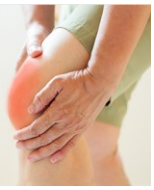
Exploring Best Practices for Diagnosis and Management of Adult-Onset Still's Disease



OVERVIEW

Adult-onset Still's disease (AOSD) is a rare, polygenic auto-inflammatory syndrome with a pathogenesis similar to systemic juvenile inflammatory arthritis. Join Petros Efthimiou, MD and Olga Petryna, MD as they discuss making the diagnosis of AOSD through interpretation of clinical and laboratory findings and careful exclusion of other diseases. The faculty review the evidence related to the variety of medications often used to treat patients with AOSD, focusing on canakinumab, the only medication approved in the United States for the disease. Case studies are utilized to share the faculty's experience in diagnosis and treatment, so as to facilitate integration into clinical practice.

CONTENT AREAS

- Pathogenesis
- Clinical Features
- Diagnosis
- Treatment
- Patient Burden of Disease
- Multidisciplinary Care

LEARNING OBJECTIVES

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

- Describe the optimal pathway of diagnosis for a patient presenting with possible Adult-onset Still's Disease (AOSD), using resources available in the average clinical setting
- Develop a treatment strategy for AOSD, taking into consideration a patient's subtype and risk assessment for systemic complications
- Describe the mechanism of action, safety and efficacy of new and emerging biologic treatments for AOSD
- Consider patient HRQoL as part of an AOSD treatment monitoring protocol

FACULTY

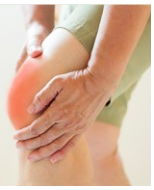
Petros Efthimiou, MD, FACR
New York Rheumatology Care, PC
New York, New York
Clinical Professor of Medicine
Ross University School of Medicine
Miramar, Florida

Olga Petryna, MD, FACR
Clinical Assistant Professor
Division of Rheumatology
NYU Grossman School of Medicine
New York, New York

TARGET AUDIENCE

This activity is intended for rheumatologists, rheumatology advanced practice providers, dermatologists, primary care physicians, and other clinicians involved in the care of patients with adult-onset Stills disease.

Exploring Best Practices for Diagnosis and Management of Adult-Onset Still's Disease



ACCREDITATION AND CERTIFICATION

The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Annenberg Center for Health Sciences at Eisenhower designates this enduring material for a maximum of 1.25*AMA PRA Category 1 Credits*™ and 1.25 ANCC Contact Hour for nurse practitioners and nurses. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

DISCLOSURE STATEMENT

It is the policy of the Annenberg Center for Health Sciences to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All faculty and planners participating in sponsored programs are expected to identify and reference off-label product use and disclose any relationship with those supporting the activity or any others with products or services available within the scope of the topic being discussed in the educational presentation.

The Annenberg Center for Health Sciences assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of CE/CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by the Annenberg Center for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. The Annenberg Center is committed to providing its learners with high-quality CE/CME activities and related materials that promote improvements or quality in health care and not a specific proprietary business interest of a commercial interest.

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosures have been made:

Faculty

Petros Efthimiou, MD, FACR
Consultant/speaker: Novartis, Kiniksa, AbbVie, Horizon, Amgen, Pfizer, Sanofi, UCB, Mallinckrodt

Olga Petryna, MD, FACR
Consultant/speaker: Nothing to disclose

The faculty for this activity have disclosed that there will be no discussion about the use of products for non-FDA approved applications.

Additional content planners:*The following have no significant relationship to disclose:*

- Gregory Scott, PharmD (medical writer)
- Eugene Cullen, MD (peer reviewer)

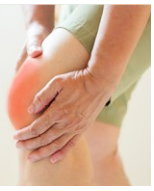
Annenberg Center for Health Sciences

Staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.

The ideas and opinions presented in this educational activity are those of the faculty and do not necessarily reflect the views of the Annenberg Center and/or its agents. As in all educational activities, we encourage practitioners to use their own judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. The Annenberg Center disclaims all liability and cannot be held responsible for any problems that may arise from participating in this activity or following treatment recommendations presented.

This activity is supported by an independent educational grant from Novartis Pharmaceutical Corporation.

This activity is an online enduring material. Successful completion is achieved by reading and/or



viewing the materials, reflecting on its implications in your practice, and completing the assessment component.
The estimated time to complete the activity is 1.25 hours.

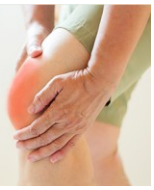
This activity was released on June30, 2021 and is eligible for credit through June30, 2022

OUR POLICY ON PRIVACY
Annenberg Center for Health Sciences respects your privacy. We don't share information you give us, or have the need to share this information in the normal course of providing the services and information you may request. If there should be a need or request to share this information, we will do so only with your explicit permission. See Privacy Statement and other information at https://annenberg.net/pages/privacyPolicy.php

CONTACT INFORMATION
For help or questions about this activity please contact Continuing Education:

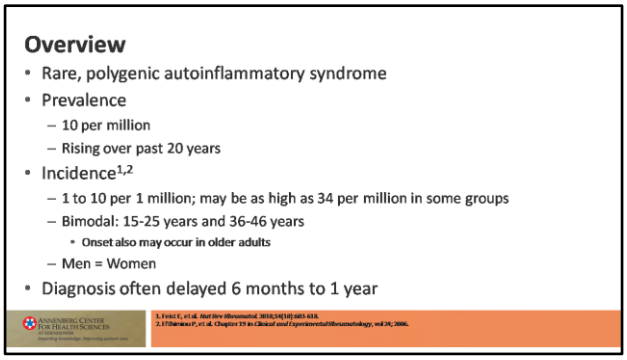
ce@annenberg.net
Annenberg Center for Health Sciences

Exploring Best Practices for Diagnosis and Management of Adult-Onset Still's Disease

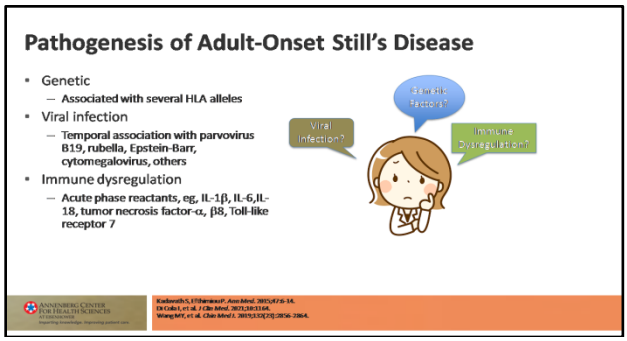


Editor's Note: This is a transcript of a CME presentation. It has been edited and condensed for clarity.

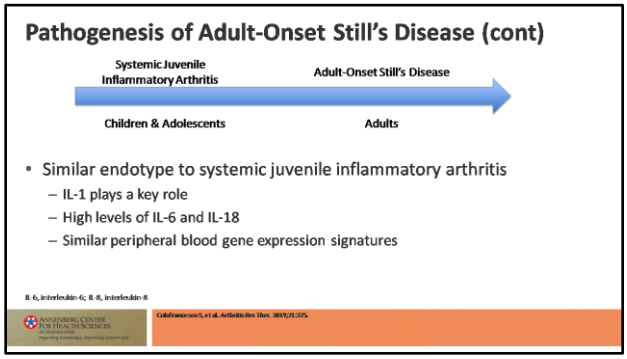
Overview and Pathogenesis of Adult-Onset Still's Disease



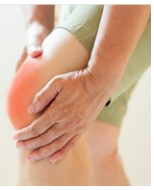
Olga Petryna, MD, FACR: First and foremost, it's important to mention that adult-onset Still's disease is a rare, polygenic auto-inflammatory syndrome. It has a prevalence of 10 per million and the prevalence number tends to be rising over the last 20 years. The incidence rate varies from study to study; has been described from 1-10 per 1 million population, but may be as high as 34 per million in some category of patients where disease is more prevalent. It has bimodal presentation, usually spiking between 15 and 25 years of age and a second spike happens between 36 and 46 years. The onset can be acute and mostly occurs as a gradual onset in older adults. It is equally distributed between male and female patients, and often, due to complexity of the disease and issues with diagnosis, the diagnostic pathway takes a while.



