

Aerospace Medicine Clinic

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You are an aviation medicine provider newly assigned to a military aviation unit. You are sitting down with the departing flight surgeon to review a list of patients on flight status who are followed for ongoing medical concerns. During this hand-off, your attention is drawn to a 38-yr-old fixed-wing pilot with “chronic lower back pain.” Lower back pain (LBP) is quite common in military pilots, but this tracker entry seems a bit different from the usual.

The left-sided pain began in the left buttock “several years ago” and has progressed upward to the left lower back. It was once intermittent, worse at night, and improved with light exercise. However, the pain is now constant and unrelenting. Discussing this with your colleague, he relates that the patient stated he was an avid, daily runner, but has not been able to run for the last few months due to the 7 out of 10 aching pain. Conservative treatments including acetaminophen (paracetamol) and rest have not improved his pain and “stiffness” in his lower back. In addition, he has been having increasing gastrointestinal (GI) symptoms including intermittent diarrhea and bloating and has been avoiding the use of nonsteroidal anti-inflammatories (NSAIDs). He has no history of acute trauma to the affected area. The pilot has a current X-ray, and he received an MRI of the pelvis yesterday due to suspicions by his primary care manager of a possible injury to, or around, the sacrotuberous ligament. Results of the MRI are pending. The pilot is currently in a “duties not to include flying” status.

After reviewing the remaining patients, the outgoing provider hands over the responsibility of the aviation medical section and wishes you well. Thinking about your new patient population, you wonder how common LBP may be in this unit.

1. What is the prevalence of LBP in the U.S. military flight community?
 - A. Approximately 85%.
 - B. Less than 20%.
 - C. Approaching 89%.
 - D. Approximately 53–64%.

ANSWER/DISCUSSION

1. A. LBP is a significant issue for U.S. military flight crews. It is reported to have a prevalence of 84.6% among fighter, helicopter, and transport pilots. The high rate of LBP in U.S. military flight crews is multifactorial; however, ergonomic support and the total load the spine is subjected to seem to be leading contributors. In one study, 67.2% of U.S. Army aircrew reported that the amount of flight and combat gear they wore contributed to LBP, and 64.4% reported that lack of lumbar support was a leading contributor to their symptoms of LBP. Servicemembers also found a link between flight hours and LBP, with the median time in flight before experiencing LBP being 60 min.¹ B, C, and D either underestimate or overestimate the current knowledge of the prevalence of LBP.

The next day you see the imaging results for your patients in your inbox. Looking at the MRI for the pilot, results include a decreased fat signal (T1 image) and increased fluid signal (short tau inversion recovery) due to bone marrow edema adjacent to the left sacroiliac (SI) joint. The radiographs from 4 wk previous indicate inflammation of the SI joints and support the MRI finding of left-sided sacroiliitis. Based on the history and imaging studies, you begin to formulate a differential diagnosis.

2. Considering the history and imaging results, what is the most likely diagnosis?
 - A. Sciatica.
 - B. Pott's disease.
 - C. Ankylosing spondylitis.
 - D. Pelvic ring stress fracture.

ANSWER/DISCUSSION

2. C. Ankylosing spondylitis (AS) is a spondyloarthropathy that begins with inflammation in and around the SI joint and

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progresses to restriction and fusion of the spine. This end state can be spotted radiographically by identifying what is commonly referred to as a “bamboo spine” on plain film.² In addition to spinal immobility, patients may experience uveitis and peripheral arthritis. Acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated in 50–70% of patients experiencing active disease.³ There is clinical suspicion for AS in this patient due to the presentation of chronic LBP, which began with involvement of the SI joint and progressed to the upper back, combined with the imaging study results and GI issues. Sciatica commonly involves impingement of the sciatic nerve or compression injury to the L4-S3 nerve roots. Radiating pain from the buttocks down the ipsilateral lower extremity to the compression in a sciatic distribution is pathognomonic for this issue.⁴ While the patient does present with pain in the gluteal region, he does not experience radiation down either lower extremity. Pott’s disease is also known as spinal tuberculosis. Pott’s disease is a process by which disseminated *Mycobacterium tuberculosis* causes osseous infection of the lumbar spine via the anterior and posterior venous plexuses. The most common initial presenting symptom is back pain.⁵ Other symptoms, including night fevers, neuropsychiatric involvement, and either an anterior or posterior spinal abscess seen on imaging are common but are absent in this patient. Pelvic ring stress fractures in younger adults such as this patient are commonly associated with high-energy trauma and often have a component of acute blood loss that may be life-threatening. The mortality rate is approximately 7.9% for stable injuries and 11.5% for unstable injuries.⁶ The progression of symptoms over the course of years for this patient makes this unlikely.

