Fever and Rheumatology

11

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11.1 Introduction

In all the patients with rheumatic diseases, fever should prompt an immediate and thorough evaluation. There are different disorders that can cause fever and arthritis. Fever that is thought to be due to active rheumatic disease is seen in over 50% of patients with SLE30. However, it can be also related to or a sequel of an infectious process. There are many infectious diseases with rheumatological manifestations. The aim of this chapter therefore is to address variable relationships of fever with patients with arthritis. Fever of unknown origin will be addressed as some systemic rheumatic disease may present with fever. It is always a dilemma when an established patient with arthritis presents with fever. What should you do? This issue is addressed with a suggested diagnostic approach that guides you in a stepwise manner until you reach to the definitive diagnosis.

A quick review of rheumatological manifestations of some infections is presented. This is to

widen your knowledge about this area in medicine and not to ignore common viruses, for example, in your differential diagnosis of fever and arthritis. Vaccination is quite an ignored aspect of clinical practice among patients with arthritis.

The objective of this chapter is to provide a systemic approach to patient with fever and arthritis.

Specific objectives:

By the end of the chapter the reader should be able to:

- Approach a patient with fever of unknown origin.
- Approach a patient with known rheumatological disease presenting with fever and recognize the common infections that affect immunocompromised patients.
- Recognize the rheumatological manifestations of common infectious diseases.
- Provide a safe and proper method of vaccinations to patients with rheumatological disease.

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11.2 Fever of Unknown Origin (FUO)

11.2.1 Definition [28]

- Temp >38.3 on several occasions.
- Duration ≥ 3 weeks.
- No clear diagnosis after 1 week of in-hospital investigation.

11.2.2 Epidemiology

The epidemiology of FUO has changed over time due to scientific and technologic advances (better imaging, more advanced organism isolation, and more understanding of connective tissue disease). A prospective multicenter study on fever of unknown origin showed the following distribution: connective tissue diseases 22%, infection 16%, malignancy 7%, miscellaneous 4%, no diagnosis 51%.

Box 11.1 Initial evaluation for FUO

- Comprehensive History (Table 11.2)
- Detailed Physical examination (Table 11.2)
- CBC with differential & Blood film
- U&E–LFTs–LDH–ESR - CRP
- hepatitis A, B, and C serologies if LFTs are abnormal
- Blood cultures (X3 - different sites - several hours between each set - off antibiotics)
- HIV antibody assay and HIV viral load for patients at high risk
- Urinalysis + microscopic examination + urine culture
- CXR

11.2.3 General Principles in the Treatment of FUO (Table 11.2)

Physician should explain to the patient that FUO is a well-known entity, and it needs time for investigation to decrease anxiety of the patient. Empiric therapy with antimicrobial or glucocorticoids *should not* be given to stable patients with FUO because it often obscures or delays the diagnosis [29]:

- The diagnostic yield of some investigation like cultures will be reduced after starting antimicrobial.
- Empiric treatment of a certain infection can affect other infection (e.g., therapeutic trial for tuberculosis with rifampicin may suppress staphylococcal osteomyelitis or diminish the ability to detect difficult to isolate organisms causing endocarditis).
- The duration of a therapeutic trial is also unclear.
- Initiation of glucocorticoid without ruling out infection can lead to severe life-threatening infections.

There are some exceptions where patient with FUO should be treated empirically. The exceptions are:

1. Septic or hemodynamically unstable patient → empirical treatment.
2. Immunocompromised or neutropenic patient → empirical treatment.
3. Query giant cell arteritis → treat with corticosteroids until biopsy result → risk of visual loss.

Figure 11.1 shows a suggested algorithm to approach a patient with FUO.

Epidemiology: Table 11.1 shows the etiologies of FUO.

Table 11.1 Etiologies of FUO [1–27]

