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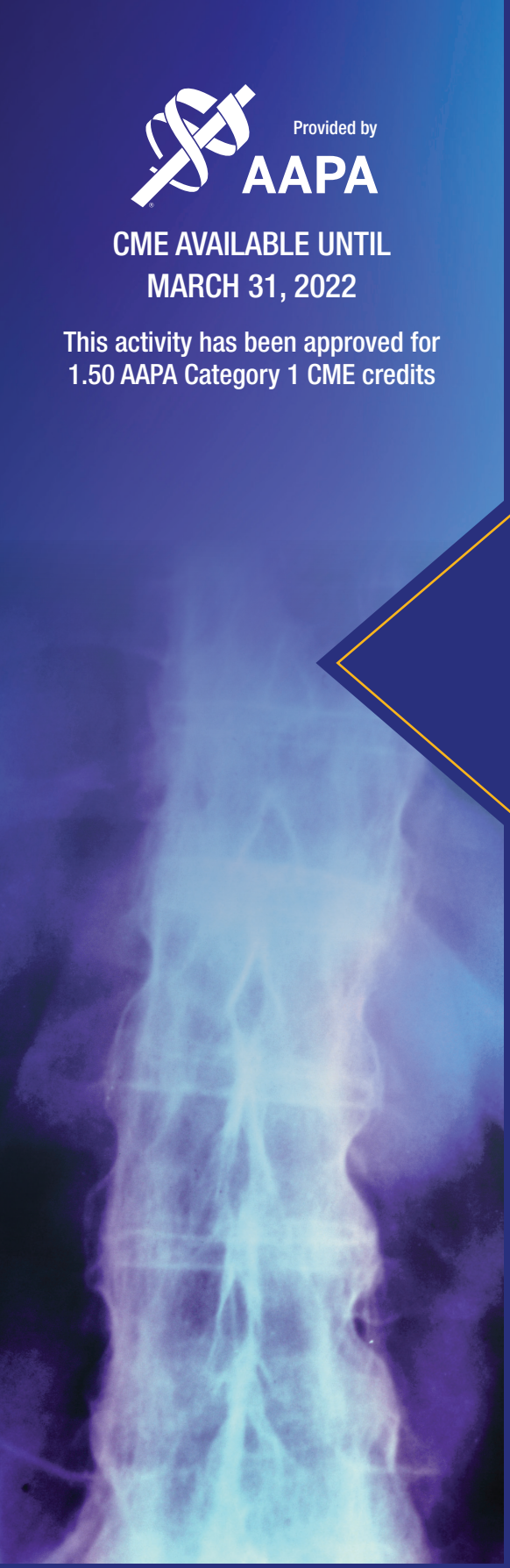
MARCH 2021

BACK IN BUSINESS

Strategies for the Diagnosis and Management of Patients with Ankylosing Spondylitis



Contents

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Produced by MedicalLogix

ACCREDITATION INFORMATION

ACTIVITY OVERVIEW

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the axial skeleton and to a lesser extent the peripheral skeleton. It is characterized by lower back pain from chronic inflammation that may progress to structural damage in the sacroiliac joints and spine. Ankylosing spondylitis is now classified as part of the broader disorder of axial spondyloarthritis, an umbrella term that includes both AS and non-radiographic axial spondyloarthritis (nr-axSpA). Ankylosing spondylitis encompasses patients with visible structural damage as seen on radiographs, whereas nr-axSpA encompasses patients without this visible structural damage. In the U.S., AS affects approximately 0.5% of the population, which equates to 1.5 million people. To provide quality care for patients with AS, PAs and other healthcare providers must remain up to date on all aspects of disease management. In 2019, the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (ACR/SAA/SPARTAN) updated their guidelines, highlighting the need for continuing education on AS management.

AAPA TAKES RESPONSIBILITY FOR THE CONTENT, QUALITY, AND SCIENTIFIC INTEGRITY OF THIS CME ACTIVITY.

EDUCATIONAL OBJECTIVES

At the conclusion of this activity, the PA should be better able to:

- Use knowledge of clinical characteristics of AS and differential diagnosis from mechanical back pain when evaluating patients.
- Utilize appropriate imaging for the diagnosis of AS.
- Outline therapies available to treat AS, including recommendations for therapy escalation based on established guidelines.
- Manage patients with stable disease appropriately.
- Apply knowledge of common comorbidities, particularly cardiovascular disease when managing patients with AS.

ACCREDITATION STATEMENT

This activity has been reviewed by the AAPA Review Panel and is compliant with AAPA CME Criteria. The activity is designated for 1.50 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation. Approval is valid through March 31, 2022.

Estimated time to complete this activity: 90 minutes.

HOW TO RECEIVE CREDIT

There are no fees for participating and receiving CME credit for this activity. Participants must: 1) read the educational objectives and faculty disclosures; 2) study the educational materials; 3) go to **www.aapa.org/AS2021** to complete the post assessments in Learning Central.

In order to receive credit, participants must complete the post-test and evaluation. You will be able to access your certificate of completion in Learning Central as soon as you complete the post-test with a minimum score of 70%. Your certificate will be available under "Transcript" for your records.

DISCLOSURE POLICY STATEMENT

All individuals in a position to control the content of this activity have disclosed their relevant financial relationships with commercial interests. Disclosures from the author(s) are listed below.

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OFF-LABEL/UNAPPROVED PRODUCT(S) DISCUSSION

This program discusses the off-label use of methotrexate and sulfasalazine and the potential use of tofacitinib and upadacitinib pending FDA review.

DISCLAIMER

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LAWRENCE HERMAN, DMSC, MPA, PA-C, DFAAPA

Hello, and welcome to this *Clinical Dialogue* and *eCase Challenge* program, "Back in Business: Strategies for the Diagnosis and Management of Patients with Ankylosing Spondylitis." I'm Dr. Lawrence Herman, President of Palantir Healthcare, LLC in Boiling Springs, South Carolina, and a Past President of the American Academy of PAs in Alexandria, Virginia.

Joining me in this conversation are two expert clinicians, Dr. Benjamin Smith and Dr. Atul Deodhar. Ben is an Assistant Professor and Director of Didactic Education for Florida State University College of Medicine in Tallahassee, Florida. Atul is a Professor of Medicine in the Division of Arthritis and Rheumatic Diseases for Oregon Health and Science University School of Medicine in Portland, Oregon. My thanks to both of you for your involvement in this important continuing medical education activity.

So, let's get started. Ben, let's begin with a definition of ankylosing spondylitis, as well as describing its prevalence in the United States, please.

BENJAMIN SMITH, DMSC, PA-C, DFAAPA

Ankylosing spondylitis is a chronic inflammatory arthritis. It most commonly presents with persons having low back pain, although peripheral inflammatory joint symptoms can also occur.

When we talk about ankylosing spondylitis, now, in 2020, we must recognize that it fits under an umbrella of a larger family of inflammatory arthritis, which we call axial spondyloarthritis. Axial spondyloarthritis includes ankylosing spondylitis, which by definition is when we find radiographic changes in the sacroiliac joints, therefore that is ankylosing spondylitis.

There's a cousin, if you will, or someone else in the family under the axial spondyloarthritis with ankylosing spondylitis, and that's non-radiographic spondyloarthritis, as well. Again, the difference here is no radiographic changes in that condition.

Another key point to make is the idea of gender distribution of this condition. Axial spondyloarthritis or ankylosing spondylitis is more prevalent in men, but we must not forget as clinicians that women can also be affected by this condition. It's so important that we remember that.

LAWRENCE HERMAN

And why the change in terminology, briefly?

ATUL DEODHAR, MD, MRCP

One of the things that we had the problem with ankylosing spondylitis was that to diagnose ankylosing spondylitis one has to have changes of sacroiliitis on the x-ray. And what we found out is that when somebody develops the symptoms of ankylosing spondylitis, it may take 2 years, 6 years, even 10 years before x-rays change. And as Ben said, you need to have definitive changes of sacroiliitis on the axial skeleton on the sacroiliac joint x-rays, pelvic x-rays, and it doesn't change that quickly.

And so we were not able to diagnose those patients for a prolonged period of time. And what do we call them? We cannot call them ankylosing spondylitis, because their x-rays haven't changed, but we know they have the disease. By the science progressing now with MRI of the sacroiliac joint, you can find those patients early.

ANKYLOSING SPONDYLITIS (AS)

- Chronic, inflammatory arthritis[1,2]
- Can present as low back pain or peripheral joint symptoms[1,2]
- Included in the umbrella term, *axial spondyloarthritis* **(axSpA)**[1,2]
  - Ankylosing spondylitis **(AS)** – radiographic changes in the sacroiliac joints
  - Non-radiographic axial spondyloarthritis **(nr-axSpA)** – joint symptoms without radiographic changes in the sacroiliac joints
- More prevalent in men, AS also occurs in women[1]
  - Approximately 2:1 ratio

1. Taurog JD, et al. *N Engl J Med.* 2016;374(26):2563-2574.
2. Sieper J, Poddubnyy D. *Lancet.* 2017;390(10089):73-84.

AS – EVOLVING DEFINITIONS

- Remember, a diagnosis of AS requires detection of sacroiliitis by x-ray[1]
- However, symptoms of AS may develop several years before changes are seen on x-ray[1]
  - By definition, these patients would not have AS
- In the early stages, x-ray is normal but the MRI is abnormal – this is nr-axSpA[1]
- Both AS and nr-axSpA are included in the spectrum of axSpA[1]
- AxSpA affects 0.9-1.4% of the U.S.[2]
  - 50% AS, and 50% nr-axSpA

1. Taurog JD, et al. *N Engl J Med.* 2016;374(26):2563-2574.
2. Reveille JD, Weisman MH. *Am J Med Sci.* 2013;345(6):431-436.

