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Continuing Medical Education

Rheumatological disorders and fever



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ABSTRACT

Causes of pyrexia in patients are mainly categorized in four major sub-groups, they are due to infections, malignancies, autoimmune conditions or due to miscellaneous causes. A physician needs to work like a detective to diagnose the etiology of fever. Other rheumatological causes of fever are usually less likely to be considered during workup for patients. The rheumatological disorders associated with pyrexia include inflammatory joint diseases, connective tissue disorders, vasculitides, infections of joints (viral arthritis, septic arthritis) and crystal induced arthritis. This article elucidates important rheumatological causes of fever in adults and children.

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1. Introduction

Pyrexia is not uncommon in rheumatological conditions and despite the fact that in many series it is the second commonest non-infectious causes of pyrexia¹ many physicians do not consider this as an important differential in a patient with pyrexia. The Rheumatological conditions which may be associated with fever include:

1. Rheumatoid arthritis and other synovial disorders like Adult Onset Still's disease.
2. Connective tissue disorder like Systemic Lupus Erythematosus, Scleroderma.
3. Spondyloarthropathies like Ankylosing Spondylitis, SAPHO.
4. Vasculitides like polyarteritis nodosa, microscopic polyangiitis, Giant cell arteritis.
5. Infection related rheumatic diseases such as septic arthritis, Mycobacterial, Brucella infection, Acute Rheumatic fever, reactive arthritis.
6. Other systemic illnesses like sarcoidosis.

7. Pediatric Rheumatological disorders such as juvenile idiopathic arthritis and autoinflammatory disorders.
8. Crystal induced arthropathies.

2. Definition

The normal body temperature is in the range of 36.5°–37.5 °C and is maintained by the hypothalamus. There is usually a diurnal variation with highest at 4–6 p.m. Fever is defined as any temperature >37.2° in morning or 37.7 °C in evening. The advantages and disadvantages of fever are enumerated (Table 1).

3. Pathophysiology of fever in rheumatic diseases

Fever as a presenting symptom of a rheumatological disease can be difficult to evaluate as the patient may not have any

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Table 1 – Advantages & disadvantages of fever.

Advantages	Disadvantages
Inhibition of pathogenic microbes	Accelerated metabolism
Enhanced antibody production	Tissue damage
Destruction of pathogenic microbes	

other systemic symptoms at the onset and also there is a lack of awareness about these conditions among the treated physicians.

Pyrogens are any substance which causes fever. If the substance causing fever is from outside, it is called exogenous pyrogen (e.g. endotoxin produced by gram negative bacteria or super antigen produced by gram positive bacteria) and if the substance is in the body it is called pyrogenic cytokine (formally called endogenous pyrogen). The pyrogenic cytokines include Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor necrosis factor (TNF) and Interferon- α . Many microbes (bacterial, viral and fungal) induce pyrogenic cytokines production. Immuno-inflammatory condition (such as connective tissue disorders) also enhances the production pyrogenic cytokines in absence of micro-organism. The augmented production of Interleukin-1, Interleukin-6 and Tumor necrosis factor acts either together or individually to cause fever by acting on the hypothalamus.² Fever occurs due to increase production of prostaglandin E in endothelium of hypothalamus. The pyrogenic cytokines also increase levels of prostaglandin E in peripheral tissue which are responsible for non-specific myalgias and arthralgias seen in patients with fever. Arachidonic acid metabolites are other contributors to hyperpyrexia associated with many forms of acute and chronic inflammation. Fig. 1 depicts schematic pathophysiology of fever. The mechanism of autoinflammatory fevers have been discussed separately below.

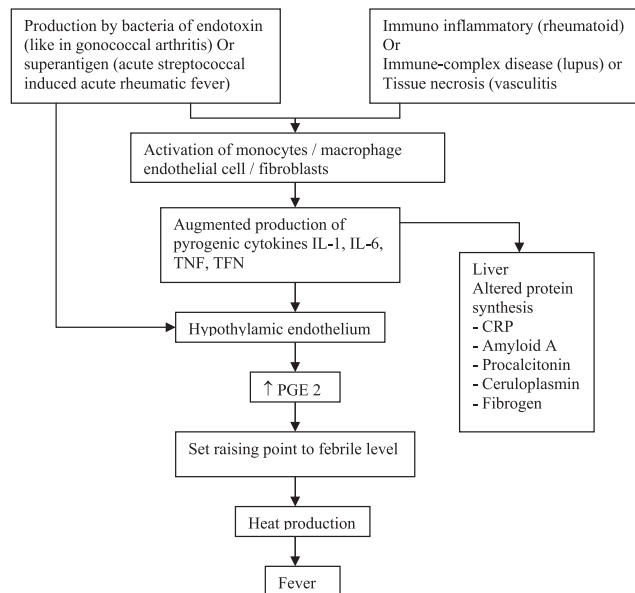


Fig. 1 – Pathogenesis of fever in rheumatic disease.

4. Patterns of fever in rheumatological conditions

Fever patterns can be considered as:

1. Intermittent – when the temperature is swinging greater than 1 °C but returns to normal in between. Systemic onset juvenile idiopathic arthritis in the child or Adult Onset Still's disease is examples of this pattern.
2. Continuous – when the temperature varies less than 1 °C and does not return to normal. It is seen in conditions like brucellosis, Lyme's disease and certain forms of vasculitis like Kawasaki's disease.
3. Remittent – when the temperature varies greater than 1 °C and does not return to normal.
4. Periodic or recurrent fever – alternating febrile and afebrile episodes lasting over days. Still's disease, Behcet's disease, and familial periodic fever syndromes are some of the examples.

5. Disorders of immune mediated injury

5.1. Rheumatoid arthritis

Fever has been historically associated with rheumatoid arthritis in earlier reports of 1920, where it was considered as a chronic infectious arthritis, but was also considered as a therapeutic agent by way of inducing fever as a vasodilatory response to increase blood supply to joint and disease activity thereby suppressing inflammation.³

Low grade fever is not uncommon in rheumatoid arthritis and it usually represents ongoing synovitis in joints and disease activity. It may be associated with other non-articular constitutional features like malaise, fatigue, myalgias, tiredness, and weakness along with loss of appetite. The low grade pyrexia in rheumatoid arthritis responds to controlling disease activity with disease modifying agents and does not require antipyretic agents.

Whereas majority of patients of rheumatoid arthritis have insidious onset fever (more than 50%), occasionally patient of rheumatoid may have very acute onset of fever with polyarthrits and extra-articular manifestations (10–25%).⁴ Systemic features of serositis like pericarditis or pleuritis if presently acutely can also be associated with fever.

5.2. Systemic lupus erythematosus

Majority of patients with lupus present with fever at diagnosis both in Indian and Western series.^{5,6} No pattern of fever is characteristic of lupus. Fever may be sole presentation in lupus.⁷ Low grade fever in lupus is related to disease activity. The important causes of fever in lupus patient includes: i. Dermatitis, ii. Arthritis and iii. Pleuropericardial disease.

Fever in a treated case of SLE should be attributed to opportunistic infections until proved otherwise.⁸ Infection in lupus is difficult to diagnose because both disease activity and infection can give rise to fever. Table 2 gives the differentiation of lupus activity from infection. Procalcitonin is a useful

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