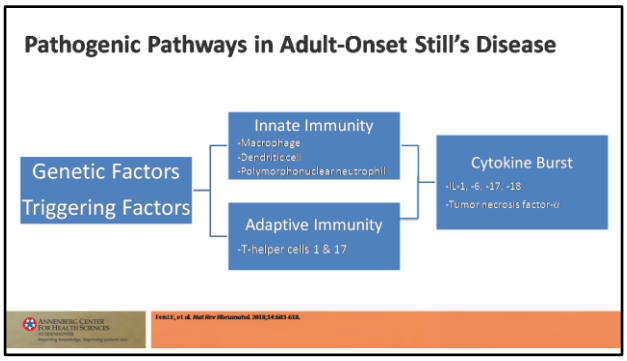
When it comes to pathogenesis of the condition, there are several factors that play a role. The belief is that several *human leukocyte antigen* (HLA) alleles are associated with genetic disposition to the disease, but it also takes a trigger to start the cascade of inflammatory reactions—often a trigger considered to be a viral infection, most of all parvovirus B19, rubella, Epstein-Barr, cytomegalovirus (CMV), and several other types of viruses. As a result of genetic predisposition and environmental triggers, the immune reaction cascade leads to the release of acute phase reactants, such as interleukin-1, interleukin-6, interleukin-18, tumor necrosis factor-alpha (TNF-alpha), and toll-like receptor 7 and leads to organ damage and disease manifestations.



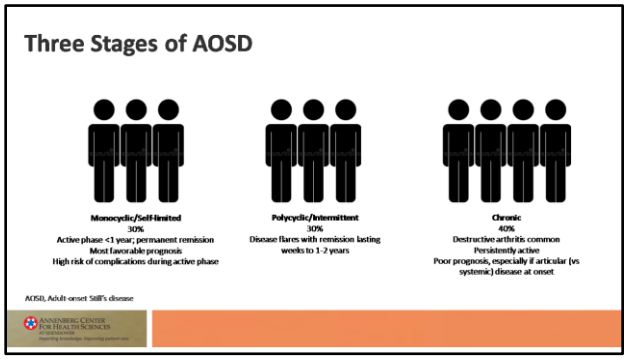
The pathogenesis of adult-onset Still's disease can take different paths, depending on time of the presentation. Oftenthe disease starts in childhood. We call it *systemic juvenile inflammatory arthritis* (SJIA). It can go into remission for a prolonged period of time and then manifest again in adulthood. In other subgroups of patients, the disease starts in adulthood without the childhood period of illness



and, in this category of patients, we call it *adult-onset Still's disease*. A similar endotype to SJIA leads us to believe that it may be a continuum of the same condition, different only by the age of presentation. It is known from the studies that in both conditions, interleukin-1 plays a key role and also increased levels of interleukin-6 and interleukin-18 as cytokines that present as a result of downstream regulation have been observed in both adult and childhood cases. Both childhood and adult patients share similar peripheral blood gene expression signatures that also supports the belief of the continuum of the same disease.



When looking at the pathogenic pathway in adult-onset Still's disease, genetic background obviously plays a role. HLA-BW35, DRB1 and 15, DRB1 04 play a role in manifestation of the disease, as well as triggering factors that lead to over-expression of interleukin-1 and interleukin-18, which triggers the cascade of inflammatory reactions. The belief is that the main pathway is led by activation of innate immunity cells, such as macrophages, dendritic cells, and neutrophils which leads to over-expression of nuclear cytokines and release of pro-inflammatory cytokines, such as interleukin-1, -6, -18, TNF-alpha, and interleukin-17. The adaptive immunity part plays a role as well, especially through T-helper cells 1 and 17, which, again, augment the release of cytokines that I mentioned earlier. That leads to a shift of the balance towards the pro-inflammatory pathway and suppression of the anti-inflammatory pathway expressed by interleukin-10, TNF, tumor growth factor beta, and other regulatory cells. This shift from an anti- to a pro-inflammatory cytokine profile leads to the inflammatory phase of the disease, which is responsible for the main manifestations in this condition.

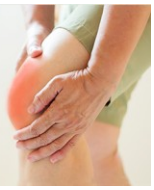


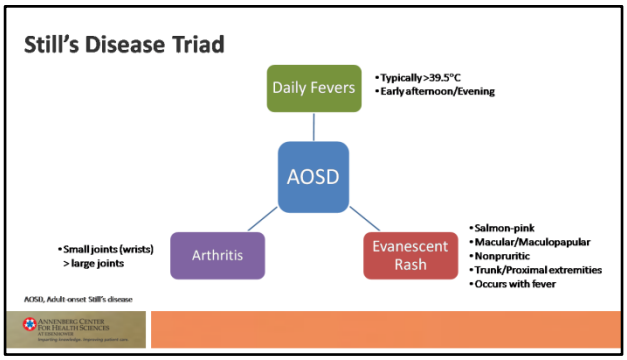
The belief is that adult-onset Still's disease may present in 3 different ways or 3 different stages. The *monocyclic* or *self-limited stage* is one of the fairly common ways to present. It happens in 30% of patients. It typically lasts about a year or less and results in a permanent remission. This type of presentation has the most favorable prognosis for patients with adult-onset Still's disease, although patients can experience a high risk of complications in the active phase of the condition where they are at high risk for macrophage activation syndrome and other serious life-threatening complications.

The second way of presentation is the *polycyclic*or *intermittent stage*where patients present with disease flares and periods of remission. Periods of remission in this type of presentation may last from several weeks to several years at a time and it is impossible to predict how to progress without ongoing observation.

The third stage is the *chronic ongoing presentation,*which is typical for about 40% of patients. It predominantly presents as destructive inflammatory arthritis, persistently active disease with some systemic inflammatory symptoms as well. This type of presentation has the poorest prognosis, especially in the articular stage where patients develop chronic erosions and mobility-limiting deformations of their joints.

Exploring Best Practices for Diagnosis and Management of Adult-Onset Still's Disease

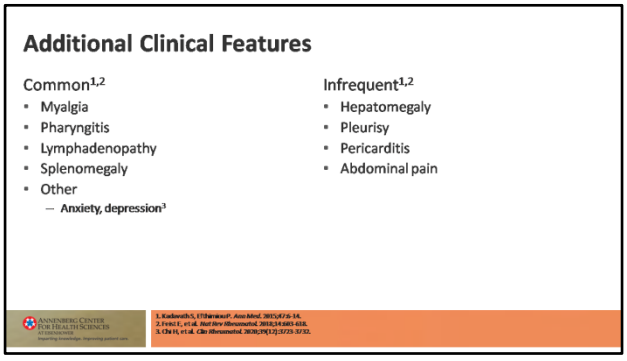




Speaking of the initial presentation of Still's disease, we typically mention the so-called Still's disease triad which presents in the form of daily fevers, typically more than 39.5°C. Usually, fevers are quotidian and cyclic. They can present in early afternoon or evening, but can be seen in other times of the day.

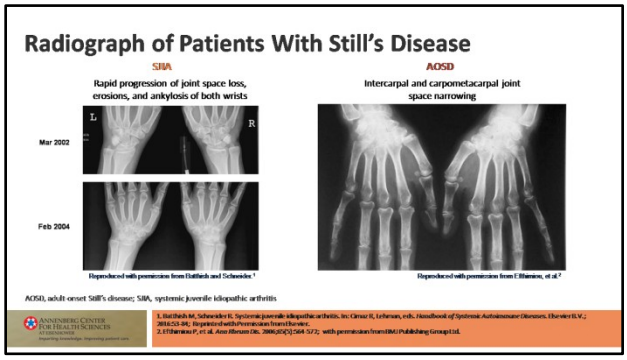
Evanescent rash is the second component of the Still's triad and it is a salmon-colored or pink rash which presents as maculopapular, non-pruritic eruptions, mainly on the trunk and proximal extremities, and often coincides with episodes of fever.