And so that's why now this early stage, when the x-rays are normal but MRI is abnormal, and the later stage, which we call ankylosing spondylitis, to put all of them together, the terminology changed, and we call it axial spondyloarthritis with AS at one end and the non-radiographic axial SpA or non-radiographic axial spondylo-arthritis at the other end. So, the same spectrum of the disease.

So there was this NHANES study, which is the National Health and Nutritional Examination Survey. And in that, what they found out was the axial, the bigger axial spondyloarthritis is anywhere between 0.9 to 1.4%. That's the kind of average. About 1% of the U.S. population has axial spondyloarthritis. Half of them are probably ankylosing spondylitis, half are non-radiographic axial SpA.

LAWRENCE HERMAN

Atul, then if we talk about axial changes, peripheral changes, extraarticular manifestations, how common is this?

ATUL DEODHAR

This ankylosing spondylitis, people think they only have involvement of the axial skeleton, but that's not true. About 40 to 50% of the patients with ankylosing spondylitis will have peripheral inflammatory arthritis, knees swelling up, ankles swelling up. So that's the joint problem.

Then there is also enthesitis, which is where the tendons insert into the bone. So, Achilles tendon insertion into the heel or plantar fascia insertion into the heel.

AS – PERIPHERAL AND EXTRAARTICULAR MANIFESTATIONS[1]

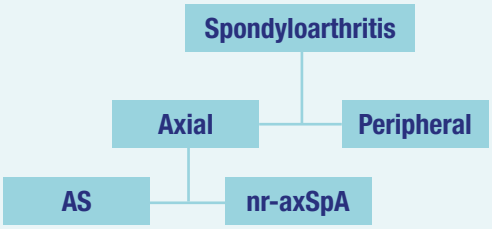
- 40-50% – peripheral inflammatory arthritis or enthesitis
  - Commonly at the Achilles tendon insertion or plantar fascia insertion
- 40% – acute uveitis
- 10% – psoriasis
- 5-10% – inflammatory bowel disease (IBD)

1. Taurog JD, et al. *N Engl J Med.* 2016;374(26):2563-2574.

And then you also mentioned about the extraarticular manifestation. This is acute anterior uveitis. This is one of the commonest presentations that patients might in fact have even before their back starts hurting. And that's seen in about 40% of all AS patients in their lifetime. About 10% of patients can have even psoriasis. About 5 to 10% of patients can have inflammatory bowel disease.

So the family of spondyloarthritis has got axial and peripheral, and under axial is AS and non-radiographic. But all of these things makes it a family and a disease which has got multiple manifestations.

FAMILY OF SPONDYLOARTHRITIS[1]



1. Taurog JD, et al. *N Engl J Med.* 2016;374(26):2563-2574.

LAWRENCE HERMAN

Interestingly enough, one of my students years ago presented with repeated episodes of anterior uveitis, and I mentioned to her, I said, "Has your ophthalmologist considered working you up for AS?" And it was only at that point in time that the student was in fact diagnosed with AS. So there are many things that can masquerade as initial symptoms. These are a result of different metabolic pathways that are inflammatory in nature?

ATUL DEODHAR

Yes, so I would say that the pathophysiology of axial spondyloarthritis, or ankylosing spondylitis, has evolved over the years, and we have understood what are the cellular mechanisms and what are the cytokines which are important in the pathogenesis of ankylosing spondylitis?

Tumor necrosis factor, we knew, was an important cytokine in the production of inflammation. But I would say in the last, oh, about 10 years we have found out another cytokine pathway, interleukin-23 and interleukin-17. And this IL-23/IL-17 pathway is an important pathway — we have been thinking it is even more important than the TNF pathway — in perpetuating the inflammation, perpetuating the signs and even the symptoms of pain and fatigue and stiffness and bone damage and new bone formation, and also the eye

PATHOPHYSIOLOGY OF AXIAL SPONDYLOARTHRITIS/AS[1]

- Several cytokines are involved in inflammation
  - Tumor necrosis factor
  - Interleukin (IL) – 23 and IL – 17 pathway
- Newer therapies block these pathways

1. Taurog JD, et al. *N Engl J Med.* 2016;374(26):2563-2574.

inflammation, and also the gut inflammation and psoriasis, et cetera.

So, these are important new pathways that have been found out in the pathogenesis, and then they obviously then have led to treatments, which we will come to later, how to block those pathways.

LAWRENCE HERMAN

Now, what you've hinted at is really a larger umbrella of diseases. However, there are a plethora of comorbidities.

ATUL DEODHAR

Right. And great point, Larry. The rheumatologists are waking up to the idea that all of our inflammatory diseases — rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis — the inflammation is the driver of some of these comorbidities, such as heart disease, such as the metabolic syndrome.

So obesity, diabetes, hypertension, heart disease, this is quite common in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, and controlling the inflammation is so important to reduce the other comorbidities.

The other ones, the renal complications and osteoporosis, the osteoporosis part is also linked to the inflammation. Renal complications are one of them. Amyloidosis, very rare now, but if you don't treat these patients aggressively, that's also linked to inflammation. So ultimately, everything boils down to significant amount of immune-mediated inflammation.

COMORBIDITIES OF AS[1]

- Inflammation: the driver of many comorbidities
- Common comorbidities of AS include:
  - Heart disease
  - Metabolic syndrome
  - Obesity
  - Diabetes
  - Hypertension
  - Renal complications
  - Osteoporosis
  - Amyloidosis

1. Strand V, Singh JA. *Mayo Clin Proc*. 2017;92(4):555-564.

LAWRENCE HERMAN

Ben, this is not an easy diagnosis to make. It is extremely ambiguous and nonspecific, especially early on in the disease state. How can we differentiate the patient who comes into a primary care office and complains about what appears to be one of the most common complaints, which is mechanical lower back pain, and how do we differentiate that from AS?

BENJAMIN SMITH

So, this is a great segue from our discussion about the molecular changes that are happening within the body. We have to be aware, when someone comes in with low back pain, you know, there's more than just mechanical or degenerative changes that potentially can occur. Certainly, a majority of patients with back pain come with those types of symptoms.

Let us also not forget those pathologic causes of low back pain, whether it be infection or malignancy or fracture, perhaps. But about 5% of persons presenting with low back pain come with this inflammatory back pain, the way that we might describe it, you know, symptomatically. Let us be aware of that. Let's not place that out of our minds.

Similar to other types of inflammatory arthritides, we need to think about inflammatory back pain as someone coming in perhaps with atraumatic symptoms, maybe symptoms have been insidious in onset. They tend to have morning stiffness that may be prolonged, greater than 30 minutes.

Additionally, they will provide to us through the history a description that their symptoms may be worse when they're sitting or at rest or inactive. And the symptoms may actually improve when they engage in physical activity — exercise, stretching, those types of things.

Patients may describe that morning stiffness is, again, a part of what they experience, and that may even wake them up in the early hours of the morning.

DIAGNOSING AS

- Differentiating inflammatory back pain from mechanical back pain[1,2]
  - Symptoms without trauma
  - Symptoms with insidious onset
  - Prolonged morning stiffness, >30 minutes
  - Worse symptoms when at rest or inactive
  - Symptoms that improve with activity
  - Symptoms that awaken the patient at night
  - Symptom onset <40-45 years of age
- Take a thorough history and ask questions
  - All back pain is not mechanical

1. Taurog JD, et al. *N Engl J Med*. 2016;374(26):2563-2574.
2. Strand V, Singh JA. *Mayo Clin Proc*. 2017;92(4):555-564.

I think a key point here, knowing these symptoms and knowing these characteristics of inflammatory back pain is to simply ask the questions. Be aware. Be thinking about these things. All back pain is not mechanical. It is a smaller percentage of patients who present, but it's a patient group that we should consider.

LAWRENCE HERMAN

So, Ben, when we talk about this — and my memory says this is about 5% of patients with back pain who have AS — and if I think about a typical primary care office, it's pretty common for me to have a patient every single day, you know, one — maybe not every day, some days two, who present with what appears to be mechanical back pain.

That means in the course of certainly a period of perhaps 3 weeks, I've got to be seeing somebody statistically who has AS. So, this is not one of those rare diseases. This is something we simply need to be on the lookout for, or else this is a patient who could go 3, 6, 9 months or longer before diagnosis.

BENJAMIN SMITH

Excellent point. And we certainly could discuss patients presenting in a primary care setting with back pain. But let us also consider those who work in other specialty settings, such as dermatology — psoriasis. Those who work in a gastroenterology clinic, that's inflammatory bowel disease.

So it's something we all should be alert to regardless of our practice setting. We will see it at some point in time.

AS PRESENTATION

- Consider the other peripheral and extraarticular manifestations
- Patients with back pain could present to:
  - Primary care
  - Chiropractors
  - Osteopaths
  - Physical therapy
  - Spine centers
  - Orthopedic surgeons

ATUL DEODHAR

Back pain patients go to primary care. They go to a chiropractor. They go to osteopath. They might certainly go to physical therapy directly. They might go to a spine center. They may go to orthopedic surgeon, spine center, orthopedic surgeon or a neurosurgeon.

