Diagnosis and Management of Adult Onset Still's Disease (AOSD)

Clinical Review

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Abstract

Context: Adult Onset Still’s Disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology that is responsible for a significant proportion of cases of fever of unknown origin and can also have serious musculoskeletal sequelae.

Objective: To assess and synthesize the evidence regarding optimal diagnosis and management of AOSD.

Data Sources, Selection, and Extraction: Using the key terms Adult Onset Still’s Disease, AOSD, Adult Still’s Disease, ASD, Still’s disease, we searched MEDLINE (1966-2005) and PUBMED (1966-2005) for all available articles in the English language. Clinically relevant articles were subsequently selected. Bibliographies, textbooks and websites of recent rheumatology conferences were also assessed to identify relevant information.

Data Synthesis: Data on diagnosis and treatment of AOSD are limited in the medical literature and consist mainly of case reports, small series and modest-scale retrospective studies. Diagnosis is clinical and necessitates the exclusion of infectious, neoplastic, and other autoimmune diseases. Laboratory tests are non specific and reflect heightened immunologic activity. Treatment consists of non-steroidal anti-inflammatories, corticosteroids, immunosuppressives (methotrexate, leflunomide, gold, azathioprine, cyclosporine A, cyclophosphamide), and intravenous gamma globulin (IVIG). The recent successful application of biologic (anti-TNF, anti-IL1, anti-IL6) agents, often in combination with traditional immunosuppressives, has been very promising.

Conclusions: AOSD often poses a diagnostic and therapeutic challenge and there is a lack of clinical guidelines. The emergence of validated diagnostic criteria, discovery of better serologic markers and the application of novel biologic medications may all provide the clinician with significant tools for the diagnosis and management of this complex systemic disorder.

Key Terms: Adult Onset Still’s Disease, AOSD, Still’s disease, Biologic medications, anti-cytokine therapy

Introduction

Adult Onset Still’s Disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology, characterized by quotidian or double-quotidian spiking fevers with an evanescent rash, arthritis, and multiorgan involvement. It owes its name to George Still who published in 1897 his monograph “On a Form of Chronic Joint Disease in Children” describing 22 children with signs and symptoms of the disease entity currently known as systemic onset juvenile idiopathic arthritis. In 1971, Eric Bywaters described 14 adults with similar presentation with pediatric Still’s disease, convincingly establishing the new disease entity. However, the first description of an adult patient with signs and symptoms of AOSD, erroneously labeled rheumatoid arthritis, was published in the Lancet in 1896, one year prior to George Still’s monograph. Since then multiple reports of fever
of unknown origin or “rheumatoid arthritis” that we would call AOSD appeared in the literature. In the French and German literature there were occasional reports of AOSD then called “subsepsis allergica” or “Wissler’s syndrome” and later the “Wissler-Fanconi syndrome”.3

Methods
We searched MEDLINE using the key terms Adult Onset Still’s Disease, AOSD, Adult Still’s Disease, ASD, Still’s disease, we searched MEDLINE (1966-2005) and PUBMED (1966-2005) for all available articles in the English language, utilizing the filters “human” and “adult”. Reference lists of identified trials, review articles and papers proposing diagnostic criteria were reviewed. In addition, textbook chapters (both printed and electronic) were assessed to identify additional relevant information. Websites of recent rheumatology conferences (including those of the American College of Rheumatology and the European League against Rheumatism [EULAR]) were searched for recent studies presented but not yet published. Approximately 200 references in the English language were initially retrieved based on their clinical relevance and the reference list was subsequently modified during the peer-review process on the basis of comments from the reviewers, to include 107 papers. No randomized controlled trials (RCTs) were identified which could be explained by the rarity of the disease. The existing body of clinical literature consists of case reports, small series and modest-scale retrospective studies.

Epidemiology
Adult Onset Still’s disease is rare, not readily diagnosed and currently there is no consensus on the incidence and/or prevalence rates in different populations. Based on the larger reviews from the 1980s it appears that it occurs worldwide and affects women slightly more frequently than men. The disease characteristically affects younger individuals, with three quarters of the patients reporting disease onset between 16 and 35 years of age.4, 5 In a Dutch retrospective review of 45 patients, 60% of the patients were women and the median age of onset was 25 years (range 16-65) with 27% of the patients showing the first symptom after the age of 35.6 In a retrospective study of 62 patients from western France, the incidence was estimated to be 0.16 per 100,000 inhabitants with a bimodal peak at ages 15-25 and 36-46 without a sex bias.7 However, an epidemiological survey from Japan reported that 67% of the cases presented after the age of 35, the majority (65-70%) being women.8 AOSD affects all ages and several cases have been reported after the age of 60.4, 9 Stress has been suggested as an important risk factor for all ages.10

