Arthritis Update

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AUTHORS

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Foreword

Arthritis is a ubiquitous disease. It seems that every family in my practice, in my neighborhood, perhaps in the world, has at least one member with one of the types of arthritis discussed in this edition of *FP Essentials™*. My earliest memory of a chronic illness was watching my grandmother, with her fingers pointing in every direction, making a pie. By the time I was in high school, pain limited her movements; when I entered college, she could no longer knit. There wasn’t much anyone could do but treat her pain (and inadequately at that). Fortunately, many effective treatment options are available today.

According to the Centers for Disease Control and Prevention, one of every five US adults has arthritis, the nation’s leading cause of disability. Data from the 2003 Behavioral Risk Factor Surveillance System survey showed that between 25% and 51% of working-age adults with physician-diagnosed arthritis were limited in their work by this disease. Treating arthritis is a health priority for the nation, with *Healthy People 2010* calling for a reduction in these numbers. With the tremendous increase in our understanding about arthritis and ability to intervene, I believe we are ready to answer this call.

In reading this edition of *FP Essentials™*, I was impressed at the wide range of therapeutic options for our patients. For patients with rheumatoid arthritis, disease-modifying drugs allow us to tailor treatment and prevent the devastating consequences of this condition. These same concepts are being applied to osteoarthritis, with exciting early results in disrupting inflammatory cells and protecting cartilage. For the acutely swollen joint, I found *Figure 1* particularly useful in leading me through the maze of symptoms and conditions.

The discussion of lifestyle modifications, the key to prevention and management of all of these diseases, was an excellent reminder for me to be ever more encouraging to patients about the evidence-supported treatments that can make a difference in their lives.

Mindy A. Smith, MD, MS, Associate Medical Editor
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Learning Objectives

1. Summarize diagnostic criteria for osteoarthritis (OA).
2. Describe the types of exercise that are beneficial in OA management.
3. Cite evidence-supported nonpharmacologic OA treatments.
4. Describe the circumstances in which x-rays are useful in the diagnosis of rheumatoid arthritis (RA).
5. Cite factors that should be considered in tailoring RA therapy.
6. Cite the role of disease-modifying anti-rheumatic drugs for patients with newly diagnosed RA.
7. Summarize the components of baseline RA management.
8. Distinguish between nonbiologic and biologic drugs for RA management.
9. Describe when and how nonbiologic and biologic drugs for RA management should be combined.
10. Cite the risk factors for septic arthritis in adults.
11. Describe the role of imaging in the evaluation of acutely swollen joints.
12. Summarize the role of joint aspiration in the diagnosis of monoarticular arthritis.
15. Cite treatment options for lowering uric acid levels in patients with gout.
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Physicians should independently verify the extent of FDA-approved uses for drugs and devices, just as physicians should use their individual professional judgment in determining the appropriate course of treatment or care in each clinical situation.
1. In a patient older than 50 years, which one of the following additional clinical features contributes to the diagnosis of osteoarthritis based on American College of Rheumatology clinical criteria?
   - A. Pain while standing.
   - B. Crepitus on motion of the knee.
   - C. A give-way sensation while walking.
   - E. Morning stiffness lasting hours.

2. You are concluding your visit with a 62-year-old patient with newly diagnosed knee osteoarthritis. Which one of the following should you emphasize as a core treatment component?
   - A. Regular doses of ibuprofen.
   - B. An exercise program.
   - C. A custom orthotic.
   - D. Knee bracing.
   - E. Glucosamine with chondroitin.

3. In patients with rheumatoid arthritis, x-rays of the hands and wrists might show which one of the following?
   - A. Joint space narrowing.
   - B. Bony erosions.
   - C. Previous fractures.
   - D. Sclerotic bone.
   - E. Both A and B.

4. For patients with newly diagnosed rheumatoid arthritis, which one of the following should be instituted within 3 months of diagnosis?
   - A. Regular physical activity.
   - B. Disease-modifying anti-rheumatic drugs.
   - C. Testing for serum antibodies.
   - D. Adequate doses of acetaminophen.
   - E. Work schedule changes.

5. The three most common causes of acutely inflamed joints are infection, trauma, and which one of the following?
   - A. Hemarthrosis.
   - B. Crystal-induced arthropathy.
   - C. Malignancy.
   - D. Rheumatologic disease.
   - E. Osteoarthritis.

6. A 28-year-old woman presents to the emergency department with an acutely hot, painful, swollen knee. You suspect septic arthritis. Which one of the following tests should be performed promptly to confirm the diagnosis?
   - A. Cervical culture to test for sexually transmitted infection.
   - B. White blood cell count and differential.
   - C. Arthrocentesis.
   - D. C-reactive protein.
   - E. Magnetic resonance imaging study.

7. Definitive diagnosis of gout requires which one of the following?
   - A. Hyperuricemia.
   - B. Identification of monosodium urate crystals in synovial fluid.
   - C. Podagra.
   - D. Acute gout.
   - E. Monoarticular arthritis.
Pretest Answers

**Question 1:** The correct answer is B.
According to American College of Rheumatology clinical criteria, the diagnosis of knee osteoarthritis requires three of the following: age older than 50 years, morning stiffness for less than 30 minutes, crepitus on motion of the knee, bony tenderness, bony enlargement, and/or lack of palpable rheumatoid nodules. See page 13.

**Question 2:** The correct answer is B.
Weight loss and exercise are the foundations of osteoarthritis (OA) prevention and management. The American College of Rheumatology, Royal College of Physicians/National Institute for Health and Clinical Excellence, European League Against Rheumatism, American Academy of Orthopedic Surgeons, and the Osteoarthritis Research Society International all recommend aerobic exercise and/or muscle-strengthening exercises for OA treatment. See page 16.

**Question 3:** The correct answer is E.
X-rays of the hands and wrists in patients with rheumatoid arthritis might show periarticular osteopenia, or, later, joint space narrowing or bony erosions. See page 20.

**Question 4:** The correct answer is B.
Treatment with disease-modifying anti-rheumatic drugs should be initiated within the first 3 months of rheumatoid arthritis diagnosis. See page 23.

**Question 5:** The correct answer is B.
The 3 most common diagnoses to consider in the case of an acutely inflamed joint are trauma, crystalline disease, and infection. See page 25.

**Question 6:** The correct answer is C.
For any patient with suspected septic arthritis, a prompt attempt should be made to aspirate the joint. Arthrocentesis is essential for microbiologic diagnosis, which must be made early to allow prompt treatment to prevent joint damage. See pages 26-27.

**Question 7:** The correct answer is B.
The gold standard for gout diagnosis is microscopic evaluation of a sample of synovial fluid for monosodium urate crystals. Definitive diagnosis depends on joint aspiration and crystal identification. See pages 29-30.
Key Practice Recommendations

1. For patients with osteoarthritis, institute exercise as a core treatment, including local muscle strengthening exercises and general aerobic activity.

2. For patients with newly diagnosed rheumatoid arthritis, institute treatment with disease-modifying anti-rheumatic drugs within the first 3 months of diagnosis.

3. Perform arthrocentesis in the evaluation of patients with possible septic arthritis.

4. For patients with suspected crystal-induced arthritis, obtain synovial fluid to assess for presence of crystals in the definitive diagnosis of gout.

5. Evaluate patients with gout for other health risk factors and associated comorbidities (eg, metabolic syndrome, obesity, hyperglycemia, hypertension, hyperlipidemia).

Resources

1. Strength of evidence: SORT A

2. Strength of evidence: SORT C

3. Strength of evidence: SORT A
   Web site: http://jama.ama-assn.org/cgi/reprint/297/13/1478

4. Strength of evidence: SORT A

5. Strength of evidence: SORT C

Strength of Recommendation Taxonomy (SORT)

<table>
<thead>
<tr>
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<th>Definition</th>
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<tr>
<td>A</td>
<td>Recommendation based on consistent and good-quality patient-oriented evidence. a</td>
</tr>
<tr>
<td>B</td>
<td>Recommendation based on inconsistent or limited-quality patient-oriented evidence. a</td>
</tr>
<tr>
<td>C</td>
<td>Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, a or case series for studies of diagnosis, treatment, prevention, or screening.</td>
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aPatient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvement in patient outcomes (eg, blood pressure, blood chemistry, physiologic function, pathologic findings). (From Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy [SORT]: a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. 2004;69:548-556.)
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Starting in June 2011, double credit will no longer be awarded for FP Essentials™.
Preface

This edition of *FP Essentials™* reviews recent updates in the management of arthritis. Although this group of diseases was first described in ancient times, there recently have been great advancements in the knowledge and technologic capabilities available to manage these conditions.

In the past, much emphasis was placed on joint replacement or joint injection of various drugs to treat arthritis. Today, new drugs and a greater understanding of the pathophysiology of arthritis have caused a paradigm shift in the management of this group of diseases. In addition to discussing these advancements in osteoarthritis and rheumatoid arthritis treatment, this text provides a logical, evidence-based approach to the treatment of patients with acutely nontraumatic swollen joints in an outpatient setting, helping family physicians to differentiate between septic and crystalline arthropathy.
Arthritis Update
Nonpharmacologic and Nonsurgical Osteoarthritis Treatments

Case 1. Ellen is a 55-year-old woman who presents to your office with a 3-year history of progressively worsening knee pain. She is obese (body mass index is 30 kg/m²) and moderate osteoarthritis (OA) of both knees was diagnosed based on her age, tenderness over both patellas and joint lines, and crepitus on motion of the knee.

Standing x-rays of the knees are obtained and reveal joint space narrowing of both medial compartments of the knees. Ellen does not wish to take any prescription drugs, if possible, and does not want to undergo surgery. She asks about other treatments to manage knee OA.

Overview

Osteoarthritis (OA) is a metabolically active process that affects all joint tissues. Key pathologic changes include degeneration of articular cartilage and remodeling of adjacent bone with new bone formation. OA is not a single condition but a complex condition with multiple risk factors, including genetic, constitutional, and biomechanical factors.¹

Diagnosis

According to American College of Rheumatology (ACR) clinical criteria, the diagnosis of knee OA requires 3 of the following: age older than 50 years, morning stiffness for less than 30 minutes, crepitus on motion of the knee, bony tenderness, bony enlargement, and/or lack of palpable rheumatoid nodules.²

A second diagnostic technique known as the classification and regression tree (CART) adds laboratory test results and radiographic information to clinical data.³ These findings are placed on a flow diagram and the physician follows a classification tree to make the diagnosis.