LAWRENCE HERMAN

And there are a few tip-offs here that point towards AS as opposed to mechanical back pain or other forms of back pain. You mentioned no improvement with rest, and rest tends to worsen it. But there are a couple of questions. If a patient says to me, "I get up halfway through the night and that's when my back bothers me," is that the case, Atul?

ATUL DEODHAR

Great point. And, I mean, Ben actually covered it a little bit earlier, is that one of the tip-offs that this could be not your typical mechanical back pain could be in fact this question, that, "What happens when you go to bed at night?" Generally, people with mechanical back pain will sleep through the night, and in fact, if their back is hurting, they would rather lie in bed.

Inflammatory back pain, which is still a misnomer, because it doesn't necessarily mean there is inflammation -- and I'll come to that in a minute — but inflammatory back pain is (A) "Does your back — back pain get better with activity?" And (B) "What happens at nighttime?"

And the answer to the first question is, "I get better with activity, worse with rest," or, "It doesn't get better with rest," and, "My nights are the worst." That is very typical of inflammatory back pain.

Now, inflammatory back pain itself is not a disease. Inflammatory back pain is a symptom. And if you take 100 patients with inflammatory back pain, only 15 of them would have either axial spondyloarthritis or ankylosing spondylitis. But that would give you the tip-off.

But if they just took this history, "Tell me about your back pain. How long is it going on? And insidious onset Ben has already mentioned. "Was there any reason?" I mean,

AS PRESENTATION (CONT.)

- Mechanical back pain:
  - *What happens when you go to bed at night?*
  - Typically, patients with mechanical back pain sleep through the night and they would rather lie in bed
- Inflammatory back pain (IBP):
  - *Does your back pain get better with activity? What happens at night?*
  - AS patients get better with activity, worse with rest, and nights are the worst
- **Remember: IBP is not a disease** – it is a symptom that may suggest the presence of axSpA. A referral to a specialist is necessary in a patient with IBP.

if somebody fell off the ladder and it started a backache, that's acute. No acute pain, but it started before the age of 40, 45 for no apparent reason, insidious onset, worse with rest, better with activity, wakes them at night, these are a tip-off. And then they should start considering there may be something else going on.

LAWRENCE HERMAN

Ben, this diagnosis we said was challenging in any setting. But in a busy primary care office, what kind of — I mean, I would love to have a single blood test that would give me a thumbs-up saying that that's what this patient has. But that is not simply available. How should I begin to work this patient up in terms of H&P and then ancillary laboratory tests in determining the constellation of symptoms that this patient is exhibiting, is prototypical for AS?

BENJAMIN SMITH

You're exactly right, Larry. There is not one lab test or one study that can be done that perhaps makes the diagnosis. As with all that we do in medicine, it falls back to that initial history and physical exam that must be conducted.

We've shared with you some characteristics tonight that should be included in the history, some questions to be asked. But I would also highlight the absolute importance of the past medical history, the family history, the review of systems, as well.

Patients will often come because their back hurts or they have some type of peripheral joint symptom it may be focused on. And when we ask those other questions about inflammatory eye disease, we must ask about those other important features in the past medical history and family history.

We ask about past history of inflammatory eye disease, about skin rashes, about bowel changes and bowel habits. All of those things will help us, to support us and lead us to begin to think about axial spondyloarthritis as a potential diagnosis in our differential.

We support that with our physical exam. Please complete an appropriate peripheral joint physical exam, an examination of the spine, including range of motion and palpation. And then support those details that you obtained in your history, as well. History and physical are absolutely vital, and they really are our best tools I think we have.

Ancillary tests can also be helpful, as well. Acute phase reactants play a role. They are a piece of the puzzle. As we know, they are very nonspecific but can be helpful.

There is a lab test that is commonly associated with ankylosing spondylitis or axial spondyloarthritis, and that's the HLA-B27, a genetic marker. It's helpful, can be found in other conditions. As we know with other laboratory, the sensitivity and specificity is not 100%. So bringing all these things together, these tools, history and physical and ancillary tests that we've mentioned, are helpful.

When working someone up that we're considerant of this condition, I would also include system review lab, just to cover the bases with blood counts and chemistries, as well.

ATUL DEODHAR

HLA-B27 doesn't really diagnose anything, because if I take 100 people, 100 white people in the U.S. with HLA-B27, only five of them are going to have axial spondyloarthritis. 95 of 100 are going to have just HLA-B27. So, I would not order HLA-B27 tests willy-nilly.

I would order HLA-B27 if, as Ben was saying, the history and the physical exam is suggestive. If the pretest probability is high, then I would order the HLA-B27 test.

LABORATORY WORK-UP[1]

- AS diagnosis is not dependent on a specific lab test
- More importantly, look at patient history and physical exam, as well as family history and symptoms
  - Patient history – peripheral manifestations
  - Physical exam – spinal range of motion and palpation at entheseal sites
- HLA-B27 – marker associated with AS
  - Order if history and physical exam is suggestive of AS

1. Taurog JD, et al. *N Engl J Med*. 2016;374(26):2563-2574.

LAWRENCE HERMAN

Then that begs the question in terms of what we start with in terms of imaging studies. Do we begin with plain radiographs, and are we ordering the correct radiograph when we begin trying to make this diagnosis?

ATUL DEODHAR

As we were saying earlier, x-rays have been our friend for a long time. X-rays are simple. They are cheap, and unfortunately, when somebody goes with back pain, the commonest x-ray that is done is that of lumbar spine. And lumbar spine x-ray does not include sacroiliac joints.

So, once you take the history, once the patient has inflammatory back pain, once you start suspecting there is something more, "This is not my usual mechanical back pain patient," then the first imaging to order is plain x-ray of the pelvis, just one view, PA view, is enough. You do not

need sacroiliac joint films where you get these three views, one from the front, the AP view, and then the views from the side, and those are really not required. That increases the radiation to the pelvic area three times, and it doesn't really add too much to the diagnostic certainty.

So the first thing to do is x-ray of the sacroiliac joint. If that shows sacroiliitis, you've got your diagnosis of ankylosing spondylitis. If that does not, and your suspicion is still high, that is when in fact I will go to the HLA-B27 test and then, if that is also negative, then I might go to MRI scan of the sacroiliac joint.

IMAGING FOR AS[1,2]

- Start with plain x-ray of the pelvis – AP view
  - X-ray of lumbar spine is not needed
  - X-ray of sacroiliac joints with 3 views (front, AP, side) are not required
- If x-ray shows sacroiliitis – AS is confirmed
- If x-ray is negative and clinical suspicion is still high:
  - HLA-B27 can be ordered
  - If negative, order an MRI of the sacroiliac joint (contrast not required)
  - MRI can detect early non-radiographic axial SpA

1. Sieper J, Poddubnyy D. *Lancet*. 2017;390(10089):73-84.
2. Mandl P, et al. *Ann Rheum Dis*. 2015;74(7):1327-1339.

MRI scan of the sacroiliac joint has in fact changed the whole field, and that's when all this — we were discussing earlier the nomenclature change, because we are able to find these patients early.

LAWRENCE HERMAN

Atul, I think it's important for us to remember that the changes that we may see on imaging may not occur for up to 10 years. So, when we do a plain film or we do even an MRI, and we do not see any changes on imaging, it does not rule out the disease per se. It's simply that we're catching it earlier than we can see on radiographic imaging.

In my practice, if I have one or two negative tests, but I still have a high level of suspicion, before I begin to order additional imaging studies, I want to consult with my expert, and that would be a rheumatologist. Is that premature? Is that an appropriate referral to make at that point in time?

ATUL DEODHAR

Great point. That is a perfectly appropriate referral to make if you have suspicion of axial SpA, the patient has inflammatory back pain, the patient may have psoriasis, may have history of uveitis and may have IBD, et cetera, plain x-ray is normal. That is a perfect time to send the patient to a rheumatologist, who will, again, do the whole history and physical examination, and the rheumatologist may then order HLA-B27 or the MRI.

APPROPRIATE REFERRAL

- Referral to a rheumatologist should be done if initial tests are negative, but suspicion for AS is still high
  - Especially if the patient has inflammatory back pain with psoriasis, uveitis, or IBD and the plain x-ray is normal
- The rheumatologist may order HLA-B27 or MRI

And let me jump in here with what we see on the MRI of the sacroiliac joints, because MRIs are extraordinarily sensitive. They are not always specific. So here, again, the person who's ordering the MRI should know what they are looking for.

So, MRIs which are ordered by the rheumatologists, there are two types of scans or two types of images we order. One is called T1-weighted image, and the second is T2-weighted image. And I won't go into too much detail, but the T1-weighted image shows you about the damage, so about sclerosis, about erosions, about fusion.

And the T2 fat-suppressed image is extremely important. That shows bone marrow edema. That's what it is called. Bone marrow edema is a fluid signal on both sides of the sacroiliac joint, and there is no real fluid. If you biopsy that, you in fact find the inflammatory cells, the lymphocytes and all those things that we were talking earlier, which generate

MRI IMAGING

- MRIs are sensitive but not always specific[1,2]
- 2 types of images to order[1,2]
  - T1-weighted image
    - Can show sclerosis, erosions, fusions
  - T2-weighted image
    - Can show bone marrow edema
      - Looks like fluid around the sacroiliac joint, but instead of fluid it is inflammatory cells
  - Image can show edema that would signal inflammation of the sacroiliac joint even when the x-ray is normal

1. Mandl P, et al. *Ann Rheum Dis*. 2015;74(7):1327-1339.
2. Khmelinskii N, et al. *Front Med*. 2018;5.

all those cytokines. But on the MRI, that looks like a fluid signal.

