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Still Disease

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Still Disease

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Introduction

Adult Onset Still's Disease (AOSD) is a rare systemic inflammatory disorder characterized by daily fever, inflammatory polyarthritis, and a transient salmon-pink maculopapular rash. AOSD is alternatively known as systemic onset juvenile idiopathic arthritis. Even though there is no specific diagnostic test, a serum ferritin level more than 1000ng/ml is common in AOSD.

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Etiology

The etiology of AOSD is unknown. The hypothesis remains that AOSD is a reactive syndrome in which various infectious agents may act as triggers in a genetically predisposed host. Both genetic factors and a variety of viruses, bacteria like *Yersinia enterocolitica* and *Mycoplasma pneumonia* and other infectious factors have been suggested as important[1][2]. There is uncertainty regarding the presence of same etiopathogenic factors among all the AOSD patients. A French study of 62 patients showed the association of AOSD with HLA antigen subtypes[3].

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Epidemiology

Adult-onset Still's disease is a very uncommon disease. Its annual incidence has been estimated to be 0.1 to 0.4 cases per 100,000 people in Europe. Females are affected slightly more than males. It has bimodal age distribution, the first peak between the ages of fifteen to twenty-five and the second between thirty-six to forty-six. However, about three-quarters of the patients report the onset of disease between sixteen and thirty-five years of age.

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Pathophysiology

There are two immune dysregulations described in the pathogenesis of AOSD. Innate immunity with neutrophil and macrophage activation under the effect of proinflammatory cytokine IL-18 is one pathway. A study has shown the upregulation of CD64 in active ASD which is a marker of neutrophil activation[4]. Secondly, CD4+ T helper (Th) cells may also play a role in the pathogenesis of AOSD with the predominance of Th1 subset over Th2 as seen in a study which showed significantly higher expression of interferon-gamma mRNA expression than interleukin-4 in tissue biopsies[5]. Moreover, the role of Th-17 responses is emerging in the pathogenesis of AOSD, and levels of Th-17 related cytokines, interleukins-1,6,17,18,21 and 23 are elevated.

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History and Physical

There are three main patterns of the clinical course of adult-onset Still's disease (AOSD) namely monophasic, intermittent, and chronic [3][6][7]. There is an approximately equal distribution in each category however some studies have shown a chronic articular pattern to be more common. It is not uncommon for the first two patterns to evolve into chronic articular [3][8].

The primary clinical features are seen in adult-onset Still's disease (ASD) are fever, rash, and arthritis or arthralgia. They are seen in about 75 to 95 percent of patients [9]. Other common symptoms are myalgia, pharyngitis, lymphadenopathy, and splenomegaly. Less commonly observed symptoms are hepatomegaly, pleurisy, pericarditis, and abdominal pain. Fever is usually quotidian (daily recurring fever with temperature returning to normal between fever spikes) most often occurring late during the day and generally precedes other symptoms. The temperature can change by 4°C within four hours [10]. Approximately 20 percent of cases do not have complete defervescence as fever persists between spikes or an additional spike occur in the morning(double quotidian fever). It may also present as fever of unknown origin (FUO), and a temperature of more than 39.5°C suggests monophasic pattern more strongly [7]. A rash is classically evanescent, salmon-colored, macular or maculopapular which is usually nonpruritic and occurs with the fever. It is mainly seen on the trunk and extremities but can also be seen on palms, soles, and the face. The rash can sometimes be induced by heat(hot shower or towel) or by rubbing the skin(Koebner phenomenon). Arthritis can initially be mild, transient, and oligoarticular and may evolve to severe, destructive and symmetric polyarticular forms.[11]. Commonly involved joints are the knees, wrists, and ankles, although elbows, proximal interphalangeal joints, shoulders, metacarpophalangeal, metatarsophalangeal, hips, distal interphalangeal and temporomandibular joints can also be involved. Fusion of the wrist joint is characteristic of AOSD but is seen in only a few patients. Myalgia often gets worse with fever spikes. It may sometimes be severe and debilitating. Muscle weakness is not present, but case reports have described a slight elevation of serum creatine kinase and aldolase. Usually, electromyographic studies and muscle biopsies are either normal or may show a nonspecific inflammatory myopathy.

