



# CLINICAL PRACTICE GUIDELINE

# **Ultrasound in**

# **Rheumatological Settings**

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## Table of Contents

<b>Introduction .....</b>	<b>6</b>
<b>Diagnostic Musculoskeletal Ultrasound .....</b>	<b>10</b>
Definition of Important Ultrasound Findings .....	11
Rheumatoid Arthritis .....	11
Ultrasound Follow-up and Monitoring in Rheumatoid Arthritis .....	13
Future Directions of Ultrasound in Rheumatoid Arthritis .....	15
Limitations of Ultrasound in Rheumatoid Arthritis .....	16
Ultrasound in Rheumatoid Arthritis (Summary/Conclusions) .....	17
Psoriatic Arthritis .....	17
Ultrasound for the Diagnosis of Psoriatic Arthritis .....	17
Ultrasound in the Distinction of Psoriatic Arthritis from Rheumatoid Arthritis and Other Forms of Inflammatory Arthritis .....	19
Ultrasound Findings in Patients with Psoriasis Without Psoriatic Arthritis .....	20
Ultrasound Monitoring in Psoriatic Arthritis .....	20
Ultrasound in Psoriatic Arthritis (Summary/Conclusions) .....	21
Osteoarthritis .....	21
Ultrasound in the Diagnosis of Osteoarthritis .....	21
Ultrasound in Osteoarthritis (Summary/Conclusions) .....	23
Gout .....	23
Ultrasound for the Diagnosis of Gout .....	24
Ultrasound Monitoring in Gout .....	25
Ultrasound in Gout (Summary/Conclusions) .....	25
Calcium Pyrophosphate Dihydrate Deposition Disease.....	26
Polymyalgia Rheumatica .....	27
Additional Applications of Diagnostic Ultrasound in Rheumatology .....	29
<b>Interventional Musculoskeletal Ultrasound .....</b>	<b>31</b>
<b>Summary and Conclusions .....</b>	<b>35</b>
<b>Glossary.....</b>	<b>36</b>

<b>References .....</b>	<b>37</b>
<b>Appendix A—Giant Cell Arteritis .....</b>	<b>44</b>
References .....	46
<b>Appendix B—Sjögren’s Syndrome.....</b>	<b>47</b>
References .....	50
<b>Document Updates .....</b>	<b>51</b>

## List of Tables

Table 1. EULAR-OMERACT scoring system for RA .....	9
Table 2. EULAR/ACR scoring system for polymyalgia rheumatica (PMR) without ultrasound .....	28
Table 3. EULAR/ACR classification system for polymyalgia rheumatica (PMR) with ultrasound .....	29
Table 4. Some additional indications for diagnostic ultrasound .....	30
Table 5. Proposed reporting system for parenchymal echogenicity and homogeneity .....	48

## Abbreviations

ACPA	Anticitrullinated protein antibody
ACR	American College of Rheumatology
anti-CCP	Anti-cyclic citrullinated peptide
CD	Cluster of Differentiation
CDAI	Clinical Disease Activity Index
CPDD	Calcium pyrophosphate dihydrate deposition disease
CRP	C-reactive protein
CT	Computed tomography
CTS	Carpal tunnel syndrome
CXC13	C-X-C motif chemokine ligand 13
DAS28	Disease Activity Score based on 28 joints
DECT	Dual energy computed tomography
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GCA	Giant cell arthritis
Ig	Immunoglobulin
LDA	Low disease activity
MHz	Megahertz
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MSU	Monosodium urate
MSUS	Musculoskeletal ultrasound
OA	Osteoarthritis
OMERACT	Outcome Measures in Rheumatology
PD	Power Doppler
PET-CT	Positron emission tomography computed tomography
PMR	Polymyalgia rheumatica
PRF	Pulse repetition frequency
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RA-GLOSS	Rheumatoid Arthritis Global Synovitis Score
RF	Rheumatoid Factor
SH	Synovial Hypertrophy
sUA	Serum uric acid

T2T	Treat-to-target
UCLA	University of California at Los Angeles
ULT	Urate-lowering therapy
US	Ultrasound
USSONAR	Ultrasound Society of North American Rheumatologists
XBP1	X-box binding protein 1

## Introduction

Diagnostic imaging has become an important part of the diagnosis and management of many musculoskeletal and rheumatologic disorders. Over the past several decades, ultrasound (US, sonography) has been demonstrated to be a safe, cost-effective, and accurate method of imaging many rheumatic diseases; it also has helped to improve the results of invasive procedures by providing real-time guidance for needle placement. Ultrasound does not use ionizing radiation, and it is currently the only modality capable of dynamic imaging.

Ultrasound was enthusiastically adopted in Europe but was slow to take hold in the United States. A prospective study published in 1999 showed the importance of an imaging approach for obtaining accurate findings. It compared musculoskeletal US, plain X-ray, magnetic resonance imaging (MRI), and three-phase bone scintigraphy of the fingers in patients with arthritis to determine which imaging modality was best at detecting both bone erosions and synovitis in patients with normal and abnormal X-rays.<sup>1</sup> The study found that US, MRI, and three-phase bone scans were more sensitive than plain films for detecting synovitis. However, scintigraphy had a low specificity and therefore was thought to be inadequate as a screening test for patients with early inflammatory arthritis. The study also reported that US using a 7.5-megahertz (MHz) transducer was more sensitive than MRI in detecting synovitis but not at detecting bone erosions. In an earlier report using a higher frequency 13-MHz transducer, Grassi et al.<sup>2</sup> had described visualization of both cartilage and bone erosions in patients with rheumatoid arthritis (RA). The difference in results between the two studies demonstrates the importance of using the correct equipment, especially the highest-frequency transducer possible.

More widespread adoption of US in rheumatologic practices in the United States has occurred over the recent past, but its growth has been limited by several factors. Perhaps the most significant initial limitation was the lack of fellowship training and training courses for practicing rheumatologists in the United States. Additional factors have included a limited standardized lexicon of terms, inadequate guidelines for the appropriate use of US, inadequate protocols for performing US examinations in an active office environment, absence of validated scoring systems, inadequate knowledge of the standards for reporting results, and lack of validated recommendations for repeat studies.

Several organizations have attempted to address this lack of US training opportunities; including the European League Against Rheumatism (EULAR), the American College of Rheumatology (ACR), the American Institute of Ultrasound in Medicine (AIUM), and the Ultrasound Society of North American Rheumatologists (USSONAR). There has also been an increase in the number of rheumatology fellowship programs that included US training as part of their curricula. Since 1998, EULAR has offered beginner-, intermediate-, and advanced-level US training courses. In 2008, it also published requirements for musculoskeletal US training courses describing requirements for the content and conduct of these courses. For example, regardless of the level of training, EULAR indicated that there should be no more than six students per faculty member and that no less than 50% to 60% of the course time should be spent on actual scanning. Each course should include at least 20 hours of training over 3 days. The ACR introduced its first US course in 1999 and has continued to offer US training courses for rheumatologists.<sup>3</sup>

The USSONAR is a relatively new organization founded in 2006. Since 2008, it has offered an eight-month US training course for rheumatologists in the United States.<sup>4</sup> This course prepares both rheumatology fellows and practicing rheumatologists for the ACR credentialing examination. In addition, the USSONAR has developed a training curriculum for rheumatology fellows that can be helpful to directors of training programs.

More importantly, a large number of rheumatology fellowships now include US training. In 2017, Torralba et al<sup>5</sup> published the results of a survey of 113 rheumatology training programs. Surveys were sent to 113 program directors; responses were received from 108. Of the 108 responses, 94% stated that their fellowship programs included training in musculoskeletal US. This was a marked improvement when compared to a survey taken in 2008 in which, of 135 fellowship directors surveyed, only 46 had responded and, of those, 41% had indicated that there was some US training in their programs. In addition, 33% had indicated that they had some resources to send fellows to US training courses.<sup>3</sup>

The first guidelines for US in rheumatology were published by EULAR in 2001.<sup>6</sup> The paper reviewed some of the technical advances in US at that time; which included improved visualization of soft tissues, fluid collections, cartilage, and bone surfaces.<sup>6</sup> The authors described the pathologic conditions that could be imaged with US in the shoulder, elbow, hand, wrist, hip, knee, ankle, heel, and foot as well as the proper positioning of the patient and the views that should be obtained for different joints. Recently, EULAR has published two excellent updates to these original guidelines—the *EULAR Ultrasound Scanning Guide* and the *EULAR Imaging Library*.<sup>7,8</sup> The former document includes images of probe position during actual scans based on anatomic site, normal US anatomy, and cine clips of the scan itself; the latter document contains multiple images of abnormal scans with explanations.

Over the past decade there have been significant advancements in US technology, particularly with the introduction of high-frequency linear array transducers that produce very detailed images. The introduction of extended-field-of-view imaging provides more complete visualization of an anatomic area on a single image. The current equipment is also more user friendly and less costly than in the past. As a result, in many clinical contexts, US has become more widely accepted as an alternative to MRI. The soft-tissue resolution of US is superior to that of radiography; even bone erosions in patients with normal radiographs can be detected. Though not widely in clinical use, with the introduction of 3D- or volume imaging, US can now provide multi-planar imaging, enabling the user to determine the optimal image plane for visualizing an abnormality.

Among the most important clinical applications of US technology in rheumatology is the detection of synovitis and bone erosions in patients with inflammatory arthritis. The use of power Doppler (see additional definitions in the Glossary) imaging identifies areas of increased vascularity that are consistent with inflammatory changes such as synovitis, before they can be identified on physical examination.<sup>9-11</sup> Wakefield et al.<sup>12</sup> found that US detected more bone erosions in patients with RA than X-ray. Power Doppler evaluation of erosions seen on gray-scale sonography can determine if there is active synovitis in an erosion by demonstrating increased vascularity in the hypertrophied synovium (pannus) within the erosion.<sup>13</sup>

Another significant advantage of US as an imaging modality is its ability to perform dynamic imaging. Ultrasound permits real-time evaluation of fluid collections in soft tissues and joints as well as in muscles.



Joint movement can also be visualized on dynamic US imaging. Ultrasound can distinguish between synovial fluid/joint effusion, which is compressible, and synovial hypertrophy, which is not,<sup>14</sup> although both may appear hypoechoic on gray-scale sonography. Ultrasound can also detect intraarticular crystals.

Unlike MRI, US evaluation of joints and soft tissues can be performed without sedation or anesthesia, which is often required when performing MRI on children or very anxious adults.

Diagnostic musculoskeletal US is cost effective. In 2008, a paper in the *Journal of the American College of Radiology* estimated that substituting US for MRI, when appropriate, in the Medicare population alone could result in savings of more than \$6.9 billion between 2006 and 2020.<sup>15</sup> In 2017, a different study of the use of US and MRI looked at the actual utilization trends of MRI and US for musculoskeletal problems in the Medicare fee-for-service population. The study reported that, between 2003 and 2007, MRI use increased about 9.5% per year but after 2007, MRI use increased only .6% per year. Between 2003 and 2015, the use of US for musculoskeletal problems increased by 347%. Unlike MRI, US utilization continued to increase during the study period. The authors concluded that US had not decreased the use of MRI as much as was predicted in 2006 but rather had slowed its growth.<sup>16</sup>

The clinical use of US for the evaluation of musculoskeletal disorders is still in the relatively early stages of development. Indications for its use continue to grow as the equipment improves, the images become easier to interpret, and US training becomes more widely available and is incorporated into more rheumatology fellowship programs. At this time, the literature consists mostly of small studies, often using only one manufacturer's US equipment. Larger, multicenter studies are needed to standardize both image acquisition and interpretation and to clarify the precise clinical scenarios wherein US adds value to care.

