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Stéphane Mitrovic, Bruno Fautrel

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Stéphane Mitrovic[1,2], MD, MSc, Bruno FAUTREL[1,3,4], MD, PhD

Affiliations:
[1]Department of Rheumatology, Pitié-Salpêtrière Hospital, AP-HP, Paris France
[2]Department of Internal Medicine, Institut Mutualiste Montsouris, Paris, France
[3]Sorbonne Université, Faculté de Médecine et Institut Pierre Louis d'Epidémiologie et Santé publique, GRC 08, Paris France
[4]CRI-IMIDIATE, a FCRIN Clinical Research Network network

Corresponding author for submission: Dr Stéphane Mitrovic, Hôpital Pitié-Salpétrière, Service de Rhumatologie, 47-83, boulevard de l'Hôpital - 75013 Paris France. Mail: stephane.mitrovic@yahoo.fr
http://orcid.org/0000-0001-5244-7881
Tel: +33 1 42 17 76 20 Fax: +33 1 42 17 79 59

Corresponding author: Pr Bruno FAUTREL, Hôpital Pitié-Salpétrière, Service de Rhumatologie, 47-83, boulevard de l'Hôpital - 75013 Paris France. Mail: bruno.fautrel@aphp.fr
https://orcid.org/0000-0001-8845-4274
Tel: +33 1 42 17 76 20 Fax: +33 1 42 17 79 55

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Abstract (180 words)

Introduction: Adult-onset Still's disease (AOSD) is a rare systemic auto-inflammatory disorder whose management and treatment have considerably progressed over the past decade. Despite wide use of interleukin (IL)-1 or IL-6 inhibitors, serious complications remain possible.

Areas covered: A comprehensive literature search in MEDLINE via Pubmed was performed to review AOSD severe and sometimes life-threatening complications: reactive hemophagocytic lymphohystiocytosis, coagulation disorders, fulminant hepatitis, cardiac or pulmonary complications and amyloid A amyloidosis.

Expert commentary:
Early recognition and prompt management is essential to significantly decrease morbi-mortality. The key question is to determine whether the complication is related to the disease itself or related to or favored by (e.g., infection) the ongoing treatment.
For all severe AOSD-related complications, high-dose corticosteroids and supportive measures remain the first-line treatment. In case of inadequate response, combination with IL-1 or IL-6 blockers is justified. Cyclosporine A and etoposide remain of interest, especially in case of reactive hemophagocytic lymphohysitocytosis. Plasma exchange may be useful in case of thrombotic microangiopathy. In the near future, new biologic or non-biologic drugs targeting IL-18 or other cytokines or kinases could be of help.

Keywords: adult-onset Still's disease; reactive hemophagocytic lymphohistiocytosis; disseminated intravascular coagulation; thrombotic microangioapathy; hepatitis; pericarditis; pulmonary arterial hypertension; biological agents; interleukin-1 inhibitors; interleukin-6 inhibitor

1. Introduction

Adult-onset Still's disease (AOSD) is a rare systemic auto-inflammatory disorder (SAID) that was first described in the early 1970s (1), about a century after the description of its childhood counterpart, the systemic form of juvenile inflammatory arthritis (sJIA). In most patients, AOSD is characterized by four cardinal symptoms: spiking fever, an evanescent salmon-pink maculopapular rash, arthralgia or arthritis and white blood cell count $\geq$10,000/mm^3, mainly neutrophilic polymorphonuclear cells (2). Other features are sore throat or pharyngitis, myalgia, lymphadenopathy, hepatosplenomegaly, serositis, multivisceral involvement and other hematologic abnormalities (2,3).

The mechanisms underlying AOSD are not completely understood (2–5). The levels of most proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-18, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, have been found elevated during the disease. This "cytokine storm" is thought to play a pivotal role, along with an excessive activation of innate immunity, which might be triggered by danger signals (viral, bacterial or other pathogenic organisms), on a susceptible genetic background (3,5) **(Figure 1)**.

AOSD is heterogeneous in terms of clinical presentation, evolution and severity, which suggests different pathogenic mechanisms (2,3). Different phenotypes have been suggested, ranging from very explosive systemic forms to more chronic articular subtypes (4–6) **(Figure 2)**. The prognosis is triple:

Vital: although the disease course is often favorable, especially in Western countries, where the mortality rate is low (3,7,8), AOSD may present several rare manifestations that can limit life expectancy (3,9,10). A recent retrospective work identified 26 reported fatalities among 932 patients with AOSD in 18 cohorts published over 25 years, including at least 14 patients (mortality 2.75%, range 0–9.8%) (10). Hence, physicians should know about these manifestations, since early recognition and prompt management in a monitored setting can significantly decrease morbidity and mortality (11). Reactive hemophagocytic lymphohstiocytosis (RHL) is the most frequent (3,12). Altogether, these complications of systemic AOSD concern about one third of AOSD patients seen in a tertiary center of internal medicine (9).

Functional: related to joint damage in chronic articular AOSD, which affects approximately one-third of patients (2).