Patients can present with a sore throat at the time of initial evaluation and it frequently recurs during a disease flare. Examination in those cases typically reveals severe, nonsuppurative pharyngitis with negative bacterial cultures. A review of 341 cases of AOSD has described a sore throat in 69% of the patients [12]. Symmetrical slightly tender lymphadenopathy is reported in

one-third to two-thirds of patients, and splenomegaly in one-third to one-half of patients. Liver abnormalities include hepatomegaly ranging from 12 to 45 percent[9] and more commonly modest elevations of serum hepatic transaminases and alkaline phosphatase. About 30 to 40 percent of patients with AOSD have pericarditis, pleural effusions, and transient pulmonary infiltrates[8][9][13]. Macrophage activation syndrome occurs in a small minority of patients but it may be underdiagnosed as suggested by retrospective studies in which MAS occurred in six out of 50 patients and 21 out of 109 patients [14]. Abdominal pain occurs in 1 to 48 percent of the patients. Nausea, anorexia, and weight loss can also be seen.

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Evaluation

At least seven different variety of classification criteria for AOSD are there for use in research. The Japanese standards termed the Yamaguchi criteria has the highest sensitivity amongst them [15][16]and is the most commonly used.

Total of five or more criteria including 2 or more significant criteria have a sensitivity of 96% and specificity of 92% to classify a patient as having AOSD.

Major criteria are as follows:

- Fever of at least 39°C for at least one week
- Arthralgia or arthritis for at least two weeks.
- Nonpruritic salmon-colored rash on trunk/extremities.
- Granulocytic leukocytosis (10,000/microL or greater).

Minor criteria are as follows:

- A sore throat.
- Lymphadenopathy.
- Hepatomegaly or splenomegaly.
- Abnormal liver function tests.Negative tests for RF and ANA.

The lab findings discussed below are characteristic of AOSD, but not pathognomonic and hence their presence along with clinical manifestations will help the clinician in establishing the diagnosis after ruling out alternate causes.

Inflammatory markers, ESR and CRP are elevated in almost all the patients [3]. Leukocytosis, generally more than 15,000 cells/microL with a predominance of neutrophils greater than 80%, normocytic normochromic anemia and thrombocytosis are the hematological findings. These hematological abnormalities can be severe enough to mimic primary hematologic disease. Bone marrow biopsy has been reported to show hyperplasia of granulocytic precursors and hypercellularity and hemophagocytosis in some cases. Hepatic transaminases can be elevated in 75 percent of patients and aldolase can also elevate in some due to liver inflammation.

Ferritin levels are generally higher than five times the upper limits of normal in patients with AOSD. Elevated ferritin suggests the presence of the disease with an 80% sensitivity and 46% specificity. If combined with a decrease in the proportion of glycosylated ferritin <20%, the specificity will rise to 93%.

Less than 10% of the patients have Antinuclear antibodies (ANA) and rheumatoid factor (RF) but generally only in low titer.

The synovial fluid is usually inflammatory with a mean leukocyte range of 100 to 48,000 cells/microL [3].

Radiographs early in the disease typically are either normal or show slight joint space narrowing or periarticular osteopenia. Narrowing of the wrist carpometacarpal and intercarpal joint spaces which may progress to bone ankylosis is a classic radiographic finding of adult-onset Still's disease (AOSD) [17][18].

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Treatment / Management

The goals of therapy include controlling symptoms and physical signs of inflammation as well as laboratory markers of inflammation. It also includes preventing end-organ damage and keeping the long term effects of therapy to the minimum.

The efficacy of treatment interventions for ASD is derived from observational studies and clinical experience [6][8][19][20][21].

The initial therapeutic decisions are based upon the degree of disease activity and the subsequent ones based on the clinical response.

The mild disease presents with fevers, rash, arthralgias or mild arthritis. The patients with mild disease may respond to NSAIDs alone, but most of them require at least a low dose of glucocorticoid for better control. The dose of NSAIDs is in anti-inflammatory range.

The moderate disease presents with debilitating joint symptoms, high-grade fever or internal organ involvement which is not life-threatening. The patients with moderate disease severity are initially treated with glucocorticoids initiated with prednisone 0.5 to 1 mg/kg per day, depending upon disease severity. Biologic, as well as non-biologic disease-modifying antirheumatic drugs, might be needed if the steroids cannot be successfully tapered. Anakinra is favored as the initial agent in patients without joint erosions, and methotrexate is preferred in patients with prevalent joint disease.

Those with severe disease have life-threatening organ involvement like cardiac tamponade, disseminated intravascular involvement or severe hepatic involvement. Those with severe disease require initial therapy with pulse IV methylprednisolone 1000 mg daily for three days, and this approach has been proven effective in many case reports and series [19][22][23]. Early

use of biologic therapy is also recommended in severe disease. Among biologics, IL-1 inhibitor Anakinra and IL-6 inhibitor Tocilizumab are more effective than TNF inhibitors. Limited evidence suggests that Canakinumab, Rilonacept, Rituximab, and Abatacept may be effective in treating patients who are refractory to therapies as mentioned above.