Arthritis is the third component of this triad that usually presents as inflammatory arthritis of the smaller joints and, in many cases, large joints in the body. Most often, in adult cases, we see wrists and knee joints being affected most severely.



Additional features that we can observe in patients with adult-onset Still's disease at initial presentation are myalgia, pharyngitis, lymphadenopathy, spleno-megaly, and also feelings of anxiety and depression.

A lot of times you can see the patient with episodes of frequent nasopharyngitis or tonsillitis with negative cultures and poor response to antibiotic therapy. It always raises the concern for possible adult-onset Still's disease as a manifestation of systemic inflammation. Less frequent manifestations are hepatomegaly, pleuritic pain, pericarditis and abdominal pain.



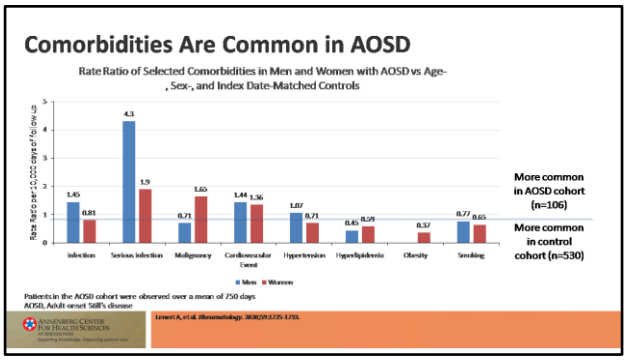
When it comes to describing the triad of Still's disease, there are certain differences in childhood and adult presentation of the condition. Joint damage is a common feature of Still's disease for either adults or kids and typically erosions and ankylosis occur early in the disease course.

On the left, you see the image of a 15-year-old girl with SJIA who experienced rapid progression of joint space loss and you see, between 2002 and 2004, she developed significant loss of joint space, erosions, and ankylosis of both wrists.

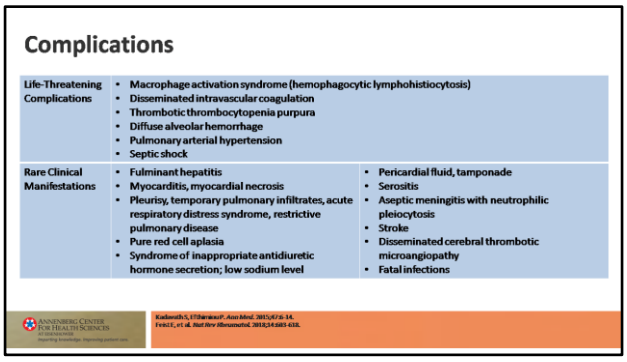
On the right side, you see the case of an adult patient with Still's disease, which has a distinct pattern of inter-carpal and carpal-metacarpal joint space narrowing and also resulting in pericapitate ankylosis.

So, as you see in both adult and adult cases, arthritis of Still's disease progresses very fast and often leads to irreversible joint deformities.

Exploring Best Practices for Diagnosis and Management of Adult-Onset Still's Disease



Other common comorbidities in Still's disease are outlined in this slide. Most often, the disease gets complicated by infections or even serious infection and it happens as a result of altered or impaired immunity, as well as therapies patients receive which are typically immunosuppressive therapy. Other common co-manifestations are malignancy, cardiovascular events, hypertension, dyslipidemia. Often patients suffer from smoking and obesity and that also leads to worse outcomes in this category of patients. It's always important to keep in mind potential comorbidities that can complicate the disease course and affect the treatment course.



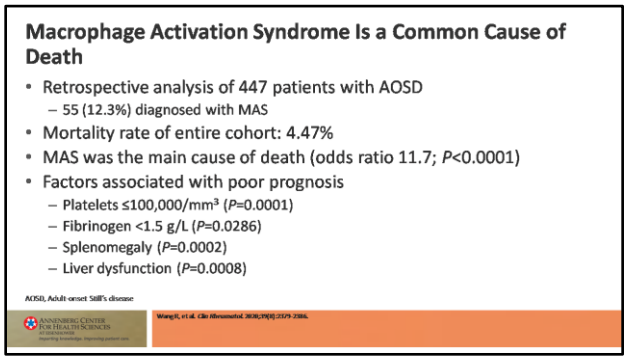
Speaking of less common manifestation of Still's, you would always want to keep in mind the life-threatening manifestations or conditions that you should be on high alert for.

One of the most common manifestations is*macrophage activation syndrome*. Macrophage activation syndrome, while it doesn't occur in necessarily every patient with Still's disease, can be life-threatening and lead to mortality up to 40% of cases. Early recognition of macrophage activation syndrome is important in Still's patients. It can be a life-changing decision when it comes to treatment options.

Other life-threatening complications to keep in mind are disseminated intravascular coagulation, TTP or thrombotic thrombocytopenia purpura, diffuse alveolar hemorrhage, pulmonary hypertension, and septic shock.

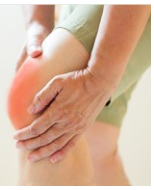
Some of the less threatening, but nonetheless important and severe, rare manifestations of the disease are fulminant hepatitis, myocarditis, myocardial necrosis, pleuritis or pleuropericarditis, as well as pure red cell aplasia.

It is important to monitor patients for these complications with laboratory screening and even imaging studiesif the level of clinical suspicion is high, in order to prevent and treat these conditions early.



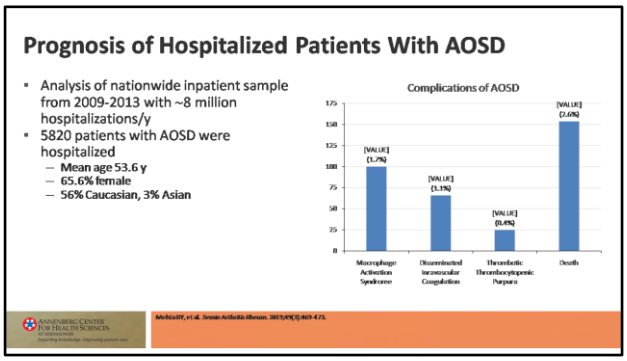
Let's focus on macrophage activation syndrome since it is one of the most common causes of death in patients with adult-onset Still's disease.

A retrospective analysis of 447 patients with Still's disease showed that 12.3% of patients in the study were diagnosed with this complication and the mortality rate of the entire cohort was 4.47% which corresponds with about a third of the patients who were diagnosed with the condition. As I mentioned before, it's one of the main causes of death in this condition with an odds ratio of 11:7 and early



diagnosis and treatment is crucial in changing the outcome.

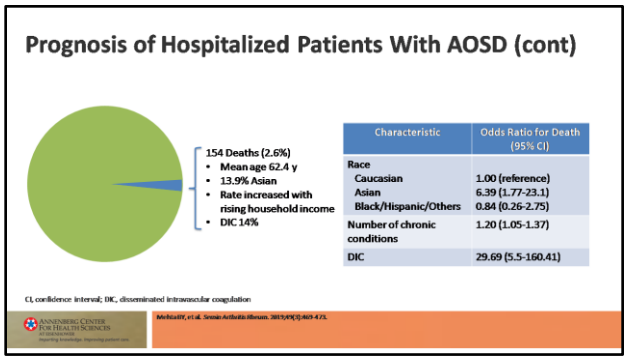
What are the factors to keep in mind? If your patient has platelets of less than 100,000/mm^3, fibrinogen of less than 1.5 g/L; if they present with splenomegaly or liver dysfunction, that rate is of concern for poor prognosis and requires more aggressive approach to treatment. A lot of times, patients with rising ferritin levels, dropping cell counts, and a drop in fibrinogen are starting treatment, even before they develop any clinical symptoms, out of concern for possible progression of the disease.



Another study on the prognosis of hospitalized patients with adult-onset Still's disease, which is an analysis of nationwide in-patient samples from 2009 to 2013, included 8 million hospitalizations from almost 6,000 patients with Still's disease.

