Rheumatology questions are FUN

- Specific autoantibodies
- Quirky findings
- Must know your disease scripts!
- It is entirely possible to do really well on the rheumatology section
Approaching board-type questions

• Read the stem
• Pay attention to:
  • Age
  • Gender
  • Occupation
  • Current complaint
  • Geographical area
  • PMHx
  • FHx
  • Labs

• What is the dx, is this a particular subset of the disease (severe, etc.)?
• Now read the question and the answer options – don’t get distracted!
<table>
<thead>
<tr>
<th>Disease(s)</th>
<th>Antibody</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE, Scleroderma, Sjögren’s, MCTD, DILE, RA, PAN, poly/dermatomyositis</td>
<td></td>
<td>Notable if &gt;1:80, does NOT correlate with ds activity</td>
</tr>
<tr>
<td>SLE</td>
<td></td>
<td>Specific for lupus – low sensitivity. More likely to have lupus nephritis, <a href="#">correlates with disease activity</a> – helps to confirm a flare</td>
</tr>
<tr>
<td>SLE, Sjögren’s</td>
<td></td>
<td>Neonatal lupus erythematosis, Congenital heart block</td>
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<tr>
<td>SLE, MCTD</td>
<td></td>
<td>Does NOT correlate w/ds activity</td>
</tr>
<tr>
<td>SLE</td>
<td></td>
<td>Highly specific for SLE. Does NOT correlate w/disease activity</td>
</tr>
<tr>
<td>Drug-induced SLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td></td>
<td>Non-specific.</td>
</tr>
<tr>
<td>RA</td>
<td></td>
<td>More specific, more severe ds.</td>
</tr>
<tr>
<td>LcSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DcSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DcSS</td>
<td></td>
<td>Increased risk renal ds; less pulmonary fibrosis, better survival than anti-ScL 70</td>
</tr>
<tr>
<td>Dermatomyositis/Polymyositis</td>
<td></td>
<td>Predicts ILD</td>
</tr>
<tr>
<td>GPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGPA</td>
<td></td>
<td>also microscopic polyangiitis, RPGN</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Synovial fluid review

<table>
<thead>
<tr>
<th>Color</th>
<th>WBC</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear/pale yellow, transparent</td>
<td>&lt; 200</td>
<td></td>
</tr>
<tr>
<td>Clear/yellow</td>
<td>&lt; 2K</td>
<td></td>
</tr>
<tr>
<td>Yellow/white, cloudy</td>
<td>2K → 100K</td>
<td></td>
</tr>
<tr>
<td>White, opaque</td>
<td>&gt; 100K</td>
<td></td>
</tr>
</tbody>
</table>

*Synovial fluid: 3 Cs – cell count, crystals, culture*
Gonococcal arthritis

Who: young, sexually active person
Joints: knee, elbow, distal joints. spares axial skeleton
Disseminated: bacteremia, rash, fever, polyarthralgia, tenosynovitis
DX: blood, GU, rectal, pharyngeal cultures +, (synovial cx usually neg.)
RX: CTX or cefotaxime

Purulent joint only: 1-2 joints, synovial fluid cultures +
A 35-year-old man is evaluated for a 2-month history of abrupt left knee swelling. He notes prominent stiffness of both joints but no significant pain. He previously felt well. He lives in Vermont and goes hiking during the summer. He has not had any episodes of diarrhea or abdominal pain and reports no trauma to the knee, fever, rash, or known insect bites. He does not have a history of sexually transmitted infections. He has no history of injection drug use and does not take any medications.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 115/70 mm Hg, pulse rate is 82/min, and respiration rate is 12/min. BMI is 20. There is a large effusion over the left knee with warmth and mild tenderness but no overlying erythema; range of motion is limited by swelling, but stability is intact. There is no heart murmur. Lung and abdominal examinations are normal. There are no skin lesions.

Laboratory studies reveal an erythrocyte sedimentation rate of 12 mm/h and a leukocyte count of 6000/µL (6.0 × 10⁹/L).

Radiograph of the left knee shows a large effusion but is otherwise unremarkable.

First step: what is the diagnosis?
Question 1

A 35-year-old man is evaluated for a 2-month history of abrupt left knee swelling. He notes prominent stiffness of both joints but no significant pain. He previously felt well. He lives in Vermont and goes hiking during the summer. He has not had any episodes of diarrhea or abdominal pain and reports no trauma to the knee, fever, rash, or known insect bites. He does not have a history of sexually transmitted infections. He has no history of injection drug use and does not take any medications.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 115/70 mm Hg, pulse rate is 82/min, and respiration rate is 12/min. BMI is 20. There is a large effusion over the left knee with warmth and mild tenderness but no overlying erythema; range of motion is limited by swelling, but stability is intact. There is no heart murmur. Lung and abdominal examinations are normal. There are no skin lesions.

Laboratory studies reveal an erythrocyte sedimentation rate of 12 mm/h and a leukocyte count of 6000/µL (6.0 × 10⁹/L).

Radiograph of the left knee shows a large effusion but is otherwise unremarkable.

Which of the following is most likely to provide the diagnosis?
Question 1

A. Blood Cultures
B. Lyme serologic testing
C. MRI of the knee
D. Synovial fluid cultures
A. Blood Cultures
B. Lyme serologic testing
C. MRI of the knee
D. Synovial fluid cultures

Synovial fluid culture not helpful in Lyme Disease!
Correct Answer: B

Educational Objective: Diagnose Lyme arthritis.

Key Point
In patients with risk factors for Lyme arthritis (even without a history of a tick bite), serologic tests showing an immunologic response to *Borrelia burgdorferi* are indicated to establish the diagnosis.

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In patients with risk factors for Lyme arthritis (even without a history of a tick bite), serologic tests showing an immunologic response to *Borrelia burgdorferi* are indicated to establish the diagnosis.
Serologic testing for Lyme disease is appropriate for this patient with arthritis characterized by prominent swelling with stiffness without significant joint pain. He has a risk factor for Lyme arthritis, given his frequent hiking in an endemic area. Patients may not recall a tick bite; therefore, Lyme disease should be suspected even without this history. The knee is most commonly affected, although other large joints can also be involved, usually in a monoarticular or oligoarticular pattern. Serologic testing for *Borrelia burgdorferi* is the diagnostic test of choice for this disease and is typically done with an enzyme-linked immunosorbent assay (ELISA) screening test, followed by confirmation by Western blot.

Blood cultures should always be obtained when there is a suspicion for bacterial infectious arthritis. This patient does not have risk factors for infectious arthritis, with Lyme being the most compelling diagnosis. Arthrocentesis is recommended for routine synovial fluid analysis and symptomatic relief, but blood cultures will not provide the correct diagnosis.

An MRI of the knee is unlikely to have diagnostic benefit in new-onset Lyme arthritis (and even in recurrent cases, it tends to be a nonerosive arthritis). MRI can be helpful in cases in which mechanical damage needs to be excluded or if there is concern for osteomyelitis or other bone pathology.

*Synovial fluid cultures tend to be negative in Lyme arthritis.* Synovial fluid will show inflammatory fluid with a neutrophil predominance. *B. burgdorferi* can be detected by polymerase chain reaction in synovial fluid.
MEMORIZE

Hereditary Hemochromatosis: 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th} MCPs
(OA is rare in MCPs)
DIPs

gull wing
(OA)

pencil-in-cup
(PsA)
“pencil in cup”: 

“squaring of thumb”: 

“Overhanging bony erosions” (aka rat bite): 

“hooked-shaped osteophytes”: 

Marginal erosions, periarticular osteopenia:
“pencil in cup”: PA

“squaring of thumb”: OA

“Overhanging bony erosions” (aka rat bite): GOUT

“hooked-shaped osteophytes”: HH

Marginal erosions, periarticular osteopenia: RA
# Categories of Inflammatory Arthritis

<table>
<thead>
<tr>
<th>Category</th>
<th># Joints</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoarthritis</td>
<td></td>
<td>Infectious. Staph/strep cause joint destruction.</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td></td>
<td>SLE (asymmetric), spondyloarthritis (HLA-B27, reactive arthritis), disseminated GC, rheumatic fever, Lyme</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td></td>
<td>Involves hands. RA is paradigm. Also SLE, psoriatic arthritis. Viral infections: hepatitis, parvovirus, rubella, herpes, HIV, adenovirus, mumps, enterovirus. Drug-induced serum sickness.</td>
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Duration of stiffness in inflammatory arthritis?
# Categories of inflammatory arthritis

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<th># joints</th>
<th>examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoarthritis</td>
<td>1</td>
<td>Infectious. Staph/strep cause joint destruction.</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>2-4</td>
<td>SLE (asymmetric), spondyloarthitis (HLA-B27, reactive arthritis), disseminated GC, rheumatic fever, Lyme</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>5+</td>
<td>Involves hands. RA is paradigm. Also SLE, psoriatic arthritis. Viral infections: hepatitis, parvovirus, rubella, herpes, HIV, adenovirus, mumps, enterovirus. Drug-induced serum sickness.</td>
</tr>
</tbody>
</table>

**Duration of stiffness in inflammatory arthritis?** $\geq 1$ hour
Question 2
A 50-year-old woman is evaluated for slowly worsening joint pain in her fingers for the past 5 years. She notes swelling, morning stiffness lasting 10 minutes, and pain that is worse after housework or typing. She has no other joint pain and otherwise feels well. She reports no fevers, weight loss, rashes, alopecia, oral ulcers, dyspnea, chest pain, or abdominal pain. The patient takes no medications. On physical examination, vital signs are normal. There is squaring, crepitus, and tenderness of the first carpometacarpal joints. Bony enlargement and tenderness over all distal interphalangeal (DIP) joints are present. Limited range of motion of the thumbs and DIP joints is noted. There is no joint warmth, redness, or effusions. The remainder of the joint examination is normal.