Pathogenesis
The etiology of AOSD, like most rheumatic diseases, is currently unknown. A genetic component has been suggested by many studies, linking the disease with a number of HLA antigens. In a retrospective review of 62 patients from Canada, 55 underwent immunogenetic studies and HLA B17, B18, B35, and
DR2 were associated with a relative risk ranging from 2.1 to 2.9. However, other studies did not confirm these findings and other associations were reported, including HLA B14 and DR7, or Bw35 and Cw4, or DR4 and Dw6. The hypothesis that AOSD may be a reactive syndrome, where various infectious agents may act as disease triggers in a genetically predisposed host has been very popular and a variety of organisms has been proposed. Some clinical manifestations of AOSD are reminiscent of those seen in self-limited viral infections. Viruses such as rubella, mumps, echovirus 7, CMV, EBV, parainfluenza, Coxsackie B4, adenovirus, influenza A, HHV6, parvovirus B19, hepatitis B, and hepatitis C have all been implicated in case reports and small series. Other studies have proposed microbial triggers, including Mucoplasma pneumoniae, Chlamydia Pneumoniae, Yersinia enterocolitica, Brucella abortus, and Borrelia burgdorferi in the pathogenesis of AOSD. The observation that many different infectious agents may act as disease triggers, suggests a similarity with reactive arthritis. More recently, alterations in cytokine production have been suggested to have an important pathophysiologic role in AOSD. A predominance of Th1 cytokines was shown in the peripheral blood and tissues of patients with active untreated AOSD. Th1 immune response is characterized by increased production of IL-2, IFNγ and TNFα cytokines that steer B-cells toward IgG2a production, activate macrophages and NK cells and promote cell-mediated immunity. Serum levels of IL-6, TNFα, and INFγ were significantly increased in 12 patients with active AOSD when compared to controls. IL-18 is another pro-inflammatory cytokine closely related to the AOSD pathogenesis, as it is overproduced in the acute phase of the disease and is believed to be the cytokine initiating the inflammatory cascade that includes IFNγ, IL-6, and TNFα. Genetic polymorphisms of the human IL-18 gene have been described and the S01/S01 diplotype conferred disease susceptibility in a Japanese study. In another Japanese study, serum levels of soluble IL-2 receptors (sIL2-R), IL-4 and IL-18 correlated with chronic arthritic AOSD activity, while IFNγ and IL-8 levels were persistently elevated, even in disease remission. TNFα, soluble TNF receptor 2, and IL-18 were also persistently elevated in both the systemic and the chronic articular forms of AOSD. There seems to be an increased activation of γδ T-cells of the Vγ9/Vδ2 type in active vs inactive AOSD.

**Clinical Manifestations**

AOSD typically manifests as a triad of symptoms that include high-spiking fevers, a characteristic rash, and arthritis/arthralgias. Fever generally exceeds 39°C and is transient, lasting typically under 4 hours, and is most commonly quotidian or double quotidian in pattern, with the highest temperatures seen in the late afternoon or early evening. Fever can herald the onset of other manifestations as well, with serositis, sore throat, myalgias, and arthralgias described. Overall incidence of fever across five of the largest retrospective studies was 95.7%.
Table 1. AOSD Clinical Manifestations in the largest series (% patients)

<table>
<thead>
<tr>
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<th></th>
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<tbody>
<tr>
<td>Sore throat</td>
<td>68</td>
<td>68</td>
<td>70</td>
<td>92</td>
<td>67</td>
<td>71</td>
<td>38</td>
<td>35</td>
<td>74</td>
</tr>
<tr>
<td>Myalgia</td>
<td>75</td>
<td>62</td>
<td>56</td>
<td>84</td>
<td>61</td>
<td>12</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>100</td>
<td>94</td>
<td>100</td>
<td>100</td>
<td>85</td>
<td>82</td>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>68</td>
<td>69</td>
<td>72</td>
<td>94</td>
<td>89</td>
<td>100</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>11</td>
<td>0</td>
<td>64</td>
<td>53</td>
<td>100</td>
</tr>
<tr>
<td>Rash</td>
<td>54</td>
<td>85</td>
<td>87</td>
<td>87</td>
<td>94</td>
<td>88</td>
<td>51</td>
<td>76</td>
<td>73</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>54</td>
<td>48</td>
<td>69</td>
<td>74</td>
<td>56</td>
<td>47</td>
<td>32</td>
<td>35</td>
<td>61</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>14</td>
<td>22</td>
<td>65</td>
<td>55</td>
<td>56</td>
<td>29</td>
<td>32</td>
<td>44</td>
<td></td>
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<tr>
<td>Pleuritis</td>
<td>25</td>
<td>15</td>
<td>12</td>
<td>53</td>
<td></td>
<td></td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td>25</td>
<td>23</td>
<td>10</td>
<td>37</td>
<td></td>
<td></td>
<td>15</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

The typical rash is an evanescent, salmon-pink, maculopapular eruption, predominantly found on the proximal limbs and trunk, with rare involvement of the face and distal limbs. Often accompanied by fever, the rash can be mildly pruritic, and confused with a drug allergy. A Koebner phenomenon has been described. Histology reveals perivascular inflammation of the superficial dermis with invasion of lymphocytes and histiocytes, with immunohistochemistry sometimes positive for complement and immunoglobulin. Incidence ranges from 51-87%, with an average of 72.7%. In three cases, a vasculitic purpuric rash has also been described and an association with mixed cryoglobulinemia has been suggested in one of them.

