrile convulsions is still relatively unknown, although there does appear to be a link with a rising, rapid elevation of temperature exceeding 38.8°C rather than a prolonged elevation (Berg 1997). The literature varies on an exact incidence of febrile convulsions in childhood but it appears that around 3 per cent of children between the age of six months and six years are at risk (Pang *et al* 2005). This age range coincides with a period of physiological development where the child's seizure tolerance is relatively low (Champi 2001) and also their exposure to a variety of pathogens is at its highest. Febrile convulsions are generally self limiting and

BOX 1

Naturally Ocurring Anti-pyretics

- Anti-diuretic Hormone,
- α-melanocyte stimulating hormone, produced by the intermediate lobe of the pituitary and involved in the production and release of melanin in the skin and hair
- corticotrophin releasing factor, produced by the neuroendocrine cells of the hypothalamus are released during a febrile episode.

Time out 4

Up until this point the article has dealt with the beneficial effects of fever. List the harmful effects of a fever and in particular what clinical features cause you concern.

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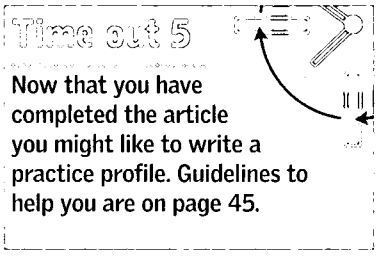
a review of the literature by Russell *et al* (2003) found no evidence that anti-pyretic treatment reduces the incidence of febrile convulsions.

In rare cases, where the body temperature continues to elevate beyond 40°C, there is a greater risk of irreversible cell damage. Neuronal damage occurs above 43°C and thermoregulation ceases with cell destruction around 45°C. Proteins that make up the cell structure and the enzymes responsible for cellular growth and metabolism change shape and ultimately their function deteriorates or denatures as cellular temperature increases (Martini 2006).

One aspect of febrile management that should not be over looked is the burden placed on the body by the fever. A rising metabolic rate places a great demand on the body's energy stores resulting in a high degree of stress throughout the child's body. Some children are at higher medical risk and may need more rigorous assessment, and include those with:

- a fever greater than 41°C
- known bacterial sepsis
- sickle cell anaemia
- suppressed immunity
- congenital heart disease
- a severe head injury.



Conclusion

The NICE (2007) guideline introduces a 'traffic light' system to help assess the risk of serious illness in a child with fever. This allows assessment and management to be directed according to the level of risk. Understanding the physiology of fever supports the application of the NICE guideline: knowing how the body reacts to the presence of pathogens allows you to make informed decisions about the actions to take in caring for the child. A further learning exercise that you could undertake now is to apply the physiological principles explored in this article to the assessment and management guidelines specified in the NICE document.

Now do Time out 5.

References

Berg AT *et al* (1997) Predictors of recurrent febrile seizures. A prospective cohort study. *Archives of Pediatrics and Adolescent Medicine.* 151, 4, 371-378.

Biddle C (2006) The neurobiology of the human febrile response. *AANA Journal.* 74, 2, 145-150.

Casey G (2000) Fever management. *Paediatric Nursing.* 12, 3, 38-42.

Champi C (2001) Managing febrile seizures in children. *Dimensions of Critical Care Nursing.* 20, 5, 2-7.

DiMicco JA, Zaretsky DV (2005) The mysterious role of prostaglandin E_2 on the medullary raphe: a hot topic or not? *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology.* 289, 6, 1589-1591.

Huether SE, McCance KL (2000) *Understanding Pathophysiology. 3rd Edition.* Mosby, Missouri.

Jiang Q *et al* (2000) Febrile core temperature is essential for optimal host defense in bacterial peritonitis. *Infection and Immunity.* 68, 3, 1265-1270.

Kayman H (2003) Management of fever: making evidence-based decisions. *Clinical Pediatrics.* 42, 5, 383-392.

Mackowiak PA (1981) Direct effects of hyperthermia on pathogenic microorganisms: Teleologic implications with regard to fever. *Reviews of Infectious Diseases.* 3, 3, 508-520.

McCance KI, Huether SE (2002) *Pathophysiology: The biologic basis for disease in adults and children.* Mosby, Missouri.

Martini FH (2006) *Fundamentals of Anatomy and Physiology. International Edition. 7th Edition.* Pearson, San Francisco.

Montague SE *et al* (2005) *Physiology for Nursing Practice.* Elsevier, Edinburgh.

National Institute of Health and Clinical Excellence (2007) *Feverish Illness: Assessment and initial management in children younger than five years of age.* www.nice.org.uk

Pang D *et al* (2005) *Paediatrics. 2nd edition.* Mosby, Edinburgh.

Richmond CA (2003) The role of arginine vasopressin in thermoregulation during fever. *The Journal of Neuroscience Nursing.* 35, 5, 281-286.

Roth J (2006) Endogenous antipyretics. *International Journal of Clinical Chemistry.* 371, 1-2, 13-24.

Russell FM *et al* (2003) Evidence on the use of paracetamol in febrile children. *Bulletin of the World Health Organization.* 81, 5, 367-372.

Skills for Health (2004) EC11l: Investigate and diagnose an individual presenting for emergency assistance with fever. http://www.skillsforhealth.org.uk/tools/viewcomp.php?id=2704 [Last accessed: 7 June 2007]

Stanley SK *et al* (1990) Heat shock induction of HIV production from chronically infected promonocytic and T cell lines. *Journal of Immunology.* 145, 4, 1120-1126.

Tatro JB (2000) Endogenous Antipyretics. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America.* 3, 5, 190-201.

Thibodeau GA, Patton KT (2007) *Anatomy and Physiology. 6th edition.* Philadelphia, Mosby.

Thompson HJ (2005) Fever: a concept analysis. *Journal of Advanced Nursing.* 51, 5, 484-492.

Tortora GJ, Derrickson B (2006) *Principles of Anatomy and Physiology. International Edition. 11th edition.* John Wiley and Sons, New Jersey.

Vertree RA *et al* (2002) Whole-body hyperthermia: a review of theory, design and application. *Perfusion.* 17, 4, 279-290.

Walsh AM *et al* (2005) Fever management: paediatric nurses' knowledge, attitudes and influencing factors. *Journal of Advanced Nursing.* 49, 5, 453-464.

Walsh A, Edwards H (2006) Management of childhood fever by parents: literature review. *Journal of Advanced Nursing.* 54, 2, 217-227.