OVERALL 2019 CONFERENCE NEEDS ASSESSMENT

PROGRAM OVERVIEW

Rheumatology News, Internal Medicine News, and ***Family Practice News*** present the **12th Annual Perspectives in Rheumatic Diseases**, a continuing medical education conference that explores the latest advances in the treatment and management of rheumatic diseases. This activity has been designed to provide a forum for rheumatologists, family practice physicians, internists, nurses, nurse practitioners, pharmacists and physician assistants to receive relevant and timely information regarding the most recent developments in managing patients with rheumatic diseases. By remaining current on the advances in the treatment of rheumatic diseases—particularly the newest evidence regarding the optimum use of the biologic agents—clinicians will be able to provide state-of-the-art therapeutic options to their patients.

A nationally renowned group of faculty leaders will analyze the many areas of research relevant to, and best practices in management of, a wide range of rheumatologic conditions including ankylosing spondylitis, gout, myositis, osteoporosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, and vasculitis. Faculty will also discuss management of comorbidities associated with rheumatic diseases, including gastrointestinal complications, dermatologic manifestations, and pain. All sessions offer evidence-based lectures from leading experts while providing an opportunity for participants to engage in interactive case presentations and panel discussions. This conference will help clinicians who manage patients with various rheumatic diseases maintain and improve their clinical diagnostic and therapeutic skills, leading to improved patient care and optimal patient outcomes.

Practice surveys indicate that more than half of patients' rheumatologic conditions receive their care from family physicians, many of whom are not familiar with or comfortable using current medications to treat these diseases and are not aware of the recent innovations in management. In response to this finding, this meeting offers attendees the opportunity to follow their choice of agendas with small group breakouts: one track is designed for the rheumatologist, and one track targeted to the primary care clinician.

Learning Objectives

After completing this live activity, participants should be better able to:

- Review new and emerging ACR/EULAR guidelines for rheumatic disorders.
- Describe the screening assays for ANA and how to interpret the results.
- Match specific cutaneous manifestations with the various connective tissue diseases.
- Distinguish between gout and other crystalline-induced arthropathies and their respective treatments.
- Differentiate the clinical manifestations of gout, calcium pyrophosphate and basic phosphate induced arthritis.
- Describer the appropriate use of synovial fluid analysis in the diagnosis of acute arthritis.
- Identify the role of color duplex sonography in the diagnosis of giant cell arteritis.
- Describe the current and emerging treatment options for giant cell arteritis.
- Integrate imaging options to aid in the diagnosis of gout.
- Recognize evidence-based recommendations for dosing urate-lowering therapies to optimize efficacy in patients with gout.
- Establish treatment plans for gout that achieve targeted levels of serum uric acid.
- Prescribe management options for patients with complex medical conditions that complicate the management of their gout.
- Describe therapeutic options for patients who do not reach target serum urate levels with usual dosing of allopurinol.
- Discuss the value of dramatic lowering of the serum urate to <1 mg/dL in selected patients with gout.
- Describe the role of the microbiome in eliciting the immune response.
- Identify mechanisms by which the microbiome could cause rheumatic disease.
- Discuss how greater understanding of the relationship between the microbiome and rheumatic diseases could inform future therapies.
- Describe how myositis-specific autoantibodies define different types and subtypes of inflammatory myopathy.
- Develop strategies for managing patients with the different types of inflammatory myopathy.
- Describe current therapeutic approaches to symptomatic OA.
- Determine the relative value of currently popular unconventional approaches to OA.
- Identify important targets of OA therapy currently under development.
- Review the diagnostic evaluation for osteopenia and osteoporosis.
- Identify appropriate candidates for treatment and available treatment options**.**
- Identify how current and emerging agents might fit in the treatment strategy for osteoporosis.
- Identify the underlying mechanisms responsible for chronic pain.
- Compare and contrast the safety, efficacy, and mechanisms of various agents available for managing pain in the context of autoimmune disorders.
- Determine the optimal manner to incorporate non-pharmacological treatment of pain into clinical practice.

- Demonstrate awareness of current guidelines for management of psoriasis.
- Outline treatment plans for psoriasis that consider the use of new agents, with new mechanisms, and that include strategies for modifying treatment as needed based on results and patient satisfaction.
- Create a treatment plan for psoriatic arthritis that incorporates tools for assessing the impact of psoriatic arthritis and that anticipates the potential need to switch or augment therapy.
- Describe the safety and efficacy of available agents for psoriatic arthritis.
- Discuss the signs and symptoms suggestive of developing or early psoriatic arthritis.
- Develop a treatment strategy for patients with psoriatic arthritis.
- Identify the features of a patient who has difficult-to-treat (D2T) RA.
- Understand the factors that underlie D2T RA.
- Generate a clinical management plan to address the needs of people with D2T RA.
- Design effective treatment strategies for the various manifestations of localized and systemic scleroderma.
- Discuss current understanding of the screening, diagnosis and management of lung disease in scleroderma.
- Develop a strategy for identifying and managing cutaneous adverse reactions.
- Summarize the diagnosis and management of different types of statin-related muscle complaints.
- Summarize current and emerging research on the mechanisms of the pathology of systemic lupus erythematosus and treatment of lupus nephritis.
- Review data from clinical trials – including failed trials – on candidate therapies that target various pathways involved in systemic lupus erythematosus.

AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM: UPDATES

Gap: Clinicians may not be current with new guidelines for management recommendations of rheumatologic diseases.

Learning objective: Review new and emerging ACR/EULAR guidelines for rheumatic disorders.

The American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) recently updated recommendations for the management of Behçet's syndrome (BS).[Hatemi 2018] The update includes evidence-based recommendations involving control new treatment modalities with novel mechanisms of action, and recommends multidisciplinary treatment strategies based upon the location and severity of disease.[Hatemi 2018]

New classification criteria for systemic lupus erythematosus were presented at the 2017 ACR/EULAR Annual Meeting; they were to be voted on in late 2018. The goal of these new criteria is to achieve higher sensitivity and specificity compared with the 1997 and 2012 criteria; as presented, they will represent a "paradigm shift" for future research.[Zoler 2018] A critical aspect of the recommended re-classification concerns ANA positivity as the entry criterion.[Leuchten 2018; Zoler 2018] Prior criteria focused on a yes/no decision regarding whether or not the patient had a minimum number of characteristic signs or symptoms; the recommended revisions will replace this yes/no decision with a point system that assigns varying weight to each of 22 criteria.[Zoler 2018] As of February 2019, the recommendations have not been approved, but clinicians should be aware of potential revisions and their potential impact on diagnosis and management of SLE.

References: ACR/EULAR

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ANTINUCLEAR ANTIBODIES

Gap: Clinicians may be unfamiliar with the evolving terminology surrounding ANA and the interpretations of the presence of ANA.

Learning objective: Describe the screening assays for ANA and how to interpret the results.

The presence of antinuclear antibodies (ANAs) in serum may indicate an autoimmune connective tissue disease (CTD). However, ANAs are also found in healthy individuals, in persons with chronic infectious diseases or cancers, or as a result of medication-related adverse events.[Grygiel-Górniak 2018; Sur 2018] As ANAs increase with aging, up to one-third of adults over age 65 may have a positive ANA result. There is also the possibility of false positive results, perhaps associated with the method used to determine antibodies.[Grygiel-Górniak 2018] Consequently, it can be challenging for clinicians to interpret whether the presence of ANAs has diagnostic value.[Grygiel-Górniak 2018]

Emerging evidence suggests comparable efficacy between the screening enzyme immunoassay (SEIA) and indirect immunofluorescence (IIF) as ANA screening assays for patients with systemic rheumatic diseases such as systemic lupus erythematosus (SLE), Sjögren syndrome (SS), and systemic sclerosis (SSc).[Jeong 2018] Two recent systematic reviews and meta-analyses reported that IIF is more sensitive than SEIA for SLE,[Jeong 2018; Leuchten 2018] but the two approaches are essentially comparable in specificity and standardization.[Jeong 2018] The patterns of ANAs are also evolving to include both nuclear staining and cytoplasmic and mitotic cells patterns (CMPs); as such, it is believed that new nomenclature guidelines will recommend that non-nuclear patterns should be considered as a positive ANA for patients with CONTrol.[Choi 2018; Sur 2018] Evidence is also emerging to support the potential value of trait ANA as a new index for diagnosis of SLE.[Wan 2018]

Clinicians would benefit from education that makes them aware of recent findings regarding the role and diagnostic approaches for ANA findings.

References: Antinuclear Antibodies

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Wan L, Zhu H, Gu Y, Liu H. Diagnostic value of trait antinuclear antibodies and multiple immunoglobulin production in autoimmune diseases. J Clin Lab Anal. 2018 May;32(4):e22361.

CONNECTIVE AUTOIMMUNE DISEASES

Gap: Dermatologists and other clinicians may not be aware of the specific cutaneous manifestations of connective tissue diseases and their treatments.

Learning objective: Match specific cutaneous manifestations with the various connective tissue diseases.

Connective tissue or autoimmune diseases (CTDs) comprise a heterogeneous group of autoimmune disorders that affect both the skin and other organs and systems.[Dourmishev 2018] The most common CTDs include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, and Sjogren syndrome. CTDs, also referred to as collagen vascular diseases, require clinical, serologic, and pathologic evaluation; however, precise diagnosis may be challenging owing to the overlap of clinical and histologic features.[Laga 2017] Histopathologic assessment confirms or rules out CTD, but does not provide evidence for a definitive diagnosis of a specific CTD.[Laga 2017]

Cutaneous manifestations are an important component of CTDs; consequently, there is value in adopting a multidisciplinary team approach to the diagnosis and management of these various diseases. Dermatologists may thus play an important role in the early diagnosis and treatment of these diseases, as some of the earlier manifestations of the diseases may be cutaneous.[Ferreli 2017; Jhorar 2018; Smith 2018] The role of high-dose intravenous immunoglobulins (IVIG) varies dependent upon the specific CTD, as either first-line or second- or third-line therapy.[Dourmishev 2018; Hoffmann 2017] Dermatologists and other clinicians should be well-versed in the manifestations, diagnosis, and management of cutaneous manifestations of CTDs.

References: Connective Tissue Diseases

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CRYSTALLINE ARTHRITIS

Gap: Clinicians may be unfamiliar with the diagnosis and management of crystalline arthritis that is not gout.

Learning objectives:

- *Distinguish between gout and other crystalline-induced arthropathies and their respective treatments.*
- *Differentiate the clinical manifestations of gout, calcium pyrophosphate, and basic phosphate-induced arthritis.*
- *Describe the appropriate use of synovial fluid analysis in the diagnosis of acute arthritis*

Crystalline-induced arthropathies, including gout (monosodium urate deposition), calcium pyrophosphate dihydrate deposition (CPPD), and hydroxyapatite deposition disease, are associated with substantial morbidity, most often associated with bone health and risk of fractures.[Buckens 2017; Chang 2018] The different diseases are challenging to diagnose, particularly during their early phases. Newly approved and emerging medications may provide more curative approaches; many current approaches are limited by poor long-term adherence.

Radiographic differences may help distinguish between the various crystalline arthropathies, in addition to analysis of crystals in synovial fluid.[Buckens 2017; Jacques 2017; Muangchan 2018; Stirling 2018] Dual-source CT (dual-energy CT, or DECT) can help selectively identify crystalline deposits.[Buckens 2017] Musculoskeletal ultrasound (MSUS) is another modality that can accurately assess intra- and peri-

articular abnormalities, and can be used to guide musculoskeletal aspirations and/or therapeutic injections.[Naredo 2017] Gout is characterized by hyperuricemia, whereas pseudogout involves a monoarticular attack with periarticular soft tissue swelling.[Muangchan 2018]

Emerging urate-lowering therapies include lesinurad, preferably in combination with a xanthine oxidase inhibitor (XOI) to minimize serum creatinine elevations, and arhalofenate.[Abhishek 2018] A particular challenge for clinicians is the lack of concordance between various clinical practice guidelines for gout and crystal-associated diseases.[Dalbeth 2017] Notably, the recently published clinical practice guideline from the American College of Physicians differs substantially from that of the ACR/EULAR, leading a group of experts (the Gout, Hyperuricemia and Crystal-Associated Disease Network, G-CAN) to develop its own consensus evidence-based statement.[Dalbeth 2017]

Clinicians would benefit from expert guidance to help interpret the various radiographic features of the differing crystalline-induced arthropathies as well as the current and emerging treatments for these disorders.

