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**Original Article**

# Assessment of Infections in Autoimmune Rheumatic Patients Treated With Disease Modifying Antirheumatic Drugs

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## Abstract

**Background:** Autoimmune rheumatic diseases (ARDs) are chronic inflammatory disorders that often require long-term treatment with disease-modifying antirheumatic drugs (DMARDs) to control disease activity and prevent organ damage. However, due to their immunosuppressive effects, DMARDs may increase patients' susceptibility to various infections.
**Objective:** To assess various types of infections occurring among patients of autoimmune rheumatic diseases receiving disease-modifying antirheumatic drugs in the Department of Rheumatology at Pakistan Institute of Medical Sciences (PIMS), Islamabad
**Methods:** A cross-sectional study was conducted in Department of Rheumatology, Pakistan Institute of Medical Sciences, Islamabad during April to October 2023. Data of 150 patients having autoimmune rheumatic diseases who were receiving disease modifying antirheumatic drugs was collected after taking informed consent and ethical approval. Frequency of various infections in patients with autoimmune rheumatic diseases on disease-modifying antirheumatic drug therapy was observed. Data was analyzed in Statistical Package for Social Sciences version 23.0.
**Results:** The mean age was 40.7±17.1 years and most of study patients were females 129 (86.0%). All patients experienced infection. Of total, 60 (40.0%) had lower respiratory tract infections, and 45 (30.0%) had skin/soft tissue infections. Other frequent infections were upper respiratory tract infections 24 (16.0%), gastrointestinal tract infections 14 (9.3%) and sepsis found in 7 (4.6%) of study cases. None of the patients had pneumococcal or influenza vaccination.
**Conclusion:** An absolute infection rate was found among ARDs patients under DMARDs therapy. This is alarming situation and underscores the need for risk stratification and preventive measures before initiation of therapies.
**Key words:** Infection, disease modifying antirheumatic drugs, autoimmune rheumatic diseases.

## Introduction

The ARDs is a set of different diseases which exhibit comparable clinical, immunologic and pathological symptoms.[1] ARDs represent conditions such as rheumatoid arthritis, systemic sclerosis, lupus erythematosus, and Sjögren's syndrome that affects up to 5% of global population.[2]

In ARDs patients suffer from pain, swelling, and stiff joints, where these patients often present with the conditions of fatigue, febrile and weight loss.[3] It's key pathobiological insight is as emergence of an excessively self-reactive response to immunes that is driven by an antigen. It is widely believed that its pathogenesis is caused by a combination of infections, genetic history, as well as physical or chemical reactions, stressful condition and hormonal imbalance based on clinical and translational research investigations.[4] Infection remains to be the predominant factor causing illness, hospital admissions and death in ARD cases. Genetic, immunological abnormalities, damaged organ systems, disease activity, and drug

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**Authors Contribution**

SM, SZ & UR conceptualized the project. SM, SG & GH did the data collection. SZ & UR performed the statistical analysis. SM & SZS did the literature search. Drafting, revision & writing of manuscript were done by SM, SZS, SG & GH.

use, particularly corticosteroids and immune-suppressants like cyclophosphamide (CF), stand out as risk factors for this consequence.[5]

The DMARDs are immunomodulatory and immunosuppressive drugs which are either conventional or biologic DMARDs. The goal of DMARDs therapy is based on achieving complete remission or reducing the activity of disease and avoiding its further progress. Therapeutic advancements in terms of disease-modifying antirheumatic medicines that act biologically, reduction of swelling have been achieved, that led to decrease in severe morbidity and mortality. However, due to mechanism of action of drugs some concerns regarding risk of infection have been mentioned.[6] Data from few studies reflected that Streptococcus pneumoniae, Herpes zoster virus (HZV), Candidiasis, Salmonella, Toxoplasmosis, Tuberculosis (TB), Pneumocystis jirovecii (PCJ), Influenza and Human papillomavirus (HPV) are most commonly found microorganisms among ARDs patient suffering from preventable serious infections.[7] Recently, Gupta P et al studied ways to rule out the different infections occurring among ARDs patients who were taking DMARDs and they found that 34.5% of patients were infected with RTI, 24.5% with genitourinary tract infection, 20.5% had skin and soft tissue infections, 14.5 % suffered with GIT and 1% patients developed sepsis during the study period.[8] In another study, Ichinose K et al reported that 10.9% of their patients suffered with bacterial infections after DMARD therapy. Among these 73.3% patients had bacterial RTI, 6.6% of patients had sepsis and soft tissue infections each. While, acute sinusitis, UTI and digestive tract infection were reported in 3.3% of their patients.[9]

