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Fever and musculoskeletal symptoms in an adult: differential diagnosis and management

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Fever in the context of a patient with musculoskeletal symptoms is a sign of systemic inflammation. Initial management should be targeted at the identification of the organ systems affected and the search for a precise diagnosis. The main challenge is to differentiate between an infectious aetiology from an immune-inflammatory cause. Patient history and physical examination are key elements in the diagnostic work-up in order to direct appropriate laboratory investigations, as well as radiological and biopsy procedures. Advances in microbiological techniques and molecular genetics have provided additional tools for the clinician. Unfortunately, there is no simple algorithm to direct the diagnostic work-up, which still largely depends on the recognition of patterns of clinical presentations and the corresponding laboratory abnormalities.

Key words: fever; musculoskeletal system; management; clinical approach.

Fever is a systemic manifestation of inflammation and is an important symptom although it is non-specific. Its presence, which sometimes needs to be confirmed personally by the clinician in order to rule out factitious causes, is a strong indication of an inflammatory pathological process, and alerts the clinician to a range of differential diagnoses, especially when it occurs in the context of musculoskeletal symptoms.

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The regulation of body temperature and its dysregulation in febrile illnesses are summarized in Figure 1.[1] Pyrogens, either exogenous or endogenous, act on the hypothalamic endothelium that is central to thermoregulation. Inflammatory cytokines [e.g. tumour necrosis factor (TNF)-α, interleukin (IL)-1, IL-6], as well as microbial toxins, induce secretion of prostaglandin E2 by the hypothalamus, that in turn leads to increased levels of cAMP. The result is an alteration of the hypothalamic thermoregulatory set point and fever. Experimental evidence for the role of cytokines has been confirmed by direct injection of cytokines into the cerebral ventricles and by gene knockout mice, which showed that both IL-1 and TNF act proximally to IL-6 in order to induce fever.

In clinical practice, the presence of fever alerts the clinician to two broad pathological groupings: infection or a non-infectious source of systemic inflammation. This chapter will concentrate on those aspects that appear to be the most relevant to practicing rheumatologists in developed countries, as the patterns of infectious diseases will be very different in developing or undeveloped countries. The clinical approach

