RHEUMATOLOGY NURSE
PRACTICE

Inside this Issue

ISSUE **3** | VOLUME **2**

- What are the most common types of sleep disturbance issues among patients with rheumatoid arthritis (RA)?
- How can multidisciplinary management of RA patients with sleep and/or respiratory issues improve their overall well-being?
- What are the most common types of pulmonary manifestations of RA?
- What are some effective management strategies that may help alleviate the severity of respiratory issues in patients with RA?

HELPING PATIENTS

SLEEP

AT NIGHT AND

BREATHE

DURING THE DAY

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Learning Objectives

1. *Discuss the impact of sleep loss on RA patients' reported levels of pain, fatigue, depression, and anxiety*
2. *Review pharmacologic and nonpharmacologic strategies that may alleviate the impact of common sleep issues in patients with RA*
3. *Assess the impact of RA on the lungs*
4. *Describe multidisciplinary management strategies that have proven efficacy in categorizing and treating RA patients with comorbid pulmonary disease*

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HELPING PATIENTS SLEEP AT NIGHT AND BREATHE DURING THE DAY

Few patients with rheumatoid arthritis (RA) consistently sleep well, and those with chronic sleep deprivation can experience severe fatigue, heightened pain intensity, and worse disease activity.[1] Many RA patients also develop respiratory symptoms associated with their autoimmune disease, which in severe cases can increase the risk for morbidity and mortality.[2] Sleep disturbances and respiratory issues can be treated, but these extraarticular manifestations of RA must first be recognized and diagnosed.

Part 1: Sleep Issues in RA

Restorative sleep is essential for maintaining health and general well-being. According to the American Academy of Sleep Medicine (AASM), adults who routinely sleep fewer than 7 hours per night have an increased susceptibility to acute illnesses (e.g., upper respiratory infection, pneumonia) compared with adults who sleep for 7–8 hours per night.[3] Ongoing sleep deprivation contributes to the development of chronic conditions such as cardiovascular disease, diabetes, and increased pain symptoms.[3]

Approximately 80% of RA patients experience some degree of disrupted sleep.[4,5] Among RA patients with poor sleep quality, the most common types of disturbances are 'waking in the middle of the night or early morning' (97%), 'pain' (95%), and 'cannot get to sleep within 30 minutes' (91%).[6] Joint pain interferes with sleep quality, and sleep disturbance in turn exacerbates fatigue, depression, and pain intensity.[7] Poor sleep quality also interferes with immune system regulation, leading to heightened inflammatory disease activity.[8] Risk factors for worse sleep in RA patients include greater pain severity, higher RA disease activity (i.e., higher DAS28 scores), longer duration of RA, depression, physical limitations, and higher daily dose of prednisone.[4-6,9] Sleep abnormalities in RA adversely affect quality of life.[4]

Measuring Sleep Quality

Before exploring sleep issues in RA, it is important to understand how sleep quality is measured. Patient-reported questionnaires such as the Pittsburgh Sleep Quality Index (PSQI) are commonly used in the research setting to evaluate sleep quality.[10] With the PSQI, patients answer 19 questions about their sleep over the past month. The questions fall into 7 categories: subjective sleep quality, sleep latency (the time it

ACTIVITY SUMMARY

In this issue of Rheumatology Nurse Practice, we will explore the underlying causes of sleep disturbances and respiratory conditions in RA, discuss opportunities for collaborative diagnosis and management, and review additional insights that may impact clinical practice and patient quality of life.

takes to transition from sleep to full wakefulness), sleep duration, habitual sleep efficiency (the percentage of time in bed that one is asleep), sleep disturbances, use of sleeping medication, and daytime dysfunction. Each of the 7 categories is scored on a scale from 0 to 3, for a total score of 0 to 21. In general, patients with a total PSQI score of >5 are considered to have poor sleep.[10] In one study of 384 RA patients, the prevalence of poor sleep (PSQI score >5) was 61%, and the mean total PSQI score for all patients in the study was 7.5.[11]

Sleep Loss in RA: More Than Just a Bad Night

Even 1 night of disrupted sleep is more detrimental to RA patients than to healthy individuals.[12] In a 2012 sleep study, 27 RA patients and 27 healthy volunteers spent 4 nights in a sleep lab: 1 night to get acclimated, 1 night to record baseline sleep, 1 experimental night, and 1 recovery night. On the acclimation, baseline, and recovery nights, participants were allowed uninterrupted sleep between 11 p.m. and 7 a.m. During the experimental night, participants were kept awake between 11 p.m. and 3 a.m. to simulate partial sleep deprivation (PSD). After 1 night of PSD, RA patients were significantly more likely than healthy controls to have increased self-reported pain, fatigue, depression, and anxiety. Patients with RA also experienced significant increases in joint pain severity, self-reported tender/swollen joint count, and clinician-rated tender/swollen joint count after 1 night of PSD. The clinicians who performed the joint count were blinded to the experimental conditions of the RA patients.

Together, these findings show that patients with RA feel worse after sleep loss than control subjects, and that sleep loss results in objective evidence of increased disease activity.[12] This highlights the vicious cycle of sleep deprivation and pain in RA, where sleep loss activates disease activity and clinical symptoms of pain, which then contribute to further sleep loss.[12] Despite the prevalence of sleep disturbances in RA patients, few rheumatology providers ask their patients about sleep. In a survey of 28 providers with an average of 10 years of experience working in rheumatology, only half reported asking their RA patients about their sleep quality, even when patients complained of fatigue.[13]