The European League Against Rheumatism (EULAR) evidence-based diagnostic guidelines list 3 symptoms (ie, persistent knee pain, limited morning stiffness, decreased function) and 3 signs (ie, crepitus, restricted movement, bony enlargement) as most useful in the diagnosis of OA.⁴ For patients 45 years and older, the estimated probability of radiographic evidence of knee OA was found to be 99% when all 6 symptoms and signs were present.

Study results from the ACR found that the addition of laboratory test results and x-rays to clinical criteria did little to improve diagnostic accuracy in patients with hand and wrist OA.⁵ Although the diagnosis of knee OA can be made on clinical grounds alone, diagnostic accuracy was increased modestly using laboratory and standing x-ray findings.² Radiographic findings significantly improve diagnostic accuracy in hip OA.³,⁶

Traditional Treatments

Most patients with OA are offered the options of lifestyle change; traditional drugs for pain management, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs); and targeted physical therapy. If these modalities are ineffective, joint replacement is considered. Several difficulties might be encountered with this approach.

Nonsteroidal anti-inflammatory drugs, although typically well tolerated in younger patients, are associated with increased risk of gastrointestinal upset and bleeding, renal failure, hypertension, coagulability, and cardiovascular events in older patients.¹ NSAIDs also negate the effects of enteric-coated aspirin. Finally, the use of these drugs might shift focus away from evidence-based, patient-centered treatment plans that recommend patient activity, muscle-strengthening programs, aerobic fitness, and weight loss as the most effective long-term treatments.¹

Evidence-Based Treatment Guidelines

Evidence-based guidelines for the treatment of patients with OA from the American Academy of Orthopedic Surgeons (AAOS), Royal College of Physicians (RCP)/National Institute for Health and Clinical Excellence (NICE), EULAR, and Osteoarthritis Research Society International (OARSI) are summarized in Table 1. The recommendations address lifestyle, pharmacologic, and nonpharmacologic options.

The guidelines differ with respect to joint injection and nonpharmacologic recommendations. For example, AAOS found insufficient evidence to recommend for or against intra-articular hyaluronic acid joint injections or bracing for patients with knee OA.⁷ RCP/NICE recommends against the use of hyaluronic
### Table 1
Evidence-Based Recommendations for Osteoarthritis Management

<table>
<thead>
<tr>
<th>Option</th>
<th>AAOS (knee)</th>
<th>RCP/NICE&lt;sup&gt;a&lt;/sup&gt;</th>
<th>EULAR (knee or hip)</th>
<th>OARSI (knee and hip)</th>
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<td>Recommended (A&lt;sup&gt;h&lt;/sup&gt;)</td>
<td>Education, advice, access (A)</td>
<td>Recommended (A)</td>
<td>Self-management, telephone contact (B)</td>
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<tr>
<td>Diet (weight loss)</td>
<td>≥5% body weight if BMI &gt;25 kg/m&lt;sup&gt;2&lt;/sup&gt; (A)</td>
<td>Especially if obese (A)</td>
<td>For hip (D)</td>
<td>Recommended (B)</td>
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<td>Exercise (aerobic)</td>
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<td>Aerobic fitness (A)</td>
<td>Not addressed for hip (D)</td>
<td>Recommended (B)</td>
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<td>Strengthening exercises (A)</td>
<td>Not addressed</td>
<td>Muscle strengthening (B)</td>
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<td>Not addressed</td>
<td>Not addressed</td>
<td>Not addressed</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>Not addressed</td>
<td>Education (A)</td>
<td>Not addressed</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td><strong>Pharmacologic Interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>First line (A)</td>
<td>Second line (A)</td>
<td>First line for knee (A)</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>NSAID</td>
<td>First line (A)</td>
<td>Third line (B)</td>
<td>Recommended (A)</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>COX-2 inhibitor</td>
<td>For GI risk (A)</td>
<td>Third line (B)</td>
<td>Recommended (A)</td>
<td>For GI risk (B)</td>
</tr>
<tr>
<td>Topical NSAID</td>
<td>For GI risk (A)</td>
<td>Second line (A)</td>
<td>Recommended (A)</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Not addressed</td>
<td>Third line (B)</td>
<td>For hip (B)</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>Recommended against (A)</td>
<td>Recommended against (A)</td>
<td>For hip recommended neither for nor against (B)</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>Intra-articular corticosteroids</td>
<td>Recommended (A)</td>
<td>Third line (C)</td>
<td>For hip recommended against (C)</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>Intra-articular hyaluronates</td>
<td>Recommended neither for nor against</td>
<td>Recommended against (A)</td>
<td>For hip (C)</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td><strong>Nonpharmacologic Interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthroscopy and joint lavage</td>
<td>Recommended against</td>
<td>Recommended against</td>
<td>Not addressed</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>Arthroscopy and debridement</td>
<td>Recommended against</td>
<td>Recommended against</td>
<td>For knee (C)</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Not addressed</td>
<td>Insufficient evidence</td>
<td>For knee (B)</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>Bracing</td>
<td>Recommended neither for nor against</td>
<td>Third line (C)</td>
<td>For knee (B)</td>
<td>Recommended: walking aids, knee braces (B)</td>
</tr>
</tbody>
</table>
acid joint injection in patients with OA based on lack of long-term effectiveness and cost, whereas EULAR and OARSI recommend its use.1,8,9

Use of the RCP/NICE guideline is recommended for several reasons.1 The guideline is patient-centered, multidisciplinary, considers costs, and includes a suggested holistic assessment of patients with OA. In addition, the RCP/NICE guideline uses a tiered approach that emphasizes healthy lifestyle changes and arthritis education in the context of the patient’s belief system and expectations. Pharmacotherapy is a secondary option offered to patients who do not benefit from primary modalities. Treatments such as knee braces, orthotics, manipulative therapy, or intra-articular injections are considered adjuvant because there are limited data for their use, they are less effective or are of only short-term benefit, or they have associated risks.

Table 1 (continued)
Evidence-Based Recommendations for Osteoarthritis Management

<table>
<thead>
<tr>
<th>Option</th>
<th>AAOS (knee)</th>
<th>RCP/NICEa</th>
<th>EULAR (knee or hip)</th>
<th>OARSI (knee and hip)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonpharmacologic Interventions (continued)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Custom foot orthotics</td>
<td>Recommended against</td>
<td>Third line (C)</td>
<td>For knee (B)</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>Osteotomy</td>
<td>Not addressed</td>
<td>Not addressed</td>
<td>For hip (C)</td>
<td>Recommended (C)</td>
</tr>
<tr>
<td>Manipulative therapy</td>
<td>Not addressed</td>
<td>Third line (C)</td>
<td>Not addressed</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Thermal therapy</td>
<td>Not addressed</td>
<td>Third line (C)</td>
<td>Not addressed</td>
<td>Recommended (B)</td>
</tr>
<tr>
<td>TENS</td>
<td>Not addressed</td>
<td>Third line (C)</td>
<td>For knee (B)</td>
<td>Recommended (B)</td>
</tr>
</tbody>
</table>

**Guideline Types**

- Equally weighted orthopedic subspecialist
- Subspecialty guideline, includes cost-benefit ratio
- Weighted, primarily rheumatology subspecialists
- Weighted, primarily rheumatology subspecialists

aNICE categorizes recommended therapy for OA into primary recommendations (ie, lifestyle recommendations), secondary recommendations (ie, pharmacologic options for those for whom primary recommended treatments have been ineffective), and adjunctive recommendations (for which evidence is less well studied or limited or there is evidence of short-term effectiveness).
bStrength of Recommendation rating: A = consistent, good quality, patient-oriented evidence; B = inconsistent or limited quality patient-oriented evidence; C = consensus, disease-oriented evidence, expert opinion, or case series.

AAOS = American Academy of Orthopedic Surgeons; BMI = body mass index; COX-2 = cyclooxygenase-2; EULAR = European League Against Rheumatism; NSAID = nonsteroidal anti-inflammatory drug; GI = gastrointestinal; OA = osteoarthritis; OARSI = Osteoarthritis Research Society International; RCP/NICE = Royal College of Physicians/National Institute for Health and Clinical Excellence; TENS = transcutaneous electrical nerve stimulation.

**Lifestyle Modifications**

Weight loss (if the patient is overweight) and exercise are the foundations of OA prevention and management.

**Weight Loss**

The American College of Sports Medicine (ACSM) and all of the previously mentioned guideline developers recommend weight-loss programs for overweight patients. The Framingham study showed an increased risk of knee OA development in patients with high body mass index (ie, 25 kg/m² or greater)(odds ratio = 1.5 in women; 2.1 in men), supporting the significance of weight loss for these patients. One study that monitored patients for 10 years showed that a 4.5-kg (10-lb) weight loss decreased the likelihood of knee OA development by 50%. The relationship between amount of weight loss and the incidence of OA appears to be linear, suggesting even modest weight loss is beneficial.

Although weight loss can be challenging, physicians should assess patient stage of change and assist with goal setting through negotiation. Follow-up visits and referral to other trained professionals can also be helpful. Follow-up and continuity are key.

**Exercise**

The ACR, RCP/NICE, and all of the guideline developers recommend aerobic exercise and/or muscle-strengthening exercises for OA treatment. One randomized clinical trial and one large meta-analysis found benefits of exercise in patients with knee OA. In the clinical trial, patients with documented knee OA were randomized to either participate in a combined program of supervised fitness walking and education or to receive routine medical care. Patients in the treatment group experienced improved walking distance (20%) and functional status (29%) and decreased pain (30%) compared with those in the control group.

Data are less clear for benefits of exercise in patients with hip OA; pain levels might be decreased. The ACSM has implemented an Exercise is Medicine program that assists physicians in providing individualized exercise programs for all patients, including patients with OA (available at http://www.exerciseismedicine.org). Physicians should begin with risk assessment so that patients with high-risk symptoms (eg, exertional chest pain, arrhythmias) or conditions (eg, cardiovascular, metabolic, pulmonary diseases) can be identified and undergo further testing before starting exercise programs. Patients at moderate risk (ie, those with 2 or more cardiovascular risk factors) can begin light or moderate exercise programs, and those at low risk can begin unrestricted exercise programs.

Patients with OA frequently experience deficiencies in gait, strength, flexibility, aerobic fitness, balance, and exercise capacity. Closed kinetic chain exercises, which allow the foot or hand to stay in constant contact with a surface, support joint stability and have been shown to be of benefit in patients with OA symptoms. Examples of closed kinetic chain exercise include tai chi, bicycling, swimming, hand wall slides, and resistance training using elastic tension bands. This is in contrast to open kinetic chain exercise, such as walking and running. These exercises only allow the foot to have intermittent contact with a surface and can cause shear forces on joints, which can aggravate OA symptoms.