First step: What is the diagnosis?
A 50-year-old woman is evaluated for slowly worsening joint pain in her fingers for the past 5 years. She notes swelling, morning stiffness lasting 10 minutes, and pain that is worse after housework or typing. She has no other joint pain and otherwise feels well. She reports no fevers, weight loss, rashes, alopecia, oral ulcers, dyspnea, chest pain, or abdominal pain. The patient takes no medications. On physical examination, vital signs are normal. There is squaring, crepitus, and tenderness of the first carpometacarpal joints. Bony enlargement and tenderness over all distal interphalangeal (DIP) joints are present. Limited range of motion of the thumbs and DIP joints is noted. There is no joint warmth, redness, or effusions. The remainder of the joint examination is normal.

Which of the following is the most appropriate next step in management?
Question 2

A. Anti-double-stranded DNA antibody testing
B. Antinuclear antibody testing
C. Radiography of the hands
D. Rheumatoid factor testing
E. No further testing
A. Anti-double-stranded DNA antibody testing
B. Antinuclear antibody testing
C. Radiography of the hands
D. Rheumatoid factor testing
E. No further testing

OA of hands is a clinical diagnosis
OA stiffness < 30 min
OA symptoms worse w/activity
Educational Objective: Clinically diagnose osteoarthritis of the hands.

Key Point
Additional testing such as autoantibody measurements or radiography is unnecessary in patients with clinically diagnosed hand osteoarthritis.

No further testing is necessary for this patient who clinically appears to have hand osteoarthritis. Osteoarthritis is a clinical diagnosis, and the cardinal symptom is pain with activity that is relieved with rest. Affected patients also typically experience morning stiffness that lasts for less than 30 minutes daily. Bony hypertrophy is commonly detected in the fingers, and Heberden and Bouchard nodes may be easily palpated. Osteoarthritis also may cause squaring or boxing of the carpometacarpal joint at the base of the thumb.

This patient has no clinical signs or symptoms suggestive of a systemic inflammatory disease and therefore does not require diagnostic testing with antinuclear antibodies (ANA) or anti–double-stranded DNA antibodies. A positive ANA test result has low predictive value when the pretest probability of systemic lupus erythematosus or a related disease is low. Therefore, this test should not be used to screen indiscriminately for the presence of rheumatologic disease. The American College of Rheumatology recommends not testing ANA subserologies such as anti–double-stranded DNA without the combination of a positive ANA and elevated clinical suspicion of autoimmune disease, which is not present in this patient.

Radiography is not needed to confirm the diagnosis of osteoarthritis in patients with a history and physical examination compatible with this condition. Clinical examination is more sensitive and specific for the diagnosis of hand osteoarthritis compared with radiography.

The key features of rheumatoid arthritis (RA) are swelling and tenderness in and around the joints. Prominent morning stiffness that usually lasts more than 1 hour characterizes early RA. Rheumatoid factor positivity is characteristic of RA, although rheumatoid factor has a low specificity for diagnosis of RA. Rheumatoid factor may be present in healthy persons, especially at older ages. Because this patient has no clinical evidence of RA, testing for rheumatoid factor is unnecessary.
Question 3:
A 55-year-old woman is evaluated for a 3-year history of gradual left knee pain. She reports increased difficulty with stair climbing and an increase in pain over the past 6 months. She has no history of injury. She was prescribed acetaminophen, 1000 mg three times daily, and an exercise program 3 months ago but continues to have activity-limiting symptoms. Family history is notable for her mother who had a total knee replacement at the age of 65 years.

On physical examination, vital signs are normal. BMI is 31. There is bony hypertrophy of the left knee and the first metacarpophalangeal joints without warmth, erythema, swelling, or effusion. Laboratory studies, including an erythrocyte sedimentation rate and serum creatinine, are normal. Knee radiographs (including standing views) show medial joint-space narrowing and small osteophytes of the left knee; there is no periarticular osteopenia or marginal erosions.

First step: what is the diagnosis?
Question 3:
A 55-year-old woman is evaluated for a 3-year history of gradual left knee pain. She reports increased difficulty with stair climbing and an increase in pain over the past 6 months. She has no history of injury. She was prescribed acetaminophen, 1000 mg three times daily, and an exercise program 3 months ago but continues to have activity-limiting symptoms. Family history is notable for her mother who had a total knee replacement at the age of 65 years. On physical examination, vital signs are normal. BMI is 31. There is bony hypertrophy of the left knee and the first metacarpophalangeal joints without warmth, erythema, swelling, or effusion. Laboratory studies, including an erythrocyte sedimentation rate and serum creatinine, are normal. Knee radiographs (including standing views) show medial joint-space narrowing and small osteophytes of the left knee; there is no periarticular osteopenia or marginal erosions.

Which of the following is the most appropriate next treatment?
Question 3
A. Capsaicin
B. Diclofenac
C. Duloxetine
D. Hyaluronic Acid
E. Hydrocodone
A. Capsaicin

B. Diclofenac

C. Duloxetine

D. Hyaluronic Acid

E. Hydrocodone

Approach to treatment:

1. Acetaminophen
2. NSAID (oral or topical) +/- PPI (topical NSAID if ≥ 75 yo)
3. Tramadol
4. Duloxetine

Can use intraarticular glucocorticoids for acute exacerbation
Correct Answer: B

Educational Objective: Treat a patient who has inadequately controlled knee osteoarthritis.

An NSAID such as diclofenac is indicated for this patient with knee osteoarthritis. In addition to the implementation of nonpharmacologic measures such as an exercise regimen and/or assistive devices, the initial pharmacologic management of osteoarthritis recommended in guidelines issued by various societies is acetaminophen in doses ≤3 g/d. If this offers inadequate relief, NSAIDs can be used. NSAIDs are more efficacious than acetaminophen in the relief of osteoarthritis pain. Treatment guidelines suggest using the lowest possible effective dose for the shortest time period because side effects are common and occasionally severe. However, many patients require years of NSAID use given the prolonged timeframe over which the disease is symptomatic and the small number of alternative pharmacologic treatments. NSAIDs are associated with important toxicities, particularly with prolonged exposure. The risk of peptic ulcer disease and gastrointestinal bleeding can be reduced with concomitant use of proton pump inhibitors. Cardiovascular risks can be mitigated by appropriate patient selection for chronic NSAID use.

Topical capsaicin can be used at any time to treat osteoarthritis as well; however, in the absence of an effect from acetaminophen, an NSAID is likely to give this patient more substantial relief of symptoms.

Duloxetine is a serotonin-norepinephrine reuptake inhibitor approved to treat osteoarthritis pain but is slower acting than NSAIDs and requires ongoing, rather than intermittent and as-needed, administration.

Hyaluronic acid injections have shown only a minimal degree of benefit in the treatment of knee osteoarthritis; they also require an invasive procedure for administration and are expensive. Therefore, they would not be preferred to treatment with an NSAID.