Outcome Measures in Rheumatology (OMERACT) established the OMERACT Ultrasound Task Force in 2004. In 2005, the group published its first report, which included definitions of terms commonly used in US (see Glossary).<sup>17</sup> In 2007, the Ultrasound Task Force reported on a systematic review of the literature to determine if US could be reliably used to measure synovitis in inflammatory arthritis involving the hand, wrist, elbow, shoulder, knee, ankle, and posterior foot.<sup>18</sup> The findings indicated that additional study of US scanning protocols and interpretation was needed. At OMERACT 9, the Task Force also reported an insufficient number of quality studies of US scanning protocols and the lack of definition of terms in the literature.<sup>19</sup> The Task Force noted that individual centers or practices used scanning protocols, definitions, and scoring systems developed at their own centers or practices and that standardization of protocols and definitions was lacking, making the comparison of studies very difficult. (For more information on the findings of OMERACT 9, see D'Agostino et al.<sup>19</sup>). The Task Force also decided to initially focus on RA and develop standards for scanning and reporting results, including a scoring system for synovitis.

In 2017, the EULAR-OMERACT Ultrasound Task Force published two important papers describing the methodology used in the development of a scoring system for the evaluation of synovitis in patients with RA. The scoring system is consensus-based and has been reported to be reliable.<sup>11, 20</sup>

The use of this system can provide an objective outcome measure for synovitis. It includes four grades of synovitis (0-3), each of which has two components: gray-scale ultrasound, also referred to as synovial hypertrophy (SH), and power Doppler (PD). The scores are added to determine the severity of synovitis

(Table 1).<sup>11, 20</sup> The scoring system does not assess for the presence of effusions and is based on bilateral longitudinal US studies.<sup>11, 20</sup> For more detail on the scoring system and excellent demonstrations of the US images, the reader is referred to the EULAR-OMERACT Ultrasound Task Force articles by D’Agostino et al. and Terslev et al.<sup>11, 20</sup>

**Table 1. EULAR-OMERACT scoring system for RA**

Synovial Grade	Synovial Hypertrophy (SH)	Power Doppler (PD)	Combined Score
0	0	None	0
1 (minimal)	Hypoechoic SH up to a line drawn connecting the dorsal surfaces of the head of the metacarpal bone and the proximal phalanx	<ul style="list-style-type: none"> <li>• Up to 3 Doppler spots Or</li> <li>• Up to 1 confluent spot and 2 single spots Or</li> <li>• Up to 2 confluent spots</li> </ul>	<ul style="list-style-type: none"> <li>• Grade 1 hypoechoic SH and &lt; Grade 1 PD</li> </ul>
2 (moderate)	Hypoechoic SH that extends above a line drawn connecting the dorsal surfaces of the head of the metacarpal bone and the proximal phalanx with the upper surface being flat or concave	<ul style="list-style-type: none"> <li>• Doppler signal &gt; Grade 1 but &lt; 50% of the SH-containing Doppler signals</li> </ul>	<ul style="list-style-type: none"> <li>• Grade 2 SH and &lt; Grade 2 PD Or</li> <li>• &lt; Grade 1 SH and Grade 2 PD</li> </ul>
3 (severe)	Hypoechoic SH which extends above a line drawn connecting the dorsal surfaces of the head of the metacarpal bone and the proximal phalanx with a convex upper surface	<ul style="list-style-type: none"> <li>• &gt;50% of the SH-containing Doppler signals</li> </ul>	<ul style="list-style-type: none"> <li>• Grade 3 SH and &lt; Grade 3 PD Or</li> <li>• Grade 1 or 2 SH and Grade 3 PD</li> </ul>

EULAR, European League Against Rheumatism; OMERACT, Outcome Measures in Rheumatology; RA, rheumatoid arthritis

The grading system for synovitis in patients with RA in Table 1 is an important first step in US reporting and standardization. Unfortunately, at this time, there is no guidance on how to incorporate this scoring system into an overall determination of disease activity. Many practicing rheumatologists may interpret the presence of any Doppler signal in an area of synovial hypertrophy as inconsistent with complete remission despite a clinical score indicating remission. Others may consider a score of 1 as evidence of low disease activity (LDA) in a patient with full remission according to a clinical scoring system. However, there **is no validated** method for using the grade of synovitis along with the clinical score to guide management at this time.

## Diagnostic Musculoskeletal Ultrasound

When a new imaging modality is introduced to any medical practice, there must be good evidence that it improves patient care. Over the last 2 years; many reports have indicated the superiority of US when compared to plain films and even MRI for the diagnosis of synovitis; bone erosions; and pathology of tendons, ligaments, cartilage, and even peripheral nerves.<sup>21</sup> However, additional research is needed to determine when and how often US is optimally employed for the diagnosis of rheumatic diseases or for monitoring therapeutic response.

In 2012, the ACR issued their *Report on Reasonable Use of Musculoskeletal Ultrasonography in Rheumatology Clinical Practice*.<sup>22</sup> The authors did not use the term “appropriateness” as defined by the RAND Healthcare/University of California at Los Angeles (RAND/UCLA) *Appropriateness Methodology*, because the Task Force Panel was of the opinion that the published literature was incomplete. Instead, decisions were based on a review of the literature and expert consensus. According to the ACR, “reasonable” indications for diagnostic US represent clinical circumstances when the “evidence and/or consensus of the Task Force Panel supported the use of ultrasound for the described scenario” (Page 1626).<sup>22</sup>

The ACR Task Force Panel found that the use of US is reasonable in the following clinical scenarios, when the diagnosis is uncertain:<sup>22</sup>

- Joint pain and swelling or mechanical complaints
- Arthralgia(s)
- Known inflammatory arthritis, together with new or continuing symptoms (to evaluate for disease activity, and bone or cartilage erosions)
- Hip pain or mechanical symptoms (to evaluate for fluid, intra- or periarticular lesions, or surrounding soft-tissue abnormalities)
- Periarticular pain (to evaluate for tendon and soft-tissue disease)
- Probable inflammatory enthesal, sacroiliac, or spine pain (to evaluate for enthesopathy)
- Shoulder pain or mechanical symptoms (to evaluate for structural disease, but not to evaluate for adhesive capsulitis or preoperative evaluation)
- Regional mechanical complaints (to evaluate for inflammation, or tendon and soft-tissue abnormalities)

- Regional neuropathic pain (to diagnose carpal tunnel syndrome [CTS], or ulnar- or posterior tibial-nerve entrapment)
- Monitoring of disease activity or structural progression in patients with inflammatory arthritis
- Anatomic limitations to physical examination of a joint due to obesity or local abnormalities of the surrounding soft tissues
- Image guidance for periarticular or articular injections or aspirations
- Image guidance for a synovial biopsy
- Evaluation of the parotid or submandibular glands in patients being evaluated for Sjögren's syndrome

The Task Force Panel indicated that US should not be used for the evaluation of the temporomandibular joint and the costochondral joints, unless otherwise indicated.<sup>22</sup>

### *Definition of Important Ultrasound Findings*

The OMERACT definitions<sup>17</sup> for the most important US findings in rheumatologic diseases are provided in the Glossary.

### *Rheumatoid Arthritis*

There is no definitive test for the diagnosis of RA. The diagnosis is based on clinical evaluation. Early in the course of the disease, symptoms may be subtle, and X-rays (which are currently standard for RA) may be normal. Current diagnostic criteria depend on the identification of at least one joint with clinical evidence of synovitis with no other clinical explanation (see the *United Rheumatology Clinical Practice Guideline—Rheumatoid Arthritis—Adult*). Recent publications have demonstrated that the clinical evaluation for synovitis can miss significant inflammation when compared to US, potentially delaying diagnosis and treatment.<sup>23-25</sup> In its most recent set of criteria for the diagnosis of RA, the ACR defines an “involved joint” as “any joint with swelling or tenderness on examination that is indicative of active synovitis” (Page 2576).<sup>26</sup> The criteria further state that US can be used to confirm the clinical diagnosis. However, US can diagnose synovitis in clinically normal joints. Using the ACR definition, some joints with active synovitis can be missed, if US is not performed.

In patients with RA, US is used primarily to detect and assess joint inflammation and damage manifested by synovial hypertrophy, synovial fluid/effusion, and synovitis.<sup>21</sup> Synovial fluid usually appears as an anechoic, compressible collection within the joint capsule at US. However, at times, synovial fluid may appear hypoechoic. Synovial hypertrophy is typically hypoechoic, although it may appear as either anechoic or hyperechoic material within and/or adjacent to the joint capsule. Synovial hypertrophy is non-compressible. Both synovial fluid and synovial hypertrophy are initially evaluated on gray-scale US. Power Doppler is then used to further evaluate the synovial space. Increased Doppler signal (increased vascularity) in an area of synovial hypertrophy indicates that there is active synovitis rather than simple hypertrophy. Power Doppler signal is not found in synovial fluid or a joint effusion. Sonography can also be used to detect bone erosions, if the proper equipment is used (high-frequency transducers).

Establishing the presence of both synovitis and bone erosions in early RA can be challenging. Already in the year 2000, Wakefield et al.<sup>12</sup> published a study comparing US to plain films for the diagnosis of erosions at the metacarpal phalangeal joints in 100 patients with RA. Of these patients, 40 had early disease and 60 had late disease. The control group included 20 patients with no evidence of RA. The study used a complete video (real-time examination) of the sonogram rather than hard copies, with selected images by the person performing the examination. Ultrasound found 127 erosions in 56 of the 100 patients with RA. Plain films found only 32 erosions in 17 of these patients. Of the erosions detected on X-ray, 81% were also seen on US. In the group of patients with early RA (n=40), US found 39 erosions; plain films only 6. In the group of patients with late RA (n=60), US found 88 erosions and plain films only 26. The study concluded that US detected more erosions in both early and late disease than plain films.

A case-controlled study of 40 patients with RA and 20 controls evaluated the sensitivity, specificity, and accuracy of US versus other imaging modalities for the evaluation of bone erosions and inflammation in finger joints.<sup>27</sup> The study demonstrated that US has greater sensitivity and accuracy than either clinical examination or radiographs for the detection of bone erosions and/or synovitis in the fingers. In this study, erosive disease was found in 13 patients on X-ray and in 20 patients with both MRI and US.

Another study also involving 40 patients with RA found that power Doppler detected synovitis better than clinical examination (swollen and/or tender joints).<sup>28</sup> In this study, one proximal interphalangeal or metacarpophalangeal joint was evaluated in each patient. Patients were equally divided into four groups: tender joint only, swollen joint only, tender and swollen joint, and clinically unremarkable joint. Power Doppler demonstrated that the tender-joint-only group showed less vascularity than patients in either the swollen-joint-only or the tender-and-swollen-joint groups. Power Doppler also found synovitis in joints that were clinically unremarkable (neither tender nor swollen), again demonstrating that clinically normal joints may have active synovitis.

Ten Cate et al.<sup>29</sup> published a systematic review of the role of US in the diagnosis of early RA and remission; and concluded that power Doppler of metacarpophalangeal joints, the wrist, and metatarsophalangeal joints was helpful in establishing the diagnosis of RA by demonstrating clinically silent synovitis. The review also found that power Doppler scanning of the metacarpophalangeal joints of the dominant hand had value when assessing patients for remission.<sup>29</sup> Some patients in clinical remission actually showed signs of inflammation on US.<sup>30</sup>

In 2016, a systematic review of US for the detection of bone erosions was published.<sup>31</sup> Fifty-eight publications were selected for review, with 79% of the papers defining bone erosions, but only 17 using the OMERACT definition of erosions. The most common joints scanned were finger and toe joints; wrists, shoulders, and knees were investigated less frequently. The review found a lack of agreement among researchers on how to score erosions. The review also identified a lack of consensus on how to evaluate progression of erosions. The authors suggested that US was useful for the detection of bone erosions but additional work was needed to develop a valid system for scoring them. In 2013, EULAR published ten *Recommendations for the Use of Imaging of the Joints in the Clinical Management of Rheumatoid Arthritis* that included the following information regarding US:<sup>32</sup>

- Imaging with conventional X-ray, US, or MRI provides information that can improve the certainty of the diagnosis of RA, when the clinical information is unclear.
- US (and MRI) can demonstrate inflammation that is helpful in predicting which patients will progress from early, undifferentiated inflammatory arthritis to RA.
- **Joint inflammation is better detected with US (or MRI) than with X-ray or clinical examination.**
- Initial imaging of patients with clinically definite or possible RA should be done with X-rays of the hands and feet. **If these films are negative then US (or MRI) may be useful to detect joint damage before it can be seen on plain films resulting in earlier, more intense treatment with the goal of preventing joint destruction.**
- Imaging can be used to predict response to treatment. Inflammation seen on US (or MRI) may be a better predictor of response than clinical evidence of disease activity.
- **US (and MRI) may be used to monitor disease activity, because they detect inflammation earlier than clinical examination.**
- Interval radiographs of the hands and feet may be helpful in evaluating joint damage, but because **US and MRI are both more sensitive than X-ray at detecting joint damage, they can be used to monitor disease activity.**
- **US (and MRI) can detect inflammation, even in a subset of patients determined to be in clinical remission.**

Baseline X-rays of the hands and feet should be obtained at the time of initial evaluation for suspected RA. However, because US has been demonstrated to be more accurate than radiographs in identifying erosions, it may be considered in addition to plain films, especially when the diagnosis is uncertain or radiographs are normal.