References: Crystalline Arthritis

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GIANT CELL ARTERITIS (GCA)

Gap: Clinicians may be unfamiliar with the use of ultrasound instead of biopsy to assess giant cell arteritis.

Learning objective: Identify the role of color duplex sonography in the diagnosis of giant cell arteritis.

Gap: Clinicians may not be aware of the current and emerging non-corticosteroid treatment options for giant cell arteritis.

Learning objective: Describe the current and emerging treatment options for giant cell arteritis.

Giant cell arteritis (GCA), the most common large vessel vasculitis, is characterized by headaches, scalp tenderness, visual loss, and muscle stiffness and pain.[Winkler 2018] Historically, diagnosis of GCA has

required biopsy, and treatment has involved high-dose corticosteroids. GCA is associated with a risk of irreversible vision loss and substantial morbidity as a consequence of corticosteroid treatment.[Winkler 2018] Recent developments support the use of noninvasive vascular imaging using color duplex sonography (CDS) or high-resolution cranial MRI instead of biopsy.[Monti 2018a; Monti 2018b; Sammel 2018] Treatment for GCA is evolving as well; various biologic agents are under investigation, or have been approved, for the treatment of GCA.

Color duplex sonography (CDS) has become an emerging diagnostic tool for GCA.[Monti 2018a] It is noninvasive and is able to detect wall edema (halo). In cases of bilateral halos, CDS has a specificity of nearly 100%.[Monti 2018a] Despite this, its use is not widespread, and many clinicians are not trained sonography.[Monti 2018a] A recent study involving nearly 300 patients, of whom 118 had clinically confirmed GCA, demonstrated the high positive predictive value of CDS, facilitating a reduced need for temporal artery biopsies.[Monti 2018b] Clinicians would benefit from education regarding how to integrate CDS or other vascular imaging techniques into the diagnostic assessment of patients with suspected GCA, and for which patients these options are most appropriate.[Sammel 2018]

GCA shares similarities with the other main large vessel vasculitis, Takayasu arteritis (TAK), but their different underlying pathophysiologies requires different treatment approaches.[Samson 2018] Both are traditionally treated with glucocorticoids; however, the high morbidity associated with high-dose corticosteroid treatment led clinicians to investigate alternative, biologic treatments for both TAK and GCA.[Koster 2016; Samson 2018] While TNFα inhibitors have shown effectiveness in the treatment of TAK, they appear to have little benefit in GCA.[Koster 2016] Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R), was recently approved by the FDA for management of GCA. It has been shown to significantly decrease the relapse rate and lower steroid cumulative doses and to sustain glucocorticoid-free remissions through 52 weeks.[Schmalzing 2018; Winkler 2018; Sammel 2018]

Abatacept shows little benefit in TAK, and there is minimal evidence supporting the use of tocilizumab in TAK, whereas there does appear to be benefit with infliximab.[Samson 2018] A variety of other biologic agents are currently under investigation for treatment of GCA. Ustekinumab appears to have promising results in refractory or relapsing GCA; trials are ongoing.[NCT02955147] Other agents under investigation for GCA include baricitinib for relapsing GCA,[NCT03026504] abatacept [NCT00556439; Langford 2017] and upadacitinib.[NCT03725202] Some of these agents are also under consideration for the management of rheumatoid arthritis.[Serhal 2018] With greater understanding of the immunopathology of GCA, including the role of Th1 and Th17 lymphocytes, it is hoped additional treatments may be forthcoming.[Sammel 2018]

It is challenging for clinicians to keep current with emerging recommendations and treatment options for GCA; expert guidance regarding the use of imaging and emerging treatments is needed.

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GOUT

Gap: Clinicians need education on the various imaging options to aid in the diagnosis of gout.
Learning objective: Integrate imaging options to aid in the diagnosis of gout.

Gap: Clinicians do not always measure serum urate levels and may not be aware of the target levels of serum urate to control hyperuricemia.
Learning objective: Recognize evidence-based recommendations for dosing urate-lowering therapies to *optimize efficacy in patients with gout.*

Gap: Clinicians need to develop comprehensive treatment plans that address gout as a curable chronic disease requiring the appropriate first-line treatment as well as ongoing monitoring and management.
Learning objective: Establish treatment plans for gout that achieve targeted levels of serum uric acid.

Gap: Clinicians are challenged to manage patients with difficult-to-treat gout so as to achieve optimal outcomes.
Learning objectives:

- *Prescribe management options for patients with complex medical conditions that complicate the management of their gout.*
- *Describe therapeutic options for patients who do not reach target serum urate levels with usual dosing of allopurinol.*
- *Discuss the value of dramatic lowering of the serum urate to <1 mg/dL in selected patients with gout.*

Gout is the most common inflammatory arthritis among adults in Western nations; its prevalence exceeds that of rheumatoid arthritis.[Singh 2016; Doherty 2012] The underlying pathophysiology of gout

is well understood: It is a disease of crystal deposition caused by persistent elevation of serum urate (sUA) levels above the saturation point for monosodium urate (MSU) crystal formation.[Doherty 2012] Following a period of asymptomatic hyperuricemia, sodium urate crystals gradually accumulate in and around peripheral joints, tendons, and bursae. This accumulation is initially "silent" – that is, it does not cause symptoms – but over time, as urate crystals are shed from articular cartilage into the joint spaces, patients typically experience acute attacks, or flares, of painful synovitis. Left unchecked, this buildup of MSU crystals induces inflammation and eventually causes accumulations of densely packed crystals (tophi) on articular cartilage and bone, resulting in irreversible joint damage, pain, and other chronic symptoms.

A leading risk factor for development of gout is lifestyle, especially obesity and excessive intake of purines, alcohol, and fructose.[Fay] Use of certain medications (eg, diuretics) can increase risk, as can the presence of comorbid conditions such as diabetes, metabolic syndrome, hypertension, cardiovascular disease, and chronic kidney disease.

Up to 40% of patients with hyperuricemia have asymptomatic sUA deposits around joints. The risk for recurrent attacks of gout is associated with sUA levels above approximately 6.0 mg/dL; but, according to an MD-IQ quiz, 37% of respondents did not know the level of sUA that is associated with higher risk for recurrent attacks. Recent research indicates that even "normal" levels of sUA may play a role in cardiovascular, renal, skeletal, and metabolic disorders and that levels <6.0 mg/dL should be considered as normal for healthy individuals. According to recent practice data, an estimated 40% to 70% of patients with gout who are receiving the accepted current standard of care are not being successfully treated to low enough target levels of sUA. Clinicians would benefit from education that reviews the target levels of serum uric acid to minimize gout attacks and related consequences.

Diagnosis of gout can be confirmed through visualization of monosodium urate crystals in the synovial fluid through such modalities as conventional radiography, ultrasonography, and MRI. However, aspiration of synovial fluid, although the standard of care, is often deferred because of inaccessibility of small joints, patient assessment during intervals between flares, or clinicians' unfamiliarity with the technology. Dual energy computed tomography (DECT) is a relatively new imaging modality that provides a noninvasive alternative to synovial fluid aspiration. In addition to providing greater sensitivity for erosion detection compared to conventional radiography, DECT can identify and color-code tophaceous material and provide an overview of the tophus burden of a joint area. Clinicians need education about new and emerging imaging modalities to better diagnose gout.

Gout is a highly treatable disease; in many cases appropriate management can prevent future attacks and can often lead to a cure.[Doherty] Because the disease usually remains unrecognized unless symptoms develop, most patients do not seek treatment until they experience an acute flare. Patients often will present to a primary care provider (PCP) (eg, internist, family doctor, or podiatrist), whose approach is aimed at treating current symptoms using NSAIDs and corticosteroids. Ideally, the importance of lifestyle changes, including diet and alcohol consumption, is included in the overall treatment plan. Often, however, PCPs fail to offer comprehensive treatment that is aimed at long-term management or cure.

Use of available medications can achieve sUA targets if the treatment plan follows an evidence-based approach. Unfortunately, many clinicians fail to prescribe medications at effective doses, and they are hesitant to titrate the dosage to achieve optimal results. The label for allopurinol, a xanthine oxidase inhibitor (XOI) that has become a standard urate-lowering treatment for gout, indicates that the minimal

effective dosage is 100-200 mg per day. However, per labeling, the average daily dose to achieve benefit is 200-300 mg for mild gout and 400-600 mg for moderate to severe disease. Some patients will require the maximum approved daily dose of allopurinol (800 mg in the United States; 900 mg in Europe).

Many clinicians prescribe a fixed dose of allopurinol and are subsequently hesitant to titrate to doses higher than 300 mg.[Doherty] However, allopurinol given at 300 mg per day achieves target sUA levels in only 21% to 50% of patients.[Fay 2010; Singh 2016] A dose escalation study found that increasing the dose of allopurinol to 600 mg/day in patients with relatively preserved renal function significantly increased the percentage of patients achieving target sUA to 85%.[Fay 2010] Despite such evidence, most clinicians in a recent survey reported that they started their patients on 100 mg or less of allopurinol, and that only about half reported that the would subsequently increase the dose.[Vaccher]

Even with the use of maximum doses of a single agent, many patients may not achieve their treatment goals. For these individuals, ACR guidelines recommend the use of a combination urate-lowering strategy that includes an XOI such as allopurinol to reduce formation of sUA plus a uricosuric agent such as lesinurad to increase excretion of sUA.[Khanna + Fitzgerald] Clinicians need guidance to understand how best to use the available therapies for gout and to adjust the regimen as needed to achieve treatment targets.

Part of the confusion among clinicians on how best to treat gout arises from the fact that different specialty societies – including the American College of Physicians (ACP), The American College of Rheumatology (ACR), and the European League Against Rheumatism (EULAR) – have produced guidelines that offer conflicting recommendations.[Qaseem; Khanna + Fitzgerald 2012; Khanna + Khanna 2012; Kiltz] Of these, the EULAR guidelines recommend a treat-to-target approach. In addition, it is necessary to treat gout not as an episodic attack but rather as a chronic disease. Clinicians need education about the similarities and differences between the various guidelines, as well as the need to develop long-term strategies that both address acute flares and prevent future ones**.**

Despite the availability of various medications and recommendations for treating gout, management of the disease remains poor. At least 3 population-based studies (in the United States, United Kingdom, and Taiwan) have reported that gout is significantly undertreated. In a 2016 survey among primary care physicians and rheumatologists, 89% of respondents agreed that achieving serum uric acid levels <6 mg/dL – the goal established by ACR – is imperative, yet only 51% reported that their patients achieve this goal. Nearly 9 out of 10 clinicians said they wished there were additional treatment options available. New agents or combinations have been introduced, including febuxostat, pegloticase, lesinurad, a combination of lesinurad and allopurinol, and canakinumab. Other agents are under investigation. Unfortunately, many clinicians fail to prescribe gout medications at guideline-recommended effective doses, and they are hesitant to titrate the dosage to achieve optimal results. Clinicians would benefit from education that reviews the efficacy and safety of each of the available and emerging agents, including appropriate dosages.

Several comorbidities are commonly associated with gout. For example, patients with gout have higher rates of diabetes, metabolic syndrome, cardiovascular disease, chronic kidney disease, and hypertension. More than 25% of patients with gout report having 4 or more comorbidities.[Vaccher] Left untreated, the hyperuricemia and the inflammation that underlie the development of gout may also contribute to the formation, or the severity, of these other conditions. Clinicians should be aware of the risk for potential adverse events and other complications arising from the presence of comorbidities in a patient who is being treated for gout. For example, some medications used for gout, like allopurinol and

probenecid, may interfere with renal excretion of other drugs, such as ACE inhibitors used in the treatment of hypertension. Clinicians need guidance to make sure decisions about gout management take place within the broader context of the patient's overall health.

