

BULLETIN ON THE Rheumatic Diseases

Adult-Onset Still's Disease

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SUMMARY POINTS

- AOSD presents with a triad of quotidian fever, evanescent rash, and polyarthriti*s*.
- The etiology of AOSD is unknown, but circadian release of cytokines accounts for many features.
- Morbidity is largely linked to chronic arthritis, which may be destructive in 20% to 25% of patients with AOSD.

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Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown cause. The clinical course is dominated by systemic activity with exacerbations and/or chronic arthritis. There is no diagnostic test or pathognomonic histopathology, so the diagnosis of AOSD is often a diagnosis of exclusion.

Etiology

No etiologic trigger has been proven for AOSD; however, an infectious agent has been inferred based on symptom complex (ie, sore throat, fever). Many of the clinical manifestations are reminiscent of those seen during self-limited viral infections. Investigators have also demonstrated the persistence of viral antigens, especially rubella, in patients with juvenile arthritis and

Comment [S1]: involvement of multiple joints by inflammation or arthritic changes. The most important cause of polyarthriti*s* is rheumatoid arthritis, although this entity is seen in gout and several other diseases. Widespread involvement of joints is typical in rheumatic fever and systemic lupus erythematosus. Polyarthriti*s* is also a feature of several other diseases.

Comment [S2]: used to describe a pattern repeated approximately every 24 hours

Comment [S3]: chemicals produced by the immune system that stimulate white blood cells to attack and kill viruses, bacteria, foreign cells, or cancer cells

Comment [S4]: the relative frequency of occurrence of a particular disease in a particular area

Comment [S5]: medicine used to describe a symptom or sign that indicates almost beyond doubt the correct diagnosis of a disease

Comment [S6]: a branch of pathology concerned with the study of the microscopic changes in diseased tissues

Comment [S7]: the causes or origin of a disease or disorder; the study of the factors that cause disease and the method of their introduction to the host

AOSD. The circadian release of proinflammatory cytokines (especially interleukin 6) appears to account for many features of AOSD.

Comment [S8]: used to describe a pattern repeated approximately every 24 hours

Comment [S9]: tending to cause inflammation

Comment [S10]: chemicals produced by the immune system that stimulate white blood cells to attack and kill viruses, bacteria, foreign cells, or cancer cells

Demographics

AOSD has been described in nearly all countries and races. Few (n = 13) large-series studies (>10 patients) have been undertaken. From these series we estimate that AOSD is a relatively rare condition and that major academic medical centers may see 1-3 new cases of AOSD per year. In several large series of people with fever of unknown

origin (FUO), AOSD was consistently the most common rheumatic cause of FUO, ranging from 5% to 9% of all FUOs.

AOSD is typically a disease of young adults, affecting men and women equally. Disease onset is before age 35 years in nearly 76% of patients. From a review of the medical literature it can also be estimated that fewer than 10% of patients will have disease onset after 50 years of age. AOSD in the elderly may be difficult to diagnose, primarily

because of comorbid conditions, a wider age-related differential diagnosis, atypical cutaneous features, and fevers that tend to be lower.

Comment [S11]: relating to the skin

Disease Onset

The onset of AOSD is often heralded by a sore throat and other constitutional symptoms.

A prodromal sore throat occurring days to weeks before the onset of fever or rash is seen in more than 70% of patients. It is typically nonexudative, lasts for several days, and is unresponsive to antibiotics.

Comment [S12]: a symptom indicating the start of a disease

Comment [S13]: does not result in a discharge

Whether this represents a triggering mucosal infection or is a manifestation of lymphoid activity and inflammation is unknown.

Comment [S14]: mucous membrane

Comment [S15]: lymphatic tissue

Constitutional

features soon follow and may include severe myalgias or arthralgias, fatigue, anorexia, nausea, and rapid weight loss. Weight loss is seen in 50%-60% of patients, may be dramatic and rapid, and tends to parallel inflammatory activity as measured by dropping hemoglobin and serum albumin values.