Disease activity, comorbidities, and the use of immunosuppressive medications increase the risk of infections in patients with ARDs. Therefore, healthcare professionals managing these patients must be aware of the infection risks associated with various therapies, as this knowledge is essential for appropriate monitoring and treatment decisions. Limited global evidence and a lack of local data exist regarding the pattern of infections in ARD patients receiving DMARD therapy. This study was conducted to assess the spectrum of infections among ARD patients on DMARDs, with the objective of identifying common infections to inform preventive and clinical management strategies.

## Methods

This cross-sectional study was conducted in the Department of Rheumatology, PIMS, Islamabad, over a six-month period from April to October 2023. A total of 150 patients were enrolled through non-probability consecutive sampling. The sample size was statistically calculated using a 95% confidence level, 5% absolute precision, and an expected population proportion of 10.9%.[9]

Patients aged 18-70 years of either gender with a confirmed diagnosis of ARDs and receiving DMARD therapy were included. ARDs were defined as systemic inflammatory disorders characterized by immune dysregulation leading to organ damage. The initial clinical diagnosis was made by a consultant rheumatologist with at least three years of teaching experience who was independent of the study data collection. Disease-specific diagnostic criteria were applied: SLE according to ACR 1987 revised criteria or the 2010 ACR/EULAR criteria;[10] primary Sjögren's syndrome using the Revised American–European Consensus Group or European classification criteria; systemic sclerosis according to the 1980 classification criteria;[11] and polymyositis/ dermatomyositis using the Bohan and Peter criteria.

Patients with more than one ARD, a history of infection within the preceding three months, diabetes mellitus, heart failure, renal failure, liver failure, tuberculosis, AIDS, malignancy, pregnancy, lactation, or those lost to follow-up were excluded. Infections were assessed in patients with confirmed ARDs receiving DMARD therapy and were diagnosed clinically within three months of enrollment. These were categorized as LRTI, URTI, GIT, GUT, UTI, skin and soft tissue infections, and sepsis. Recurrence of infections was also recorded. The written informed consent was obtained from all participants. Clinical history and physical examination were performed by a postgraduate trainee. Laboratory investigations including CBC, CRP, rheumatoid factor with titer, LFT, RFT, and ECG were performed. Patients were followed on a fortnightly basis during the study period to monitor for infections.

Data were entered and analyzed using SPSS version 17. Quantitative variables were expressed as mean±standard deviation, while qualitative variables were presented as frequencies and percentages. Associations between types of infections and age groups or gender were assessed using the chi-square test, with a *p*-value <0.05 considered statistically significant.

## Results

In this study a total of 150 cases of ARDs were enrolled. The mean age of patients was 40.7±17.1 years with a female majority 129 (86.0%). Of the total, most patients i.e. 60 (41.3%) were

found between 41 to 60 years of age, followed by 26 to 40 years 51 (34.0%). The average BMI was found out to be 21.1±2.0.Most of the study patients were living in the urban area 126 (84.0%) (Table-1).