Aquatic exercise has been shown to benefit patients with severe arthritis or patients who are unaccustomed to exercise. The buoyancy of the water decreases the effects of body weight on joints. A Cochrane review showed a small to moderate effect of aquatic exercise on function and quality of life in patients with OA, although data are limited.

Patients might further benefit from supervised exercise with a training partner. Supervised resistance training, such as aerobic and muscle-strengthening exercises, can provide symptomatic relief for patients without causing OA progression. A simple way patients can monitor the intensity of their exercise is to use the talk-sing rule. While exercising, patients should be able to talk but not sing. This allows each patient to exercise below their maximum effort level but with sufficient intensity. Table 2 provides recommendations for exercise participation for patients with OA.

**Case 1, cont’d.** You evaluate Ellen for her ability to start an exercise program using the American College of Sports Medicine questionnaire and find that she is at moderate risk based on her age and body mass index. Ellen is encouraged to start a light (ie, able to talk and sing while exercising) or moderate (ie, able to talk but not sing) exercise program. You discuss options with her and she signs up for a tai chi class. She also joins a local community-supported agriculture group, which provides more fresh food choices.
<table>
<thead>
<tr>
<th>Exercise Type</th>
<th>Recommended Duration and Intensity</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic Exercises</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking</td>
<td>30 min, 5 days/week</td>
<td>Easy to perform</td>
<td>Easy performed with partner</td>
</tr>
<tr>
<td></td>
<td>Talk-sing rule</td>
<td>Stress reducer</td>
<td>Environmental factors can limit</td>
</tr>
<tr>
<td>Water aerobics or swimming</td>
<td>60 to 90 min, 5 days/week</td>
<td>Buoyancy reduces joint stress</td>
<td>Swimsuit anxiety</td>
</tr>
<tr>
<td></td>
<td>Talk-sing rule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicycling</td>
<td>30 min, 5 days/week</td>
<td>Alternative exercise to walking</td>
<td>Wearing helmet</td>
</tr>
<tr>
<td></td>
<td>Talk-sing rule</td>
<td>Well tolerated by most patients</td>
<td>Balance issues</td>
</tr>
<tr>
<td><strong>Gait and Balance Exercises</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tai chi</td>
<td>30 min, 5 days/week</td>
<td>Helps balance</td>
<td>Not readily available or accepted by some patients</td>
</tr>
<tr>
<td></td>
<td>Talk-sing rule</td>
<td>Core strength</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Social—can be done in group setting</td>
<td></td>
</tr>
<tr>
<td><strong>Flexibility Training</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoga</td>
<td>Speak with physician before starting program</td>
<td>Core strength</td>
<td>Not readily available or accepted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stress reducer</td>
<td>Patient might not be able to tolerate certain positions</td>
</tr>
<tr>
<td><strong>Strength Training</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Machine-based</td>
<td>Not more than 3 days/week</td>
<td>Easy for beginners</td>
<td>Machines are not designed for all body types and sizes</td>
</tr>
<tr>
<td></td>
<td>Start with light weight and small number of repetitions and slowly increase</td>
<td>Ensures proper form</td>
<td>Machines act on a single joint</td>
</tr>
<tr>
<td></td>
<td>Speak with physician before starting program</td>
<td>Isolates specific muscle groups</td>
<td>Most machines allow movement along only one plane</td>
</tr>
<tr>
<td>Free weights</td>
<td>Not more than 3 days/week</td>
<td>Provides effective range of motion exercise</td>
<td>Requires greater hand and wrist strength</td>
</tr>
<tr>
<td></td>
<td>Start with light weight and small number of repetitions and slowly increase</td>
<td>Improves coordination and balance through use of synergistic and stabilizer muscles</td>
<td>If exercises are performed incorrectly from a standing position, they can place excessive strain on the lower back</td>
</tr>
<tr>
<td></td>
<td>Speak with physician before starting program</td>
<td>Provides greater exercise diversity, workouts can be customized</td>
<td>Requires strict form to be safe and effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires involvement of a spotter</td>
<td>Requires supervisor for greatest effect</td>
</tr>
</tbody>
</table>

*Patient should be able to talk but not sing.*

After 3 months, she reports feeling better and has lost 4.5 kg (10 lb). She brings in some information about acupuncture and avocado and soybean unsaponifiables and wants your opinion about their use as treatments for OA.

**Integrative Medicine Treatments**

Many patients are interested in integrative medicine treatments for OA. In the United States, the annual number of outpatient visits to integrative medicine practitioners is greater than the number of outpatient visits to mainstream physicians. In addition, out-of-pocket expenditures for integrative medicine are greater than those for hospitalization.

**Manipulative Therapy**

Manipulative therapy includes all techniques in which the hands are used to touch, feel, massage, or manipulate tissue therapeutically. It is difficult to assess effectiveness of manipulative therapy for OA as most studies of manipulative therapy also include therapeutic exercise. RCP/NICE recommends manipulative therapy as an adjuvant to exercise for all patients with arthritis. There is some evidence for use of manipulative therapy for treatment of hip OA but not for knee or ankle OA.

Because these studies were conducted with physical therapists trained in manual medicine, it is unclear what benefit manipulative therapy might have for patients under the care of other types of practitioners. In addition, no specific treatment protocols were provided.

**Acupuncture**

The Council of Acupuncture and Oriental Medicine Associations and the Foundation for Acupuncture Research have published evidence-based treatment guidelines for acupuncture and electroacupuncture. The guidelines provide general recommendations but none is specific for patients with OA. RCP/NICE found insufficient evidence to recommend use of acupuncture for the treatment of OA, but EULAR and OARSI recommend its use. RCP/NICE recommends against the use of electroacupuncture for treatment of patients with arthritis based on cost threshold for quality-adjusted life-years.

A randomized trial compared 3 treatment modalities in more than 1,000 patients with chronic knee OA: conservative treatment with NSAIDs and physical therapy, the same treatment and 10 acupuncture sessions, or the same treatment and 10 sham acupuncture sessions. The improvement rates were similar in sham and actual acupuncture groups (53% improvement) and both groups of patients experienced better outcomes than patients who underwent conservative treatment alone (29% improvement).

The RCP/NICE guidelines found the results of acupuncture studies mixed. Data from studies conducted over a time period of 26 weeks does not support the effectiveness of acupuncture over placebo for patients with OA. Acupuncture might provide some short-term benefit, but it is unclear which joints and which groups of patients with OA might benefit.

**Thermal Therapies**

The evidence for thermal therapies for arthritis treatment is limited to 3 small studies on cold application for pain relief. None showed a significant effect on pain relief or function. Superficial cooling should not be used in patients with Raynaud phenomenon, cryoglobulinemia, or cold hypersensitivity. If heat is used, application should not exceed 20 minutes at one time; it is suggested that patients use hot water bottles to avoid the possibility of thermal burn from heating pads.

Ultrasound diathermy is a therapeutic modality in which heat is applied to deep tissues. This modality is claimed to increase level of muscle function, but data are lacking.

Use of lasers as a form of heat has been studied in patients with OA. Although a systemic review showed insufficient evidence to support use of laser therapy, a more recent study found a decrease in pain with therapeutic laser treatment when the laser was applied to acupuncture points in patients with knee pain.

**Transcutaneous Electrical Nerve Stimulation**

Transcutaneous electrical nerve stimulation uses electrodes placed on the skin to stimulate superficial nerves to decrease pain. Although short-term decrease in pain has been claimed, the effect appears to cease as soon as the stimulation device is disengaged. A Cochrane review of 18 small trials could not confirm pain relief for knee OA with this modality because of poor quality trials and heterogeneity.

**Nonprescription Dietary Supplements**

At one time, use of glucosamine sulfate and chondroitin was recommended to decrease pain and progression of OA. It has been difficult to assess studies...
of these agents because of concerns about blinding in early trials and the multiple forms of glucosamine available (hydrochloric acid versus sulfate form). A Cochrane review found that only the Rotta preparation (ie, crystalline glucosamine sulfate) was associated with greater effectiveness of glucosamine than placebo in reduced pain and functional impairment in patients with symptomatic OA. RCP/NICE and AAOS recommend against the use of these agents and EULAR recommends neither for nor against use of glucosamine for hip OA.

A recent Cochrane review showed that the intake of avocado and soybean unsaponifiables provides long-term symptom relief for patients with OA, particularly those with hip OA. Other studies using willow bark and homeopathic remedies appear promising.

Addressing Functional Capacity and Considering Joint Replacement

It is important to assess and discuss functional level in patients with OA. Patients with OA in the hands have a good prognosis, whereas function for patients with knee OA is more variable. Approximately 66% of these patients’ conditions improve or remain stable over 5 years. Patients with hip OA have the worst prognosis, and many of these patients progress to discomfort that adversely affects their activities of daily living. In one longitudinal study of patients with moderate hip OA, 24% of symptomatic patients underwent hip replacement surgery and only 3% remained asymptomatic over an 8-year period.

When patients have exhausted pharmacologic and nonpharmacologic treatments but remain symptomatic, surgical options should be discussed. The inability to perform activities of daily living, increasing pain, and impaired sleep are all indications for referral for joint replacement. The previously discussed treatments also are important parts of treatment for patients with artificial joints.

Case 1, cont’d. Ellen returns for follow-up and is pleased with the symptom reduction that she attributes to the use of avocado and soybean unsaponifiables, acetaminophen, and monthly acupuncture treatments. Her weight loss has slowed but she continues to adhere to the diet. You encourage Ellen to pursue a greater level of exercise now that her symptoms have improved, and you schedule her for another follow-up in 6 months.
Advances in Rheumatoid Arthritis Management

Case 2. Sally is a 45-year-old English professor with seropositive rheumatoid arthritis diagnosed 2 months ago. She smokes approximately 1 pack/week of cigarettes. She is single and new to the area. She has no other health issues. She reports experiencing at least 1 hour/day of morning stiffness in the hands.

On physical examination, you find involvement of both wrists and metacarpophalangeal joints of the index and middle fingers. Rheumatoid factor and cyclic citrullinated peptide (CCP) antibody test results are positive, but results of x-rays of the hands are normal. Sally has no systemic signs of complications. She says she has tried nonsteroidal anti-inflammatory drugs with some success, but the treatment was not entirely effective. She asks you if there are any new drugs that can help.

Overview

Rheumatoid arthritis (RA) is a disease of chronic polyarticular inflammation primarily affecting peripheral joints, with proliferation of the synovium and the potential for joint destruction. RA is associated with a twofold increase in mortality rate. This is thought to be because of increased risks of myocardial infarction, infection, and certain malignancies.

Rheumatoid arthritis results in disability early in the disease process. One study showed that 80% of patients with RA of less than 2 years’ duration exhibited joint space narrowing on x-rays of the hands and wrists. Almost 66% of these patients had bony erosions.

