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

**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.

**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.

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

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.

**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
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 >40ºC), 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 monarthriti has not been observed in AOSD.
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.
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 alvelolar 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), and C-reactive protein.
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.

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

Radiographs will reveal the distinctive pattern of intercarpal pericapitate 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.

**Diagnosis**

The differential diagnosis of AOSD is
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, Coxackie, 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, rash, serositis).
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)
will evolve into chronic inflammatory 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.

**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.

**Bibliography**

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