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ORIGINAL ARTICLE

Respiratory Infections in the Rheumatic Patients: Epidemiology, Pathogenesis, Prophylaxis and Management

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ABSTRACT

Pulmonary infections are an important consideration in the management of patients with rheumatological diseases, especially in those with associated lung disease. Underlying altered immune status and administration of immunomodulatory drugs are thought to be the primary drivers of increased susceptibility to infection. Multiple studies have suggested that rheumatic patients, especially those taking biologic agents such as tumor necrosis factor-alpha (TNF-α) inhibitors, are at an increased risk of infection. Clinicians can attenuate the risk of serious infections by ensuring appropriate vaccination and by screening patients carefully for opportunistic infections prior to initiating therapy with biologic agents. Any signs or symptoms of pulmonary infection should be taken seriously, and both common and uncommon pathogens must be considered in the differential diagnosis. The management of pulmonary infections in rheumatic patients can be challenging, sometimes requiring cessation of immunomodulatory therapy and consultation with infectious diseases specialists andshould be tailored to the individual patient.

Keywords: Respiratory, Infections, Rheumatic.

INTRODUCTION

Significant morbidity and death are associated with systemic rheumatic disorders because of these consequences and, in particular, because of concomitant infections [1]. Patients diagnosed with rheumatic illnesses frequently experience respiratory tract infections. Both common pathogens, such as viruses and bacteria, and opportunistic diseases can cause pneumonia in these patients. In wealthy nations, the latter are starting to account for a significant portion of deaths [2].

The primary risk factors for individuals with rheumatoid arthritis include immuno-regulation changes, disease severity, debility, co-occurring conditions, and immuno-suppressive drug use **[3].**

Biological agents and immuno- suppressive therapy have demonstrated to elevate the likelihood of infection by common respiratory pathogens, both bacterial and viral, in addition to opportunistic pathogens such as Mycobacterium species, Pneumocystis jiroveci, Histoplasma- capsulatum, Coccidio-idesimmitis, Aspergillus species, and Nocardia species **[4,5,6].**

Epidemiology

The evidence linking rheumatic disease to infection risk has been studied extensively; however, in those suffering with inflammatory arthritis, the evidence is

strongest. According to a sizable prospective investigation, individuals with newly diagnosed inflammatory polyarthritis have an infection risk that is at least 2.5 times higher than that of the general population. Patients with inflammatory polyarthritis were even more at risk for respiratory tract infections; they had a 3.5-fold increased chance (95 percent confidence interval [CI] of 2.3–5.4) compared to the general group **[7].**

A well-known retrospective matched cohort study of patients with rheumatoid arthritis (RA) treated at the Mayo Clinic over a roughly 40-year period similarly revealed higher infection risks. Upon adjusting for several risk factors, such as the use of corticosteroids, the researchers discovered that individuals with RA had an objectively diagnosed infection 1.7 times (95 percent confidence interval [CI] 1.4–2.0) higher than those in the same cohort without RA. Additionally, they had a 1.7-fold (95% CI 1.5-2.0) increased risk of pneumonia **[8,9].**

Pathogenesis

It is believed that immunological modulatory medication effects and underlying compromised host defenses play a significant part in the rheumatoid arthritis infection's etiology patients. Even while complement insufficiency and other mechanisms in SLE are well-documented immune system abnormalities in rheumatoid arthritis patients [**10],** there is still much to learn about the pathophysiology of rheumatic disorders **[11].**

Structural defects linked to Rheumatoid arthritis may also increase the risk of infection in addition to immune system dysfunctions. Rheumatoid nodules and chronic lung disease were linked in a multivariate model to a higher risk of infection in RA patients. Furthermore, environmental factors that may possibly contribute to the development of rheumatic fever may result in an increased risk of infection disorders **[12].**