Arthralgia and arthritis is found in the majority of patients with Adult Onset Still’s Disease, with incidences ranging from 64-100%. Joints affected most frequently are the knees, wrists, and ankles, although involvement of the elbow, shoulder, proximal and distal interphalangeal joints, metacarpophalangeal and metatarsophalangeal joints, TMJ, and hip have been described as well. In particular, carpal and pericapitate abnormalities are typically higher than in cases of rheumatoid arthritis, offering a means to clinically differentiate the two entities. Of note, changes in the wrist typically present 6 months after disease onset, with progressive joint-space narrowing in a pericapitate or carpometacarpal distribution, with ankylosis developing after 1.5-3 years. The pattern of arthritis is typically symmetrical, with the majority developing polyarthritis and joint pain associated with fever spikes. As such, complaints are often short-lived, resolving as fever diminishes. Joint aspiration fluid often reveals marked leukocytosis, with a neutrophilic predominance.
Table 2. Articular Manifestations in Chronic Articular AOSD (% patients)

Results from 2 large series

<table>
<thead>
<tr>
<th>Series (# of pts)</th>
<th>Pouchot (62)^11</th>
<th>Masson (65)^23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>82</td>
<td>69</td>
</tr>
<tr>
<td>Wrist</td>
<td>73</td>
<td>67</td>
</tr>
<tr>
<td>Ankle</td>
<td>55</td>
<td>38</td>
</tr>
<tr>
<td>PIP</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td>Elbow</td>
<td>44</td>
<td>29</td>
</tr>
<tr>
<td>Shoulder</td>
<td>40</td>
<td>24</td>
</tr>
<tr>
<td>MCP</td>
<td>35</td>
<td>42</td>
</tr>
<tr>
<td>MTP</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Hip</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>DIP</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>PIP</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>TMJ</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Myalgia is another frequent manifestation, with incidences ranging from 56-84%. Distribution remains generalized, and most often appears with exacerbations in fever. Inflammatory myopathy is rarely a finding, although a number of case reports have described an elevation of muscle enzymes in patients’ sera.30, 31

Liver abnormalities, predominantly hepatomegaly and abnormalities in liver biochemistry, are present in approximately 50-75% of patients, but it has been suggested that liver dysfunction secondary to NSAID use may be a significant co-factor AOSD can present with a pseudo-angiocholitis picture.33 Jaundice and acute hepatitis leading to hepatic failure and requiring liver transplantation remain exceedingly rare.34, 35

Less frequent manifestations include pleuritis (26.4%), pericarditis (23.8%), and splenomegaly (43.9%). Additional cardiac complications that have been noted to a lesser extent include tamponade and myocarditis.37 Pulmonary manifestations include fibrosis, pleural effusions, and, rarely, ARDS.38-40 Renal involvement is rare and can manifest as interstitial nephritis, subacute glomerulitis, renal amyloidosis and the more recently described collapsing glomerulopathy. The latter is a relatively newly recognized entity, originally described in HIV patients (HIV-associated nephropathy) in the 1970s, but is also seen in non HIV patients and is characterized by heavy proteinuria and rapidly progressive renal failure with poor outcome.41-44 Hematologic complications (thrombotic thrombocytopenic purpura (TTP), pure red cell aplasia), and neurologic complications (cranial nerve palsies, seizures, asceptic meningoencephalitis, Miller-Fisher Syndrome) are rarer still.11, 14, 43-47
Laboratory and Radiographic Findings