Comment [S16]: pain or tenderness in a muscle or group of muscles

Comment [S17]: pain in a joint

Comment [S18]: Tiredness

Comment [S19]: persistent loss of appetite

Comment [S20]: the unsettling feeling in the stomach that accompanies the urge to vomit

Quotidian Fever

A quotidian fever is a once daily febrile spike >39°C (102.2°F) with intervening afebrile intervals. Nearly two-thirds of patients will have peak temperatures greater than 40°C (104°F). More than 94% of patients will demonstrate a quotidian or double-quotidian (twice daily spikes) fever pattern. A minority of patients may exhibit a remittent pattern with febrile spikes and an

Comment [S21]: substance in the red blood cells that supplies oxygen to the cells of the body

Comment [S22]: clear fluid in the blood

Comment [S23]: water soluble protein

Comment [S24]: med a fever in which attacks of the illness recur daily

Comment [S25]: relating to, involving, or typical of fever

Comment [S26]: having no fever, or marked by absence of fever

Comment [S27]: lessening and then intensifying again at intervals

elevated baseline temperature. Thus, one of the more distinctive features of AOSD is the occurrence

of fever at nearly the same time every day, usually late at night or, less commonly, late morning or afternoon. This circadian feature may be diagnostically important. Fevers are heralded

by the onset of shaking chills, followed by 2-4 hours of high fever (often >40°C), and then defervescence with drenching sweats.

It is also common for fever to be accompanied by the appearance or exacerbation of rash, myalgias, arthralgias, headache, nausea, or serositis. Quotidian fever is most prominent during disease onset and flares of systemic activity.

Evanescent Rash

The characteristic rash of AOSD has been called the Still's rash, or juvenile rheumatoid arthritis (JRA) rash, in the literature. Rash is seen in more than 92% of patients. It is evanescent, frequently appears during febrile attacks, lasts for hours, and tends to change from day to day. It is typically a faint salmon-colored (infrequently erythematous), morbilliform exanthem found on the extremities (extensor surfaces), trunk, and neck. Koebner phenomenon, dermatographism, pruritis, and/or urticaria are

commonly seen. Involvement of the face, palms, or soles is exceedingly rare. Cutaneous manifestations of AOSD are most prominent early in the disease and tend to decline with time. In nearly all instances, skin biopsies and immunofluorescent studies are nondiagnostic. Pathology of lesional skin reveals a nonspecific chronic inflammatory picture with a perivascular mononuclear (and seldom polymorphonuclear) infiltrate, vascular dilatation, and dermal edema.

Articular Manifestations

Arthritis is found in nearly 93% of people with AOSD, and is usually the last feature of the triad to appear. The early clinical picture is likely to be dominated by complaints of arthralgia, myalgia, morning stiffness, and less commonly, synovitis. Although the arthritis may begin as oligoarticular and migratory, it will develop into an additive polyarthritis that will affect both small and large joints if the AOSD is persistent. Chronic monarthritis has not been observed in AOSD

Comment [S28]: the stage of an illness during which fever subsides

Comment [S29]: an increase in the severity of a disease or disorder, or a worsening of its symptoms

Comment [S30]: pain or tenderness in a muscle or group of muscles

Comment [S31]: pain in a joint

Comment [S32]: Serositis is inflammation of one of the sacs around the heart, lungs or abdomen

Comment [S33]: affecting the whole body as distinct from having a local effect

Comment [S34]: disappearing after only a short time

Comment [S35]: relating to, involving, or typical of fever

Comment [S36]: redness of the skin as a result of a widening of the small blood vessels near its surface.

Comment [S37]: of a rash that resembles that of measles

Comment [S38]: the appearance of lesions along a site of injury

Comment [S39]: an exaggeration of the wheal response following scratching of the skin eg when towelling dry after a bath

Comment [S40]: Pruritus is the medical word for itch

Comment [S41]: a skin rash, usually occurring as an allergic reaction, that is marked by itching and small pale or red swellings and often lasts for a few days

Comment [S42]: relating to the skin

Comment [S43]: the removal of a sample of tissue from a living person for laboratory examination

Comment [S44]: the labelling of antibodies or disease-causing agents (antigens) with a fluorescent dye in order to identify or locate them in a tissue sample