The many pharmaceuticals used to treat rheumatic disorders fall into three general categories: biologic agents, corticosteroids and disease-modifying anti-rheumatic medications (DMARDs). Although several of these drugs have obvious immune-modulatory effects, there is frequently conflicting data to suggest a link between their usage and illness. Although observational evidence consistently shows a relationship between infection and corticosteroid treatment **[12],**There was no increased risk in randomized trials, according to a recent meta-analysis assessing infection risk in RA patients using glucocorticoids **[13].**

Each medication has a different risk of infection, but methotrexate, the most widely used DMARD, inhibits lymphocyte proliferation. Large-cohort studies have not consistently shown an increased risk of infection in patients receiving low-dose methotrexate, even though multiple Patients with rheumatoid arthritis who take it have been reported to have opportunistic infections [14]. Cyclophosphamide use was associated with the highest risk of infection among standard DMARDs in a large case control investigation of RA patients treated between 1980 and 2003, with a relative risk of 3.26 (95% CI 2.28–4.67). Azathioprine was associated with a moderately increased relative risk of 1.52 (95 % CI 1.18–1.97), but antimalarial agents, leflunomide, sulfasalazine, cyclosporine, and others were not in the same study **[15].** Among the DMARDs, this observational data confirms that clinicians must be especially wary of infection with cyclophosphamide and azathioprine.

Each medication has a different risk of infection, but methotrexate, the most widely used DMARD, inhibits lymphocyte proliferation. Large-cohort studies have not consistently shown an increased risk of infection in patients receiving low-dose methotrexate, despite the fact that multiple case reports have shown opportunistic infections in rheumatic patients taking it **[14].**

In a large case control analysis of RA patients treated between 1980 and 2003, cyclophosphamide use was linked to the highest risk of infection among standard DMARDs, with a relative risk of 3.26 (95% CI 2.28–4.67). Leflunomide, sulfasalazine, cyclosporine, and other antimalarial

medications were not linked to a substantially increased relative risk of 1.52 (95% CI 1.18–1.97) for azathioprine in the same study **[15].** This observational data across DMARDs validates that clinicians need to be particularly cautious for infection with azathioprine and cyclophosphamide **[16].**

Screening and Prophylaxis for Infections

Before starting immune modulatory medications, doctors should thoroughly screen patients due to concerns about increased infection risks. Before beginning leflunomide and methotrexate treatment in high-risk individuals, the American College of Rheumatology advises testing for the hepatitis B and C viruses (HBV and HCV, respectively) [17]. All patients should undergo testing for latent tuberculosis infection (LTBI), HBV, and HCV prior to beginning TNF-α antagonists**[18].**

The more modern interferon-γ release assays (IGRAs), such as QuantiFERON ® -TB Gold (Cellestis Ltd, Victoria, Australia), or the more conventional tuberculin skin testing (TST), can be used to screen for LTBI **[19].**

Patients who are unlikely to return for a TST reading or who have already received the Bacillus Calmette-Guérin (BCG) vaccination are typically better candidates for IGRAs. Individuals who get positive findings from an LTBI screening should obtain a chest X-ray to detect any active cases of tuberculosis (TB) and be assessed for clinical indications of active disease. If the chest X-ray is not informative, they should be treated for LTBI with weekly isoniazid and rifapentine for a period of nine months or using the just-approved 12-week schedule **[20].**

TNF-α antagonists should ideally be started after LTBI treatment has been completed, yet many doctors start TNF-α antagonists a few months following treatment with LTBI. Prophylactic itraconazole treatment should be administered to patients for at least three months before and one year following starting biologic therapy if a chest X-ray reveals evidence of histoplasmosis or if clinical data supports a histoplasmosis diagnosis made in the two years before biologic therapy **[21].**

Clinicians who practice in endemic areas of coccidioidomycosis, before starting biologic usage, patients in regions like Arizona, New Mexico, central and southern California, or southern Texas should get chest X-rays and anti-coccidioidal antibody serology. For patients receiving biologics, we recommend treating them with preventative fluconazole for a minimum of 6–12 months if they have a history of coccidioidomycosis, which is now gone, or if the chest X-ray or serology show signs of the illness. Although there is substantial debate regarding the best course of action for patients receiving biologics for asymptomatic coccidio-idomycosis, a suggested care plan was recently published. **[22].**