One special challenge associated with gout management is the fact that effective sUA therapy lowers the saturation point for monosodium urate crystal formation, leading to dissolution of the deposits. During the early stages of treatment, the crystals break off and enter synovial spaces, causing flares of gout symptoms. Patients need to be counseled about this seemingly paradoxical aspect of initial gout therapy, so they do not conclude that treatment is ineffective and thus become nonadherent. Clinicians should educate their patients to understand that "Things may get worse before they get better – and that's one way we know your drug therapy is working." What's more, anti-inflammatory prophylaxis against acute attacks, for example through the use of a corticosteroid or colchicine, is an integral part of effective gout management.[Singh + Uhlig 2016]

A comprehensive and optimal treatment plan for gout incorporates pharmacologic and nonpharmacologic strategies, including patient education, access to expert advice, lifestyle counseling, appropriate upward titration of sUA-lowering medications, and increased frequency of visits until target sUA concentrations are achieved.[Kiltz] Drug therapy is but one component of comprehensive gout management. Patients need guidance and support to make necessary changes in lifestyle, specifically by reducing consumption of alcohol (especially beer) and purine-rich foods (such as shellfish and red meat). Fructose, in the form of high-fructose corn syrup, is directly implicated in the rising incidence of obesity and diabetes. By interfering with the function of adenosine triphosphate (ATP), fructose promotes hyperuricemia and thus is thought to be a cause of gout. In one survey, men with the highest fructose consumption had twice the risk of developing gout, independent of body mass index, alcohol use, and other risk factors.[Choi] Unfortunately, however, studies show that only a minority of patients with gout receive effective lifestyle advice and urate-lowering therapy.[Doherty]

Patients with difficult-to-treat gout may be particularly challenging to manage. New and emerging agents, such as pegloticase, lesinurad, and arhalofenate, in combination with xanthine oxidase inhibitors, may afford benefit for patients with severe or refractory cases that fail to respond to traditional therapies.[Pascart 2017; Soskind 2017] Canakinumab, which blocks IL-1, was initially rejected by the FDA in 2009; recent evidence from the CANTOS multicenter randomized trial involving more than 10,000 patients demonstrated that it reduced gout flares by about 50%.[Barding 2015; mdedge.com] However, it has been associated with substantial safety concerns. While canakinumab suggests potential benefit of this target, other IL-1 blocking agents may be more appropriate.

On February 21, 2019, the FDA mandated a black-box warning for febuxostat, noting it poses a significantly higher risk of all-cause and cardiovascular-related mortality compared with allopurinol.[MDEdge.com] The FDA recommended that use of this agent, which has been on the market for more than a decade, should now be limited to patients who have failed or do not tolerate allopurinol.

Clinicians should be educated about the risks and benefits of available gout therapies. They should also be aware of the risk for potential adverse events and other complications arising from the presence of comorbidities in a patient who is being treated for gout. Clinicians would also benefit from education that provides clear guidance about the appropriate use of available medications, that addresses myths and misconceptions about the disease, and that presents evidence-based strategies for nonpharmacologic and supportive care for patients with gout.

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MICROBIOMES AND RHEUMATIC DISEASES

Gap: Many clinicians may lack understanding of the relationship between the microbiome and immune disorders, including rheumatic diseases.

Learning objectives:

- *Describe the role of the microbiome in eliciting the immune response.*

- *Identify mechanisms by which the microbiome could cause rheumatic disease.*
- *Discuss how greater understanding of the relationship between the microbiome and rheumatic diseases could inform future therapies.*

The microbiome refers to the collection of micro-organisms that cohabit a species.[Rosenbaum 2016] The microbiome "educates" the immune system. Because most rheumatic diseases are immune-mediated, it is critical to understand the role of the microbiome in altering the immune response and thus contributing, positively or negatively, to immunological disease.

Increasing evidence supports modulation of the immune system by gastrointestinal (GI) microbes as a key factor in the onset, course, and outcome of rheumatic diseases.[Ostrov 2017] In addition, bacterial communities outside the GI tract – in the mouth, lung, and skin – have been associated with pathogenesis of some rheumatic diseases.[Rosenbaum 2016] It remains unclear, however, if this association is bidirectional.[Scher 2016] For example, it is known that patients with ankylosing spondylitis and psoriatic arthritis are at increased risk for developing clinical irritable bowel disease.[Scher 2016] It is believed that the GI microbiome, along with genetic and environmental factors, may trigger rheumatic diseases, and that management of the microbiome may be influential in treating these diseases.[Ostrov 2017; Rosenbaum 2016; Scher 2016; Zegarra-Ruiz 2019; Zhong 2019]

Greater understanding of how immune pathways are modulated by the microbiota may help inform treatment development. Investigations currently focus on induction of T helper 17 (Th17) cell immunity and secretory immunoglobulin A.[Viladomiu 2017] At this time, much of the research focuses on clinical and immunological associations and the pathogenesis of rheumatic diseases, with a lesser focus on applying this information for management strategies.[Ostrov 2017; Zhong 2018]

Clinicians would benefit from a greater understanding of the GI microbiome and how it may be associated with the development and possible treatment of rheumatic disorders.

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MYOSITIS: INFLAMMATORY MUSCLE DISEASES

Gap: Many clinicians may lack clinical experience in the diagnosis and management of the various inflammatory muscle diseases.

Learning objectives:

- *Describe how myositis-specific autoantibodies define different types and subtypes of inflammatory myopathy.*
- *Develop strategies for managing patients with the different types of inflammatory myopathy.*

The inflammatory myopathies (IMs) are a heterogeneous family of diseases ("myositis"), and each type has different clinical features, optimal management strategies, and prognosis. They all share symptoms of muscle weakness, fatigue, and inflammation.[Lundberg 2016; Selva-O'Callaghan 2018] Idiopathic IMs are somewhat rare, with a prevalence of about 10 in 100,000 individuals.[Lundberg 2016] Many clinicians do not know how to properly classify patients with IMs, which in turn can affect their ability to provide optimal care.

Advances in muscle histology and immunology have provided greater understanding regarding chronic inflammatory muscle diseases (IMDs), such as polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM). As with inflammatory joint diseases, IMDs encompass a highly heterogenous groups of conditions, all of whose main target is the skeletal muscle.[Meyer 2017;Tournadre 2010] Most forms of myositis are connective tissue disorders involving multiple organs, including skin, joints, and lungs. Initially, IMs were classified as either dermatomyositis (if there were characteristic rashes with the muscle involvement) or polymyositis (if rashes were absent).[Selva-O'Callaghan 2018; Tournadre 2010] Currently, in addition to polymyositis, there are 4 main types of idiopathic IMs – dermatomyositis, immune-mediated necrotizing myopathy, sporadic inclusion-body myositis, and overlap myositis (including antisynthetase syndrome).[Mariampillai 2018; Selva-O'Callaghan 2018] Each of the 4 "clusters" of idiopathic IM is associated with unique characteristics and myositis-specific autoantibodies (MSAs).[Mariampillai 2018] MSAs provide information about distinct clinical phenotypes and provide support to a myositis diagnosis as well as the subgroups, each of which have different patterns of extramuscular organ involvement.[Lundberg 2016] For example, IBM, which may be inherited, manifests with asymmetrical muscle involvement, along with possible involvement of distal limb muscles, and absence of autoantibodies. Notably, IBM is unresponsive to glucocorticoid and immunosuppressant therapies.[Tournadre 2010] However, the etiologies of IMDs are not well known.[Castro 2012]

Diagnosis of IBMs typically involves a multidisciplinary team, and requires imaging studies, laboratory evaluation, histologic examination, and possibly genetic studies to differentiate between the various disorders.[Castro 2012; Tournadre 2010] There may be elevations in serum muscle enzyme levels (creatine kinase, aldolase, and transaminases); electromyogram demonstrates polyphasic, low amplitude and short duration motor-unit action potential, spontaneous fibrillation potentials, and positive sharp waves; and MRI may demonstrate edema and/or fatty infiltration of the skeletal muscles. MRI may be used to guide the muscle biopsy, which is used to identify inflammation and exclude noninflammatory myopathies.[Lundberg 2016] Histologically, there may be inflammatory infiltrate and/or muscle fiber necrosis.[Meyer 2017] However, none of these findings is specific for IMD; diagnosis requires further findings of muscle abnormalities, extramuscular manifestations, and immunologic changes.[Meyer 2017]

Treatment is generally empiric, often based on expert opinion; no large trials have been performed owing largely to the low prevalence of the diseases.[Selva-O'Callaghan 2018; Tournadre 2010] Typically, treatment begins with glucocorticoids and/or methotrexate. Intravenous immunoglobulin infusion is

reserved for specific situations. Other treatments can include methotrexate with azathioprine, mycophenolate mofetil, or rituximab.[Tournadre 2010] However, there are cases of paradoxical exacerbation of muscle involvement associated with TNF-alpha–antagonist therapies.[Tournadre 2010] Clinicians would benefit from education regarding these somewhat rare disorders, with emphasis on their differential diagnosis and management.

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OSTEOARTHRITIS

Gap: Clinicians are inadequately familiar with current and emerging treatment options for osteoarthritis.

Learning objectives:

- *Describe current therapeutic approaches to symptomatic OA.*
- *Determine the relative value of currently popular unconventional approaches to OA.*
- *Identify important targets of OA therapy currently under development.*

Osteoarthritis (OA) is the most common arthritis and results in vast societal costs and substantial morbidity.[Hermann 2018; Mandl 2019] Nonetheless, many physicians still consider it to be simply part of aging, and optimal treatment remains poorly understood. Clinicians would benefit from education regarding appropriate treatment approaches, including emerging therapeutics.

Despite greater understanding of the underlying disease pathogenesis, there are currently no disease-modifying drugs for OA.[Hermann 2018] Current consensus guidelines recommend a combination of conservative measures (physical therapy), analgesia, and surgical interventions (arthroplasty).[Wu 2018] Standard treatment remains pain control and agents to manage the inflammation (nonsteroidal anti-inflammatory drugs [NSAIDs], analgesics including opioids, and intra-articular corticosteroids), as well as intra-articular hyaluronic acid (HA).[Hermann 2018] There is a great need for the development of novel safe and effective therapies to alleviate the pain and inflammation.[Miller 2018]

A variety of potentially promising new strategies focus on serotonin-norepinephrine reuptake inhibitors (SNRIs), IL-1 antagonists, antibodies to nerve growth factor (NGF), cryoneurolysis, and regenerative medicine approaches using stem cells, platelet rich plasma (PRP), amniotic fluid, and cytokine modulation.[Spasovski 2018; Wu 2018; Zhao 2018]

Blockade of nerve growth factor with antibodies appears to be among the most promising new strategies.[Miller 2018; Miller 2017] Initial trials on anti-NGF antibodies revealed serious adverse effects, including rapidly progressive OA and osteonecrosis, leading to a moratorium on research from 2010 until 2015.[Miller 2017] Currently, there are 2 anti-NGF antibodies in development: tanuzemab and fasinumab. While preclinical testing has demonstrated substantial beneficial analgesic effects, detrimental effects on joint integrity in animals and humans have emerged.[Miller 2017; Wu 2018]

A recent small study on 9 patients with knee OA has shown significant and persistent benefits with a single injection of adipose-derived mesenchymal stem cells (AD-MSCs) over 18 months, warranting additional investigation.[Spasovski 2018] Initial studies on MSCs from bone marrow were associated with substantial improvements in pain scores as well as improvements in cartilage quality.[Wu 2018] However, harvesting MSCs from bone marrow is difficult and painful, leading investigators to obtain MSCs from adipose tissue. Results from studies using AD-MSCs appear encouraging but are less consistent.[Wu 2018]

Prior findings that osteoarthritis is associated with central (and not peripheral) sensitization led to investigations into the benefits of SNRIs for pain management. Duloxetine has subsequently been approved by the FDA for the treatment of chronic knee OA, and additional trials on milnacipran are ongoing.[Wu 2018]

Trials on IL-1 receptor antagonists were initiated based on evidence of significantly elevated levels of IL-1 in the synovial fluid of humans with OA.[Wu 2018] Initial studies with the IL-1 receptor antagonist AMG 108 suggest pain improvement, particularly in patients with more severe pain, the safety profile, including a decreased neutrophil count, necessitates additional investigation.[Wu 2018]

Studies on hydroxychloroquine (HCT) are ongoing, but have not yet demonstrated superiority over placebo in analgesia or reduction of radiographic progression.[Hermann 2018] Similarly, current data regarding potential benefits of TNF-alpha blockers for OA have not been promising. Initial results with strontium ranelate is promising, as do results with the intra-articular administration of PRP. Additionally, clinical trials are examining a number of mechanism-based interventions, such as cytokine inhibition, selective μ, δ or κ opioid receptor agonists, zoledronate and intra-articular capsaicin.[Miller 2018]

It is challenging for clinicians to remain current with research regarding the wide range of potential treatments for OA, and with the number of ongoing clinical trials. Clinicians would benefit from expert review of the trials, including the most current findings, and how to match patient characteristics to potential treatments.