So that STIR image shows subchondral or periarticular bone marrow edema, and that is classic for inflammation in the sacroiliac joint when the x-ray can be completely normal. But I would agree that this should be ordered by a specialist after the patient has been referred to them and they have gone through the initial stages of history and physical examination.

LAWRENCE HERMAN

Ben, let's switch gears and talk about available therapies. And we would of course begin with nonpharmacologic therapies, and then move on to pharmacologic therapies. What does the American College of Rheumatology and the other guidelines say about what we should be doing?

BENJAMIN SMITH

When we think about these guidelines, let us first think about the nonpharmacologic approach, which I think is tremendously important in the condition that we're talking about today. When we do this, we're going to help patients achieve goals and remain patient-centered as providers. We aim to reduce pain, we aim to help patients to maintain function, continue to do the things that they both need and want to do.

These are things that we desire. We're always cognizant of other comorbidities and coexisting things that can go along with the inflammatory arthritis, as well. I think that highlights the absolute necessity and importance for us to work as a team, a team of health care providers, PAs, physicians in multiple specialties, to help and stay focused on the patient. We must extend the opportunities that exist also to our other health professional colleagues.

NONPHARMACOLOGIC THERAPIES[1]

- Goals of treatment
  - Reduce pain
  - Maintain function
  - Decrease disease complications
- A multidisciplinary care team approach should be taken
  - Primary care, rheumatology, physical therapists, occupational therapists
  - Maintain flexibility and physical activities
    - Promote activities that improve the range of motion

1. Ward MM, et al. *Arthritis Rheumatol.* 2019;71(10):1599-1613.

One of the things we often encourage patients to do is to maintain flexibility through stretching and maintaining physical activities. Certainly, many subsets of patients will find a referral to a physical therapist to be very helpful in encouraging and establishing a pattern for this. So the guidelines support the idea of a multidisciplinary approach with our colleagues, certainly, as well.

LAWRENCE HERMAN

Atul, we use a number of different drugs in RA that we would think might work in AS. But we've got to divide this into two different areas. We've got to talk about axial disease, and we've got to talk about peripheral disease, because not all of these drugs work in one or the other, correct?

ATUL DEODHAR

Great point, and absolutely correct. The drugs — our conventional synthetic DMARDs, as we call them, like sulfasalazine, methotrexate — they work beautifully in rheumatoid arthritis, but they have no effect on the axial disease. And for the peripheral disease that we see in ankylosing spondylitis, like the arthritis or the enthesitis or dactylitis, which is kind of swollen digits, sulfasalazine is the adjunctive therapy that has been recommended by the ACR/SAA/SPARTAN treatment guidelines. Methotrexate is not recommended.

PHARMACOLOGIC THERAPIES[1]

- Peripheral disease
  - Arthritis, enthesitis, dactylitis
  - Conventional synthetic DMARDs (sulfasalazine, methotrexate) – no effect on axial disease
  - Sulfasalazine – adjunctive therapy for peripheral disease only
  - Methotrexate – NOT recommended
  - Local glucocorticoid injections
    - Can be used in joints but not weight-bearing enthesis
  - Systemic glucocorticoids – NOT recommended

1. Ward MM, et al. *Arthritis Rheumatol.* 2019;71(10):1599-1613.

One could use local glucocorticoid injections into the joints, but not into the weight-bearing enthesis. And the treatment guidelines also say that — do not use systemic glucocorticoids. They are in fact strongly recommended against. And that's mainly because of glucocorticoids (A) don't really work, and secondly, there are all kinds of side effects, as we know. I mean, already these people are getting osteoporosis, and they can have worse osteoporosis.

LAWRENCE HERMAN

Ben, I typically would start somebody on an NSAID, and if after a relatively brief period of time, one category of NSAID did not work, I might switch them to a different NSAID, or if it didn't work over a period of a couple of months, I then need to escalate therapy. At what point do I talk about escalating them to another category of drug, second-line therapy, besides NSAIDs?

BENJAMIN SMITH

It's remarkable, and perhaps a surprise to some, the effect that people get with NSAIDs. They can be effective. They can be helpful. They can reduce symptoms for many patients.

However, after we try them and try a second nonsteroidal anti-inflammatory drug continuously — and I think that's a key point to make — and perhaps after a couple of rounds, if the patient is not having adequate symptom control, they're just not making the improvement functionally or symptomatically that we would expect, certainly a referral would be in order at that point in time.

Because at that point, we're going to begin to think about these other medications that potentially can be very helpful for patients who have failed the initial anti-inflammatory trial.

FIRST-LINE THERAPY[1]

- Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Can be used for both axial and peripheral disease
  - Reduce symptoms in many patients with AS
    - Less effective with mechanical back pain
  - Failure of NSAIDs with inadequate symptom control or functional improvement would prompt referral and consideration of a biologic therapy

1. Ward MM, et al. *Arthritis Rheumatol.* 2019;71(10):1599-1613.

LAWRENCE HERMAN

Curiously, Atul, you hinted at two specific pathways that we can attack with pharmacotherapy, the pathophysiology that we understand, TNF-alpha as well as interleukin-17.

Can you speak a little bit, if I were to refer a patient to either Ben or yourself — because I'm not going to start that biologic, to be perfectly honest. I don't care how comfortable I am, I'm going to refer him to you to make that choice. What do you do at that point in time?

ATUL DEODHAR

So, the first biologic class, which is our go-to class, is the TNF-alpha inhibitors, and they have been approved for the ankylosing spondylitis diagnosis since 2003. There are five different drugs. All five have been tried in ankylosing spondylitis. All five have been shown to be very effective. They are adalimumab and certolizumab and etanercept and golimumab and infliximab. Four of these are monoclonal antibodies. Etanercept is the solo, soluble receptor construct. But they all work very well on the axial disease and the peripheral disease, and those are the ones that we will first go to.

BIOLOGIC THERAPIES FOR AS

- Tumor necrosis factor (TNF)-alpha inhibitors
  - Monoclonal antibodies:[1,2]
    - Adalimumab
    - Certolizumab
    - Golimumab
    - Infliximab
  - Soluble receptor construct: etanercept[1,2]
  - All have shown similar efficacy in axial and peripheral disease in clinical trials[3]

1. Ward MM, et al. *Arthritis Rheumatol.* 2019;71(10):1599-1613.
2. Soriano ER, et al. *Best Pract Res Clin Rheumatol.* 2014;28(5):793-806.
3. Van den Bosch F, Deodhar A. *Best Pract Res Clin Rheumatol.* 2014;28(5): 819-827.

The treatment guidelines say that if you start those drugs most of the patients will do well. But if somebody absolutely has zero effect — that is called primary failure — after 3 months of TNF inhibitor, no effect whatsoever, then do not go to another TNF inhibitor, jump onto IL-17 inhibitor. This is that pathway that I was talking earlier.

Whereas, patient does very well on one TNF inhibitor for a year, for 2 years, and then it starts wearing off, the effect, then we should go to a second TNF inhibitor, because that is called a secondary failure. But that's the way I would look at these biologic DMARDs.

LAWRENCE HERMAN

If I refer to Ben or yourself, I'm thinking that what I want to

FAILURE OF TNF INHIBITORS[1]

- Primary failure
  - No effect after 3 months of therapy
  - Switch to an IL-17 inhibitor
- Secondary failure
  - Response to TNF inhibitor for 1-2 years, then waning response
  - Switch to a second TNF inhibitor

1. Hunter T, et al. *Rheumatol Ther.* 2019;6(2):207-215.

do ahead of time just to make your life a little bit easier is screen them for a past history of hep B and then go ahead and do a QuantiFERON-Gold to rule out TB. Do I need to do anything else beyond that to kind of get them ready for your decision?

SAFETY CONSIDERATIONS OF TNF INHIBITORS

- Prior to their use[1]
  - Screen for hepatitis B virus and tuberculosis
  - Provide all appropriate vaccinations
- Other safety considerations[2]
  - Contraindicated in patients with chronic, serious, or recurring infections
  - Rarely, increased risk of bacterial, viral, invasive fungal, and mycobacterial infections
  - Reactivation of hepatitis B virus

1. Taurog JD, et al. *N Engl J Med.* 2016;374(26):2563-2574.
2. Ali T, et al. *Drug Healthc Patient Saf.* 2013;5:79-99.

ATUL DEODHAR

Well, that's fantastic if you did that. That will make our life really easy. I probably would suggest also to give them all the vaccines that they are supposed to take, flu vaccine and pneumonia vaccine, and et cetera. And the only reason is that there is some indication that our biologics might reduce the efficacy of vaccines. So, if they are fully vaccinated, then I'm even more delighted, and then we can start them on our biologics.

LAWRENCE HERMAN

Ben, do you want to make any comment? If you have started them on a TNF-alpha inhibitor and they have been one of those patients who's failed that, are there any other considerations when you start them on IL-17 and the efficacy, how many choices? Can you speak a little bit about that?