RA, Poor Sleep Quality, and Fatigue: A Mechanistic Model

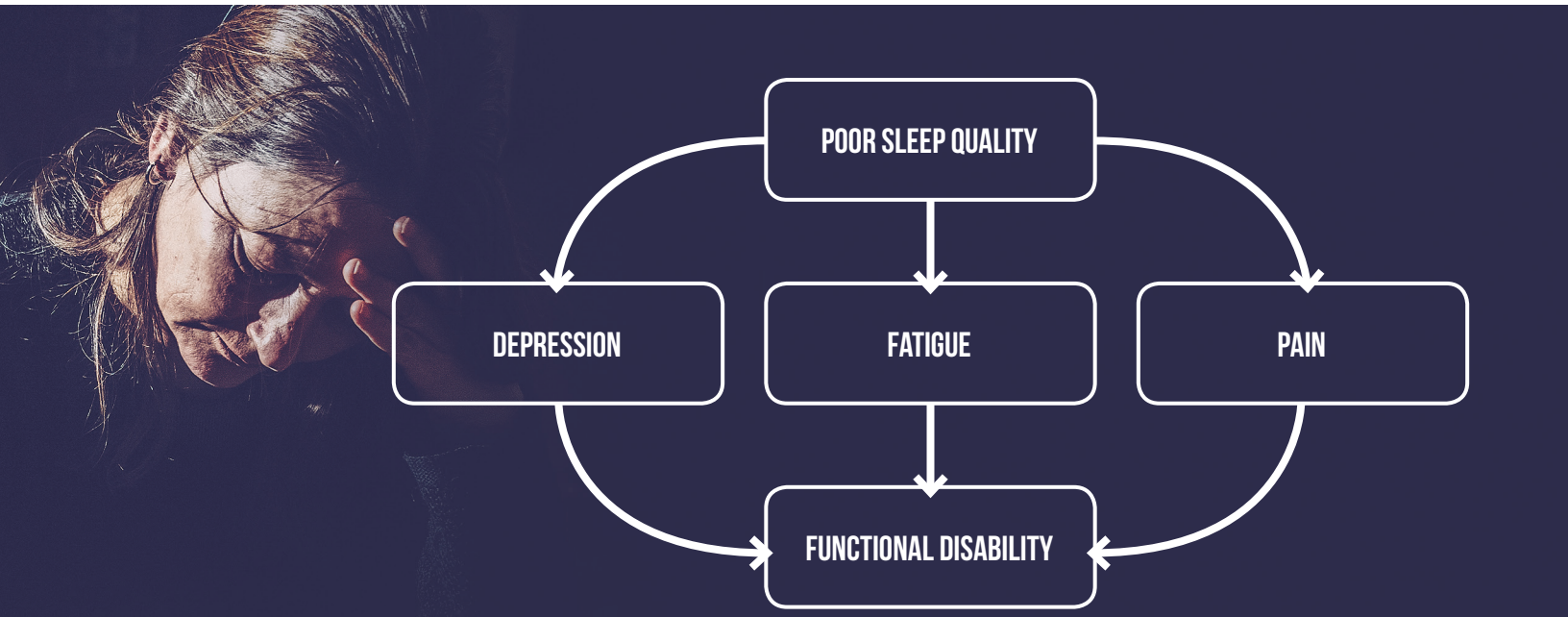
Approximately 50% of patients with RA report some degree of fatigue.[14] In patients with RA and other rheumatic diseases, the experience of fatigue tends to follow 1 of 3 major patterns, depending on whether the underlying cause is primarily physical or mental:[14]

- Tiredness related to biochemical processes that expend extra energy (e.g., inflammation), deficient energy production (e.g., endocrine disorders such as hypothyroidism), or inadequate recovery (e.g., sleep disorders)
- Muscle weakness due to motor function failure or peripheral neuropathy
- Weariness due to the impact of stress and depression on quality of life

For many patients, fatigue symptoms can be debilitating. In a study of 542 patients with RA, 41% met the criteria for severe fatigue, which is defined as a score of ≤35 on the RAND version

Figure 1

Depression, Fatigue, and Pain: Mediators of the Relationship Between Sleep Quality and Functional Disability in RA[16]



of the 36-item Short-Form Health Survey.[15] For reference, approximately 10% of adults in the general population and 82% of those with fibromyalgia have severe fatigue.[15] For patients with RA, poor sleep quality (PSQI >5) significantly correlates with both general fatigue and mental fatigue.[11]

Given the adverse effects of poor sleep quality on fatigue, depression, and pain severity, sleep disturbances also contribute to functional disability in patients with RA (see Figure 1).[16] In one study of 162 RA patients, the relationship between poor sleep (PSQI >5) and functional disability persisted even after controlling for patient age, duration of RA, number of comorbidities, prednisone use, and anti-TNF use.[16]

Other Sleep-Related Issues in RA

In addition to the cycle of pain, fatigue, and sleep loss associated with RA, many patients with RA have other sleep-related comorbidities. These conditions may occur in RA patients due to similar inflammatory disease processes, shared risk factors, or both. Importantly, these comorbidities can be treated to improve sleep quality in patients with RA.

RESTLESS LEGS SYNDROME

Approximately 30% of RA patients meet the diagnostic criteria for restless legs syndrome (RLS), compared with approximately 5-15% of adults in the general population (see Table 1).[17,18] Patients with RLS experience an uncomfortable "creepy-crawling" sensation in their legs and an irresistible desire to move them. Symptoms are common during periods of rest or inactivity and worsen at night, disrupting sleep. In most cases, patients with both RA and RLS can distinguish their RLS symptoms from their RA symptoms. For RA patients with sleep abnormalities, screening for RLS can be helpful to confirm or rule out the disorder as a potential contributing factor.[17]

SLEEP APNEA

Obstructive sleep apnea (OSA) describes the partial or complete obstruction of the upper airway during sleep, leading to sleep loss and daytime sleepiness. Approximately 12% of adults in the general population—or 29.4 million patients in the United States—are affected by OSA. The cost burden of OSA is huge, accounting for $12.4 billion in direct medical costs in 2015 and $150 billion in lost productivity and associated comorbidities.[19]

OSA is common among patients who are obese, including RA patients who gain weight because of limited capacity for physical activity.[20] The prevalence of OSA is also higher in patients with autoimmune diseases than in healthy controls, suggesting a common underlying disease process.