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OSTEOPOROSIS

Gap: Clinicians are inadequately familiar with guidelines for distinguishing between and diagnosing osteopenia and osteoporosis.
Learning objective: Review the diagnostic evaluation for osteopenia and osteoporosis.

In the US, an estimated 16% of women and 4% of men over the age of 50 have osteoporosis.[Altkorn 2015] Additionally, an estimated 1.5 to 2 million osteoporosis-related fractures occur annually, 70% of them in women [AACE/ACE Guidelines 2016] Screening, diagnosis, and treatment of osteoporosis are lagging behind compared to other chronic disease states.[Rice 2014] For example, among patients with a fragility fracture, only 2.3% of men and 20% of women are screened for osteoporosis, and less than 10% of men and 20% of women are treated for osteoporosis.[Papaioannou 2004] Low bone density is the primary risk factor for osteoporotic fractures.[Altkorn 2015]

There are large gaps in the diagnosis, management, and treatment of osteoporosis among health care providers. Clinicians can help narrow these gaps by playing an integral role in the identification, risk stratification, and treatment of patients at risk for osteoporosis and fractures.[Rice 2014; Greene 2010] Increased education on how to perform a focused history and physical examination in patients at risk for osteoporosis will help clinicians better determine appropriate screening tests and fracture risk that will help in guiding treatment decisions[Rice 2014] In fact, interventions designed to improve osteoporosis disease management are associated with improved treatment and decreased hip fracture rates.[El Miedany 2006]

Osteoporosis, menopause, kidney disease, and calcium-related endocrinopathies can all contribute to bone fragility. In peri- and postmenopausal white women, the lumbar spine and femoral neck show bone loss of at least 9% cumulatively over 10 years; Asian women experience an even greater loss.[Cauley 2015] However, there is a dearth of data concerning bone size, structural, and geometric changes in postmenopausal women, and there are several complexities with risk factors. Existing screening methods for osteoporosis in postmenopausal women are often inadequate, thus hindering appropriate diagnosis and monitoring.[Cauley 2015]

Calcium-related endocrinopathies can also result in bone fragility. For example, hypercalcemia can accompany hyperthyroidism or primary hyperparathyroidism, which in turn can result in increased fragility.[Zanocco] These hormones are important for calcium regulation and bone turnover, and have been associated with decreasing bone mineral density.[Ziegler 2001; Zanocco 2017]

Gap: Many clinicians may lack awareness of current treatment guidelines for osteoporosis.
*Learning objective: Identify appropriate candidates for treatment and available treatment options***.**

There are gaps in osteoporosis treatment, reflected in the recent 50% decrease the use of available antiresorptive therapy.[Lems 2017] Similarly, patients with high fracture risk do not receive adequate treatment; a range of European countries showed that 40% to 95% of patients at high risk do not receive treatment with any anti-osteoporosis therapies.[Lems 2017]

In 2014, the National Osteoporosis Foundation released guidelines on the prevention and treatment of osteoporosis.[NOF 2014] In 2016, clinical guidelines for the treatment of postmenopausal osteoporosis were published by the American Association of Clinical Endocrinologists/American College of Endocrinology.[AACE/ACE 2016] Clinicians need education to keep abreast of the most current recommendations for managing bone conditions.

There is evidence that the microbiome plays a role in bone health, and research suggests probiotics may help protect against bone loss and increase bone mineral density.[Collins 2017] Exercise may also help mitigate bone mineral density loss, though exercise regimens should be tailored and adjusted for each patient as needed. Clinicians require knowledge of conditions that can affect bone health and should be aware of guidelines that outline current effective strategies for preventing and managing these conditions.

Gap: Clinicians may lack knowledge of the current and emerging antiresorptive and anabolic agents for osteoporosis and their optimal sequencing.
Learning objective: Identify how current and emerging agents might fit in the treatment strategy for osteoporosis.

Currently available agents include anabolic therapies (parathyroid hormone 1-34 [teriparatide] and the 34-amino acid peptide abaloparatide) and antiresorptive agents.[Chew 2017] Romosozumab, an antibody to sclerostin shown to repair skeletal defects and restore skeletal integrity, was approved by the FDA in January 2019 for treatment of osteoporosis in perimenopausal women at high risk for fracture.[Rossi] Current agents, alone or in combination, have a greater efficacy on vertebral versus non-vertebral fracture reduction, and have potential adverse effects when used for long durations.[Tabatabaei-Malazy 2017]

Combination therapy with anabolic and non-bisphosphonate antiresorptive agents, such as SERMs and denosumab, appears to afford superior benefit over monotherapy in improving BMD and reducing fracture risk, whereas combination of anabolic agents with bisphosphonates appears to reduce the anabolic effects of anabolic agents.[Lou 2017; Shen 2017] However, evidence now suggests greater benefit with sequential treatments when anabolic therapy precedes treatment with potent antiresorptive therapies, noting that switching to TPTD after patients have an inadequate response to antiresorptive therapy is not optimal, and may result in transient loss of hip BMD and strength.[Cosman 2017] In addition, research notes that BMD gains abruptly decrease upon discontinuation of teriparatide and denosumab, necessitating immediate and prompt initiation of antiresorptive therapy.[Leder 2017] Clinicians need guidance on the importance of timely and appropriate medication transitions.[Leder 2017]

Despite remarkable advances in the management of osteoporosis, many patients at high risk who would likely benefit from drug therapy are not taking appropriate agents, often owing to fear of rare side effects or the absence of evidence of long-term efficacy.[Khosla 2017] Patient acceptance and compliance remains suboptimal. Clinicians would benefit from expert guidance regarding how to engage

patients to facilitate effective and consistent treatment with agents to manage osteoporosis.

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PAIN MANAGEMENT IN RHEUMATIC DISEASES

Gap: Many clinicians may lack adequate experience with the full spectrum of pharmacologic modalities of pain management.

Learning objectives:

- *Identify the underlying mechanisms responsible for chronic pain.~*
- *Compare and contrast the safety, efficacy, and mechanisms of various agents available for managing pain in the context of autoimmune disorders.*
- *Determine the optimal manner to incorporate non-pharmacological treatment of pain into clinical practice.*

Most practitioners have historically considered chronic pain to be largely from peripheral nociceptive input (ie, damage or inflammation).[Clauw 2015] If they consider central nervous system (CNS) involvement in pain, they typically focus entirely on psychological factors. We now understand that non-psychological CNS factors can markedly increase (sensitization) or decrease pain sensitivity, in that the CNS is now thought of as "setting the volume control" or gain on pain processing and determining what nociception is felt as pain.[Schrept 2018] The most highly prevalent pain conditions in younger individuals are now thought to be more central than peripheral, and centralized pain or central sensitization can also be identified in subsets of individuals with any nociceptive or neuropathic pain state. This is not currently appreciated in clinical practice so there is marked overuse of treatments for acute/nociceptive pain (opioids, injections, surgery) for treating centralized pain, and underuse of non-opioid centrally-acting analgesics and non-pharmacological therapies.[Clauw 2015]

According to the American College of Rheumatology Pain Management Task Force, pain plays a central role in the clinical spectrum of rheumatic disorders and is the most common complaint of patients presenting to a rheumatologist. Non-severe acute pain represents one of the most frequent complaints of patients presenting to primary care physicians (PCPs), accounting for nearly 50% of all patient visits.[Masala 2017; McCarberg 2011] Despite the ubiquity of pain as a symptom, few clinicians have adequate experience with nonopioid pharmacologic and nonpharmacologic modalities of pain management. Instead, they may concentrate on reducing inflammation and modifying the disease. Importantly, in the absence of timely pain assessment and treatment, central nociceptive pathways may undergo potentially irreversible changes that sensitize the system to subsequent inputs and exaggerate pain responses over the long term. About 15% to 30% of patients with autoimmune or rheumatic disorders have a centralized pain state. However, clinicians may not be aware that opioid medications – besides posing a significant risk for addiction and dependence – often are ineffective in central pain states. And yet, despite increasing evidence questioning the benefits and highlighting the risks of opioids for OA, epidemiologic evidence demonstrates that prescriptions for opioids for joint OA remained stable between 2007 to 2014.[DeMik 2017]

The goals of treatment for pain associated with rheumatic conditions are to improve function and reduce global complaints. The ACR Pain Management Task Force published a report in 2010 categorizing pain by mechanism (inflammation, joint degeneration, or abnormalities of central pain processing) to help guide treatment selection; however, this approach minimizes the overlap between the categories.[Borenstein 2017]

Effective pain management usually involves combination strategies using pharmacologic analgesics and anti-inflammatories as well as nonpharmacologic interventions such as cognitive-behavioral therapy, exercise, hydrotherapy, massage, mindfulness-based stress reduction (MBSR), and other palliative measures.[Anheyer 2017; Maserejian 2014] This multidisciplinary approach has proved to be highly effective. Effective treatment stratification requires a full assessment of pain mechanisms by clinical history and examination, as well as objective assessment of synovitis and joint damage. Treatments vary from person to person, and treatment choices may change as the underlying disease progresses. Even though two patients receive the same diagnosis, they may be given different treatments based on the severity and types of problems each one experiences. However, despite current recommendations, fewer than 1 in 3 PCPs would provide advice on exercise, and newer physicians are more likely to provide guidance on lifestyle changes than those in practice for longer durations.[Maserejian 2014] Clinicians must better inform their patients about the key role they play in managing their own pain therapy, for example by reminding them of the importance of adhering to their therapeutic regimens and by tracking and communicating their progress.

Several categories of drugs are available to treat pain resulting from rheumatic diseases. A number of pharmacologic agents have been studied for central pain; the strongest evidence exists for dual reuptake inhibitors (including tricyclic compounds and highly selective reuptake inhibitors of serotonin or norepinephrine or both; SSRI, SNRI) and the anticonvulsants gabapentin and pregabalin. Other data recommend against the use of gabapentinoids for chronic back pain.[Shanthanna 2017] Modest evidence exists for tramadol, older less-selective serotonin reuptake inhibitors, gamma-hydroxybutyrate, and low-dose naltrexone. Three medications, duloxetine, pregabalin, and milnacipran, have received FDA approval for fibromyalgia. However, a recent retrospective analysis found that treatment of fibromyalgia pain is suboptimal.

Numerous agents are currently under investigation for management of pain. Patients may present with acute and/or chronic pain; treatment may need to be approached based more on the way in which a patient perceives pain than the location of the pain.[Masala 2017] In fact, chronic pain has become recognized as a disease per se.[Masala 2017] In addition, emerging evidence suggests that a subset of patients with RA may also have coexisting fibromyalgia, which appears to account for ongoing pain and RA treatment resistance.[Basu 2018]

A recent study found intra-articular injection of onabotulinumtoxinA reduced pain sensitization and improved function in patients with knee OA.[Arendt-Nielsen 2017] Numerous studies have examined the value of cannabis-based medicines, with inconsistent findings.[Hauser 2018] An emerging approach focuses on the role of nerve growth factor (NGF) in the generation and maintenance of pain, leading to research into anti-NGF monoclonal antibodies (anti-NGF mAbs). However, early clinical trials reports serious joint-related adverse effects, including rapid progression of osteoarthritis and osteonecrosis. Consequently, the FDA placed a clinical hold on studies from 2010 through March 2015. Currently, studies are ongoing involving tanezumab and fasinumab, predominantly for pain relief in patients with symptomatic OA.[Bannwarth 2017; Jayabalan 2017] Positive results from a phase 3 trial of tanezumab – which had been granted fast-track approval status – were announced in July 2018. Similarly, top-line results from a phase 3 trial of fasinumab were announced in August 2018, showing that the drug met efficacy end points in patients with OA of the knee or hip.