With a strong suspicion for AS, you call the pilot to discuss ordering a referral to rheumatology. The pilot agrees and asks if there is a definitive test for verifying the diagnosis. You discuss with the pilot that there is no pathognomonic test for the suspected condition. Rather, it is a combination of the patient’s history, the physical exam, imaging, and blood work that determines the diagnosis.

3. Which of the following blood tests is least helpful in forming a diagnosis of AS?
 - A. ESR.
 - B. Rheumatoid factor (RF).
 - C. Genetic test for human leukocyte antigen B27 (HLA-B27).
 - D. CRP.

ANSWER/DISCUSSION

3. **B.** RF should not be ordered if the provider is only thinking about AS and not rheumatoid arthritis (RA) or connective tissue disease. In general, these two diseases do not coexist. RF is an antibody test found in RA and other rheumatologic (e.g., Sjogren’s syndrome) and nonrheumatologic (e.g., hepatitis C) diseases but not AS. RF and HLA-DR4 are seropositive in patients presenting with RA, while HLA-B27 is seropositive in

patients presenting with AS.⁷ ESR and CRP are acute phase reactants that are seropositive in many acute inflammatory conditions including both RA and AS. These markers are nonspecific. Genetic testing for HLA-B27 would be helpful to solidify a diagnosis of AS in light of the current symptoms, as approximately 90% of AS patients are seropositive for the HLA-B27 allele.⁸

After meeting with the rheumatologist, the patient meets with you for a follow-up. Test results show elevated ESR and CRP and the presence of HLA-B27. The rheumatologist has agreed with your preliminary diagnosis of AS and also recommends the pilot be started on adalimumab. You discuss with the patient that adalimumab is a biological medication and tumor necrosis factor (TNF) blocker that reduces inflammation. You relate that it can be used to reduce pain and swelling due to certain types of arthritis such as rheumatoid, psoriatic, juvenile idiopathic, as well as AS. Specifically for your own knowledge, you note that adalimumab is a fully human, high-affinity, recombinant immunoglobulin G anti-TNF-alpha (TNF- α) monoclonal antibody. The pilot is not too fond of the medicine being injectable. However, he is willing to try the medication to help relieve his symptoms and possibly get back to flying.

Looking into the aeromedical regulations for pilots and flight crew who have a diagnosis of AS and are on a biological, the Air Force Aerospace Medicine Waiver Guide addresses AS as a disqualifying condition “if the condition results in duty restriction, or frequent absences from duty, or ongoing specialist follow-up more frequently than annually.”⁹ The condition is potentially waivable for flight classes II/III, among other specialties, if factors indicate the patient experiences stable remission on an approved, sustainable treatment with good drug tolerance, along with a lack of significant nonorthopedic disease manifestations.⁹ Waiver authority-approved NSAIDs are preferred for the flight-safe treatment of AS, but several biologicals including adalimumab are approved with a waiver.

The U.S. Navy Aeromedical Reference and Waiver Guide addresses AS such that “an established diagnosis with symptoms is CD [conditionally disqualifying]. Waiver is possible in early cases with normal mobility and no complications.”¹⁰ This guide specifically notes that strict adherence to a regular exercise routine and physical rehabilitation for flare-ups is a cornerstone for treatment, with chronic therapy with NSAIDs generally not being conducive to a waiver.¹⁰

The Army Aeromedical Policy Letters and Aeromedical Technical Bulletins address AS with waivers being “recommended on a case-by-case basis for select aircrew with early stage, mild or inactive disease, who have minimal symptoms, require minimal medications for symptom control, have had no recurrent symptoms or extra-spinal manifestations, who continue to have normal spinal mobility, and job environmental safety risk remains acceptable.”¹¹ As with the Air Force, nonorthopedic disease manifestations indicate poor prognosis and lower chance of waiver approval.¹¹ As with the Navy, the Army waiver guide emphasizes regular exercise and other lifestyle health modifications along with NSAID treatment. Biologicals are noted to be waivable but have the potential to impact the ability to deploy.