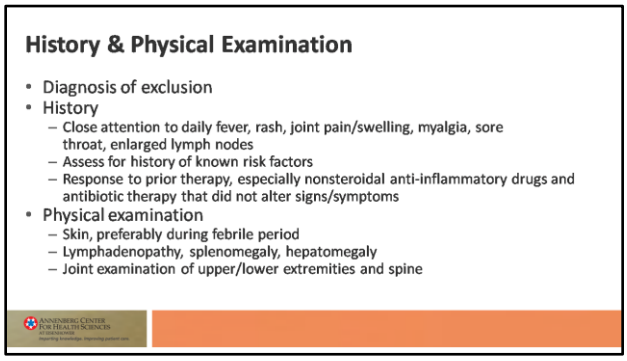
In this analysis, the average age at presentation was 53 years. About 65% of the patients were female and 56% of the patients were Caucasians. When you look at the complications that led to hospitalization or were seen in these hospitalized patients, the most common complication was actually macrophage activation syndrome. It was followed by disseminated intravascular coagulation (DIC), and the third most common one was thrombotic thrombocytopenic purpura.

As we see from this cohort, 2.6% of the cases resulted in death of the patient, which emphasizes the seriousness of Still's complications and the importance of early diagnosis and treatment.



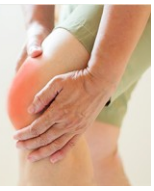
When it comes to prognosis of hospitalized patients from this same study, 2.6% of the patients who died had a mean age of 62.4 years, 13.9% of those patients were Asian and the rate increased with rise in household income. DIC was seen in 14% of the patients.

Diagnosing Adult-Onset Still's Disease



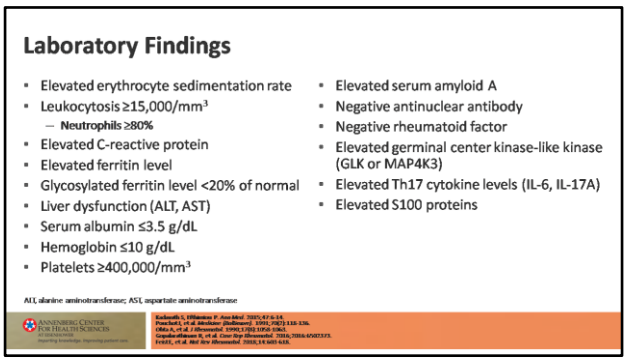
Petros Efthimiou, MD, FACR: Adult-onset Still's disease remains a diagnosis of exclusion., so we pay close attention to the patient's history, which usually includes daily spike in fever, a rash, usually gets worse around the time of the febrile episode, joint pain and swelling in multiple joints, including the small joints of the hands and the wrists. It includes myalgia, sore throat, generalized malaise and sometimes history of enlarged lymph nodes.

The clinician will assess the history of known risk factors and look for common diseases that should be excluded. A very important point is response to prior therapy, especially non-steroidal anti-inflammatory



drugs (NSAIDs), but also a history of antibiotic use that did not change the febrile episodes.

The physical examination is really important in the diagnosis of Still's disease. We're looking at multiple organ systems, including the skin, which may present with classic salmon-colored maculopapular rash that gets exacerbated during the febrile period, but can be present throughout. A careful physical exam should look for diffuse lymphadenopathyand alsoorganomegaly including splenomegaly and hepatomegaly. And, of course, a very careful joint examination, looking at the upper and lower extremities, andthe central skeleton.



Laboratory findings are important, although there's not a diagnostic test that can make the diagnosis of Still's disease. However, laboratory tests play an important role in assessing disease severity, organ complications and ruling out other more common conditions that can present in a similar fashion.

Typically, we will consider the sedimentation rate since the elevated erythrocyte sedimentation rate can be frequently seen. An important clinical note here is that if there is a rise in the sedimentation rate and then we experience a drop, the clinician should think about macrophage activation syndrome since this is a paradoxical phenomenon that's seen in this very important and life-threatening complication.

A very commonly seen laboratory finding is *leukocytosis*, which can exceed 15,000/mm^3 white cells. Of those, more than 80% are neutrophils. There is elevated C-reactive protein and elevated serum ferritin which is known to be acute phase reactant. It is cytokine-driven and is produced in the liver. Some laboratories in Europe have proposed a glycosylated ferritin level since glycosylation of ferritin is paradoxically low in adult-onset Still's disease which is usually less than 20% of normal and that distinguishes it from other inflammatory conditions. Unfortunately, this test is not commonly seen commercially, so it's not always available.

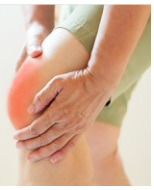
We always look for liver dysfunction and look for transaminasemia, for example, elevated alanine aminotransferase (ALT) and aspartate amino-transferase (AST). Serum albumin is often equal to or less than 3.5 grams per deciliter. We can see anemia, sometimes less than 10 g/dL, which is related to a generalized inflammatory response. Elevated platelets, more than 400,000/mm^3 at times, again that's a finding associated with generalized inflammation. And when it's commercially available, elevated serum amyloid A.

Of course, we're going to look for common auto-immune diseases and that should be excluded., so a negative antinuclear antibody and a negative rheumatoid factor is an important factor and has found its way in some of the classification criteria for adult-onset Still's disease.

Some laboratories offer cytokine levels which are not always standardized, but in recent laboratories they have found an elevation of Th17 cytokine levels, including interleukin-17, but also elevated interleukin-6 and elevated S100 proteins.

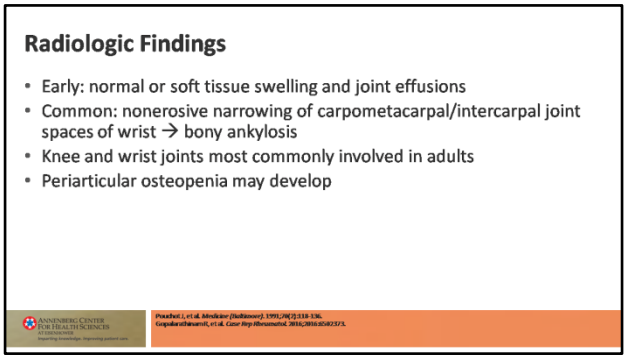
Is there a good biomarker for adult-onset Still's disease? The majority of clinicians use serum ferritin as a biomarker. I would like to caution the audience that serum ferritin is not always elevated and a normal ferritin should not exclude the presence of adult-onset Still's disease. When it's elevated, though, we often follow that and often in response to anti-inflammatory treatment.

Exploring Best Practices for Diagnosis and Management of Adult-Onset Still's Disease



We can follow inflammatory markers such as C-reactive protein, sedimentation rate and, when available, usually in a research setting, S100 proteins or cytokines such as interleukin-18, interleukin-6 or interleukin-17A.

The laboratory work is important, but it's not diagnostic. It complements the clinical picture and the clinical assessment.



How about radiography? Radiologic findings in adult-onset Still's disease are often absent in the early stages and can be seen later on, especially involvement of the wrist joint where there can be ankylosis and loss of joint space.

In some aggressive cases, that can be seen early on, so it's important to screen for that and look for that. It causes irreversible joint damage that can be prevented with treatment. When disease becomes more extensive, wrist and knee joints, but also ankles, can also be involved, and this should be screened.

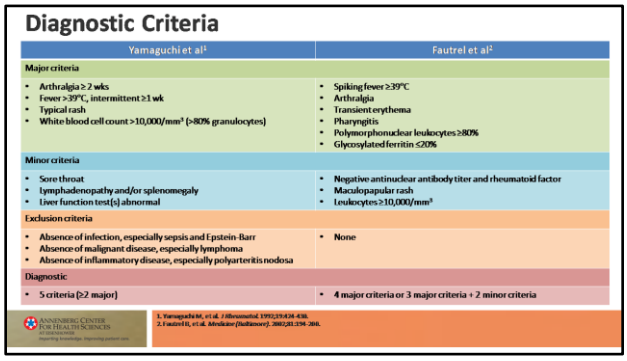
There can be periarticular osteopenia and a frequent finding is inflammatory arthritides. And other modalities have been used recently, for example, MRIs and PET/CT scans where they can show some uptake of the isotope in target organs such as lymph nodes, spleen, and liver.