Despite the ACR Pain Management Task Force recommendations, and the variety of options for pain management, clinicians have inadequate training and poor understanding and appreciation of the benefits of pain management.[Borenstein 2017] A recent study of patients with RA found that many

patients reported reliance on alternative therapies owing to poor pain management from their medications; further, many patients admitted they do not talk about their pain, despite reporting significant pain.[Schlaeger 2018] Clinicians would benefit from education that reviews the available (and emerging) pharmacologic interventions for pain management, including how to determine appropriate candidates for each option.

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PSORIASIS

Gap: Many clinicians fail to apply updated treat-to-target guidelines for diagnosis, treatment, and assessment of progress in patients with psoriasis.
Learning objective: Demonstrate awareness of current guidelines for management of psoriasis.

Gap: Because psoriasis is a chronic condition and most patients with psoriasis are dissatisfied with their treatment, clinicians must be prepared to make ongoing modifications in their therapeutic approach.
Learning objective: Outline treatment plans for psoriasis that consider the use of new agents, with new mechanisms, and that include strategies for adjusting treatment as needed based on results and patient satisfaction.

Psoriasis is an inflammatory chronic, immune-mediated systemic disease affecting 3.2% of the adult US population (approximately 8 million people). Characterized by pruritic inflammatory plaques with a chronic remitting and relapsing disease course, psoriasis is associated with significant comorbidities including obesity, metabolic syndrome, cardiovascular disease, psoriatic arthritis, autoimmune disease, psychiatric illness, liver disease, malignancy, chronic obstructive pulmonary disease, sleep apnea, and alcohol abuse, resulting in a markedly decreased quality of life.[Oliveira Mde 2015; Kim 2010] Psoriatic arthritis develops in 10% to 30% of these patients approximately 10 years after the onset of skin disease.[Mease 2014; Young 2017]

Clinicians may lack a thorough understanding of psoriasis beyond its dermatologic manifestations. For example, in a recent survey, 75% of dermatologists and rheumatologists acknowledged that psoriatic arthritis may be underdiagnosed because of a failure to connect skin and joint symptoms. Fewer than half of primary care physicians reported screening psoriasis patients for cardiovascular risk factors, as recommended by National Psoriasis Foundation guidelines.[Parsi]. Thus, accurate diagnosis and effective management of psoriasis and its comorbidities requires a deeper understanding of its pathophysiology.

In a survey of dermatologists, 92% acknowledged that the disease burden of psoriasis is frequently underestimated and that the condition is undertreated.[van de Kerkhof 2015] Among patients with psoriasis, 24% to 35% of those with moderate psoriasis, and 9% to 30% with severe psoriasis, were untreated.[Armstrong 2017] In a 2016 survey, only 1 in 3 patients were satisfied with their treatment plan, and more than 80% reported emotional impact resulting, in part, from lack of knowledge about what to expect.[Gould 2016] Barriers to guideline adherence frequently cited by clinicians include lack of knowledge and fear of side effects, suggesting the need for further educational strategies.[van de Kerkhof 2015]

Clinicians also need expanded knowledge and improved clinical confidence in assessing disease severity, treatment results, and quality of life.[Gottlieb 2016] Clinicians should discuss treatment goals with patients, stressing that control of the disease is the primary aim and that remission may be achievable with appropriate use of therapies in appropriately chosen patients. Treatment goals for psoriasis include rapidly controlling the disease process; achieving and maintaining remission; minimizing adverse events; and enhancing quality of life. For mild-to-moderate disease, topical therapies may suffice. Severe psoriasis (affecting >5% to 10% of body surface area) requires phototherapy or systemic therapies such as retinoids, methotrexate, cyclosporine, apremilast, or biologic immune modifying agents.[Young 2017] Keeping the regimen simple and acceptable to the patient can maximize adherence.

The National Psoriasis Foundation (NPF) suggests that clinicians need to understand and use defined treatment targets, citing clinical assessment tools including changes in BSA (Body Surface Area), Psoriasis Area and Severity Index (PASI), Physician Global Assessment (PGA), and Dermatology Life Quality Index (DLQI).[Armstrong 2017] The treat-to-target strategy allows patients and their health care providers to take better control of psoriatic disease by setting specific targets and goals for improved health outcomes.[NPF Treat to Target, 2017] However, many clinicians have not adopted treat-to-target strategies for their patients and thus are not evaluating progress and adjusting treatments as recommended.[Duffy 2016]

The advent of biologic agents has allowed treatment goals for psoriasis to be more aggressive and has made remission a potential and realistic goal.[Feldman 2017] Biologic immune-modifying agents act through targeted inhibition of specific cytokines associated with inflammatory immune responses and skin lesions.[Leonardi 2015, Young 2017] Several biologic agents have already been approved for the treatment of psoriasis, including the biosimilars adalimumab and tildrakizumab-asmn, which was approved in March 2018 (Table 1); other agents are currently under investigation (Table 2).

Table 1: Agents Approved for Psoriasis

Biologic	Target	Year Approved for Psoriasis
Adalimumab	TNF-α	2008
Apremilast	PDE-4	2014
Brodalumab	IL-17A	2017

Certolizumab pegol	Anti-TNF	2018 psoriasis, PsA
Etanercept	TNF-α	2004
Golimumab	TNF-α	2009
Guselkumab	IL-23	2017
Infliximab	TNF-α	2006
Ixekizumab	IL-17	2016
Secukinumab	IL-17A	2015
Tildrakizumab	IL-23p19	2018
Ustekinumab	IL-12/IL-23 p40	2009

Source: Blauvelt JAAD 2016; Blauvelt Br J Derm 2017; Reich 2017

Table 2: Agents Under Investigation for Psoriasis

Biologic	Status	Target/Mechanism
Bimekizumab	Phase 3 for PsA; phase 2 for psoriasis	IL17A, IL17F
Namilumab	Phase 2	Human monoclonal antibody; inhibits granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling by binding the soluble cytokine
Neihulizumab	Phase 2	Preferentially induces apoptosis of late-stage activated T cells, effectively eliminating chronic pathogenic T cells while fully maintaining host defense
Risankizumab	Phase 3	IL-23

In September 2018 it was reported that namilumab at any dose tested failed to provide significant benefit compared with placebo in patients with moderate-to-severe plaque psoriasis.[Papp 2018] Risankizumab is under review by the FDA; approval is expected in the April 2019 following positive results from phase 3 studies and data supporting its positive impact on quality of life for patients with psoriasis.

However, despite the availability of guidelines and effective treatments, a substantial number of patients with moderate-to-severe psoriasis are not receiving appropriate, aggressive management.[Eissing 2016] Barriers to providing optimal care include lack of knowledge (regarding the guidelines and treatments) and poor understanding and appreciation of psoriasis comorbidities.[Eissing 2016] Clinicians need education on these topics so they can to optimally manage their patients with psoriasis. Primary care clinicians would also benefit from guidance regarding when to refer patients with psoriasis to specialists.[Gottlieb 2016]

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PSORIATIC ARTHRITIS

Gap: Clinicians may lack understanding of the pathophysiology of psoriatic arthritis.
Learning objective: Describe the underlying pathological heterogeneity of psoriatic arthritis.

Gap: Clinicians must make ongoing modifications to treatment strategies based on assessment of joint symptoms and comorbidities to maximize outcomes and to increase patient satisfaction.
Learning objective: Create a treatment plan for psoriatic arthritis that incorporates tools for assessing the impact of psoriatic arthritis, comorbid conditions, and that anticipates the potential need to switch or augment therapy.

Gap: Clinicians need to stay current on the growing armamentarium of agents for the treatment of PsA to provide optimal care to patients.
Learning objective: Describe the safety and efficacy of available agents for psoriatic arthritis, including their strategic place in treatment.

The scientific understanding of psoriatic arthritis (PsA) – its natural history, pathogenesis, treatment, and clinical sequelae – continues to advance. However, PsA, as part of the axial SpA spectrum, remains a major clinical challenge driven by its heterogeneous presentation, highly variable response to current therapeutics, and extensive impact on quality of life on the basis of the foregoing, together with the presence of significant comorbidities. This growing body of knowledge mandates that clinicians who care for patients with PsA must keep abreast of results of clinical trials exploring new therapeutic options.

PsA is a clinically diverse inflammatory arthritis that can affect peripheral joints and the axial skeleton. Up to 40% of patients with psoriasis also develop PsA, and many suffer from pain, physical limitations, and disability. If untreated, PsA can cause irreversible damage.[Mease 2014] Duration of disease does not correlate with how rapidly joint destruction may progress; some patients demonstrate progressive disease within the first year after diagnosis. Unless PsA is treated effectively, patients may experience persistent inflammation, progressive and debilitating joint destruction, and increased mortality.[Gottlieb 2016] Furthermore, many patients with PsA have serious comorbidities, primarily cardiovascular disease and inflammation-related insulin resistance leading to diabetes, but also including autoimmune ophthalmic disease, inflammatory bowel disease, and osteoporosis.[Coates 2014]

Clinicians must be prepared to address the identification, assessment, and treatment of PsA; the similarities and differences in the treatment of cutaneous and musculoskeletal manifestations of the disease; and comorbidities and quality-of-life issues. However, persistent gaps in clinicians' awareness of appropriate treatment options means there are unmet needs in the management of PsA. According to the Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP), a population-based survey that included 1005 patients, 101 dermatologists, and 100 rheumatologists, more than one third of dermatologists reported that their greatest challenging in managing PsA patients was in differentiating between PsA and other arthritic diseases.[van der Kerkhof, MAPP]

There also is a gap between patients' and clinicians' perceptions of PsA. In the MAPP survey, nearly half of patients with a diagnosis of psoriasis reported pain in more than 4 joints, while dermatologists reported that only about 19% of their psoriasis patients complained of joint pain. About 87% of dermatologists and 85% of rheumatologists acknowledged that PsA is likely underdiagnosed because clinicians may not assess joint pain effectively (or at all) in patients with skin symptoms. Only about 7% of dermatologists thought they would need to refer to or involve other specialists in the care of their PsA patients, while 1 in 4 rheumatologists said that delayed referral by dermatologists of patients with PsA is one of their greatest challenges.[MAPP]

Different sets of PsA treatment recommendations have been developed. The European League Against Rheumatism (EULAR) published an algorithm that guides the clinician through serial treatment steps and choice of medications based on the severity of clinical domains involved (ie, arthritis, enthesitis, and spondylitis) and on the patient's response to therapy.[Gossec, EULAR 2016] The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) developed its recommendations based on evidence derived from a literature review of treatment of the various clinical domains, including skin.[GRAPPA] The American Academy of Dermatology (AAD) guidelines recommend that clinicians first ascertain whether a patient with psoriasis also has PsA; patients who have PsA should receive systemic medications that treat both psoriasis and PsA.[Gottlieb 2008] Clinicians need to become familiar with these guidelines and with strategies for optimally applying them in their clinical practice.

For patients with localized mild PsA that affects only 1 or 2 joints, the recommended treatment is NSAIDs with or without intra-articular injections of corticosteroids.[Gossec/Smolen CER2015] Patients whose PsA involves 3 or more joints are at greater risk for joint erosion and functional disability. Experts advise that patients who do not respond adequately to treatment with NSAIDs may need treatment with disease-modifying antirheumatic drugs (DMARDs) such as methotrexate; immunosuppressant medications such as azathioprine, cyclosporine, or leflunomide; or biologic agents to control signs and symptoms. Many of the same medications that are effective in psoriasis are also beneficial in PsA. Anti-tumor necrosis factor (anti-TNF) agents such as certolizumab pegol have emerged as a pivotal treatment for many patients More education is needed about the role of anti-TNF therapy in the management of PsA.

