Back-to-basics: Fever is a syndrome and not just pyrexia

Lucien Wasingya-Kasereka and John Kellett

Kitovu Hospital Study Group, Kitovu Hospital, Masaka, Uganda

Correspondence:
John Kellett
kellettjg@gmail.com

Submitted: December 2021
Accepted: January 2022
Published: February 2022

ABSTRACT

Fever is a common presenting complaint in sub-Saharan Africa. Although it has many causes, the symptoms of fever, with or without an elevated body temperature, should always make the clinician suspect infection. The other presentations associated with fever often help identify its likely cause. However, the features of fever that make it life-threatening continue to bedevil physicians.

Key words: fever, pyrexiaa, sepsis, assessment, monitoring

INTRODUCTION

"Fever" is a common presenting complaint, especially in sub-Saharan Africa. Equating "fever" with pyrexia (raised body temperature) is of questionable value. In some African languages the word "fever" is used to describe malaria, or indeed any acute illness. Symptoms reported by patients as "fever" vary and include anorexia, headache, fatigue, rigors, or chills with shivering, feeling hot and then cold, and anxiety.[1]

During exercise heat production increases the body core temperature above the thermoregulatory reference temperature, which results in vasodilatation and sweating. In illnesses this reference temperature may be re-set to a higher level[2] so that heat loss is inhibited by skin vasoconstriction accompanied by chills, shivering and rigors and the patient feeling cold. If the 'set-point' falls, heat is lost by skin vasodilatation, and the patient feels hot and sweaty. The febrile response may also be accompanied by anorexia, headache, malaise, and other cognitive symptoms caused by pyrogenic cytokines.[3]

There are many causes of a raised and prolonged body temperature, which include:

- Infective and inflammatory conditions:
  - Pneumonia and pneumonitis,
  - Urinary tract infections including pyelonephritis,
  - Dysentery,
  - Venous thromboembolic disease / phlebitis,
  - Pancreatitis,
  - Ulcerative colitis and Crohn's disease,
  - Sarcoidosis.
- Connective tissue disorders.
- Meningeal and cerebral haemorrhages.
- Skin conditions: pemphigus, bullous pemphigoid, exfoliative dermatitis.

Citation: Wasingya-Kasereka and Kellett. Back-to-basics: Fever is a syndrome and not just pyrexia. South Sudan Medical Journal 2022;15(1):33-38 DOI: https://dx.doi.org/10.4314/ssmj.v15i1.8

- Primary and secondary malignancies.
- Allergic conditions.
- Drug reactions e.g., malignant hyperthermia.
- Fictitious fever in mentally disturbed patients.

The clinical value of the symptoms of "fever", with or without an elevated body temperature, is that they should always make the clinician suspect infection.[4,5] In addition to the symptoms of fever several other features also suggest infection, which include:

- Skin or soft tissue changes: hyperaemia and oedema, or chronic ulcerations,
- Airway symptoms: sore throat, rhinorrhoea, cough, sputum, or respiration dependent chest pain,
- Gastrointestinal symptoms: diarrhoea or abdominal pain,
- Genitourinary symptoms: dysuria, frequent or abnormal urination, low back pain,
- Feeling faint.[5]
- Myalgia is a common symptom with viral infections (especially SAR-Cov2), influenza and dengue fever and is also seen in many other infections (Lyme disease, malaria, and pneumonia).

Most "fevers" arise acutely and are often upper respiratory tract viral infections, which are recovered from within a week. However, this is not always so. There are no bedside findings that reliably distinguish between viral and bacterial infections. Bacteria are always present in the healthy body, and a bacterial infection only occurs when bacteria are in areas of the body in which they are not normally present. Usually, the body will confine these infections to a painful local area of inflammation, but the development of "fever" symptoms and/or a pyrexia suggests that the infection has become systemic. In contrast, there should be no viruses anywhere in the body, so all viral infections are likely to have systemic manifestations even if rapidly contained within their area of entry to the body (i.e., usually the respiratory or gastro-intestinal tract). The interval between the early nonspecific symptoms and the development of specific symptoms and signs may be minutes in meningococcal sepsis, and hours or even days in other conditions. Therefore, every patient presenting with fever needs an immediate careful bedside assessment, which considers the likely infectious agent, anticipates the likely course of the illness and the monitoring required to follow its clinical progress.