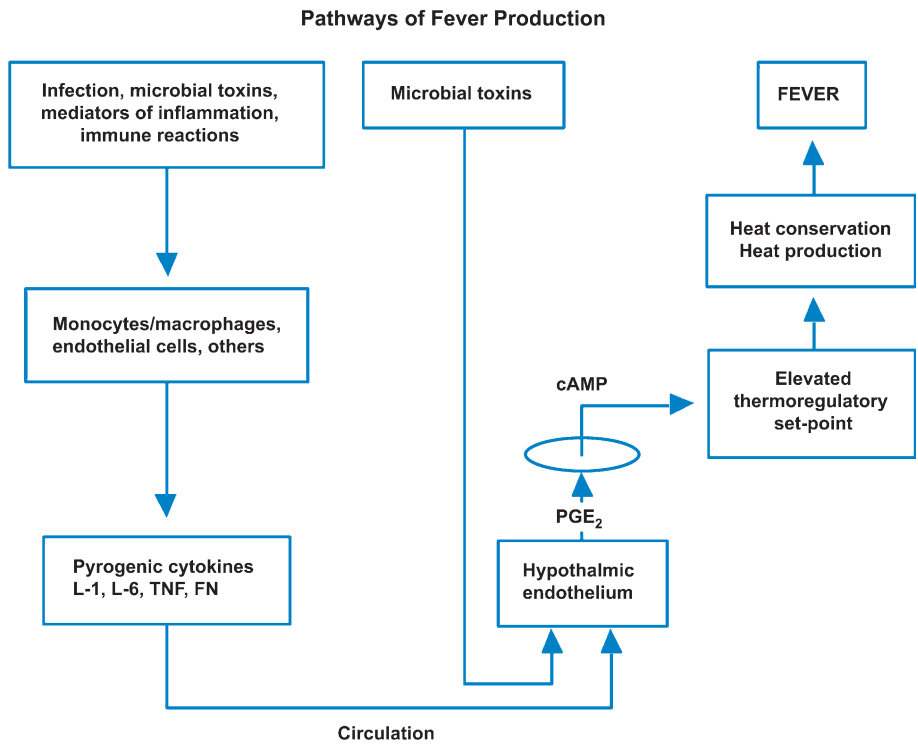

Figure 1. Pathophysiology of fever.[1] Starting from the upper left, infections, microbial toxins, and other macrophage activators stimulate the production of pyrogenic cytokines. These, in turn, gain access to the circulation and interact with specific receptors (each cytokine has its own receptor) on the hypothalamic endothelium. In addition, microbial toxins can directly trigger receptors on the same endothelium in the hypothalamus and these receptors are also specific for each class of toxins. The response of the hypothalamic endothelium to either cytokines or toxins is the same, that is, the production of prostaglandin E2. Cyclic AMP is released by PGE2 and acts as a neurotransmitter. Elevated cAMP raises the set-point and triggers peripheral heat conservation and production.

to a patient who presents for the first time with fever and musculoskeletal symptoms will be reviewed here. This chapter will not cover the problem of infection in immunosuppressed patients with musculoskeletal diseases, although many of the diagnostic steps are similar.

DIFFERENTIAL DIAGNOSIS

In the investigation of fever of unknown origin (FUO), three broad categories of disease represent most of the diagnoses: infectious diseases; systemic auto-inflammatory diseases; and neoplastic diseases. In a review of previous published studies, between 13% and 29% of FUO cases reported in studies since the 1980s are accounted for by collagen vascular diseases, and 21–54% are due to infectious causes. However, up to 30% of FUO cases resist diagnosis despite advances in diagnostic technology such as imaging or biological techniques.[2] In adults presenting with fever and musculoskeletal symptoms, the differential diagnosis is similarly broad (Table 1), and an extensive review of all possible causes of fever associated with musculoskeletal symptoms is beyond the scope of this chapter.

Primary articular diseases may be associated with fever, especially during an acute excacerbation. Fever is present in about 50% of cases of polyarticular gout[3], and a clinical presentation mimicking meningitis has been described in calcium pyrophosphate deposition (CPPD) disease affecting the cervical spine.[4] Rheumatoid arthritis (RA) can present with fever, especially in elderly patients with features of weight loss and lymphadenopathy. RA complicated by vasculitis can also present with systemic signs. In these cases, the underlying diagnosis is usually obvious and the main question is if there is also a septic state. A low-grade indolent fever accompanied by asthenia and weight loss is a common presenting symptom in polymyalgia rheumatica, and the diagnosis has to be guided by the typical clinical features as well as the exclusion of other diseases such as endocarditis or neoplastic conditions.

Fever frequently accompanies systemic lupus erythaematosus (SLE) and related connective tissue disease, although arthralgia and arthritis are still the most common manifestations.[5] All forms of vasculitis may present with fever. In general, fever is mild and clearly differentiated from the high fevers seen in sepsis or the periodic syndromes. Pattern and recurrence are the key elements that suggest these diagnoses.[6]

The other causes are likely to be less frequent than the two broad groups described above. However, a number of well-recognized clinical syndromes need to be considered. In sarcoidosis, fever commonly accompanies Löfgren's syndrome, the triad of acute arthritis, erythaema nodosum and bilateral hilar adenopathy. Uveoparotid fever (Heerfordt's syndrome) is a manifestation of sarcoidosis that is more common in men, presenting with a febrile arthropathy, enlarged parotid glands and uveitis.[7] Whipple's disease is a rare infectious disease due to *Tropheryma whippeli*, a Gram-positive actinomycetes.[8] Articular manifestations are common at initial presentation, often preceding intestinal signs, and may be accompanied by fever. Schnitzler's syndrome is a rare condition that presents with immunoglobulin M monoclonal gammapathy, intermittent fever, chronic urticaria, bone pains, arthralgia or arthritis. Fever is the cardinal symptom and musculoskeletal manifestations are present in 80% of patients.[9] Adult-onset Still's disease (AOSD) has a diagnosis of exclusion as no specific tests are available (see later for discussion on role of ferritin measurements). The classical case of high spiking fevers, evanescent rash and arthritis should not pose a major diagnostic challenge, but incomplete forms of the disease have also been described and the

Table 1. Differential diagnosis of fever and musculoskeletal symptoms.