For individuals undergoing therapy for rheumatic disease, immunization is a crucial intervention in addition to the preventive measures already discussed **(Table 1).** It is advised that persons taking minocycline or hydroxychloroquine get the influenza vaccine. Vaccinations against pneumococcal disease and influenza are advised for people on sulfasalazine. It is advised that patients receiving leflunomide, methotrexate, or biologic medicines also have influenza, pneumococcal, and hepatitis B vaccinations. Vaccinations that are live, such as the measles, mumps, rubella, and zoster vaccines, should be avoided by patients on biologic drugs. Notably, the American College of Rheumatology has recently recommended that patients obtain the herpes zoster vaccine prior to starting biologic medicines **[23].**

Additionally, prophylaxis against Pneumocystis pneumonia (PCP) should be given to individuals on moderate- and high-dose glucocorticoids. We advise for patients taking glucocorticoids equivalent to at least 20 mg of prednisone for at least a month, or glucocorticoids in combination with another immunosuppressive medication such as a TNF-α antagonist, PCP prophylaxis with trimethoprim-sulfamethoxazole (at least one double-strength tablet, three times a week), even though consensus guidelines are lacking in this area. Methotrexate toxicity is more

common in individuals using trimethoprim-sulfamethoxazole (TMP-SMX) in addition to methotrexate; nevertheless, compared to twice daily therapeutic doses, methotrexate is typically well tolerated in patients taking prophylactic doses of TMP-SMX **[24].**

Table (1): Recommendations for vaccinations in patients with RA starting or currently taking DMARDs or biologic agents **[24].**

	Pneumococcal (a)	Influenza (b)	Hepatitis (c)	Live attenuated vaccinations
***Before initiating therapy**				
DMARD monotherapy d	X	X	X	X
Combination DMARDs	X	X	X	X
All biologics e	X	X	X	X
***While already taking therapy**				
DMARD monotherapy	X	X	X	X
Combination DMARDs	X	X	X	X
All biologics	X	X	X	Not recommended

X = recommend vaccination when indicated (based on age and risk)

a. The Centers for Disease Control and Prevention also recommends a one-time pneumococcal revaccination after 5 years for persons with chronic conditions such as RA. For persons ages ≥65 years, one-time revaccination is recommended if they were vaccinated ≥5 years previously and were age <65 years at the time of the primary vaccination

b. Intramuscular

c. If hepatitis risk factors are present (e.g., intravenous drug abuse, multiple sex partners in the previous 6 months, healthcare ersonnel)

d. DMARDs include hydroxychloroquine, leflunomide, methotrexate, minocycline, and sulfasalazine

e. Biologics include TNF-α antagonists (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) and other agents (abatacept, rituximab, and tocilizumab)

Clinical syndromes

Hospitalisation, morbidity, and mortality are significantly influenced by pulmonary infections, which make up a significant fraction of infections in those suffering from rheumatoid arthritis. One study found that in multiple cohorts of SLE patients, lung infections accounted for 21–25% of all infections. Numerous respiratory illnesses, such as pneumonia, the most frequent pulmonary infection, and tuberculosis (TB), which should be considered in patients on TNF-α antagonists, have been observed in rheumatoid arthritis patients **[25].**

Pneumonia

When rheumatoid arthritis patients exhibit symptoms suggestive of pneumonia,

particular care should be given to them, especially if they are on biologic drugs. It is possible for imaging tests to come back falsely negative and for the usual pneumonia symptoms and indicators to be minor or nonexistent. Common bacterial pathogens include Legionella spp., Haemophilusinfluenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, and Streptococcus pneumonia, should be assessed and treated in patients with probable pneumonia. We typically start treating rheumatic individuals with community-acquired pneumonia with an advanced-generation macrolide (like azithromycin) in addition to either a betalactam or a respiratory fluoroquinolone (such as levofloxacin or moxifloxacin). It is recommended that hospitalized rheumatic patients who have either hospital-acquired or healthcare-associated pneumonia receive first antibiotic therapy that includes nosocomial infections such methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa **[26].**

Typical regimens include a combination of three antibiotics as follows:

1) Piperacillin-tazobactam, an antipseudomonal carbapenem (imipenem or meropenem), or an antipseudomonal cephalosporin (ceftazidime or cefepime)

(2) Vancomycin

(3) An aminoglycoside or an antipseudomonal fluoroquinolone (levofloxacin, ciprofloxacin, etc.).