The diagnostic approach to adult-onset Still's disease is a complex process. It involves a very careful clinical examination and a heightened index of clinical suspicion. It's important to exclude more common conditions, such as infections, malignancies, but also other autoimmune or auto-inflammatory conditions.

When there's a high index of suspicion for adult-onset Still's disease, laboratory findings can help outline the suspicion, assess the level of inflammation, and help us focus on potential complications with the disease.

Finally, a radiographic assessment can be helpful when there's suspicion of articular involvement, damage, and ankylosis which again is preventable.

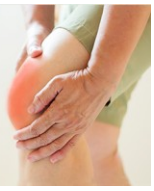
There have been several classification criteria for adult-onset Still's disease. I would like to caution the audience that these are not necessarily diagnostic criteria because sometimes they're not sensitive enough or, in early cases, the patient will not fulfill the criteria. Nevertheless, they're important because it teaches about the disease, and they can help us classify that and potentially do clinical research.



The more commonly seen criteria and more commonly referenced are the Yamaguchi criteria which were the first comprehensive criteria to be introduced for adult-onset Still's disease. Even today, almost 50 years later, they hold a value with a very high sensitivity and specificity.

Typically, Yamaguchi criteria are divided in major criteria that would include:

- Arthralgia that lasts 2 weeks or more



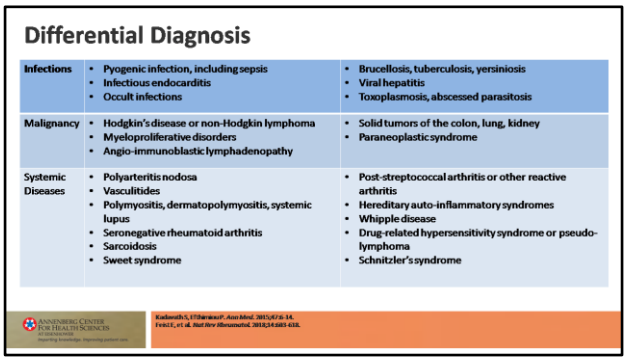
- Febrile episodes of 39°C, intermittent for 1 week or more
- The typically-described rash
- Elevated white blood cell count more than 10,000/mm^3, of which 80% or more should be granulocytes

Then there are the minor criteria. They include sore throat, lymphadenopathy, splenomegaly, and abnormal liver function tests.

Of course, those criteria can only be applied if there has been careful exclusion of infections, malignancies, and other inflammatory diseases.

In order to make the classification and diagnosis of adult-onset Still's disease using the Yamaguchi criteria, you should have at least 5 criteria, of which 2 or more should be major criteria.

There have been other sets of classification criteria, including criteria proposed by Bruno Fautrel in Paris. Those criteria do not include exclusion criteria and also include some of the more recently described serologic criteria that include, for example, serum ferritin.



When the patient gets admitted to the hospital, there's often a multi-specialty approach because the patient will present with febrile episodes. Often, the initial approach is to rule out infection, especially sepsis, so it's not uncommon for patients to undergo a very elaborate infectious disease work-up in an effort to rule out occult infections, brucellosis, tuberculosis, yersiniosis, viral infections, opportunistic infections, and infectious endocarditis.

If infectionsare excluded, often the patient will be screened for malignancies. Hodgkin's lymphoma and non-Hodgkin's lymphoma are notoriously known to cause similar symptoms, including fever, but don't show elevation of serum ferritin. It's important to rule out myeloproliferative disorders and angioimmunoblastic lymphadenopathy.

There are also other systemic diseases typically seen by rheumatologists that can cause fever, rash, and arthritis. Some commonly considered conditions could be vasculitis, polyarteritis nodosa, inflammatory myopathies, seronegative rheumatoid arthritis, and spondyloarthridites, especially in the chronic articular pattern, but also sarcoidosis and Sweet syndrome. A rheumatologist will carefully exclude those before making a diagnosis.

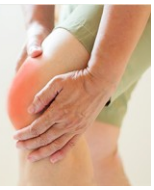
We shouldn't forget some of the other auto-inflammatory conditions, such as drug-related hypersensitivity syndrome or Schnitzler's syndrome that can present in a similar fashion. Genetic testing can be helpful when you're trying to eliminate some of those monogenic inflammatory conditions.

Treating Adult-Onset Still's Disease

Petros Efthimiou, MD, FACR: The next step is to design an appropriate therapeutic regimen for the patient. The patient may be very symptomatic with findings of systemic inflammation, extreme malaise, and can be in pain.

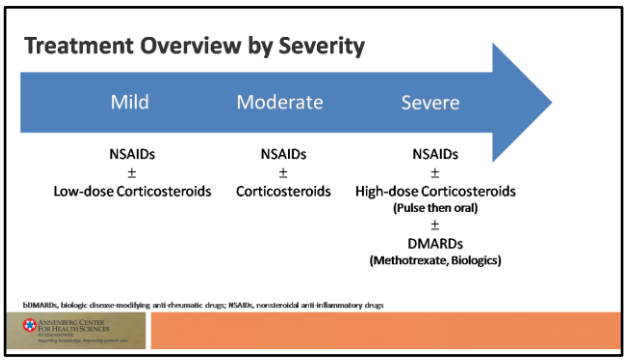
What are our goals? Well, the first goal should be to control the systemic inflammation. Findings that suggest systemic inflammation include fever, rash, morning stiffness, polyarticular joint pain, swelling, but also elevation of some of the serologic markers of inflammation, including sedimentation rate and C-reactive protein.

Exploring Best Practices for Diagnosis and Management of Adult-Onset Still's Disease

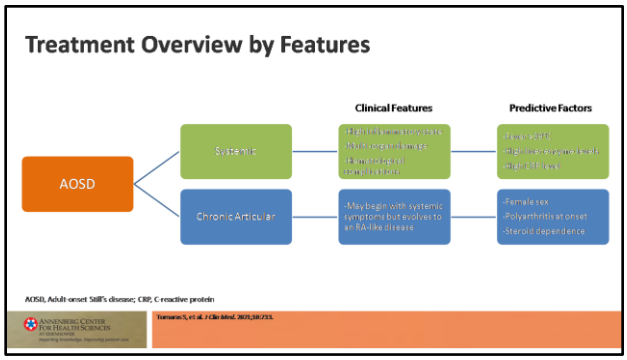


After we control the systemic inflammation, if the patient has systemic findings, then our next goal should be to treat the arthritis and prevent irreversible joint injury. We should always keep in the back of our mind some of the well-known and often life-threatening complications of Still's disease, such as macrophage activation syndrome, and we should have a high index of suspicion when findings suggesting those complications ensue.

When we design the therapeutic regimen, we should always keep the risk/benefit ratio in mind and try to minimize the risk of treatment-related adverse events, taking into consideration the patient's concerns, burden of disease, and long-term goals.



One more consideration when we think about treatment is adjusting the treatment to the disease severity. In the past, many patients were treated with NSAIDs and maybe low-dose corticosteroids for mild cases. In 2021, most of the treatment for moderate-to-severe disease has shifted to a more targeted approach that includes disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, with or without low-dose corticosteroids, and NSAIDs play only an adjunct role. And, of course, we have the development of biologic treatments.



In this slide, I would like to show you the 2 major subtypes of adult Still's disease, the *systemic* and the *chronic articular*, and how the clinical presentation of those 2 important subtypes can direct the appropriate treatment.

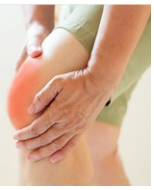
When a patient has a lot of systemic findings—the fever, the rash, the malaise—we often choose treatments that can be appropriate for that systemic presentation. When they go to the chronic articular pattern, many times they lose those systemic findings, so they may not have a fever or a rash. Maybe there's a distinct remote history of that, but the burden of disease is the chronic polyarticular inflammatory seronegative arthritis.