Diagnosis

The American Rheumatism Association diagnostic criteria can be useful in assisting the physician with diagnosis of RA. If the patient has at least 4 of the findings noted in Table 3 that are present for at least 6 weeks, there is a high probability of RA. The revised American College of Rheumatology (ACR) classification criteria also can be used.

X-rays of the hands and wrists might show periarticular osteopenia, or, later, joint space narrowing or bony erosions. In addition, RA can be staged by observing bone erosion and ulnar deviation of the wrist.

Between 70% and 80% of patients with RA have positive rheumatoid factor test results, but the test has poor specificity. Most patients with RA have positive cyclic citrullinated peptide (CCP) antibody test results. The presence of CCP antibodies is useful in predicting which patients with RA will likely develop erosive disease. CCP antibody test results can be useful in distinguishing early RA from primary Sjögren syndrome or systemic lupus erythematosus because the test results usually are negative in patients with the latter.

Acute phase reactant tests such as erythrocyte sedimentation rate or C-reactive protein are not specific for RA. They can be useful in distinguishing between inflammatory arthritis and osteoarthritis (OA). These

### Table 3

American Rheumatism Association Diagnostic Criteria for Rheumatoid Arthritis

- Patients with RA will have 4 or more of the following:
  - Morning stiffness for at least 1 hour before improving of 6 or more weeks’ duration
  - Arthritis with soft tissue swelling affecting 3 or more joints for 6 or more weeks’ duration
  - Arthritis for 6 or more weeks’ duration affecting at least 1 of the following: wrist, metacarpophalangeal joint, or proximal interphalangeal joint
  - Symmetric involvement of the same joint on both sides of the body of at least 6 weeks’ duration
  - Nodules palpated over bony prominences or subcutaneously (rheumatoid nodules)
  - Abnormal amounts of serum rheumatoid factor
  - Radiographic bony changes (eg, erosions, decalcification) typical of RA

*Fourteen possible joint areas, including the hand (eg, metacarpophalangeal joints, proximal interphalangeal joints), wrist, elbow, knee, ankle, and metatarsophalangeal joints.

RA = rheumatoid arthritis.

tests might be more useful in monitoring disease activity than in diagnosing RA, but physical examination findings at the joints are more significant.

**Disease Assessment for Tailored Therapy**

The updated ACR guideline summarizes the newest pharmacotherapy information for patients with RA. The emphasis is on early use of disease-altering drugs and tailored therapy based on 3 aspects of the disease: duration, activity, and the presence of adverse prognostic factors. Table 4 summarizes the tools used for this assessment.

Disease stage is classified as early, intermediate, or late. Assessment of disease activity includes a review of symptoms, functional status, joint evaluation, extra-articular manifestations, laboratory markers, and radiographic studies.

Several tools have been developed for assessment of patient symptoms and physical findings, including joint involvement and extra-articular manifestations of disease. These tools have been validated in research settings but their use can be cumbersome in clinical settings. The most user-friendly are the Disease Activity Score 28 (DAS28), recommended by the European League Against Rheumatism (EULAR), and the Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI), recommended by the ACR. These tools provide cutoff points to aid in treatment decision-making. For example, SDAI scores of less than 11 indicate low disease activity and scores greater than 26 reflect high disease activity.

Factors associated with poor prognosis are listed in Table 4. These include concurrent medical conditions, cigarette smoking, lack of formal education, and lower socioeconomic status.

After assessment is complete, the ACR recommends classifying patients into 1 of 3 disease severity categories: mild, moderate, or severe (Table 5). Patients with mild disease typically have fewer than 6 inflamed joints, no extra-articular joint disease, and no evidence of erosions or cartilage loss on x-ray. Patients with severe disease typically have more than 20 inflamed joints, elevated inflammatory marker levels, and extra-articular manifestations of disease.

**Case 2, cont’d.** Although Sally could be classified as having early mild disease based on the clinical assessment and negative x-ray findings, the results for rheumatoid factor and CCP antibody tests are positive. These positive results indicate the possibility of future severe disease.

---

**Table 4**

American College of Rheumatology Recommendations for Rheumatoid Arthritis Assessment

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Early: &lt;6 months</th>
<th>Intermediate: 6 to 24 months</th>
<th>Long term: &gt;24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurement of disease activity</strong></td>
<td>Patient and physician assessment of symptoms and functional status</td>
<td>Simplified Disease Activity Index</td>
<td>Clinical Disease Activity Index</td>
</tr>
<tr>
<td>Evaluation of joint involvement and extra-articular manifestations</td>
<td>Disease Activity Score 28</td>
<td>Physical examination for rheumatoid nodules, evaluation for dermal or pleural involvement</td>
<td></td>
</tr>
<tr>
<td>Laboratory markers</td>
<td>C-reactive protein</td>
<td>Serum hemoglobin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CCP antibody</td>
<td>Serum albumin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythrocyte sedimentation rate</td>
<td>RF titers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum albumin</td>
<td>Platelet count</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>X-ray of both hands and wrists (only postero-anterior view needed)</td>
<td>In future, musculoskeletal ultrasound</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X-ray of both feet (only antero-posterior view needed)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Factors associated with poor prognosis**

Functional limitations
Extra-articular disease
Positive RF and CCP antibody test results
Bony erosions documented on x-ray

CCP = cyclic citrullinated peptide; RF = rheumatoid factor.

The ACR recommends a team approach to the treatment of patients with RA. At different times during the disease process, one physician might be more involved in patient management than another.

The first therapeutic action provided to patients with RA should be patient education. Data from 17 studies showed that patients with RA experienced significant decreases in pain and disability when they participated in detailed discussion and were given patient education.

Behavioral counseling also can significantly decrease patient pain and feelings of low self-esteem. Rheumatoid arthritis produces fatigue, and this makes the performance of many activities of daily living more difficult for patients with RA. These patients should be encouraged to make appropriate scheduling changes and consider workplace modifications, such as shorter work weeks, to improve function and performance.

Certain isometric, isotonic, and isokinetic exercises can improve patient function. Physical and occupational therapy also can be prescribed. In one randomized clinical trial, patients participating in an Arthritis Foundation exercise program who attended at least 9 of 16 sessions experienced decreased pain and stiffness that lasted at least 6 months, even if the patients stopped exercising.

Immunizations often are overlooked in patients with chronic conditions, but are particularly important for patients with RA. The ACR guideline recommends influenza vaccination for patients with RA before starting therapy with nonbiologic disease-modifying anti-rheumatic drugs (DMARDs). Hepatitis B vaccine should be administered if risk factors exist, and if vaccine has not previously been administered. In addition to receiving appropriate vaccinations, all patients who might be candidates for immunosuppressive treatments should be tested for tuberculosis.

Pain treatment is an important component of therapy. Acetaminophen, nonsteroidal anti-inflammatory drugs, and topical creams such as capsaicin can be used to manage pain and improve function. However, these drugs do not influence the RA disease process. A decrease in pain should not be interpreted as improved disease status and result in delayed use of DMARDs.

Treatments Tailored by Disease Severity

Case 2, cont’d. Sally returns to your office after visiting the rheumatology subspecialist, who prescribes methotrexate and recommends she take folic acid supplements to minimize adverse effects. She is counseled to abstain from drinking alcohol and to quit smoking.

Early and Mild Disease

The ACR strongly recommends that patients with possible RA be evaluated as candidates for use of DMARDs in the early stages of disease to attempt to prevent progression.

Corticosteroids suppress inflammation and are sometimes used early in the disease process to treat symptoms and improve function. The usual oral dose is equivalent to 5 to 7.5 mg/day of prednisone, a dosage that is relatively safe and can be used for an extended period. Corticosteroids do not prevent disease progression and most commonly are used in conjunction with DMARDs until a patient’s condition is stable. Patients with a single inflamed joint who are in otherwise healthy condition might benefit from intra-articular injections of depot corticosteroids.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Classification of Rheumatoid Arthritis Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Patient meets ACR criteria for diagnosis of rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>Fewer than 6 joints affected</td>
</tr>
<tr>
<td></td>
<td>No extra-articular disease</td>
</tr>
<tr>
<td></td>
<td>No bony erosions or cartilage loss on x-ray</td>
</tr>
<tr>
<td>Moderate</td>
<td>Does not meet criteria for mild or severe disease</td>
</tr>
<tr>
<td>Severe</td>
<td>More than 20 inflamed joints</td>
</tr>
<tr>
<td></td>
<td>Elevated ESR and/or CRP levels</td>
</tr>
<tr>
<td></td>
<td>AND 1 OR more of:</td>
</tr>
<tr>
<td></td>
<td>• Anemia and/or hypoalbuminemia</td>
</tr>
<tr>
<td></td>
<td>• Positive RF and/or CCP antibody test results</td>
</tr>
<tr>
<td></td>
<td>• Extra-articular disease</td>
</tr>
<tr>
<td></td>
<td>• Bony erosions or cartilage loss on x-ray</td>
</tr>
</tbody>
</table>

ACR = American College of Rheumatology; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor.

Information from Harris ED Jr, Schur PH, Maini RN. General principles of management of rheumatoid arthritis. UpToDate. Available by subscription at http://www.uptodate.com/online/content/topic.do?topicKey=rheumart/7684&selectedTitle=1~150&source=search_result#H11.
Treatment with DMARDs should be initiated within the first 3 months of RA diagnosis.\textsuperscript{52} The ACR divides DMARDs into nonbiologic (traditionally available) and biologic drugs (newer drugs).

**Nonbiologic disease-modifying anti-rheumatic drugs.** Nonbiologic DMARDs are a mainstay of RA treatment. They affect the entire infiltrating disease process, whereas newer biologic drugs target specific sites. DMARDs include methotrexate, leflunomide (Arava), hydroxychloroquine, and sulfasalazine. There is no evidence that differences in effectiveness or safety exist among methotrexate, leflunomide, and sulfasalazine.