Inflammatory disorders	
Auto-inflammatory diseases	Adult-onset Still's disease Periodic syndromes (Mediterranean fever, tumour-necrosis-factor-associated periodic syndrome, Muckle-Wells syndrome etc.)
Rheumatic inflammatory diseases	Rheumatoid arthritis Reactive arthritis including rheumatic fever, and the spondylarthropathies Polymyalgia rheumatica
Connective tissue diseases	Systemic lupus erythaematosus Inflammatory myopathy Mixed connective tissue disease Polychondritis
Vasculitis	Wegener's granulomatosis Microscopic polyangeitis Churg-Strauss's syndrome Henoch-Schönlein purpura Polyarteritis nodosa Behçet's disease Sweet's syndrome Temporal arteritis Takayasu
Granulomatous diseases	Sarcoidosis Crohn's disease
Infectious diseases	Bacterial endocarditis Bacterial infection (gonococcaemia, meningococcaemia, brucella, Lyme's disease, syphilis) Viral (hepatitis C virus, parvovirus B19, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, influenza, coxsackie, adenovirus) Tuberculosis Dengue fever and other flaviviruses Alphaviruses (Sindbis, O'nyong-nyong, Ross river, etc.) Whipple's disease Rat bite fever
Malignancies	Multiple myeloma Lymphoma, leukaemia Disseminated metastasis Atrial myxoma Schnitzler's syndrome
Metabolic	CPPD disease Gout
Miscellaneous	Facticious fever Haemophagocytosis Sickle cell crisis

This table is not exhaustive and should be considered as examples and reminders of some large groups of diseases where fever associated with musculoskeletal symptoms may be part of the clinical presentation.

rash may not always be typical.[10] Finally, there is increasing awareness of the hereditary periodic fever syndromes in the differential diagnosis.[11] A positive family history is not always present, even in familial Mediterranean fever, but the availability of a genetic diagnosis has greatly advanced its identification. The other syndromes [e.g. tumour-necrosis-factor-associated periodic syndrome (TRAPS) and chronic inflammatory neurological cutaneous and articular syndrome/Muckle-Wells syndrome] are rare, but the increased understanding of their molecular pathology has also enabled more accurate diagnosis.

Although tuberculosis is not a common infectious disease in developed countries, there have been a number of recent reports of a possible recrudescence. In an elderly patient presenting with an indolent fever and arthritis, infection by *Mycobacterium tuberculosis* has to be considered.[12] Finally, in times of mass tourism and migration, it is important to consider some 'exotic' infectious diseases, even if they are uncommon and extremely rare in the local practice setting. Dengue fever[13] and other flavi- and alphaviruses are associated with severe myalgias and arthralgias.[14,15] Most are endemic in popular tourist destinations, and the possibility of such diseases should certainly be raised in the case of recent travel.

HOW USEFUL IS PATIENT HISTORY?

The first and probably most important clinical step is to obtain a detailed history from the patient. Although the precise history of a fever is not as useful a diagnostic tool as was once thought, it can still provide useful diagnostic pointers. Fever is seldom continuous and unabating, and it is important to establish if there is a periodic pattern to the symptom. Its onset may be acute or insidious, and the timing of its appearance in the context of musculoskeletal symptoms may be helpful in the diagnostic process. High peaking quotidian fever ($>38\ ^{\circ}C$) presenting at the same time as acute joint symptoms would suggest an infectious process or a severe auto-inflammatory disease, such as systemic vasculitis or AOSD. A low-grade continuous fever is a common presenting symptom of systemic inflammatory diseases, such as SLE and RA. In the latter case, an elderly patient presenting with fever, joint pains and lymphadenopathy can justifiably raise concerns about a paraneoplastic process, but these symptoms can also be a manifestation of the systemic phase of RA.

A systematic history is an essential part of the evaluation. Age, gender, ethnic origin and the geographical areas where the patient has visited may provide clues to the aetiology of the disease. Presence of symptoms such as weight loss, asthenia and night sweats may suggest diseases such as malignancies or severe inflammatory systemic diseases such as vasculitis. A detailed drug history is vital, as drug reactions are common and are often overlooked initially.