### *Ultrasound Follow-up and Monitoring in Rheumatoid Arthritis*

The earlier the diagnosis of RA is established and treatment initiated, the better the outcome.<sup>33-35</sup> When treating patients with RA, the target is complete remission or LDA (see the *United Rheumatology Clinical Practice Guideline—Rheumatoid Arthritis—Adult*). Current therapy can achieve remission in many patients; others may achieve LDA, which is also an acceptable target in those with complicated comorbidities or in patients who cannot reach remission.

Synovitis detected on US but not diagnosed on clinical evaluation can progress to X-ray-detectable joint destruction, even in patients who meet the ACR definition of remission. A study with a cohort of 90 patients with RA in clinical remission reported that, over time, 63% had radiographic joint changes, 68% had US evidence of bone erosions, 89% had US detectable synovial hypertrophy, and 63% had power Doppler evidence of increased blood flow (hyperemia) consistent with synovitis not found on clinical examination.<sup>36</sup> This study demonstrated that US was more sensitive than either clinical examination or radiography for the diagnosis and management of patients with RA, and that US may be helpful for the identification of patients who, despite clinical remission, are at risk for the development of bone destruction and flares.

Nguyen et al.<sup>37</sup> published a systematic literature review that included 19 studies involving 1618 patients with RA, 1369 of whom were in remission. The analysis found that 44% of patients in clinical remission had power Doppler evidence of synovitis. The presence of power Doppler signal (synovitis) in patients in clinical remission can predict which patients may relapse, develop flares, or experience progressive bone destruction. This problem was addressed in the EULAR recommendations for imaging in RA (see above).<sup>32</sup>

Molenaar et al.<sup>38</sup> followed 187 patients with RA who had been in clinical remission (according to both, ACR criteria<sup>39</sup> and the Disease Activity Score based on 28 joints [DAS28]) for 2 years with plain films. At the end of 2 years, only 52% of these patients remained in remission. In 15% of those who remained in remission, erosions developed in previously normal joints. The radiographic progression seen in patients in clinical remission may be related to the presence of synovitis that is not detected on clinical evaluation but is detected on power Doppler.

A recent study comparing clinical and imaging remission in patients with early RA, who were managed with a treat-to-target (T2T) approach, demonstrated that 43% achieved a clinical remission as defined by DAS28 and C-reactive protein (CRP).<sup>40</sup> However, within this group, only 42% had no power Doppler activity in the synovium when in clinical remission. This finding is consistent with the other studies cited above and suggests that a significant number of patients with RA who have achieved clinical remission may not actually be in complete remission but rather in a subclinical remission. These patients may require a different treatment approach to achieve a complete remission.

Tenosynovitis is another manifestation of RA that can lead to discordance between clinical remission and symptoms.<sup>41</sup> In fact, US evidence of tenosynovitis was recently found to predict a shorter duration of clinical remission in 427 patients with RA.<sup>41</sup>

Many papers have recognized the significantly increased risks for patients with RA in clinical remission but with US evidence of subclinical synovitis, particularly as identified by power Doppler signal.<sup>36, 37, 42, 43</sup> Related risks include RA flares, development of radiographic erosions, and failure to maintain remission upon tapering of medications. However, studies are lacking that demonstrate the appropriate interval at which US should be repeated.

Two recent studies (TaSER and ARTIC) compared clinical remission by DAS28 to imaging remission with US in a T2T strategy and reported that using US did not lead to significantly better outcomes than conventional disease-activity assessment (clinical remission).<sup>44, 45</sup> A trend towards improved clinical outcomes in the US-directed treatment group was identified in one of the studies.<sup>44</sup> Both studies reported increased use of biologics and increased cost of treatment for the US groups when compared to the clinical disease-activity groups. Thus, neither the TaSER<sup>44</sup> nor the ARTIC<sup>45</sup> study supported the use of US remission as the end point for achieving the treatment target in patients with early RA. Each study has been criticized for issues related to the methodology employed. The TaSER study,<sup>44</sup> which demonstrated a trend towards better outcomes among those treated according to a US-T2T approach was likely under-powered. When coupled with the trend toward better remission rate for the US group, the results suggest that a larger sample size may have demonstrated superiority of US over clinically-driven T2T. In the ARCTIC trial,<sup>45</sup> every inflamed joint was treated with a US-guided steroid injection at each study visit, an approach that diverges significantly from and is not reflective of RA treatment practices in the United States. The aggressive,

longitudinal, intraarticular corticosteroid injection treatment was applied asymmetrically to the treatment arms of the trial; as all joints with Doppler activity in the US-T2T arm were injected; while all patients in either arm with overt, clinical evidence of synovitis were injected. The impact of longitudinal US-guided steroid injection on the long-term course of RA, and the resulting impact on the ARCTIC trial results, remains unclear. Regardless, there are other studies (cited above) that document disease progression (development of bone erosions) in patients in clinical remission but with evidence of subclinical synovitis on US. Therefore, in patients with RA who are in clinical remission, screening with US may be considered, because it provides additional data to assist in treatment decision making, including drug escalation or tapering.

Another study described the histologic differences of the synovium in patients with RA who were in clinical remission but had no power Doppler evidence of synovitis compared to patients with RA who were in clinical remission with power Doppler evidence of synovitis.<sup>46</sup> The latter group showed evidence of high macrophage infiltration of the synovium, which is usually seen in patients with active RA. However, unlike patients with active RA, other patients had either reduced levels of lymphocyte and/or mast cell infiltration or demonstrated fibroblastic hyperplasia in the synovium. The authors postulated that the persistently increased level of macrophages in the synovium may be responsible for flares and continued bone destruction in this subset of patients (see below).

### *Future Directions of Ultrasound in Rheumatoid Arthritis*

Four distinct synovial phenotypes have been described in another study of the synovium of patients with RA:

1. Lymphoid (B cell and plasmablast dominated)
2. Myeloid (macrophage dominated)
3. Low-inflammatory
4. Fibroid (hyperplastic tissue and little evidence of immune deposits)

Interestingly, all patients with either lymphoid or myeloid synovium types tested positive for rheumatoid factor (RF), 75% of the low-inflammatory phenotype patients were RF positive, but none of the fibroid phenotype patients. Each phenotype was defined by the presence of a distinct pattern of gene expression. Myeloid-type synovium was identified as having the highest levels of nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB). The lymphoid-synovial type had the highest expression of B cell- and plasmablast-associated genes that included Cluster of Differentiation (CD) 19, CD20, X-box binding protein 1 (XBP1), immunoglobulin (Ig) heavy and light chains, CD38, and C-X-C motif chemokine ligand 13 (CXCL13). In the fibroid-synovial type, there was low or no expression of these B cell-lineage activation markers. Rather, increased expression of genes associated with fibroblast and osteoclast/osteoblast regulation was found. Each phenotype responded differently to specific biologics used to treat RA.<sup>47</sup>

A more recent paper described only three synovial phenotypes in RA.<sup>48</sup>



1. High-inflammatory phenotype, which likely corresponds to what other authors have described as a myeloid phenotype, as it is characterized by infiltration of white cells
2. Low-inflammatory phenotype
3. Mixed phenotype

These groups were based on clustering of gene expression data designed to reflect specific, characteristic histopathologic features of rheumatoid as opposed to osteoarthritic synovium. The identified synovial subtypes bear similarities but are not identical to those described by Dennis et al.<sup>47</sup> above. Patients with the high-inflammatory synovial subtype had high serum levels of autoantibodies, acute-phase reactants, RF, and anti-cyclic citrullinated peptide (anti-CCP) antibodies.

Presently, synovial phenotypes cannot be determined without a biopsy; furthermore, although longitudinal studies of the response of patients with RA by synovial subtype have not been published, such studies will determine whether or not this observation is valuable for the treatment and monitoring of patients with RA. If such studies demonstrate a gradation in the aggressiveness of synovitis by synovial subtype (as is strongly suggested by the gene expression and pathologic differences based on which the subtypes were identified), then the utility of US for monitoring disease activity in RA will be determined largely by the ability of US to distinguish the sonographic features of more aggressive synovitis associated with a risk of progression to erosions from sonographic features of more inert synovitis with less aggressive potential.

United Rheumatology will continue to review the literature for studies that correlate US-signatures of specific synovial phenotypes that impact the management of patients with RA and recommend specific US protocols that best identify the sonographic features of synovitis associated with the risk of disease progression.

### *Limitations of Ultrasound in Rheumatoid Arthritis*

A validated US scoring system for RA and synovitis along with a standardized protocol for imaging and repeat imaging is needed. In addition, a standardized method for incorporating the US results into disease activity scores is needed.<sup>40,41</sup> Also see the above discussion of the OMERACT/EULAR US scoring system and the joint papers on this issue by D'Agostino et al. and Terslev et al.<sup>11, 20</sup> The most commonly utilized US scoring system<sup>49</sup> at this time is the approach described by Szkudlarek et al.<sup>50</sup> This approach scores synovitis using power Doppler and gray-scale imaging for synovial fluid/hypertrophy according to separate scales. However, United Rheumatology suggests adoption of the OMERACT/EULAR system (see above), although that there is no current guidance on how to incorporate the results into disease activity scores. It is important to begin the process of standardization of synovitis scoring so that clinical results can be compared, both in practice and clinical studies.

### *Ultrasound in Rheumatoid Arthritis (Summary/Conclusions)*

Ultrasound is a useful adjunct to the clinical parameters used to establish the diagnosis of RA. Although imaging protocols of the hands, wrists, and feet are still evolving; US can be particularly effective in

resolving uncertainty in patients with joint complaints but no evidence of synovitis on clinical examination. Ultrasound may also be helpful in evaluating patients in clinical remission (US demonstrates synovitis and possible new erosions better than clinical examination or plain films) to determine which patients are in a more robust, clinical and imaging remission as opposed to those who continue to demonstrate subclinical inflammation. The standardization of a scoring system for synovitis for patients with RA,<sup>20</sup> which is in an early stage of development, holds great promise to assist rheumatologists in determining which patients are truly in remission or at LDA by combining the Clinical Disease Activity Index (CDAI) scoring system (preferred by United Rheumatology) with a US scoring system.

United Rheumatology will continue to monitor the literature and update these guidelines as appropriate. The *United Rheumatology Clinical Practice Guideline—Rheumatoid Arthritis—Adult* provides a more complete discussion of the diagnosis and management of patients with RA.

## *Psoriatic Arthritis*

Psoriatic arthritis (PsA) affects up to 30% of patients with psoriasis.<sup>51, 52</sup> A wide spectrum of musculoskeletal changes can be seen in patients with PsA; including arthritis of the distal interphalangeal joints of the hands and feet, sacroiliitis, seronegative symmetric polyarthritis (which is indistinguishable from RA), oligoarthritis, spondyloarthritis, enthesitis, and dactylitis<sup>14</sup> (see the *United Rheumatology Clinical Practice Guideline—Psoriatic Arthritis*).