**Table 1: Demographic characteristics. (n=150)**

| *Characteristics* | | *No. of Cases* | *%* |
|---|---|---|---|
| Gender | Males | 21 | 14.0 |
| | Females | 129 | 86.0 |
| Age (years) | 16 to 25 | 37 | 24.7 |
| | 26 to 40 | 51 | 34.0 |
| | 41 to 60 | 60 | 41.3 |
| | Mean ± SD | 40.7 ± 17.1 | |
| Body Mass Index | Mean ± SD | 21.1 ± 2.0 | |
| Living area | Urban | 126 | 84.0 |
| | Rural | 24 | 16.0 |

In this study the majority of patients 61 (40.7%) were diagnosed to have Systemic lupus erythematosus Lupus Nephritis while another 30 (20.0%) had Rheumatoid Arthritis (RA) and 24 (16.0%) were diagnosed with Rheumatoid Arthritis Hypertension. The other frequent conditions were polymyositis 8 (5.4%), Scleroderma Interstitial Lung Disease 7 (4.7%) and Juvenile Idiopathic Arthritis 7 (4.7%). There were 6 (4.0%) cases of Propionic Acidemia too. The mean duration of Antirheumatic Drugs (ARDs) was 95.4±53.3 months in this study. While on the other hand the mean duration of Disease Modified Antirheumatic Drug (DMARD) treatment was 59.3±41.9 months (Table-2).

**Table 2: Diagnosis of patients. (n=150)**

| *Characteristics* | | *No. of Cases* | *%* |
|---|---|---|---|
| Diagnosis | Systemic lupus erythematosus + Lupus Nephritis | 61 | 40.7 |
| | Rheumatoid Arthritis | 30 | 20.0 |
| | Rheumatoid Arthritis + Hypertension | 24 | 16.0 |
| | Polymyositis | 8 | 5.4 |
| | Scleroderma + Interstitial Lung Disease | 7 | 4.7 |
| | Juvenil Idiopathic Arthritis | 7 | 4.7 |
| | Propionic Acidemia | 6 | 4.0 |
| | Scleroderma & Sclerotic sclerosis | 7 | 4.7 |
| Duration of disease (mon) | Mean ± SD | 95.4 ± 53.3 | |
| Duration of DMARD therapy (mon) | Mean ± SD | 59.3 ± 41.9 | |

When the management of patients was assessed. It was noted that most of the patients 68 (45.3%) were taking anti-rheumatic Methotrexate treatment. There were 45 (30.0%) patients on Hydroxychloroquine and 22 (14.7%) were taking Leflunomide. Tumor Necrotic Factor Alpha (TNF α) therapy of Etanercept was taken by (4.7%) patients while a similar number was taking non-TNF α therapy. There were more than 80.0% of the present study patients who were taking steroids DMARDs. When the status of vaccination in the study patients was assessed, it was noted that 126 (84.0%) had their COVID vaccination while only 14 (9.3%) had influenza vaccination. None of the study patients had pneumococcal or meningococcal vaccine (Table-3).

**Table 3: Management details of study patients. (n=150)**

| *Characteristics* | | *No. of Cases* | *%* |
|---|---|---|---|
| Conventional | Methotrexate | 68 | 45.3 |
| | Leflunomide | 22 | 14.7 |
| | Hydroxychloroquine | 45 | 30.0 |
| | Azathioprine | 7 | 4.7 |
| | Mycophenolic acid | 8 | 5.3 |
| TNF α | None | 142 | 94.4 |
| | Infliximab | 1 | 0.6 |
| | Etanercept | 7 | 4.7 |
| Non TNF α | None | 143 | 95.3 |
| | Secukinumab | 7 | 4.7 |
| Steroids + DMARDs | Yes | 121 | 80.7 |
| | No | 29 | 19.3 |
| Recurrence of disease | Yes | 47 | 31.3 |
| | No | 103 | 68.7 |
| Covid vaccination | Yes | 126 | 84.0 |
| | No | 24 | 16.0 |
| Pneumococcal vaccination | Yes | 0 | 0.0 |
| | No | 150 | 100.0 |
| Influenza vaccination | Yes | 14 | 9.3 |
| | No | 136 | 90.7 |
| Meningococcal vaccination | Yes | 150 | 100.0 |
| | No | 0 | 0.0 |