The armamentarium for PsA is rapidly expanding, with additional agents constantly being approved (Table 1) and others being investigated.[Hilton 2016; Leonardi 2017] As is true of treatment for psoriasis, challenges to the optimal use of therapies for PsA include cost, lack of long-term safety, and lack of efficacy. PsA is undertreated; half of the patients with PsA who participated in the MAPP survey reported they received no treatment or that they were prescribed topical medications only. Among PsA patients, 40% reported being dissatisfied with the long-term safety of conventional oral therapy and 25% reported dissatisfaction with biologic therapy. More than 4 out of 10 PsA patients said that their primary goals of therapy were not met with their current treatment. Tellingly, 88% of patients and 98%

of clinicians felt there was a strong or moderate need for better therapy. Nearly half of dermatologists and nearly one third of rheumatologists reported that patients leave their practice because of frustration or dissatisfaction with current therapies.

Table: Biologics Approved for the Treatment of Psoriatic Arthritis

Abatacept	T-cell costimulation modulator	2017
Adalimumab	TNF-alpha	2008
Apremilast	PDE-4	2014
Brodalumab	IL-17A	2017
Certolizumab pegol	TNF-alpha	2013
Etanercept	TNF-alpha	2004
Golimumab	TNF-alpha	2009
Guselkumab	IL-23	2017
Infliximab	TNF-alpha	2006
Ixekizumab	IL-17	2016
Secukinumab	IL-17A	2015
Tofacitinib	JAK-1, -2, -3, TAK inhibitor	2017
Ustekinumab	IL-12/IL-23 p40	2009

Finally, there are no treatment algorithms or typical patient profiles to help guide clinicians when switching patients between biologic DMARDs, and only limited data are to be found in the clinical literature.[Merola 2017] Evidence from the Tight Control of Psoriatic Arthritis (TICOPA) study found greater ACR responses when treatment was adapted for tight control versus standard care.[Ramiro 2016] Clinicians typically consider disease characteristics, comorbidities, cardiometabolic risk factors, treatment history, and patient preference when selecting or switching between agents. While the literature suggests that switching between TNF inhibitors may be effective for many patients, switching biologic DMARDs with different mechanisms of action may afford superior outcomes.

The heterogeneity of PsA leads to delayed diagnosis, incorrect diagnoses (as RA), and challenges to treatment selection.[Mahmood 2018; McCardle 2018] Despite similarities with RA, the differences in their underlying pathophysiology require different treatments.[McCardle 2018] However, there are as yet no PsA-specific biomarkers. Increased knowledge regarding prognostic markers may help optimize treatment selection, and early aggressive treatment may minimize joint damage progression.[Mahmood 2018; McCardle 2018] Clinicians need guidance in selecting initial therapy and in switching therapies when indicated.

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PSORIASIS AND PSORIATIC ARTHRITIS: A DERMATOLOGIC PERSPECTIVE

Gap: Although dermatologists are often uniquely positioned to recognize and manage early PsA, they may not be aware of common signs and symptoms of PsA or how to optimally manage this disease.
Learning objective: Discuss the signs and symptoms suggestive of developing or early PsA
Learning objective: Develop a treatment strategy for patients with PsA.

Psoriasis affects about 2% of the world's population, and 1 in 5 patients with psoriasis have psoriatic arthritis (PsA).[Thio 2018] In fact, nearly 30% of patients with psoriasis who are being seen by dermatologists have undiagnosed PsA.[Raposo 2015; Villani 2014] Most often, cutaneous lesions precede presentation of articular manifestation.[Hoelt 2017[As such, dermatologists are ideally situated to recognize, diagnose, and manage PsA, often in early stages during routine visits and

screening.[Gisondi 2018; Hoelt 2017] Consequently, optimal management of psoriasis and PsA involves collaboration between dermatologists and rheumatologists.[Okhovat 2017]

Early diagnosis and treatment of PsA are associated with improved joint and skin outcomes; it is important for dermatologists to be able to recognize signs and symptoms not only of psoriasis, but also of PsA.[Villani 2014] Towards that end, an expert group consensus determined that patients with psoriasis who have peripheral inflammatory pain, axial inflammatory pain, dactylitis, and buttock and sciatic pain should be evaluated for PsA. Other manifestations strongly suggestive of PsA included involvement of distal interphalangeal joints, talalgia, swollen Achille's tendon, costo-chondral involvement, uveitis, and mouth ulcerations.[Villani 2014] Nail psoriasis may also be predictive of psoriatic arthritis.[Raposo 2015] Similarly, a consensus from an expert panel of dermatologists and rheumatologists identified practical implications to help diagnose and manage (early) PsA in the dermatology setting, ranging from signs and symptoms of joint disease, important differential diagnoses, appropriate screening and diagnostic strategies and tools, management strategies, and when referral to a rheumatologist may be warranted.[Gisondi 2018]

Greater understanding of pathogenesis of psoriasis led to the development of important new therapies, including TNF-inhibitors, ustekinumab, IL-17 inhibitors, and guselkumab.[Amin 2018] Dermatologists can rely upon recent treatment recommendations for PsA from both EULAR and GRAPPA, which recommend progression from nonsteroidal anti-inflammatory drugs, to conventional synthetic DMARDs such as methotrexate, and lastly biological DMARDs.[Hoelt 2017] However, traditional agents have not been shown to slow down radiographic progression of PsA.[Raychaudhuri 2017] Anti-TNF agents, including adalimumab, certolizumab, etanercept, golimumab, infliximab, and tofacitinib are more effective in this regard.[Raychaudhuri 2017] Additional novel or emerging agents for PsA include apremilast, brodalumab, ixekizumab, secukinumab, and ustekinumab.[Abrouk 2017; Keating 2017; Raychaudhuri 2017; Wang 2017]

Dermatologists and rheumatologists alike must be cognizant of the various comorbidities in patients with PsA, as well as the increased risk of CV morbidity, when selecting appropriate treatments.[Hoelt 2017; Roubille 2015] An international task force emphasized the importance of shared decision-making, and reinforced the importance of remission or low disease activity as the optimal target for treatment of SpA.[Smolen 2018] Lastly, a novel approach involved combined dermatology-rheumatology clinics to care for patients with psoriasis and PsA. Currently there are 20 such clinics in the US, and evidence suggests improved outcomes, patient and physician satisfaction, and efficiency associated with these clinics.[Soleymani 2017]

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RHEUMATOID ARTHRITIS

Gap: Clinicians lack awareness of the latest understanding of the pathophysiology of rheumatoid arthritis (RA), including the role of interleukin-6 and its receptors (IL-6/IL-6R).
Learning objective: Identify the various cytokine pathways that underlie the process by which rheumatoid arthritis develops and progresses and that serve as potential targets for therapy.

Gap: Clinicians may not be effectively using laboratory studies or appropriately applying the results to monitor outcomes and adjust therapy as needed for patients with rheumatoid arthritis.
Learning objective: Develop effective protocols for conducting laboratory studies and incorporating their results to improve outcomes in patients with rheumatoid arthritis.

Gap: Clinicians may be uninformed about the rapidly evolving guidelines for managing patients with RA.
Learning objective: Discuss current ACR/EULAR guidelines for managing rheumatoid arthritis, including the treat-to-target approach.

Gap: Clinicians may lack guidance in designing appropriate treatment strategies that align individual patient needs with various therapeutic options for RA.
Learning objective: Design effective treatment strategies for managing rheumatoid arthritis.

Rheumatoid arthritis (RA) is a complex disease with multiple mechanisms that result in a spectrum of articular and systemic manifestations and associated comorbidities. Treatment of RA is similarly

complex, requiring appropriate assessment and evaluation to identify which therapies offer the greatest benefit for individual patients.

The most recent diagnostic criteria are the 2010 RA classification criteria from the ACR/EULAR collaborative initiative, which continue to be extensively validated and well-integrated into clinical practice.[Aletaha 2010; Radner 2014] ACR/EULAR treatment guidelines were most recently updated in 2015, and thus do not include all of the most current available treatment options.[Singh 2015] These guidelines focus on pharmacologic treatment decisions and emphasize the importance of facilitating discussion about individualized decision-making between patients and their clinicians.[Singh 2015] Rheumatologists and primary care providers (PCPs) would benefit from education that keeps them abreast of the latest specialty consensus statements so as to be better prepared to manage patients with RA.

The interpretation of laboratory tests used in the diagnosis of such conditions as diabetes or hyperlipidemia is relatively straightforward. In contrast, analysis of laboratory test results for the diagnosis of rheumatoid arthritis is less clear-cut. Most adult patients with RA test positive for rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies (ACPA), or they have elevations in erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).[Pincus 2014] However, about 1 in 3 patients with RA test negative for RF or ACPA; more than 40% have normal ESR or CRP; and many people without RA test positive for RF or ACPA.[Pincus 2014] Similarly, a large percentage of healthy pediatric patients test positive on the antinuclear antibody (ANA) or human leukocyte antigen (HLA)-B27 assays, minimizing their diagnostic value.[Correll 2016] These tests are often useful in categorizing disease, or in helping to offer prognostic information, but they are less useful in establishing a diagnosis on their own.[Correll 2016] Clinical findings must be considered in the diagnostic process. Nevertheless, some laboratory tests (RF and ACPA) are of significant benefit in predicting radiographic progression or identifying patients with “poor prognosis RA.”[Pincus 2014] Lastly, a number of laboratory tests are critical to help clinicians monitor risk of safety concerns or other adverse effects for patients receiving RA medications.[Rigby 2017] Physicians would benefit from education that reviews the available laboratory tests, including how best to interpret the results on an individualized basis.

The advent of DMARDs represented a significant advance in the management of RA. However, the probability of achieving American College of Rheumatology criteria (ACR50) with methotrexate alone is about 40%.[Hazlewood 2016] Since research unveiled the role of the proinflammatory cytokine tumor necrosis factor alpha (TNFa) in the pathophysiology of RA, anti-TNFa drugs have become a mainstay of RA treatment. However, up to two-thirds of RA patients have no or only partial response to anti-TNF therapy.[Calabrese; Hetland 2010; Kim 2015; Tanaka 2014]. An even greater percentage lose response over time or experience significant adverse events following treatment with a TNF inhibitor.[Rubbert-Roth 2009] Lack of response means that many patients will need to be switched to another therapy or to treatment with a combination of two or more agents, which increases the risk for adverse events.[Pavelka 2012]

Greater understanding of the underlying pathophysiologic mechanisms of rheumatoid arthritis has led to the development and introduction of new therapies with unique mechanisms of action, including tofacitinib, the first Janus kinase (JAK) inhibitor for use in RA, and tocilizumab, the first biologic DMARD (bDMARD) monoclonal antibody (mAb) targeting the IL-6 receptor. JAK inhibitors work in a novel way by regulating intercellular gene transcription cytokine signaling, thereby reducing the extracellular release of cytokines and immune complexes. Filgotinib is a selective JAK1 inhibitor that may limit toxicity owing to its selectivity, but requires investigation in large-scale studies.[Taylor 2017] Both IL-6 and the IL-6

receptor (IL-6R) have been identified as pathways in RA, leading to investigation of additional IL-6/IL-6R inhibitors such as olokizumab. Other newer agents include abatacept (now available in 3 modes of delivery), anakinra, golilumab, infliximab, rituximab, and sarilumab. Sarilumab, a fully human mAb, has a unique mechanism of action: it targets the alpha subunit of membrane-bound and soluble IL-6R (IL6Ra), thereby blocking both cis- and trans–IL-6 medicated signaling.[Cooper 2015; Genovese 2016] The discovery of other pathways has led to the development of additional agents. Abatacept, an injectable anti-CD80/86 fusion protein, was approved in 2005 for use in RA. Rituximab is a CD20-directed cytolytic antibody approved for use in combination with MTX for patients who had inadequate response to 1 or more anti-TNFa agents. The B-cell-depleting CD20 antibody ofatumumab, already approved for chronic lymphocytic leukemia, has shown promise for RA.[Pers 2016] Canakinumab, which demonstrates anti–IL-1 beta activity, is approved for systemic juvenile idiopathic arthritis.