### *Ultrasound for the Diagnosis of Psoriatic Arthritis*

Ultrasound findings in the peripheral joints of patients with PsA are nonspecific, as they may be seen in other forms of inflammatory arthritis such as RA and gout. Three of the most important areas to evaluate in patients with PsA are joints (including but not limited to an evaluation for erosions, synovitis, and fluid), entheses, and tendons.<sup>53, 54</sup> Gutierrez et al.<sup>53</sup> also suggested that evaluation of the skin and nail beds should be considered; however, this remains controversial.

Conventional X-rays are very often used to assist in the diagnosis and monitoring of PsA. However, both US and MRI have been found to be more sensitive than either plain films or clinical evaluation for the detection of inflammatory joint changes (synovitis, tenosynovitis), enthesitis, new bone formation, bone erosions, destructive bone lesions (osteolysis), and dactylitis.<sup>52, 55-57</sup> Ultrasound can be employed for the diagnosis of PsA as well as for monitoring therapeutic responses.<sup>53</sup>

Ultrasound findings in PsA include:<sup>56</sup>

- Synovial fluid collections—usually anechoic compressible collections within the joint
- Synovial hypertrophy—commonly hypoechoic material in and/or around the joint that is not compressible and rarely may be hypo- or hyper-echoic and does not contain power Doppler signal
  - Synovitis—gray-scale and/or power Doppler signal in areas of synovial hypertrophy
- Tenosynovitis—hypoechoic or anechoic thickening of the tendon, which may be accompanied by anechoic fluid in the tendon sheath. The findings must be seen in two orthogonal planes. Power Doppler signal may or may not be present.

- Tendinosis—disruption of the normal echotexture of the tendon
- Enthesitis—hypoechoogenic and/or thickened entheses with power Doppler signal
- Dactylitis—flexor tenosynovitis of a digit plus metacarpophalangeal and/or metatarsophalangeal, proximal interphalangeal, and distal interphalangeal synovitis

Gutierrez et al.<sup>53</sup> have reported that synovitis in the small joints of the fingers and toes is best imaged with a high-frequency probe.

A high-frequency transducer is also required for the evaluation of inflammatory changes at the entheses. Ultrasound may show thickening or hypoechoogenicity or intratendinous edema. In later stages, bone erosions or enthesophytes may be seen.<sup>53</sup>

D'Agostino and Terslev<sup>58</sup> have described enthesitis on gray-scale US as the presence of any of the following findings demonstrated within 2 mm of the bone surface:

- Hypoechoogenicity of the insertion of the tendon/ligament or capsule into the bone
- Increased thickness of the tendon/ligament or capsule at the point of insertion into the bone when compared to the body of the tendon/ligament or capsule with or without blurring of the margins of the tendon/ligament or capsule
- Calcifications or fibrous scars in the tendon/ligament or capsule insertion into bone (demonstrated in two orthogonal planes)
- Erosions (defect in the bony cortex) in two perpendicular planes
- Cortical irregularities with loss of the normal bone contour and no sign of an erosion or enthesophytes
- Doppler signal detected at the cortical insertion of an enthesis

The clinical significance of these findings is unclear, especially in asymptomatic patients.

Dactylitis or so-called “sausage digit” occurs in up to 48% of patients with PsA and is described as inflammation of the entire digit with diffuse swelling, pain, and tenderness.<sup>59</sup> It is one of the **CIAS**sification criteria for **P**soriatic **AR**thritis (CASPAR) classification criteria for the diagnosis of PsA and is often associated with progressive disease. On US, dactylitis appears as diffuse swelling of the subcutaneous soft tissues with flexor tenosynovitis and synovitis.<sup>60</sup>

In a systematic review of the literature, Bakewell et al.<sup>61</sup> reported that flexor-tendon tenosynovitis and joint synovitis were the most common MRI and US findings in dactylitis. This is considered to be an important imaging feature of PsA; however, according to Husic et al.,<sup>56</sup> it is diagnosed more frequently on clinical examination than on US.

Delle Sedie et al.<sup>62</sup> published a study of both knees in 83 patients with known PsA and reported that, on clinical examination, 62 of the 168 knees examined had evidence of active arthritis. Ultrasound with power Doppler found evidence of active synovitis in 70 knees, once again indicating that US detects subclinical active disease in clinically unremarkable joints. In addition, enthesitis was found in 39.7% of the patients.

### *Ultrasound in the Distinction of Psoriatic Arthritis from Rheumatoid Arthritis and Other Forms of Inflammatory Arthritis*

A number of studies have attempted to distinguish the US appearance of patients with PsA from those with RA. Using gray-scale and power Doppler, synovitis of the metacarpal phalangeal joints was found less often in PsA than in RA.<sup>63</sup>

Fournié et al.<sup>64</sup> studied the US findings in 25 fingers of patients with PsA and 25 fingers of patients with RA to determine whether power Doppler imaging of the finger (a common place for bone erosions and destruction in both PsA and RA) could demonstrate differences between these two types of inflammatory arthritis. The scans were performed with a high-frequency transducer and included imaging of the dorsal, volar, and lateral aspects of the fingers. Ultrasound detected extrasynovial abnormalities (enthesitis, enthesopathy of the deep flexor tendon insertion) in many of the PsA fingers but in none of the RA fingers. Based on these findings, the authors concluded that erosive synovitis and tenosynovitis occur equally in both PsA and RA. However, enthesopathy of the fingers was only seen in patients with PsA and thus may distinguish the two conditions.

Another study comparing US findings in patients with PsA and RA reported that PsA was associated with more bone erosions, bone destruction, and synovitis in the distal interphalangeal joints than RA. Hyperostosis was also shown to occur more frequently in PsA than RA.<sup>55</sup>

A 2015 study found that the prevalence of synovitis, bone erosions, and joint effusions were similar in patients with RA and those with PsA.<sup>65</sup> However, the authors also reported no evidence of tenosynovitis in the RA group as compared to a 69.9% incidence of tenosynovitis in the PsA group. In addition, soft-tissue inflammation was found in none of the patients in the RA group but in a large number of those in the PsA group. No dactylitis was seen in the RA group, but many patients in the PsA group had soft-tissue inflammation and thickening with increased blood flow on power Doppler consistent with dactylitis. Enthesitis was found in 34.5% of the patients with PsA and in none of those with RA.

In addition, Gutierrez et al.<sup>53</sup> reported evidence of peritendinous inflammation in only 4 of 83 patients with RA, whereas it was found in 54 of 82 patients with PsA. The authors proposed that the finding of peritendinous inflammation strongly suggests a diagnosis of PsA (and not RA) in clinically difficult or confusing cases.

Enthesitis may be asymptomatic or present clinically with pain and tenderness when pressing on the enthesis. In a study of 40 patients with PsA, 40 with RA, and 80 control subjects, US was found to detect the presence of enthesitis more accurately than clinical examination.<sup>66</sup> In this study, sonography was performed in both the transverse and longitudinal planes using a high-frequency transducer. The quadriceps enthesis was examined with the knee extended at rest, with contraction, and in 30° flexion. The authors considered enthesitis to be present, if US showed at least one of the following:<sup>66</sup>

- Heterogeneous decreased echogenicity and thickening of the enthesis
- A >2-mm irregularity of the patella
- Enthesophytes >5 mm in size
- Bone erosions

Additional studies are needed to determine whether PsA can be differentiated from other forms of inflammatory arthritis by the anatomic distribution of the involved joints using US.<sup>55, 67</sup>

### *Ultrasound Findings in Patients with Psoriasis Without Psoriatic Arthritis*

In 2011, Naredo et al.<sup>68</sup> published the results of a study designed to evaluate the presence of synovitis, tenosynovitis, and enthesitis diagnosed by US in patients with psoriasis but no clinical evidence of PsA in comparison to a group of age-matched controls with other skin disorders and no known musculoskeletal disorders. Synovitis, although generally low in both the psoriasis cohort and the control group, was almost three times greater in psoriasis group than the control group (3.2% vs 1.2%). Enthesopathy was found by US in 11.6% of the patients in the psoriasis group and 5.3% of those in the control group. Increased vascularity detected by US in the studied entheses was seen only in the psoriasis group. The authors suggested that additional studies are needed to investigate whether the presence of synovitis and enthesopathy in patients with psoriasis and no musculoskeletal problems could be predictive of developing PsA in the future.

### *Ultrasound Monitoring in Psoriatic Arthritis*

A recent study suggests utility of US monitoring patients with PsA who appear to be responding well to treatment. Of 54 patients with PsA in clinical remission or with minimal disease activity at baseline, power Doppler evidence of synovitis predicted the need for advancing treatment due to an increased risk of disease flare over the next 6 months. Of those with synovitis at baseline detected by power Doppler, 65% (13 of 20) required escalation of treatment as opposed to just 5.9% (2 of 34) of those without synovitis.<sup>69</sup>

Additional studies are needed to score US findings in patients with PsA and to compare them to other disease activity scores, to determine when a patient is in complete remission.

### *Ultrasound in Psoriatic Arthritis (Summary/Conclusions)*

The use of US for the diagnosis and assessment of response to treatment in patients with PsA is still evolving. Currently, there is little standardization of technique and reporting. Most of the more recent studies indicate the need for >10-MHz transducers to perform an accurate US examination of small joints for synovitis.<sup>65</sup>

United Rheumatology believes that sonographic evaluation of patients with known or suspected PsA may be helpful for establishing a diagnosis and following response to treatment. United Rheumatology will continue to monitor the literature and update the guideline as appropriate. The *United Rheumatology Clinical Practice Guideline—Psoriatic Arthritis* provides a more complete discussion of the diagnosis and management of patients with PsA.

## *Osteoarthritis*

Osteoarthritis (OA) is the most common form of arthritis and the most common cause of disability, loss of productivity, and absenteeism from work due to a rheumatological disorder.<sup>70</sup> It is characterized by osteophyte formation; loss of cartilage; and damage to ligaments, tendons, menisci, joint capsules,

bursae, and synovial tissue. Under normal conditions, there is an equilibrium between cartilage destruction and cartilage synthesis in joints. When cartilage destruction exceeds synthesis, OA can develop.<sup>71</sup>

### *Ultrasound in the Diagnosis of Osteoarthritis*

Conventional X-rays have been the most common imaging modality used for evaluating joint changes in OA. X-rays can demonstrate joint-space narrowing, bone erosions, and osteophyte formation. However, unlike MRI and US, X-rays cannot evaluate joint cartilage, periarticular soft tissue, joint capsules, tendons, ligaments, bursae, menisci, and synovium. Narrowing of the joint space thought to be secondary to loss of cartilage is one of the earliest conventional X-ray findings in OA.