The diagnosis of AOSD remains a clinical one. Unlike other systemic rheumatic diseases, it is not associated with RF or ANA positivity, and this fact has been used in various sets of criteria used to define the disease. In fact, the laboratory profile of the disease is a reflection of the systemic inflammation and cytokine cascade present. The ESR is elevated in virtually all patients in three of the largest series described.6, 11, 48 C reactive protein can also be found elevated.49 Common hematologic abnormalities include leukocytosis, which often accompanies increased disease activity, anemia and thrombocytosis.5, 6, 11 Leukocytosis is the result of a striking neutrophilia that is likely secondary to bone marrow granulocyte hyperplasia.11, 50 In a series of 62 patients, 50% of the patients had peripheral leukocyte counts above 15,000, and 37% had WBC counts exceeding 20,000 cells/dL.11 Anemia of chronic disease is seen with active disease that often returns to normal when the disease subsides.11 Reactive thrombocytosis is common. Pancytopenia should alert to the presence of hemophagocytic syndrome which has been reported in AOSD and necessitates prompt immunosuppressive therapy.50 Coagulation abnormalities are rare and consist of prolongations of partial thromboplastin time (PTT) or prothrombin time (PT); cases of disseminated intravascular coagulation (DIC) have been described that have led to fatalities.11 Elevations in LDH, AST, ALT, GGT, and bilirubin can be seen in up to three quarters of patients and frequently occur concomitantly with fever and exacerbations of arthritis.4 Liver biopsy typically shows mild peri-portal inflammation with monocyte infiltration.11 Lately, serum ferritin and glycosylated ferritin have received a lot of attention as diagnostic and disease activity markers. Ferritin, an acute phase reactant, is intimately involved in inflammatory processes, including the mechanisms underlying oxidative stress. Inflammation is associated with increased production of ferritin by the histiocyte-macrophage system and/or increased release from damaged hepatocytes. Several cytokines seem to drive the increased production of ferritin, mainly IL-1β, IL-18, TNFα, and IL-6.51 Ferritin levels in AOSD are usually higher than those found in patients with other autoimmune or inflammatory diseases. In most studies, the threshold above which serum ferritin levels suggest AOSD has been placed at 1000 ng/mL, five times the upper limits of normal (40-200 ng/mL).51 Very high levels ranging from 4,000-30,000ng/mL are not uncommon and even extreme levels as high as 250,000 ng/mL have been recorded.52 Furthermore, serum ferritin levels correlate with disease activity and often normalizes when the disease goes to remission.53-55 Hyperferritinenemia’s validity as a diagnostic tool was evaluated in a retrospective French study56 with 49 patients, whereas a fivefold increase in serum ferritin had 80% sensitivity and 41% specificity and similarly in a Japanese study57 with (82% sensitivity, 46% specificity). The usefulness of serum ferritin is limited by the fact that very high levels can also be seen in other diseases, such as liver disease (hemochromatosis, Gaucher’s disease), infections (sepsis, HIV), malignancies (leukemia, lymphomas), and especially in the hemophagocytic syndrome.51, 52
A more specific diagnostic marker than ferritin may be its glycosylated fraction. In healthy individuals, 50-80% of ferritin is glucosylated, a process that provides protection from proteolytic enzymes. In inflammatory diseases, saturation of glycosylation mechanisms causes the glycosylated fraction to drop to 20-50%. This phenomenon is particularly prevalent at AOSD, where the glucosylation of the ferritin often is less than 20%. Interestingly, defective glycosylation of other acute-phase reactants has been reported as well in AOSD. It has been suggested that, in addition to the saturation of the glycosylation mechanisms, other more disease-specific mechanisms might be in place, such as decreased clearance of non-glycosylated proteins by the histiocyte-macrophage system. Glycosylated ferritin cannot be used to monitor disease activity or response to therapy, as it remains low for many months after the disease goes to remission. When combined with five-fold serum ferritin elevation, sensitivity fell to 43% and specificity rose to 93%. Better diagnostic tests are clearly needed and new immunologic tests, still in the research setting, such as IL-18 may prove very useful in the near future for diagnosis as well as disease activity and response to therapy monitoring. Until the development of these tests, clinicians will continue to use the currently available tests: Complete blood count and differential, ESR, CRP, ANA and RF (both negative), LFTs and albumin, ferritin, and glucosylated ferritin (if available).

Radiographs during the initial acute phase of the disease aren’t usually very helpful in establishing the diagnosis, being either normal or showing soft-tissue swelling, joint effusion, or mild periarticular demineralization. Radionuclide bone scan and gadolinium-enhanced MRI were assessed in small series and may prove to be more sensitive imaging modalities for early diagnosis and successful therapy in follow up. In one study, 41% of patients developed a distinctive pattern of intercarpal and carpometacarpal joint space narrowing (bilateral in 69%), that led to pericapitate ankylosis in 25% of the cases. Other investigators have also reported a tendency for distal interphalangeal, interscalene, and cervical zygapophyseal ankylosis. Patients that fall into the chronic articular disease pattern often present with joint erosions. A French group reported frequent severe involvement of the hip requiring total hip replacement, a finding that wasn’t replicated in a Japanese study. (See Figure 1 for radiographic manifestations of AOSD arthritis)

There is currently no consensus in the literature whether AOSD and its juvenile counterpart (systemic-onset juvenile idiopathic arthritis, formerly known as pediatric Still’s disease) represent the same clinical continuum vs being distinct entities. The diagnosis of SoJIA is clinical based on the presence of characteristic disease manifestations, distinct from other forms of JIA, and an age of onset < 16 years of age, while diagnosis of AOSD requires an age of onset>18 years. Both entities share typical clinical features such as the abruptness of onset, the fever patterns, the transient nature of the rash, the near equal female to male ratio, the arthritis, and the neutrophilia. Furthermore, recent research has shown that a similar pattern of cytokines (IL-6, IL-18, TNF-α) may be involved in the pathogenesis of both disorders. Despite those
similarities, other studies have reported differences in levels of acute phase reactants (ferritin, chymotrypsin)⁶³ and, especially, prognosis. In children, systemic disease onset is typically between 3-5 years, and organ involvement is frequently present. Children severely affected by SoJIA are at significant risk for life-long disability and up to 50% develop 5-10 years after diagnosis a chronic, destructive polyarthritis⁶⁴, ⁶⁵ that often appears to be less responsive to treatment, even with anti-TNF therapy.⁶⁶, ⁶⁷