In the presence of fever, infection is the obvious diagnosis to exclude. The history should include major risk factors for infection such as recent surgery or dental treatment, as well as potential immunosuppressive agents and history of past infections. It may be relevant to ask about the history of recent travel, bites by animals or insects, contact with sick animals or people, sexually transmitted diseases, drug abuse etc. These details, which may often provide clues to a potential source of infection, are frequently overlooked and their relevance is only established retrospectively.[16]

Finally, the duration of symptoms should be evaluated. It is unlikely that an infection would persist for months or years without some other localizing symptoms to indicate the site of sepsis. The exceptions to this are, of course, chronic infections such as

tuberculosis and chronic osteomyelitis. In most cases of infectious aetiology, fever is of shorter duration and is not accompanied by signs such as weight loss unless there is a high fever and loss of appetite.

HOW USEFUL IS PHYSICAL EXAMINATION?

A thorough physical examination is mandatory. Clinical identification of the organs involved allows pattern recognition, which is essential for diagnosis of systemic diseases (see Table I) and to direct the appropriate supplementary investigations. Similarly, the pattern of joints or muscles involved may give a clue to the underlying diagnosis.

Cardiac, pulmonary and abdominal examinations are essential to define the presence of any organ participation that could necessitate immediate treatment measures. Cardiac auscultation may reveal the presence of heart murmur or pericardial rub, while cardiac failure could be a sign of underlying myocardial involvement. Chest examination may reveal signs of interstitial lung disease, pulmonary fibrosis or serositis, while abdominal examination may reveal organomegaly, signs of peritonitis or intestinal ischaemia.

Presentations associated with organ involvement or symptoms.

Organ involved or symptoms	Common presentation	Uncommon presentation
Raynaud's phenomenon	SLE Systemic sclerosis Cryoglobulinaemia	Vasculitis Rheumatoid arthritis
Aphtous lesions	Reiter's syndrome and spondylarthropathies Behçet's disease Viral diseases	Rheumatoid arthritis Vasculitis
Urticaria lesions	Periodic syndrome (Muckle-Wells) Schnitzler's syndrome	
Renal involvement	Vasculitis SLE Cryoglobulinaemia	Systemic sclerosis Rheumatoid arthritis
Pulmonary involvement	Sarcoidosis Wegener's granulomatosis Connective tissue diseases	Rheumatoid arthritis Spondylarthropathies
Serositis	SLE Periodic syndromes Adult-onset Still's disease	
Ocular involvement	Sarcoidosis Infection Behçet's disease Reiter's syndrome and spondylarthropathies Lymphoma Temporal arteritis	Vasculitis Rheumatoid arthritis

SLE, systemic lupus erythaematosus.

Musculoskeletal examination should include the peripheral and axial joints. Again, the pattern of joint involvement may be helpful in establishing the differential diagnosis. Septic arthritis is usually monoarticular unless there is overwhelming septicaemia, with the exception of neisseriae septicaemia (*Neisseria meningitidis* or *Neisseria gonorrhea*) which may present with a polyarthritis affecting the small joints of the hands. Septic arthritis usually involves the large joints, particularly the knee, and local symptoms typically identify the site of infection. However, non-infectious causes of joint inflammation can occasionally present with fever. Examples are gout and chondrocalcinosis in elderly patients. Infection of a joint such as the hip is more difficult to recognize clinically, and requires a high index of clinical suspicion. Examination of the axial skeleton should include the sacroiliac joints, the sternoclavicular joints and the vertebral column. Infectious spondylodiscitis may present with radicular symptoms, signs of local inflammation or vertebral collapse depending on its localization, although it is rarely found at multiple levels unless there is an underlying disorder of immune function. Pyogenic infection of muscle is rare and is often clinically evident, although low-grade myositis, which may be a sign of a systemic connective tissue disease, can sometimes be difficult to differentiate from myalgias presenting in the context of a chronic viral infection.