The diagnosis of OA is often delayed (see the *United Rheumatology Clinical Practice Guideline—Osteoarthritis of the Knee*). Initially, patients may be asymptomatic, despite cartilage loss and joint-space narrowing, and do not seek medical care until they experience pain and/or stiffness or decreased function in one or more joints. Less commonly, in earlier stages of the disease, patients with symptoms may have normal X-rays, and OA is not recognized, unless additional clinical examination findings are present or advanced imaging testing is pursued. Ultrasound can be used as an adjunct to conventional X-rays and clinical examination, especially when there is a need to visualize soft tissue of the joints.<sup>72</sup> On US, normal articular cartilage appears as a homogeneous anechoic curved band, which has a sharp, regular, anterior margin. The posterior margin is more echogenic and represents the interface between the articular cartilage and the bone.<sup>73</sup> Early anatomic changes of OA in asymptomatic patients can be seen as areas of increased echogenicity within the anechoic band of articular cartilage, with loss of the sharp superficial margin. Destruction progresses to focal thinning of the articular cartilage, readily visible on US but not necessarily on conventional X-ray. Later in the disease process, there may be episodes of synovitis (areas of synovial hypertrophy with increased vascularity on color Doppler) and accumulation of joint fluid/effusion, all of which can be documented by US. Joint-capsule thickening and osteophytes can also be detected with US.<sup>73</sup>

The knee is commonly involved in patients with OA. To visualize the maximum amount of weight-bearing cartilage, it is helpful to scan the knee flexed to the greatest pain-free position possible. Ultimately, the articular cartilage becomes narrowed or completely destroyed. Intermittent synovitis can be diagnosed and monitored by visualizing thickening of the synovium (usually measured in the suprapatellar bursa, and measuring 2-3 mm) and evidence of increased vascularity on power Doppler. Ultrasound evaluation of the lateral and medial joint margins can demonstrate bone irregularities of both the distal femur and proximal tibia. In addition, joint effusions are often detected. Small effusions may be missed on clinical examination but can be seen with US. Most frequently, effusions are anechoic, but loose bodies may be seen. Proteinaceous material or crystals in a joint effusion result(s) in a heterogeneous appearance on US. Fine debris in an effusion may be seen after intraarticular steroid injections. Baker's cysts (popliteal cysts), which can vary in size, may also be seen in patients with OA of the knee. At times, US can demonstrate communication of these cysts with the knee joint.<sup>74</sup>

Naredo et al.<sup>75</sup> published the results of a study of 50 patients with OA of the knee, ten of whom were asymptomatic in one knee. The asymptomatic knees were used as controls. The investigators compared

the results of clinical examination (including the anserine insertion), plain films, and US. All US examinations were performed with high-frequency linear array probes using a predefined protocol. Details of the US technique can be found in the Naredo et al. paper.

The following findings were detected in the 90 symptomatic knees of patients participating in this study and were associated with both mechanical knee pain and pain at rest:<sup>75</sup>

- Effusions 47.7% (maximum anteroposterior diameter of the suprapatellar recess >4 mm)
- Baker's cyst (fluid in the gastrocnemius-semi-membranous bursa) with a transverse diameter of >4 mm); when ruptured, it usually points distally 22.2%
- Protrusion (extrusion) of the medial meniscus (distance from the peripheral border of the meniscus to the outline of the tibial plateau >2 mm) and displacement of the medial collateral ligament 61.6%

The authors reported that all of these findings were associated with knee pain in OA. In this study, the presence of an effusion was associated with pain on motion and at rest, regardless of the radiographic findings. In addition, the authors suggested that protrusion or extrusion of the medial meniscus may, in part, explain the joint-space narrowing seen on plain films. Further study is required.

A more difficult diagnostic problem is the evaluation of the painful hip with normal plain films. Hip effusions or synovitis may be detected by US in these patients. A distance of >7 mm between the hip joint capsule and the femur, or a difference of >1 mm distance between the joint capsule and the femur between the left and right hips indicate the presence of synovial fluid or synovial hypertrophy. Irregularity of the femoral head and neck and marginal osteophytes can also be seen on US of the hip. Anatomically, the articular cartilage of the hip cannot be visualized in its entirety by US.<sup>73</sup>

Sonography has been found to be helpful in the evaluation of other joints, including the wrist and hand; especially of the first carpometacarpal joint, which is commonly one of the first joints to be affected by OA. This joint is usually scanned in anterior, lateral, and posterior longitudinal planes.

### *Ultrasound in Osteoarthritis (Summary/Conclusions)*

The role of US in the evaluation of OA is evolving. There is no standardized protocol for imaging and no validated US-based scoring system. In addition, there is no standard for when and how often US imaging should be performed. United Rheumatology recognizes that, despite these limitations, US can be a valuable adjunct to clinical and radiographic evaluations early in the course of the disease, especially when the diagnosis is unclear. It should **not be used routinely** for every patient with OA and, at this time, does not replace conventional radiographs for the evaluation of OA.

United Rheumatology will continue to monitor the literature and update the guideline as appropriate. The *United Rheumatology Clinical Practice Guideline—Osteoarthritis of the Knee* provides a more complete discussion of the diagnosis and management of patients with OA of the knee.

## Gout

Gout is an inflammatory arthritis with recurrent episodes of synovitis, joint swelling, and pain. It is most common in joints of the lower extremities, especially the first metatarsophalangeal joint. An estimated 4% of the United States population is affected by gout (see the *United Rheumatology Clinical Practice Guideline—Gout*).

Although flares may occur in patients with normal serum uric acid (sUA) levels, gout is typically associated with elevated levels of sUA (>6.0 mg/dL), which can be due to the overproduction of uric acid or decreased excretion by the kidneys. When the sUA concentration exceeds 6.0 mg/dL, crystals of monosodium urate (MSU) may be deposited in synovial fluid or in the soft tissues resulting in tophi. Not all patients with hyperuricemia or elevated sUA levels develop gout and, conversely, not all patients with gout have hyperuricemia.<sup>76</sup>

Currently, the definitive diagnosis of gout is established by demonstrating MSU crystals (intra- or extracellular) in synovial fluid or soft-tissue tophi. However, aspiration of an involved joint or soft-tissue mass is not always necessary, because the diagnosis may be established based on clinical presentation alone. In certain clinical circumstances; an attack of pain, swelling, and tenderness of a lower-extremity joint that reaches maximum intensity within 6 to 12 hours is highly suggestive of crystal-inflammatory arthritis and, if the first metacarpophalangeal joint is involved, particularly of gouty arthritis.<sup>77, 78</sup>

The 2015 Gout Classification Criteria (endorsed by both EULAR and the ACR)<sup>79</sup> require a score of ≥8 to establish a diagnosis of gout (see the *United Rheumatology Clinical Practice Guideline—Gout*). The demonstration of urate deposits in joints or bursae that have been symptomatic by either US or dual energy computed tomography (DECT) is equal to four points. The criteria also assign four points, if there is evidence of at least one gout-like erosion in either the hands or feet on conventional radiography (see the *United Rheumatology Clinical Practice Guideline—Gout*). Neither US (or DECT) nor conventional X-rays of the hands and/or feet are required to establish the diagnosis by these classification criteria, but they should be strongly considered when evaluating a patient with a clinical suspicion of gout.

### *Ultrasound for the Diagnosis of Gout*

Musculoskeletal US in gout may demonstrate any of a number of pathologic changes characteristic of gout. In addition to the detection of intraarticular urate deposits; US may also demonstrate intraarticular and/or periarticular abnormalities; including effusions, synovitis, bone erosions, tendonitis, bursitis, and changes in hyaline cartilage. In addition, soft-tissue changes such as tophi can be seen. The most common US findings in patients with gout include:<sup>80</sup>

- The “double contour sign” of the hyaline cartilage—focal or diffuse hyperechoic anterior margin of the hyaline cartilage, which may be slightly irregular. This sign is highly suggestive of gout, with a 43.7% sensitivity and 99% specificity for gout.<sup>81</sup> It is best seen in the knees and metatarsal and metacarpal joints. This sign may be present in asymptomatic hyperuricemic patients.



- Crystal deposition in synovial fluid, seen as hyperechoic spots measuring <1 mm floating in the synovial fluid, which may cause posterior acoustic shadowing, which is sometimes called a “starry sky.” When pressure is gently applied to the joint and then released, the hyperechoic foci will move, creating the appearance of a “snowstorm.”
- Tophus, seen as a hyper- or hypoechoic soft-tissue mass, which may result in posterior acoustic shadowing and is located in the soft tissue around a joint.
- Synovial hypertrophy, seen commonly as hypoechoic material in and/or around the joint, which is not compressible and rarely is iso- or hyperechoic without power Doppler signal. This is a nonspecific finding that can be seen in any inflammatory arthritis.
- Bone erosions, seen as breaks in the bony cortex, which can be very destructive. The sonographic findings of bone erosions must be visible in two perpendicular planes.<sup>6</sup>

A recent study compared the sensitivity and specificity of US to the gold standard, arthrocentesis, in 824 patients with possible gout. In patients with at least one swollen joint or a palpable subcutaneous nodule, the presence of either a double contour sign, a snowstorm appearance in the joint fluid, or a tophus on US accurately identified gout with a specificity of 84.3%, a sensitivity of 76.9%, a positive predictive value of 83.3%, and a negative predictive value of 78.2%.<sup>82</sup>

Effusions may be present in any inflammatory arthritis and are not specific for gout. They can be completely anechoic; as seen in RA, PsA, and the earliest stages of gout; however, with time, urate deposits in the joint fluid can be seen as hyperechoic foci.

Synovial hypertrophy is nonspecific for gout and, if power Doppler signal is detected, then synovitis is present. Synovitis is usually detectable before erosions are seen.<sup>80</sup> As in RA, small erosions are detected with US before they can be seen on conventional X-ray. The erosions in gout are usually deeper and more destructive than those in RA.

### *Ultrasound Monitoring in Gout*

In 2010, Thiele and Schlesinger<sup>83</sup> published a study of five patients with documented gout and evidence of MSU crystals in the joints who were treated with urate-lowering therapy (ULT). The researchers found that when sUA levels were 6 mg/dL or less for at least 7 months, US was able to demonstrate clearing of urate deposits in both synovial fluid and articular cartilage. The authors cautioned that a larger study was needed to establish whether or not US may be used to determine response to ULT. In addition, demonstration of the double contour sign may allow the provider to avoid arthrocentesis in acutely painful joints. However, if arthrocentesis is not done, it is important to be confident that the painful joint is not infected.

As with many patients with a rheumatologic disorder, adherence to pharmacologic therapy is frequently an issue in gout treatment. Ultrasound has been proposed as a means of following patients on ULT. A study published in 2015 indicated that US may have the potential to determine if a patient is adherent to treatment.<sup>84</sup> Sixteen patients with gout (all with elevated sUA levels) were studied with US at baseline and

at 6 months after starting ULT. At baseline, US demonstrated tophi or a double contour sign in 62.5% to 75% of the patients. At 6 months, four patients who had not achieved normal sUA levels had no changes in the US findings; however, in eleven of the twelve patients who had achieved normal sUA levels, the US findings of tophi or double contour sign had either disappeared or decreased. The authors suggested that a larger controlled study be performed to determine whether US could be used to monitor patients who are on ULT and possibly identify patients who are non-compliant with medication.

### *Ultrasound in Gout (Summary/Conclusions)*

Unfortunately, there is no standardized protocol for imaging patients with suspected gout. One investigative group has proposed a simple and reasonable approach, which includes:<sup>85</sup>

- Bilateral US of one joint
- US of three articular cartilages
- US of two tendons

Further evaluation is required to validate this suggestion.

United Rheumatology encourages the use of US to assist in establishing a diagnosis of gout and will continue to monitor the literature for significant advances in the use of US for patients with gout. The *United Rheumatology Clinical Practice Guideline—Gout* provides a more complete discussion of the diagnosis and management of patients with gout.

### *Calcium Pyrophosphate Dihydrate Deposition Disease*

A complete discussion of the diagnosis and management of calcium pyrophosphate dihydrate deposition disease (CPDD, also called “pseudogout”) is beyond the scope of this guideline. Briefly, CPDD affects approximately 3% of the United States population between 60 and 70 years of age. Calcium pyrophosphate crystals are deposited in the cartilage (**not on the surface**) and, when released into synovial fluid, cause very painful synovitis. Such an attack is generally accompanied by swelling, redness, warmth, and joint pain. Attacks may also be brought on by trauma or surgery.<sup>86</sup> However, most people with evidence of calcium pyrophosphate crystals in joint cartilage will never develop symptoms.

The causes of CPDD are not known; but it is believed that it involves a combination of factors, including genetics and age; and occurs as a consequence of a variety of comorbid systemic diseases; including hemochromatosis, hypercalcemia, hypothyroidism, hyperparathyroidism, or hypomagnesemia.<sup>87</sup> The most common joint involved is the knee, which is affected in 50% of acute attacks; the wrist is the second most commonly involved joint.<sup>88</sup> Shoulders, ankles, elbows, hands, and feet may also be affected. Acute attacks of CPDD can last from a few days to a several weeks.<sup>86</sup> Calcium pyrophosphate crystals may also be seen in the joints of patients with OA or gout.