Iatrogenic: although the AOSD prognosis has been greatly improved by biological therapies (13), the current treatments of AOSD are a source of many complications (2,3) **(Table**

1). They include well-known corticosteroid-induced complications — infections favored by immunosuppression, which can be bacterial (pyogenic or tuberculous), parasitic (pneumocystosis), or viral reactivations (mainly Eipstein Barr virus [EBV] or cytomegalovirus [CMV]) and may play the role of triggering factors of systemic complications such as RHL (11,12). Finally, biological agents can be responsible for various intensity hypersensitivity symptoms, ranging from local reactions to site injections to severe systemic reactions, such as Drug Rash with Eosinophilia Symptoms (DRESS) syndrome, which can sometimes represent a differential diagnosis issue with other AOSD complications.

This article reviews the main serious complications of AOSD and their management and offers new therapeutic perspectives and research agendas.

2. Prognostic factors

A prognosis is difficult to establish during the initial presentation of the disease. The identified prognostic criteria are heterogeneous and are based on retrospective studies (3,9). These unfavorable prognostic factors that have been suggested from the analysis of large patient cohorts should make clinicians aware of a possible negative evolution, because such cases are more prone to become refractory to treatment over the course of disease. They include rash, polyarthtitis, root joint arthritis (hips and shoulders), pleuritis, interstitial pneumonia, elevated ferritin levels, and failure of fever to subside after 3 days of systemic corticosteroid treatment (9,11,14,15). In 1991, Pouchot et al. described 12 items comprising the main signs and symptoms of disease that may reflect its activity (8). A retrospective cohort study suggested that Pouchot's "systemic score" could predict a poor outcome in AOSD: a score ≥ 7 and the presence of any complications (RHL, kidney failure or myocarditis) at diagnosis are associated with mortality (16). However, this score does not predict the occurrence of a complication, which may occur at any step of the disease and its management.

3. Serious complications

The life prognosis is dominated by the severity of the following visceral involvements, in isolation or combination, which can lead ultimately to systemic inflammatory response syndrome (SIRS) and multi-organ failure (17). Importantly, exacerbation of these serious symptoms has been reported within the first days of initiating treatment, especially biologic agents (2,11,18). This situation necessitates a close and very careful monitoring of such patients at the start of treatment.

3.1 Reactive hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is an immune-mediated syndrome that has previously been given several names, including macrophage activation syndrome, and is clinically characterized by fever, hepatosplenomegaly, and cytopenia, and the finding of activated macrophages in hematopoietic organs (12) **(Table 2)**. It is characterized by an uncontrollable activation of the reticulo-endothelial system within the bone marrow, reticuloendothelial system and central nervous system, with subsequent phagocytosis of hematopoetic cells by tissue macrophages (histiocytes) (11). HLH is not specific to AOSD. Indeed, it has traditionally been classified according to the cause of disease and is divided into primary (genetic, mainly in children) and secondary (reactive) HLH, which are subclassified as infectious (viral, bacterial, parasites and fungi), drug-induced, autoimmune or autoinflammatory, or neoplasia-related **(supplementary Table 1)**, even though nearly one third of reported cases in adults have more than one underlying cause (12). Although reactive HLH (RHL) is, overall, a very rare condition, it is not uncommon in AOSD, with an incidence of 12% to 14% in several recent series (9,12,18–22) but is probably more prevalent in patients with persistent or refractory forms of the disease (5,20–22). Of note, this rate is higher than in other rheumatic diseases: systemic lupus erythematosus (SLE) is the second systemic disease that is well associated with RHL, but its prevalence is much lower in this disease (4%) (12). RHL is one of the most-feared life-threatening complications of AOSD (2,3,11), with a reported mortality rate ranging from 10% to 20% (11,12).

Strikingly, RHL and AOSD share several common features, including clinical and biological features, and very similar pathophysiological mechanisms have been described (5). In both conditions, a defect in granule-mediated cytotoxicity, in perforin and FAS systems in natural killer cells has been reported, leading to enhanced antigen presentation and repeated IFN-γ–dependent stimulation, and thus uncontrolled activation of macrophages, histiocytes and T cells as well as "cytokine storm" production **(Figure 1)**. This latter, with a potential predominant role of IL-18, could be responsible for the development of the main clinical and laboratory features of both conditions and contribute to tissue damage and progressive systemic failure (5,12). Hence, most authors suggest that RHL and AOSD could share the same disease spectrum, with AOSD representing the milder form (5). It is not unusual for a patient to simultaneously have both diagnoses, and less severe or "subclinical" cases of RHL may not be

diagnosed if they respond to immunosuppressive treatments given for a presumed flare of AOSD (11,23,24). Importantly, RHL has been described in patients with AOSD under IL-1 and IL-6 inhibitors (25–27). Whether this complication is directly imputable to the introduction of those drugs, which might induce an imbalance within the cytokine storm, with an excess of IL-18 (28–30), or just reflects a more active disease is still controversial (31). Indeed, RHL is a frequent complication of AOSD, and many patients receive a combination of treatments, so formally implicating biologics is difficult, especially because these latter agents were usually prescribed for an underlying refractory AOSD: RHL might have been only the evolution of an uncontrolled disease. A recent study showed no increased risk of RHL in patients with sJIA receiving tocilizumab as compared with control patients not treated with tocilizumab (32). Finally, the immunodeficiency state induced by AOSD treatments may lead to reactivation of latent viruses or an increased vulnerability to viral or bacterial infections (2,33). These latter manifestations may act as triggers that can exacerbate the already abnormal immune system activation.