BENJAMIN SMITH

So perhaps someone has not gained adequate efficacy or beneficial effect with one or maybe two TNF agents, or maybe there's been some intolerant symptoms that have occurred for whatever reason, we have a second class of medications that we could consider at that point, and that's the IL-17 medications. There now are two of those which are approved for either ankylosing spondylitis or non-radiographic axial spondyloarthritis, as well.

These are efficacious. The previous studies have suggested that to us. And these medications are generally tolerated very well. Atul spoke earlier about the importance of IL-17 in the pathophysiology of the condition which we're focused on tonight, and this has presented a great opportunity for treatment target.

IL-17 INHIBITORS[1]

- If TNF inhibitor fails or patient is intolerant, an IL-17 inhibitor should be considered
- Secukinumab[2] and ixekizumab[3] are available
  - Approved for use in AS and non-radiographic axial SpA
  - Similar efficacy in clinical trials
  - Generally, well tolerated

1. Ward MM, et al. *Arthritis Rheumatol.* 2019;71(10):1599-1613.
2. Secukinumab. Prescribing information. 2020
3. Ixekizumab. Prescribing information. 2020.

LAWRENCE HERMAN

And the same issues in terms of vaccines and the potential of an infection holds true for those drugs. The one difference is, you can see an exacerbation of inflammatory bowel disease and primary care providers should be aware of that in patients who are taking either secukinumab or ixekizumab, correct?

ATUL DEODHAR

The other common comorbidity in patients with axial spondyloarthritis or ankylosing spondylitis — in fact, the commonest — would be uveitis. And if somebody's getting recurrent uveitis, IL-17 inhibitors won't make it worse, but IL-17 inhibitors won't make it better, either.

So for IBD, they would be contraindicated, because they are known to worsen IBD, whereas with uveitis, they may not help as much as the TNF inhibitors. So that would be another reason why we would be going to TNF inhibitors.

SAFETY CONSIDERATIONS OF IL-17 INHIBITORS[1]

- Common adverse events:
  - Nasopharyngitis
  - Upper respiratory tract infections
  - Gastrointestinal symptoms
- TNF inhibitors are recommended over IL-17 inhibitors for those with:
  - IBD – IL-17 inhibitors can exacerbate symptoms
  - Uveitis – IL-17 inhibitors have limited efficacy

1. Ward MM, et al. *Arthritis Rheumatol.* 2019;71(10):1599-1613.

LAWRENCE HERMAN

I know you've been involved in a number of clinical trials in the past. We have some interesting drugs coming down the pipeline, specifically JAK inhibitors. Can you speak about those?

ATUL DEODHAR

The JAK inhibitors have already been approved for the treatment of rheumatoid arthritis and psoriatic arthritis. And interestingly, they are now coming into ankylosing spondylitis, and the phase 2 trials on tofacitinib and upadacitinib have been done.

Both of those look very promising. The American College of Rheumatology meeting, which is about to happen, the tofacitinib phase 3 trial will also be presented.

None of these are approved by FDA as yet for the treatment of ankylosing spondylitis, but that did not stop American College of Rheumatology to put them into their treatment guidelines as if everything fails. So, TNF inhibitors have failed and IL-17 inhibitors have failed or there is nothing that you cannot give them for some reason, JAK inhibitors would be the next class of drugs to go to. And as I already said, tofacitinib and upadacitinib are the ones which are currently being tried for this indication.

LAWRENCE HERMAN

Atul, for those who are not intimately familiar with the clinical trials on JAK inhibitors, there are a couple of unusual adverse events that have been noted. What are those?

ATUL DEODHAR

Yes. So JAK inhibitors have been associated with an important side effect, and that is the VTE, or venous thromboembolism. So, they may get deep vein thrombosis, and they may get pulmonary embolism. And that's the reason that the doses of JAK inhibitors, the lower doses have been approved by the FDA.

The other interesting and unusual side effect with the JAK inhibitors has been increased creatinine phosphokinase, or CK levels. The patients were not weak, and they did not really have myositis. But the CK levels were high, and patients continued through the trials, and the CK levels normalized.

AGENTS IN CLINICAL DEVELOPMENT

- Janus kinase (JAK) inhibitors: tofacitinib and upadacitinib
  - Approved for use in RA and PsA[1,2]
  - As of December 2020, no current approval in AS but clinical trials are ongoing[3]
  - Considered for AS if TNF inhibitors and IL-17 inhibitors have failed[4]
  - Safety considerations[1,2]
    - Risk of venous thromboembolism
    - Increased creatinine phosphokinase

1. Tofacitinib. Prescribing information. 2020.
2. Upadacitinib. Prescribing information. 2020.
3. ClinicalTrials.gov
4. Ward MM, et al. *Arthritis Rheumatol.* 2019;71(10):1599-1613.

LAWRENCE HERMAN

So, Ben and Atul, I know in my practice, I know that these patients have an increased risk of cardiovascular disease, and some estimates are up to 50% increased risk of events, including a doubling of risk of death associated with AS. As a result, I am extremely aggressive in monitoring and treating and, wherever possible, ameliorating any of the risk factors that I possibly can associated with CV events — smoking, controlling their diabetes, dyslipidemia, hypertension, all of the things that we are responsible for in primary care.

COMORBIDITIES OF AS

- Broad increase in inflammatory pathways in those with AS[1]
- Cardiovascular disease (CVD)[2,3]
  - Up to 50% increased risk of cardiovascular event and 2x the risk of cardiovascular/cerebrovascular death
  - Aim to control CV risk factors
  - AS disease activity should also be controlled to lower CVD risk

1. Hreggvidsdottir HS, et al. *Mol Immunol.* 2014;57(1):28-37.
2. Heslinga SC, et al. *BMC Musculoskelet Disord.* 2015;16.
3. Eriksson JK, et al. *Ann Rheum Dis.* 2017;76(2):364-370.

Ben, let's talk about the ongoing management of patients, even those with stable disease. What do the guidelines indicate we should be doing?

BENJAMIN SMITH

So this is a question that patients will often ask, as well, if perhaps they've achieved stability with a treatment regimen, they're doing well, they're happy with the way things are going, they're more functional, certainly have less pain, perhaps are maintained with a biologic, a TNF and an anti-inflammatory drug — so patients will ask, for numerous reasons — cost or route of administration — they may ask, can they back away from their medication regimen?

And generally, this should be discouraged. If we decide to back away from a medication, instead of the continuous use of the anti-inflammatory, the NSAID, we could go to perhaps a PRN or less frequent dosing of the NSAID. But studies have shown us that, once we commit to the biologic, assuming that it's tolerated and we're not noticing any ill effects from that, those will need to be maintained over time.

If patients come off their biologics, oftentimes frequently even greater than 60% of them will flare, perhaps within a few months.

One of the educational opportunities we have is to help patients understand that once they commit to biologic treatment, it's something that we would expect that they will use for an extended period to help maintain disease control.

Certainly, as patients continued maintaining and doing well, flares might occur at times. And one of the points to make about flares is — which may be a surprise to many, is really oral steroid has really a very limited role in this condition.

MANAGEMENT OF STABLE DISEASE[1]

- Discontinuation or tapering of a biologic is NOT recommended as a standard approach, unless the patient has prolonged stable AS
  - Shared decision making should be used
- On-demand or less frequent dosing of NSAID can be considered
- >60% of those on TNF inhibitor who discontinue will flare within a few months
- Long-term treatment with a biologic is recommended in the absence of toxicities
- Oral steroids have a limited role in reducing flares

1. Ward MM, et al. *Arthritis Rheumatol.* 2019;71(10):1599-1613.

LAWRENCE HERMAN

Typically, if somebody has a chronic disease, we follow them with some sort of test along the way. Should we be following these patients who are on biologics or other drug choices? And if so, how should we follow them? And is it my responsibility in primary care, or your responsibility as the rheumatologist?

ATUL DEODHAR

Well, it's definitely, definitely my responsibility as a rheumatologist. We wouldn't expect primary care doctors to follow with any particular test.

The only blood test that the specialist would be doing to follow these patients would be C-reactive protein to look for inflammation. We would not repeat the MRI in day-to-day practice just to see that the patient is doing well. There are certain indications when the MRI would be repeated, and that is if the patient comes and complains that they're not doing well, and you are positive as to why the patient is not doing well.

So, to find whether the disease is really active or not active, that may be the only time you would do the MRI, but it is certainly not a routine test that needs to be repeated.

And let me quickly add here, x-rays definitely should not be repeated. We repeat the x-rays in rheumatoid arthritis to look for new erosions and et cetera. But in ankylosing spondylitis, repeating the x-ray of the spine -- I mean, it takes 2 years or even longer to get some small syndesmophyte formation, and we don't really need to know that, because what are we going to do if the patient is already on a biologic? We are not really going to do anything differently.

So, the American College of Rheumatology treatment guidelines specifically mention that, don't do x-rays, and use the MRIs only sparingly, only in situations when you are not sure about the disease activity.

LAWRENCE HERMAN

And I know Ben alluded to this quite clearly earlier, but I want to reiterate that this is a disease that takes a village. This is a multidisciplinary team. And we need to continue communicating with primary care specialists, our physical therapy and occupational therapy colleagues and others. And the specialists would include folks like ophtho and derm and gastro, as well as cardiology when warranted. So this is not something that is done in a silo.

And with that being said, what I'd like to ask each of you — and I'm going to start with you, Ben — your closing thoughts or a clinical pearl for our audience in terms of diagnosing and managing patients with ankylosing spondylitis.