Infection	<ul style="list-style-type: none"> • Tuberculosis: require high clinical suspicion as patient can have normal PPD or interferon gamma release assay and may require biopsy to yield diagnosis. • Abscesses: Intra-abdominal, pelvic, dental, or paraspinal. • Osteomyelitis: some sites can have no localized symptoms like vertebral and mandibular osteomyelitis. • Endocarditis: consider culture negative organism → <i>HACK</i>, <i>Coxiella</i>, <i>Bartonella</i>, <i>T. whipplei</i>, <i>Brucella</i>, <i>Mycoplasma</i>, <i>Chlamydia</i>, <i>Histoplasma</i>, and <i>Legionella</i>. • Other causes: Brucellosis, HIV, sinusitis, CMV, EBV, secondary syphilis, Lyme disease, prostatitis, visceral leishmaniasis, <i>Q</i> fever, leptospirosis, psittacosis, tularemia, melioidosis, disseminated gonococcemia, chronic meningococcemia, Whipple's disease, and yersiniosis.
Connective tissue disease	<ul style="list-style-type: none"> • Adult Still's disease: evanescent rash, arthritis, lymphadenopathy, and high ferritin. • Giant cell arteritis: >50y, headache, scalp pain, visual disturbances, myalgias, arthralgias, high ESR. • Other: polyarteritis nodosa, granulomatosis with polyangiitis, RA, SLE, psoriatic or reactive arthritis, PMR, Takayasu's arteritis, mixed cryoglobulinemia.
Malignancy	<ul style="list-style-type: none"> • Lymphoma (especially non-Hodgkin's). • Leukemia. • Myelodysplasia. • Renal cell carcinoma (increase HCT, microscopic hematuria). • Hepatocellular carcinoma or other tumors metastatic to the liver. • Multiple myeloma. • Pancreatic and colon cancers, sarcomas, mastocytosis. • Atrial myxomas (arthralgias, emboli, and hypergammaglobulinemia).
Miscellaneous	<ul style="list-style-type: none"> • Drug-induced fever. • DVT/PE. • Hematoma. • Thyroid storm, thyroiditis, adrenal insufficiency, pheochromocytoma. • Sarcoidosis. • Alcohol or granulomatous hepatitis. • Hereditary periodic fever syndromes: FMF, TRAPS, hyper-IgD syndrome, muckle-Wells syndrome, and familial cold autoinflammatory syndrome.

Table 11.2 Initial evaluation for FUO

History	Physical examination
<p>Careful and thorough history including:</p> <ul style="list-style-type: none"> • Any localizing symptoms. • Travel Hx (TB, malaria, hepatitis, typhoid fever, parasitic infections, Rocky Mountain spotted fever, or Lyme disease). • Exposure to TB patient. • Unpasteurized milk and cheese, • Animal and insect exposure. • Immunosuppression (medication or diseases). • Sexual contacts. • New unusual activity. • Drug and toxin history including alcohol, illicit drug use, over-the-counter medications and recent antimicrobial. • Ethnic background. 	<p>Complete physical examination including:</p> <ul style="list-style-type: none"> • Skin, mucous membranes, and lymphatic system. • Abdominal palpation for masses or organomegaly. • Joint examination and the back → Pott's disease. • Heart auscultation → new murmur (infective endocarditis). • Sinuses. • Prostate examination.

Fig. 11.1 Suggested algorithm to approach patient with FUO

11.2.4 Tips in FUO

- Think of uncommon presentations of common diseases rather than thinking of uncommon diseases.
- <40 Y → infection > rheumatological > malignancy.
- >40 Y → Infection > Malignancy > Rheumatological.
- Rheumatological disease usually present in stable condition.
- Empiric treatment not recommended unless there is an indication.
- If empiric treatment is a must avoid quinolone (TB resistance).
- Chills, rigors, night sweat (infection > rheumatological).
- Most of undiagnosed cases of FUO are related to viruses that we don't usually investigate.
- Viral infections can give a temperature up to 40–41 °C and can persist up to 3 weeks (average 9 days).

2. The typical signs and symptoms of infection may be absent because of concomitant immunosuppressive therapies [56–58].
3. The anti-inflammatory and antipyretic effects of glucocorticoids may diminish the usual systemic and localizing signs of infection.
4. With the immunosuppressive impact of the medication and the disease itself, the spectrum of potential pathogens is large, making empiric treatment difficult.

In patient with rheumatoid arthritis, bone and joints, skin, soft tissues, and the respiratory tract are the most frequently involved sites in infectious processes [33]. In patients with chronic inflammatory rheumatic or autoimmune diseases without arthritis, infections of the respiratory tract are the most common site. **Finally, ascribing fever to the underlying rheumatological disease itself in an immunosuppressed patient should be done only after reasonable and good efforts have been made to exclude infection.** Figure 11.2 shows suggested algorithm to approach a patient with rheumatic disorder presenting with fever.

Risk factors for infection in a patient with rheumatic disease include:

11.3 Fever and Rheumatology

11.3.1 Introduction

Approach to fever is a very challenging in a patient with rheumatic disease as it could be an infection, disease activity, or medication side effect. Fever that is thought to be due to active disease is seen in over 50% of patients with SLE [30]. On the other hand, fever is a rare presentation of RA disease activity. Infections are often difficult to diagnose and treat in this group of patient because of the following reasons:

1. Clinical manifestations of infections are often indistinguishable from the underlying disease and vice versa [52–55].

- Active disease.
- Long-term disease damage.
- Neutropenia.
- Lymphopenia.
- Hypocomplementemia.
- Renal involvement.
- Neuropsychiatric manifestations.
- Use of glucocorticoids and other immunosuppressive drugs.
- Arthrocentesis [23].