Thorough examination of the skin is essential, as skin involvement is seen in a number of systemic inflammatory diseases, often with fairly specific features. Examples include the malar 'butterfly' rash associated with SLE, although one has to remember that it is a presenting feature in less than one-third of patients.[17] An evanescent cutaneous rash of the limbs and trunk typically characterizes AOSD, but many different forms of mucocutaneous eruptions have also been described. Purpura is a feature of systemic vasculitis as well as septicaemia and panniculitis, and subcutaneous nodules with erythaema nodosum are features of sarcoidosis, rheumatic fever, Crohn's disease and Behçet's disease. Skin involvement is relatively common in sarcoidosis, being found in about 30% of cases.[18] Urticaria is seen in some of the periodic fever syndromes, as well as in paraneoplastic conditions such as Schnitzler's syndrome. In familial Mediterranean fever, TRAPS and Muckle-Wells syndrome, skin rashes have been described. Other periodic manifestations are panniculitis, nodular lesions of the lower limbs and diffuse erythaema of the palms and soles. Finally, skin rashes can also be a presenting sign of infection, ranging from viruses such as parvovirus B19, human immunodeficiency virus and measles, to bacterial infections such as borellia and rickettsia.

Neurological examination should include a careful assessment of the peripheral nervous system, as mononeuritis multiplex is a frequent sign of a vasculitic process although it may also be found in infections such as borreliosis and hepatitis C. Ocular involvement is often overlooked and is an important window on systemic processes. Conjunctivitis, keratitis, episcleritis, periorbital oedema, anterior uveitis and retinal haemorrhages may be detected during clinical examination and provide valuable diagnostic clues. Visual loss requires an urgent assessment by a specialist as it could be the expression of a posterior uveitis or retinal involvement by vasculitis or an embolic process.

HOW USEFUL ARE LABORATORY TESTS?

General laboratory tests

C-reactive protein (CRP) and erythocyte sedimentation rate (ESR) are standard tests that distinguish between inflammatory and non-inflammatory conditions. As ESR can

also be elevated non-specifically by anaemia and age, CRP appears to be a more reliable measure of inflammation.

Other non-specific tests that may be useful in the assessment of inflammation include immunoglobulin levels, measurement of complement C3 and C4, and measurement of fibrinogen. As inflammation generally increases the levels of the above proteins, a lowered level may be helpful in orientating the clinician to a particular diagnosis, such as lowered complement levels in SLE and lowered fibrinogen levels in the macrophage activation syndrome.

A very simple and specific diagnostic test in the febrile patient with musculoskeletal symptoms is the analysis of synovial fluid. The identification of crystals by polarizing light microscopy as well as a microbiological analysis could differentiate rapidly between an inflammatory cause and an infectious cause. However, it must be borne in mind that septic arthritis and crystals (gout as well as CPPD) can co-exist in the same joint[19], and clinical acumen has to be exercised when the diagnosis is not clear.

Microbiological examination of blood, synovial or other tissue samples is required to establish if an infectious agent is present; if negative, serological analyses may provide indirect evidence of infection (see below). Recent advances in detection of infection, such as the use of polymerase-chain-reaction-based techniques and the lymphocyte-cytokine assay[20], have made diagnosis of tuberculosis more rapid and reliable. For viral infections, the combination of molecular and serological techniques has also increased the diagnostic capacity.

Specialized laboratory tests

For certain diseases, more specialized tests have been developed. However, they generally suffer from restricted availability and are not always as specific as initially reported. One such example is the diagnosis of AOSD. Although the diagnosis is typically reached by exclusion, very high serum ferritin levels are often found and were thought at one time to be diagnostic. However, the rise is not specific for AOSD and may also be found in inflammatory rheumatic diseases, hepatic diseases, lymphoma, systemic infections and patients who develop fever after multiple blood transfusions. New disease markers that may be more specific include haem oxygenase-1, the levels of which are increased in AOSD and are correlated with disease activity and ferritin levels[21], and glycosylated ferritin, an isoform of ferritin. In one study, reduced levels of glycosylated ferritin of less than 20% are highly suggestive of AOSD, while levels between 20% and 40% are seen in other systemic inflammatory states. A new diagnostic and classification score that incorporates glycosylated ferritinaemia appears to be more accurate for the diagnosis of AOSD.[22] These claims need to be substantiated in other patient cohorts.

