# ADULT-ONSET STILLS DISEASE (AOSD)

**BOTTOM LINE**

Adult-onset Still's Disease (AOSD) is an inflammatory disorder characterized by a syndrome of quotidian fever, inflammatory arthritis, and evanescent rash . Additional features include pharyngitis, lymphadenopathy, leukocytosis with neutrophilia, and high ferritin (usually at least >1000ug/mL). Macrophage activation syndrome (MAS) is a life threatening complication and should be considered in patients presenting acutely ill with multiorgan failure alongside typical AOSD features (especially anemia and thrombocytopenia). Diagnosis is considered in patients presenting with cardinal AOSD features after excluding differentials in particular infection and lymphoma. Mild disease may only require NSAIDs. More persistent or severe disease require steroids and steroid sparing therapies including methotrexate, leflunomide, IL-1 or IL-6 inhibitors.

## EPIDEMIOLOGY

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| Incidence, prevalence | • Incidence: 0.16-0.62/100,000 annually<br>• Prevalence: 0.73-6.77/100,000 |
| Age | • Bimodal peak: 16-25 years > 36-46 years<br>• Onset after age 60 years rare, though reported up to 10% in some case series<br>• AOSD and systemic juvenile inflammatory arthritis (SJIA) likely exist as related disease on a "Still's disease spectrum" |
| Sex | • Slight female predominance |
| Risk | • Infectious trigger: described after viral or bacterial infections; various pathogens described<br>• Genetic risk: HLA-DR4, HLA-Bw35, or HLA-DRB1 haplotype; polymorphisms in genes encoding IL-18, and MIF |

## CLINICAL MANIFESTATIONS

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| Cardinal | • Cardinal symptoms: skin rash, fever ≥39$^0$C, Leukocytes >10,000/mm$^3$ Neutrophils >80%, Arthritis and/or arthralgia | |
| Clinical Pattern | Monocyclic | • Disease lasts weeks-months and completely resolves<br>• Systemic features common (fever, rash, serositis, hepatosplenomegaly) |
| | Polycyclic | • Disease flares with complete remission for weeks to 1-2 years between flares<br>• Subsequent flares tend to be less severe and shorter duration |
| | Chronic | • Persistently active disease; predominantly erosive inflammatory arthritis.<br>• More common if persistently high ferritin and if diagnostic delay |
| Fever | • High spiking (≥39$^0$C) quotidian or double quotidian fever (i.e.: fever spike once or twice daily). (46-100%).<br>• Onset is acute and duration lasts a few hours; ~20% may not completely defervesce between spikes | |
| Rash | • Morphology: evanescent "salmon-coloured" macular or maculopapular rash<br>• Timing: appears during fever episode, typically late afternoon or evening<br>• Distribution: trunk, extremities; can involve palms, soles, face. Some have Koebner phenomenon/dermatographism<br>• Histopathology: non-specific perivascular lymphohistiocytic infiltration and dermal edema.<br>• Immunofluorescence: May show slight C3 deposition | |
| MSK | • Mild/transient oligoarticular arthralgias that can progress to severe and erosive polyarthritis. (40-100%)<br>• Joints: knees, wrists, ankles elbows, PIPs; typically spares DIPs and shoulders<br>• Myalgias (during fever spike) | |
| Pharyngitis | • Severe nonsuppurative pharyngitis; common. Typically coincides or precedes fever/rash. (up to 90%) | |
| Lympha-denopathy | • Slightly tender cervical lymphadenopathy. (50%)<br>• Lymphadenopathy: typically symmetrical, commonly cervical (~50%). Important to consider lymphoma differential.<br>• Splenomegaly (44-80%)<br>• Biopsy: paracortical immunoblastic reactive hyperplasia with polyclonal B-cells; send for lymphoma protocol. | |
| Hepatic | • Hepatomegaly; common, with mild elevation in ALT (6-70%). Can have rare fulminant hepatitis. | |
| Cardio/ resp | • Pericarditis/pericardial effusion, myocarditis, pleural effusions, pleuritis, pulmonary infiltrates. (30-40%)<br>• Rarely reported cardiac tamponade, interstitial lung disease, pulmonary arterial hypertension, acute ARDS | |
| GI | • Abdominal pain, nausea, weight loss. Rarely reported peritonitis. | |
| Coag-ulopathy | • DIC: combination of thrombosis and cutaneous/mucosal bleeding with organ dysfunction (ex: hepatitis) (1-5%)<br>• TMA: multiple small thrombi causing multi-organ failure with hemolytic anemia, schistocytes, and low ADAMSTS13 | |