MONITORING DISEASE ACTIVITY[1]

- Typically managed by the rheumatologist
- C-reactive protein can be monitored for inflammation
- MRI should not be repeated in routine practice
  - MRI only repeated if patient is symptomatic to determine disease activity
- X-rays should not be repeated as done with rheumatoid arthritis
  - Remember – changes can take years to develop
- Continue to work with the multidisciplinary care team

1. Ward MM, et al. *Arthritis Rheumatol.* 2019;71(10):1599-1613.

BENJAMIN SMITH

Well, there are two clinical pearls that I hope those who are attending will take home with them. First, the absolute necessity of early detection of ankylosing spondylitis, axial spondyloarthritis and these family of conditions, as well. Be sensitive to have these things in the back of your mind as you're seeing folks with low back pain, both men and women.

Second, we now have many treatment options which make a tremendous difference in the lives of those with these conditions. It may require referral, but these things can be really life-changing in helping someone remain functional and, again, doing the things they both need and want to do. A happy patient is what will come.

LAWRENCE HERMAN

And Atul, what would you like to leave our audience with, in terms of your closing thoughts or a clinical pearl?

ATUL DEODHAR

Yeah, I would echo exactly what Ben has said, is that these patients do not come to rheumatologists, and it's the primary providers where these patients are going. And primary care providers should keep this in their mind, that every patient with back pain does not necessarily have mechanical back pain, and they need to look for some of the pointers that there may be an immune system dysfunction going on here by asking them questions about their eyes and their gut and their skin and their peripheral joints, et cetera. And history and physical examination is so very important. So that will be my first thought.

And the second thought is — and Ben has mentioned this also — this space is expanding. In rheumatoid arthritis, we have got probably 13 or 14 different biologics available. We are behind here in ankylosing spondylitis and axial spondyloarthritis, but as the knowledge base about the pathophysiology is expanding, we are finding newer and newer pathways of the cytokines which are important and the inflammatory markers – or inflammatory pathways that are important in developing this disease.

The newer therapies are also coming along, and very soon we are actually going to find three, four, five different classes of drugs added to our already increasing armamentarium to treat these patients successfully.

CLINICAL PEARLS

- To promote early detection, be mindful of AS and axial spondylarthritis when seeing patients with low back pain
- Refer, when necessary, to provide patients with effective treatment options
- AS patients are often seen in primary care first
  - Ask the right questions to determine if there is immune system dysfunction associated with the back pain
  - Take a thorough clinical history and physical exam
- New inflammatory markers are being discovered, which will lead to new, targeted therapies

LAWRENCE HERMAN

I would like to thank both of our expert faculty, Drs. Ben Smith and Atul Deodhar, for their great insights and discussion. And I'd like to thank you, our audience, for participating in this *Clinical Dialogue*.

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CASE PRESENTATION
Julie

Julie is a 32-year-old admissions counselor at a local university who has progressively worsening lower back pain. She describes the pain as being persistent from deep in her low back and from within her buttocks. Julie describes the pain as first occurring in her early 20s, which at first was variable and sporadic. As a former collegiate volleyball player, Julie attributed the pain to the general wear and tear from the sport.

Initially, she managed the pain with the nonsteroidal anti-inflammatory drug (NSAID), ibuprofen 400 mg, three to four times daily. However, after a few years, Julie began to have gastrointestinal (GI) side effects that became intolerable. At that time, she switched to naproxen 250 mg twice daily, which managed the pain initially. Over time, she needed to increase the dose to 500 mg twice daily to better control her symptoms. Now, Julie reports that the naproxen is not adequate to control her pain. Previous evaluations by her primary care clinician were inconclusive and did not determine an underlying cause.

Julie states that her pain interferes with her ability to sleep at night and is worse in the mornings with lasting discomfort after awakening. Over the years she has tried chiropractic manipulation and massage for the back pain — none of them resulting in significant symptom relief. She does exercise three times a week and that offers temporary subsidence of her symptoms. You note from her history that she has a history of plantar fasciitis in her right heel. On physical examination she has tenderness on the right plantar fascia insertion and tenderness and swelling at the insertion of the right Achilles tendon. She also has some tenderness over the bilateral sacroiliac joints.

Her medical chart reveals the following:

BIOMETRICS
- Height: 5 feet 9 inches
- Weight: 154 lbs
- BMI: 22.7 kg/m^2

VITAL SIGNS
- Pulse: 68 bpm
- BP: 119/72 mmHg
- Respirations: 15/minute

PAST MEDICAL HISTORY
- 11-year history of intermittent back pain
- 2-year history of plantar fasciitis in the right heel

PAST SURGICAL HISTORY
- None

FAMILY HISTORY
- Mother, psoriatic arthritis
- Sister, inflammatory bowel disease

SOCIAL HISTORY
- Never-smoker
- Alcohol use: social/on occasion (1-2 glasses of wine/week)
- Occupation: admissions counselor
- Unmarried

CURRENT MEDICATIONS
- Naproxen, 500 mg twice daily

KNOWN ALLERGIES
- None

QUESTION 1

Which of the following characteristics would be consistent with inflammatory back pain rather than mechanical back pain?

A. Acute onset of symptoms
B. Discomfort that gets better with activity
C. Discomfort that gets better with rest
D. Morning stiffness lasting <30 minutes

Differentiating inflammatory back pain from mechanical back pain can be challenging because symptoms may be nonspecific and heterogenous. One type of inflammatory joint disease is ankylosing spondylitis (AS), which can have significant negative effects on patient quality of life if left undiagnosed or untreated. AS is a chronic and often debilitating inflammatory disease that can affect the axial skeleton and the peripheral skeleton to a lesser extent.[1,2] AS is included within the broader disorder of axial spondyloarthritis (axSpA). This umbrella term has evolved over time, stratifying patients based on the degree of sacroiliitis and visible structural damage observed by conventional radiography. Radiographic axSpA, or AS, encompasses patients with definitive evidence of sacroiliitis by radiography, while non-radiographic axial spondyloarthritis (nr-axSpA) encompasses patients without this visible structural damage.[2]

Unfortunately, many patients with AS experience a delay in diagnosis of a decade or more, leading to potentially avoidable structural damage from persistent disease activity.[3,4] The inflammatory back pain of AS may not be recognized as a hallmark symptom of the disease, leading to high rates of misdiagnosis.[5] As such, clinicians should review and understand the signs and symptoms of AS and how to differentiate AS from mechanical back pain, which is more common.

Characteristics of inflammatory back pain include:[1,6]

- Age of onset <40-45 years
- Duration of >3 months
- Insidious onset
- Morning stiffness lasting >30 min
- Improvement with exercise/activity
- No improvement with rest
- Awakening with pain during sleep, especially during the second half of the night, which improves on arising
- Alternating buttock pain

The presence of two or more features is usually suggestive of inflammatory back pain, while the presence of four or more features may be considered diagnostic of inflammatory back pain.[1] In contrast, patients with mechanical back pain would present with discomfort that typically improves with rest, only mild or transient morning stiffness, and the onset of symptoms at any age.[6] For these reasons, the correct answer is B, inflammatory back pain is associated with discomfort that improves with activity. However, note that inflammatory back pain in itself does not make the diagnosis of axial spondyloarthritis or AS; only 15-20% of patients with inflammatory back pain have axial spondyloarthritis.[7]

CASE PRESENTATION CONTINUES

Julie presents with several of the characteristics that are consistent with inflammatory back pain. These include her age, symptom duration, persistent morning stiffness, improvement of symptoms with exercise, awakening with pain during sleep, and alternating buttock pain. You look at her patient history again and note the plantar fasciitis. You also recognize that many patients with AS have additional extra-articular manifestations and/or peripheral spondyloarthritis. For example, about 50% of patients also present with peripheral arthritis, enthesitis, or dactylitis; 30-40% present with acute anterior uveitis; 10% present with psoriasis; and 5-10% present with inflammatory bowel disease (IBD).[1] Enthesitis occurs most frequently, with common sites of inflammation including the Achilles tendon insertion, the plantar fascia insertion, the base of the fifth metatarsal head, the tibial tuberosity, and the superior and inferior poles of the patella.[8] Julie has enthesitis in her Achilles tendon insertion and right plantar fascia, further raising your strong clinical suspicion of AS.

QUESTION 2

Which of the following methods is the initial step to confirm a diagnosis of AS?

A. CT imaging of the lumbar spine
B. MRI with gadolinium
C. MRI without gadolinium
D. Plain film x-ray of the sacroiliac joints

In many patients with AS, the sacroiliac joints are affected first and conventional radiography (plain film x-ray) is recommended as the initial imaging method to detect

sacroiliitis. While spinal imaging can help with a differential diagnosis, it is usually not required for the initial diagnosis. CT imaging is typically not part of the initial evaluation and is not currently recommended to confirm the diagnosis unless conventional imaging is inconclusive or MRI cannot be performed.[2,9] MRI would be appropriate for a patient suspected of nr-axSpA, who is in early stages of the disease and would not have developed the sacroiliac changes that are detectable by x-ray. Typically, gadolinium is not necessary and would not improve diagnosis over T1-weighted and fat suppressed T2-weighted images.[9,10] Taken together, the correct answer is D, plain film x-ray is sufficient to make the diagnosis.