### Table 6

**Drugs for Rheumatoid Arthritis Management**

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Dosage</th>
<th>Common Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-inflammatories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid (prednisone equivalent)</td>
<td>5 mg/day to 7.5 mg/day PO</td>
<td>GI upset, hypertension, hyperglycemia</td>
<td>Does not prevent disease progression</td>
</tr>
<tr>
<td>Corticosteroid (triamcinolone equivalent)</td>
<td>10 mg to 40 mg IA (depends on size of joint)</td>
<td>GI upset, hypertension, hyperglycemia</td>
<td>Useful if a single joint is involved</td>
</tr>
<tr>
<td><strong>Nonbiologic DMARDs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>7.5 mg/week PO initially, then titrate to 12.5 mg to 20 mg/week PO</td>
<td>Nausea, stomatitis, bone marrow suppression</td>
<td>Add folic acid supplementation 1 mg/day or 5 mg/week, FDA pregnancy category X</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>100 mg/day for 3 days, then 20 mg/day PO</td>
<td>Nausea, stomatitis, bone marrow suppression</td>
<td>More expensive</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>0.5 to 1 g/day PO for first week, then titrate by 500 mg each week to 2 g/day in 2 divided doses</td>
<td>Headache, diarrhea, reversible oligospermia</td>
<td>FDA pregnancy category B</td>
</tr>
<tr>
<td><strong>Biologic DMARDs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab (TNF inhibitor)</td>
<td>3 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks</td>
<td>Headache, nausea, infection</td>
<td>Usually used with methotrexate</td>
</tr>
<tr>
<td>Etanercept (TNF inhibitor)</td>
<td>50 mg/week or 25 mg 2 times/week SC</td>
<td>Headache, injection site reaction, respiratory tract infection</td>
<td>Can cause false-positive ANA test results</td>
</tr>
<tr>
<td>Rituximab (monoclonal antibody)</td>
<td>1,000 mg IV on days 1 and 15</td>
<td>Headache, fever, thrombocytopenia</td>
<td>Methylprednisolone usually given 30 min before rituximab infusion, usually given with methotrexate</td>
</tr>
<tr>
<td>Tocilizumab (monoclonal antibody)</td>
<td>4 mg/kg IV every 4 weeks, maximum dosage of 8 mg/kg IV every 4 weeks</td>
<td>Headache, hypertension, hypersensitivity reaction, GI perforation</td>
<td>Recently approved by FDA</td>
</tr>
</tbody>
</table>

**ANA = antinuclear antibody; DMARD = disease-modifying anti-rheumatic drug; FDA = Food and Drug Administration; GI = gastrointestinal; IA = intra-articular; IV = intravenous; PO = oral; SC = subcutaneous; TNF = tumor necrosis factor.**

zine based on comparative trials. The ACR guidelines use expert consensus to differentiate among these drugs. They recommend use of methotrexate and leflunomide over sulfasalazine in all patients, including those with significant disease activity.

Methotrexate is the drug of choice in early disease because it is well known and less expensive than leflunomide. It usually is started at a low dosage (eg, 7.5 mg/week), then the dosage is titrated until there is significant benefit or the maximum dosage of approximately 20 mg/week is achieved. Leflunomide is started at 100 mg/day for 3 days, then the dosage is decreased to the maintenance dosage of 20 mg/day.

Adverse effects of methotrexate and leflunomide include gastrointestinal upset, stomatitis, and bone marrow suppression. It is recommended that patients take folic acid to decrease these effects. Intake of alcoholic beverages should be avoided while a patient is taking methotrexate because of increased risk of liver damage.

Women who are pregnant or planning pregnancy should not take methotrexate or leflunomide. Women should discontinue methotrexate for 1 full menstrual cycle before attempting to conceive. For women considering pregnancy, sulfasalazine with a folic acid supplement can be prescribed.

A combination of 3 DMARDs (ie, methotrexate, hydroxychloroquine, sulfasalazine) has been found to be more effective than single drugs and should be considered. The goal of nonbiologic DMARD treatment should be remission or at least a decrease in disease activity.

**Biologic drugs.** These drugs include those that inhibit cytokines, such as tumor necrosis factor (TNF) (eg, infliximab [Remicade], etanercept [Enbrel], adalimumab [Humira]) and interleukin (IL) (eg, anakinra [Kineret]), and those that deplete B cells (rituximab [Rituxan]). In general, patients with mild disease who tolerate nonbiologic DMARDs should be treated with these drugs alone. If a patient does not tolerate a drug or has poor prognostic factors (eg, tobacco smoking, positive rheumatoid factor and CCP antibody test results), one of the biologic drugs can be added to the patient’s regimen.

Before starting these drugs, patients should undergo chest x-ray, be tested for tuberculosis, and receive vaccinations as previously discussed. Use of live virus vaccines (eg, herpes zoster, polio, rabies) is contraindicated.

Drugs that inhibit TNF have been shown to be more effective when combined with methotrexate. Observational data show that a TNF inhibitor can be combined with another DMARD if methotrexate is not tolerated. In contrast, combining 2 biologic drugs is not recommended because this is associated with increased frequency of adverse effects.

**Moderate or Severe Disease**

For patients with moderate to severe disease, glucocorticoids (eg, prednisone) can rapidly decrease symptoms when used in combination with methotrexate. The dosage of glucocorticoid should be gradually decreased as the patient’s condition improves.

Biologic drugs that suppress B cells (eg, rituximab) should be considered for patients with moderate to severe disease who do not benefit from methotrexate and a TNF inhibitor. Use of the TNF inhibitor should be discontinued before another biologic drug is started. Rituximab usually is administered as 2 1,000 mg intravenous infusions separated by 2 weeks. Prednisolone or its equivalent can be used in the infusion to decrease the intensity of adverse effects. Patients can continue methotrexate while taking this drug. Patients with active infection or severe heart failure or who are considering pregnancy should not take rituximab.

Another biologic drug option is the IL-1 receptor antagonist anakinra. This drug inhibits the binding of the cytokines produced in RA to receptors on the lymphocytes.

Tacitizumab (Actemra) is a humanized IL-6 receptor antibody recently approved by the Food and Drug Administration. In Europe, it is often used in combination with methotrexate in patients with moderate to severe RA who have not benefited from other drugs. Patients taking this drug should undergo monitoring of serum transaminase and cholesterol levels.

**Case 2, cont’d.** Sally’s symptoms and swollen joints have persisted despite use of methotrexate. The rheumatology subspecialist decides to add infliximab to Sally’s drug regimen after tuberculosis test results are negative. At this visit to your office, you provide the recommended vaccinations. Sally has started attending a local Living With Arthritis program. She reports this program is helpful because it offers an exercise program, counseling, and a support group. She says she is interested in smoking cessation and you prescribe bupropion.
Advances in Evaluation and Management of the Acutely Swollen Joint

Case 3. Robert is a 65-year-old man with a history of diabetes who presents to your office with an acutely swollen and painful right knee. On physical examination, he walks with an antalgic gait with limited ability to bear weight on the right leg. He has a temperature of 39°C (102.2°F). The right knee is swollen, erythematous, and extremely tender to palpation. He denies any recent trauma or skin lacerations in the area.

Differential Diagnosis

The differential diagnosis of an acutely inflamed joint includes trauma, crystal-induced arthropathy, infection, hemarthrosis, tumor, systemic rheumatologic disease, osteoarthritis, and torn meniscus or ligament. The 3 most common diagnoses to consider are trauma, crystalline disease, and infection. Arthritis attributable to systemic conditions also represents a significant subset; this can usually be identified by obtaining a complete history. Using data from 14 studies of 6,242 patients who met criteria for acute monoarticular synovitis (eg, swollen, warm joint), one review found that 653 (10.5%) had culture-diagnosed septic arthritis.

Trauma

Most patients with acute joint effusions from trauma recall the event. Certain high-risk patients, such as those with dementia or concussion or those who have ingested alcohol or illicit drugs, might not remember the trauma. If any possibility of trauma is suspected in a patient presenting with acute monoarticular arthritis, the affected joint should be imaged immediately.

Crystalline-Induced Arthropathy

Crystalline disease can be difficult to distinguish from septic arthritis; a subgroup of patients has both. Patients with crystalline disease have inflamed synovium that is characterized by severe pain reaching its peak in 6 to 12 hours, accompanied by swelling and redness of the joint. At times, the inflammation extends beyond the confines of the joint. Eighty percent of initial attacks of crystalline arthropathy involve a single joint, most commonly the metatarsophalan-geal joint of the first great toe (podagra) or the knee. It is impossible to differentiate clinically between acute gout (ie, monosodium urate crystals) and acute pseudogout (ie, calcium pyrophosphate crystals).

Septic Arthritis

The most common cause of septic arthritis in which an organism cannot be cultured on routine culture media is disseminated gonococcal infection. Women are 2 to 3 times more likely than men to present with this infection. The classic presentation is a triad of tenosynovitis, vesicular pustular skin lesions, and polyarthritis; some patients present only with monoarthritis.

Synovial fluid cultures test positive for Gonococcus in only 10% of patients with gonococcal arthritis, so a high index of suspicion must be maintained. Any skin lesions and clinically relevant areas, such as the genital and anus, should be cultured when this condition is suspected. Fortunately, patients with gonococcal arthritis do not develop the massive joint damage that is common with other causes of bacterial arthritis.

Although septic arthritis can result from introduction of bacteria from a bite, trauma, joint surgery, or osteomyelitis, the most common cause of bacterial arthritis is hematologic spread to the joint. The most common predisposing factors for hematologic spread are invasive procedures, such as central line placement, urinary catheter placement, and surgery. Patients with a history of joint or synovial inflammation (eg, rheumatoid arthritis, crystal-induced arthritis) are at increased risk of developing a septic joint.

Other risk factors for septic arthritis include age older than 80 years, diabetes, prosthetic joint, recent joint surgery, and skin infection. Among these, only recent joint surgery was associated with a high likelihood ratio (LR) of septic arthritis (positive LR = 6.9; 95% confidence interval [CI] = 3.8 to 12). However, combinations of these risk factors were found to substantially increase the risk. For example, a patient with a prosthetic joint and evidence of a skin infection who presented with acute joint pain was found to have a positive LR for a septic joint of 15 (95% CI = 8.1 to 21).

Patients with suspected septic arthritis and immuno-
compromise (eg, diabetes, HIV) should be evaluated for atypical causes of articular infection, including tuberculosis and fungi. Patients with histoplasmosis or coccidioidomycosis often present with pulmonary symptoms. Fungal organisms should be suspected in patients presenting with erythema nodosum.

**Evaluation of Patients With Suspected Septic Arthritis**

American College of Radiology guidelines for the initial evaluation of patients with acute musculoskeletal symptoms state that determining the presence or absence of synovitis is a critical initial step in differentiating septic arthritis from other causes of acute joint pain. Hallmarks of synovitis include soft tissue swelling, warmth over the joint, and joint effusion.

**Key Features of History and Physical Examination**

Septic arthritis can occur in any joint. Signs and symptoms vary and only 50% of patients with septic arthritis present with the classic hot joint. One literature review showed that joint pain was absent in 15% of patients presenting with septic arthritis (95% CI = 78% to 90%) and that joint swelling was absent in 12% of patients (95% CI = 71% to 85%). In another study of 80 patients presenting with joint symptoms and fever, only 46% had culture results that supported a diagnosis of bacterial arthritis.