Diagnosis

The clinical presentation of AOSD is heterogeneous, and the spectrum of differential diagnoses is wide, including infectious, neoplastic, and autoimmune disorders, which should be ruled out before the diagnosis of AOSD can be made. Viral syndromes (e.g. rubella, CMV, EBV, mumps, coxsackie, adenovirus) can be excluded if the symptoms persist beyond three months. Infectious surveys, including cultures and serologies can be especially helpful early in the disease. Neoplastic disorders that can mimic AOSD include leukemia, lymphoma, and angioblastic lymphadenopathy. However, the clinical presentation can differ substantially with atypical rashes and/or isolated lymph node enlargement. The hematologic profile can help differentiate the disease entities, but occasionally bone marrow and/or lymph node biopsy may be needed.⁵² Occasionally, the constellation of findings (fever, abdominal pain, and mesenteric lymphadenopathy) has led to exploratory laparotomy before the diagnosis of AOSD was entertained.¹¹ Conditions commonly confused with the AOSD include reactive arthritis and the other spondyloarthropathies, hemophagocytic syndrome, dermatomyositis, Kikuchi’s syndrome, Sweet’s syndrome, granulomatous disorders, and the vasculitides.⁵², ⁶⁸

Another category of syndromes that may mimic the clinical manifestations of AOSD are the periodic fever syndromes and in particular, in this age group, Familial Mediterranean fever (FMF) and TNF receptor-associated periodic syndrome (TRAPS). FMF patients often presents with acute, self-limited episodes of fever accompanied by signs of peritonitis, pleuritis, or acute synovitis, mainly of the knee, ankle, or hip. Erysipelas-like erythema can accompany the fever, which does not have the quotidian pattern of AOSD and usually lasts for 1-3 days. The disease often starts in childhood or early adolescence. The significant family history (and ethnic background) together with the distinct clinical characteristics and response to colchicine can direct the clinician toward the correct diagnosis, which can be verified, in many cases, with genetic analysis for the MEFV gene. TRAPS commonly starts in childhood and also has a strong familial distribution. Fever attacks last longer, 21 days on average, and are associated with ocular involvement and is associated with a distinctive centrifugal, erythematous patch.⁶⁹

Several sets of classification criteria have been published for AOSD. They have all been developed from retrospective data and classify criteria as major or minor. One study attempted to validate these classification criteria: Yamaguchi’s criteria⁵⁷ were shown to be the most sensitive (93.5%), followed by Cush’s⁷⁰ (80.6%) and Calabro’s⁷¹ (80.6%). As there was no control group, no validation of
More recently, a French group has proposed a new set of criteria that, unlike the previously described ones, does not contain exclusion criteria and takes into consideration the two novel disease markers: serum ferritin and its glucosylated fraction. This set provided a sensitivity of 80.6% and a specificity of 98.5%, which remains to be validated in a different population before becoming widely accepted. Table 3 compares Yamaguchi criteria with the widely used Cush clinical criteria and the newly proposed criteria by Fautrel et al.

Table 3. AOSD Diagnostic Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yamaguchi et al&lt;sup&gt;57&lt;/sup&gt;</th>
<th>Cush&lt;sup&gt;62&lt;/sup&gt;</th>
<th>Fautrel et al&lt;sup&gt;24&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td><strong>Major</strong></td>
<td>• Arthralgia &gt;2 weeks&lt;br&gt;• Fever &gt;39°, intermittent, ≥ 1 week&lt;br&gt;• Typical rash&lt;br&gt;• WBC&gt;10,000 (&gt;80% Granulocytes)</td>
<td>(2 points)&lt;br&gt;• Quotidian fever &gt;39°&lt;br&gt;• Still's (evanescent) rash&lt;br&gt;• WBC&gt;12.0+E SR&gt;40 mm/h&lt;br&gt;• Negative RF and ANA&lt;br&gt;• Carpal Ankylosis</td>
<td>• Spiking fever≥39°&lt;br&gt;• Arthralgia&lt;br&gt;• Transient erythema&lt;br&gt;• Pharyngitis&lt;br&gt;• PMN≥80%&lt;br&gt;• Glycosylated ferritin ≤20%</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td>• Sore throat&lt;br&gt;• Lymphadenopathy and/or spleenomegaly&lt;br&gt;• LFT abnl&lt;br&gt;• (-)ve ANA and RF</td>
<td>(1 point)&lt;br&gt;• Onset age&lt;35 years&lt;br&gt;• Arthritis&lt;br&gt;• Prodromal sore throat&lt;br&gt;• RES involvement or abnl LFTs&lt;br&gt;• Serositis&lt;br&gt;• Cervical or tarsal ankylosis</td>
<td>Maculopapular rash&lt;br&gt;Leukocytes≥10000/mm³</td>
</tr>
<tr>
<td><strong>Diagnostic combination</strong></td>
<td><strong>Exclusion Criteria</strong>&lt;br&gt;• Infections&lt;br&gt;• Malignancies&lt;br&gt;• Rheumatic diseases</td>
<td><strong>Probable AOSD</strong>: 10 points with 12 weeks’ observation</td>
<td>4 major criteria</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>• 5 criteria (at least 2 major)</td>
<td>• <strong>Definite AOSD</strong>: 10 points with six months’ observation</td>
<td>3 major+2 minor</td>
</tr>
</tbody>
</table>
Course and Prognosis