The gold standard for the diagnosis of CPDD in a patient with a warm, painful, swollen joint is arthrocentesis demonstrating calcium pyrophosphate crystals from a synovial fluid aspirate. X-rays may

show chondrocalcinosis (calcium deposits **in** the joint cartilage), which is suggestive of, but not specific for CPDD.

Ultrasound has been found to be useful in establishing a diagnosis of CPDD. Filippucci et al.<sup>81</sup> published a study of the US findings in 30 patients with gout and 70 patients with CPDD. All of the patients were clinically evaluated by an experienced rheumatologist prior to having US of both knees. Among the 100 patients (with 200 knee US studies), the most common sonographic finding was an effusion, seen in 35% of the gout knees and 37% of the CPDD knees. Seventeen percent of the gout knees and 15% of the CPDD knees showed synovial hypertrophy with or without power Doppler signal. Meniscal calcification was found in 77% of the CPDD knees and in none of the gout knees. The double contour sign (described in the section on gout) was present in 41.6% of the gout knees and in only .7% of the CPDD knees.<sup>81</sup> The coexistence of CPDD and gout in certain patients, a so-called “mixed crystalline” presentation, may affect the clinometric performance of US in distinguishing the conditions.

Another study published in 2006 compared the US findings in patients with CPDD and gout (both proven by arthrocentesis and microscopic evaluation of synovial fluid).<sup>89</sup> In gout, MSU crystals were deposited **on the surface** of the articular cartilage (double contour sign); in CPDD, the crystal deposition was **within** the articular cartilage. In addition, calcium pyrophosphate crystals were seen in tendons and fibrocartilage.

In a study published in 2014, Gutierrez et al.<sup>90</sup> compared US and X-rays in the diagnosis of CPDD. This study included 74 patients with CPDD and 83 control patients with a variety of other chronic arthritides. In addition to a clinical evaluation and synovial fluid analysis, all patients had X-rays and US of both knees. Hyperechoic spots consistent with crystal deposition within hyaline cartilage were found in at least one knee in 59.5% of the CPDD patients with US but were detected by X-ray in only 45.9% of the patients.

Detection of calcification in the menisci was seen with US in 90.5% of the CPDD patients; however, X-ray detected it in only 83.7%. The authors concluded that CPDD could be detected more reliably with US than with X-ray.<sup>90</sup>

United Rheumatology supports and encourages the use of US, when available, for the diagnosis of CPDD, because it appears to be more reliable than X-ray and may avoid arthrocentesis in acutely painful joints. However, if arthrocentesis is not done, it is important to be confident that the painful joint is not infected.

### *Polymyalgia Rheumatica*

The diagnosis and management of polymyalgia rheumatica (PMR) is outside the scope of this document. However, a brief discussion of the role of US in establishing the diagnosis is appropriate.

About half of the patients with giant cell arteritis (GCA) will develop PMR before, after, or at the time of the diagnosis of GCA. Like GCA, PMR usually affects people 50 years of age or older and is more common in women. The diagnosis may be difficult to establish, because the presenting symptoms such as pain and stiffness in the shoulders and hips are seen in many rheumatologic disorders.

In 2012, the ACR and EULAR published classification criteria for PMR.<sup>91</sup> Like all other classification criteria in rheumatology, these are designed for use in clinical research studies and not for diagnosis. However,

they are a helpful guide to the rheumatologist faced with a confusing clinical situation. Unfortunately, there is no one test that can establish the diagnosis of PMR. The published classification criteria can be used with or without US, but US use does increase the specificity and sensitivity.

According to the ACR and EULAR, there are two ways to use the PMR classification system. When using either system; **all patients must be 50 years of age or older and have elevated acute-phase reactants (erythrocyte sedimentation rate [ESR] and/or CRP), aching of both shoulders**, and optional classification criteria equaling a score of 4 or more.<sup>92, 91</sup> No other joint pain can be present.

The first way to use the EULAR/ACR scoring system does not include US findings and requires a score of  $\geq 4$  to classify a patient as having PMR (Table 2).

**Table 2. EULAR/ACR scoring system for polymyalgia rheumatica (PMR) without ultrasound**

Clinical Findings	Points
Morning stiffness for more than 45 minutes	2
Normal RA serology (negative RF and negative ACPA)	2
Hip pain or limited range of motion	1
No other joint pain	1

**Note: patients must be >50 years of age, have an abnormal ESR and/or CRP, and complain of bilateral shoulder aches.**

A score of 4 or more classifies a patient as having PMR. The specificity of this scoring system is best when trying to tell the difference between PMR and other shoulder problems (79%) except when trying to differentiate between PMR and RA where the sensitivity is only 61%.

ACR, American College of Rheumatology; ACPA, anticitrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European Leagues Against Rheumatism; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; RF, rheumatoid factor

The committee developing the classification criteria found that, when US was added to the standard scoring system, the sensitivity of the criteria improved from 79% to 86% for differentiating PMR from other shoulder disorders except RA; in RA, sensitivity of the criteria improved from 61% to 65%.<sup>92</sup> When using the system with US findings, scores of 1 can be obtained for demonstrating either (Table 3):

- One shoulder with either subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis AND one hip with at least synovitis and/or trochanteric bursitis OR
- Both shoulders with subdeltoid bursitis and/or biceps tenosynovitis or glenohumeral synovitis

The second way to use the EULAR/ACR scoring system for PMR diagnosis does require the use of US. It has the same requirements for use as the non-US-based system with respect to patient age, elevated acute-phase reactants, and bilateral shoulder aches. This system requires a minimal score of 5 for a patient to be classified as having PMR (Table 3).

**Table 3. EULAR/ACR classification system for polymyalgia rheumatica (PMR) with ultrasound**

Clinical Findings	Points
Morning stiffness for more than 45 minutes	2
Normal RA serology (negative RF and negative ACPA)	2
Hip pain or limited range of motion	1
No other joint pain	1
Ultrasound Findings	
One shoulder with either subdeltoid bursitis, and/or biceps tenosynovitis and/or glenohumeral synovitis <b>AND</b> one hip with synovitis or trochanteric bursitis	1
<b>Both</b> shoulders with subdeltoid bursitis and biceps tenosynovitis or glenohumeral synovitis	1

**Note:** patients must be >50 years of age, have an abnormal ESR and/or CRP, and complain of bilateral shoulder aches. A score of 5 or more classifies a patient with PMR, when US is included in the classification criteria scoring system.

ACR, American College of Rheumatology; ACPA, anticitrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European Leagues Against Rheumatism; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; RF, rheumatoid factor

In a US, tenosynovitis is seen as hypoechoic or anechoic material in the tendon sheath that is compressible and has no flow on power Doppler examination. The findings must be seen in two perpendicular views.

Synovitis (non-compressible hypoechoic soft tissue with increased power Doppler signal) in a joint may be seen in the glenohumeral- or hip-joint(s). These findings also must be confirmed on two orthogonal views.

Hypoechoic compressible fluid collections consistent with joint effusions may also be seen, especially in the shoulder or hip,<sup>93, 94</sup> and must also be confirmed on two perpendicular views.

Bursitis, especially at the subacromial-subdeltoid or trochanteric bursa in the hips, may also be demonstrated. On US, bursitis appears as an anechoic or hypoechoic collection distending the bursa. There may be synovial hypertrophy and/or thickening of the bursal wall. The changes must be seen on two orthogonal views.

Patients suspected of having GCA as well as PMR should be evaluated as described in Appendix A—Giant Cell Arteritis.

### ***Additional Applications of Diagnostic Ultrasound in Rheumatology***

This guideline focuses on the use of US in the evaluation of some of the most common causes of rheumatologic disorders. There are many other indications for US that are beyond the scope of this guideline. Some additional indications for US that may be of interest to rheumatologists are listed in Table

4.<sup>95</sup> The list is incomplete, because appropriate indications for diagnostic and interventional US are constantly evolving. It is important to note that, although rheumatologists most commonly perform US or refer patients for US of the musculoskeletal system, it may be appropriate for them to perform US for other indications (some of which require specific training outside the usual musculoskeletal imaging courses and certification) at the point of care. In Table 4, indications marked with an asterisk require more training and experience than that required to pass the current ACR certification examination.

**Table 4. Some additional indications for diagnostic ultrasound**

Anatomic Location	Indications	
<b>Shoulder</b>	<ul style="list-style-type: none"> <li>• Rotator cuff tears (partial and full • thickness)*</li> <li>• Postoperative rotator cuff failure*</li> <li>• Bursitis</li> <li>• Calcific tendonitis</li> </ul>	<ul style="list-style-type: none"> <li>• Pectoralis/deltoid tear*</li> <li>• Tendinopathy, dislocation, rupture of long head of biceps*</li> <li>• Septic arthritis</li> <li>• Sternoclavicular joint disease*</li> </ul>
<b>Elbow and wrist</b>	<ul style="list-style-type: none"> <li>• Lateral epicondylitis</li> <li>• Septic arthritis</li> <li>• Medial epicondylitis</li> <li>• Tenosynovitis</li> <li>• Tendon rupture</li> <li>• Ganglion</li> </ul>	<ul style="list-style-type: none"> <li>• Radial nerve compression*</li> <li>• Median nerve entrapment*</li> <li>• Ulnar nerve neuropathy*</li> <li>• Ulnar nerve subluxation*</li> <li>• Foreign body</li> <li>• Olecranon bursitis</li> </ul>
<b>Hip</b>	<ul style="list-style-type: none"> <li>• Effusion</li> <li>• Extraarticular snapping hip</li> <li>• Sports hernia*</li> </ul>	<ul style="list-style-type: none"> <li>• Muscle injuries (high grade)</li> <li>• Evaluation of lateral femoral cutaneous and femoral nerves*</li> </ul>
<b>Knee</b>	<ul style="list-style-type: none"> <li>• Patellar tendinopathy or tear</li> <li>• Quadriceps tendinosis or tear</li> <li>• Medial collateral ligament</li> <li>• Effusion or synovitis</li> <li>• Pes anserinus tendino-bursitis</li> </ul>	<ul style="list-style-type: none"> <li>• Baker's cyst</li> <li>• Periarticular ganglion</li> <li>• Periarticular bursitis</li> <li>• Osgood Schlatter's disease*</li> </ul>
<b>Ankle</b>	<ul style="list-style-type: none"> <li>• Tendon tears</li> <li>• Sheath effusions</li> <li>• Calcific tendinitis</li> <li>• Retrocalcaneal bursitis</li> <li>• Peroneal tendon dislocation*</li> <li>• Anterior talofibular ligament • injury*</li> <li>• Entrapment</li> </ul>	<ul style="list-style-type: none"> <li>• Morton's neuroma</li> <li>• Calcaneofibular ligament injury*</li> <li>• Effusion</li> <li>• Deltoid ligament injury</li> <li>• Plantar fasciitis</li> <li>• Ganglion cyst</li> <li>• Achilles' tendinopathy or tear</li> <li>• Haglund disease</li> </ul>
<b>Miscellaneous</b>	<ul style="list-style-type: none"> <li>• Sjögren's syndrome* (see Appendix B—Sjögren's Syndrome)</li> </ul>	

\*Denotes conditions that require that both the individual performing and/or interpreting the examination have additional training in US specific to the condition to be evaluated.

## Interventional Musculoskeletal Ultrasound

Rheumatologists routinely perform joint aspirations and injections in the office setting. In addition to intraarticular injections of steroids or hyaluronic acid (or other agents), aspirations of an effusion are commonly performed for diagnostic purposes or to relieve symptoms. Many rheumatologists use palpation to identify a joint for injection and/or aspiration. Not all of these procedures are successful and, when the target is missed, repeat procedures may be needed. After a therapeutic injection, the patient may not have the expected improvement in symptoms or may even have an occasional adverse event secondary to an extraarticular injection, such as local soft-tissue damage. When procedures are performed with palpation guidance alone, there is a risk of injuring a blood vessel, tendon, or nerve when passing a needle or other device into the soft tissue or joint. This can almost always be avoided, if US guidance is used.