One recent study examined adults with OSA and no baseline diagnosis of autoimmune disease (n=105,846) and a comparison group of healthy age- and sex-matched controls (n=423,384).[21] During the 9-year follow-up period, patients with OSA were twice as likely as controls to develop any autoimmune disease. In particular, OSA patients were 33% more likely to develop RA. OSA patients also had an increased risk of developing Sjögren's syndrome and Behçet's disease during follow-up. Of note, treating OSA appeared to mitigate the risk of developing RA.[21] Among all OSA patients, those who were receiving treatment had a 78% lower risk of developing RA compared with those who were not receiving OSA treatment. Left uncontrolled, the underlying disease process eventually manifested as RA in many untreated OSA patients.

NARCOLEPSY

Although the pathogenesis of narcolepsy is not well understood, some evidence suggests that this chronic sleep disorder is an autoimmune disease that arises from the selective destruction of neurons involved in sleep.[22] One case study described a 78-year-old male patient with a 20-year history of REM sleep behavior disorder and narcolepsy who was diagnosed with RA in late life.[23] His case led researchers to propose a

Table 1

Diagnostic Criteria for Restless Legs Syndrome[18]

1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable or unpleasant sensations in the legs.
2. The urge to move the legs and any accompanying unpleasant sensations beginning or worsening during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations that are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity that only occur or are worse in the evening or night than during the day.
5. The occurrence of the previous features that are not solely accounted for as symptoms primary to another medical or behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, and habitual foot tapping).

common underlying autoimmune process that triggered the development of both narcolepsy and RA.[23] Additional links between narcolepsy and other potentials triggers, such as infections, are also being evaluated.

Medication-Induced Sleep Disturbances

Glucocorticoids such as prednisone may exacerbate sleep issues in some RA patients.[24] For patients prescribed twice-daily glucocorticoid therapy, the doses taken at night can interfere with their circadian rhythm and disrupt sleep. Patients can avoid this effect by taking glucocorticoids in a single morning dose.[24]

Pharmacologic Management of Sleep in RA

First and foremost, controlling RA disease activity with standard RA medications can improve sleep for some RA patients.[1,25] Patients whose RA is uncontrolled may be awakened in the night by pain, or wake in the morning with pain and stiffness. In two prospective studies, RA patients with uncontrolled RA disease activity and poor sleep reported significant improvements in sleep quality after starting treatment with anti-tumor necrosis factor (TNF) therapy.[25,26] RA patients with sleep disturbances also reported improvements in pain, fatigue, and health-related quality of life after starting treatment with a TNF inhibitor.[26] While the effects of other biologic DMARDs on sleep endpoints has not yet been examined in large-scale clinical trials, in a study of 172 RA patients, those treated with biologic DMARDs achieved a significantly greater reduction in RA disease activity and a significantly greater reduction in PSQI scores than those treated with conventional DMARDs.[1]

Beyond RA therapies, other medications may also have beneficial effects on sleep quality in RA. For instance, managing common comorbidities such as fatigue and depression are key steps in improving sleep. Selective serotonin reuptake inhibitors (SSRIs) can improve overall health-related quality of life in patients with fatigue through positive effects on mental status and systemic inflammation.[14] Pregabalin, an analgesic medication approved for use in fibromyalgia, neuropathic pain, and partial-onset seizures, but also used off-label in patients with anxiety, RLS, and other disorders, appears to have a positive effect on sleep maintenance (i.e., staying asleep).[27]

Multidisciplinary collaboration with psychiatrists, sleep specialists, and other healthcare professionals can also be helpful to ensure that patients' comorbidities are well controlled and to determine whether patients may benefit from over-the-counter (OTC) or prescription sleep aids.[28] It is important to ask patients about their approaches to sleep management. In one study, 67% of RA patients with sleep disturbances reported taking OTC or prescription medications to help with their sleep.[13]

Table 2

Sleep Hygiene Recommendations[29]

- Maintain a consistent sleep schedule. Wake up at the same time each day, even on weekends or during vacations.
- Set your bedtime early enough to get at least 7 hours of sleep.
- Don't go to bed unless you feel sleepy.
- Get out of bed if you don't fall asleep within 20 minutes.
- Find bedtime rituals that you find relaxing.
- Use your bed only for sleep and sex.
- Keep your bedroom quiet and maintain the room at a cool, comfortable temperature.
- Avoid caffeine in the late afternoon or evening.
- Limit your exposure to light in the evenings.
- Avoid eating a large meal before bedtime. Eat a light, healthy snack if you are hungry before bed.
- Avoid consuming alcohol before bedtime.
- Reduce your fluid intake before bedtime.
- Maintain a healthy diet and exercise regularly.

Nonpharmacologic Management of Sleep in RA

The nonpharmacologic management of sleep disorders begins with a review of basic sleep hygiene recommendations (see Table 2).[29] Simple changes such as going to bed at the same time every day, using the bed only for sleep and sex, and avoiding large meals and excessive fluid intake before bedtime can improve nighttime sleep quality in patients with RA.[29] In a study of 54 patients with RA, poor sleep hygiene behaviors were associated with the following:[30]

- Higher PSQI scores, indicating worse sleep quality
- More severe RA disease activity, as measured by RAPID3 scores
- Worse patient-reported outcomes, including pain and patient global assessment scores

Exercise has also been shown to improve sleep quality, fatigue, and related outcomes in patients with RA. In one prospective study, 40 patients

with RA were randomly assigned to an exercise intervention while 38 maintained their usual RA care.[31] The exercise intervention was a 12-week, home-based program with tailored exercises designed to target individual deficiencies in health-related quality of life, as measured by the Health Assessment Questionnaire (HAQ). After 12 weeks, RA patients in the exercise group demonstrated significant improvements in pain, stiffness, sleep quality, fatigue, and HAQ scores compared with baseline. By comparison, RA patients managed with usual care had no improvements in any sleep or fatigue measures.[31]