Comment [S45]: area of affected skin

Comment [S46]: lasts over a long period

Comment [S47]: Around the blood vessels

Comment [S48]: blood vessels

Comment [S49]: enlarged

Comment [S50]: abnormal buildup of fluid in the skin, i.e. swelling

Comment [S51]: a medical condition affecting a joint or joints, causing pain, swelling, and stiffness

Comment [S52]: inflammation of the sinovial membrane of a joint, contains the lubricating fluid in joints

Comment [S53]: affecting a few joints

Comment [S54]: moves from one part of the body to another

Comment [S55]: multiple joints are affected simultaneously

Comment [S56]: Arthritis pain, which affects only one joint

and should prompt other diagnostic considerations.

The most commonly involved joints at the outset include the knee, wrist, ankle, elbow, shoulder, proximal interphalangeal joints (PIP), and cervical spine. If the arthritis becomes chronic (lasting longer than 6 months) the wrists are prominently affected, with less common involvement of the tarsal, cervical, and PIP joints. Neck pain is seen in nearly half of patients.

AOSD is associated with carpal or carpopmetacarpal ankylosis (wrist fusion).

Nearly 50% of people with systemic JA or AOSD will develop carpal ankylosis that will become painless once fused. A lesser tendency for ankylosis has also been noted in the tarsal joints and cervical spine.

The risk of chronic, destructive, and disabling polyarthritis is quite high in both systemic JA and AOSD, occurring in 20%-25% of cases. Disability and significant joint damage may result from early, progressive inflammatory arthritis and, later, secondary degenerative changes. Erosive disease has the greatest impact on weightbearing joints (hips and knees), shoulders, and hands. Synovial biopsies have not revealed a distinctive pathology but instead demonstrate chronic synovitis with proliferation of the synovial lining layer and perivascular infiltration of mononuclear cells (eg, lymphs, plasma cells).

Other Systemic Features

Lymphadenopathy (65%), splenomegaly, (42%) and hepatomegaly (40%) are very common early in the disease and reflect tissue infiltration with inflammatory cells and heightened immunologic activity within the reticuloendothelial system (RES). More than 70% of patients will exhibit some degree of liver dysfunction as demonstrated by elevation of hepatic enzymes (eg, AST, ALT, alkaline phosphatase).

Liver biopsies have demonstrated periportal mononuclear infiltrates (lymphocytes, plasma cells) and Kupffer cell hyperplasia. Hypoalbuminemia is often impressive and is seen in 76% of people with AOSD. Lymphadenopathy is usually generalized and manifests as mild-to-moderate, painless nodal enlargement. Isolated or focal lymph node enlargement is rare and should question the diagnosis and may require lymph node biopsy.

Comment [S57]: Finger

Comment [S58]: relating or belonging to the bones of the ankle joint

Comment [S59]: relating to the bones in the wrist

Comment [S60]: inflammation of the sinovial membrane of a joint

Comment [S61]: any disease, disorder, or enlargement of the lymph nodes

Comment [S62]: abnormal enlargement of the spleen

Comment [S63]: enlargement of the liver

Comment [S64]: Of, relating to, or being the widely diffused bodily system constituting all phagocytic cells except certain white blood cells

Comment [S65]: relating to or affecting the liver

Comment [S66]: a complex protein produced by living cells that promotes a specific biochemical reaction by acting as a catalyst

Comment [S67]: abnormal growth in a part of the body, caused by an excessive multiplication of cells

Comment [S68]: An abnormally low blood level of albumin. Normally, albumin is the most plentiful protein in human blood and the key to the regulation of its osmotic pressure