Auto-antibodies

Measurement of auto-antibodies is a common test in diagnostic work-up. It must be borne in mind that false-positive auto-antibody results may be due to infectious diseases, so the results have to be interpreted in their clinical context. Conditions besides RA that can cause elevated rheumatoid factor include sarcoidosis, viral hepatitis, mycobacterial diseases, endocarditis, syphilis and old age. Similarly, antinuclear antibody (ANA) positivity can be found in a variety of clinical settings in addition to SLE. Chronic bacterial infections and viral infections can give false-positive ANA and

anticardiolipin antibody results, although assays for dsDNA and anti-b2GPI may give higher specifity for SLE compared with infectious diseases.

Antineutrophil cytoplasmic antibodies (ANCAs) are frequently found in vasculitic syndromes, and c-ANCAs, directed against proteinase-3, are highly specific for Wegener's granulomatosis and microscopic polyarteritis. Sensitivity is close to 90% in patients with severe classical systemic disease, but is much lower in patients with limited forms of Wegener's granulomatosis.

Infectious disease serology

In case of suspicion of viral or bacterial infection, serology can be very useful and can complement direct microbiological methods. In the context of this chapter, relevant assays include serology for parvovirus B19, cytomegalovirus, influenza and hepatitis C virus, and antibodies against streptolysine O, brucella, borrelia and campylobacterial infection. Although rheumatic fever is now much less common, post-streptoccal arthritis and post-streptococcal vasculitis are not infrequent problems, and may sometimes present with features of vasculitis and fever.[23] Patients with this syndrome characteristically have very high anti-streptolysine O titres that descend when the inflammation is treated.

HOW USEFUL ARE RADIOLOGICAL AND OTHER PROCEDURES?

In addition to standard radiographs, specialized radiological examinations such as computer tomography (CT) and magnetic resonance imaging (MRI) have contributed enormously to rapid diagnosis in this group of patients. High-resolution CT has been show to be superior to plain chest X-rays in demonstrating pulmonary pathology[24], and whole-body CT has been invaluable in the search for occult infections or neoplasms. MRI is more sensitive and specific than CT in identifying deep-seated infection/inflammation, as it is able to image soft tissue structures. The ability of MRI to visualize inflammation has made early diagnosis of spondylodiscitis possible, and has been particularly helpful in identifying sacroiliac inflammation. MRI imaging of blood vessel inflammation has also been successful in identifying sites of vasculitis in Takayasu's disease and in giant cell arteritis. Occasionally, MRI is not able to distinguish between a septic or a non-septic origin of inflammation, in which case a guided biopsy of the involved region under radiological control should provide the definitive diagnosis. With the generalization of MRI, nucleotide bone scanning has become less important. However, it still has a place in the diagnostic work-up of a possible neoplastic disease and in the generalized search for sites of bone and joint inflammation.

Finally, in some systemic diseases, the final diagnosis is often dependent on histology. Histological signs of blood vessel involvement are still the gold standard for the diagnosis of vasculitis, and muscle biopsy is essential in the evaluation of muscle pathology. Radiology can be extremely helpful to guide the clinician to an appropriate site of biopsy to provide the final diagnosis.

CONCLUSION

There is no simple algorithm to approach an adult with systemic febrile illness and musculoskeletal symptoms. The key is a systematic, logical approach combining the

information gathered during history taking and physical examination to direct selected biological, radiographic or other more invasive procedures.

The first purpose is to establish the spectrum of affected systems and their relative gravity to initiate the immediate treatment required to prevent irreversible end organ damage, while initiating simple symptomatic measures for pain and fever. The definite diagnosis will mainly be useful for the long-term planning of management and treatment, as well as to better define prognosis.

Practice points

- potentially lethal diseases could present with fever and musculoskeletal symptoms, and the initial purpose is the prevention of irreversible end organ damage
- history and physical examination should be systematic to avoid overlooking any diagnostic clues
- there are no simple algorithms or screening tests to approach an adult with systemic febrile illness and musculoskeletal symptoms. The key is a systematic, logical and progressive clinical approach to direct selected biological, radiographic or other more invasive procedures

Research agenda

- validation of simpler new diagnostic and classification criteria for AOSD, which remains a difficult diagnosis of exclusion

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