Fig. 11.2 Suggested algorithm to approach a patient with rheumatic disorder presenting with fever

Points to consider in the approach to this group of patients:

- Respiratory viral infections are the most common cause of fever in rheumatological patient as non-rheumatological patient.
- There is no single clinical or laboratory finding that can differentiate between infection, disease activity, or drug-induced insult as a cause of

fever. It is rather a collective clinical and laboratory finding with good clinical judgment.

- One of the crucial points in determining the cause of fever is to know the patient's disease activity status prior to presentation and if he is on immunosuppressive therapy or no.
- Both the patient's underlying rheumatic disease and its therapy need to be taken into con-

sideration when evaluating the white blood cell count in a febrile immunosuppressed patient because:

- Glucocorticoids therapy can cause a neutrophilic leukocytosis.
- Cytotoxic drug therapy can impair a patient's ability to mount a neutrophilic leukocytosis in response to infection.
- Neutrophilic leukocytosis may be a manifestation of certain rheumatic diseases, such as active granulomatosis with polyangiitis [101].
- Recent systemic review and meta-analysis for the utility of procalcitonin as a diagnostic marker for bacterial infection in patients with autoimmune disease showed that:
 - Procalcitonin has higher diagnostic value than CRP for the detection of bacterial sepsis in patients with autoimmune disease, and the test for procalcitonin is more specific than sensitive 32.
 - Procalcitonin test is not recommended to be used in isolation as a rule-out tool 32.

11.4 Fever in Rheumatology Patient

11.4.1 History

Careful and thorough history including:

- Medication history → immunosuppressed (type and for how long)→ suspect new infection, particular if other signs of active disease have begun to remit.
- Onset of symptoms → few days → infection.
- Days to weeks → disease activity/opportunistic infection
- Fever pattern → episodic → disease activity/infection.
- Sustained → drug/CNS involvement
- Shaking chills occurred in significantly more patients with proven infections (68% versus 27% non-infectious).
- Contact with children (viral infection).
- Recent travel and exposure to TB.
- Vaccination history.

11.4.2 Physical Examination (Table 11.3)

Complete physical examination includes:

- Oral mucosal candidiasis → significant immunodeficiency → increased risk of opportunistic infections, such as PCP [36].
 - Erythematous necrotic cutaneous lesions→? Gram-negative sepsis, in particular *P. aeruginosa*.
 - Cutaneous vesicular rash → varicella.
 - Pulmonary infiltrates + cutaneous lesions→? Disseminated histoplasmosis, *Cryptococcus*, and nocardiosis (Table 11.4).
 - Pulmonary infiltrates + focal neurologic deficits→? Disseminated infection with mycobacteria, fungi (*C. neoformans*, *Aspergillus* spp.), or *Nocardia* spp. (Table 11.5).
 - A detailed neurologic examination should be performed and repeated frequently to monitor the patient's progress.
 - Each patient should undergo a careful ophthalmologic examination looking for papilledema, signs of retinal and choroid infection (e.g., cryptococcosis, toxoplasmosis), and proptosis (suggestive of orbital infection or cavernous sinus involvement).
 - Parotid gland enlargement → mumps.
- [39–57, 59–99].

Table 11.3 Possible pathogens by the predominant immune system defect caused by pharmacological agent used in the treatment of rheumatic disease [37–38]

Abnormality	Agent	Infection	
Qualitative defect of phagocytic function Or neutropenia	Corticosteroids Cyclophosphamide and other alkylating agents Azathioprine	Bacterial	Gram positive Coag (–) staph, <i>Staphylococcus aureus</i> , <i>Streptococcal</i> spp., <i>Corynebacterium</i> spp., <i>Bacillus</i> spp., <i>Nocardia</i> spp.
			Gram negative <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i>
		Viral	VZV, HSV1&2, CMV
		Fungal	<i>Candida</i> spp., <i>Aspergillus</i> spp.
Defective cell-mediated immunity	Corticosteroids Cyclophosphamide Other alkylating agents Azathioprine Methotrexate Cyclosporine A	Bacterial	<i>Salmonella</i> spp., <i>Campylobacter</i> , <i>Listeria</i> , <i>Yersinia</i> , <i>Legionella</i> , <i>Rhodococcus</i> , <i>Nocardia</i> , TB, non-TB <i>Mycobacterium</i> spp.
		Viral	CMV, EPV, VZV, HSV, JC virus, BK virus
		Fungal	<i>Candida</i> , Histo, crypto, Coccidio, <i>Aspergillus</i> , pneumocystis, <i>Zygomycetes</i> spp., and other mold
		Parasites	<i>Toxoplasma</i> , <i>Cryptosporidium</i> , <i>Isospora</i> , <i>Microsporidia</i> , <i>Babesia</i> , <i>Strongyloides</i>
Defective humoral immunity and asplenia	Cyclophosphamide Corticosteroids (high dose) Azathioprine	Bacterial	Encapsulated bacteria: <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Neisseria meningitidis</i> Other bacteria: <i>E. coli</i> And GNRs
		Viral	VZV, Echovirus, Enterovirus
		Parasites	<i>Babesia</i> , <i>Giardia</i>