Comment [S69]: any disease, disorder, or enlargement of the lymph nodes

Lymph node biopsies in AOSD patients are nondiagnostic and tend to show reactive hyperplasia or lymphadenitis. At least six cases of Kikuchi's syndrome, or necrotizing lymphadenitis, have been described in AOSD. Kikuchi's syndrome is a benign disorder that is usually associated with viral infection, and may manifest as fever, tender lymphadenopathy, hepatomegaly, leukopenia, and elevated ESR. Pleuritis (40%) and pericarditis (30%) occur in AOSD and may be one of the presenting complaints. Thoracentesis or pericardiocentesis often yields exudative effusions. Although uncommon, a worrisome manifestation of AOSD is acute pericardial tamponade. In such cases emergent drainage and high-dose corticosteroids are indicated. Pneumonitis is found in more than 20% and may present as bilateral alveolar and interstitial infiltrates on radiographs. Abdominal pain has also been described in 30% of people with AOSD and may be ascribed to several etiologies, including serous peritonitis, mesenteric adenitis, hepatic or splenic distention, and ileus or small bowel obstruction. Renal involvement is not usually seen in AOSD, although minor degrees of proteinuria may be noted during febrile episodes. Other uncommon or rare findings in AOSD include sensorineural hearing loss, aseptic meningitis, meningoencephalitis, orbital pseudotumor, disseminated intravascular coagulation, hemophagocytic syndrome, and keratoconjunctivitis sicca.

Laboratory and Radiographic Findings

Despite the systemic inflammatory features present in AOSD, patients are uniformly seronegative for RF and ANA. Laboratory findings in AOSD reflect the degree of inflammatory and cytokine activity present. The majority of people with AOSD will have a neutrophilic leukocytosis, with white blood cell counts usually ranging from 12,500 to 40,000 cells/mm³. Leukopenia or extreme leukocytosis are rare in AOSD and should raise the possibility of another diagnosis (eg, leukemia; lymphoma; Kikuchi's or hemophagocytic syndrome). Nearly all patients will have marked elevations of the acute phase reactants, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum amyloid A (SAA),

Comment [S70]: abnormal growth in a part of the body, caused by an excessive multiplication of cells

Comment [S71]: inflammation of lymph nodes

Comment [S72]: Development of lesions in the lymph node characterized by infiltration of the cortex or paracortex by large collections of proliferating histiocytes and complete or, more often, incomplete necrosis of lymphoid tissue

Comment [S73]: any disease, disorder, or enlargement of the lymph nodes

Comment [S74]: enlargement of the liver

Comment [S75]: an abnormally low number of white blood cells in the circulating blood

Comment [S76]: erythrocyte sedimentation rate

Comment [S77]: an inflammation of the pleura, the lining of the lungs, with subsequent pain.

Comment [S78]: inflammation of the pericardium

Comment [S79]: a surgical procedure in which a needle is inserted through the chest wall in order to withdraw fluid, blood, or air.

Comment [S80]: the use of a needle to withdraw fluid from the pericardial sac

Comment [S81]: the oozing of fluids from blood or lymph vessels into body cavities or intercellular tissue spaces as a result of inflammation, or the presence of excess blood or tissue fluid

Comment [S82]: intrapericardial pressure due to fluid accumulation in the **sack surrounding the heart**

Comment [S83]: any inflammation of the air sacs in the lungs

Comment [S84]: the study of the causes and origins of disease

Comment [S85]: relating to or affecting the kidneys

Comment [S86]: the presence of protein in the urine, usually indicating disease

Comment [S87]: relating to, involving, or typical of fever

Comment [S88]: involving or relating to sensory nerves

Comment [S89]: **Meningitis** is an illness in which there is inflammation of the tissues that cover the brain and spinal cord. Viral or **aseptic meningitis**, which is the most common type

Comment [S90]: an inflammation of the brain and the meninges

Comment [S91]: **Orbital pseudotumor** is a **swelling** of the **orbital** tissues behind the eye, but unlike cancerous tumors, it cannot invade tissues or spread elsewhere

Comment [S92]: activated **coagulation** that manifests with bleeding or thrombosis

Comment [S93]: persistent dryness of the cornea and **conjunctiva** due to decreased function of the tear glands or increased evaporation of tears

Comment [S94]: after a blood test, showing no immunological evidence of infection, either current or previous, with a particular bacterium, virus, or other infective agent

Comment [S95]: the most common type of white blood cell

Comment [S96]: an increased white blood cell count

Comment [S97]: Low white blood cell count

Comment [S98]: a measurement of how quickly red blood cells fall to the bottom of a test tube. When swelling and inflammation are present, the blood's proteins clump together and become heavier than normal.

serum complement levels, **haptoglobin**, and serum ferritin. It may be helpful to note that 90% of AOSD patients have an ESR >50 mm/h and 50% have an ESR >90 mm/h. Other signs of systemic inflammation during the early active systemic stage include drop in hemoglobin and hematocrit, anemia of chronic disease, and thrombocytosis.