Referral to a Sleep Specialist

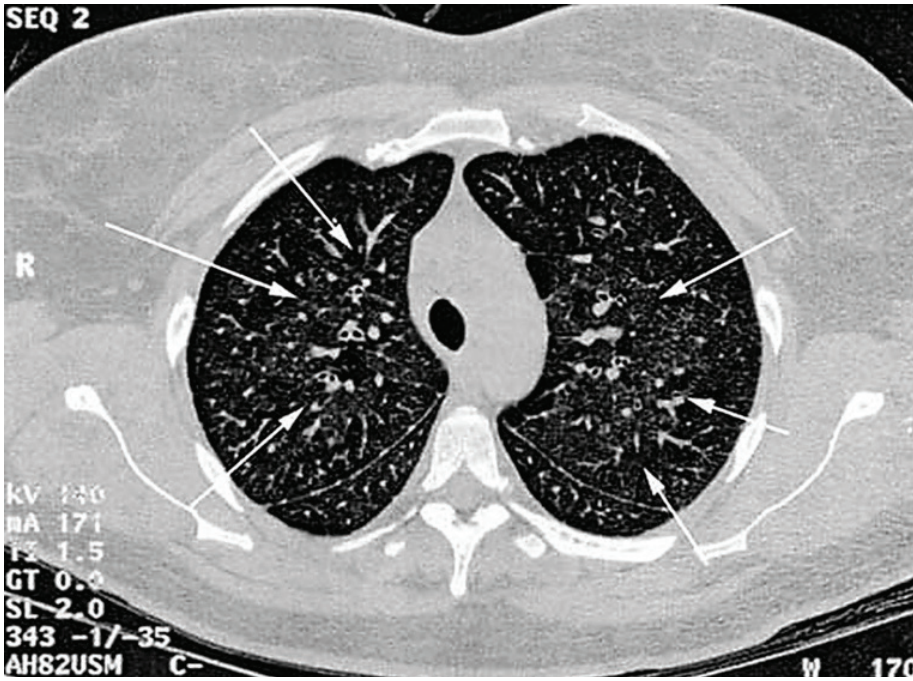
RA patients with signs and symptoms of sleep abnormalities should be referred to a sleep disorder center or sleep specialist as early as possible. The AASM clinical practice guidelines (www.aasmnet.org) provide referral recommendations for specific diagnoses such as OSA. For patients with geographic barriers to specialist care, the AASM also provides guidance on the use of telemedicine to diagnose and manage sleep disorders.[32]

Part 2: Respiratory Issues

Patients with RA are susceptible to a wide range of respiratory diseases with diverse symptoms and clinical manifestations (see Table 3).[33,34] In a study of 2,053 veterans with RA, 34% had a diagnosis of comorbid chronic lung disease. This included chronic obstructive pulmonary disease (COPD) in 18% of RA patients and asthma in 4%; an additional 23% of patients in the study were diagnosed with 'other' chronic lung diseases such as interstitial lung disease (ILD). The presence of subclinical respiratory symptoms among RA patients may be higher. In one study, two-thirds of RA patients showed evidence of shortness of breath (dyspnea), cough, wheezing, or phlegm. Laboratory testing confirmed widespread lung involvement among RA patients, with 64% having abnormal pulmonary function test (PFT) results and 47% showing signs of pulmonary involvement on high-resolution computed tomography (CT) scans.[35]

How Does RA Affect the Lungs?

Although the pathogenesis of lung disease in RA remains unclear, new insights suggest a potential role of the lung as a key organ in the development of autoimmune disease. Smoking has long been recognized as a major risk factor for anticyclic citrullinated protein antibody (ACPA)-positive RA. Based on this observation, researchers have recently focused on the lung as the initial site of autoimmune antibody generation in ACPA-positive RA.[36] Respiratory conditions in patients



Computed tomography scan showing extensive, bilateral ground-glass opacity.

with RA may arise due to genetic predisposition, environmental risk factors (eg, smoking), and other processes linked to RA disease activity.[36]

Interstitial Lung Disease

ILD is the most common pulmonary manifestation of RA. Approximately 30% of RA patients have subclinical evidence of RA-related ILD (RA-ILD) such as distinct radiologic patterns on imaging tests or abnormal PFT results.[34] In addition, approximately 10% of RA patients will develop clinically significant ILD.[34] Risk factors for RA-ILD include smoking, ACPAs, and rheumatoid factor.[37,38]

For most patients with RA-ILD, lung manifestations appear only after a diagnosis of RA has been established. In one study of 35 patients with RA-ILD, only 8 patients (13.6%) were diagnosed with ILD prior to being diagnosed with RA.[39] This suggests that most patients who develop RA-ILD will be diagnosed with RA and under the care of a rheumatologist when their lung symptoms begin to appear.

The disease course of RA-ILD depends on the subtype. Unfortunately, approximately 60% of patients with RA-ILD will have the usual interstitial pneumonia (UIP) subtype, which is associated with a more aggressive disease course and worse overall survival. In one study, RA patients with the UIP subtype had a significantly greater number of respiratory hospitalizations, were more likely to require oxygen therapy, and were more likely to experience a decline in lung capacity than RA patients with non-UIP subtypes. Patients with the UIP subtype were also more likely to have

comorbidities such as hypertension, diabetes, coronary artery disease, COPD, and asthma. The median overall survival was 92 months (7.6 years) for UIP patients compared with 137 months (11.4 years) for those with non-UIP subtypes.[39] Clinical features associated with more severe disease, including greater extent of lung fibrosis and lower diffusion capacity for carbon monoxide, predict shorter survival regardless of RA-ILD subtype.[40] Male patients and older patients with RA-ILD also tend to have worse outcomes.[40]