Narcotics such as hydrocodone should be reserved for patients who have not responded to nonpharmacologic measures in addition to NSAIDs. An alternative to hydrocodone is tramadol, a centrally acting synthetic opioid analgesic that binds to µ-opioid receptors and inhibits reuptake of norepinephrine and serotonin. It can be used for analgesia when NSAIDs are not tolerated or are contraindicated. Side effects include headaches and dizziness. Tolerance can occur with long-term use; withdrawal symptoms can occur with discontinuation.
Question 4:
A 40-year-old woman is evaluated for a 6-month history of pain and swelling in her left thumb, left fifth finger, and left foot. She also has morning stiffness lasting 2 to 3 hours. She has a 4-year history of lumbar and thoracic back pain that is worse with bending and lifting and is better with rest. Naproxen is only mildly helpful for the pain. On physical examination, vital signs are normal. Patches of erythema and scaling behind the right ear and on the scalp at the occiput are noted. Fusiform swelling of the left thumb and left fifth finger is present. Tenderness and swelling at the left third metatarsophalangeal joint are noted. There is mild lumbar tenderness, and full range of motion of the lumbar spine and cervical spine is noted. No other joint swelling or tenderness is present. Nail findings are shown.

Laboratory studies, including complete blood count with differential, comprehensive metabolic panel, rheumatoid factor, and urinalysis, are normal; HLA-B27 testing is positive.

First step: What is the diagnosis?
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A 40-year-old woman is evaluated for a 6-month history of pain and swelling in her left thumb, left fifth finger, and left foot. She also has morning stiffness lasting 2 to 3 hours. She has a 4-year history of lumbar and thoracic back pain that is worse with bending and lifting and is better with rest. Naproxen is only mildly helpful for the pain. On physical examination, vital signs are normal. Patches of erythema and scaling behind the right ear and on the scalp at the occiput are noted. Fusiform swelling of the left thumb and left fifth finger is present. Tenderness and swelling at the left third metatarsophalangeal joint are noted. There is mild lumbar tenderness, and full range of motion of the lumbar spine and cervical spine is noted. No other joint swelling or tenderness is present. Nail findings are shown.
Laboratory studies, including complete blood count with differential, comprehensive metabolic panel, rheumatoid factor, and urinalysis, are normal; HLA-B27 testing is positive.
Which of the following is the most likely diagnosis?
Question 4

A. Ankylosing spondylitis
B. Inflammatory bowel-disease-associated arthritis
C. Psoriatic arthritis
D. Reactive arthritis
A. Ankylosing spondylitis
B. Inflammatory bowel-disease-associated arthritis
C. Psoriatic arthritis
D. Reactive arthritis
Educational Objective: Diagnose psoriatic arthritis.

The most likely diagnosis is psoriatic arthritis. Although estimates of the prevalence of psoriatic arthritis in patients with psoriasis vary, more recent studies using standardized diagnostic criteria indicate that psoriatic arthritis is present in approximately 15% to 20% of those with psoriasis. Patients who have features consistent with psoriatic arthritis should be examined closely for psoriasiform skin lesions on the umbilicus, gluteal cleft, extensor surfaces, posterior auricular region, and scalp. Nails should be examined for pitting or onycholysis.

Characteristic features of psoriatic arthritis include enthesitis, dactylitis, tenosynovitis, arthritis of the distal interphalangeal joints, asymmetric oligoarthritis, and spondylitis. The recently developed Classification Criteria for Psoriatic Arthritis (CASPAR) have a sensitivity and specificity of more than 90%, especially for the diagnosis of early psoriatic arthritis. This patient fulfills the CASPAR criteria because she has inflammatory articular disease with psoriasis, psoriatic nail dystrophy, dactylitis, and a negative rheumatoid factor. This patient does not have symptoms or findings of inflammatory back pain associated with ankylosing spondylitis; her back pain is related to use and improves with rest, which is noninflammatory. HLA-B27 positivity alone is insufficient to diagnose this disease, and peripheral articular disease is not typical for ankylosing spondylitis.

Nearly 50% of patients with inflammatory bowel disease (IBD) develop musculoskeletal symptoms. Peripheral arthritis may be acute and remitting with a pauciarticular distribution commonly involving the knee. Peripheral arthritis can also be chronic or relapsing, with prominent involvement of the metacarpophalangeal joints and less correlation with intestinal inflammation. IBD-associated arthritis is also unlikely because this patient has no symptoms of bowel disease.

Reactive arthritis (formerly known as Reiter syndrome) is a postinfectious arthritis triggered by infections causing urethritis or diarrhea, although patients may be asymptomatic. Arthritis, usually oligoarticular, develops several days to weeks after the infection. Reactive arthritis can cause dactylitis; however, this patient has no history of a preceding infection, making this an unlikely diagnosis.
**Question 5:** A 25-year-old woman is evaluated during a follow-up visit for **systemic lupus erythematosus**. She was feeling well until 2 weeks ago when she developed increased fatigue and diffuse arthralgia. Medications are **hydroxychloroquine and ibuprofen** as needed.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 140/80 mm Hg, pulse rate is 80/min, and respiration rate is 16/min. There is diffuse alopecia of the scalp. Malar erythema is noted. Heart sounds are normal, and the chest is clear. Examination of the abdomen is normal. Tenderness with minimal swelling of the proximal interphalangeal joints is present bilaterally. Small effusions on both knees with pain on range of motion are noted.

**Laboratory studies:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>Leukocyte count</td>
<td>3000/µL (3.0 × 10⁹ /L), with 900 lymphocytes</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Normal</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Normal</td>
</tr>
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**First step:** What is the diagnosis?
Question 5:
A 25-year-old woman is evaluated during a follow-up visit for systemic lupus erythematosus. She was feeling well until 2 weeks ago when she developed increased fatigue and diffuse arthralgia. Medications are hydroxychloroquine and ibuprofen as needed.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 140/80 mm Hg, pulse rate is 80/min, and respiration rate is 16/min. There is diffuse alopecia of the scalp. Malar erythema is noted. Heart sounds are normal, and the chest is clear. Examination of the abdomen is normal. Tenderness with minimal swelling of the proximal interphalangeal joints is present bilaterally. Small effusions on both knees with pain on range of motion are noted.

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Which of the following tests should be obtained next?
A. Anti-double-stranded DNA antibodies
B. Antinuclear antibodies
C. Anti-Ro/SSA and anti-La/SSB antibodies
D. Anti-Smith antibodies
E. Anti-U1-ribonucleoprotein antibodies
A. **Anti-double-stranded DNA antibodies**
B. Antinuclear antibodies
C. Anti-Ro/SSA and anti-La/SSB antibodies
D. Anti-Smith antibodies
E. Anti-U1-ribonucleoprotein antibodies

Anti-dsDNA is only test that correlates with disease activity!
Correct Answer: A

**Educational Objective**: Confirm a flare of systemic lupus erythematosus with an anti–double-stranded DNA antibody measurement.

Measurement of anti–double-stranded DNA antibodies is appropriate for this patient who is having a flare of systemic lupus erythematosus (SLE). She has symptoms of **fatigue, joint pain, rash, leukopenia, and lymphopenia**. Urinalysis shows **proteinuria and hematuria**, indicating that she may have glomerulonephritis as well. Levels of anti–double-stranded DNA antibodies correlate with SLE disease activity; in particular, they correlate with active kidney disease or glomerulonephritis and might prompt further evaluation such as kidney biopsy. Thus, measuring anti–double-stranded DNA antibody titers may be useful in assessing this patient's recent symptoms. Following anti–double-stranded DNA antibody titers over time can be useful because it is a marker for risk of developing lupus nephritis.

Antinuclear antibody (ANA) testing is a useful screening tool for SLE because more than 95% of patients with SLE are positive for ANA; however, ANA does not correlate with disease activity. Anti-Ro/SSA and anti-La/SSB antibodies can be present in patients with Sjögren syndrome as well as SLE. These antibodies correlate with SLE rashes and photosensitivity and are a risk factor for the development of neonatal lupus erythematosus; however, they do not correlate with disease activity. Anti-Smith antibodies are highly specific for the diagnosis of SLE; however, these antibodies also do not correlate with disease activity. Anti-U1-ribonucleoprotein antibodies are found in patients with SLE and with mixed connective tissue disease but do not correlate with disease activity.

**Key Point**

Anti–double-stranded DNA antibodies correlate with systemic lupus erythematosus disease activity, particularly active kidney disease or glomerulonephritis.
Question 6:
A 30-year-old woman is evaluated during a follow-up visit for systemic lupus erythematosus. She was diagnosed 3 months ago after presenting with pericarditis and arthritis. She was initially treated with prednisone, 40 mg/d, with improvement of her presenting symptoms. The prednisone has been tapered over 3 months to her current dose of 10 mg/d with no recurrence. She also takes vitamin D and a calcium supplement. On physical examination, vital signs are normal. BMI is 25. Cardiac examination is normal. There is no evidence of arthritis. The remainder of the examination is normal.

First step: What is the diagnosis?
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On physical examination, vital signs are normal. BMI is 25. Cardiac examination is normal. There is no evidence of arthritis. The remainder of the examination is normal.