Real-time US image guidance for joint aspirations, injections, aspiration of soft-tissue collections, and joint biopsies is gaining more acceptance in the rheumatology community. This approach has the advantage of providing visualization of the needle in real time, as it passes from the skin to the target joint or soft tissue. As a result, US-guided procedures are less time-consuming, usually less painful, more accurate, and safer than those performed with palpation alone.<sup>96-98</sup> In addition, they can usually be performed at the point of care. A US scan can be used prior to needle entry to determine whether free fluid for aspiration is available within a joint, thereby preventing the discomfort associated with futile “dry” taps when no fluid is present. When very little fluid is present, US guidance allows rapid and accurate localization and evacuation of the fluid while limiting the trauma associated with “searching” for the joint fluid by blindly moving the needle tip under the skin as is often necessary with palpation-guided aspiration. By visualizing the path of the needle and the target, the operator is able to avoid puncturing blood vessels, which could result in a post-procedure hematoma, especially in patients on anticoagulants or with a bleeding diathesis. In addition, direct injection into tendons, which may be associated with tendon rupture, can be avoided with an image-guided procedure. Finally, when aspirations and/or injections are performed with direct US visualization of the target, the accurate placement of the needle and injection of therapeutic agents can be confirmed.

Finnoff et al.<sup>99</sup> published a systematic review comparing the value of US guidance versus palpitation alone for diagnostic or therapeutic injections, aspirations and tenotomies, releases, and hydrodissection. The authors concluded that US-guided interventions involving painful or inflamed joints were more accurate (95% for US-guided vs 81% for palpation), less painful, and more effective than palpation-guided procedures.

In a study with 108 patients, (44 with RA, 52 with OA, and 13 with other diseases) different joints were injected using only palpation to guide the needle.<sup>100</sup> Unfortunately six patients were lost to follow up. The study found that half of the needles and injections were not inserted into the target; the injections were administered by rheumatologists. Another study compared the accuracy of needle placement into small joints (proximal interphalangeal joints and metacarpophalangeal joints) in patients with synovitis in at least one joint.<sup>101</sup> Seventeen patients had a needle placed by an experienced rheumatologist using palpation. Fifty-three small joints of the hand (in 30 patients) were accessed using US image guidance.

The position of the needle tip was evaluated by sonography and distention of the joint capsule after injection. In the group accessed by palpation, the needle tip was in the joint in 59% of cases, but no fluid could be aspirated. In joints accessed with real-time US guidance, the needle tip was inserted into the joint in 96% of the patients. In the US-guided group, joint lavage was performed to obtain samples of synovial fluid.

A report by Balint et al.<sup>102</sup> compared the accuracy of joint aspiration using US-guided needle placement to joint aspiration using palpation-guided needle placement. The patients in this study had either RA, OA, or seronegative arthritis. The joints accessed in both groups included shoulders, elbows, knees, ankles, carpometacarpal joints, metacarpophalangeal, and proximal interphalangeal joints. In the group accessed with US guidance, the success rate was 97%; in the group accessed by palpation, the success rate was only 32%. In the palpation-guided group, joints in the wrist were accessed successfully in 25% of cases. The US-guided group included soft-tissue collections, which were successfully aspirated 100% of the time. Difficulty with accessing joints was encountered not only in the small joints of the hand and wrist but also in larger joints such as the knee (95% success with US guidance vs 40% success by palpation) and shoulder (100% success with US guidance vs 25% success with palpation).<sup>102</sup> All of these studies were small, but all showed that US-guided joint aspiration was more successful than palpation-guided aspiration.<sup>100-102</sup>

In 2012, Sibbitt et al.<sup>103</sup> published a randomized controlled study comparing US-guided aspiration and steroid injections to those performed by palpation. They found that US guidance resulted in 48% less pain, a 183% increase in the volume of fluid aspirated, and overall better outcomes 2 weeks after the procedure when compared to procedures performed without US guidance. It is important to note that, in this study, aspirations performed with US-guidance were done with specialized, and not widely utilized equipment in the form of controlled mechanical aspirating syringes.

The most common indications for US-guided needle placement into a joint include:<sup>104, 98</sup>

- Injection of diagnostic or therapeutic agents such as steroids or hyaluronic acid into a joint
- Aspiration of joint fluid prior to the injection of a diagnostic or therapeutic agent
- Aspiration of fluid prior to the injection of steroids into a Baker's cyst
- Aspiration of joint fluid for analysis
- Aspiration of joint fluid for symptom relief
- Aspiration of joint to exclude infection
- Failed non-image-guided injection or aspiration
- Inability to localize the target by palpation due to body habitus; deep location such as the hip; or anatomic variants, which could be congenital or secondary to surgical intervention or trauma

The most common indications for US-guided interventions of tendon, ligament, bursal, and muscle disorders include:<sup>104, 98</sup>



- Tendinopathy and partial-thickness tears, including but not limited to rotator-cuff tendinopathy •  
Calcific tendinitis of the rotator cuff
- Enthesopathy
- Tenosynovitis
- Tendon snapping
- Tendon subluxation or dislocation
- Trigger-point injections
- Trigger finger
- Lateral epicondylitis
- Contusions of muscles
- Trochanteric bursitis
- Olecranon bursitis
- Tenotomy

The most common indications for US image-guided drainage procedures include:<sup>98</sup>

- Undiagnosed soft-tissue collection such as a cyst, abscess, or liquefied hematoma
- Suspicion of abscess, to obtain fluid for culture
- Treatment of an abscess with aspiration and placement of drain
- Aspiration of a ganglion or synovial cyst

According to the 2016 *American Academy of Orthopaedic Surgeons Evidence-Based Clinical Practice Guideline for the Management of Carpal Tunnel Syndrome*,<sup>105</sup> there is strong evidence to support the use of steroid injections into the carpal tunnel to treat CTS. According to this guideline, CTS is defined as follows:

Carpal Tunnel Syndrome is a symptomatic compression neuropathy of the median nerve at the level of the wrist, characterized physiologically by evidence of increased pressure within the carpal tunnel and decreased function of the nerve at that level. Carpal Tunnel Syndrome can be caused by many different diseases, conditions and events. It is characterized by patients as producing numbness, tingling, hand and arm pain and muscle dysfunction. The disorder is not restricted by age, gender, ethnicity, or occupation and is associated with or caused by systemic disease and local mechanical and disease factors.” (Page 24)

A detailed description of CTS and its diagnostic criteria, treatment, and monitoring is beyond the scope of this guideline. However, US-guided injection procedures have become increasingly popular in recent years and are therefore included in this section. Ultrasound-guided injection of steroids for the management of CTS is safer than palpation-guided injections and was found to be more accurate.

A controlled clinical study comparing patients injected (without US guidance) with either 80 mg of methylprednisolone, 40 mg of methylprednisolone, or placebo followed these patients at 10 weeks for severity of disease and again at 1 year for rate of surgery.<sup>106</sup> It found that improvement in symptoms 10 weeks after injection was greater in the patients who had received methylprednisolone than in those who had received a placebo. Improvement was noted to be better in those patients treated with 80 mg of methylprednisolone than in those treated with 40 mg. At 1 year, the 80-mg methylprednisolone group had less surgery than the 40-mg group, which, in turn, had less surgery than the placebo group. Although the blind injections were effective at 10 weeks, they were not very durable, and most patients had surgery by the end of 1 year. Makhoul et al.<sup>107</sup> reported the results of a randomized controlled study comparing the results of US-guided steroid injections for CTS to conventional palpation-guided steroid injections. They reported that patients in the US-guided injection group had less procedural pain than those in the palpation-guided group. In addition, the US group had less pain immediately after the injection, as well as 2 weeks and 6 months later than those in the palpation-guided group. The average time to reinjection was 9.1 months in the US-guided group and 7.0 months in the palpation-guided injection group. In some patients, CTS can spontaneously resolve and for those individuals, steroid injections may help avoid surgery.

A more recent study compared the effectiveness of US-guided injections to blind injections for CTS and found that US-guided procedures were safer than blind injections.<sup>108</sup> In addition, US patients were less likely to need repeat injections within 1 year when compared to patients who had blind injections. Of the patients injected with US guidance, only 44% eventually required surgery; of those who had a blind injection, 64% required surgery.

Ultrasound-guided injection of the carpal tunnel requires detailed understanding of the target anatomy and special training and technique, and should not be performed by anyone without appropriate expertise.

Contraindications to US-guided interventions are:<sup>84,85</sup>

- Active infection over the puncture site
- Tumor or mass overlying the site
- Rash over the sampling site
- Inaccessible site (inadequate acoustic window or visualization of the target)

United Rheumatology strongly encourages the use of US guidance (when available) for all interventions, unless contraindicated.

## Summary and Conclusions

United Rheumatology encourages the use of US in the practice of rheumatology. Ultrasound can assist rheumatologists in establishing a diagnosis when the clinical diagnosis is unclear. It can also be used to monitor patient response to treatment and is an extremely effective tool when used to guide biopsies, injections, and/or aspirations; improving accuracy and decreasing the need for repeat procedures. The EULAR-OMERACT scoring system for synovitis in patients with RA is a novel instrument that may be helpful

to clinicians, but further evaluation with larger randomized controlled studies is needed to validate and/or modify it.

This guideline is designed to assist the practicing rheumatologist in determining the appropriate use of US. United Rheumatology will continually monitor the literature and update this guideline as appropriate.

## Glossary

### Erosion

An intraarticular discontinuity of the bone surface that is visible in two perpendicular planes.<sup>17</sup>

### Joint effusion or synovial fluid

Abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal.<sup>17</sup>

### Synovial hypertrophy

Abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intraarticular tissue that is not displaceable and poorly compressible and may exhibit Doppler signal.<sup>17</sup>

### Tenosynovitis

Hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath that is seen in two perpendicular planes and may exhibit Doppler signal.<sup>17</sup>

### Enthesopathy

Abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification) seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes such as enthesophytes, erosions, or irregularity.<sup>17</sup>

## Additional Definitions

### Color flow Doppler

Technique that “estimates the average velocity of flow within a vessel by color coding the information. The direction of blood flow is assigned the color red or blue, indicating flow toward or away from the ultrasound transducer.” The color is superimposed on a gray-scale image. Color flow is often combined with **pulsed Doppler** or **spectral Doppler**, which “allows a sampling volume or ‘gate’ to be positioned in a vessel visualized on the gray-scale image and displays a graph of the full range of blood velocities within the gate versus time. The amplitude of the signal is approximately proportional to the number of red blood cells and is indicated, not in color but simply as a shade of gray.”<sup>109</sup>

### Power Doppler

This technique “depicts the amplitude, or power of Doppler signal rather than the frequency shift”, which permits the detection of a larger range of Doppler signal and allows for the visualization of vessels with very low flow velocities; however, it cannot be used to determine direction of flow.<sup>109</sup>

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## Appendix A—Giant Cell Arteritis

A detailed description of giant cell arteritis (GCA) as well as classification criteria, diagnostic criteria, treatment and monitoring of this disorder is beyond the scope of this guideline.

Giant cell arteritis is an auto-inflammatory and autoimmune disorder<sup>1</sup> that results in inflammation within the blood vessel walls. According to the *2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides*,<sup>2</sup> GCA is a large-vessel vasculitis that most often involves the temporal and scalp arteries with sparing of the intracranial vessels.<sup>3</sup> However, the disease can also involve the thoracic aorta as well as the brachial, axillary, and subclavian arteries. Approximately half of the patients with GCA also have polymyalgia rheumatica.<sup>4</sup> Giant cell arteritis usually occurs in patients over the age 50 years and is more common in women.