The clinical course can fall into three distinct patterns, with significant prognostic implications, each affecting approximately one third of AOSD patients.\textsuperscript{52, 73}

- The \textit{self limited} or \textit{monocyclic} pattern is characterized by systemic symptoms (fever, rash, serositis, and organomegaly). Most patients achieve remission within a year (median time is 9 months) from the first and only disease episode.\textsuperscript{6}

- The patients with the \textit{intermittent} or \textit{polycyclic systemic} pattern experience recurrent flares with or without articular symptomatology. There is complete remission between the flares, that may be years apart and tend to be milder than the initial episode.\textsuperscript{11}

- The \textit{chronic articular} pattern is dominated by the articular manifestations that can be severe and lead to joint destruction. In one series, 67\% of patients in this group required at least one total joint replacement, after a median of 28 (13-60) months from disease onset.\textsuperscript{6}

Patients with chronic articular disease generally have more disability and worse prognosis than patients with only systemic symptoms. Rash, polyarthritis and root joint (shoulder, hip) involvement at disease onset, were predictors of a chronic articular pattern in one retrospective study.\textsuperscript{11} Patients with systemic disease have a favorable prognosis, with only rare serious complications from the disease (pericarditis, tamponade, diffuse intravascular coagulation, amyloidosis, hepatic, and respiratory failure) or the treatment (infections, gastrointestinal bleeding, etc).\textsuperscript{6}

Treatment

Treatment in Adult Onset Still’s Disease has been exclusively empirical, with data on treatment efficacy extrapolated from case reports and small-scale retrospective studies. These have been further confounded by frequently inconsistent treatment regimens and a proliferation of qualitative descriptions of the data. While the low incidence of AOSD places a burden on the execution of prospective, clinically-controlled treatment trials, higher standards are needed in the interpretation and presentation of existing retrospective data.

The treatment of AOSD has centered around the use of NSAIDs, steroids, and anti-rheumatic agents to control fever, arthritis, and systemic disease, beginning with the treatment of AOSD by Bywaters in 1971.\textsuperscript{1} Evidence of the varying efficacies of these treatments in AOSD was later elucidated in several retrospective studies, including a multicenter study in France of 65 patients with ASD.\textsuperscript{74} Initial treatment in these patients consisted of aspirin in 23 patients, NSAIDs in 21 patients, and a glucocorticoids in 21 patients. Approximately 12\% of patients were controlled on NSAID monotherapy, compared to 7\% and 15\% from earlier studies.\textsuperscript{11, 14} 88\% of patients required prednisone in addition to NSAIDs at some point, with 46\% of patients requiring maintenance prednisone
therapy. A subsequent study emphasized the relative inefficacy of salicilates and suggested indomethacin and naproxcen as more useful class representatives. As NSAID monotherapy is effective in controlling disease in only 7-15% of patients, most patients are treated with steroids at some point in their disease course, with responses ranging from 76-95%. The efficacy of glucocorticoids was demonstrated by Wouters et al, who showed that 16 out of 21 (76%) patients responded favorably to glucocorticoids administered for the control of systemic and joint disease. However, eight of those on a maintenance dose of 10-15 mg/day of prednisone for arthritic symptoms developed severe joint destruction despite steroid treatment. In the study by Masson et al, maintenance prednisone therapy on top of NSAID use was required in 30 patients (46%), with 57 patients (89%) requiring prednisone at some point during their disease. Similar requirements for steroid use were found by Larson and Bywaters in 50% and 54% of their patient cohorts, respectively. There seems to be an increasing need for steroid therapy based on the disease pattern. Prednisone was required for 57% of patients with self-limited, 67% with intermittent, and 77% with chronic articular AOSD. The utility of intravenous pulse methylprednisolone to treat disease refractory to oral prednisone and the availability of dexamethasone as a prednisone alternative have also been demonstrated in case reports and small series. As a whole, studies indicate the need for steroid treatment in the majority of patients with AOSD. Within this population, the majority of patients are well-controlled. Guidelines for the use of steroids are derived from their use in juvenile Still’s. Large doses of prednisone should be limited to 6 months for the treatment of NSAID refractory systemic disease, presenting with persistent anemia, pericarditis, serositis, and elevated liver enzymes.