The Infectious Diseases Society of America has comprehensive antibiotic guidelines **[27].**

It is imperative to consider uncommon pathogens, particularly considering the mounting observational data that associates the use of biologic agents with pneumonias caused by bacteria, fungi, and viruses. There have been numerous reports of fungal pneumonia to the AERS. The FDA has added a black box warning to TNF-α antagonists for blastomycosis, coccidioidomycosis, and pulmonary and disseminated histoplasmosis **[28]** in reaction to the 240 documented cases of histoplasmosis **[29].**

Compared to etanercept, infliximab seems to carry a greater risk of histoplasmosis development **[30].**

Antifungal therapy should be started as soon as possible in rheumatic patients with recently confirmed histoplasmosis, commonly with amphotericin B or itraconazole after seeing an infectious diseases expert. Additionally, we advise discontinuing,if possible, use TNF-α antagonists in these patients until the clinical infection is under control closely monitoring them for indications of an immune reconstitution inflammatory syndrome (IRIS), which has been documented in case studies, after stopping the TNF-α antagonist **[21].**

Tuberculosis

TNF-α antagonist-using rheumatoid arthritis patients appear to be at higher risk of TB reactivation, and this risk may be higher for rheumatoid arthritis patients overall. Patients using TNF-α antagonists have a higher chance of developing tuberculosis (TB), most likely because TNF-α is crucial for the previously discussed creation and maintenance of granulomas. Among RA patients not on TNF-α antagonists, the risk ratio for tuberculosis (TB) was 8.9 (95% CI 4.6–17.2) in Korean research, but it was 30.1 in patients receiving infliximab. The most frequent cause of LTBI reactivation in US patients is other TB, although primary TB development should also be considered, particularly in those with risk factors for recent TB exposure. Patients on TNF-α antagonists seem to have a higher risk of extrapulmonary tuberculosis than the general population **[31].**

Research with 112,300 RA patients found that 386 instances of tuberculosis (TB)

occurred after RA medication. RA patients treated with biologic drugs had a 1.5 (95 % 1.1–1.9) relative risk of getting tuberculosis (TB) compared to RA patients not treated with biologics or DMARDs. A total of 2,57 (95 % 1.89–3.26) cases of tuberculosis per 1,000 person-years were seen in patients receiving TNF-α antagonist treatment. 73% of these individuals experienced pulmonary tuberculosis (TB), a median presentation time of 79 weeks (range 3–168 weeks) after the first prescription for etanercept and 17 weeks (range 1–71 weeks) after the first prescription for infliximab. **[32].**

It's interesting to note that people using corticosteroids concurrently had a lower probability of contracting tuberculosis. A recent meta-analysis also revealed variations in TNF-α antagonists; compared to etanercept, Adalimumab and infliximab were associated with a 3.4-fold increased risk of tuberculosis (TB). The typical time for TB symptoms to appear for infliximab, etanercept, and adalimumab was 5.5 months, 13.4 months, and 18.5 months, respectively, which is consistent with our results. In 62% of instances, the TB was extrapulmonary **[33].**

Upon diagnosis of tuberculosis, the patient should begin multidrug therapy according to a history of exposure and pharmacological sensitivity, and cease using TNF-α antagonistsif possible. Notably, rheumatoid arthritis patients with recently diagnosed tuberculosis have been reported to experience an IRIS-like response following TNF-α antagonist withdrawal **[34].**

CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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