More recently, there is interest in the granulocyte macrophage-colony stimulating factor pathway, Bruton's tyrosine kinase pathway, phosphoinositide-3-kinase pathway, neural stimulation and dendritic cell-based therapeutics.[Cheung 2017] A phase IIb study of mavrilimumab, a monoclonal antibody to granulocyte-macrophage colony-stimulating factor receptor α, and golimumab, a monoclonal antibody to TNF (anti-TNF), in patients with RA who had an inadequate response to DMARDs or to other anti-TNF agents found regimens with both agents were well tolerated and demonstrated clinical efficacy, warranting additional investigation.[Weinblatt 2018] Another potential target is the eicosanoid pathway, which is responsible for the progressive destruction of bone and cartilage.[Hoxha 2018] With these and numerous other agents and pathways under investigation, it is very challenging for clinicians to remain current on emerging agents and their place in treatment strategies.[Ferro 2017]

The goals of RA therapy include achieving remission or low disease activity using a treat-to-target approach.[Smolen 2014] Although biomarkers have not yet been identified that would help determine which patients are likely to respond to a specific therapy, some progress has been made toward the development of a personalized approach to treatment. However, there is still controversy regarding the most appropriate treatment strategy for patients who fail on specific biologic agents.[Mehta 2017] Clinicians need education to keep abreast of the current scientific rationale for use of combination therapy, dose escalation, or switching between or among classes of DMARDs and biologic agents.

A particular challenge in the management of patients with RA is the high rate of comorbidities associated with the disease. Among the more common comorbid conditions are diabetes and insulin resistance,[Nicolau 2017] lung disease,[Bluett 2017; Hyldgaard 2017] cardiovascular comorbidities, including numerous components of metabolic syndrome,[Gualtierotti 2017; Müller 2017] and possibly gallstones in women.[Garcia-Gomez 2017] Historically gout was not considered to be a usual comorbidity of RA, but a large population database study in Israel reported a significant proportion of gout in patients with RA versus controls.[Merdler-Rabinowicz 2017] Of concern is an increased risk of disease malignancies, including non-Hodgkin lymphoma. In addition to the association between RA and these conditions, biologic agents used in the management for RA can increase susceptibility to infection, tuberculosis, and malignancies. Clinicians must be aware of the elevated risk of comorbid conditions and should continually monitor patients for these diseases throughout the course of treatments.

Recent research has identified an elevated risk of inflammatory and/or rheumatoid arthritis in patients with cancer who are receiving the new immune checkpoint inhibitor drugs (including nivolumab and ipilumumab), which are now the most widely used precision immunotherapy treatments for cancer. Cappelli and colleagues identified 13 patients receiving this treatment who developed rheumatologic complications, including 9 who developed inflammatory arthritis.[Cappelli 2017] They noted that

inflammatory arthritis is underappreciated and may have clinically severe consequences. As many as 10% to 15% of patients being treated with immune checkpoint inhibitor drugs may have inflammatory arthritis.[Cappelli 2017] Rheumatologists must therefore be aware of all treatments their patients are receiving and should directly inquire about symptoms of IA in patients undergoing immune checkpoint inhibitor therapy.

Rheumatologists and other clinicians involved in the care of patients with RA are constantly challenged with staying current with new clinical data. Optimal care is hampered by delayed diagnoses, challenges with adherence to treat-to-target strategies, and consequences of comorbid conditions.[Burmester 2017] Data from a retrospective cohort study found that applying a treat-to-target approach is feasible in real-world clinical practice, noting that only about 25% of all visits over a 3 year period represented protocol deviations.[Wabe 2015] Further, guidelines are not able to keep current with the approval of new agents. Clinicians would benefit from education that provides the most up-to-date information on the guidelines, diagnosis, and management of RA.

Gap: Clinicians may be challenged to manage patients with difficult-to-treat RA so as to achieve optimal outcomes.

Learning objectives:

- *Identify the features of a patient who has difficult-to-treat RA*
- *Understand the factors that underlie D2T RA*
- *Generate a clinical management plan to address the needs of people with D2T RA*

Despite remarkable progress in the treatment of rheumatoid arthritis in the last decade, driven by new therapeutic and advanced treatment strategies, there now remains a smaller group of people with treatment-resistant disease. Patients with difficult-to-treat rheumatoid arthritis represent a substantial clinical challenge, comprising a significant unmet need.

To begin with, there is a wide variation in the criteria experts use to describe difficult-to-treat RA.[Buch 2018; Roodenrijs 2018] Notably, 50% of the more than 400 rheumatologists who responded to an international survey identify difficult-to-treat RA based on disease activity score or the presence of signs suggestive of active disease; 42% selected fatigue as a determining factor, 48% based their assessment on failure to at least 2 conventional synthetic DMARDs and at least 2 biological/targeted DMARDs; almost all rheumatologists included an inability to taper glucocorticoids below 5-10 mg/day.[Roodenrijs 2018] Current evidence suggests that one in 5 patients with RA progress to a third bDMARD.[Buch 2018]

In addition, clinicians have noted that interfering comorbidities, extra-articular manifestations, and polypharmacy are not adequately addressed in current management guidelines. [Albrecht 2017; Roodenrijs 2018] For example, poor prognostic factors are defined heterogeneously; the relevance of any individual prognostic factor remains unclear.[Albrecht 2017] Some clinicians propose that there are many patients with difficult-to-treat RA, who comprise an unmet clinical need that require evaluation of all contributing factors; careful assessment to determine underlying cause of persistent signs and symptoms; and a management approach that addresses symptoms as well as comorbidities.[De Hair 2017]

A recent literature review reports that pain, fatigue, and impairments to physical and mental function remain unmet needs in the management of RA.[Taylor 2016] This study highlights the ongoing need for treatment of these quality-of-life burdens resulting from RA. Similarly, interim results of a study on refractory RA that were presented at the 2016 ACR annual meeting concluded that there are different

types of patients who are being identified as refractory, despite different signs and symptoms.[Unger 2016] Half of the patients who had failed 3 treatment courses, including at least one biological DMARD, over 18 months continued to demonstrate radiographic progression, and 87% of these patients showed signs of ultrasound activity. Half of the patients who did not demonstrate progression met the criteria for fibromyalgia, which accounted for their high patient global scores and tender joint counts. The remaining patients had active synovitis. Most non-progressing patients are thus diagnosed with refractory RA owing to pain and not disease progression.[Unger 2016]

Clinicians would benefit from expert guidance regarding how to identify and manage patients with D2T rheumatoid arthritis, despite the absence of clear criteria or targeted treatments.

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SCLERODERMA AND LUNG DISEASE

Gap: Physicians would benefit from education regarding available treatments for the various manifestations of localized and systemic scleroderma.
Learning objective: Design effective treatment strategies for the various manifestations of localized and systemic scleroderma.

Scleroderma refers to a heterogeneous group of chronic autoimmune rheumatic disorders characterized by hardening of the skin.[Brady 2016; Fett 2013] It affects an estimated 300,000 Americans, and about one-third of them have the systemic form. There are 2 major classifications: localized scleroderma (LoS), which is generally benign and is limited to the skin and/or underlying tissues; and systemic sclerosis (SSc), which manifests with cutaneous sclerosis and visceral involvement.[Careta 2015] Each major classification is further subdivided into its own subclassifications: LoS into plaque morphea, generalized morphea, bullous morphea, linear scleroderma, and deep morphea; and SSc into limited cutaneous SSc, diffuse cutaneous SSc, and SSc sine scleroderma.[Fett 2013; Careta 2015] However, it can be challenging to distinguish between the different types of morphea.[Beilsa Marsol 2013] ACR/EULAR guidelines for classification of SSc, published in 2013, were designed for use as entrance criteria into SSc clinical trials; these classifications are not diagnostic, and may overlook early patients.[Vanden Hoogen 2013] They incorporate important elements not previously included: proximal scleroderma, sclerodactyly, digital pit, pulmonary fibrosis, Raynaud phenomenon, and Sc-specific autoantibodies.[Johnson 2015]

The symptoms of scleroderma vary greatly, often depending on the parts of the body affected and the extent to which they are affected. Consequently, scleroderma can range from very mild in severity to a life- threatening disorder. Generally, localized scleroderma affects children and SSc is more common in adults. While morphea (LoS) is associated with substantial morbidity but does not affect mortality, SSc has the highest disease-specific mortality of all autoimmune rheumatologic diseases.[Fett 2013] The etiology and pathogenesis of this disease remain unclear.

Diagnosis is based on the individual's symptomatic manifestations; blood work, specialized imaging (Doppler, laser Doppler) and other tests may be necessary depending upon the organs affected.[Zulian 2013] Because many symptoms of scleroderma are similar to those of autoimmune diseases, diagnosis can be difficult, leading to misdiagnoses or missed diagnoses.[Brady 2016] It is important for clinicians to be educated on the most recent recommendations for diagnostic assessment in order to be able to provide an early diagnosis and promptly initiate treatment.

Currently there is no cure for scleroderma. Treatment is based on symptomatic manifestations, although some patients benefit from treatments that decrease the activity of the immune system, such as methotrexate.[Zulian 2013] SSc that involves the lung, kidney, and heart is frequently treated with corticosteroids and immunosuppressives; in contrast, there are limited options to manage the cutaneous manifestations.[Kuhn 2016] A survey of pediatric rheumatologists and dermatologists who manage children and young adults with juvenile localized scleroderma (JLS) in the UK found substantial variation in their respective use of monitoring tools and treatment approaches.[Hawley 2014] Hematopoietic stem cell transplantation (HSCT) has been shown to prevent disease progression in some SSc patients but is associated with a high incidence of treatment-related mortality.[Farge 2017] The European Society for Blood and Marrow Transplantation (EBMT) recently published guidelines to evaluate SSc patients undergoing HSCT; careful patient selection is needed to minimize mortality.[Farge 2017; Sullivan 2018] Lack of universal guidelines and identification of appropriate candidates can interfere with diagnosis, monitoring, and selection of treatment strategies, leading to suboptimal outcomes.

Gap: Lung disease in scleroderma is a primary source of morbidity and mortality, yet little is known regarding risk factors, diagnosis and management.
Learning objective: Discuss current understanding of the screening, diagnosis and management of lung disease in scleroderma.

One of the most challenging aspects of managing rheumatic and connective tissue diseases involves lung ailments, including interstitial lung disease (ILD) and pulmonary artery hypertension (PAH).[Dellaripa 2018; Doyle 2017; Schoenfeld 2017] Screening and diagnosis frequently involve serologies, pulmonary function testing, high-resolution imaging, and echocardiography.[Caron 2018; Giacomelli 2017; Schoenfeld 2017]

Particularly challenging is that lung disease is more difficult to recognize and treat within the context of a systemic disease. Of these, SSc has the highest fatality rate, and ILD is the most frequent cause of death.[Giacomelli 2017; Schoenfeld 2015; Schoenfeld 2017; Volkmann 2016] An estimated 40% of patients with SSc have some degree of ILD.[Ueda 2018] However, ILD and PAH are under-reported in SSc, highlighting the importance of regular screening to detect lung diseases early and optimize outcomes.[Schoenfeld 2017]

Lung diseases are a source of significant morbidity and mortality; however, there is an absence of high-level data identifying which patients are at greatest risk, and which therapies are most effective and have a sufficient safety profile.[Dellaripa 2018; Doyle 2017] Traditionally, lung manifestations have been treated with anti-inflammatory therapies; more recently, anti-fibrotics, oral cyclophosphamide and mycophenolate mofetil (MMF) have shown effectiveness.[Dellaripa 2018; Tashkin 2016; Ueda 2018] Although cyclophosphamide was historically the preferred treatment, it is associated with a complex adverse event profile. Recent data demonstrate comparable effectiveness with a better safety profile.[Ueda 2018; Volkmann 2016] Other agents under investigation include rituximab, tocilizumab, pirfenidone, and nintedanib.[Koo 2017; Volkmann 2016] Nintedanib is a tyrosine-kinase inhibitor that blocks several profibrotic pathways, and is approved for idiopathic pulmonary fibrosis. Data suggests it may be a promising agent for SSc-associated lung fibrosis.[Duarte 2018] In March 2018 nintedanib was granted fast-track approval status for this indication.