Which of the following is the most appropriate next step in treating this patient?
Question 6

A. Add azathioprine
B. Add hydroxychloroquine
C. Add mycophenolate mofetil
D. Add a scheduled NSAID
A. Add azathioprine
B. **Add hydroxychloroquine**
C. Add mycophenolate mofetil
D. Add a scheduled NSAID

**Hydroxychloroquine:**
- Decreases risk for flares
- Glucocorticoid-sparing agent
- Decreases overall morbidity and mortality
- Safe in pregnancy
- Helps to reduce flares during pregnancy
- Decreases risk for neonatal lupus and congenital heart block
- Decreases thromboembolic events (MI, stroke)
- Improves glucose tolerance and insulin resistance
**Drugs for SLE**

**All:** hydroxychloroquine. OK w/pregnancy. Monitor for retinopathy. (NSAID-sparing)

**Mild to Moderate Disease** (rash, arthritis, pericarditis, pleuritis, mild cytopenias)
- Prednisone
- Hydroxychloroquine
- NSAIDs for arthritis

**Moderate to Severe Disease** (nephritis, severe pleural or pericardial disease, or if fail hydroxychloroquine)
- Mycophenolate mofetil – not w/pregnancy
- Azathioprine – not used much anymore, can be used w/pregnancy if absolutely necessary (some risk)
- Belimumab (add on therapy for incomplete response to therapy)

**Severe or life-threatening disease** (severe active nephritis, acute CNS lupus, pulmonary hemorrhage, myocarditis)
- High-dose corticosteroids
- Cyclophosphamide
- Azathioprine
- Mycophenolate mofetil
Hydroxychloroquine is an appropriate agent to address milder systemic manifestations of systemic lupus erythematosus (SLE) such as arthritis and pericarditis, and it can act as a glucocorticoid-sparing agent. All patients with SLE who can tolerate it should be taking hydroxychloroquine. Antimalarial therapy such as hydroxychloroquine in SLE has documented benefit for reducing disease activity, improving survival, and reducing the risk of SLE-related thrombosis and myocardial infarction.

Azathioprine is generally reserved for more severe manifestations of SLE not responsive to low-dose prednisone and hydroxychloroquine but can be associated with serious toxicity. Azathioprine has generally been supplanted by the use of mycophenolate mofetil in SLE.

Mycophenolate mofetil may be appropriate for this patient if she had more serious disease activity such as nephritis or if her arthritis or pericarditis recurred while taking hydroxychloroquine.

NSAIDs, often with colchicine, are first-line therapy for most patients with pericarditis, although glucocorticoids may be indicated in patients with pericarditis associated with a systemic inflammatory disease such as in this patient. However, there is no indication to start an NSAID now given resolution of her symptoms, and doing so would increase her risk of gastrointestinal complications if used along with her daily glucocorticoid.

**Key Point**
Antimalarial therapy such as hydroxychloroquine in systemic lupus erythematosus (SLE) has documented benefit for reducing disease activity, improving survival, and reducing the risk of SLE-related thrombosis and myocardial infarction.
# S/S of active disease in SLE

<table>
<thead>
<tr>
<th>Cell counts</th>
<th>cytopenias</th>
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<tbody>
<tr>
<td>urinalysis</td>
<td>Protein, blood, casts</td>
</tr>
<tr>
<td>Renal function</td>
<td>Rising creatinine</td>
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<tr>
<td>Inflammatory markers</td>
<td>Elevated ESR, CRP</td>
</tr>
<tr>
<td>antibodies</td>
<td>↑ ds DNA (especially w/kidney disease)</td>
</tr>
<tr>
<td>Complement (C3, C4)</td>
<td>Decreases w/disease activity</td>
</tr>
<tr>
<td>ANA</td>
<td>No change – does not correlate with disease activity</td>
</tr>
</tbody>
</table>
Question 7: A 28-year-old woman seeks preconception counseling. She has a 5-year history of systemic lupus erythematosus, which initially presented with nephritis, rash, and arthritis. Her disease has been well controlled for 1 year with hydroxychloroquine, mycophenolate mofetil, and prednisone, 5 mg/d.

On physical examination, vital signs are normal. BMI is 28. There is a discoid rash on the ear pinna, unchanged since the last examination. No other rashes or ulcers are noted. The remainder of the examination, including cardiopulmonary examination, is normal. Laboratory studies, including complete blood count, chemistry panel, liver chemistries, complement levels, and urinalysis, are normal.

Which of the following is the most appropriate next step in management?
Question 7

A. Discontinue hydroxychloroquine
B. Discontinue mycophenolate mofetil
C. Discontinue prednisone
D. Continue current regimen
E. Stop all medications
A. Discontinue hydroxychloroquine
B. **Discontinue mycophenolate mofetil**
C. Discontinue prednisone
D. Continue current regimen
E. Stop all medications

Mycophenolate mofetil must be stopped 3 months before becoming pregnant – teratogenic!!

Pregnancy outcomes better in SLE patients if disease is well-controlled for 6 months prior to becoming pregnant

Up to 1/3 of SLE patients will have worsening disease w/pregnancy, hydroxychloroquine reduces this risk
Correct Answer: B

**Educational Objective:** Manage pregnancy planning in a patient with systemic lupus erythematosus who is taking mycophenolate mofetil.

Discontinuation of mycophenolate mofetil is indicated for this patient with systemic lupus erythematosus (SLE) who plans to become pregnant. **Pregnancy outcomes in patients with SLE are better if their disease has been well controlled for 6 months prior to becoming pregnant.** SLE can worsen during pregnancy in up to one third of patients, and hydroxychloroquine can reduce this risk. In addition, **most rheumatologists continue stable low-dose prednisone during the pregnancy.** Many medications used in SLE are contraindicated in pregnancy; permitted medications include prednisone, hydroxychloroquine, and azathioprine. Mycophenolate mofetil was developed to prevent transplant rejection but in recent years has been used as a treatment for SLE. Mycophenolate works by inhibiting the purine pathway in nucleotide synthesis and may be at least as effective as cyclophosphamide for SLE (including lupus nephritis) but with fewer and milder side effects. **This agent is teratogenic and must be stopped for 3 months prior to becoming pregnant.** Mycophenolate mofetil use may also be associated with difficulty in conception in some cases. This patient with SLE plans to become pregnant and has stable disease, and her laboratory parameters show no significant activity. Stopping mycophenolate is the only necessary intervention, and both hydroxychloroquine and prednisone should be continued unchanged. Stopping all three medications would put this patient at unnecessary increased risk of a flare-up during pregnancy.
Systemic sclerosis

<table>
<thead>
<tr>
<th></th>
<th>Limited (LcSS)</th>
<th>Diffuse (DcSS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin thickening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibodies</td>
<td></td>
<td></td>
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<tr>
<td>Pulmonary disease</td>
<td></td>
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<tr>
<td>Scleroderma Renal</td>
<td></td>
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<tr>
<td>Crisis</td>
<td></td>
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<tr>
<td>CREST*</td>
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</tbody>
</table>

C  
R  
E  
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T
Systemic sclerosis

**Limited (LcSS)**
- Skin thickening: face & distal to elbows/knees, no organ fibrosis
- Antibodies: ANA, anti-centromere
- Pulmonary disease: Pulmonary arterial hypertension (PAH)
- Scleroderma Renal Crisis: infrequent
- CREST*: frequent (annual echo, PFTs)

**Diffuse (DcSS)**
- Skin thickening: face & proximal to elbows/knees, early organ involvement (htn, kidney ds, ILD, malabsorption d/t SIBO)
- Antibodies: ANA, Anti-ScL70, RNA polymerase III
- Pulmonary disease: ILD
- Scleroderma Renal Crisis: frequent
- CREST*: usually absent

**Calcinosi**
**Raynaud’s**
**Esophageal dysmotility**
**Sclerodactyly**
**Telangiectasias**
Question 8:
A 52-year-old woman is evaluated for an 8-week history of fatigue and shortness of breath. She has gastroesophageal reflux disease, hypertension, and a 3-year history of limited cutaneous systemic sclerosis. Medications are omeprazole, nifedipine, lisinopril, and aspirin. On physical examination, temperature is 36.4 °C (97.6 °F), blood pressure is 126/72 mm Hg, pulse rate is 114/min, and respiration rate is 20/min. BMI is 24. Oxygen saturation is 88% on ambient air. A prominent single S₂ is heard. The chest is clear on auscultation. Sclerodactyly and multiple healed digital pits are noted. There is no rash. Chest radiograph is normal.