The use of remittive drugs in AOSD is marked by an absence of prospective, clinically-controlled trials, which has proven additionally problematic because of the unclear efficacy of anti-rheumatics in anecdotal case studies and small-scale retrospective studies. Broadly, these studies suggest that the use of anti-rheumatics should be reserved for cases in which the combination of NSAIDs and steroids fails, or in which a reduction in the requirement for steroids is desired, either due to tolerance or adverse events. Anti-rheumatic agents that have been studied include cyclosporin A, hydroxychloroquine, gold, penicillamine, azathioprine, cyclophosphamide, and methotrexate, with modest success and overall response across studies at approximately 40%. In a study by Wouters et. al., of 18 trials of anti-rheumatics used in 13 patients with NSAID- and corticosteroid-refractory disease, only 8(44%) proved clinically efficacious. The list of anti-rheumatics used included hydroxychloroquine (0/3 respondents), gold (6/8 respondents), penicillamine (4/6 respondents), and azathioprine (0/1 respondents). Masson et. al. demonstrated that 22/65 patients(34%) required additional remittive therapy to maintain disease control, 20(91%) of whom were concomitantly receiving prednisone. Of the 13 patients receiving methotrexate (MTX) as the remittive agent in that group, 11(85%) were able to taper the prednisone dose. Similarly, Fautrel et. al., in a study of 26 patients diagnosed...
with refractory AOSD, found that 23 (88%) patients responded to treatment with low-dose methotrexate (11.5 +/- 3.6 mg/wk), with 18/23 (78%) entering complete remission. In addition, daily prednisone intake decreased by 69% and 11 (42%) of these 26 patients were able to discontinue prednisone altogether. Polyarthritis was particularly susceptible to MTX treatment and resolved completely in many cases, while the effect of methotrexate on non-articular manifestations of AOSD was less well defined. Side effects of MTX treatment included mild elevations in LFTs, gynecomastia, nausea and vomiting, and varicella zoster infection. Serious infections (Legionella pneumonitis and cerebral nocardiosis) occurred when higher doses of methotrexate (40 and 50 mg/day) were used.

The use of IVIG in AOSD has been described as well in the treatment of flares and disease refractory to NSAIDs, with responses (13/15, cumulatively) seen at doses ranging from 0.4-2 g/kg/day for 2-5 days, with remission lasting for 2-53 months. Interestingly, IVIG may serve a role in the induction of remission and control of early disease prior to the use of steroids, with Vignes et al. demonstrating an absence of flares in 4/7 patients after the cessation of IVIG to the end of the study period, with three of those responders able to ultimately discontinue the use of NSAIDs. All 7 patients were relatively newly diagnosed, with an average duration of AOSD prior to the first IVIG infusion of 32.5 +/- 22 days. The results must be interpreted with caution, as the early treatment group may include the patients that will go into spontaneous remission and the efficacy of any therapeutic agent can be overestimated. Whether remission can be induced in patients diagnosed with chronic AOSD remains to be studied. Additionally, IVIG in combination with mycophenolate mofetil were used successfully in a case of severe collapsing glomerulopathy associated with AOSD.

TNF blocking agents have also been employed in uncontrolled studies. Etanercept in conjunction with MTX and corticosteroids was used successfully by Asherson et al in a single patient who had failed multiple immunosuppressives and plasmapheresis. In an open-label trial of etanercept (25mg twice-weekly, with an increase to 3 times per week at 8 weeks if no improvement was seen) in a cohort of 12 patients, addition of the soluble TNF receptor to the pre-study regimen of prednisone, MTX and NSAIDs led to a 67% improvement in the number of tender joints and a 63% improvement in the number of swollen joints at the end of the 6 month trial. Furthermore, etanercept use in a Still's disease patient with nephrotic syndrome due to renal AA amyloidosis, a rare complication of the disease, resulted in amelioration of proteinuria. Side effects associated with etanercept treatment in AOSD include injection site reactions, paradoxical disease flares, cutaneous eruption, infectious complications (sinusitis, listeriosis, skin abscesses), upper respiratory tract illness, and diarrhea. Use of infliximab, the monoclonal chimeric anti-TNFα antibody has also been reported in various open label trials to be effective in AOSD. In a study of 3 patients with chronic AOSD unresponsive to a conventional therapy of prednisone and MTX, addition of infliximab (3mg/kg at weeks 0, 2, 6, and once
every 8 weeks) led to decreases in ESR, CRP, serum ferritin, and fever and improvements in both the patient’s and physician’s global assessment by week 2 and extending to the end of the trial at week 50. Clinical improvement also allowed for a gradual decrease in prednisone dose, from 15-30 mg/day to 7-12 mg/day. In a Greek case series, four patients refractory to high doses of corticosteroids and MTX responded favorably to treatment with infliximab 3-mg/kg. All four patients went into remission soon after their first infusion and serum inflammation indices followed closely the clinical improvement. Systemic corticosteroids were quickly tapered off and long-term remission was sustained. Efficacy of infliximab in MTX+corticosteroid resistant AOSD was also reported by Huffstutter et al (2 patients), Bonilla-Hernan et al (2 patients), Caramaschi et al (1 patient), and Dilhuydy et al (1 patient). Infliximab at a dose of 5mg/kg was found to be effective in a patient with early AOSD who was steroid resistant and ineligible for MTX treatment. A European series of 8 patients (3 male, 5 female) diagnosed with AOSD, attempted to evaluate the long term outcome of patients treated with infliximab (3-5mg/kg) after having failed corticosteroids and traditional DMARDs. Seven out of eight patients experienced a positive response with rapid improvement in both clinical and serological response and five (4 in acute and 1 in chronic articular phase) went into long term remission, even after discontinuation of therapy. The responders that did not go into long term remission included a patient with intermediate disease who was switched to etanercept after experiencing an infusion reaction and a second patient with chronic articular disease who required continuous treatment with infliximab in order to control the severe arthritis. The one patient that did not respond to infliximab (and subsequently neither to etanercept nor to adalimumab) had chronic articular disease. A larger (20 patients) observational study reported the French experience with the use of TNF inhibitors in corticosteroid (and MTX)-resistant AOSD. The disease manifestation was systemic in 5 and polyarticular in 15 patients. Ten patients received only infliximab, 5 only etanercept and 5 were treated with both medications consecutively. After a mean follow up of 13±14 months, complete remission was observed in 5 patients (1 treated with etanercept and 4 treated with infliximab). Most patients (16 of 25 treatments) achieved a partial remission: 7/10 on etanercept and 9/15 on infliximab. Although the study design does not allow for definitive comparisons between the two agents (infliximab vs etanercept), there appeared to be a trend of differential efficacy of anti-TNF agents. Infliximab induced 4 complete and long lasting remissions, while etanercept produced one, albeit on a patient treated concomitantly with 80 mg of prednisolone/day and 100mg azathioprine/day. There were four treatment failures equally divided among both treatments and they all occurred in patients with childhood onset of disease, likely representing cases of systemic-onset juvenile idiopathic arthritis (or Juvenile Still’s), a condition that has been shown to be less responsive to anti-TNF therapy. The use of infliximab in AOSD has been associated with rare, albeit occasionally serious, side effects including infusion reactions, cutaneous eruptions, recurrent bronchitis & pneumonia, pneumonitis, heart failure, blurry vision, and fulminant hepatitis in a patient with concomitant hepatitis B.
IL-6 is thought to be an important pro-inflammatory cytokine in the disease pathogenesis and a promising target, especially with the development of anti-IL-6 therapies. One case report demonstrated a marked decrease in CRP, defervescence, and improvements in arthralgia in ASD refractory to methotrexate, cyclosporin A, and prednisolone, after the administration of anti-human IL-6 monoclonal antibody (MRA). 103