Despite the high morbidity and mortality associated with lung disease in scleroderma, little is known regarding risk factors, diagnosis, and treatment. The prevalence of these diseases, including ILD and PAH, necessitates ongoing and targeted education for clinicians who treat these patients.

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SKIN REACTIONS TO DRUGS

Gap: Patients on medications for rheumatic disorders may experience cutaneous adverse reactions, necessitating immediate diagnosis and management.
Learning objective: Develop a strategy for identifying and managing cutaneous adverse reactions.

The majority of immune-mediated adverse drug reactions involve the skin, often along with other features.[Peter 2017] Severe cutaneous adverse reactions, while uncommon, include a heterogeneous group of often delayed and potentially life-threatening hypersensitivity reactions, most often to drugs.[Adler 2017; Peter 2017] It can be challenging to differentiate between cutaneous adverse drug reactions and systemic illness, particularly in older patients.[Young 2017]

A multidisciplinary approach is recommended to address the diagnosis and management of the skin reactions, including whether or not to cease the offending medication. [Matsuda 2018; Peter 2017] For example, mild cutaneous reactions without other systemic involvement may not necessitate treatment cessation; in contrast, Stevens-Johnson syndrome or toxic epidermal necrolysis require immediate withdrawal and management.[Matsuda 2018; Peter 2017]

Some medications, including hydroxychloroquine, interferons, and monoclonal antibody- and small molecule based targeted therapies (such as TNF-alpha antagonists and ICIs) can exacerbate rheumatic disorders such as pre-existing psoriasis.[Balak 2017] However, it can be particularly difficult to distinguish between drug-related psoriasis and induction of psoriasis, as both manifest with similar histopathological and clinical features.[Balak 2017] TNF-alpha blockers have also been linked with development of cutaneous sarcoidosis.[Park 2017] Although rare, biologics used in the management of RA have also been linked with eosinophilia.[Azuma 2017] In some cases, switching to another biologic with a lower immunogenicity may be appropriate.

Clinicians may encounter cutaneous adverse reactions to medications used in the management of rheumatic diseases. It is important to have the knowledge and access to a multidisciplinary team to be able to accurately determine the cause and to appropriately treat the adverse reaction in a timely fashion.

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STATIN-INDUCED MYOPATHIES

Gap: Clinicians may not be aware of how to diagnose and manage muscle complaints related to statins.
Learning objective: Summarize the diagnosis and management of different types of statin-related muscle complaints.

Statins can cause mild muscle symptoms, severe muscle damage, and even an autoimmune myopathy requiring immunosuppressive therapy. Although clinicians often see patients who develop muscle complaints while on statins, many do not know how to diagnose and manage these patients.

According to the CDC, using data from the NHANES studies 2005-2012, about 50% of Americans with cholesterol readings that increase the risk of heart attack or stroke are not taking medication to reduce their cholesterol and risk.[ACSH 2015] In 2014, 28% of Americans over age 40 were taking cholesterol-lowering medications. Statin drugs are first-line therapy, as they are highly effective for preventing cardiovascular (CV) events by inhibiting HMG-CoA reductase which helps reduce low-density lipoprotein cholesterol (LDL-C).[Nazir 2017; Rosenson 2017; Taylor 2018] Unwarranted fears of statins may

contribute to the underuse of these potentially life-saving agents. While statins may be associated with an increased incidence of exercise-related muscle complaints, they have not been found to reduce muscle strength, endurance, overall exercise performance, or physical activity.[Noyes 2017]

Of concern are reports of statin-associated symptoms (SAS), including statin-associated muscle related symptoms (SAMS), which are the most common SAS.[Thompson 2016] SAMS are associated with poor adherence to statin medications, thereby increasing risk of CV events.[Rosenson 2017] Mild statin-related myalgia may affect between 5% to 10% users,[Thompson 2016] and between 2% to 20% of patients develop toxic myopathies.[Nazir 2017] Rare but clinically important symptoms include rhabdomyolysis and statin-induced necrotizing autoimmune myopathy (SINAM).[Thompson 2016] Many SAMs resolve once statin treatment has been discontinued, but some SAMS require additional treatment.[Nazir 2017] In addition, clinicians need to identify alternative lipid-lowering therapies for these patients, and reintroducing statins is often unsuccessful. [Nazir 2017]

SAMS are challenging to treat in part because there is a lack of conclusive evidence linking statins to them.[Thompson 2016] Further, there are no validated biomarkers or tests to confirm patient self-reported SAMS, and some muscle pain is, in fact, not attributable to statins.[Taylor 2018] The European Atherosclerosis Society Consensus Panel Statement on SAMS notes that between 1/1000 to 1/10,000 people on standard statin doses will have a significant elevation of serum creatine kinase leading to statin-associated myopathy; other patients with SAMS manifest with a broad range of clinical manifestations.[Stroes 2015] As such, diagnosis often requires review of symptoms and their temporal association with statin use.

In light of the absence of clear diagnostic and management recommendations, clinicians are challenged to care for patients with potential SAMS and would benefit from education on the topic.

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SYSTEMIC LUPUS ERYTHEMATOSUS

Gap: Clinicians may not be using current findings on the underlying pathophysiological mechanisms of

SLE and its various biomarkers to design treatment strategies.
Learning objective: Summarize current and emerging research on the mechanisms of the pathology of systemic lupus erythematosus and treatment of lupus nephritis.

Gap: Clinicians who are unable to keep abreast of results of clinical trials of targeted therapies for SLE may not be providing optimal treatment for their patients.
Learning objective: Review data from clinical trials – including failed trials – on candidate therapies that target various pathways involved in systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is an autoimmune disease with a polymorphic presentation. The various forms of this inflammatory connective tissue disorder – systemic, discoid (cutaneous), drug-induced, and neonatal – can follow an unpredictable pattern of flares and remission. About half of SLE cases progress to involve the kidneys (lupus nephritis). The Lupus Foundation of America estimates that 1.5 million Americans, and at least 5 million people worldwide, have some form of chronic SLE. More than 16,000 new cases of lupus are reported annually in the US.

The complex immunopathology of SLE, the variability in its clinical expression and severity, and the unpredictable response to treatment poses significant challenges to rheumatologists, PCPs, and other clinicians responsible for managing the disease.

Education is needed to help clinicians keep current on research into the pathophysiology of the disease; its potential therapeutic targets; safety and efficacy findings from the latest clinical trials; and strategies for choosing appropriate therapy. The ultimate goal is to develop a personalized approach to diagnosing and managing SLE, one that identifies the specific biomarkers and disease mechanisms active within a given individual and that supports therapeutic choices to offer the best hope for treating SLE.

The Systemic Lupus International Collaborating Clinics (SLICC) group developed a set of diagnosis criteria that include 17 variables derived by expert consensus and statistical analysis using real-life patient scenarios. SLICC criteria require that at least 4 criteria need to be met – including at least 1 clinical criterion and 1 immunologic criterion – to establish a classification of SLE.[Petri 2012] The SLICC criteria demonstrate greater sensitivity (97% vs 83%, $P<0.0001$) but less specificity (84% vs 96%, $P<0.0001$) than the current ACR criteria. The SLICC criteria are considered to be more clinically relevant and will probably identify more patients with clinically defined SLE than would the current ACR criteria. Similarly, validated diagnostic recommendations and disease-specific indices for lupus nephritis in children with SLE have been developed and are evolving into consensus treatment practices.[Wenderfer 2016] Most recently, the British Society for Rheumatology published guidelines on non-renal manifestations of SLE. Unlike prior guidelines, the British Society's version uses clinical descriptions for disease activity severity and offers treatment approaches for each disease activity category.[Gordon 2018a; Gordon 2018b] PCPs are often the initial physicians to evaluate patients with possible SLE; as such, they need to be familiar with the many manifestations of SLE to facilitate early diagnosis.[Pramanik 2014] PCPs also need familiarity with warning signs that warrant referral to a rheumatologist.[Lam 2016] Clinicians would benefit from education on these new guidelines, including means for integrating them into clinical practice.

Research into the immunopathology of SLE is expanding at rapid pace. These emerging findings, as they become validated, have enormous potential for improving the ability of clinicians to recognize patients at risk for SLE, for recognizing SLE earlier in the disease process, and for identifying potential therapeutic targets. For example, researchers are investigating possible biomarkers and genetic markers that may

enable better understanding of the underlying pathophysiology of SLE, while identifying potential targets for emerging therapies.[Wang; Motawi; Navarro Quiroz; Lee; Sá; Kröger; Patra; Hu; Rai; Mahieu] Clinicians would benefit from education that summarizes the most relevant current research findings on the mechanisms of SLE pathology and that provides expert perspectives on the clinical utility of emerging data.

The most recently approved drug for treatment of SLE in the United States is belimumab, a fully human IgG1-lambda recombinant monoclonal antibody directed against B-lymphocyte stimulator that was approved in 2011. Before that, the only approved agents were aspirin (1948) and hydroxychloroquine and corticosteroids (1955). Not all patients respond to belimumab treatment. Given that SLE is a highly heterogeneous disease with variable response to treatment, clinicians may be challenged to find optimal treatment for patients on an individualized basis. In order to optimize ongoing treatment, PCPs and rheumatologists need to work together and communicate to best coordinate care.[Lam 2016]

Recent clinical trials have produced mixed results. Many once-promising drug candidates have proved disappointing, and the search for optimal therapy is ongoing and is exploring a number of pathways.[Merrill 2010; Rovin 2012; Mota 2017; Haarhaus; Mysler; Isenberg 2016; Isenberg 2015; Clause; Scheinberg; Zimmer; Kalunian] Clinicians need to keep abreast of the latest developments in this fast-moving field.

The kidney is one of the most common target organs of lupus; as such, a diagnosis of lupus nephritis (LN) has a substantial impact on treatment and clinical outcomes.[Bawazier 2017] A retrospective observational study of 176 patients with LN found that renal remission status at 24 months following a diagnosis of LN was a significant predictor of long-term renal survival.[Davidson 2018] However, the treatment of LN is an unmet need in the management of patients with SLE.[Margiotta 2018] Typically, diagnosis of LN requires renal biopsy, although research has been investigating noninvasive techniques, including possible urinary biomarkers.[Urrego 2018] Induction therapy focuses on achieving partial or complete remission; maintenance treatment aims to maintain remission and avoid relapses. Earlier remission is correlated with better prognosis and fewer relapses. Current pharmacotherapies include cyclophosphamide (CPM), mycophenolate mofetil (MMF), azathioprine, cyclosporine (CYC), and tacrolimus.[Bawazier 2017] While MMF and CYC are traditionally used as standard induction therapy, they are often ineffective or poorly tolerated.[Jesus 2018; Margiotta 2018] A recent small study reported that adding cyclosporine A to MMF led to complete renal remission in 4 of 6 patients and partial remission in another within 6 months, without any adverse effects.[Jesus 2018] A recent study that compared CYC, MMF, and CMP-based regimes found comparable rates of (complete and partial) remission with each of the regimens, as well as similar rates of end-stage renal disease.[Sahay 2018] Other research suggests belimumab, in combination with low-doses of MMF, may be an effective induction option.[Margiotta 2018] Rheumatologists and nephrologists need to work together to optimize management of lupus nephritis on an individualized basis.

Recent advances in the understanding of SLE disease mechanisms have raised interest in the role the interferon pathway plays in the pathogenesis of SLE.[Kalunian; Merrill 2010; Khamashta 2016; Furie 2015] Clinicians would benefit from education that helps provide context for the flood of data – positive and negative – emerging from clinical trials and that helps them incorporate newly available drugs into treatment plans for appropriately selected patients.

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