First step: What is the diagnosis?
Question 8:
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Which of the following is the most appropriate diagnostic test to perform next?
Question 8

A. Bronchoscopy with bronchoalveolar lavage
B. Doppler echocardiography
C. N-terminal proBNP (B-type natriuretic peptide)
D. Right heart catheterization
A. Bronchoscopy with bronchoalveolar lavage  
B. **Doppler echocardiography**  
C. N-terminal proBNP (B-type natriuretic peptide)  
D. Right heart catheterization

![sclerodactyly](image1.png)
![Digital pits](image2.png)
Educational Objective: Diagnose pulmonary arterial hypertension in a patient with limited cutaneous systemic sclerosis.

Doppler echocardiography is the most appropriate test to perform next in this patient with a 3-year history of limited cutaneous systemic sclerosis (LcSSc) who now presents with shortness of breath and fatigue, a prominent single S₂, and a normal pulmonary examination and chest radiograph. LcSSc is characterized by isolated distal skin thickening (face, neck, and hands distal to wrists), is typically not accompanied by internal organ fibrosis, and is more likely to be associated with pulmonary arterial hypertension (PAH). The initial screening test for those with systemic sclerosis who have suspected PAH is echocardiography, which can rapidly and noninvasively estimate elevated pulmonary pressure as well as rule out some etiologies in the differential diagnosis such as intracardiac shunts, valvular heart disease, or heart failure. A moderate to high tricuspid gradient correlates well with PAH confirmed with gold standard right heart catheterization, which is 97% specific but may not be sensitive.

Bronchoscopy with lavage is often used in immunocompromised patients with rapidly deteriorating lung function to assess for infection and/or pulmonary hemorrhage. This test is not indicated in a patient with findings suggestive of PAH.

B-type natriuretic peptide (BNP) or N-terminal proBNP levels should be assessed in patients suspected of having heart failure. Preliminary data suggest that N-terminal proBNP may be helpful in the assessment of PAH and may provide prognostic information. BNP and N-terminal proBNP measurement cannot be recommended at this time until further studies validate their usefulness in patients with PAH.

In patients with echocardiographic findings suggesting PAH, an array of studies (such as imaging of the chest to assess parenchymal lung disease; V/Q scanning to assess potential chronic thromboembolic disease; pulmonary function testing with DLCO; serologic studies for connective tissue disease, liver disease, and HIV; and sleep studies) are helpful in selected patients. All patients suspected of having PAH should be considered for right heart/pulmonary artery catheterization to confirm the diagnosis suggested by clinical presentation, echocardiography, and pulmonary function tests and to accurately measure the arterial pressure. It is also very useful in evaluating responsiveness to therapeutic medications and helps guide therapy. However, right heart catheterization follows these preliminary diagnostic tests and would not be done next.
Question 9:
A 31-year-old woman is evaluated in the hospital for headache, blurred vision, and nausea occurring for the past 12 hours. She has a 2-year history of diffuse cutaneous systemic sclerosis with recent worsening of Raynaud phenomenon that is treated with nifedipine.

On physical examination, the patient is alert but is somnolent and has altered sensorium. Temperature is normal, blood pressure is 150/92 mm Hg, pulse rate is 104/min, and respiration rate is 16/min. BMI is 22. Oxygen saturation is 95% on ambient air. Cardiopulmonary examination is normal. Examination of the skin reveals diffuse skin thickening of the face, anterior chest, and distal extremities; sclerodactyly; and multiple healed digital pits. Neurologic examination is nonfocal.

Labor:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
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<td>Normal</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.0 g/dL (30 g/L)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>32 mEq/L (32 mmol/L)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>4.2 mg/dL (371.3 µmol/L); baseline, 0.8 mg/dL (70.7 µmol/L)</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>2+ protein; 3 erythrocytes/hpf; 5 leukocytes/hpf; few granular casts</td>
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<td>Urine protein-creatinine ratio</td>
<td>1200 mg/g</td>
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Chest radiograph is normal. Noncontrast CT of the head is normal. MRI of the brain shows bilateral parietal lobe white matter prominence.

First step: what is the diagnosis?
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Chest radiograph is normal. Noncontrast CT of the head is normal. MRI of the brain shows bilateral parietal lobe white matter prominence.

Which of the following is the most appropriate treatment?
A. Captopril
B. Cyclophosphamide
C. Methylprednisolone
D. Sildenafil
A. Captopril
B. Cyclophosphamide
C. Methylprednisolone
D. Sildenafil

Scleroderma Renal Crisis (SRC)
HTN (10% will have normal BP)
MAHA
Thrombocytopenia
Proteinuria
Oliguric kidney disease

RX: ACEi

Steroids are risk factor.
Do not give steroids to patients with systemic sclerosis
The ACE inhibitor captopril is the most appropriate treatment for this patient who most likely has scleroderma renal crisis (SRC) in the setting of diffuse cutaneous systemic sclerosis (DcSSc). SRC occurs in 10% to 15% of patients with systemic sclerosis and is more frequent in DcSSc compared with limited cutaneous systemic sclerosis. Vascular involvement of afferent arterioles leads to glomerular ischemia and hyperreninemia. The typical presentation is acute onset of oliguric kidney disease and severe hypertension, mild proteinuria, urinalysis with few cells or casts, microangiopathic hemolytic anemia, and thrombocytopenia. Some patients develop pulmonary edema and hypertensive encephalopathy. Normal blood pressure may be present in up to 10%. This patient presents acutely with a rapid rise in serum creatinine consistent with acute kidney injury, with a bland urinalysis and non–nephrotic-range proteinuria as well as neurologic symptoms suggestive of encephalopathy. Although her blood pressure is almost normal, these findings are highly suggestive of SRC. Treatment with an ACE inhibitor is essential to restore kidney function and manage hypertension associated with SRC. Captopril is the preferred ACE inhibitor because it has been the most extensively studied agent in this clinical setting, and its short half-life allows rapid titration. Cyclophosphamide is a potent immunosuppressant used to treat severe or life-threatening manifestations of certain diseases such as systemic lupus erythematosus or systemic vasculitis. It is ineffective in treating SRC, which is vascular and noninflammatory. This patient does not have inflammatory end-organ involvement; therefore, methylprednisolone is not needed. Glucocorticoids are not useful in SRC, and intravenous glucocorticoids may cause worsening symptoms. Sildenafil can be used to treat pulmonary hypertension or finger ulcerations but is not appropriate for SRC, which is primarily mediated through the renin-angiotensin axis.
Question 10:
A 76-year-old man seeks advice regarding dietary modifications to help prevent gout flares. He recently experienced his first episode of podagra. At his initial visit, serum urate level was 7.2 mg/dL (0.42 mmol/L). History is also significant for hypertension, for which he takes losartan.
On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 135/80 mm Hg, pulse rate is 80/min, and respiration rate is 15/min. BMI is 27. The remainder of the examination is unremarkable.
In addition to meat restriction, increased intake of which of the following may help to decrease this patient's risk of gout flares?
A. Leafy green vegetables
B. Low-fat dairy products
C. Red Wine
D. Shellfish
A. Leafy green vegetables
B. Low-fat dairy products
C. Red Wine
D. Shellfish
The addition of low-fat dairy products is appropriate for this patient with gout. Low-fat dairy products have been shown to decrease the risk of gout flares both through uricosuric and anti-inflammatory properties. He should also be advised to reduce intake of high-fructose beverages such as soft drinks because they are associated with gout flares due to metabolic pathways utilized in the metabolism of fructose, which lead to increased uric acid generation. **Obesity is also a risk factor for gout** and should be addressed as needed. Some leafy green vegetables are high in purines, the nucleic acid component that is metabolized to uric acid. Thus, **a recommendation to increase leafy greens as a dietary approach to gout treatment would be incorrect**. However, intake of leafy green vegetables has not been shown to increase the risk of flares in population-based studies. **Alcohol is a well-established trigger for gout**, probably due to several mechanisms, including uric acid production and kidney urate handling. Although **wine has been found less likely to trigger gout flares than beer**, alcohol consumption of any sort will increase the risk of flares overall. **Shellfish have long been established as a food that is likely to trigger a gout flare due to the high purine load** and should therefore be restricted in this patient's diet.