These data suggest that a patient’s history and physical examination findings often are not helpful in the diagnosis of septic arthritis. The assessment of patients with these findings should be approached in a systematic way with consideration of risk factors to prevent excessive testing and overlooked diagnoses.

**Laboratory Tests**

White blood cell count, erythrocyte sedimentation rate, and C-reactive protein have limited diagnostic value in predicting which patients have septic arthritis because of the low specificities of these tests.

For any patient with suspected septic arthritis, a prompt attempt should be made to aspirate the joint. In the past, much emphasis was placed on physical aspects of the aspirate (eg, color, turbidity) and its glucose, protein, and lactate dehydrogenase content. However, studies have shown poor discriminative ability of these tests.

Synovial leukocyte count is useful in diagnosing septic arthritis in adults. An elevated synovial leukocyte count proportionately increases the likelihood of septic arthritis. A synovial leukocyte count of 25,000/mm$^3$ or greater was found to have a positive LR of 2.9. A count of 50,000/mm$^3$ or greater increased the positive LR to 7.7, and a count greater than 100,000/mm$^3$ increased the positive LR to 28 (high likelihood). The ability of this test to rule out septic arthritis is poor; the negative LR of septic arthritis with a synovial leukocyte count of less than 25,000/mm$^3$ was found to be 0.32. A polymorphonuclear (PMN) leukocyte proportion of 90% or more was shown to be associated with a relatively low positive LR for septic arthritis of 3.4 (95% CI = 2.8 to 4.2).

When aspiration is performed in the office setting, fluid should be sent immediately for culture and synovial leukocyte count with an indication as to which organisms could be present. Fluid can then be refrigerated if needed for later assessment.

**Imaging**

There is a paucity of data in this area, but an x-ray of the affected joint can be helpful in patients presenting with acute monoarticular joint pain in the following cases: history of significant trauma or focal bone pain; evaluation of the joint effusion when clinical evaluation is difficult, especially in the ankle and hip; or evaluation of chondrocalcinosis, tophaceous erosions, or joint space narrowing. In patients with bacterial infection of the joint, initial x-ray results can be normal or show swelling of soft tissue or joint effusion. Joint space narrowing and erosions are nonspecific findings that occur later in the disease process and have no role in acute evaluation.

Magnetic resonance imaging study has been suggested as the most effective imaging modality for septic joints because of its high sensitivity and high-quality soft tissue resolution. In the future, with appropriate physician training, office ultrasound might have great utility in identifying effusions and assisting in aspiration of joints.
Joint Aspiration

Arthrocentesis is essential for microbiologic diagnosis, which must be made early to allow prompt treatment to prevent joint damage. If a large amount of fluid is obtained, the diagnostic arthrocentesis can be therapeutic. It is unclear whether it is most effective to drain the joint with single or multiple arthrocenteses versus the use of arthroscopy or open drainage. An appropriate subspecialist should be consulted, as acute bacterial arthritis is a medical emergency.

One recommendation is to use single needle aspiration for a peripheral joint. The wrist or ankle can be most effectively aspirated with multiple joint aspirations. The knee and the shoulder are more suitable for arthroscopic drainage, and some experts advocate that synovium be removed in these patients.

Some experts recommend that open arthrotomy be performed on the axial joints, such as the hip and shoulder. These are all consensus-based recommendations.

Controversy exists about the subgroup of patients that, despite early treatment, goes on to develop severe arthritis. This can be secondary to bacterial DNA in the synovium causing an inflammatory response, even in the absence of signs of infection.

Evaluation of Patients With Monoarthritis

The physician should follow a systematic approach in the evaluation of patients with monoarthritis with acutely swollen joints (Figure 1). If there is a history of trauma, the joint should be x-rayed and evaluated for other pathology. The physician also should consider recent travel abroad and medical conditions including reactive arthritis (eg, recent diarrhea, other types of infection), sickle cell disease, and Lyme disease. In young patients, gonococcal arthritis should be considered.

Septic arthritis should be suspected when patients with risk factors present with joint pain. The physician should immediately aspirate the joint or refer the patient for prompt aspiration, and send the resulting fluid for culture and synovial leukocyte count with a differential cell count. The probability of a septic joint is increased when there are more than 90% PMN leukocytes in the fluid.

Case 3, cont’d. Robert is considered at high risk of a septic joint based on the presence of fever and diabetes. Aspiration of the right knee is performed and the specimen is sent for crystal analysis, synovial leukocyte count with differential cell count, and culture. He is sent to the hospital to receive intravenous antibiotics.

Management of Suspected Septic Arthritis

High-risk patients with suspected septic arthritis should be treated empirically with intravenous antibiotics, even if the Gram stain is negative, until culture results return. The decision to not treat empirically can be made in patients with negative Gram stain who are classified at low risk after evaluation of the synovial fluid leukocyte count and percentage of PMN leukocytes.

There is little data to guide treatment duration for septic joints. Some experts recommend 14 days of intravenous therapy followed by 14 days of oral therapy. Treatment should be based on culture results and local antibiotic sensitivities. Staphylococcus aureus infections can require longer treatment.
Figure 1. Evaluation of Patients With Monoarthritis

- **High-risk patients include those older than 80 years and those with diabetes, rheumatoid arthritis, prosthetic joint, recent joint surgery, or skin infection.**
- **Synovial WBC count ≥25,000/mm³.**

CBC = complete blood count; INR = international normalized ratio; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; PMN = polymorphonuclear; PT = prothrombin time; STI = sexually transmitted infection; WBC = white blood cell.
Advances in Gout Management

Case 4. Teng is a 42-year-old man with no significant medical conditions who presents to the emergency department with an acutely swollen and painful right toe. He takes no drugs and denies any recent trauma. He noticed that the pain started the night after he attended a wedding ceremony.

On physical examination, Teng has an erythematous, swollen, and exquisitely tender right first metatarsophalangeal joint. Any passive movement of this joint aggravates the pain.

Gout is a metabolic disease associated with increased intra-articular uric acid level; episodic acute and chronic arthritis; and deposition of monosodium urate (MSU) crystals in joints, connective tissue (tophi), and the kidneys. Recently, it has been suggested that gout be used as a general term to describe all crystal-induced arthropathies, including those involving calcium pyrophosphate dihydrate (pseudogout), calcium hydroxyapatite, and calcium oxalate. This was suggested because all are associated with similar clinical findings and definitive diagnosis requires joint fluid aspiration. However, for the purpose of this section, the narrower definition of gout as MSU-crystal arthropathy is used.

Hyperuricemia can be caused by underexcretion or overproduction of uric acid, contributed to by ingestion of purine-rich foods that are metabolized into urate. Other mammalian species are able to transform uric acid into allantoin, a highly soluble substance that can be excreted by the kidneys. Humans lack an active uricase gene that allows for this conversion and, as a result, have serum uric acid concentrations approaching the theoretical limit of solubility (6.8 mg/dL). Without the ability to metabolize urate, it must be eliminated daily by the intestines (a passive process) and the kidneys, where most uric acid excretion occurs.

Diagnosis

The gold standard for gout diagnosis is microscopic evaluation of a sample of synovial fluid for MSU crystals. The aspirate can be centrifuged into a button that can be viewed first under regular light and, if available, under a polarizing microscope. The MSU crystals appear as bright yellow needle-like crystals when parallel to a marked axis termed negatively birefringent under compensated polarized light.

However, the majority of patients with crystal-induced arthritis are diagnosed presumptively without joint aspiration. Many patients present with acute joint inflammation in the lower extremity, most commonly the first metatarsal joint. Most patients with gout are treated by family physicians. One study found that only 10% of patients with gout were referred to rheumatology subspecialists, and the vast majority were diagnosed and treated without joint aspiration. There are many reasons for this, including failed arthrocentesis, physician discomfort with joint aspiration, and time or resources needed to evaluate synovial fluid. Another issue that can complicate diagnosis is that uric acid levels are not always elevated during episodes of acute gout.

For these reasons, the European League Against Rheumatism (EULAR) developed criteria for the presumptive diagnosis of crystal-induced arthritis. These expand on the earlier criteria for gout published by the American College of Radiology (ACR) in 1977. The initial ACR guideline was criticized because not all patients present with 6 of the 12 criteria and radiologic findings are difficult to interpret unless the patient has chronic uric acid arthropathy. The sensitivity of the initial diagnostic guideline (ie, 6 criteria present) was found to be only 88%.

In the family medicine setting, it is reasonable to use the EULAR guideline for a presumptive diagnosis of gout. The guideline states that for typical presentations of gout (eg, recurrent podagra with hyperuricemia), a clinical diagnosis alone is reasonably accurate but is not definitive without confirmation of presence of crystals.

Risk Factors

There are many risk factors, conditions leading to hyperuricemia, and triggers associated with acute gout (Table 7). In addition to several inherited enzyme defects, such as glucose-6-phosphate dehydrogenase deficiency, conditions or drugs that increase uric acid production or decrease urate excretion increase the risk of gout. Obesity, diabetes, hypertension, and hyperlipidemia are all associated with an increased risk
of gout; thus, patients with gout should be evaluated for other health risk factors and associated comorbidities. As these diseases become more prevalent in the population, so will gout.

Although hyperuricemia is the biologic precursor of gout, many patients with hyperuricemia remain asymptomatic. The annual incidence of gout in patients with elevated uric acid levels increases from 0.5% in individuals with uric acid levels between 7 and 8.9 mg/dL to 4.5% in those with levels higher than 8.9 mg/dL. Men primarily are affected, but after middle age, women are twice as likely as men to be hyperuricemic and the incidence of gout increases.

### Differentiating Gout and Pseudogout

Pseudogout or calcium pyrophosphate dihydrate arthritis clinically is indistinguishable from acute gout. However, the knee is more often affected in pseudogout (more than 50% of acute gout). Pseudogout can be associated with severe patellar arthritis. Calcification of cartilage or meniscus on x-ray is pathognomonic for diagnosis of pseudogout. Definitive diagnosis depends on joint aspiration and crystal identification. Gout and pseudogout are treated similarly in the acute setting, but long-term management strategies differ.

Patients with pseudogout should be screened for hemochromatosis, hyperparathyroidism, hypomagnesemia, hypophosphatemia, hypothyroidism, and familial hypercalcemia. Uric acid, calcium, phosphorus, magnesium, alkaline phosphatase, ferritin, iron, and thyroid-stimulating hormone levels should be evaluated.