Other Pulmonary Comorbidities

Patients with RA are twice as likely as non-RA patients to develop COPD.[41] However, rather than being linked biologically, COPD and RA appear to be linked through one of their shared risk factors—smoking. In patients who develop COPD, smoking triggers an autoimmune reaction that leads to chronic airway inflammation that persists even after patients stop smoking.[41] Although the underlying pathophysiology of COPD in patients with RA remains unclear, comorbid lung conditions are possible. In one study, 29% of patients with RA-ILD had comorbid COPD.[39] RA patients with comorbid COPD have significantly increased risk of mortality relative to RA patients without COPD.[2]

Asthma is another common pulmonary comorbidity that occurs twice as often in patients with RA as in the general population.[42] Asthma also occurs in the presence of other lung conditions. Approximately 20% of patients with RA-ILD also have a diagnosis of asthma.[39]

Table 3

Pulmonary Manifestations of RA[33,34]

Interstitial Lung Diseases	• Usual interstitial pneumonia • Nonspecific interstitial pneumonia • Organizing pneumonia • Lymphocytic interstitial pneumonia • Acute interstitial pneumonia
Airway Diseases	• Follicular bronchiolitis • Constrictive (obliterative) bronchiolitis • Bronchiectasis • Cricoarytenoid arthritis
Pleural Diseases	• Pleuritis • Pleural effusion • Pneumothorax • Empyema
Nodules	• Rheumatoid nodules • Rheumatoid pneumoconiosis (Caplan syndrome)
Vascular Diseases	• Pulmonary hypertension • Rheumatoid vasculitis
Other Manifestations	• Drug toxicity • Infection • Amyloidosis • Fibrobullous disease • Thromboembolic disease • Thoracic cage restriction

Treatment Options for Pulmonary Disease

Treatment of RA patients with pulmonary disease requires close collaboration between rheumatology providers and lung specialists.[43] Specific considerations for the management of RA-ILD are described in the following section. RA patients with other pulmonary comorbidities such as COPD or asthma also require multidisciplinary management and individualized care.

Pharmacologic Management of RA-ILD

The choice of therapy for RA-ILD depends on the severity of disease. For many patients with subclinical or asymptomatic RA-ILD, continued monitoring with chest radiographs, CT imaging, and/or pulmonary function testing is an appropriate management option. For patients who show evidence of an aggressive disease course and/or develop bothersome respiratory symptoms, immunosuppressive therapy is the treatment cornerstone.[43,44]

High-dose glucocorticoids are often used in patients who are starting treatment for RA-ILD.[37] An example of a standard treatment course may include oral prednisolone 0.5-1.0 mg/kg/day, given with or without other agents (e.g., cyclophosphamide, azathioprine, cyclosporine, or mycophenolate mofetil). For patients who respond to glucocorticoids treatment, the prednisolone dose is gradually adjusted to 5-10 mg/day over the course of 6 to 12 months.[45] In some cases, synthetic DMARDs such as methotrexate and leflunomide have been beneficial.[37] On the other hand, given the link between RA medications and lung toxicity, patients taking nonbiologic or biologic DMARDs to manage their RA should be monitored for the possibility that treatment is exacerbating their RA-ILD.[44]

Nonpharmacologic Management of RA-ILD

Nonpharmacologic strategies focus on minimizing the impact of RA-ILD on general health and preventing further complications. Smoking cessation is critical for improving prognoses in patients with RA-ILD. Keeping up to date with vaccinations against pneumococcal disease and seasonal influenza is also recommended for all patients with RA-ILD, particularly for those treated with immunosuppressive therapy. For patients with hypoxemia, supplemental oxygen therapy can be beneficial. Finally, lung transplantation may be an option for patients who progress to severe respiratory failure.[45]

Models of Collaborative Rheumatology/ Pulmonology Care

Multidisciplinary ILD clinics offer patients with RA an opportunity for improved diagnosis and treatment.[46] One study examined management patterns among 50 patients with RA who were referred to the multidisciplinary ILD clinic at Brigham and Women's Hospital in Boston, MA, with a preliminary diagnosis of ILD or idiopathic pulmonary fibrosis (IPF). All patients underwent a comprehensive evaluation by a rheumatologist and a pulmonologist with expertise in connective tissue disease (CTD)-related ILD. As a result of this evaluation, 27 patients (54%) had their initial diagnosis changed to an alternate form of lung disease. In total, 25 patients (50%) were diagnosed with CTD-ILD, 15 (30%) were diagnosed with IPF, and 10 (20%) were diagnosed with another form of lung disease (e.g., cryptogenic organizing pneumonia, drug-induced ILD, and vasculitis). The multidisciplinary clinic team recommended treatment adjustments for 80% of the RA patients with CTD-ILD and for 27% of those with IPF. Common treatment changes for patients with CTD-ILD included the initiation of glucocorticoids and/or mycophenolate mofetil.[46]

Specialized CTD-ILD clinics are emerging at several other academic medical centers, including the University of California-Los Angeles (UCLA), the University of California-San Francisco (UCSF), and the Cleveland Clinic.[47-49] At UCLA, patients attending the CTD-ILD clinic can arrange to see a rheumatologist and pulmonologist as part of the same visit. Radiologists, pathologists, nurses, and other clinicians with expertise in CTD-ILD also contribute to integrated patient care.[48] At the Cleveland Clinic CTD-ILD program, a team of rheumatologists, pulmonologists, thoracic radiologists and pulmonary pathologists conduct weekly case reviews to collaborate on treatment plans for patients with CTD-ILD.[47] Multidisciplinary teams with specialized training in CTD-ILD are also involved in pulmonary rehabilitation, oxygen therapy, and lung transplantation.[47] With access to clinical trials of investigational ILD therapies, the CTD-ILD programs are a valuable resource for patients who are interested in participating in clinical trials.