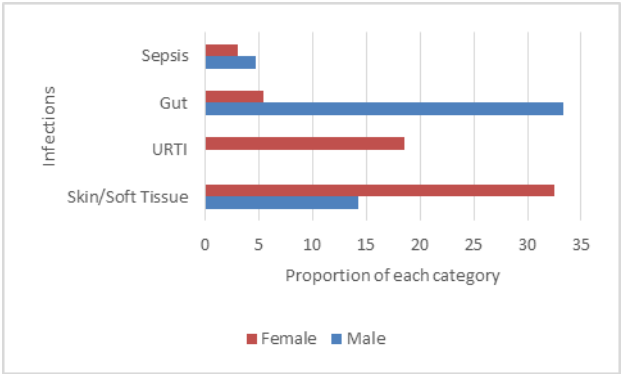


**Figure: Type of infections according to gender (n=150)**

In the current study, all the cases had experienced infections during DMARDs therapy. Frequency of infections was distributed according to gender and age. It was noted that except for GUT infections which were similarly distributed in both genders (*p*-value, >0.05), all other infections were found significantly associated with female gender in this study (*p*-value, <0.001) (Figure).

Moreover, when distribution of infections was assessed according to age it was noted that LRTI and sepsis were significantly associated with older age (*p*-value, <0.001). On the other hand, skin/soft tissue, and GUT infections were common in younger age categories (*p*-value, <0.001). Moreover, URTIs were found equally distributed in different age categories (*p*-value, >0.05) (Table-4).

**Table 4: Type of infections according to age in years. (n=150)**

| *Infections* | *Age Group (Years) n (%)* | | | *Total* |
|---|---|---|---|---|
| | *16-25* | *26-40* | *41-60* | |
| LRTI | 0 | 21 (14.0) | 39 (86.0) | 60 |
| Skin/Soft Tissue | 15 (33.3) | 22 (48.9) | 8 (17.8) | 45 |
| UTI | 8 (33.3) | 8 (33.3) | 8 (33.3) | 24 |
| Gut | 14 (100.0) | 0 | 0 | 14 |
| Sepsis | 0 | 0 | 7(100) | 7 |

## Discussion

In the current study all patients experienced infections of varying types. Lower respiratory tract infections (LRTI) were the most common (40.0%) in this study followed by skin/soft tissue infections and upper respiratory tract infections (URTI). Similarly, Gastrointestinal (GUT) infections and sepsis were also experienced by a few patients but still at significant rate in the present study. Many previous investigators have found similar findings, a large European study reported similar prevalence rates; 42% for LRTI, 28% for skin infections, and 18% for URTI.[12] Another study by Frede N et al witnessed LRTIs in 31.1% patients while URTI were experienced by around 90.0% of their cases and other infections were found in 18.0% of their cases.[13] They also witnessed a recurrence of more than 3 episodes of respiratory tract infections in 18.0% cases. In the current study too we witnessed recurrent LRTI in almost 30.0% patients. Gupta et al also witnessed that after DMARDs therapy LRTI were the most common infections in their patients while other frequent infections were GUT 24.5%, skin/soft tissue 20.5% while 14.5% suffered with GIT and 1% of their study patients developed sepsis.[8] Ichinose K et al also witnessed that bacterial RTI was the most common infection while GUT and UTIs were less frequent in their study patient taking DMARDs.[9] This trend of infections has been reported by many other too.[14-16] The overall aggregate evidence suggests a global trend of increased susceptibility of infections across diverse populations.