**Key Point**
In patients with gout, lifestyle and dietary modifications, including weight loss if appropriate, reduction of high-fructose and high-purine foods, alcohol restriction, and increased low-fat dairy intake, may help decrease the risk of gout flares.
Gout

Negative birefringent needle-shaped crystals

Tophaceous gout
Treatment of gout

Flare:

<table>
<thead>
<tr>
<th>NSAID</th>
<th>1st line; not with CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>colchicine</td>
<td>2nd line; not with CKD, not w/clarithromycin, anti-retrovirals, cyclosporine</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>If NSAID contraindicated</td>
</tr>
<tr>
<td>Intra-articular corticosteroids</td>
<td>If single joint and others contraindicated; r/o infection 1st</td>
</tr>
</tbody>
</table>

Urate lowering therapy: start after attack has resolved
- Who: ≥ 2 attacks/year, 1 attack/year + CKD2+, tophi or stones
- Target urate: <6
- What

<table>
<thead>
<tr>
<th>Allopurinol</th>
<th>OK with CKD</th>
<th>Not with azathioprine, 6-MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febuxostat</td>
<td>If can’t tolerate allopurinol, OK w/CKD</td>
<td>Not with azathioprine, 6-MP; $$$</td>
</tr>
<tr>
<td>Pegloticase</td>
<td>If fail above rx; refractory tophaceous gout</td>
<td>Not with G6PD deficiency, lowers uric acid, immunogenic</td>
</tr>
</tbody>
</table>

Anti-inflammatory prophylaxis: begin colchicine w/urate lowering therapy to prevent flare.
Do not stop & do not start urate lowering therapy during acute attack!
Question 11:
A 59-year-old man is evaluated for a 6-month history of gout. He was doing well on colchicine and allopurinol but developed hypersensitivity to allopurinol, which resolved with cessation of the agent. He then began to have more frequent gout flares; two flares occurred in the past month and were treated with prednisone. History is also significant for hypertension, chronic kidney disease, and dyslipidemia. Current medications are colchicine, lisinopril, metoprolol, and simvastatin.
On physical examination, temperature is 37.2 °C (98.9 °F), blood pressure is 142/86 mm Hg, pulse rate is 64/min, and respiration rate is 12/min. BMI is 30. The remainder of the examination is normal.
Laboratory studies reveal a serum creatinine level of 2.3 mg/dL (203.3 µmol/L), a serum urate level of 9.2 mg/dL (0.54 mmol/L), and normal liver chemistry studies; estimated glomerular filtration rate is 48 mL/min/1.73 m².

Which of the following is the most appropriate next step in management?
A. Discontinue colchicine
B. Start febuxostat
C. Start pegloticase
D. Start pobenecid
A. Discontinue colchicine
**B. Start febuxostat**
C. Start pegloticase
D. Start pobenecid

Allopurinol and febuxostat are OK with mild CKD!
Correct Answer: B

**Educational Objective:** Treat hyperuricemia with febuxostat in a patient with an adverse reaction to allopurinol. Febuxostat is indicated for this patient with frequent gout attacks. He had been taking allopurinol, a first-line agent for serum urate reduction in patients with gout. Urate-lowering therapy is indicated for patients with gout who experience repeated attacks (≥2 per year), have one attack in the setting of chronic kidney disease (CKD) of stage 2 or worse, have tophaceous deposits found on examination or imaging, or have a history of urolithiasis. This patient developed an adverse reaction to allopurinol but still needs urate-lowering therapy. Febuxostat is a newer non-purine, non-competitive xanthine oxidase inhibitor, which is a viable alternative to allopurinol. It can be used in patients with mild to moderate CKD and is safe to try after an adverse reaction or failure of allopurinol. Anti-inflammatory prophylaxis to prevent gout attacks is recommended when urate-lowering therapy is initiated because of the paradoxical increased risk of acute gout attacks when serum urate levels are rapidly decreased by medication. Prophylaxis should be continued in the presence of any active disease (tophi or flares). Colchicine is a first-line option for gout prophylaxis and should not be discontinued in this patient who requires flare prophylaxis during urate-lowering therapy.

Pegloticase is an intravenous synthetic uricase replacement approved for treatment-failure gout. Pegloticase is immunogenic, and the development of antibodies eventually occurs in most patients taking the drug, which leads to reduced effectiveness and increases the risk of hypersensitivity reactions. The uricosuric drugs probenecid and sulfinpyrazone promote kidney clearance of uric acid by inhibiting urate-anion exchangers in the proximal tubule responsible for urate reabsorption. These agents are relatively contraindicated in patients with impaired kidney function or those at risk for kidney stones.

**Key Point**
In patients with gout who require urate-lowering therapy, febuxostat is a viable alternative for those who have an adverse reaction to allopurinol.
Question 12:
A 65-year-old woman is evaluated for bilateral hand and wrist pain that worsens with activity. She reports no swelling or redness but has morning stiffness lasting less than 30 minutes. History is also significant for hypertension and diabetes mellitus. There is no personal or family history of psoriasis. Medications are hydrochlorothiazide and metformin.

On physical examination, vital signs are normal. BMI is 29. The right wrist has a mild effusion and slightly reduced range of motion. There is mild pain with range of motion of both wrists. The hands have bony hypertrophy of the proximal and distal interphalangeal joints, with mild tenderness to palpation but no swelling. Bilateral crepitus of the knees is noted. There are no rashes or nail changes.

Laboratory studies reveal a negative rheumatoid factor, and erythrocyte sedimentation rate, C-reactive protein, and serum urate levels are within normal limits.

A radiograph of the wrist is shown.
Aspiration of the wrist is performed, and results are pending.

Which of the following is the most likely diagnosis?
A. Chronic gouty arthropathy
B. Osteoarthritis with calcium pyrophosphate deposition
C. Psoriatic arthritis
D. Rheumatoid arthritis
A. Chronic gouty arthropathy
B. Osteoarthritis with calcium pyrophosphate deposition
C. Psoriatic arthritis
D. Rheumatoid arthritis

chondrocalcinosis
Correct Answer: B

**Educational Objective:** Diagnose osteoarthritis with calcium pyrophosphate deposition.

This patient most likely has pyrophosphate arthropathy, specifically osteoarthritis with calcium pyrophosphate deposition (CPPD). She has symptoms consistent with degenerative arthritis (pain worse with activity, brief morning stiffness) and signs of osteoarthritis of her hands. Her radiograph shows calcification (also known as chondrocalcinosis) of the triangular fibrocartilage, seen as calcific densities in the region of the distal ulna and ulnar styloid, consistent with CPPD; there is also some narrowing of the carpal metacarpal joints consistent with osteoarthritis. In osteoarthritis with CPPD, patients often have osteoarthritis in joints not typically involved with traditional osteoarthritis, including non–weight-bearing joints such as the shoulders and wrists.

This patient has risk factors for gout (postmenopausal woman, hypertension and taking a diuretic, diabetes mellitus, overweight). However, she lacks a history of episodic joint inflammation that typically precedes chronic gouty arthropathy. The distribution of involved joints, including the distal interphalangeal (DIP) joints, is consistent with psoriatic arthritis; however, there is no evidence or symptoms of inflammatory arthritis. This patient also has no skin or nail findings to support the diagnosis of psoriasis. Although some patients develop skin involvement after the onset of arthritis, psoriatic arthritis cannot account for the finding of chondrocalcinosis seen in this patient.

The absence of synovial thickening and limited morning stiffness are not consistent with inflammatory arthritis such as rheumatoid arthritis. Rheumatoid factor is also negative, and inflammatory markers are within normal limits. Finally, examination and radiographic findings indicate involvement of the DIP joints, which tend to be spared in rheumatoid arthritis.

**Key Point**

Osteoarthritis with calcium pyrophosphate deposition is a form of pyrophosphate arthropathy in which patients often have osteoarthritis in joints not typically involved with traditional osteoarthritis, including non–weight-bearing joints such as the shoulders and wrists.
Calcium Pyrophosphate Deposition (CPPD)

• “pseudogout”, “pseudoOA”
• Pain, swelling
• Inflammation
• After surgery, atypical non-weight bearing locations (shoulders, wrists)
• Chondrocalcinosis
• RX: NSAIDS, colchicine, intraarticular corticosteroids
• Clues:
  • > 65 have OA
  • <50 look for HH, hyperparathyroidism, hypothyroidism, gout

Calcium Phosphate Deposition

• “Milwaukee shoulder”
• Pain, stiffness, swelling with h/o trauma
• Women > 70yo
• Non-inflammatory
Calcium Pyrophosphate Deposition (CPPD)

- Positive birefringent rhomboid crystals
- XRAY

Calcium Phosphate Deposition

- Non-birefringent crystals
- Alizarin stain (red globular clumps)
- XRAY: narrowing of glenohumeral joint, calcification periarticular cartilage, erosive changes of humeral head, upward subluxation of humeral head d/t rotator cuff destruction, bony cysts
Question 13: A 71-year-old woman is evaluated during an office visit. Four months ago, she fell on an outstretched hand. During the next several weeks, she noted gradual pain, stiffness, and swelling of her right shoulder; the pain occurs with movement and at night. History is significant for knee osteoarthritis, gout, and hypertension. Medications are acetaminophen, colchicine, allopurinol, and lisinopril. On physical examination, vital signs are normal. BMI is 25. The right shoulder has a large effusion without warmth or overlying erythema; range of motion is limited by pain and swelling, and prominent crepitus is palpable with motion. Erythrocyte sedimentation rate, leukocyte count, C-reactive protein level, and serum urate level are within normal limits.