Summary

As providers increasingly recognize RA as a systemic inflammatory disease, extraarticular manifestations will be the next frontier of RA management. Sleep quality affects the subjective experience of RA in terms of pain and fatigue, and influences objective measures such as joint count. RA itself contributes to poor sleep quality and increases the likelihood of comorbid sleep-disrupting disorders such as OSA and RLS. Patient education around sleep hygiene can improve sleep quality for many RA patients. Optimizing RA medications to control RA disease activity and minimize sleep disturbances are additional important steps toward improved sleep. When appropriate, referring patients for the evaluation and management of OSA, RLS, and other sleep disorders can ensure that sleep-related comorbidities are addressed.

Similarly, evaluating patients for the signs and symptoms of respiratory illness can identify lung disease in its early stages and identify patients who may benefit from referral to a pulmonologist. For patients who are diagnosed with RA-ILD, collaboration between rheumatology and pulmonology providers improves the management of both joint and lung symptoms. For all RA patients, smoking cessation and timely vaccinations are key strategies for maintaining respiratory health.

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Using Your Nurse's Intuition in Patients with Cancer

by Jacqueline Fritz, RN, MSN, CNS, RN-BC

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The cyclic nature of autoimmunity and carcinogenesis is all too familiar to healthcare providers. The environment created by a chronically overactive immune response can lead the development of cancer and also be a marker of developing tumor immunity. Studies have shown that patients with chronic inflammation have a higher risk of being diagnosed with a lymphoproliferative malignancy such as lymphoma, skin, and lung cancer than the general population.[1]

The management of rheumatoid arthritis (RA) has changed dramatically since the introduction of biologic agents specifically designed to mitigate excessive cytokine or cellular activity. Studies now demonstrate that patients with RA have less than a 1% standardized incidence ratio increase in the prevalence of breast and colon cancer compared to the general population.[2] A variety of large international registries such as CORONA and ARTIS were developed to compare cancer risks among patients treated with TNF inhibitors and conventional DMARDs such as methotrexate. These databases fortunately found no increased cancer risk among RA patients treated with any of these agents. Current evidence suggests that uncontrolled inflammation and tobacco use increase the risk of cancer substantially more than the use of biologic therapies.[1]

Despite these facts, I will admit to always being on guard when one of my RA patients is diagnosed with cancer. Such was the case with K.P., a patient of mine who came into our clinic about 1 year ago and told me that she had just been diagnosed with breast cancer. K.P.'s oncologist suggested that a combination of chemotherapy, radiation, and surgery would be the most appropriate regimen. She was consequently placed on rituximab, an agent we are well familiar with in rheumatology. This choice was consistent with recommendations from the American College of Rheumatology for the management of solid malignancies in patients with RA.[3]

K.P.'s RA stayed in remission throughout the course of her therapy.

All is well! Or so we thought.

HIGH-RISK CONDITION	RECOMMENDATION	LEVEL OF EVIDENCE
Previously treated or untreated skin cancer (non-melanoma or melanoma)	• Use DMARDs over biologics in both melanoma and non-melanoma • Use DMARDs over tofacitinib in both melanoma and non-melanoma	Very Low
Previously treated lymphoproliferative disorder	***Use rituximab over TNFi***	***Very Low***
Previously treated lymphoproliferative disorder	Use combination DMARD or abatacept or tocilizumab over TNFi	Very Low
Previously treated solid organ malignancy	Same recommendation as in patients without this condition	Very Low

Table 3 *American College of Rheumatology recommendation for the treatment of solid malignancies*[3]
NOTE: bold/italic = strong recommendation

A few weeks following her surgical mastectomy, K.P. came in and asked me with a bit of concern, "Is this what the typical incision for mastectomy looks like?" I took a closer look and saw a longitudinal incision with many lobulated areas and very taught sutures. To me, it looked as if the breast had been removed without any effort to preserve the natural fold of the chest wall anatomy. My first response was horror, which was soon tempered as I reminded myself that I am not a surgeon nor even an oncology nurse. I did, however, suggest that she address her concerns with a board certified breast surgeon who could more adequately examine her.

Unfortunately, my initial suspicions were proven correct as K.P. required two additional reconstructive surgeries due to infection that also required several rounds of intravenous antibiotics and a month of gamma globulin. Not surprisingly, her RA disease activity spiked during this period, although things have fortunately stabilized to some degree.

Collaborative care is what we do best. As I noted earlier, I have no specific expertise in the treatment of breast cancer, yet through experience and observation, my "nurse's intuition" has become more finely honed. I am proud that my suggestion to K.P. that she see a breast surgeon might have saved her from so many more severe sequelae.

A decade or more of black box warnings with biologic therapies remind us that we must always be careful with the use of these agents in patients with specific types of cancer, yet it is not always (or even often) the use of the biologic that triggers the malignancy. It is vital that we as rheumatology nurses understand the risks of the treatment modalities that are prescribed for our patients, but that we also remain alert to anything that seems out of the ordinary. We may not have the knowledge to be able to fix every problem our patients come in with, but we are experts in "nurse's intuition" that can often be the greatest boon to our patients.

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RA and Shingles: No Easy Answers

by Elizabeth Kirchner, CNP, RN-BC

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Back in 2012, I was helping in the management of J.D., a longstanding patient being treated for rheumatoid arthritis (RA). At that time, J.D. was 68 years old and had been treated in our center since being diagnosed with RA 12 years before.

As this story begins, J.D. was being treated with hydroxychloroquine (200 mg per day), methotrexate (20 mg per week, oral), and prednisone (12.5 mg per day). She was unhappy with the results of this regimen, reporting to me high levels of pain as reflected in her DAS28 score of 5.5 (indicating high disease activity). While her hand x-rays were normal, she had 3 small erosions in her feet that were concerning. Clearly, J.D. was the type of patient who needed something changed in her management.