Skin and soft tissue infections were also common in this study cases, these were more frequent in patients on TNF inhibitors. Evidence reveals that skin and soft tissue infections were considered significant, as these are inhibited by TNF-α that is a crucial cytokine contributing to cutaneous endothelial activation and enhancing inflammatory cells in the skin.[17] Previous evidence suggests that TNF inhibitors have been related to cause recurrent infections.[18] In the current study almost one half of patients received Methotrexate therapy. Previous reports have found that Methotrexate is significantly associated with serious infections.[19]

The most successful shield against infections is vaccination. In the current study none of patients had pneumococcal or influenza vaccinations. The physicians must focus on this issue in the local context as DMARDs are long term treatments and protective options against infections should be a priority. In this regard, Schneeweiss et al witnessed that patients who were treated with TNF antagonists had more chances of taking minimum one dose of influenza vaccination. Vaccination has protective response in mitigating chance of infection.[20] Another study by Germano et al also suggested that vaccines are protective in patients who are compliant to long term medication.[17]

These findings suggest that DMARDs therapy may substantially elevate a patient's susceptibility to infections, rest aside the chances of other associated serious illnesses.[21] The results underscore the importance of considering infection risk when initiating DMARDs therapy. Physicians may want to develop a risk stratification approach to identify patients more susceptible to infections.[22] This could involve factors like age, underlying health conditions, and medication history. Proactive monitoring and potential preventative measures, such as vaccinations, might be warranted in high-risk patients.[23-25]

The key findings of the current study suggest that RA patients have greater chance of infection and protective techniques like vaccinations should be applied early on in these patients who need DMARDs. This study noticed that biological

therapies are on greater risk for serious infections like respiratory tracts, gastrointestinal and sepsis, however, the magnitude of spread has been found modest.

Further research is needed to explore the mechanisms by which DMARDs therapy increases infection risk. This knowledge could guide the development of more targeted strategies to mitigate infection susceptibility in patients requiring DMARDs.

## Conclusion

DMARD therapy is found associated with high rate of infections in ARDs patients. There is a need to find protective techniques to avoid serious infections during long term therapies for chronic diseases like ARDs. The role of vaccine prevention against LRTIs and skin infections should be investigated in future studies. Further large-scale studies on this topic with rigorous methods are needed to validate the current findings.

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**Availability of Data:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethical Approval:** The Ethics Research Review Board of Pakistan Institute of Medical Sciences, Islamabad approved the study via letter no. F.3-1/2023(ERRB)/Chairman.

**Conflict of Interest:** None declared.

## References

1. David T, Ling SF, Barton A. Genetics of immune-mediated inflammatory diseases. Clin Exp Immunol 2018; 193(1): 3-12.
2. Hedar AM, Stradner MH, Roessler A, Goswami N. Autoimmune Rheumatic Diseases and Vascular Function: The Concept of Autoimmune Atherosclerosis. J Clin Med 2021; 10(19): 4427- 30.
3. Angum F, Khan T, Kaler J, Siddiqui L, Hussain A. The Prevalence of Autoimmune Disorders in Women: A Narrative Review. Cureus 2020; 12(5): 8094-98.
4. Shukla SK, Singh G, Ahmad S, Pant P. Infections, genetic and environmental factors in pathogenesis of autoimmune thyroid diseases. Microb Pathog 2018; 116: 279-88.
5. Morales-Tisnés T, Quintero-Ortiz L, Quintero-Muñoz E, Sierra-Matamoros F, Arias-Aponte J, Rojas-Villarraga A. Prevalence of hospital readmissions and related factors in patients with autoimmune diseases. J Transl Autoimmun 2021; 4: 1-5.
6. Ozen G, Pedro S, England BR, Mehta B, Wolfe F, Michaud K. Risk of Serious Infection in Patients with Rheumatoid Arthritis Treated with Biologic Versus Non-Biologic Disease Modifying Antirheumatic Drugs. ACR Open Rheumatol 2019; 1(7): 424-32.
7. Rúa-Figueroa Fernández de Larrinoa Í, Carreira PE, Brito García N, Díaz Del Campo Fontecha P, Pego Reigosa JM, Gómez Puerta JA, , et al. Recommendations for prevention of infection in systemic autoimmune rheumatic diseases. Reumatol Clin (Engl Ed) 2022; 18: 317- 30.
8. Gupta P, Padhan P, Bhargava N, Behera PK, Tripathy KP, Panda SS. Spectrum of infections occurring in patients of autoimmune rheumatic diseases on treatment with biological versus conventional disease-modifying antirheumatic drugs: A comparative study. J Family Med Prim Care 2022; 11: 3575-83.
9. Ichinose K, Shimizu T, Umeda M, Fukui S, Nishino A, Koga T, et al. Frequency of Hospitalized Infections Is Reduced in Rheumatoid Arthritis Patients Who Received Biological and Targeted Synthetic Disease-Modifying Antirheumatic Drugs after 2010. J Immunol Res 2018; 2018: 6259010-4.
10. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol 2019; 71(9): 1400-12.
11. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, Rasmussen A, Scofield H, Vitali C, Bowman SJ, Mariette X; International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol 2017; 69(1): 35-45.
12. Riley TR, George MD. Risk for infections with glucocorticoids and DMARDs in patients with rheumatoid arthritis. RMD open 2021; 7(1): e001235.
13. Frede N, Rieger E, Lorenzetti R, Nieters A, Venhoff AC, Hentze C, et al. Respiratory tract infections and risk factors for infection in a cohort of 330 patients with axial spondylarthritis or psoriatic arthritis. Front Immunol 2022; 13: 1040725.
14. Richter A, Listing J, Schneider M, Klopsch T, Kapelle A, Kaufmann J, et al. Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis. Ann Rheum Dis 2016; 75: 1667-73.
15. Quartuccio L, Zabotti A, Del Zotto S, Zanier L, De Vita S, Valent F. Risk of serious infection among patients receiving biologics for chronic inflammatory diseases: Usefulness of administrative data. J Adv Res 2019; 15: 87-93.
16. Aaltonen KJ, Joensuu JT, Virkki L, Sokka T, Aronen P, Relas H, et al. Rates of serious infections and malignancies among patients with rheumatoid arthritis receiving either tumor necrosis factor inhibitor