11.5 Rheumatologic Manifestation of Infectious Diseases

11.5.1 Introduction

Rheumatologic manifestations of infectious diseases are well-recognized and relatively common. This topic will review the most common infectious diseases associated with rheumatologic manifestations. *An overview of each infectious agent is presented separately.*

11.5.1.1 Hepatitis B Virus Arthritis [104]

Evidences have shown that four rheumatologic syndromes are linked with hepatitis B virus infection.

Clinical and laboratory features of each syndrome will be described below.

11.5.1.2 Acute Hepatitis B and Arthritis

The symptoms are abrupt in onset, and they are composed of low-grade fever, a symmetrical polyarthritis which might be additive or migratory in pattern, morning stiffness, and other constitutional symptoms. The most common joints involved are the knees and small joints of the hands, but any peripheral joint might be involved with either arthralgia or frank arthritis. It may last from several days to several months.

11.5.1.3 Chronic Active Hepatitis B

Chronic active hepatitis is linked with joint discomfort and occasional rash. The joints

Table 11.4 Causes of CXR abnormalities in patient with rheumatic disease^a

Radiographic pattern	Infectious causes	Noninfectious causes
Localized infiltrates	Bacterial pneumonia (including <i>Legionella</i> spp.) <i>Mycobacteria</i> spp. Opportunistic fungi: <i>Aspergillus</i> spp. <i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i> <i>Cryptococcus neoformans</i> <i>Pneumocystis jiroveci</i> (uncommon)	Granulomatosis with polyangiitis Eosinophilic granulomatosis with polyangiitis Pulmonary embolus
Diffuse infiltrates	<i>Pneumocystis jiroveci</i> Bacterial pneumonia (haematogenous spread) <i>Mycoplasma pneumoniae</i> <i>Chlamydia</i> spp. <i>Mycobacteria</i> spp. (miliary pattern) Opportunistic fungi Viral Influenzae Cytomegalovirus Varicella-zoster virus (rare)	Systemic lupus erythematosus Rheumatoid arthritis Microscopic polyangiitis Granulomatosis with polyangiitis Eosinophilic granulomatosis with polyangiitis Scleroderma Sjogren's syndrome Dermatomyositis/polymyositis Pulmonary edema Drug induced Methotrexate Cyclophosphamide (rare) Azathioprine (rare)
Nodules or nodular infiltrates	Septic emboli <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> <i>Mycobacteria</i> spp. <i>Nocardia</i> spp. Opportunistic fungi	Granulomatosis with polyangiitis Eosinophilic granulomatosis with polyangiitis Rheumatoid arthritis Lymphoma

^aThe appearance or progression of pulmonary disease following the initiation or intensification of immunosuppressive therapy should always prompt a thorough evaluation for a possible infectious cause

Table 11.5 Infections in rheumatological patient and most common causes [34, 35, 100, 102, 103, 133–136]

Disease	Causes	Comments
Pneumonia	<ul style="list-style-type: none"> Immunocompromised patient are prone to the same pathogens acquired in the community by immunocompetent hosts. (<i>S. pneumoniae</i>, <i>S. aureus</i>, and enteric GNRs) are the most common isolated pathogens Less common organism. <p>Fungi (<i>Pneumocystis jirovecii</i>→most common OI, <i>Aspergillus</i> spp., <i>C. neoformans</i>, <i>C. immitis</i>, and <i>H. capsulatum</i>) TB & non-TB mycobacteria <i>Nocardia</i> spp. CMV HSV</p>	<ul style="list-style-type: none"> Pneumonia is one of the most frequent life-threatening infections in patients with rheumatic diseases. Pneumonia in immunosuppressed rheumatic patient is a challenging diagnosis because of: <ol style="list-style-type: none"> Pulmonary manifestations of certain rheumatic diseases and medications used to treat rheumatic diseases may produce many of the same clinical and radiographic abnormalities as pneumonia. The usual radiographic appearance of pulmonary infections can be dramatically altered by immunosuppressive therapy.