Before making any changes, we completed our usual battery of screening exams—hepatitis remote panel, TB test, etc.—which all came back negative. We therefore had no reservations about starting J.D. on a TNF inhibitor. While our office completed and submitted the necessary paperwork to J.D.'s insurance company to get her biologic agent approved, I asked J.D. to see her primary care provider (PCP) to update her vaccinations.

I kid you not: TWO DAYS after we made the decision to try an anti-TNF—before I even had a chance to complete the prior authorization form—J.D. was at her PCP's office getting diagnosed with shingles. She hadn't even had time to go in for the shingles vaccine we had discussed. It didn't seem fair, but there it was. Obviously, the shingles diagnosis put a halt on our plans to start biologic therapy. While we waited for her shingles to clear up, I still submitted the prior authorization form—no sense in stalling that effort.

It took a while for J.D.'s shingles to resolve. In the meantime, her RA remained active and continued to make her miserable. Naturally, she was also terrified that the small erosions in her feet would get worse while off treatment.

Finally, about 6 weeks after she was diagnosed with shingles (and with the pre-authorization process completed and the medication approved), we were ready to start the biologic. We made sure that J.D. was rash- and pain-free for 2 weeks before initiating biologic therapy, being cautious to make sure her bout with shingles had resolved.

Guess what happened 4 weeks after we started J.D. on an anti-TNF? Shingles. Again.

This second bout wasn't, in fact, a recurrence, but rather a breakout in a completely different dermatome on the opposite side of J.D.'s body. Was this breakout caused by the biologic? Possibly. But J.D. had also just seen her PCP for an upper respiratory infection and had been started on fluticasone nasal spray and fluticasone/salmeterol via inhalation.

And, of course, she was still on 12.5 mg of daily oral prednisone. Her new bout of shingles certainly could have been due to the steroids and not the biologic, though we'll never know for sure.

So then to recap—we have a 68-year-old woman with longstanding, active RA that is newly erosive despite full-dose dual DMARD therapy and oral prednisone. She just got over 2 cases of shingles in 3 months and is in tremendous discomfort with 17 tender and 10 swollen joints. She wants her anti-TNF desperately. But with her recent history of shingles, is it wise to restart her anti-TNF? The medical literature is no help—our team looked thoroughly, but there are no reports we could find about a patient who gets shingles one month before AND one month after starting an anti-TNF. And then what about the prednisone? If we decrease the dosage, theoretically her risk of another bout of shingles will decrease, but her RA is likely going to get worse.

Often, there are no guidelines for these unusual cases, but we can't just throw up our hands and walk away.

When discussing treatment options with my patients, I often have to tell them, "There is no Door No. 3." What this means is that we have two options—both with risks—but unfortunately no third option that carries no risk and a reasonable possibility of success.

In this case, Door No. 1 meant holding the biologic, decreasing J.D.'s prednisone to ≤10 mg per day (and ideally <5 mg per day), and then maybe—someday—restarting a biologic. The risk with Door No. 1 was an increase in RA disease activity; the benefit would be a lower chance of shingles recurrence. Door No. 2 meant restarting the biologic immediately and trying to wean J.D. off the prednisone once the biologic started working. The risk with Door No. 2 was obviously a third case of shingles.

After a long discussion, we went with No. 2, adding an extra layer of protection with shingles prophylaxis (daily acyclovir) for 6 months.

Spoiler alert! It worked. No shingles. Better RA control. Patient weaned down to 5 mg prednisone. But the real lesson here is that sometimes, our patients' physiology does strange stuff, and we just have to deal with it. Often, there are no guidelines for these unusual cases, but we can't just throw up our hands and walk away. We do the best we can, mapping out the risks and benefits for our patients, and spending however long it takes with them to make sure they understand the important factors under consideration. We may have to get creative with timing and dosing. We may have to invent our own safety nets. We definitely have to make ourselves available for updates and questions and concerns. But at the end of the day, that's why we are rheumatology nurses—because we'll do whatever it takes to make sure our patients have the best possible outcomes. Even when their bodies do weird stuff.

INFECTIONS IN RA:
Hearing the Warning Bell

by Iris Zink, MSN, NP, RN-BC

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A few years ago, I met Rhonda, a 57-year-old patient with seropositive rheumatoid arthritis (RA), for the first time. Prior to arriving in our office, Rhonda had done well on etanercept for approximately 5 years before it started having an increasingly blunted effect on her disease. That was followed by a similar response for a similar duration on adalimumab before that biologic also stopped working as well as it needed to.

Rhonda's history showed that she also previously failed both methotrexate and leflunomide due to unmanageable side effects prior to starting on biologic therapy. Her condition was further complicated by a long history of smoking (currently a pack a day) and multiple respiratory infections that frequently caused her to cycle on and off of therapy.

During her first few years at our practice, Rhonda was a typical patient, with both good and bad days that we were able to manage reasonably well, though we were never able to get her RA into remission. But that all changed approximately 1 year ago when Rhonda showed up in our office in tears due to extreme hand pain.

"I haven't been able to go to work for the last week and a half," Rhonda blurted out between sobs. "This has never happened before, and I'm really scared."

Once we were able to get her to calm down, Rhonda reported that for the last month she had been severely limited in her job as a radiology technologist at a local hospital. Due to the pain in her hands, she could no longer move patients on or off the exam table or administer IV contrast. At home, she had gone from being an avid cook and seamstress to being unable to even cut vegetables or meat to begin preparing dinner.

Clearly, her adalimumab was no longer working and it was time to try something else.

Rhonda's Vectra DA score showed a very high level of leptin, a hormone that is elevated in obese patients and those suffering high levels of inflammation. Although the Vectra DA test has not been validated for use in predicting which specific therapies to use in specific patients, we were looking for any clues we could find to help us with Rhonda. Published studies have shown that TNF inhibitors do little to help reduce leptin levels,[1] so we decided to try abatacept, a biologic with a different mechanism of action. After a week or so, Rhonda began to show some improvement in her symptoms.