Of critical importance, clinicians should remember that radiographic sacroiliitis is a late-stage finding in many patients with AS. A limitation of conventional radiography is that it may not detect structural damage in patients with early-stage disease, or nr-axSpA. Because the sacroiliac and spinal changes may take years to develop, they may not be immediately visible by conventional radiography.[11] If the x-ray is negative and the clinical suspicion is still high for nr-axSpA, then an MRI would be appropriate. Patients with early stages of the disease would require MRI to confirm any inflammatory lesions (bone marrow edema) and/or structural lesions (bone erosion or new bone formation).[9]

Another important point to remember is that there is no gold standard for an AS diagnosis. The combination of family and clinical history, laboratory work up, and imaging results must all be weighed in order to make an accurate and early diagnosis. Diagnosis can be based on a strong clinical suspicion and pattern recognition. A timely diagnosis, specialist referral, and treatment initiation are critical components of care.[1,6]

CASE PRESENTATION CONTINUES

You order plain film x-rays of the pelvis, including the bilateral sacroiliac joints. You also order a laboratory workup for HLA-B27 and C-reactive protein (CRP). HLA-B27, a variant of the major histocompatibility complex (MHC), has been identified as an important marker of AS. This allele is found in approximately 80-90% of patients with AS or nr-axSpA. Positive HLA-B27 is also associated with other inflammatory diseases, such as psoriasis, IBD, and reactive arthritis.[12] Laboratory assessment can also include other markers of inflammation such as elevated erythrocyte sedimentation rate (ESR, or sed rate) and CRP. However, these markers may also be elevated with infection and are only elevated in about one-third of patients with axSpA.[1] As such, elevated ESR and CRP should be interpreted cautiously and always evaluated together with patient history and a physical exam.

Results from the plain film x-rays show bilateral sacroiliitis, and the laboratory workup show positive HLA-B27 and elevated CRP (8.9 mg/L). These results, along with Julie's family history of other inflammatory diseases, support a diagnosis of AS.

QUESTION 3

In patients like Julie who are refractory to NSAIDs, which of the following would be the next best appropriate pharmacologic therapy?

A. Interleukin-6 (IL-6) inhibitor
B. Methotrexate
C. Systemic glucocorticoid
D. Tumor necrosis factor (TNF) inhibitor

According to American College of Rheumatology/Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network (ACR/SAA/SPARTAN) guidelines, goals of treatment are to "alleviate symptoms, improve functioning, maintain the ability to work, decrease disease complications, and forestall skeletal damage as much as possible".[13] Patients should receive both nonpharmacologic and pharmacologic interventions throughout their disease course. Nonpharmacologic interventions can include exercise, physical therapy, rehabilitation, and support from patient associations and self-help groups. These strategies can keep the patient active, help to maintain good quality of life, improve daily functioning, and decrease pain associated with AS. ACR/SAA/SPARTAN guidelines support NSAID use for pain and stiffness in the first-line setting for both axial and peripheral manifestations. NSAID use successfully reduces symptoms in 50-80% of patients with AS, and notably has much lower efficacy in those with mechanical pain.[14]

According to guidelines, second-line therapy should be started in a patient with persistently high disease activity despite conventional treatment with nonpharmacologic therapy and NSAIDs. Second-line therapy should be initiated after failure of at least 2 different NSAIDs over 1 month, or incomplete responses to 2 or more NSAIDs over 2 months and would drive escalation to a second-line therapy.[13] In daily practice, response to therapy can be assessed by asking about symptoms and functional limitations.

For those patients who have failed first-line therapy or are intolerant to first-line therapy, current ACR/SAA/SPARTAN

guidelines support initiating therapy with a biologic therapy, namely a TNF inhibitor (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) or an IL-17 inhibitor (secukinumab or ixekizumab). This makes the correct answer to the clinical question D. In clinical practice, a TNF inhibitor is preferred after nonpharmacologic therapy and NSAID failure, unless comorbidities suggest that an IL-17 inhibitor is a better choice. IL-6 inhibitors are not indicated for use in patients with AS. Methotrexate should only be considered in patients with prominent peripheral arthritis or when TNF inhibitors are not available. Systemic glucocorticoids are not recommended.[13]

When discussing available therapies, clinicians should always discuss the potential advantages and limitations. In clinical trials, both TNF inhibitors and anti-IL-17 therapies had a clinical response rate of about 60%, measured by the Assessment of Spondyloarthritis International Society 20 (ASAS20) 20 (improvement of at least 20% and an absolute improvement in three of four domains).[15] For patients without significant comorbidities, there are little differences in efficacy between the five TNF inhibitors approved for use in AS, though head-to-head clinical studies are unavailable.[13] Important safety considerations for TNF inhibitors include contraindication in patients with chronic, serious, or recurring infections, and rarely, increased risk of bacterial, viral, fungal, and mycobacterial infections and reactivation of hepatitis B virus.[16] As such, patients should be screened for tuberculosis and hepatitis B virus prior to TNF inhibitor use.[17]

Like the TNF inhibitors, secukinumab and ixekizumab both have shown an ASAS20 response rate of about 60% in clinical trials.[18–21] Important safety considerations for IL-17 inhibitors include monitoring of tuberculosis, hypersensitivity reactions, and risk of serious infections. In clinical trials of IL-17 inhibitors, injection site reactions, upper respiratory tract infections, and gastrointestinal symptoms were among the most common adverse events reported.[22,23]

Other biologic therapies, including Janus kinase (JAK) inhibitors, are being evaluated in clinical trials. Tofacitinib is approved for use in other inflammatory conditions[24] and has been evaluated in a phase 2 clinical trial of AS.[25] Upadacitinib is another JAK inhibitor approved for use in rheumatoid arthritis and has been studied in a phase 2/3 trial in AS.[26] In August 2020, an application was submitted to the FDA for a new indication in AS.[27]

ACR/SAA/SPARTAN guidelines also recommend specific therapeutic strategies for certain AS subpopulations. For example, TNF inhibitors would be recommended over other biologics for patients with recurrent iritis and coexistent IBD. In patients with greater risk of tuberculosis exposure (through travel or personal contacts) or with a history of recurrent infections, TNF inhibitors other than infliximab should be considered given the increased risks of tuberculosis and infections for that agent.[13]

CASE PRESENTATION CONTINUES

You and Julie discuss the therapeutic options, including the relative efficacy and safety profiles of the various agents. Julie is screened for tuberculosis and hepatitis B infections, and her patient history indicates that her vaccinations are currently up to date. You also discuss Julie's preferences for dosing frequency and administration methods when selecting therapies. Because Julie does not have other comorbidities that would preclude her use of TNF inhibitors, you both decide that adalimumab 40 mg biweekly is a suitable option. Julie can continue her NSAID use as needed. You also recommend that she continue with physical therapy twice weekly.

After 3 months of treatment, Julie returns to the office to evaluate her response and tolerance to adalimumab. She reports that she has been sleeping through the night and her pain and stiffness in the mornings has subsided significantly. Her physical therapist has helped her maintain her range of motion and she is also doing some recommended exercises at home as well. She is pleased so far with her progress.

QUESTION 4

Which of the following would you recommend for Julie if she continues to have stable disease?

A. Continuous use of NSAIDs over on-demand use.
B. Long-term biologic use in the absence of toxicities.
C. Repeated MRI or radiographs to confirm stable disease over time.
D. Tapering of biologic use with ongoing stable disease.

ACR/SAA/SPARTAN guidelines define stable disease as disease that is asymptomatic or causing symptoms at an acceptable level, as reported by the patient for a minimum of 6 months. Current guidelines do not recommend discontinuation or tapering of biologic therapy in those with stable AS. Observational studies indicate that discontinuing a TNF inhibitor after disease remission or low disease activity can result in relapse within a few months in 60-74% of patients. As such, long-term treatment with a biologic

is recommended in the absence of toxicities, making the correct answer B. Discontinuation would only be considered in patients with sustained remission over several years, weighing the consideration that only a third of patients do not relapse. Regarding ongoing NSAID use, on-demand use is recommended over continuous use given the potential toxicities associated with continuous NSAID treatment.[13]

In patients with stable AS, a spinal or pelvis MRI is not needed to confirm inactivity, and unnecessary imaging may increase the burden of testing and possible overtreatment. Further, repeat spinal radiographs taken at scheduled intervals are not recommended as a standard approach. In published studies, only about a third of patients show any incremental changes in spine damage over a 2-year interval. Currently, no evidence supports that monitoring serial changes in radiographs of the spine leads to better outcomes and the potential benefit would need to be weighed against the risk of radiation exposure.[13]

QUESTION 5

In addition to peripheral manifestations, which of the following conditions is a common comorbidity of AS?