(continued)

Table 11.5 (continued)

Disease	Causes			Comments
CNS Involvement	Clinical syndrome	Infectious causes	Non-infectious causes	<ul style="list-style-type: none"> • CNS involvement occurs in many rheumatic diseases, including granulomatosis with polyangiitis, polyarteritis nodosa, Behcet's disease, and most frequently SLE. • Immunosuppressive therapy increases the risk of CNS infections which may be indistinguishable from CNS manifestation of underlying rheumatic disease. • The usual signs and symptoms of life-threatening CNS infection may be greatly diminished or absent because of the effect of immunosuppressive therapy. • In lupus cerebritis, clinical and LP findings are almost similar to bacterial meningitis with the exception of: <ul style="list-style-type: none"> – Less neck stiffness in lupus cerebritis. – Normal lactic acid level (↑ bacterial). – Decreased C4 level in the CSF.
	Acute meningitis	Bacterial <i>Listeria monocytogenes</i> <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Neisseria meningitidis</i> Viral: <i>Enterovirus</i> , <i>HIV</i> , <i>HSV</i> , <i>VZV</i> , <i>CMV</i> , <i>EBV</i> , and others	NSAIDS Azathioprine IVIG Sarcoid SLE Behcet's disease	
	Sub-acute meningitis	<i>Cryptococcus neoformans</i> <i>Listeria monocytogenes</i> <i>Mycobacterium tuberculosis</i> <i>Coccidioides immitis</i> <i>Strongyloides stercoralis</i>		
	Focal brain lesion	<i>Toxoplasma gondii</i> <i>Aspergillus</i> spp. <i>Nocardia</i> spp. <i>Cryptococcus neoformans</i> <i>Mycobacterium TB</i> JC virus (PML)	Lymphoma	
UTI	<ul style="list-style-type: none"> • Usually caused by gram negative organisms and may be accompanied by septicemia. • <i>Candida albicans</i> → immunosuppressed . 			<ul style="list-style-type: none"> • The incidence of UTI in immunosuppressed patients other than diabetics or renal transplant recipients is not higher than the incidence in immunocompetent individuals. • Neutropenia blunts the clinical manifestations of UTI and predisposes to bacteremia.

Table 11.5 (continued)

Disease	Causes			Comments
Skin infection	• Staphylococcus aureus, group A streptococci, and GNR.			
	Neutropenic	Initial infection: Gram negative and gram positive		
		Subsequent infection: Antibiotic-resistant bacteria, fungi		
	Cellular immune deficiency	Bacterial	Nocardia spp., atypical mycobacteria	
		Viral	VZV, HSV, CMV	
		Fungal	Cryptococcus species Histoplasma species	
Septic arthritis	• Staphylococcus aureus (most common), other species Streptococcus pneumoniae, groups B, C, and G Strep, Haemophilus, and gram-negative bacilli. • Consider →OI such as atypical mycobacteria and Pneumocystis jirovecii immunocompromised host.			• The risk of septic arthritis in RA patient, irrespective of therapy, is increased by 4–15-fold. • Diagnosis of septic arthritis in the rheumatoid patient is often delayed. • Use of anti-TNF therapy in RA is associated with a doubling in the risk of septic arthritis. • DMARDS can predispose some patients with rheumatoid arthritis to septic arthritis.
Osteomyelitis	Haematogenous	Usually monomicrobial → S. aureus (most common), Mycobacteria		
	Contiguous	Polymicrobial or monomicrobial → Staphylococcus aureus, coagulase-negative staphylococci, and (aerobic gram + anaerobic GPC and GNR)		
	In immunocompromised patients consider →Aspergillus spp., Candida albicans, Mycobacteria spp., Salmonella spp., or Streptococcus pneumonia			

(continued)

Table 11.5 (continued)