Comment [S99]: any of several plasma proteins that combine with free haemoglobin in the bloodstream

Much has been made of the potential diagnostic utility of extreme elevations of serum ferritin. **Ferritin** is also an acute phase reactant, and extreme elevations, or

Comment [S100]: a spherical complex of iron and protein mainly found in the liver and spleen that is one of the forms in which iron is stored in the body

hyperferritinemia

Comment [S101]: high levels of ferritin, (iron), in the blood serum

(>4,000 ng/ml), are seen in fewer than 50% of patients. Extreme levels may range from 4,000 to 30,000 ng/ml, although levels as high as 250,000 ng/ml have been reported. Hyperferritinemia may also be seen in other conditions, including iron overload conditions (hemochromatosis, polytransfusions), neoplasia (eg, leukemia, lymphomas), hepatitis, pancreatitis, sepsis, other systemic inflammatory diseases (eg, rheumatoid arthritis, systemic lupus erythematosus), and hemophagocytic syndrome.

Other major laboratory abnormalities seen in people with AOSD include elevation of hepatic enzymes (70%), hypoalbuminemia (76%), and **hypergammaglobulinemia** (50%). Elevations of the hepatic

Comment [S102]: an excess of gamma globulins in the blood, seen frequently in chronic infectious diseases

enzymes may show either a cholestatic or hepatocellular pattern. Hyperbilirubinemia is very uncommon, but if present, it may indicate severe hepatic involvement and the need for high-dose **glucocorticoids**. Up to one-third of patients may have an elevated **anti-streptolysin-O titer** at disease

Comment [S103]: a steroid hormone (corticoid) that controls the metabolism of carbohydrates, proteins, and fats. Glucocorticoids have anti-inflammatory properties useful in treating rheumatoid arthritis.

onset, although throat cultures are invariably negative. Such a finding reflects nonspecific heightened immunologic activity during active disease.

Comment [S104]: Test that identifies serum antibody to streptolysin

Radiographs will reveal the distinctive pattern of intercarpal pericarpitate ankylosis will develop in nearly half of these patients and usually manifests in the first few years of disease. There is also a tendency for **intertarsal** (19%) and **cervical zygapophyseal** (12%) **ankylosis** to occur in AOSD patients. Erosive arthritis and juxta-articular osteopenia may be found in the minority who demonstrate a chronic **arthropathy**.

Comment [S105]: foot

Comment [S106]: relating or belonging to the neck

Comment [S107]: The joint that occurs between facets of the interior and superior articular processes of adjacent vertebra

Comment [S108]: stiffness or immobility in a joint caused by bones fusing together

Diagnosis

The differential diagnosis of AOSD is

Comment [S109]: a disease or medically noteworthy condition of a joint

large and has considerable overlap with other disorders capable of causing a FUO. Nonetheless, several conditions are often confused with AOSD and bear specific mention. Viral syndromes are the most common cause of misdiagnosis. In such patients the viral condition seldom persists beyond 3 months and may be confirmed by obtaining acute and convalescent viral serologies. Viral pathogens that may behave as AOSD include rubella, Epstein-Barr virus, mumps, cytomegalovirus, Coxsackie, and adenovirus. Acute leukemia and lymphoma may also mimic AOSD. Such patients are unlikely to have all three features of the diagnostic triad, often have isolated lymph node enlargement, atypical rashes, and/or hematologic abnormalities not commonly seen in AOSD. In some instances, it may be necessary to perform lymph node or bone marrow biopsies to distinguish these diagnoses.