Most recently, IL-1 blockade has emerged as a possible new therapeutic option. First, it was reported to be effective in a refractory AOSD case, where multiple DMARDs (MTX, SSZ, CyA), IVIG, and TNF inhibitors had failed to produce sustained remission and prolonged corticosteroids administration had resulted in serious side effects. When anakinra 100 mg sc/day was added to MTX 25mg/week, moderate dose of prednisolone (20mg/day) and naproxen, the patients reported a decrease of arthritic and systemic symptoms within weeks, paralleled by a normalization of serum acute phase reactants. The patient achieved a prolonged remission on MTX+anakinra. 104 In the 2004 EULAR meeting a report by Haraoui et al described the successful treatment of three patients with refractory chronic AOSD with daily subcutaneous anakinra 100mg. Clinical improvement was seen within days of initiation of therapy and eventually allowed for a significant taper of the prednisone dose. 105 Also in this meeting, Aelion et al reported the successful outcome of daily anakinra 100mg sc in two patients with persistent AOSD. Clinical improvement was again seen in days in one patient and within a few weeks in the other. The first patient was reported to be in complete remission on anakinra alone, with normalized laboratory values. The other patient was weaned off corticosteroids and remained stable on a combined regimen of anakinra and oral methotrexate (10mg/week). 106 More recently, another study also showed efficacy of anakinra in the treatment of four AOSD patients that were refractory to treatment with corticosteroids and MTX. Interestingly, two of the four patients had been unsuccessfully treated earlier with etanercept, added on the standard regimen of MTX+corticosteroids. In all four cases, patients responded quickly to anakinra; within days there was resolution of symptoms and normalization of laboratory values (WBC count, ferritin, CRP). It is noteworthy to mention that when anakinra was withheld on two occasions, the disease relapsed within days, with reappearance of fever, arthritis and rash paralleled by elevation of laboratory markers (WBC, ferritin, CRP). Both patients responded quickly to re-institution of IL-ra. Remission was prolonged and allowed for tapering of the prednisone dose and eventual discontinuation in three out of four patients. 107 Multicenter, controlled studies are needed to validate these early, open label studies.

In Figure 2 we present, in schematic form, our recommendations for a treatment strategy taking into consideration the recent data on biologic agents.

Conflict of Interests: The authors have no conflicts of interest.
References


Figure legends

Figure 1. AOSD patients often develop a distinctive pattern of intercarpal and carpometacarpal joint space narrowing that can lead to pericapitate ankylosis. (Image reproduced with permission from www.cri-net.com)

Figure 2. Therapeutic Algorithm for AOSD
Adult Onset Still’s Disease (AOSD) Treatment

Methotrexate (MTX) + low dose glucocorticoids (±NSAIDs prn)

Add biologic therapy

Anti-IL1 Rx (Anakinra)

OR

Anti-TNF Rx (Infliximab>etanercept)

-Clinical monitoring
-Observation by objective criteria (serum ferritin, Xrays)

-2nd line agents (leflunomide, IVIG, azathioprine, thalidomide, IM gold, cyclophosphamide, cyclosporine)
- Experimental agents (anti-IL6[MRA])
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