Both ACR and EULAR are in the process of developing specific guidelines to further aid in the diagnosis of pseudogout. However, the gold standard remains microscopic evaluation of synovial fluid for typical rhomboid or rod-shaped crystals that exhibit positive birefringence on compensated polarized light. Physicians who do not perform joint aspirations can refer patients to musculoskeletal subspecialists to confirm the diagnosis and to treat first-time acute pseudogout without joint aspiration.

**Case 4, cont’d.** Teng presents with classic features of crystal-induced arthritis, likely gout. Teng’s Asian ethnicity also increases the likelihood of gout. He is at low risk of an infectious process but you decide to attempt joint aspiration for a definitive diagnosis. You approach the joint laterally under the extensor tendon, successfully obtain a sample of synovial fluid, and confirm gout at follow-up.

Because he has no contraindications, you begin treatment with a nonsteroidal anti-inflammatory drug and

<table>
<thead>
<tr>
<th>Table 7 Gout-Associated Risk Factors, Conditions, and Triggers</th>
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</thead>
<tbody>
<tr>
<td><strong>Demographic factors</strong></td>
</tr>
<tr>
<td>Men and postmenopausal women</td>
</tr>
<tr>
<td>Asian or South Pacific Islander</td>
</tr>
<tr>
<td><strong>Clinical conditions directly associated with gout</strong> (purine or urate overproduction)</td>
</tr>
<tr>
<td>Malignancies</td>
</tr>
<tr>
<td>Hemolytic, lymphoproliferative, and myeloproliferative conditions</td>
</tr>
<tr>
<td>Glycogen-storage diseases</td>
</tr>
<tr>
<td>Hypoxanthine-guanine phosphoribosyltransferase deficiency</td>
</tr>
<tr>
<td>Down syndrome</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td><strong>Dietary factors associated with gout</strong></td>
</tr>
<tr>
<td>Increase risk</td>
</tr>
<tr>
<td>• Seafood</td>
</tr>
<tr>
<td>• Red meat</td>
</tr>
<tr>
<td>• Alcohol</td>
</tr>
<tr>
<td>Decrease risk</td>
</tr>
<tr>
<td>• Dairy products</td>
</tr>
<tr>
<td><strong>Drugs associated with gout</strong></td>
</tr>
<tr>
<td>Allopurinol (upon initiation or cessation)</td>
</tr>
<tr>
<td>Acetylsalicylic acid (aspirin)</td>
</tr>
<tr>
<td>Cytotoxic drugs</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Ethambutol</td>
</tr>
<tr>
<td>Nicotinic acid</td>
</tr>
<tr>
<td>Warfarin</td>
</tr>
<tr>
<td><strong>Triggers for acute gout</strong></td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Intravenous contrast material</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Psoriasis exacerbation</td>
</tr>
</tbody>
</table>

send him to a laboratory for uric acid level and creatinine testing. You ask him to return in 2 weeks for a follow-up and a second uric acid level test if the first test results are normal. You encourage him to telephone the office or return sooner if the pain does not decrease.

**Treatments for Acute Gout**

The main focus of treatment of acute gout is pain relief. Pain usually is intense and lasts 2 to 5 days in most cases, but can last up to 2 weeks. Although it has been theorized that low body temperature causes precipitation of urate crystals, there is some evidence that use of cold packs can provide pain relief after the inflammatory process starts.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been the mainstay of treatment in patients with acute gout. Cyclooxygenase-2 inhibitors also have been used. (These drugs should be used with caution in elderly patients with renal insufficiency.)

Corticosteroids, given orally or injected into the joint, also can be considered for patients with acute gout. EULAR gives a moderate strength of recommendation to intra-articular aspiration and injection of long-acting corticosteroids despite lack of evidence from randomized clinical trials. A course of oral corticosteroids is relatively safe and might be particularly helpful in patients with polyarticular gout or those unable to tolerate other forms of therapy.

Colchicine has been a mainstay of treatment for acute gout for generations. The traditional recommendation is 1 mg followed by 0.5 mg every 2 hours until symptoms abate. However, at this dosage there are high risks of gastrointestinal upset and toxicity. A recent Cochrane review showed that colchicine was cost-effective for treatment of acute gout (number needed to treat = 3). A lower dose using 0.5 mg 3 times/day is better tolerated and is a mainstay of treatment in Europe.

Research on interleukin-1 inhibition has shown some promise and the biologic drug anakinra has been used. This drug directly affects the interleukin-1 released by the leukocytes in acute gout.

**Follow-Up and Long-Term Treatment**

After acute treatment, a follow-up office visit should occur in 2 weeks to assess the patient’s progress. At this time, the uric acid level should be measured, kidney function evaluated (ie, blood urea nitrogen-creatinine ratio), and further therapy discussed. Lifestyle modifications are first-line treatment for long-term management. Concurrent treatment of hypertension, hyperglycemia, and hyperlipidemia can decrease recurrence of acute gout. The physician should review the patient’s drugs for those that increase the serum uric acid level. For patients with hypertension, low-dose losartan (Cozaar) was found to be more effective than other angiotensin receptor blockers or angiotensin-converting enzyme inhibitors in increasing renal clearance of uric acid.

A large study showed that a high-protein diet high in low-fat dairy foods decreased recurrence of acute gout. Plant-based proteins should be ingested as much as possible, as meats and certain fish can increase uric acid levels. The Mediterranean diet, often recommended for patients with metabolic syndrome, is useful in lowering uric acid levels as well. Certain types of alcohol can increase uric acid levels, especially beer, and intake of these should be discouraged; however, moderate use of wine does not appear to increase uric acid levels.

Patients with more than 2 or 3 episodes of acute gout per year should be considered for long-term treatment with uric acid level-lowering drugs. Allopurinol has been the mainstay for lowering the uric acid level and preventing recurrent episodes of acute gout. It usually is started at 100 mg/day and can be titrated to an average dosage of 300 mg/day, higher if needed (to 800 mg/day), to achieve a serum urate level of less than 6 mg/dL. At this level, crystals are resorbed and new formation is prevented.

It has been proposed that lower doses of allopurinol be used, or at least started, for patients with glomerular filtration rates less than 40 mL/min. The goal serum urate level should still be 6.0 mg/dL.

Approximately 3% to 5% of patients taking allopurinol develop a rash, leukopenia, diarrhea, or fever. A smaller number can develop allopurinol hypersensitivity syndrome, which causes eosinophilia, hepatic...
injury, and acute kidney injury in addition to rash and fever. This syndrome can be life-threatening. Allopurinol can interact with certain drugs, such as azathioprine. When allopurinol is taken with cyclophosphamide, it can cause bone marrow suppression. Allopurinol treatment also is associated with a marked increase in likelihood of an ampicillin-induced rash.

Concurrent use of NSAIDs or colchicine at low doses is recommended when starting allopurinol to prevent episodes of acute gout that can occur any time urate-lowering drugs are initiated. EULAR recommends use of NSAIDs or colchicine for a minimum of 6 months.

Patients who are unable to tolerate allopurinol might benefit from uricosuric drugs to improve uric acid clearance from the bloodstream by the kidney. Probenecid is such a drug, but it is not effective in patients with renal disease and is not used in patients who overproduce uric acid because it can cause renal stones. Probenecid usually is initiated at 250 mg 2 times/day and the dosage slowly titrated to a maximum of 3 g/day, based on serum urate levels. This drug should not be used in patients with nephrolithiasis, uric acid nephropathy, or cystinuria.

Febuxostat (Uloric) is a drug recently approved by the Food and Drug Administration to manage hyperuricemia in patients with chronic gout. This drug is a selective oxidase inhibitor that does not appear to induce hypersensitivity or cause adverse effects in patients with renal disease. Febuxostat can be initiated at 80 mg/day or 120 mg/day. It produces a rapid decrease in uric acid level, but also requires concurrent use of colchicine 0.6 mg 2 times/day to prevent episodes of acute gout. Liver function tests should be performed periodically in patients taking this drug.


Arthritis Update


References
Arthritis Update


Section One

Questions 1-5 have only one correct answer.

1. According to the European League Against Rheumatism, which 3 signs on physical examination are most useful in the diagnosis of osteoarthritis?
   - A. Crepitus, restricted movement, and bony enlargement.
   - B. Pain in the joint line, limited motion, and bony enlargement.
   - C. Antalgic gait, morning stiffness, and ligamentous laxity.
   - D. Bony enlargement, pain on palpation, and popping with motion.
   - E. Crepitus, pain on palpation, and popping with motion.

2. A 48-year-old overweight man presents for his annual physical examination. He has just been to see his mother, who has severe osteoarthritis (OA) and is recovering from knee replacement surgery. He is anxious to prevent OA. Which one of the following should you advise?
   - A. Aerobic exercise.
   - B. A 4.5-kg (10-lb) weight loss.
   - C. Avoidance of running as exercise.
   - D. Glucosamine.
   - E. Nothing can be done to prevent OA.

3. An 80-year-old woman with hip osteoarthritis continues to experience difficulty with activities of daily living because of pain. She was unable to perform prescribed exercises because of pain. She is taking acetaminophen in adequate doses. Which one of the following is a reasonable next option to reduce pain and increase her ability to exercise?
   - A. Refer her for manipulative therapy.
   - B. Prescribe a short-term narcotic drug.
   - C. Recommend a trial of acupuncture.
   - D. Prescribe a transcutaneous electrical nerve stimulation unit.
   - E. Recommend hip surgery.

Section Two

Questions 6-10 have only one correct answer.

4. A patient with osteoarthritis presents to your office for follow-up. She reports continued knee pain despite adequate doses of acetaminophen and an exercise program. She asks about other treatment options. Which one of the following should you recommend based on strong scientific evidence?
   - A. Intra-articular hyaluronic acid joint injections.
   - B. Knee bracing.
   - C. Arthroscopic debridement.
   - D. A Rotta preparation of glucosamine.
   - E. Manipulative therapy.

5. A patient with severe hip osteoarthritis presents to your office to discuss hip replacement surgery. She has tried physical therapy, manipulative therapy, and acupuncture with no sustained benefit. She is experiencing difficulty sleeping and limitations in performing daily activities. You agree to provide a referral to an orthopedic surgeon, but you suggest she try which one of the following therapies?
   - A. Transcutaneous nerve stimulation.
   - B. Continued physical therapy.
   - C. Glucosamine.
   - D. Electroacupuncture.
   - E. Avocado and soybean unsaponifiables.

6. Which one of the following tests is useful in predicting which patients with rheumatoid arthritis will likely develop erosive disease?
   - A. Erythrocyte sedimentation rate.
   - B. C-reactive protein.
   - C. Rheumatoid factor.
   - D. Platelet count.
   - E. Cyclic citrullinated peptide antibody.
7. You are seeing a patient with early rheumatoid arthritis to plan her treatment program. Which one of the following 3 aspects of the condition should be assessed to plan tailored therapy?
   - A. X-ray evidence of osteopenia, joint space narrowing, and bony erosions.
   - B. Presence of bony abnormalities, serum markers, and pain.
   - C. Disease duration, activity, and the presence of adverse prognostic factors.
   - D. Concurrent medical conditions, cigarette smoking, and alcohol consumption.
   - E. Disease duration, concurrent medical conditions, and health habits.