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Differential Diagnosis

The differential diagnosis of adult Still's disease (ASD) is very broad and includes infections, malignancy, rheumatologic disorders, and adverse drug reactions.

Among infectious etiologies, many acute viral infections including parvovirus B19, hepatitis and others may cause symptoms similar to AOSD. Bacteremia can also cause fever, elevated white cell count and acute phase reactants.

Among rheumatologic diseases include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and reactive arthritis also cause elevation of acute phase reactants. Vasculitic disorders, like polyarteritis nodosa (PAN), which present with fever, arthralgia, skin lesions, and pain in the abdomen can also mimic AOSD.

Malignancy, especially lymphomas may mimic AOSD given the features of lymphadenopathy, fever, and leukocytosis.

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Prognosis

The course of AOSD generally follows one of the three patterns - self-limited illness, intermittent flares or chronic Still's disease. There are several predictors for the chronicity of the disease and the unfavorable outcomes. It includes the presence of an erosive polyarthritis at the time of presentation and involvement of shoulders or hips [3][24][10]. The need for systemic glucocorticoids for more than two years before routine use of biologics is also considered a poor prognostic marker.

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Complications

AOSD complications include macrophage activation syndrome, amyloidosis, disseminated intravascular coagulopathy, pulmonary arterial hypertension, thrombotic thrombocytopenic purpura, and diffuse alveolar hemorrhage.

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Deterrence and Patient Education

Adult-onset Still's disease is a rare inflammatory arthritis with fevers, rash and joint pain. Sometimes people may have just one episode while in others the symptoms persist. It can affect any joint, but most commonly involved are knees, wrists, and ankles. Treatment involves nonsteroidal anti-inflammatory drugs, steroids, and biologics depending upon the disease severity

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Pearls and Other Issues

When a patient presents with fever, rash and polyarthralgia, the duration of symptoms can help in formulating differentials. Short length suggests an infectious etiology whereas a longer course should raise concerns for autoimmune causes.

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Enhancing Healthcare Team Outcomes

Adult-onset Still's disease is in part a diagnosis of exclusion and frequently poses a diagnostic challenge. While a Rheumatologist is almost always involved in the care, a team of other specialties like Cardiologists, Gastroenterologists, and oncologists plays an essential role in the management as the disease can cause complications in multiple organ systems. Nurses have an important role in monitoring the patient's vital signs and administering medications. Physical and Occupational therapy help with the rehabilitation of the patient given severe joint involvements. Since the disease has some life-threatening complications, a detailed history, and physical examination is needed for patients when there is a suspicion for AOSD to prevent complications and improve the prognosis^[25](Level V)

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Questions

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References

1. Ohta A, Yamaguchi M, Tsunematsu T, Kasukawa R, Mizushima H, Kashiwagi H, Kashiwazaki S, Tanimoto K, Matsumoto Y, Akizuki M. Adult Still's disease: a

- multicenter survey of Japanese patients. *J. Rheumatol.* 1990 Aug;17(8):1058-63. [[PubMed](#)]
2. Colebunders R, Stevens WJ, Vanagt E, Snoeck J. Adult Still's disease caused by *Yersinia enterocolitica* infection. *Arch. Intern. Med.* 1984 Sep;144(9):1880-2. [[PubMed](#)]
 3. Pouchot J, Sampalis JS, Beaudet F, Carette S, Décary F, Salusinsky-Sternbach M, Hill RO, Gutkowski A, Harth M, Myhal D. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine (Baltimore)*. 1991 Mar;70(2):118-36. [[PubMed](#)]
 4. Kontzias A, Efthimiou P. Adult-onset Still's disease: pathogenesis, clinical manifestations and therapeutic advances. *Drugs*. 2008;68(3):319-37. [[PubMed](#)]
 5. Gerfaud-Valentin M, Maucourt-Boulch D, Hot A, Iwaz J, Ninet J, Durieu I, Broussolle C, Sève P. Adult-onset still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. *Medicine (Baltimore)*. 2014 Mar;93(2):91-9. [[PMC free article](#)] [[PubMed](#)]
 6. Fautrel B. Adult-onset Still disease. *Best Pract Res Clin Rheumatol.* 2008 Oct;22(5):773-92. [[PubMed](#)]
 7. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. *Autoimmun Rev.* 2014 Jul;13(7):708-22. [[PubMed](#)]
 8. Calabro JJ, Marchesano JM. Fever associated with juvenile rheumatoid arthritis. *N. Engl. J. Med.* 1967 Jan 05;276(1):11-8. [[PubMed](#)]
 9. Elkon KB, Hughes GR, Bywaters EG, Ryan PF, Inman RD, Bowley NB, James MP, Eady RA. Adult-onset Still's disease. Twenty-year followup and further studies of patients with active disease. *Arthritis Rheum.* 1982 Jun;25(6):647-54. [[PubMed](#)]
 10. Nguyen KH, Weisman MH. Severe sore throat as a presenting symptom of adult onset Still's disease: a case series and review of the literature. *J. Rheumatol.* 1997 Mar;24(3):592-7. [[PubMed](#)]
 11. Cheema GS, Quismorio FP. Pulmonary involvement in adult-onset Still's disease. *Curr Opin Pulm Med.* 1999 Sep;5(5):305-9. [[PubMed](#)]
 12. Bae CB, Jung JY, Kim HA, Suh CH. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features, predictive factors, and prognosis in 21 patients. *Medicine (Baltimore)*. 2015 Jan;94(4):e451. [[PMC free article](#)] [[PubMed](#)]
 13. Medsger TA, Christy WC. Carpal arthritis with ankylosis in late onset Still's disease. *Arthritis Rheum.* 1976 Mar-Apr;19(2):232-42. [[PubMed](#)]
 - 14.