A radiograph of the shoulder is shown. Aspiration of the right shoulder shows blood-tinged synovial fluid with a leukocyte count of 8300/µL (8.3 \times 10^9/L); Gram stain is negative, and there are no crystals.

Which of the following is the most likely diagnosis?
A. Acute calcium pyrophosphate crystal arthritis
B. Acute gouty arthritis
C. Basic calcium phosphate deposition
D. Infectious arthritis
A. Acute calcium pyrophosphate crystal arthritis
B. Acute gouty arthritis
C. Basic calcium phosphate deposition
D. Infectious arthritis

- narrowing of glenohumeral joint
- calcification periarticular cartilage
- erosive changes of humeral head
- upward subluxation of humeral head d/t rotator cuff destruction
- bony cysts
Correct Answer: C

Educational Objective: Diagnose basic calcium phosphate deposition.

This patient has Milwaukee shoulder syndrome, caused by basic calcium phosphate deposition. Milwaukee shoulder syndrome is characterized by symptoms of pain, stiffness, and swelling that tend to occur gradually over time, often with a preceding trauma or history of overuse on the affected side, with a predilection for women older than the age of 70 years. This patient has typical features of the syndrome, including a large effusion on examination and synovial fluid that is blood tinged with a low leukocyte count. The crystals are often not visible by routine light microscopy due to their small size, and they are not birefringent (hence, not appreciated with a polarizing microscope); however, they may be revealed with alizarin red staining (with crystals visualized as red, globular clumps). This patient's shoulder radiograph reveals narrowing of the glenohumeral joint, calcification of the periarticular cartilage, and erosive changes of the humeral head, all typical findings in this syndrome. Upward subluxation of the humeral head due to rotator cuff destruction and bony cysts are also common.

Acute calcium pyrophosphate crystal arthritis (also known as pseudogout) can lead to significant joint swelling; however, the absence of inflammatory synovial fluid makes this diagnosis unlikely. This patient has a history of gout; however, her current symptoms are atypical for a gout attack, particularly the gradual onset of these symptoms. The synovial fluid is also very uncharacteristic for gout, which typically causes an inflammatory effusion. The absence of crystals in the synovial fluid further speaks against gout, although monosodium urate crystals are sometimes missed on synovial fluid analysis.

Monoarticular joint swelling must always raise suspicion for an infected joint; however, in this case, the slow onset of symptoms, lack of fever, and normal serum leukocyte count go against this diagnosis. Synovial fluid with low leukocyte count and negative Gram stain also point away from a diagnosis of an infected joint.

Key Point

Milwaukee shoulder syndrome, caused by basic calcium phosphate deposition, is characterized by pain, stiffness, and swelling that tend to occur gradually over time, often with a preceding trauma or history of overuse on the affected side, with a predilection for women older than the age of 70 years.
Rheumatoid Arthritis

- Symmetric, inflammatory, polyarthritis
- Joints: PIP, MCP, hands, feet, wrists (spares the DIP)
- AM stiffness: > 1 hour
- XRAY: periarticular and marginal erosions, bony decalcification (periarticular osteopenia)
- Spine: generally C-spine only
- Peak age: 30-60 yo
- Risk factor: smoking
Autoantibodies in RA – 40% seronegative!

• Rheumatoid Factor: RF
  • non-specific

• Anti-CCP:
  • Most specific
  • Marker of more erosive disease
Question 14:
A 52-year-old man is evaluated for a 6-month history of increasingly swollen and painful joints of the fingers of both hands, both wrists, and the left ankle associated with 90 minutes of morning stiffness. He has tried over-the-counter ibuprofen and naproxen without sustained benefit. He has no other symptoms.

On physical examination, vital signs are normal. There are swelling and tenderness of the second, third, and fifth proximal interphalangeal joints; first, second, and third metacarpophalangeal joints; both wrists; and left ankle. Decreased range of motion of the right wrist is noted. The remainder of the physical examination is normal.

Laboratory studies reveal an erythrocyte sedimentation rate of 45 mm/h and a C-reactive protein level of 5.2 mg/dL (52 mg/L); rheumatoid factor and anti–cyclic citrullinated peptide antibody tests are negative.

Hand radiographs show an erosion of the second right metacarpal head with mild symmetric joint-space narrowing and mild periarticular osteopenia of the metacarpophalangeal joints; there is no bony sclerosis or osteophytes.

Which of the following is the most likely diagnosis?
A. Osteoarthritis
B. Rheumatoid arthritis
C. Sarcoidosis
D. Systemic lupus erythematosus
A. Osteoarthritis
B. **Rheumatoid arthritis**
C. Sarcoidosis
D. Systemic lupus erythematosus
Correct Answer: B

**Educational Objective:** Diagnose seronegative rheumatoid arthritis.

The most likely diagnosis is rheumatoid arthritis (RA), which is characterized by a **symmetric inflammatory polyarthritis** of the small joints. Autoantibodies such as rheumatoid factor or anti–cyclic citrullinated peptide (CCP) antibodies may be present, although autoantibodies are neither necessary nor sufficient for diagnosis. Anti-CCP antibodies occur less frequently than rheumatoid factor, but their presence has more diagnostic specificity for RA. Some patients with RA also lack rheumatoid factor. **Seronegative RA has an identical clinical appearance as seropositive RA but is more likely to occur in men.** Despite a negative rheumatoid factor and anti-CCP antibodies, this patient’s clinical presentation of polyarticular inflammatory arthritis involving multiple and bilateral interphalangeal joints of the fingers, metacarpophalangeal joints, a wrist, and an ankle as well as prolonged morning stiffness and radiographic findings of marginal erosion and periarticular osteopenia, is characteristic of RA. Over time, some patients who are initially seronegative develop a positive rheumatoid factor. This patient does not have monoarticular or oligoarticular disease or radiographs showing bony sclerosis or osteophyte formation, all of which are typical of osteoarthritis. **This patient's symmetric polyarticular inflammatory arthritis associated with prolonged morning stiffness is not consistent with osteoarthritis, in which joint swelling is not found and morning stiffness lasts less than 30 minutes.**

Although sarcoidosis can occasionally cause joint involvement, it is unlikely to present with joint symptoms alone. Chronic sarcoid arthropathy most commonly involves the ankles, knees, hands, wrists, and metacarpophalangeal and proximal interphalangeal joints and is usually accompanied by parenchymal pulmonary disease. It is unlikely to be the cause of inflammatory polyarthritis in a previously healthy middle-aged man. Although systemic lupus erythematosus (SLE) can cause seronegative polyarticular inflammatory arthritis, the initial presentation in a middle-aged man as an explanation for polyarticular inflammatory arthritis would be exceedingly unlikely, and erosions are not seen as a result of arthritis in SLE. The patient has no signs or symptoms otherwise suggestive of SLE such as brain, kidney, lung, heart, or skin manifestations.
Treating RA: DMARDs

**Synthetic DMARDs**
- MTX (+ folate; not w/pregnancy)

OR
- Leflunamide (not w/pregnancy)

Tofacitinib (intolerant of MTX or inadequate response to MTX; inhibits JAK-1 and -3)

**Biologic DMARDs** (safe in pregnancy)
(TNF-alpha inhibitors)
- Etanercept
- Abatacept

- Rituximab (not a TNF-alpha inhibitor)
RA treatment

- Early, non-erosive/mild: hydroxychloroquine
- Erosive: MTX
- Continuing signs/symptoms: add biologics
- Moderate to severe RA with inadequate response to TNF-alpha inhibitors: rituximab + MTX

Vaccine safety:
- All vaccines safe w/MTX and leflunamide
- Never give live attenuated vaccines (nasal flu, MMR, shingles, yellow fever) with TNF-alpha inhibitors

Before starting meds:
- Screening for: TB, fungal infections, HBV, HCV, HIV, strongyloides
- Vaccinate: Tdap, Zoster, pneumonia, influenza
Updated ACR recs (2015) for treatment of early RA (≤ 6 mos)
Updated ACR recs (2015) for treatment of established RA (≥ 6 mos)
Question 15:
A 42-year-old woman is evaluated for a 6-month history of pain and swelling of several small hand joints, an elbow, and an ankle. She gets modest relief with naproxen. She has no other medical problems and takes no additional medications. On physical examination, vital signs are normal. There are tenderness to palpation and swelling of the second and third proximal interphalangeal joints bilaterally, second and fifth metacarpophalangeal joints bilaterally, left wrist, right elbow, and right ankle. The remainder of the physical examination is normal. Laboratory studies are significant for a rheumatoid factor of 85 U/mL (85 kU/L) and positive anti–cyclic citrullinated peptide antibodies. Radiographs of the hands and wrists show periarticular osteopenia at the metacarpophalangeal joints and a marginal erosion at the right second metacarpal head.