Disease	Causes	Comments
Bacteremia or fungemia	<ul style="list-style-type: none"> The presentation and etiology of bacteremia or fungemia is similar to that in other patients. Disseminated <i>Neisseria</i> and non-typhoid <i>Salmonella</i> infections are more common in SLE patients. 	<p>Salmonella:</p> <ul style="list-style-type: none"> Can cause serious infections in SLE patients. Most cases occur during periods of active SLE and may be the presenting illness of SLE. Although fever at presentation is the rule but 15% to 20% of patients may be afebrile. And most patients are not toxic or septic on admission. Clinical syndromes include gastroenteritis, arthritis, and pneumonia. Less commonly diagnoses included cellulitis, osteomyelitis, urinary tract infection, or meningitis. <p>Neisseria:</p> <ul style="list-style-type: none"> Patients are often young sexually active women with renal disease and low C3 and C4 levels. Arthritis is a common presentation of disseminated <i>Neisseria</i> infection and less commonly meningitis and endocarditis.
Viral infection	<ul style="list-style-type: none"> Viruses can cause both systemic and organ-specific disease. The most common viral infections in patients with SLE are parvovirus B19 and CMV. Other herpesviruses are common in immunosuppressed SLE patients. Viral infection can be easily confused with a lupus flare due to significant overlap in the features induced by acute viral infections (fever, arthralgia, malaise, cutaneous rash, lymphadenopathy, and cytopenia) and those observed in active SLE. Acute viral infections are not adequately investigated in SLE patients and are only suspected after ruling out other causes of fever. The differential diagnosis of SLE patients presenting with fever suspected to be of infectious origin should consider not only common bacterial infections but also opportunistic viral infections, especially in patients with severe SLE involvement or those who are on immunosuppressive therapy. This group of patient should have a detailed physical examination, serologic studies, and invasive organ-specific diagnostic procedures to rule out an underlying viral infection. 	

Table 11.6 Rheumatic manifestations of hepatitis B virus

	Acute hepatitis B	Chronic active hepatitis B	Polyarteritis nodosa	Mixed cryoglobulinemia
Rheumatic manifestation	Transient symmetrical polyarthritis	Transient asymmetrical arthritis or arthralgia	Symmetrical polyarthritis in 50%	Chronic polyarthralgia, rarely arthritis
Systemic involvement	Evanescant erythematous urticarial or petechial rash	Erythematous rash rarely reported	Peripheral neuropathy, CNS, muscle, liver, skin, intestines, kidneys, and heart	(skin: Purpura, ulceration), kidney, liver and neuropathy
Serum HBs antigen	Present during rheumatic prodrome	Variable	Up to 40%	Rarely present
Serum free antibody to HBs antigen	Present in convalescent phase	Not present	Rarely present	Present in 48%

abnormality usually manifest as arthralgias which have a fleeting nature which have a fleeting nature (Table 11.6).

11.5.1.4 Polyarteritis Nodosa

- The incidence of HBs antigenemia in polyarteritis nodosa is varied based on the criteria used for diagnosis and the sensitivity of the technique used for detection of the HBs antigen.
- Clinically, these patients might present with multisystem involvement of the skin, muscles, nervous system, lungs, and polyarthritis as well as liver disease.

11.5.1.5 Essential Mixed Cryoglobulinemia

It has the following clinical features: non-thrombocytopenic purpura upon exposure to cold, diffuse arthralgia, and generalized weakness and hepatosplenomegaly; rarely it is associated with neuropathy and gangrene.

11.5.2 Hepatitis C Virus Arthritis

Hepatitis C virus (HCV) is associated with many rheumatologic manifestations including those related to joints, muscles, and connective tissue

resulting from the body's immune system interaction with the infectious agent antigens with the subsequent immune complex formation that will be deposited in various parts of the body eliciting an inflammatory reaction that damage the involved organs. Patients who are infected with HCV often have no symptoms. Anyone newly diagnosed with arthritis or cryoglobulinemia should be tested for HCV infection. Also, there are certain drugs used in the treatment of HCV infection, e.g., interferon can worsen a related rheumatologic disease.

Arthritis is noted in 2 to 20% of HCV patients [107, 108]. The arthritis takes the form of evanescent rheumatoid-like picture in two-thirds of the cases and an oligoarthritis pattern in the rest. Rheumatologic manifestations include painful joints and muscle and fatigue, "the first and most common complain," and less commonly patients might have joint swelling and vasculitis.

Cryoglobulinemia happens when cryoglobulins (which are abnormal immunoglobulin) precipitate in cold temperature. It may affect the blood vessels specially during cold weather leading to "Raynaud's phenomenon." [105, 106] The diagnosis of HCV can be made by finding HCV Immunoglobulins or by detecting the virus RNA.

Table 11.7 Rheumatic manifestations of Parvovirus B19 infection

Rheumatologic manifestations	Parvovirus B19 arthropathy	
	Male	Female
	30%	59%
	Children [113]	Adults [112]
	<ul style="list-style-type: none">• Occur in about 8%.• Pattern: Asymmetrical or pauciarticular• Joint involved. It affects the knee most often• At times children may meet criteria of juvenile idiopathic arthritis.	<ul style="list-style-type: none">• Occur in about 60%.• Many adult have arthritis alone without other symptoms.• Typical pattern. Acute onset symmetrical polyarticular arthritis• Joints involved. Proximal interphalangeal with metacarpophalangeal most commonly

11.5.3 Parvovirus B19 Arthropathy

Parvovirus B19 is the cause of fifth disease “slapped cheeks” or erythema infectiosum. The disease manifests by rash, arthritis/arthralgia, laboratory abnormalities, and other connective tissue diseases like syndrome. It may mimic systemic lupus (SLE) both in children and adults (Table 11.7) [109, 110].