- Björkengren AG, Pathria MN, Sartoris DJ, Terkeltaub R, Esdaile JM, Weisman M, Resnick D. Carpal alterations in adult-onset Still disease, juvenile chronic arthritis, and adult-onset rheumatoid arthritis: comparative study. *Radiology*. 1987 Nov;165(2):545-8. [[PubMed](#)]
15. Fautrel B, Zing E, Golmard JL, Le Moel G, Bissery A, Rioux C, Rozenberg S, Piette JC, Bourgeois P. Proposal for a new set of classification criteria for adult-onset still disease. *Medicine (Baltimore)*. 2002 May;81(3):194-200. [[PubMed](#)]
16. Masson C, Le Loet X, Liote F, Dubost JJ, Boissier MC, Perroux-Goumy L, Bregeon C, Audran M. Comparative study of 6 types of criteria in adult Still's disease. *J. Rheumatol*. 1996 Mar;23(3):495-7. [[PubMed](#)]
17. Franchini S, Dagna L, Salvo F, Aiello P, Baldissera E, Sabbadini MG. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. *Arthritis Rheum*. 2010 Aug;62(8):2530-5. [[PubMed](#)]
18. Pouchot J, Arlet JB. Biological treatment in adult-onset Still's disease. *Best Pract Res Clin Rheumatol*. 2012 Aug;26(4):477-87. [[PubMed](#)]
19. Fitzgerald AA, Leclercq SA, Yan A, Homik JE, Dinarello CA. Rapid responses to anakinra in patients with refractory adult-onset Still's disease. *Arthritis Rheum*. 2005 Jun;52(6):1794-803. [[PubMed](#)]
20. Khraishi M, Fam AG. Treatment of fulminant adult Still's disease with intravenous pulse methylprednisolone therapy. *J. Rheumatol*. 1991 Jul;18(7):1088-90. [[PubMed](#)]
21. Bisagni-Faure A, Job-Deslandre C, Menkes CJ. Intravenous methylprednisolone pulse therapy in Still's disease. *J. Rheumatol*. 1992 Sep;19(9):1487-8. [[PubMed](#)]
22. Wouters JM, van der Veen J, van de Putte LB, de Rooij DJ. Adult onset Still's disease and viral infections. *Ann. Rheum. Dis*. 1988 Sep;47(9):764-7. [[PMC free article](#)] [[PubMed](#)]
23. Agha-Abbaslou M, Bensaci AM, Dike O, Poznansky MC, Hyat A. Adult-Onset Still's Disease: Still a Serious Health Problem (a Case Report and Literature Review). *Am J Case Rep*. 2017 Feb 03;18:119-124. [[PMC free article](#)] [[PubMed](#)]
24. Komiya A, Matsui T, Nogi S, Iwata K, Futami H, Takaoka H, Arinuma Y, Hashimoto A, Shimada K, Ikenaka T, Nakayama H, Furukawa H, Tohma S. Neutrophil CD64 is upregulated in patients with active adult-onset Still's disease. *Scand. J. Rheumatol*. 2012 Mar;41(2):156-8. [[PubMed](#)]
25. Chen DY, Lan JL, Lin FJ, Hsieh TY, Wen MC. Predominance of Th1 cytokine in peripheral blood and pathological tissues of patients with active untreated adult onset Still's disease. *Ann. Rheum. Dis*. 2004 Oct;63(10):1300-6. [[PMC free article](#)] [[PubMed](#)]

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