Which of the following is the most appropriate initial treatment?
A. Hydroxychloroquine
B. Methotrexate
C. Rituximab
D. Tofacintinib
A. Hydroxychloroquine
B. Methotrexate
C. Rituximab
D. Tofacintinib
Correct Answer: B

Educational Objective: Treat rheumatoid arthritis with methotrexate.

Treatment with methotrexate is indicated for this patient with rheumatoid arthritis (RA). She has a polyarticular inflammatory arthritis involving the small joints of the hands as well as a wrist and an ankle, with radiographically demonstrated marginal erosions and periarticular osteopenia and positive anti–cyclic citrullinated peptide antibodies and rheumatoid factor, all of which support a diagnosis of RA. Methotrexate with or without the addition of another disease-modifying antirheumatic drug (DMARD) should be instituted immediately in patients with erosive disease documented at disease onset. Methotrexate is the gold standard therapy because it is usually better tolerated than other DMARDs and has good efficacy, long-term compliance rates, and relatively low cost.

Hydroxychloroquine is indicated to treat early, mild, and nonerosive disease. Hydroxychloroquine therapy alone has not been shown to retard radiographic progression of RA and therefore should be used only in patients whose disease has remained nonerosive for several years. This patient has erosive disease, and hydroxychloroquine as a single agent is not appropriate.

Rituximab, the anti-CD20 B-cell depleting monoclonal antibody, is FDA approved for the treatment of moderately to severely active RA in combination with methotrexate in patients who have had an inadequate response to tumor necrosis factor α inhibitor therapy. Rituximab may also be considered for patients with high disease activity and poor prognostic features despite sequential nonbiologic DMARDs or methotrexate in combination with other DMARDs. It is not appropriate initial treatment for RA in a patient who has not been given a trial of methotrexate.

Tofacitinib is also indicated for use in the management of RA but only in patients who have already not responded to methotrexate alone. This relatively recent addition to the treatment armamentarium for RA is the first oral agent to be introduced in decades but is indicated for use in patients who are intolerant to or have had an inadequate response to methotrexate.

Key Point
Methotrexate is the initial treatment of choice for patients with new-onset, rapidly progressive, or erosive rheumatoid arthritis.
Question 16:
A 52-year-old man is evaluated during a follow-up visit for a 2-year history of progressively symptomatic rheumatoid arthritis. He reports increased difficulty with his job due to persistent pain and swelling in the first proximal interphalangeal joints, second and third metacarpophalangeal joints, and bilateral wrists. He also has increased difficulty climbing stairs due to persistent pain and swelling in the right knee. Medications are methotrexate, 25 mg weekly; prednisone, 10 mg/d; naproxen; and folic acid.
On physical examination, vital signs are normal. There is 1+ tenderness to palpation and 1+ swelling of the affected joints. Plain radiographs of the hands and wrists show periarticular osteopenia, multiple erosions, and carpal joint-space narrowing. Plain radiographs of the knees show medial and lateral joint-space narrowing.

Which of the following is the most appropriate next step in management?
A. Add etanercept
B. Add rituximab
C. Increase methotrexate
D. Increase prednisone
A. Add etanercept
B. Add rituximab
C. Increase methotrexate
D. Increase prednisone
Correct Answer: A

Educational Objective: Treat inadequately controlled rheumatoid arthritis.

Addition of a tumor necrosis factor (TNF)-α inhibitor such as etanercept is indicated for this patient with inadequately controlled rheumatoid arthritis (RA). He has been appropriately started on the recommended initial agent, methotrexate, with the dose appropriately titrated up because of continued disease activity. Symptomatic relief has been sought with the use of prednisone and naproxen, but he continues to have active synovitis. Because he has been given an appropriate dose of methotrexate for an adequate period of time, the most appropriate next step is to add a TNF-α inhibitor such as etanercept. TNF-α inhibitors remain the most widely used biologics for RA and are highly effective in the treatment of RA, leading to a 20% improvement in signs and symptoms of disease within weeks for over half of patients. Rituximab is indicated for use in patients with moderate to severe RA who are also taking methotrexate but have not responded to TNF-α inhibitors. Having never been treated with a TNF-α inhibitor, it is most appropriate to add a TNF-α inhibitor to this patient's regimen rather than rituximab. Other biologics are available, and a number have different mechanisms of action and can be used in combination with methotrexate.

The patient has been on methotrexate since diagnosis and is taking a dose that would be expected to improve his symptoms; however, he continues to have significant disease activity. It is unlikely that continuing to increase the dose will adequately control his disease; this will also increase the risk of toxicity. Increasing prednisone may offer short-term relief of flares in patients with RA. However, this patient has been on chronic glucocorticoids and high-dose methotrexate, yet continues to have a considerable amount of synovitis. Given the chronic nature of RA and need for long-term treatment, exposing patients to the numerous side effects associated with higher doses of glucocorticoids is not optimal. Furthermore, in this patient with known seropositive erosive disease, therapy with disease-modifying agents is required, and prednisone does not halt bony destruction.
Question 17:
A 26-year-old woman seeks preconception counseling. She has a 3-year history of rheumatoid arthritis. Medications are methotrexate, hydroxychloroquine, low-dose prednisone, and folic acid. Currently her disease is under excellent control.
On physical examination, vital signs are normal. There is no warmth, erythema, swelling, or tenderness of the joints.

Which of the following is the most appropriate next step in management?
A. Discontinue hydroxychloroquine  
B. Discontinue methotrexate  
C. Discontinue prednisone  
D. Discontinue prednisone, methotrexate, and hydroxychloroquine
A. Discontinue hydroxychloroquine
B. **Discontinue methotrexate**
C. Discontinue prednisone
D. Discontinue prednisone, methotrexate, and hydroxychloroquine
Correct Answer: B

**Educational Objective:** Manage rheumatoid arthritis medications in a patient of childbearing age. Discontinuation of methotrexate is indicated for this patient with rheumatoid arthritis (RA) who is interested in becoming pregnant. This nonbiologic disease-modifying antirheumatic drug is both highly teratogenic and abortifacient and must be discontinued 3 months prior to attempting to conceive. Although this patient is taking folic acid to help reduce her incidence of methotrexate side effects, taking folic acid supplements during pregnancy can reduce the risk of certain neural tube birth defects. Therefore, she should not discontinue folic acid even if she discontinues methotrexate.

Considerable epidemiologic evidence in patients with systemic lupus erythematosus as well as RA supports the use of hydroxychloroquine during pregnancy. The risks to mothers and their fetuses appear low, particularly when balanced against the consequences of discontinuing treatment in anticipation of pregnancy. Greater disease activity during pregnancy is associated with small gestational age and preterm delivery. In addition, patients in whom all medications are stopped, including hydroxychloroquine, run the risk of flare, which can impair their physical functioning and make coping with pregnancy more difficult. No increases in adverse maternal or fetal outcomes have been observed in a number of studies in which hydroxychloroquine has been continued throughout pregnancy.

Low-dose glucocorticoids are frequently used but should be avoided if possible before 14 weeks of gestation because of the risk of cleft palate. Glucocorticoid use can contribute to gestational diabetes and hypertension. However, they can be useful in the management of RA in pregnancy if the benefit of treatment is thought to exceed risk.

**Key Point**

Women taking methotrexate must discontinue this medication 3 months prior to attempting to conceive.
Extra-articular manifestations of RA

- Skin: subcutaneous nodules, pyoderma gangrenosum, vasculitis (purpura, petechiae, splinters, livedo)
- Eyes: keratoconjunctivitis (sicca), episcleritis
- Pulmonary: pleuritic, exudative pleural effusion, nodules, ILD (esp. smokers, sero+)
- Caplan syndrome: rheumatoid pneumoconiosis and basilar nodules
- Cardiovascular: pericarditis (most common CV manifestation), CV ds
- Felty: RA + neutropenia + splenomegaly; fever, anemia, decreased plts, vasculitis. Splenomegaly with granulocytopenia. Usually in those with severe, erosive, sero+, longstanding ds.
- Watch out for: C1-C2 subluxation. (check flexion/extension c-spine films before surgery)
Not covered in this talk:

Spondyloarthropathies
Vasculitis
Dermato/Polymyositis
Common orthopedics