Arthritis/arthralgia may accompany or follow the skin eruption. The rheumatologic symptoms may persist for weeks to rarely months with resolution, but recurrences are reported [111, 112].

The diagnosis of acute parvovirus infection is made by finding IgM antibody, while IgG antibody is evidence of preexisting exposure. Acute phase reactant, i.e., erythrocyte sedimentation rate and C-reactive protein are occasionally elevated. The leukocyte remains normal, but in some cases, rheumatoid factor and antinuclear antibody may be present in the acute period.

11.5.4 Dengue Virus

- The classical features of dengue virus (DV) are acute febrile illness, headache, and muscle and **joint pain**. It is also referred to as “break-bone fever.” [114] **Arthralgia occurs in 60 to 80% of the patients infected with DV.**

Investigations may reveal leucopenia, thrombocytopenia, and elevated liver enzymes. A small

percentage of patients may have potentially lethal forms known as hemorrhagic fever and dengue shock syndrome [115].

11.5.5 Septic Arthritis

It is a bacterial infection of the joint that is usually curable with treatment, but morbidity and mortality are still significant specially in patients who have underlying rheumatoid arthritis, patients who have prosthetic joints, elderly patients, and patients who have severe and multiple comorbidities. Incidence of septic arthritis 10 cases per 100,000 patient-years in general population in Europe [116]. Incidence of septic arthritis in patients with rheumatoid arthritis.

(Based on prospective British Society for Rheumatology Biologics Register)

1.8 cases per 1,000 patient-years in 3,673 patients taking non-biologic disease-modifying antirheumatic drugs, where 4.2 cases per 1,000 patient-years in 11,881 patients taking anti-tumor necrosis factor therapy.

Usually it is monoarthritis, but up to 20% of patients have infection in >1 joint “polyarticular.” [116] The joints mostly affected are knee (which is the most common affected joint approximately 50%) followed by the hip, shoulder, and then elbow [120]. In IV drug users, axial skeletal joints are mainly involved often with *Staphylococcus aureus*.

The most common causes of septic arthritis in adults are: [116]

- *Staphylococcus aureus* most frequent causative agent, followed by *Streptococcus*.
- *Neisseria gonorrhoeae*, but it is considered separately as disseminated gonococcal infection.
- Gram negatives, *Haemophilus*, are usually seen in older patients.

In IV drug users, septic arthritis is frequently due to methicillin-resistant *Staphylococcus* (MRSA), mixed infections, fungal infections, or unusual organisms [116]. Patients may have 1–2 weeks history of joint pain, tenderness, warmth, redness, restricted motion, loss of function, and fever. Joint-related risk factors for infection are joint prosthesis, intra-articular injection, and joint trauma [119]. **Fever occurs in about one-third of patients [116]. “Large joints in legs (hips and knees) are the typical sites of infection.” [116–118]** Septic arthritis is diagnosed by clinical signs (hot, red, tender, swollen, restricted) with any of the following:

- Pathogenic organism in synovial fluid detected by culture and gram stain.
- Pathogenic organism isolated in blood or other site.
- Turbid synovial fluid in patient with recent antibiotic treatment.
- Synovial WBC count **more than 30,000**.
- Leukocytosis.

11.5.6 Poncet’s Disease (Reactive Arthritis Associated with Tuberculosis) [121]

There is a new pattern of reactive arthritis associated with tuberculosis (TB), identified as Poncet’s disease (PD) or tuberculous rheumatism, which is a sterile reactive arthritis that can emerge during any stage of acute TB infection. In a retrospective case series study, seven cases of Poncet’s disease were identified:

- The most common presentation was extrapulmonary with involvement.
 - of multiple sites.
- Six out of seven patients developed arthritis after initiation of anti-TB drugs.
- One patient developed polyarthritis after completion of anti-TB medication.
- Asymmetrical polyarthritis was the most common pattern of joints involvement.

The resolution of the arthritis was with symptomatic treatment and continuation of anti-TB drugs. PD may manifest in a variable pattern during the course of active tuberculous infection. Physicians should be aware of this rare complication associated with a common disease to prevent delay in diagnosis and initiation of appropriate treatment.