CLINICAL ASSESSMENT

Associated symptoms and signs

The presentation of a patient with suspected infection often indicates the likely cause, and the immediate actions needed. These are key examples:

1. Breathlessness: pneumonia, which requires prompt antibiotic therapy in all age groups.
2. Cough: consider pneumonia, chronic obstructive airway disease, tuberculosis.
3. Night sweats: tuberculosis
4. Dysuria with or without loin pain: pyelonephritis.
5. Swollen tender joint: pyogenic arthritis - an emergency!
6. Tender bone: osteomyelitis (NB in diabetic feet)
7. Lymphadenopathy: lymphoma, HIV, glandular fever, early hepatitis
8. Headache: influenza, consider meningitis or sub-arachnoid haemorrhage. Bacterial meningitis usually kills within minutes or hours, while viral meningitis usually presents to hospital with a three-day history and then improve.
9. Muscle aches: influenza, but could be dengue, leptospirosis, poliomyelitis, leukaemia, polymyositis, malignant hyperthermia.
10. Diarrhoea: always consider salmonella. Do not treat diarrhoea with antibiotics. Salmonella and Shigella are often resistant, and cultures must be obtained off antibiotics. If you give antibiotics the chances are that all you will do is prevent a resistant organism from being cultured and we will remain in the dark for weeks.
11. Rash: If haemorrhagic consider Ebola or similar fevers. If like sunburn early toxic shock possible. Petechia or erythema suggest meningococcal infection.
12. Abdominal pain: gall stones, appendicitis, hernia, pancreatitis.
13. Sore Throat: streptococcal tonsillitis or infectious mononucleosis.
14. "Fever" or temperature only: If raised white cell count consider pyogenic infection, leptospirosis, or liver abscess. If no elevation of white cell count, consider viral infection, salmonella, early sepsis, pancytopenia, bacterial endocarditis, TB, auto-immune disease, and neoplasia.

Patterns of pyrexia

Many physicians have abandoned the use of the classical "fever patterns" associated with different diseases described by Wunderlich, because they are greatly influenced by antibiotic therapy and diagnostic bacteriology, if available, is a more dependable.[6] Nevertheless, fever patterns may

still be useful in low-resource settings to guide empiric treatment.

Elevated temperatures can be arbitrarily classified into:

- Acute: lasts less than seven days and is characteristics of malaria and viral upper respiratory tract infection.
- Subacute: lasts approximately two weeks, such as occurs in typhoid fever and intra-abdominal abscess.
- Chronic or persistent pyrexia lasts longer than two weeks and is seen in chronic bacterial infections e.g., tuberculosis, HIV, cancers, and connective tissue diseases.

There are three common temperature patterns:[3]

- Continuous: the temperature does not fluctuate more than 1°C during any 24-hour period but is never normal as with lobar and gram-negative pneumonia, typhoid, acute bacterial meningitis, malaria, and urinary tract infection. A slow stepwise temperature rise, and a high plateau are classical of typhoid fever. However, this pattern is often lost if anti-pyretics and antibiotics are given.
- Remittent fever is a variation with daily fluctuations exceeding 2°C but never returning to normal.
- Intermittent: a normal / low temperature in the morning and peaking in the evening often with chills occurs with localised pyogenic infections, in malaria (with spikes daily, every third or fourth day), and acute brucellosis (usually with marked sweating). Salmonellosis, miliary TB, gonococcal and meningococcal endocarditis may display two daily peaks.

• Other patterns include:

  * Saddle-back (biphasic): dengue, yellow fever, relapsing fever (Borrelia genus) and occasionally with influenza, poliomyelitis and lymphocytic choriomeningitis.
  * Pel-Ebstein: weekly or longer periods of pyrexia with intervals of normal temperature: Hodgkin's disease, brucellosis and occasionally tuberculosis
  * Reversed diurnal pattern (higher in the morning and lower temperature in the evening) may be seen in miliary TB, salmonellosis, liver abscess, bacterial endocarditis.
  * Jarisch-Herxheimer: sharp increase in temperature after penicillin treatment can occur in syphilis, leptospirosis, relapsing fever.