The International Civil Aviation Organization Manual of Civil Aviation Medicine does not specifically address AS but does have general guidelines on back problems and arthritis. These guidelines emphasize the physician's judgment on the course of the illness and the chances of acute or chronic symptoms that could impair the pilot from safely operating an aircraft.¹² It is noted that the effects of long-term treatment for these conditions must be examined for impacts on pilot readiness.

The Federal Aviation Administration Guide for Medical Examiners uses the umbrella Arthritis Worksheet to address AS, with the condition being eligible for a waiver if there is no significant disruption to daily activities for the patient, lab values are within normal limits on medication regimen, and the patient is controlled using aeromedically cleared drugs.¹³ Notably, most biologicals have a no-fly time after administration, with adalimumab having a 4-h designation.

4. As an anti-TNF agent, what are the biological effects of adalimumab?
 - A. Inhibits the interaction of TNF- α to the cell surface TNF receptors, p55 (TNFR1) and p75 (TNFR2).
 - B. Downregulates serum matrix metalloproteinases 1 and 3 (MMP-1 and MMP-3).
 - C. The resulting TNF blockade inhibits the destruction of cartilage and bone.
 - D. Has potent osteogenic properties.
 - E. All of the above.

ANSWER/DISCUSSION

4. E. Adalimumab is identical to human IgG1, which allows it to bind TNF- α with high affinity. Once adalimumab is bound, TNF- α cannot bind cell surface TNF receptors p55 (TNFR1) and p75 (TNFR2), which then downregulates cytokine-driven inflammatory processes activated by TNF- α binding p55 and p75. Furthermore, TNF- α blockade produced by adalimumab prevents TNF- α from activating nuclear factor kappa $\kappa\beta$ and receptor activator of nuclear factor $\kappa\beta$ on osteoblasts, which in turn downregulates maturation of osteoclasts, leading to decreased degradation of cartilage and bone. TNF- α blockade also downregulates expression of MMP-1 and MMP-3.¹⁴ Serum matrix metalloproteinases act to degrade extracellular matrix; specifically, MMP-1 is a collagenase and MMP-2 is a gelatinase. Together they act to degrade collagen types I, II, III, IV, V, VII, X, and XI as well as aggrecan, gelatin, elastin, fibronectin, and laminin.¹⁴ These combined factors lead to a pro-osteogenic environment, which allows adalimumab and other TNF- α blocking drugs to be used in AS, RA, and a variety of other conditions.

After doing your due diligence on how to address his service-specific aeromedical disposition, you walk over to the unit to discuss the options with the pilot. He appreciates that you checked in on him and tells you it has been a week since his first adalimumab treatment. He is a bit frustrated that he hasn't seen any changes in his symptoms.

5. Approximately how long does it take for most people with AS to benefit from adalimumab therapy?
 - A. 12 wk.
 - B. 2 wk.
 - C. 1 wk.
 - D. Within 24 h.

ANSWER/DISCUSSION

5. A. Most individuals see results within 12 wk, but it may take longer. A minority of patients will see results in 2 wk. There is little evidence to suggest mitigation of signs and symptoms in shorter periods of time. As adalimumab is a biological agent, it takes time to absorb the medication and to build significant pharmacological levels to observe clinical effect.¹⁵ Clinical information on the usage of adalimumab for AS notes that improvement in SI joint involvement and symptoms may begin at week 2 of therapy but may not reach a clinically significant level until week 12 on average.¹⁶

Monitoring the pilot's condition with monthly follow-ups, you find after 3 mo he currently has few lower back or buttocks issues and no GI symptoms to report. The patient is happy he has little to no back stiffness and can run again without restricting pain. He never had uveitis or other concerns and reports no off-nominal effects of the medication. With these positive results and support from the rheumatologist, you place a waiver request with his parent organization. After a few weeks of processing, the pilot was given a waiver with self-reporting if there are any changes in his health status and a yearly visit to the rheumatologist to screen for any disease progression or need for medication adjustment. He is returned to flying status and you add him to your waiver tracker to make sure he receives the continued follow-up his waiver requires.

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