The current gold standard for establishing the diagnosis of GCA is a temporal artery biopsy. According to a health technology assessment from the National Health Service, National Institute for Health Research published in 2016, a temporal artery biopsy may be negative in a significant population of patients with the disorder.<sup>5</sup> A prospective study, which included 381 patients, demonstrated better sensitivity but poorer specificity of ultrasound (US) when compared to temporal artery biopsy. In contrast, Delle Sedie et al.<sup>6</sup> reported that US had similar sensitivity and specificity as temporal artery biopsy. However, there has been a trend toward early imaging with US or magnetic resonance imaging (MRI) when GCA is suspected. In 2018, the European League Against Rheumatism (EULAR) published a list of recommendations for imaging, when GCA is suspected.<sup>7</sup> These recommendations include:

- Early imaging should be performed in patients with suspected GCA, but it must be performed quickly and by experienced and well-trained sonographers.
- Temporal artery biopsy is not necessary in patients in whom the clinical suspicion of GCA is high, and when there is a positive imaging test such as a noncompressible halo sign on US.
- Ultrasound of the temporal arteries with or without the axillary arteries should be the first test for suspected GCA. A noncompressible halo around either vessel is the most important sign for the imaging diagnosis of GCA (the halo sign). This sign must be demonstrated in two orthogonal planes. However, this can very quickly resolve when the patient is treated with steroids.
- If US is not available, magnetic resonance angiography (MRA) of the cranial arteries (which includes the temporal artery) should be performed.
- Conventional angiography is not recommended for the diagnosis of GCA.

OMERACT also studied the reliability of US for the diagnosis of GCA based on their definitions of normal arteries and vasculitis in temporal and axillary arteries.<sup>8</sup> This group found that temporal artery biopsy was being replaced by imaging to confirm the diagnosis of GCA by US, MRI, and positron emission tomography-computed tomography (PET-CT). Imaging was being favored, because it is non-invasive, usually immediately available, and the results are reported a short time after the test is completed. Temporal artery biopsy, on the other hand, is not immediately available, and the results are not reported for a few days. Ultrasound and MRI can visualize multiple different arteries. Ultrasound is often available at the point of care in a rheumatologist's office. It does not use any ionizing radiation and, if the proper equipment is used, it can have a resolution of 0.1 mm for superficial arteries. Ultrasound can also be used to look for the halo sign which, when present, can confirm the diagnosis of GCA in patients with a compatible history.

Outcome Measures in Rheumatology (OMERACT) performed a study of the reliability of US in the diagnosis of GCA, which was described in the *Journal of Rheumatology* in 2018.<sup>8</sup> The results indicated that, when experienced sonographers performed studies of the temporal and axillary arteries using high-quality equipment (>15 megahertz (MHz) transducers) and proper equipment settings, the results were very good.

For US examination of patients with either possible or known GCA; a linear array, high-frequency probe of >15 MHz with color Doppler is required.<sup>7</sup> The entire length of the temporal artery can usually be evaluated with US. This is important, because vessels may have so-called skip areas of involvement.<sup>4</sup> Giant cell arteritis may involve the facial, external carotid ophthalmic, brachial, and axillary arteries as well as the thoracic aorta; therefore, US imaging of patients suspected or known to have this rheumatologic disorder should also include these vessels.<sup>5, 9, 10</sup> All of the vessels imaged should be evaluated in two orthogonal planes using a linear transducer of >15 MHz with color Doppler.<sup>7</sup> When performing color Doppler, the angle of the sound waves and artery should be about 60°, and the pulse repetition frequency (PRF) should be between 2 to 3.5 kHz and 3 to 4 kHz. Power Doppler should not be used, and the color Doppler gain should be adjusted so that there is neither underfilling nor overfilling of the vessel.<sup>7</sup>

The US findings of GCA include the following:<sup>4, 11</sup>

- Hypoechoic ring in the wall of the vessel consistent with edema and swelling in acute GCA (also referred to as the “halo sign”). A meta-analysis of the sensitivity and specificity of the halo sign was published in 2010.<sup>12</sup> The authors of this study reported a sensitivity and specificity of 68% and 91%, respectively, for a unilateral halo sign; and of 43% and 100%, respectively, for bilateral halo signs when “the 1990 ACR criteria are used as the reference standard” (Page 46).<sup>12</sup>
- Noncompressible vessel acutely.
- Both the halo sign and noncompressibility rapidly disappear in most patients after 2 to 3 weeks of treatment with steroids.<sup>13</sup>
- Short-segment vascular stenosis on color flow Doppler evaluation. Aliasing and persistent blood flow in diastole are seen when a stenosis is present. The maximum systolic velocity is also increased at least two-fold in a stenosis. Stenotic areas may be seen intermittently along the course of the vessel (so-called “skip areas”).
- Vascular occlusions with absent blood flow.

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## Appendix B—Sjögren’s Syndrome

A discussion of the diagnosis, epidemiology, classification criteria, and management of Sjögren’s syndrome is beyond the scope of this guideline.

Sjögren’s syndrome is an autoimmune disease characterized by oral sicca (xerostomia) and dry eyes (xerophthalmia or keratoconjunctivitis sicca). Patients may also develop parotid gland enlargement and complain of difficulty talking and swallowing. Ocular sicca may manifest as complaints of foreign body sensation in conjunction with itchy eyes and sensitivity to light, because the disease also affects the lachrymal glands. The disease may be primary or associated with other rheumatic disorders (secondary Sjögren’s syndrome).<sup>1</sup> It primarily occurs in women between the ages of 40 to 60 years.<sup>2</sup> In the past, the gold standard for establishing the diagnosis of Sjögren’s syndrome was biopsy of a minor salivary gland.<sup>1</sup> However, more recently, classification criteria have been proposed to assist in the identification of patients for clinical trials.<sup>3</sup> It is estimated that these criteria have a sensitivity of 96% and specificity of 95%. (A complete discussion of these classification criteria is beyond the scope of this guideline; the reader is referred to the original article by Shiboski et al.) Of note is, that ultrasound (US) was not included in these classification criteria.

The clinical diagnosis of Sjögren’s may be challenging. In the past decade, the role of US in the diagnosis of Sjögren’s syndrome has become more widely accepted. The American College of Rheumatology (ACR) states that, “It is reasonable to use MSUS [musculoskeletal ultrasound] to evaluate the parotid and submandibular glands in a patient being evaluated for Sjögren’s disease to determine whether they have typical changes as further evidence of this disorder” (Page 1629).<sup>4</sup> Ultrasound is also less invasive and less costly than a salivary gland biopsy and can be performed at the point of care.

A systematic review of US in Sjögren’s syndrome was published in the May 2016 issue of *Rheumatology*.<sup>5</sup> The authors found that only 31 of 167 papers met the criteria to be included in their review. The number of patients studied ranged from a low number of 15 patients to a high number of 150. The studies varied in their description of the US findings in B-mode US; most did not use color Doppler. The authors

believed that US was useful in detecting salivary gland abnormalities in this disorder (especially in the primary form of the disease), but they also suggested that more work is needed to standardize and validate the role of US in the diagnosis of Sjögren's syndrome. A validated scoring system for parenchymal changes, which is widely used, would also be needed before US becomes routine in the evaluation of this disease.<sup>6</sup>

When US evaluation of the salivary glands is performed, it should include imaging of the parotid and submandibular glands bilaterally. It may be difficult to visualize all of the deep lobes of the parotid gland, because of acoustic shadowing from the mandible. All salivary glands studied should be imaged in two orthogonal planes using a linear array transducer of at least 10 megahertz.<sup>7</sup> Measurements should be taken in both transverse and longitudinal planes. Parenchymal echogenicity should also be evaluated.<sup>7, 8</sup> A normal salivary gland is homogeneous and hyperechoic when compared to muscle and isoechoic when compared to subcutaneous fat. There may be fine echogenic lines scattered throughout the glands. Lymph nodes may be seen in and/or around the parotid glands. They should measure no more than 6 to 8 mm in the short axis. A normal node should have an echogenic pattern, and small vessels should be present. The lacrimal ducts can also be examined through the lower lid and are usually triangular in shape and echogenic in appearance. In Sjögren's syndrome, the echotexture of the lacrimal duct is heterogeneous, and the gland is hypoechoic.<sup>9</sup> The parenchyma of a salivary gland appears inhomogeneous in patients with Sjögren's syndrome and contains multiple small, oval anechoic or hypoechoic areas. The hypoechoic (or anechoic) areas tend to represent a combination of dilated ducts, destroyed salivary gland parenchyma, and lymphatic infiltration.<sup>10</sup>

Patients with Sjögren's syndrome may have reactive and neoplastic lymphoproliferative disease, and the salivary glands should be continually monitored with US to evaluate for changes indicating possible lymphoma.<sup>10</sup>

There is no standardized reporting system for parenchymal echogenicity and homogeneity. However, Carotti et al.<sup>11</sup> proposed the system shown in Table 5. According to this system, the study is considered to be abnormal, if both parotid or submandibular glands meet the criteria for Grade >1.

**Table 5. Proposed reporting system for parenchymal echogenicity and homogeneity**

Grade	Criteria
<b>0</b>	<ul style="list-style-type: none"> <li>Glands are normal</li> </ul>
<b>1</b>	<ul style="list-style-type: none"> <li>Glands have regular margins</li> <li>Small hypoechoic areas</li> <li>Normal or increased volume of the glands and no echogenic bands</li> </ul>



<b>2</b>	<ul style="list-style-type: none"> <li>• Glands have regular margins</li> <li>• Multiple scattered hypoechoic areas measuring &lt;2 mm are present that are not uniformly distributed throughout the gland</li> <li>• Normal or increased volume of the gland and no echogenic bands</li> </ul>
<b>3</b>	<ul style="list-style-type: none"> <li>• Glands have irregular margins with multiple confluent areas of hypoechoogenicity, usually measuring 2 to 6 mm</li> <li>• Multiple cysts and echogenic bands may be detected</li> <li>• The volume of the gland may be decreased</li> <li>• The posterior margin is not detectable</li> </ul>
<b>4</b>	<ul style="list-style-type: none"> <li>• Glands have an irregular contour with large hypoechoic areas measuring more than 6 mm</li> <li>• Cysts, calcifications, and echogenic bands can be seen</li> <li>• The volume of the gland is decreased and the posterior margin is not detectable</li> <li>• Each gland is given a score equal to the parenchymal grade</li> </ul>

Evaluation of blood flow should also be undertaken in these patients using Doppler waveforms of the transverse facial artery, both before and after stimulation with lemon juice or equivalent. A resistive index (peak systolic velocity - end diastolic velocity/peak systolic velocity) should be calculated as well.<sup>8</sup> A normal salivary gland will demonstrate increased blood flow during lemon stimulation, with the peak systolic velocity increasing up to twice the peak systolic velocity in the nonstimulated state.<sup>12</sup> Blood flow or peak systolic velocity do not change significantly with lemon stimulation in either the parotid or submandibular glands of patients with long-standing Sjögren's syndrome.<sup>11</sup>

A recent study by Astorri et al.<sup>13</sup> retrospectively compared US findings in the parotid and submandibular glands to the biopsy results of labial minor salivary glands of 85 patients. The US scans were reported as "no evidence of Sjögren's syndrome", "mild disease", or "moderate/established/severe disease." Of the 85 patients, 51 had negative US scans; 49 of these patients had no evidence of focal lymphocytic infiltration. Thirty-four patients had positive US scans; 29 of these patients had positive biopsies. The authors found that the concordance between US and biopsy was 91%. However, they cautioned that prospective studies using a standardized scoring system for salivary-gland US and histology is needed. Hopefully such studies would result in a classification system that takes into account the findings of salivary-gland US.

Ultrasound may also be helpful in monitoring patients on therapy for Sjögren's syndrome by following changes in peak systolic velocity before and after exposure to lemon juice. Patient's with improvement in their disease may demonstrate an increase in peak systolic velocity after exposure to lemon juice. In addition, improvement in the echotexture of the glands (Table 5 above) may be detected. However, additional clinical studies are needed before these observations can be applied to patients in clinical care.<sup>6</sup>

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## Document Updates

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