A. Asthma
B. Cardiovascular disease
C. Epilepsy
D. Gout

AS should be recognized as a multi-organ, chronic disease that requires coordination between primary and specialty care to monitor disease progression and manage other important comorbidities. The prognosis of AS depends not only on the severity of the axial disease but also on the presence and/or severity of other existing comorbidities. AS patients with comorbidities generally have greater disability, worse quality of life, and higher rates of mortality.[28]

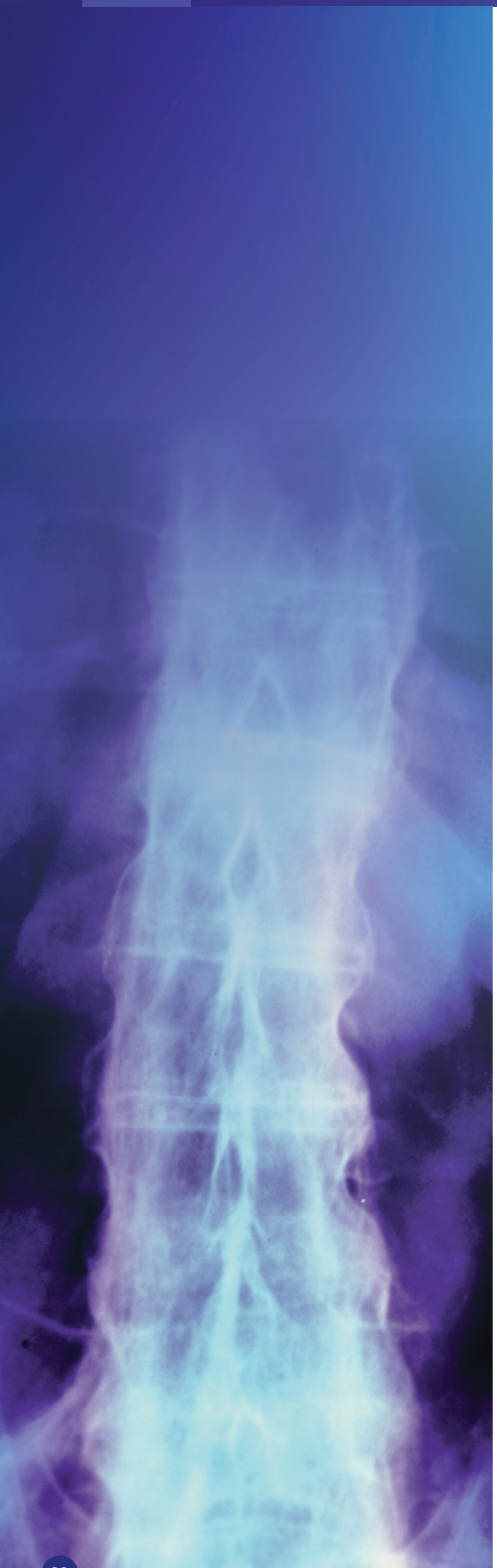
Patients with AS are at a 30-50% increased risk of incident cardiovascular events[29] and two-fold greater risk for cardiovascular death or cerebrovascular death,[30] highlighting the systemic nature of this inflammatory condition. Importantly, the most common causes of death of those with AS are cardiovascular in origin. Certain cardiovascular disease risk factors, such as hypertension, are more common in AS and such risk factors may act synergistically with chronic inflammation to drive the pathogenesis of atherosclerosis.[31] Other cardiac pathologies are linked to AS including conduction defects, valvular regurgitation, and cardiomyopathy. Additionally, patients with AS may experience other pulmonary manifestations such as apical fibrosis and interstitial lung disease.[32] Together, this indicates that B is the correct answer to the clinical question.

Given the heightened risk for cardiovascular disease, clinicians should be prepared to monitor and assess cardiovascular risk regularly in patients with AS and other inflammatory conditions. Management guidelines of cardiac conditions and inflammatory conditions are evolving. While ACR/SAA/SPARTAN has not provided specific guidelines on cardiovascular disease management, the European League Against Rheumatism (EULAR) has outlined guidance for cardiovascular risk management in patients with inflammatory joint disorders.[33] EULAR guidelines support appropriate AS disease management as part of the overall strategy to lower cardiovascular disease risk in these patients. Cardiovascular risk assessment should be completed at least once every five years in those with AS and reconsidered following any major changes in therapy.[33]

Broadly, many of the same principles to lower cardiovascular disease risk in the general population can be carried over to those with AS. These strategies include monitoring of cholesterol and lipid profiles, appropriate use of antihypertensives and statins, and lifestyle recommendations that emphasize a healthy diet, regular exercise, and smoking cessation.[33]

CASE CONCLUSION

At a follow-up appointment 6 months later, Julie reports that her back pain has continued to be controlled with the TNF inhibitor, and because she is sleeping through the night, her quality of life has improved significantly. You explain the importance of continued adherence to her current treatment regimen to reduce the risk of relapse. You also encourage Julie to continue her physical therapy, any regular exercise, and a healthy diet to maintain her overall health. You plan to continually monitor Julie for cardiovascular disease risk factors because you recognize her increased risk due to AS. Per ACR/SAA/SPARTAN guidelines, you plan to continue the adalimumab therapy unless significant toxicities arise that would warrant discontinuation. If Julie experiences a secondary failure of this initial TNF inhibitor over time and the disease remains active, she could switch to a second TNF inhibitor or an IL-17 inhibitor as needed.[13]



Ankylosing spondylitis is a chronic and often debilitating inflammatory joint disease that can have a significant negative impact on patient quality of life if left undiagnosed or untreated. The impact of AS can often be systemic, extending to many other extraarticular manifestations, including uveitis, psoriasis, inflammatory bowel disease and peripheral manifestations.

Patients with AS are also at greater risk for several comorbidities, notably cardiovascular disease, placing them at greater risk of morbidity and mortality. These factors underscore the need for early diagnosis, treatment, and monitoring.

PAs and other health care providers should review the clinical presentation of AS and how to make a differential diagnosis from the more common mechanical back pain, including the appropriate imaging methods.

While biologic agents have greatly improved the therapeutic landscape for AS, they also have increased the complexity of options and therapeutic decision-making. PAs should be knowledgeable about pharmacologic therapies, including the use of newly approved agents, and their recommended use according to ACR/SAA/SPARTAN guidelines.

Because patients with AS have an elevated risk for significant comorbidities, PAs should also regularly monitor cardiovascular disease and other high-risk comorbidities, keeping in mind that ongoing care requires coordination between primary care clinicians and specialists. Optimizing the management of these patients will lead to better clinical outcomes for those with AS.

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CME POST-TEST

PARTICIPANTS MUST:

1) Read the educational objectives and faculty disclosures
2) Study the educational materials
3) Go to **www.aapa.org/AS2021** to complete the post assessments in Learning Central. See page 2 for further information.

QUESTION 1

Which of the following characteristics would be consistent with the mechanical back pain rather than inflammatory back pain of ankylosing spondylitis (AS)?

A. Discomfort that improves with rest
B. Prolonged morning stiffness
C. Symptoms that awaken the patient at night
D. Symptoms with insidious onset

QUESTION 2

Which of the following would NOT support a positive diagnosis for AS and referral to a rheumatologist?

A. Bilateral sacroiliitis seen by plain film x-ray
B. Concomitant psoriasis, acute uveitis, or peripheral arthritis/enthesitis
C. Positive HLA-B27 biomarker
D. Symptoms that present with trauma

QUESTION 3

Which of the following statements regarding pharmacologic therapies for AS is correct?

A. An interleukin-17 (IL-17) inhibitor is recommended over TNF inhibitors in those with inflammatory bowel disease.
B. An IL-17 inhibitor should be considered if a patient fails a tumor necrosis factor (TNF) inhibitor or is intolerant.
C. Biologic therapies are the recommended first-line therapy.
D. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended only for those with peripheral disease.

QUESTION 4

Which of the following would NOT be an appropriate discussion point for a patient who has stable disease while receiving a biologic?

A. Describing the increased risk of flares with complete discontinuation of biologic therapy
B. Discussing on-demand or less frequent dosing of NSAIDs
C. Explaining that long-term treatment with a biologic is recommended once started
D. Suggesting that x-ray or MRI be repeated regularly

QUESTION 5

Which of the following statements best describes AS and its comorbidities?

A. Frank inflammatory bowel disease occurs in about 50% of patients with AS.
B. Patients with AS have twice the risk of cardiovascular or cerebrovascular death.
C. Patients with AS typically do not present with other peripheral manifestations.
D. The pathophysiologic pathways that drive inflammation are unique and non-overlapping for AS and other inflammatory diseases.

QUESTION 6

Which of the following diagnostic tests might further support an AS diagnosis?

A. Alpha-1 antitrypsin deficiency (AATD)
B. Human leukocyte antigen (HLA-B27)
C. Immunoglobulin E (IgE)
D. Rheumatoid factor

QUESTION 7

Which of the following statements is correct regarding the role of imaging in the diagnosis of AS?

A. Bilateral sacroiliitis as detected by plain film x-ray is sufficient to make the diagnosis.
B. CT imaging is routinely recommended to confirm the diagnosis.
C. Lumbar spine imaging is also required for diagnosis.
D. Patients with early stage disease will often have visual structural damage detectable by x-ray.

QUESTION 8

Which of the following therapies is the recommended first-line therapy option for patients with AS according to guidelines?

A. Interleukin-17 (IL-17) inhibitors
B. Non-steroidal anti-inflammatory drugs (NSAIDs)
C. Systemic glucocorticoids
D. Tumor necrosis factor (TNF) inhibitors

QUESTION 9

Which of the following statements is correct regarding patients with stable disease?

A. NSAIDs should be used on a continual basis rather than as needed.
B. Relapse occurs in large majority of patients who discontinue biologic therapy.
C. Repeat spinal radiographs are recommended to monitor incremental damage.
D. Therapy discontinuation is recommended for those with stable disease.

QUESTION 10

Which of the following statements is correct regarding AS and cardiovascular disease (CVD)?

A. AS and CVD have independent pathophysiologies.
B. Hypertension is less common in those with AS.
C. Patients with AS have a 50% increased risk of incident CVD events.
D. The overall CVD risk is lower in patients with AS.

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