But then something unusual happened. On the day Rhonda was scheduled to receive her second infusion of abatacept, she had her

annual Quantiferon TB test. This came back positive, which immediately set off warning bells with my medical assistant. Many infusible biologics used to treat RA include a black box warning concerning the reactivation of tuberculosis[2-4]—fortunately, as a T-cell activation inhibitor, abatacept does not carry this warning. We consequently finished the infusion, started Rhonda on daily isoniazid, and referred her to an infectious disease specialist for further follow up of her latent TB infection.

Although Rhonda was able to complete 6 months of isoniazid, the abatacept did not have a long duration of efficacy and her hands once again soon became her enemy. She reported to me that, "It feels like glass shards are being pushed into my hand joints." With her latest TB infection appropriately treated and a history of a durable response to previous anti-TNFs, we switched Rhonda to IV infliximab. She is being closely followed for reactivation of TB with annual chest x-rays and regular monitoring.

Infections in patients with RA can affect our decision-making treatment tree, but they should not interrupt the need to manage our patients' disease aggressively to maintain their quality of life and prevent deformity and disability. In an ideal situation, we would have been able to get Rhonda to quit smoking to improve her global health and risk of infection, but regular counseling and coddling have been ineffective. Rarely do patients we see regularly require a simple solution, requiring us all to stay on our toes and make sure we are communicating effectively with everyone.

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Comorbidities, Depression, and the Rheumatology Nurse

by Sheree C. Carter, PhD, RN, RN-BC

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Patients with rheumatoid arthritis (RA) rarely, if ever, have "just RA," much like a nurse is never "just a nurse." There is more depth and complexity in both accounts than the adverb "just" expresses.

On their own, patients with RA have an increased risk of mortality compared to the general population, but patients with specific comorbidities see their risk increased to an even greater degree. Several recent research studies provide evidence that introduce the obvious, and perhaps not so obvious, associated risk factors concerning patients with RA and significant comorbidities.

Even with the advances being made in identifying RA earlier in the disease process and expanding treatment options available to us, patients with RA continue to have an increased risk of mortality compared to the general population due to a variety of comorbid conditions, including respiratory, circulatory, digestive, genitourinary, and endocrine disorders.[1-4]

Comorbidities—whether pre-existing or emergent—should be assessed by the rheumatology nurse when developing an overall disease management protocol for each patient with RA. Given the holistic approach of nursing practice, utilizing critical evaluation techniques and assessment measurements are paramount to potentially impact the quality of life and reduce mortality of RA patients.

A recently-reported prospective cohort study from the Netherlands identified an association between comorbidities and mortality in patients with RA.[4] The study spanned 14 years (1997 to 2011) and yielded 882 evaluable RA patients from 7 outpatient clinics. The top two comorbidities associated with mortality in these patients were circulatory and respiratory conditions. In addition, the authors found an association between RA and other comorbidities that increased the risk of mortality, including cancer and depression.[4]

Attentive monitoring and screening for high-risk comorbid conditions, as well as depression (self-reported, subclinical, unrecognized, or officially diagnosed), has been shown in the literature to be a contributing factor in RA patients' perception of disease activity and quality of life.[1,3,4] Nurses have the ability to assess and evaluate the effects of risk factors such as obesity, nutritional status, and sleep disturbance on a patient's perception of their overall well-being.

Because RA is, at this time, incurable, painful, and progressive, the chronicity of the disease often manifests with anxiety and depression from a bio-behavioral perspective at a higher level than the general population.

A study by Benka et al examined two groups of patients with RA—one with an average age of 53 years, primarily female, and an average disease duration of 3 years. The second group had an average age of 58 years, again included mostly females, and an average disease duration of 16 years. The researchers examined levels of restriction in social participation within the two groups. They found that those individuals who reported higher restrictions in social participation also had statistically higher levels of pain, fatigue, anxiety, and depression.[1] Disease duration ***was not*** as significant a contributing factor to restrictions in social participation compared

to these psychosocial issues. It would have been interesting to note the co-morbidities associated with each individual and between the two groups, but this was not reported.

European studies have linked depression and anxiety as confounders in the subjective assessment of RA.[1-4] Matcham et al found a strong association between depression and anxiety as measured by the Hospital Anxiety and Depression Scale (HADS), using the subjective components of the DAS28.[3] However, this study found ***no significant association*** with disease activity and achievement of remission of RA. The researchers did express the possible limitation of power in this study. Moreover, it is possible that the level of severity of depression, anxiety, and other worsening health behaviors in some patients with RA could affect the probability of even participating in a clinical trial. This limits the ability to generalize results to our typical patient population.

Matcham et al recommend that depression and anxiety be routinely measured in clinical trials of patients with RA, as well as be established as a routine measurement in clinical practice.[3] This is an interesting recommendation for rheumatology nurses to consider. The challenge will be in researching and selecting valid and reliable measurement tools to use consistently and to develop a protocol that establishes their use routinely throughout an individual practice.

This year's series of *Rheumatology Nurse Practice* issues focused on comorbidities most commonly associated with RA. I encourage you to look deeper and holistically and be alert for the often-overlooked quality of life factors that impact our patient population. Readers are encouraged to routinely scan the literature for evidence that will impact your care and practice. If access to literature is limited or unavailable, there are many great resource sites in rheumatology such as the RNS website at no cost that will allow you to stay abreast of important research.

The emphasis on health outcomes in research activities is a current trend. Herein lay the pearls in our oyster. We have an open invitation to validate our unique contributions to healthcare. As nurses, we are educated to be observant—the watchdog/gatekeeper if you will—of those under our nursing care. Do not take the word lightly when "care" is used to describe nursing practice. We must ensure other colleagues in healthcare recognize our contributions. Rheumatology nurses know a depressed patient is less likely to adhere to a treatment regimen and have a poorer quality of life, which, in turn, affects the challenges already associated with RA. Let us get out there and conduct research. Your voice is needed in the literature.

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