THE BURDEN OF DISEASE: THE PATIENT EXPERIENCE

For months, Bethany Pautsch's symptoms were a mystery to the doctors she was seeing, especially when she was told she would need a hip replacement without knowing the cause of the symptoms and deterioration of her joints. Then Bethany came to the Mayo Clinic and doctors there quickly diagnosed her as having Still's Disease. Listen to her explain how this diagnosis and subsequent treatment have changed her life.

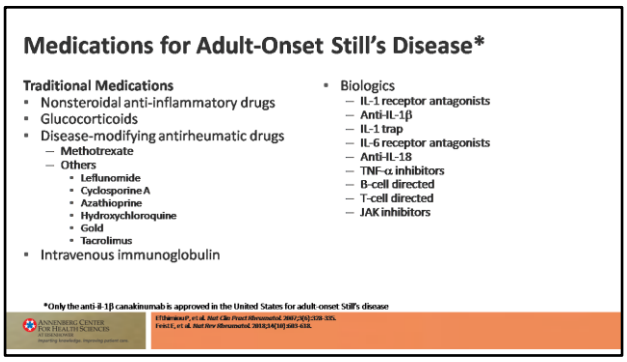
https://www.youtube.com/watch?v=ZVv0SkLXx2o

Of course, when we make the diagnosis, then we will decide which subtype is predominant. Is it the articular or is it the systemic? And that often helps

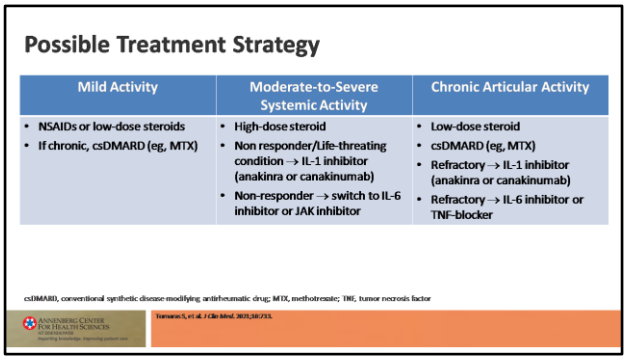


us decide what is the best possible treatment for that. There's an important overlap between those 2 subtypes because the underlying pathophysiology remains the same.

Some of the approaches may include corticosteroids, again with DMARDs, that can help not only as steroid-sparing drugs but also prevent chronic articular damage. A very important representative of that is methotrexate. Many times, this approach will be enough, but if it fails, we'll likely have targeted treatments like biologics, including the interleukin-1 and interleukin-6 inhibitors, that can provide additional efficacy and drive the patient to remission.



In this slide, I'm showing the medications that have been used and they are in the literature for the treatment of adult-onset Still's disease. *[Editor's note: Of the medications listed in the slide, only canakinumab is approved in the United States for adult-onset Still's disease.]*



Early in the 1970s, there were many publications advocating for NSAIDs, but later we found that most cases do not respond to NSAIDs alone and they need DMARDs or targeted treatment. Some of the DMARDs that have been used include methotrexate, the most commonly-used one and the most commonly-studied, but also leflunomide, cyclosporine A, azathioprine, hydroxychloroquine, gold, and tacrolimus.

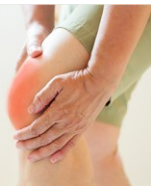
There have been publications of studies on intravenous immunoglobulin or IVIG for the treatment of adult Still's disease. The last few years, the emphasis has shifted to biologic treatments. We're likely to have several representatives of interleukin-1 inhibitors that include interleukin-1 trap, which is rilonacept, monoclonal antibodies against the subtype of interleukin-1 beta, which is canakinumab, but also interleukin receptor antagonist molecules, such as anakinra. They have transformed the treatment of moderate-to-severe adult Still's disease.

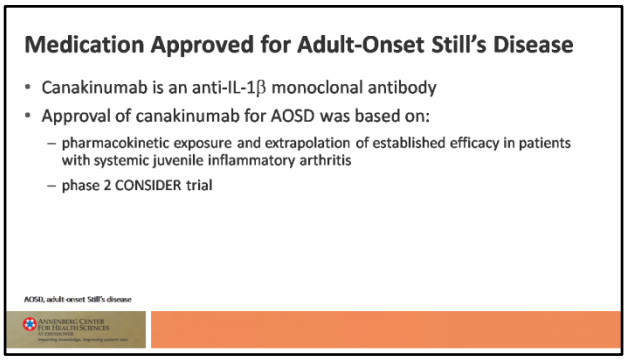
Interleukin-6 receptor antagonists, such as tocilizumab or sarilumab, have been used also successfully for treating adult Still's disease. There is ongoing research for interleukin-18 inhibitors and interleukin-18 binding proteins, but those molecules are not commercially available yet.

There have been several studies for the use of TNF inhibitors, which have shown efficacy, especially in the articular pattern, but not so much in the systemic. There are a few publications in B-cell directed and T-cell stimulation pathways and lately, Janus kinase (JAK) inhibitors.

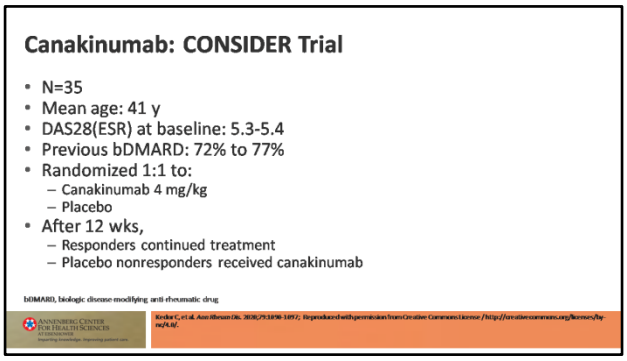
In the last 2 years, we have seen the development and approval by the US Food and Drug Administration (FDA) of a medication specifically for the treatment of adult-onset Still's disease.

Exploring Best Practices for Diagnosis and Management of Adult-Onset Still's Disease

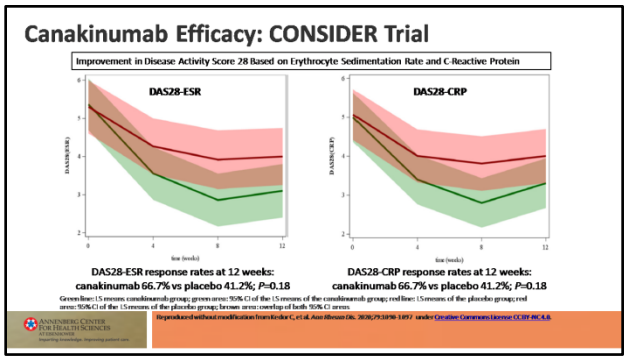




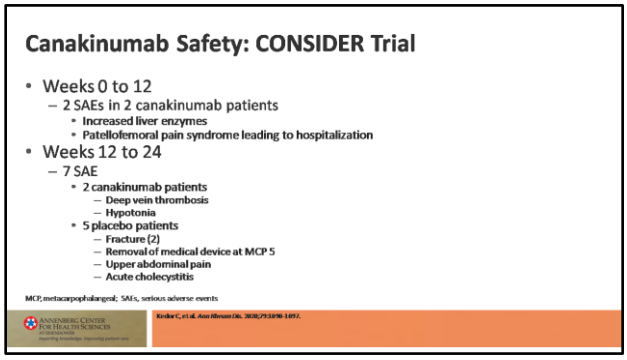
Canakinumab is an anti-interleukin-1-beta monoclonal antibody that is approved for the treatment of both SJIA but also adult-onset Still's disease. They have been investigating in a series of studies in Europe that led to the approval, but also pharmacokinetic exposure and extrapolation of established efficacy in patients with SJIA. Also, there is the phase 2 CONSIDER trial which was supportive and led to the FDA approval.