Other conditions commonly confused with AOSD include Reiter's syndrome, dermatomyositis, hemophagocytic syndrome, Kikuchi's syndrome, or a systemic febrile onset of rheumatoid arthritis. The diagnosis requires a comprehensive, noninvasive evaluation; close observation (usually during hospitalization); documentation of fever pattern, exanthem, and other systemic features; and laboratory evidence of systemic inflammation. Table 1 lists my diagnostic criteria. Patients can be diagnosed with AOSD if they possess all five major criteria (at two points each) or any combination of major and minor criteria (one point each) that yields a score of 10 points or more. The diagnosis of AOSD is probable after 3 months of clinical activity and definite after 6 months of observation.

Patients who present with several features suggestive of AOSD, but either do not have the classic triad or do not meet diagnostic criteria may be more common than those with AOSD itself. Some clinicians have referred to such patients as having a form fruste of AOSD or incomplete AOSD. Experience with people with incomplete AOSD suggests they will have more limited disease and a favorable outcome, especially with regard to their joints.

Clinical Course and Prognosis

Fewer than 20% of patients will have a self-limiting monocyclic pattern of systemic disease (eg, fever, rash, serositis).

Comment [S110]: a disease that begins as an infection in genetically predisposed people and is characterized by recurring bouts of arthritis, conjunctivitis, and urethritis

Comment [S111]: One of a group of acquired muscle diseases called inflammatory myopathies. Characterized by a short and relatively severe onset, with patchy, bluish-purple rashes and muscle weakness. Some patients develop bumps of hardened calcium deposits under the skin. Muscle weakness is the most common symptom; others include fatigue, weight loss, discomfort, and low-grade fever

Comment [S112]: disorder associated with systemic viral infection and characterized pathologically by multiple-organ infiltration of hemophagocytic histiocytes into the lymphoreticular tissues

Comment [S113]: a chronic disease of the joints that causes stiffness, swelling, weakness, loss of mobility, and eventual destruction and deformity of the joints

Comment [S114]: Rash

Comment [S115]: Serositis is inflammation of one of the sacs around the heart, lungs or abdomen

organomegaly, etc). In this group, systemic activity will last for at least 4-12 months.

A majority of patients demonstrate a pattern of recurrent systemic disease (polycyclic systemic) with or without chronic articular disease. Multiple systemic flares, may be interspersed by disease-free intervals that may last for years.

All patients should be told of the potential for disease recurrence. There is a small risk of life-threatening complications (ie, pericardial tamponade, liver or respiratory failure). However, the vast majority of patients with a predominance of systemic disease will have favorable outcomes. The infrequent causes of deaths reported in AOSD are related to either iatrogenic causes from medications (eg, infections, gastrointestinal bleeding) or to other comorbid conditions or accidents.

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Major (two points)

Quotidian fever > 39°C

Still's (evanescent) rash

WBC > 12.0 + ESR > 40 mm/h

Negative RF and ANA

Carpal ankylosis

Minor (one point)

Onset age < 35 years

Arthritis

Prodromal sore throat

RES involvement or abnormal LFTs

Serositis

Cervical or tarsal ankylosis

Proposed Criteria for AOSD Diagnosis

Probable AOSD: 10 points with 12 weeks' observation

Definite AOSD: 10 points with six months' observation

WBC, white blood cell; RF, rheumatoid factor; ANA, antinuclear antibody; RES, reticuloendothelial system (hepatomegaly, splenomegaly, generalized lymphadenopathy); LFTs, liver function tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin)

FOR EVIDENCE-BASED MANAGEMENT OF RHEUMATIC DISEASES

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A substantial minority of cases (25%)

will evolve into chronic inflammatory articular disease that can be destructive and debilitating. It has been shown that patients with a polyarticular onset and course, hip involvement, and HLA-DR4 positivity will have the poorest outcomes. In contrast, patients with an HLA-Bw35 haplotype are more likely to exhibit systemic disease and a favorable outcome.