8. Baseline treatment for all patients with rheumatoid arthritis should include which one of the following?
   - A. Patient education.
   - B. Physical therapy.
   - C. Regular dosing with acetaminophen regardless of pain.
   - D. A short course of corticosteroids.
   - E. Initiation of a biologic treatment agent.

9. You are seeing a patient with mild rheumatoid arthritis. Her rheumatology subspecialist prescribed low-dose methotrexate 1 month ago and provided patient education materials. She is experiencing only mild gastrointestinal symptoms but continued pain. You administer vaccines and agree to increase her dose of methotrexate. Which one of the following should also be instituted?
   - A. Intra-articular injection of corticosteroids.
   - B. Folic acid.
   - C. Addition of a second nonbiologic agent.
   - D. Addition of a biologic agent.
   - E. Bed rest until the pain decreases.

10. A patient with moderate rheumatoid arthritis is about to begin taking a biologic agent. He exercises regularly and his pain is well controlled. You administer vaccines and obtain which one of the following?
    - A. Cyclic citrullinated peptide antibody.
    - B. Erythrocyte sedimentation rate.
    - C. Hand x-rays.
    - D. Chest x-ray to assess for tuberculosis.
    - E. Complete blood count.

Questions 11-15 have only one correct answer.

11. A 32-year-old woman presents to your office with an acutely swollen wrist and ankle but no history of trauma. She has a vesicopustular skin rash but no other findings on physical examination. You suspect gonococcal arthritis and aspirate the wrist joint. Because you know that only 10% of synovial fluid cultures test positive for *Gonococcus* in patients with this infection, you also obtain which one of the following?
    - A. Blood cultures.
    - B. Cultures from the skin lesions.
    - C. Serum for C-reactive protein and white blood cell count.
    - D. Genital cultures.
    - E. Both B and D.

12. Of the many risk factors for septic arthritis, which one of the following is most useful in predicting the probability of a septic joint (ie, highest positive likelihood ratio)?
    - A. Recent joint surgery.
    - B. Age older than 80 years.
    - C. Presence of diabetes.
    - D. Skin infection.
    - E. HIV infection.

13. After aspirating the knee of a patient with acute monoarticular arthritis, you request the fluid be evaluated for crystals. In addition, which one of the following tests of the synovial fluid should be obtained for early confirmation of septic arthritis?
    - A. Bacterial culture.
    - B. Cytology.
    - C. Antibodies to bacterial antigens.
    - D. Synovial leukocyte count.
    - E. Lactase dehydrogenase.

14. In a patient who denies trauma or focal bone pain, which one of the following would warrant consideration of imaging an acutely swollen joint?
    - A. To protect against litigation.
    - B. When the clinical evaluation is difficult.
    - C. When hospitalization is planned.
    - D. Under no circumstances should imaging be considered.
    - E. When Lyme disease is suspected.
15. You suspect septic arthritis in a patient with diabetes and an artificial joint. Which one of the following is the appropriate treatment for this patient?

- A. Empiric treatment with oral antibiotics until culture results return.
- B. Empiric treatment with intravenous antibiotics until culture results return.
- C. Watchful waiting if the Gram stain results show no bacteria in the initial aspirate.
- D. Combination oral and intravenous antibiotics until culture results return.
- E. Intravenous antibiotics after culture results are obtained.

18. A patient presents to your office with acute gout affecting several joints. You prescribe a nonsteroidal anti-inflammatory drug and colchicine. Which one of the following additional drugs might be useful, particularly if you are concerned the patient might not tolerate colchicine?

- A. Allopurinol.
- B. Acetaminophen.
- C. Gabapentin.
- D. Oral corticosteroids.
- E. Amitriptyline.

19. You are counseling a patient with gout about diet. After a brief review of his food preferences, you recommend which one of the following dietary changes?

- A. Increase protein intake from meat sources.
- B. Increase carbohydrate intake.
- C. Increase daily intake of beer.
- D. Increase fish consumption.
- E. Increase consumption of low-fat dairy foods.

20. A patient returns for follow-up after undergoing treatment for acute gout. You discuss beginning allopurinol at 100 mg/day for the hyperuricemia, advise that she continue the anti-inflammatory drug to prevent an acute flare-up, and warn her about potential drug interactions. Which one of the following is the serum urate level target for hyperuricemia treatment?

- A. Less than 8 mg/dL.
- B. Less than 6 mg/dL.
- C. Less than 4 mg/dL.
- D. Less than 2 mg/dL.
- E. Less than 1 mg/dL.
Posttest Answers

Section One
Question 1: The correct answer is A.
The European League Against Rheumatism evidence-based diagnostic guidelines list 3 symptoms (ie, persistent knee pain, limited morning stiffness, decreased function) and 3 signs (ie, crepitus, restricted movement, bony enlargement) as most useful in the diagnosis of osteoarthritis. See page 13.

Question 2: The correct answer is B.
The American College of Sports Medicine and four guideline developers (ie, American Academy of Orthopedic Surgeons, Royal College of Physicians/National Institute for Health and Clinical Excellence, European League Against Rheumatism, and Osteoarthritis Research Society International) recommend weight-loss programs for overweight patients. One study that monitored patients for 10 years showed that a 4.5-kg (10-lb) weight loss decreased the likelihood of knee osteoarthritis (OA) development by 50%. The relationship between amount of weight loss and the incidence of OA appears to be linear, suggesting even modest weight loss is beneficial. See page 16.

Question 3: The correct answer is A.
The Royal College of Physicians/National Institute for Health and Clinical Excellence recommends manipulative therapy as an adjuvant to exercise for all patients with arthritis. There is some evidence for use of manipulative therapy for treatment of hip osteoarthritis (OA) but not for knee or ankle OA. See page 18.

Question 4: The correct answer is D.
A Cochrane review found that the Rotta preparation (ie, crystalline glucosamine sulfate) was associated with greater effectiveness of glucosamine than placebo in reduced pain and functional impairment in patients with symptomatic osteoarthritis. See page 19.

Question 5: The correct answer is E.
A recent Cochrane review showed that the intake of avocado and soybean unsaponifiables provides long-term symptom relief for patients with osteoarthritis (OA), particularly those with hip OA. See page 19.

Section Two
Question 6: The correct answer is E.
Most patients with rheumatoid arthritis (RA) have positive cyclic citrullinated peptide (CCP) antibody test results. The presence of CCP antibodies is useful in predicting which patients with RA will likely develop erosive disease. See page 20.

Question 7: The correct answer is C.
In management of rheumatoid arthritis, the emphasis is on early use of disease-altering drugs and tailored therapy based on 3 aspects of the disease: duration, activity, and the presence of adverse prognostic factors. See page 21 and Table 4.

Question 8: The correct answer is A.
The first therapeutic action provided to patients with rheumatoid arthritis should be patient education. See page 22.

Question 9: The correct answer is B.
Adverse effects of methotrexate and leflunomide include gastrointestinal upset, stomatitis, and bone marrow suppression. It is recommended that patients take folic acid to decrease these effects. See page 24 and Table 6.

Question 10: The correct answer is D.
Before starting biologic drugs, patients should undergo chest x-ray, be tested for tuberculosis, and receive vaccinations as discussed in the text. See page 24.

Section Three
Question 11: The correct answer is E.
Synovial fluid cultures test positive for Gonococcus in only 10% of patients with gonococcal arthritis, so a high index of suspicion must be maintained. Any skin lesions and clinically relevant areas, such as the genitals and anus, should be cultured when this condition is suspected. See page 25.

Question 12: The correct answer is A.
Recent joint surgery was associated with a high likelihood ratio (LR) of septic arthritis (positive LR = 6.9; 95% confidence interval = 3.8 to 12). See page 25.

Question 13: The correct answer is D.
Synovial leukocyte count is useful in diagnosing septic arthritis in adults. An elevated synovial leukocyte count proportionately increases the likelihood of septic arthritis. See page 26.

Question 14: The correct answer is B.
An x-ray of the affected joint can be helpful in patients presenting with acute monoarticular joint pain in the following cases: history of significant trauma or focal bone pain; evaluation of the joint effusion when clinical evaluation is difficult, especially in the ankle and hip; or evaluation of chondrocalcinosis, tophaceous erosions, or joint space narrowing. See page 26.
Question 15: The correct answer is B.
High-risk patients with suspected septic arthritis should be treated empirically with intravenous antibiotics, even if the Gram stain is negative, until culture results return. See page 27.

Section Four

Question 16: The correct answer is A.
The guideline states that for typical presentations of gout (e.g., recurrent podagra with hyperuricemia), a clinical diagnosis alone is reasonably accurate but is not definitive without confirmation of presence of crystals. See page 29.

Question 17: The correct answer is D.
Allopurinol, aspirin, cytotoxic drugs, cyclosporine, diuretics, ethambutol, nicotinic acid, and warfarin are associated with gout. See Table 7.

Question 18: The correct answer is D.
A course of oral corticosteroids is relatively safe and might be particularly helpful in patients with polyarticular gout or those unable to tolerate other forms of therapy. See page 31.

Question 19: The correct answer is E.
A large study showed that a high-protein diet high in low-fat dairy foods decreased recurrence of acute gout. See page 31.

Question 20: The correct answer is B.
Allopurinol usually is started at 100 mg/day and can be titrated to an average dosage of 300 mg/day, higher if needed (to 800 mg/day), to achieve a serum urate level of less than 6 mg/dL. See page 31.

Erratum

An error occurred in *FP Essentials™*, Edition No. 364, Sports-Related Conditions. The text and table on page 26 should list that the purpose of the lift-off test is to help diagnose subscapularis tendon tears.

An error occurred in *FP Essentials™*, Edition No. 366, Seizure Disorders. With regard to electroencephalogram (EEG) findings in children, page 35 should read, “A normal EEG finding at the time of discontinuation of therapy is associated with a decreased incidence of seizure recurrence.”
Notes
Notes
The following topics appear in this month’s edition of the AAFP FP Audio™ program:

**Clinical Topic:** Treatment-Resistant Hypertension

**SAM Pearls:** Postpartum Issues

**Journal Notes**

**Board Review Minute**

**Guidelines Update/Editor’s Minute**

The next edition of AAFP FP Essentials™ will be:

**Gastrointestinal Conditions**