Let's talk a little more about the CONSIDER trial. It was a small study with 35 participants. The mean age of these adult-onset Still's disease patients was 41 years. The Disease Activity Score-28 for Rheumatoid Arthritis with ESR (DAS28-ESR) at baseline showed high disease activity and that was between 5.3 and 5.4, showing very active inflammatory arthritis. Many of the patients had tried and failed other biologic DMARDs. Between 72% and 77% of those patients had tried and failed other biologics. Those patients were randomized 1:1 to either canakinumab 4 mg/kg or placebo, so after 12 weeks, responders continued treatment, where placebo nonresponders received the active treatment of canakinumab 4 mg/kg.

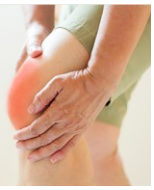


In this slide, it shows the canakinumab efficacy in the CONSIDER trial. So, there were improvements in disease activity measured by the DAS28-ESR score during treatment with canakinumab.



How about safety? That was an important consideration for the CONSIDER trial. Between weeks 0-12, there were 2 serious adverse events in 2 canakinumab patients, including an increase in the liver enzymes and patella-femoral pain syndrome leading to hospitalization. Between weeks 12-24, there were 7 serious adverse events. 2 canakinumab patients experienced deep vein thrombosis and hypotonia, while 5 placebo patients experienced side effects, such as fracture, that happened in 2 placebo patients, removal of medical device at metacarpophalangeal (MCP) joint 5, upper abdominal pain, and acute cholecystitis. Again, all of those adverse events were in the placebo group.

Exploring Best Practices for Diagnosis and Management of Adult-Onset Still's Disease



Canakinumab: Precautions

- Infection: caution; avoid during active infection requiring treatment
- Live vaccine- do not give concurrently
- Most common adverse events (≥10%)
  - Nasopharyngitis/Upper respiratory tract infection; abdominal pain; injection site reaction
- Macrophage activation syndrome
- May normalize formation of CYP450 enzymes
- Pregnancy/Lactation: no information

There are several other medications that are considered investigational at this point that can be used off-label for the treatment of adult-onset Still's disease.

Investigational Medications for Adult-Onset Still's Disease

Medication and Usual Dose*	Target	Complete Remission	Follow up (mos)
Anakinra 100 mg SC daily	IL-1 receptor antagonist	80%	>12
Rilonacept 100-320 mg SC x1, then 100-320 mg weekly	IL-1 trap	100%	>12
Infliximab 3-7.5 mg/kg IV wks 0, 2, and 6; then Q6-8 wks	TNF blocker	0-100%	>12
Etanercept 50 mg SC weekly			
Tocilizumab 8 mg/kg IV monthly	IL-6 receptor antagonist	60-85%	>12
Sarilumab 200 mg Q2 wks	sIL-6R/mIL-6R antagonist	–	–
Rituximab 1g IV days 1 and 15 every 6 months	B-cell-directed	–	–
Abatacept 500-1000 mg IV monthly or 125 mg SC weekly	T-cell-directed	–	–
Tofacitinib 5 mg QD/BID	Janus kinase inhibitor	–	–
Baricitinib 4 mg QD		–	–
Emapalumab 3 mg/kg QOD**	Interferon-γ blocker	–	–

*Not approved for use in the United States for adult-onset Still's disease. **Not approved for use in the United States for macrophage activation syndrome

There is the interleukin receptor antagonist molecule, anakinra, that has been used extensively for the treatment of adult-onset Still's disease. The usual dose is 100 mg given subcutaneously daily, and many reports show complete remission up to 80% of the cases based on follow-up of 12 months or more.

The interleukin-1 trap, rilonacept, which can block both interleukin-1-alpha and interleukin-1-beta signaling can also be used subcutaneously, usually after a loading dose of 100 to 320 mg, then given between 100 and 320 mg weekly as a subcutaneous injection. There have been small reports showing efficacy with follow-up of at least 12 weeks.

Some of the earlier attempts with TNF inhibitors showed efficacy with all 3 of them, including infliximab, etanercept, and also some cases for adalimumab.

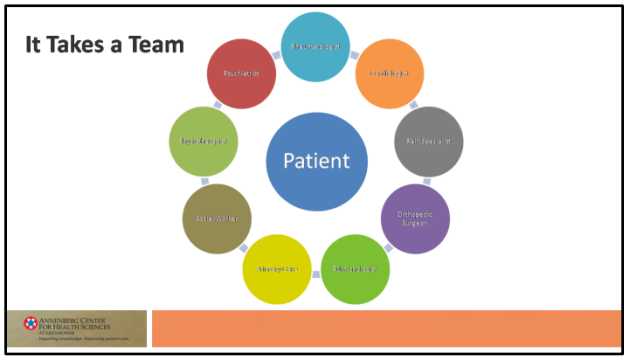
Interleukin-6 receptor antagonists, tocilizumab and sarilumab also showed benefit in small series and case reports.

Rare case reports with rituximab, abatacept suggested benefit as well.

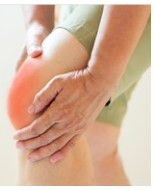
Patient Monitoring

- No standardized approach
- Assessment:
  - Impact on patient burden of disease (critical)
  - Resolution/Reduction of signs/symptoms
    - Disease remission
  - Systemic inflammation/Organ involvement
  - Early identification of complications
  - Treatment-related adverse events

What about proper monitoring? Well, monitoring means clinical monitoring—there's no standardized approach. Of course, we treat patients to remission, if possible, looking for eradication of signs and symptoms. Periodic laboratory monitoring can be quite helpful in looking at signs of systemic inflammation, but also target organ involvement, such as the liver, for example. Very close follow-up may identify cases that can go into complications, such as macrophage activation syndrome, where admission to a monitored setting, such as the ICU, is often required.



Again, it takes a team for the optimal outcome. Usually, there's the rheumatologist, but other specialties can help in preventing damage, ensuring the optimal outcome, and supporting the patient psychologically during a chronic disease process.

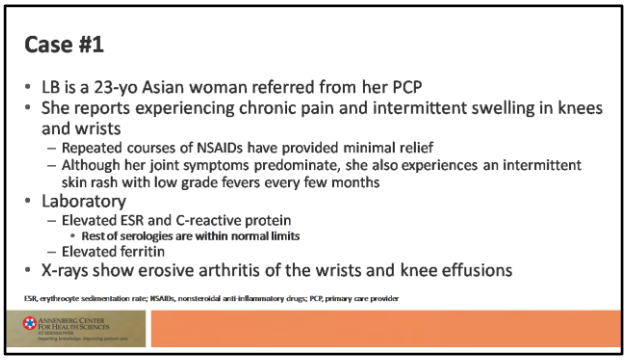


Every member of the team is a valuable member and the patient is the center of it.

Case Studies

Olga Petryna, MD, FACR

At this time, I would like to discuss several cases from real life that we encountered in our practice and that you may come across in your practice.



The first patient is a 23-year-old Asian female who was referred from her primary care physician with complaints of chronic pain and intermittent swelling, predominantly in knees and wrist joints. This patient tried and failed several courses of NSAIDs, which provided minimal relief of her symptoms. Although her joint symptoms were predominant, she also experienced an intermittent skin rash, some low-grade fevers that she couldn't explain for the last couple of months.

You see in this case, even though she does experience systemic complaints, her main concern is pain and swelling in the wrist joint and knee joint. And, apparently, she didn't respond to NSAIDs, so that's another big concern when it comes to diagnosis and treatment choice.

When this patient was seen in rheumatology clinic, she was found to have an elevated sedimentation rate and C-reactive protein, which is consistent with inflammatory arthritis. The rest of the serologies were within normal limits, meaning all the albumin antibodies, antinuclear antibody (ANA) panel, rheumatoid factor, cyclic citrullinated peptide (CCP) antibodies all came back within the normal range. Because of her systemic complaints of low-grade fevers and skin rash, [this] obviously raised the alarm for the possibility of adult-onset Still's disease. Then her ferritin level was measured and came back elevated.