Relative bradycardia

The pulse increases by approximately eight beats per minute for each degree Celsius rise. However, there are exceptions, such as yellow fever and typhoid fever, where such an increase in pulse rate does not occur i.e., there is "relative bradycardia". The latter also occurs in some viral infections (e.g., sandfly and dengue fever) and in psittacosis, Q fever, typhus, malaria, leptospirosis, and viral haemorrhagic fevers.[7] More commonly relative bradycardia occurs in infected patients taking beta-blockers. It is also a common feature of all fevers caused by drugs, lymphomas, and central nervous system disorders such as intracranial bleeds and tumours.

What makes a fever dangerous?

Identifying the features of "fever", with or without a temperature, that make it life-threatening continue to bedevil physicians. Fever and pyrexia are not the same thing. Less than 5% of patients admitted to a low-resource hospital in Uganda had a temperature >38 °C on admission, whereas 11% had a temperature ≤36 °C and more than 15% complained of fever; only 11% of patients complaining of "fever" on admission had a temperature >38°C, and 9% had a temperature ≤38 °C. Unless they had rigors, patients complaining of "fever" were no more likely to have an increased temperature on presentation than patients not complaining of "fever". Patients complaining of "fever" were younger, had shorter lengths of hospital stay, lower blood pressure and respiratory rates and higher oxygen saturations on admission than patients not complaining of fever, and did not have an increased risk of in-hospital death.[1]

Patients complaining of fever should be touched to determine if they feel hot and sweaty, or cold and clammy. Those who are cold and clammy were more likely to die.[1] Although rigors are strongly associated with bacteraemia,[4] an elevated temperature alone is a weak predictor of mortality and indeed in infected patients has been associated with a survival benefit, whereas a low temperature is associated with an increased mortality.[8]

Acute sickness may be associated with an "unhealthy" body odour,[9] altered gait patterns,[10] and the response to overt sickness behaviours, such as coughing. Conversely, supine emergency room patients with crossed ankles, crossed hands behind the neck, or folded hands over the upper abdomen have been reported to be highly unlikely to have any acute critical condition.[11] Facial cues such as paler lips and skin, a more swollen face, droopier corners of the mouth, hanging eyelids, redder eyes, less glossy and patchy skin, and appearing tired, can aid in the detection of acutely sick and potentially contagious people. Ill patients have less variability in their facial expression in response to emotional cues;[12] they may appear anxious and flushed with bright eyes, or the eyes may be congested and the facial expression dull. The alae nasi of patients with pneumonia may dilate with each inspiration and