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| Rare | • Neurological (Encephalopathy, seizures, aseptic meningitis, Posterior reversible leukoencephalopathy)<br>• Renal disease (interstitial or glomerulonephritis, secondary amyloid)<br>• Ocular disease (sicca, conjunctivitis, episcleritis, uveitis) | |
| MAS | Terms | • Macrophage activation syndrome (MAS, aka reactive hemophagocytic lymphohistiocytosis [RHL]) is hemophagocytic lymphohistiocytosis (HLH) secondary to AOSD or SJIA<br>• Aggressive life-threatening immune system activation |
| | Features | • Rare but may be under-recognized; 1.7-23.5% of ASOD patients<br>• Fever is common; typical spiking fever may become unremitting fever<br>• Rash, hepatosplenomegaly, lymphadenopathy, neurological disturbance<br>• Onset at diagnosis or during disease course |
| | Investiga-tions | • Cytopenias, high ALT, Ferritin (as in ASOD); high tryclycerides<br>• Must screen for bacterial/viral infection including HIV<br>• Hemophagocytosis may be evident in bone marrow, spleen, lymph node, or liver<br>• Special tests: Soluble IL-2, NK cell function, flow cytometry for cell surface markers, sCD163, CXCL9, IgG/IgA/IgM, lymphocyte subtypes |
| | Clues | • Quotidian fever becomes persistent, hepatomegaly, neurological symptoms<br>• Cytopenias, ↑ALT, coagulation disorders, Ferritin ≥3500ug/L |

**INVESTIGATIONS**

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| CBC | • Anemia, normocytic normochromic<br>• Leukocytosis (>15,000 cells/uL), neutrophilia,<br>• Thrombocytosis, reactive<br>• Rare: pure red cell aplasia, schitocytosis and decreased ADAMSTS13 from thrombotic microangiopathy |
| ALT | • Mild ALT elevation (75%); fulminant liver failure and hepatic necrosis is reported |
| ESR, CRP | • Elevated (70-100%) |
| Ferritin | • Elevated (70%); >1000 ng/mL (35-95%), >3000 (20-60%) |
| Serology | • No associated antibodies; may have low-positive ANA and RF by chance. |

**DIAGNOSIS**

ASOD should be suspected in patient (typically younger <50 years) presenting with syndrome of quotidian spiking fever of unknown origin with concordant rash, arthritis, pharyngitis, and lymphadenopathy. Investigations may reveal anemia, neutrophilia, thrombocytosis, or elevated ALT. Ferritin is often high, >1000 ng/mL. MAS is a severe complication and should be considered if patients present with severe multi-organ illness with cytopenias and supportive hemophagocytosis on bone marrow biopsy. Consider sending for baseline chest X-ray, blood cultures, and serology for viruses such as hepatitis B/C, parvovirus B19, EBV, and HIV. CT or PET scanning may be important to further consider malignancy differential. Tissue biopsy is typically not required unless to consider a differential (ex: lymph node biopsy for ?lymphoma, skin biopsy for ?Sweet syndrome or ?cutaneous lymphoma).

**DIFFERENTIAL DIAGNOSIS**

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| Infectious | • Acute viral: hepatitis B and C, Parvovirus-B19, HIV<br>• Bacterial: Streptococcal infection, sepsis, endocarditis<br>• Parasitic: malaria, toxoplasmosis, and trypanosomiasis |
| Auto-immune | • RA, SLE, post-strep reactive arthritis, idiopathic inflammatory myopathies, ANCA vasculitis, polyarteritis nodosa<br>• *ASOD does not present with Raynaud's, is seronegative, often has high ferritin* |
| Auto-inflammatory | • HIDS, FMF, TRAPS, CAPS, Schnitzler's syndrome<br>• Neutrophilic dermatoses and Sweet's syndrome |
| Malignancy | • Lymphoma; lymph node biopsy can help distinguish mono from polyclonal B cells<br>• Multicentric Castleman disease<br>• Myeloproliferative disorders<br>• Solid cancers or paraneoplastic syndromes |
| Drugs | • DRESS (drug reaction with eosinophilia and systemic symptoms) |
| Other | • Sarcoidosis, Kikuchi, primary HLH |