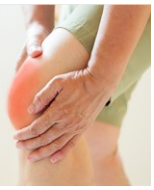
Here we have the patient's predominantly joint complaints, elevated inflammatory markers, elevated ferritin level and negative rest of the serologies. Moving forward, she had an x-ray of the joints that showed erosive arthritis of wrists and knees, effusions in both knee joints.

That supports the diagnosis of inflammatory arthritis. Moving forward, when she was diagnosed with seronegative inflammatory arthritis, she tried methotrexate first which would be the medication you typically would choose in patients with inflammatory arthritis, even if it is a seronegative one. She responded well to a steroid course, but then when she tapered off steroids, her response to methotrexate wasn't as good.

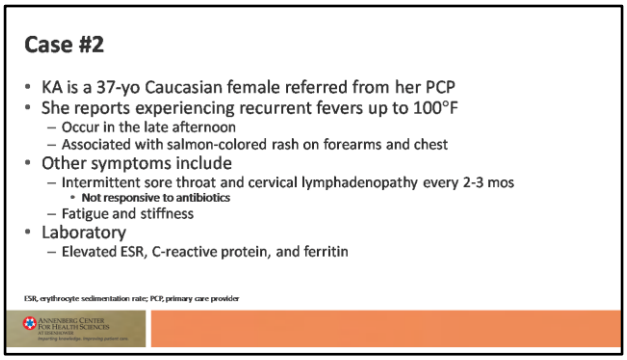
Moving forward, she went on to try TNF inhibitors, which did not help her symptoms. So now, having the patient with inflammatory arthritis, elevated ferritin level, and poor response to conventional therapy that you would use in seronegative inflammatory arthritis, you certainly want to consider adult-onset Still's disease as a possibility.

In this particular case, when the patient moved on from TNF inhibitors to interleukin-1 inhibitor, she experienced significant relief of her symptoms, and that's not something you would expect to see in rheumatoid arthritis patients, and that was in support of the diagnosis of Still's disease.

This is a great example of a patient who presents with predominantly joint symptoms, but not everything adds up when it comes to consideration of seronegative RA and there are certainly some red flags that would raise your concern for Still's, such as



elevated ferritin levels on blood work, some systemic complaints such as low-grade fevers and intermittent skin rashes, and, obviously, a typical presentation on the x-ray with rapidly progressive inflammatory arthritis with erosions and ankylosis affecting the wrists and knee joints.



The second case is a 37-year-old female, Caucasian, who is referred again by her primary care practitioner (PCP) and in this case, the patient experienced a lot of systemic complaints. She presented with recurrent fevers up to 100°F, which typically happen in the late afternoon, around 5:00 or 6:00 in the afternoon. The patient also experienced a salmon-colored skin rash on her forearms and chest that typically coincided with a spike of fever. Also, in addition to that, she experienced intermittent sore throat and cervical lymphadenopathy which started about 2-3 months before she had the rash, and she did not respond to any of the antibiotic courses that were prescribed by her doctor. In addition, she suffered from fatigue and stiffness in her body, mostly in her hand joints and larger joints. And obviously that raised a concern with the PCP in that she did not respond to any of the treatments. The patient was seen by the rheumatologist and she was found with elevated inflammatory markers, sedimentation rate, CRP, elevated ferritin level.

Here we see the joint complaints are not the big concern for the patient, but what is really bothersome is the frequent fevers, mostly at the end of the day, a skin rash that coincides with the fever, and also systemic inflammatory changes, such as lymphadenopathy, sore throat, poor response to treatment.

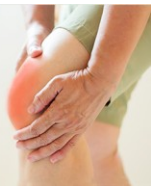
While you do want to proceed with an extensive work-up to make sure there is no mimicking condition, obviously adult-onset Still's disease shall be on your diagnostic list. In this particular case, the patient did have extensive diagnostic work-up. She had negative blood cultures, she had negative CT of the chest, abdomen and pelvis to exclude malignancy, which could also present with fevers, fatigue, and stiffness and all of those results were normal.

After exclusionary work-up ruled out other overlapping conditions, she went on to try high-dose steroids and she had a wonderful response to high-dose prednisone, but unfortunately, when she tapered her steroid dose down to a minimum, her symptoms came back again. She failed to respond to methotrexate and mainly she did not respond in terms of fevers, stiffness, and the skin rash.

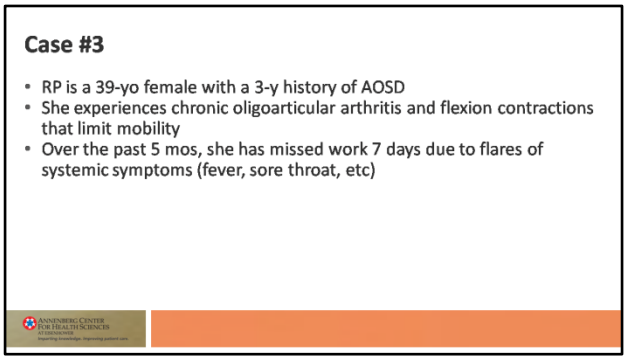
As a result of this treatment failure, she went on to try the interleukin-1 inhibitor with a wonderful clinical response. Over a short period of time, this patient experienced resolution of her daily fevers, complete resolution of the rash, and significant improvement of other systemic complaints. She went on treatment with frequent monitoring of laboratory markers which showed normalization of the sedimentation rate and C-reactive protein, as well as her ferritin level went down.

This is an example of predominantly systemic manifestation of Still's disease which also requires a complex work-up to rule out other mimicking conditions, not to miss malignancy or infection, for example. Again, while other conditions are ruled out, poor response to conventional DMARDs or requirement for high steroid dose should also raise a red flag and raise your suspicion for adult-onset Still's disease which requires more targeted anti-inflammatory therapy.

Exploring Best Practices for Diagnosis and Management of Adult-Onset Still's Disease

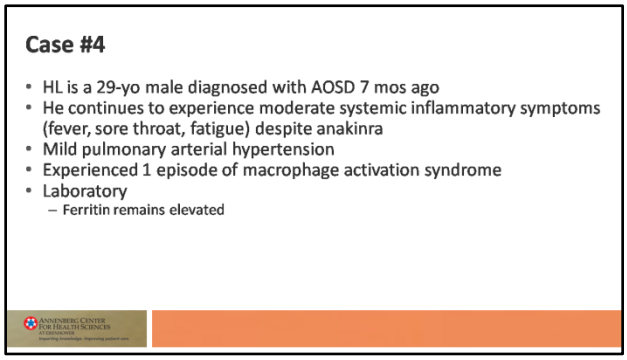


Petros Efthimiou, MD, FACR



Case 3 is a representative case of a patient with adult-onset Still's disease that has entered the chronic articular pattern. She is a 39-year-old female with a 3-year history of adult-onset Still's disease. She had a remote history of systemic findings, but currently she experiences chronic polyarticular arthritis and flexure contractures that limit her mobility, especially her wrist mobility, which is important for her because she types on a computer quite a bit. Over the past 5 months, she has missed 7 days of work, given to flares of both systemic, but also the articular symptoms.

Her disease is obviously active and she would benefit from systemic anti-inflammatory treatment that would help both the systemic and the articular patterns. This patient could be a candidate for DMARDs, such as methotrexate with or without corticosteroids, or a targeted treatment, such as interleukin-1 or interleukin-6 inhibitor. Close monitoring is required, both clinically and serologically every 2-3 months until the patient is in remission.



The next case is a representative case of a young male that was diagnosed with Still's disease 7 months ago. The patient still experiences the systemic findings despite targeted treatment with anakinra, which is a commonly-used interleukin inhibitor.

Moreover, he has end-organ damage, mild pulmonary hypertension, which has been reported in patients who have adult-onset Still's disease. In the past, he was hospitalized with a macrophage activation syndrome and his serum ferritin, despite treatment, remains elevated.

This patient has already failed a short-acting interleukin inhibitor, so his treatment choices consist of either IL-6 inhibitor, for example tocilizumab, or a long-acting interleukin inhibitor, like canakinumab at the 4 mg/kg injected every 4 weeks in order to drive him into remission.