or rituximab therapy. J Rheumatol 2015; 42: 372-8.

17. Germano V, Cattaruzza MS, Osborn J, Tarantino A, Di Rosa R, Salemi S, et al. Infection risk in rheumatoid arthritis and spondyloarthropathy patients under treatment with DMARDs, corticosteroids and TNF-α antagonists. J Transl Med 2014; 12: 77
18. Belostocki K, Leibowitz E, Tai K, Harrison M. Infections associated with etanercept treatment of Rheumatoid Arthritis:2 years of experience in the "real world". Arthritis Rheum 2001; 44: S173.
19. Haraoui B, Bykerk V. Etanercept in the treatment of rheumatoid arthritis. Ther Clin Risk Manag 2007; 3: 99-105.
20. Schneeweiss S, Setoguchi S, Weinblatt ME, Katz JN, Avorn J, Sax PE, et al. Anti–tumor necrosis factor a therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum 2007; 56: 1754 64.
21. Sasi S, Hadi HA, Chaponda M, El Ajez R, Ataelmanan M, Khasawneh S et al. Risk of Serious Infections in Patients Treated with Biologic or Targeted-synthetic Disease Modifying Antirheumatic Drugs in Qatar. Immunity, Inflammation and Disease 2025; 13(4): e70195.
22. Deane KD, Holers VM, Emery P, Mankia K, El-Gabalawy H, Sparks JA, et al. Therapeutic interception in individuals at risk of rheumatoid arthritis to prevent clinically impactful disease. Ann Rheumatic Dis 2025; 84(1): 14-28.
23. Sakai R, Tanaka E, Majima M. Unincreased risk of hospitalized infection under targeted therapies versus methotrexate in elderly patients with rheumatoid arthritis: a retrospective cohort study. Arthritis Res Ther 2022; 24: 135.
24. Isa M, Ramos MRR, Kamal S. Infection Risk in Biological Disease-Modifying Anti-rheumatic Drugs. Cureus 2025; 17(3): e80634.
25. Jani M, Barton A, Hyrich K. Prediction of infection risk in rheumatoid arthritis patients treated with biologics: are we any closer to risk stratification? Curr Opin Rheumatol 2019; 31(3): 285-92.