## CLASSIFICATION CRITERIA

AOSD is a ***clinical diagnosis***. Classification criteria are not meant as diagnostic criteria to diagnose disease in a single specific patient. Classification criteria are a standardized way of recruiting a well-defined homogenous population of patients in research studies in order to ensure comparability across studies of a heterogenous disease.

**YAMAGUCHI CLASSIFICATION CRITERIA**: Sensitivity: 96.2%, Specificity: 92.1%

| **Major Criteria** | **Minor Criteria** |
|---|---|
| • Fever ≥39°C for ≥1 week<br>• Arthralgias or arthritis for ≥2 weeks<br>• Nonpruritic macular/maculopapular salmon-colored rash usually over the trunk or extremities during febrile episodes<br>• Leukocytosis (≥10,000/uL), with ≥80% neutrophilia | • Sore throat<br>• Lymphadenopathy<br>• Hepatomegaly or splenomegaly<br>• Abnormal liver tests, particularly ALT, AST, LDH<br>• Negative ANA and RF |

- Exclusion criteria:
  1. Infections (especially, sepsis and infectious mononucleosis)
  2. Malignancy (mainly lymphoma)
  3. Other rheumatic disorders (mainly polyarteritis nodosa and rheumatoid vas□culitis with extraarticular features)
- ***For classification, patients must meet 5 or more criteria, 2 of which must be major criteria***

**FAUTREL CLASSIFICATION CRITERIA:** Sensitivity: 80.6%, Specificity: 98.5

| **Major criteria** | **Minor criteria** |
|---|---|
| 1. Spiking fever ≥39°C<br>2. Arthralgia<br>3. Transient skin erythema<br>4. Pharyngitis<br>5. Polymorphonuclear cells ≥80%<br>6. Glycosylated ferritin ≥20% | 1. Maculopapular rash<br>2. Leukocytes ≥10,000/$mm^3$ |

- ***For classification, patients must meet 4 or more major criteria OR 3 major criteria + 2 minor criteria***

## TREATMENT

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| Approach | • Screen for MAS with clinical assessment (see above)<br>• Stratify to mild, moderate, or severe disease<br>  • Ex mild-moderate: monocyclic, nondisabling fever, rash, mild arthritis, no MAS<br>  • Ex mod-severe: polycyclic, significant serositis/polyarthritis, multi-organ involvement |
| Mild-moderate | • NSAIDs<br>• If ongoing symptoms: methotrexate |
| Moderate-severe | • Combination steroids combined with a targeted advanced DMARD therapy<br>• Prednisone 20-60mg/day, tapering course<br>  • N.B.: May worsen infection or partially treat malignancy in diagnostically uncertain cases<br>• Canakinumab 4mg/kg (max 300mg) SC q4 weeks<br>• Anakinra 100-200mg SC daily/BID<br>• Rilonacept 100-320mg load, then 100-320mg/week<br>• Tocilizumab 8mg/kg IV q4 weeks or 162mg SC weekly<br>• Others described: TNF inhibitors, JAK inhibitors, abatacept, rituximab, IVIG, IL-18 inhibition |
| MAS | • High dose steroids (ex: pulse methylprednisolone 0.5-1.0g IV/day x 3 followed by prednisone 1mg/kg/day)<br>• Consider early introduction of anti-IL1 or anti-IL6 therapy<br>• If refractory, consider etoposide or ciclosporin |
| Other | • DIC: platelet transfusion, fresh frozen plasma, fibrinogen, high-dose steroids, ?IL-1 or IL-6i, IVIG, or ciclosporin<br>• TMA: high-dose steroids and plasma exchange ± haemodialysis; ?IL-1 or IL-6i, IVIG, or ciclosporin<br>• DIC and TMA are medical emergencies; often requires supportive care in ICU |

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