11.6 Vaccination in Adult Patient with Autoimmune Inflammatory Rheumatic Diseases (AIIRD)

11.6.1 Introduction

It is well known that vaccination is one of the most effective measures to prevent infections and as discussed earlier in this chapter patient with autoimmune inflammatory rheumatic diseases is at increased risk of infection compared to the normal population with the respiratory tract being the most affected organ [122, 123]. However, vaccination of immunocompromised patients is challenging both regarding efficacy and safety. The efficacy of vaccinations in patients with AIIRD may be reduced, and there is a potential risk of flares of the underlying AIIRD following vaccination. The two major issues to consider in vaccine administration of this group of patients are what is the expected immune response following vaccination and what are the potential for worsening the underlying disease.

Table 11.8 Vaccinations by type

Inactivated vaccines	Live vaccines
Tetanus	Adenovirus
Haemophilus influenzae type b	Herpes zoster (shingles)
Hepatitis A and B	Measles, mumps, rubella
Human papillomavirus (HPV)	Varicella
Japanese encephalitis	Rotavirus
Pneumococcal	Yellow fever
Meningococcal	BCG
Typhoid (IM)	Typhoid (oral)
Inactivated polio	Live polio (oral)
Inactivated influenza	Live influenza (nasal spray)
Diphtheria	
Rabies	
Cholera	

11.6.2 General Rules

All inactivated vaccines can be administered safely to persons with AIIRD whether the vaccine is a killed whole organism or a recombinant, subunit, toxoid, polysaccharide, or polysaccharide protein-conjugate vaccine. Live viral and bacterial vaccines should be avoided whenever possible in immunosuppressed patients with AIIRD because it might lead to severe infection in immunocompromised patients (Table 11.8). Table 11.9 shows vaccinations recommendations in adult patient with autoimmune inflammatory rheumatic diseases (AIIRD).

Table 11.9 Vaccination recommendation in AIIRD * [124–127]

Inactivated influenza vaccine	Give annually	Special consideration
Pneumococcal polysaccharide (PPV23)	<ul style="list-style-type: none"> Age 19 to 64 y. (one dose + revaccination dose) All adults ≥ 65 y of age. 	Minimum interval of 5 y between PPSV23 doses should be maintained
Pneumococcal 13 valent conjugate (PCV13)	<ul style="list-style-type: none"> Age 19 to 64 y. No revaccination. 	
Tetanus toxoid vaccine	Like general population	In case of major and/or contaminated wounds in patients who received rituximab within the last 24 W $\Rightarrow$ tetanus immunoglobulin's should be administered
Human papilloma virus vaccine (HPV)	Like general population	
Hepatitis A vaccine	Only recommended in patient at increased risk	Protective antibodies against hepatitis A should be absent
Hepatitis B vaccine	EULAR/ACIP $\Rightarrow$ only for patient at increased risk ACR: <ul style="list-style-type: none"> Should be given before starting DMARD or biologic drug. If not $\Rightarrow$ give to patients already on DMARD or biologic drug. 	Protective antibodies against hepatitis B should be absent

Table 11.9 (continued)

Inactivated influenza vaccine	Give annually	Special consideration
Herpes zoster vaccine (HZV)	Special circumstances	<ul style="list-style-type: none"> • Before starting DMARDS or biologic agent. • At least 14 days before initiation of immunosuppressive therapy or 3 months after immunosuppression has stopped. • The following conditions not consider sufficiently immunosuppressive to be a contraindication for HZV: <ul style="list-style-type: none"> – MTX (<0.4 mg/kg/week), AZA (<3.0 mg/kg/day) or 6-mercaptopurine (<1.5 mg/kg/day) [4]. – Short-term corticosteroid (<14 days). – Low to moderate doses of corticosteroids (<20 mg/day of prednisone or equivalent). – Long-term alternate-day treatment with short acting preparation. – Maintenance physiologic doses (replacement therapy). – Topical, inhaled, intra-articular, bursal, or tendon corticosteroids injections.
Asplenic/hyposplenic	Give: <ul style="list-style-type: none"> • Influenza vaccine. • Pneumococcal vaccine. • Meningococcal C vaccine. • Haemophilus influenzae B . 	AIIRD⇒ live in or travel to areas where other meningococcal strains are endemic (A, Y, W135), vaccination for these meningococcal subtypes is also indicated
Travelers with AIIRD	Vaccinations according to the general rules with some exception	Exceptions are: <ul style="list-style-type: none"> • BCG vaccine. • Oral poliomyelitis vaccine. • Oral typhoid fever. • Yellow fever .
PCP prophylaxis	Special circumstance	<ul style="list-style-type: none"> • Patients on a glucocorticoid dose ≥ 20 mg of prednisone daily for month or longer who also have another cause of immunocompromised .

^aVaccination in patients with AIIRD should ideally be administered during stable disease. *AIIRD* autoimmune inflammatory rheumatic disease, *MTX* methotrexate, *AZA* azathioprine [31, 128, 129, 130, 131, 132]

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