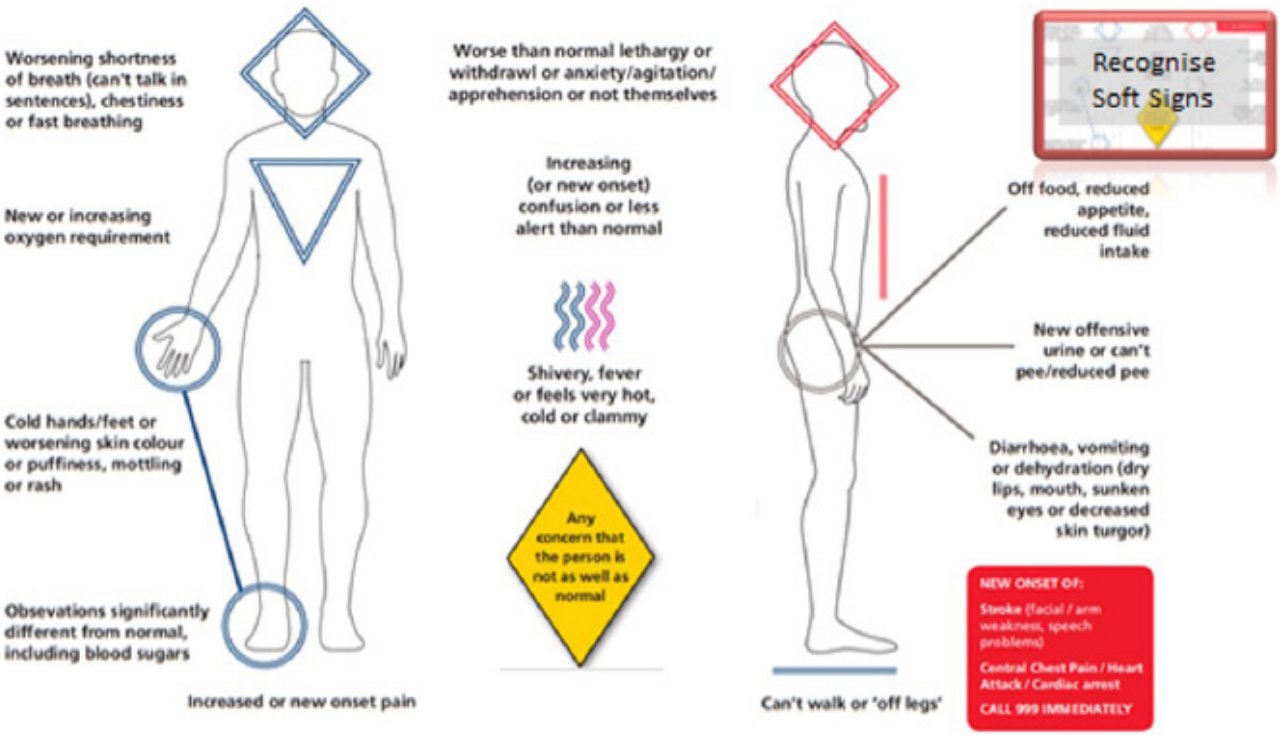

Figure 1. Soft signs to identify early indications of infection and sepsis (reproduced with permission from the Wessex Academic Health Science Network).

commonly have Herpes labialis.[13]

In a low resource hospital in sub-Saharan Africa the intuition of inexperienced clinicians accurately discriminated between patients who were likely to survive and those who were likely to die.[14] Most of these concerning patient characteristics selected by intuition are included in the Dutch Early Nurse Worry Indicator Score (DENWIS)[15] and have been adopted as "soft" vital signs of infection by Wessex Patient Safety Collaborative in the UK[16] to be used as triggers for further clinical assessment, even before there are significant vital sign changes (Figure 1).

Recognition of Sepsis

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. All deaths, including those caused by infection, are caused by hypoxia and hypoperfusion that causes multi-organ failure. Increasing oxygen and perfusion demand, therefore, produce many of the common symptoms and signs of acute illness (see Figure 1) which force the patient to rest so that perfusion and oxygen demands can again be met. As peripheral perfusion and oxygenation declines the patient may appear pale and his or her periphery becomes cold and cyanotic. Interventions that successfully increase oxygenation and cardiac output will usually improve the patient's condition. However, this improvement will only continue if the underlying causes of hypoperfusion and/ or hypoxemia are identified and overcome.

The latest definition of sepsis defines organ dysfunction as an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more. This requires laboratory tests that are unlikely to be available in low resource settings. The "quick" SOFA score is a useful alternative which indicates that sepsis is likely if two or more of the following are present:

- Alteration in mental status,
- Systolic blood pressure <100mmHg,
- Respiratory rate >22 breaths per minute.[17]

All the classic vital signs of respiratory rate, temperature, pulse rate and blood pressure are indicators of tissue perfusion and oxygen delivery. Pulse oximetry, which measures oxygenation more explicitly has become widely adopted as the fifth vital sign. Capillary refill time (CRT) and urine output are also measures of tissue perfusion. CRT monitors the perfusion of peripheral tissues: skin and muscles are the first to be affected by impaired blood flow in pre-shock states (whether caused by infection or injury) and the last to be re-perfused after resuscitation. Hypoperfusion and poor oxygenation cause fatigue, so that eventually the patient is forced to take to their bed and in severe illness becomes prostrate and often

confused. Therefore, changes in mobility[18] and mental function[19] should also be considered vital signs.