Comment [S116]: relating to or involving a joint of the body

Therapy of AOSD

For many patients, NSAIDs will be the initial choice of therapy to control both systemic and articular features. Although any NSAID therapy at anti-inflammatory doses can be used, sustained release indomethacin (75-150 mg/day) appears to be effective in 40%-60% of patients early in the disease. Aspirin is seldom effective and may be associated with salicylate-induced hepatotoxicity. Glucocorticoids are often employed, but should be reserved for those patients with markedly elevated hepatic enzymes, pericardial tamponade, severe serositis, or pneumonitis and in those resistant to NSAIDs. High-dose prednisone (40-60 mg/day) may be necessary to control systemic manifestations. Weekly oral methotrexate (7.5-20 mg/week) has successfully been used to control systemic and articular manifestations and should be used early in those with severe-to-protracted disease to limit steroid exposure. Patients who are not adequately controlled by NSAIDs, prednisone, and methotrexate appear to respond well to the addition of a TNF inhibitor (etanercept or infliximab). Unresponsive patients may also be treated with leflunomide, hydroxychloroquine, azathioprine, or cyclosporine, but there is no literature to support their use in AOSD. Chronic, progressive polyarthritis can be managed in the same manner as that employed for rheumatoid arthritis.

Comment [S117]: NSAIDs stands for nonsteroidal anti-inflammatory drugs. These are drugs, such as: aspirin, ibuprofen and naproxen, that fight inflammation

Comment [S118]: a nonsteroidal anti-inflammatory drug (trade name Indocin)

Comment [S119]: a steroid hormone (corticoid) that controls the metabolism of carbohydrates, proteins, and fats. Glucocorticoids have anti-inflammatory properties useful in treating rheumatoid arthritis

Comment [S120]: a synthetic steroid hormone produced from cortisone and used to treat allergies and autoimmune diseases

Comment [S121]: A drug which is used in the treatment of rheumatoid arthritis and other inflammatory disorders. It is a cytotoxic/immunosuppressive drug

Comment [S122]: proinflammatory cytokine that is produced by white blood cells (monocytes and macrophages); has an antineoplastic effect but causes inflammation (as in rheumatoid arthritis)

Comment [S123]: a genetically engineered anti-TNF compound (trade name Enbrel) consisting of receptors that bind TNF; it is injected twice a week in the treatment of rheumatoid arthritis

Comment [S124]: an anti-TNF compound (trade name Remicade) consisting of an antibody directed against TNF; it is given intravenously at one- to three-month intervals; used in treatment of regional enteritis and rheumatoid arthritis

Comment [S125]: an anti-TNF compound (trade name Arava) that is given orally; can slow the progression of rheumatoid arthritis by slowing the proliferation of white blood cells which reduces inflammation in the synovium

Comment [S126]: anti-inflammatory drug (trade name Plaquenil) used in the treatment of rheumatoid arthritis and malaria and lupus erythematosus

Comment [S127]: An anti-rejection drug given to transplant patients that suppresses the production of white blood cells

Comment [S128]: immunosuppressive drug which is believed to work by blocking the action of the immune cells in your blood known as the T-lymphocytes. These immune cells normally take part in the rejection process

Bibliography

1. Bywaters EG. Still's disease in the adult. *Ann Rheum Dis* 1971; 30:121-33.
2. Cush JJ, Medsger TA Jr, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease. *Clinical course and outcome. Arthritis Rheum* 1987; 30:186-94.
3. DeBeneditti F, Massa M, Pignatti P, Albani S, Novick D, Martini A. Serum soluble interleukin 6 (IL-6) receptor and IL-6/soluble IL-6 receptor complex in systemic juvenile rheumatoid arthritis. *J Clin Investigation* 1994; 93:2114-9.
4. Elliott MJ, Woo P, Charles P, Long-Fox A, Woody JN, Maini RN. Suppression of fever and the acute-phase response in a patient with juvenile

chronic arthritis treated with monoclonal antibody to tumour necrosis factor-alpha (cA2). Br J Rheumatol 1997; 36:589-93.

5. Fujii T, Akizuki M, Kameda H, Matsumara M, Hirakata M, Yoshida T, Shinozawa T, Mimori T. Methotrexate treatment in patients with adult onset Still's disease – retrospective study of 13 Japanese cases. *Ann Rheum Dis* 1997; 56:144-8.

6. Pouchot J, Sampalis JS, Beaudet F, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine*. 1991; 70:118-36.

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