The four classic vital signs reflect the continuous physiological adjustments required to maintain homeostasis, which ensures the body is alert to danger with enough mobility to avoid or confront it. The brain is the priority organ. Therefore, in any acute illness there is balance between vital sign changes, mobility, and mental alertness, which reflect the body's capacity to adjust and adapt its available resources appropriately.[20] Any patients who must be "looked after" in hospital for an acute illness has started to exceed their physiological capacity to adapt and they are far more likely to die than members of the general population of the same age.[21] The time it takes for the body to return to normal depends on the severity of the illness and their body's resilience. Until patients "get better" their vital signs, mobility and mental status may fluctuate. Therefore, their clinical course will remain unpredictable and they will require constant monitoring.

MONITORING THE COURSE OF FEVER

A high temperature in acute falciparum malaria, shigella infections and dengue fever indicates a poor prognosis but other vital sign changes are even more predictive of outcome.[3] The normal pulse to respiratory rate ratio is about 4.0 but classically falls with pneumonia and other respiratory conditions.[13] Breathlessness, respiratory distress, cyanosis, vital sign changes and altered consciousness indicate hypoxia. The oximeter is widely available, is easily used and rapidly measures oxygen saturation and pulse rate. The response of both oxygen saturation and pulse rate to exercise and change in posture can be quickly assessed. A rise in heart rate of more than 30 beats per minute on standing indicates the presence of hypovolemia, while a fall in oxygen saturation with exercise indicates a likelihood of serious lung or heart disease.[22] The ratio of oxygen saturation to respiratory rate identifies patients on supplemental oxygen who need intubation and ventilation.[23]

An increased resting heart rate is a risk factor for cardiovascular mortality and hypotension is associated with a high mortality. Once the heart rate exceeds the systolic blood pressure it is likely that the patient has a low intravascular volume or a severely depressed cardiac output. This can be distinguished by a careful fluid challenge of intravenous fluid. The ratio between pulse rate and systolic blood pressure (Shock Index) is normally 0.5 to 0.7 in adults. Persistent elevation of the Shock Index over 1.0 for several hours following trauma or acute circulatory failure has been related to a poor outcome.[24] A pulse rate below 100 beats per minute with a systolic blood pressure over 110 mmHg and a respiratory rate of 16 breaths per minute indicates a blood loss of less than 750 ml. A pulse rate over 140 beats per minute with a systolic blood pressure below 90 mmHg and a respiratory rate over 26 breaths per minute indicates severe shock (Class IV) or a blood loss of over 2000 ml.[25]

CONCLUSION

The syndrome of fever, with or without an abnormal body temperature, is common and indicates the likely presence of infection. Although identifying the infective agent causing fever can require expensive technology, which may be unavailable in low-resource settings, much can be learned from a careful history and bedside examination and then monitoring the course of the patient. Although worldwide most fevers come on acutely, are usually upper respiratory tract viral infections and patients recover within a week, this is not always the case. Temperature measurements alone are of little prognostic value. However, in combination with other vital signs the pattern of temperature recordings can provide important diagnostic clues. The severity of infection is determined by the perfusion and oxygenation of vital organs, which are best assessed by a full examination of the patient to determine and promptly correct underlying pathophysiology by the judicious use of oxygen, fluids, and appropriate antibiotics.

Acknowledgements

The authors acknowledge the help of Dr David Tibbutt in writing this paper. They also thank the members of the Kitovu Hospital Study Group whose research greatly increased the authors' knowledge and understanding of fever.

References

1. Nakitende I, Namujwiga T, Kellett J, Opio M, Lumala L.Patient reported symptoms, body temperature and hospital mortality: an observational study in a low resource healthcare environment. QJM: An International Journal of Medicine 2018 Oct;111(10):691–697.
2. Cannon JG. Perspective on fever: the basic science and conventional medicine. Complement Ther Med 2013; 21: S54–60.
3. Ogoina D. Fever, fever patterns and diseases called 'fever' – A review. J Infect Public Health 2011; 4:108–24.
4. Coburn B, Morris AM, Tomlinson G, Detsky AS. Does this adult patient with suspected bacteraemia require blood cultures? JAMA 2012; 308:502–11.
5. Martins FS, Guedes GG, Santos TM, de Carvalho-Filho MA. Suspected infection in afebrile patients: are they septic? Medicine (Baltimore) 2017; 96:e6299.

6. Musher DM, Fainstein V, Young EJ, Pruett TL. Fever Patterns - their lack of clinical significance. Arch Intern Med 1979;139:1225-1228

7. Cunha BA. The diagnostic significance of relative bradycardia in infectious disease. Clinical Microbiology and Infection 2000;6:633-634.

8. Rumbus Z, Matics R, Hegyi P, Zsiboras C, Szabo I, Illes A, et al. Fever is associated with reduced, hypothermia with increased mortality in septic patients: a meta-analysis of clinical trials. PLoS One 2017; 12:e0170152.

9. Olsson MJ et al. 2014 The scent of disease: human body odor contains an early chemosensory cue of sickness. Psychol. Sci. 25, 817–823. https://doi.org/10.1177/0956797613515681

10. Sundelin T, Karshikoff B, Axelsson E, Hoglund CO, Lekander M, Axelsson J. 2015 Sick man walking: perception of health status from body motion. Brain Behav. Immun. 48, 53–56. https://doi.org/10.1016/j.bbi.2015.03.007

11. Rapoport MJ, Leonov Y, Leibovitz A. Body language in the emergency room. Lancet 1995;345:1060

12. Kline JA, Neumann D, Haug MA, Kammer DJ, Krabill VA. Decreased facial expression variability in patients with serious cardiopulmonary disease in the emergency care setting. Emerg Med J 2015;32:3–8.

13. Osler W. The principles and practices of medicine. 4th edition. Edinburgh and London: Young J. Pentland 1901.

14. Wasingya-Kasereka L, Nabatanzi P, Nakitende I, Nabiryo J, Namujwiga T, Kellett J, on behalf of the Kitovu Hospital Study Group. Oxygen use in low-resource settings: An intervention still triggered by intuition Resusc Plus 2020 Dec 7;4:100056. https://doi.org/10.1016/j.resplu.2020.100056. eCollection 2020 Dec

15. Douw G, Schoonhoven L, Holwerda T, Huisman-de Waal G, van Zanten AR, van Achterberg T, van der Hoeven JG. Nurses' worry or concern and early recognition of deteriorating patients on general wards in acute care hospitals: a systematic review. Crit Care. 2015;19:230. https://doi.org/10.1186/s13054-015-0950-5.

16. Using Soft Signs to Identify early indications of Physical Deterioration. Wessex Academic Health Science Network. https://bit.ly/3fWsmJ4

17. Singer M, Deutschman CS, Seymour CW. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-810.

18. Brabrand M, Kellett J, Opio M, Cooksley T, Nickel CH. Should Impaired Mobility on Presentation be a vital sign? Acta Anaesthesiologica Scandinavica 2018;62(7):945-952.

19. Flaherty J.H., Rudolph J., Shay K., Kamholz B., Bookvar K.S., Shaughnessy M., Shapiro R., Stein J., Weir C., Edes T. Delirium is a serious and unrecognized problem: why assessment of mental status should be the sixth vital sign. J. Am. Med. Dir. Assoc. 2007;8:273-275.

20. Whitson HE, Cohen HJ, Schmader K, Morey MC, Kuchel G, Colon-Emeric C. Physical Resilience: Not Simply the Opposite of Frailty. J Am Geriatr Soc. 2018 August;66(8):1459–1461

21. Fløjstrup M, Henriksen DP, Brabrand M. An acute hospital admission greatly increases one-year mortality – Getting sick and ending up in hospital is bad for you: A multicentre retrospective cohort study. European Journal of Internal Medicine 2017;45: 5–7

22. Warner L., Bartlett K.A., Charles S.A., O'Brien L.M. Use of pulse oximetry with exercise in the diagnosis of PCP. Int. Conf. AIDS 1991;7:232.

23. Roca O, Messika J, Caralt B, García-de-Acilu M, Sztrymf B, Ricard JD, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: the utility of the ROX index. J Crit Care 2016;35:200–205

24. Allgower M, Buri C. Shock index. Dtsch Med Wochenschr 1967;46:1–10.

25. Fundamental Critical Care Support 3rd Edition. ed. J.L. Zimmerman. Society of Critical Care Medicine Des Plaines, Illinois; 2001, p.9-4.