Although AOSD and RHL share some similarities, they have some important differences **(Table 2)**. High fever, hepatomegaly and splenomegaly are not specific, although fever is described as persistent with hemophagocytosis (11,12). Laboratory findings of RHL include at least one cytopenia, and often bi- or pancytopenia (these cytopenias are key laboratory markers, and contrast with the hyperleukocytosis and thrombocytosis in AOSD), high serum levels of ferritin (higher than previously) and low glycosylated ferritin ≤ 20% (2), hypertriglyceridemia, and elevated liver enzyme levels, while paradoxically demonstrating normal erythrocyte sedimentation rate (ESR) (or normalization of a previously elevated ESR) (11,12). Hypofibrinogenemia is one of the most important clues for the diagnosis of RHL because patients usually have fibrinogen levels due to their underlying inflammatory disease (11,12). Increased fibrinolysis is most probably due to the uncontrolled activation of macrophages and plasminogen overproduction (11) and to liver dysfunction (12). Almost 60% of patients have coagulation disorders, and hypofibrinogenaemia (<441 mmol/L) and increased D-dimer levels (>54.76 nmol/L) are reported in 50% of adult HLH cases (12). Associated disseminated intravascular coagulation is reported in 40% of cases in some series and associated with high mortality rates, especially in patients with severe thrombocytopenia (12). Hemophagocytosis (a process involving phagocytosis of hematopoietic cells by activated macrophages) is the key marker of HLH. Bone-marrow aspiration is considered the gold standard for revealing hemophagocytosis, with positive aspirates identified in 84% of reported

adult cases (12). Bone-marrow biopsy is less effective (64% positivity) but might be useful to rule out underlying hematological neoplasia. Isolated organ-confined hemophagocytosis also occurs in lymph nodes, lung, liver, spleen, and skin (12,34–36). However, hemophagocytosis might be physiologically enhanced in some situations (blood transfusions, infections, autoimmune diseases, and other causes of bone-marrow failure) and might be absent in the initial phases of HLH or during dyserythropoiesis. Hence, revealing hemophagocytosis by bone-marrow aspiration or organ biopsy is not mandatory for a diagnosis of RHL if the clinical picture is typical.

Therefore, diagnosis of HLH relies on the coexistence of the above-cited clinical, laboratory, and histopathological findings, although none are pathognomonic alone (12). Many diagnostic criteria sets for RHL have been proposed for pediatric populations (19,37–41). They are widely used in adults, even though their sensitivity and specificity remain untested in this population (12), and they have substantial limitations: the weight of each criterion included in these scoring systems is unknown, the proposed cutoff values were empirically defined, and some of the proposed criteria (e.g., natural killer cell activity, soluble IL-2 receptor level) cannot be measured in routine practice (42). Therefore, recently, a set of 9 weighted criteria, called the HScore, was developed and validated for the diagnosis of RHL in adults (42,43). This score can be used to estimate an individual's risk of RHL **(Table 3)**.

The management of RHL requires a triple simultaneous approach (12):

- First, support measures are essential because of frequent life-threatening presentation. Supportive intensive-care guidelines should be similar to standard practice for patients with similar life-threatening diseases such as SIRS or multiple organ dysfunction syndrome; however, specific measures should be added. With hyperinflammation, coagulopathy, and thrombocytopenia, patients with HLH are at high risk of spontaneous bleeding (12); platelet transfusions, fresh frozen plasma and activated factor VII, or both, might be needed for life-threatening acute bleeding (44–46). Growth factors such as granulocyte colony stimulating factor might be used for severe neutropenia, although isolated reports have associated their administration with exacerbation of HLH (47,48).
- Second, the search for and elimination of an additional trigger (mainly infections: EBV, CMV, **supplementary table 1**) is crucial to remove potential stimuli that could have exacerbated the already abnormal immune system activation.
- Third, suppression of the inflammatory response by immunosuppressive drugs is necessary.

No randomized controlled trial has investigated potential specific treatments for RHL. Many studies of sJIA or RHL secondary to other pathologies than AOSD have been conducted but were uncontrolled and retrospective, with few patients included. Likewise, most studies have investigated drugs at different doses and in various combinations, and treatment decisions continue to be based on clinical experience, empiric data and expert opinion (12).

In our opinion, high-dose steroids remain the first-line treatment. With insufficient response, combination with IL-1 or IL-6 inhibitors should be the second step, as suggested by recent progresses in pathophysiology knowledge, especially about the central role of inflammasome activation and the cytokine storm **(Figure 1)**. Several cases of sJIA have been successfully treated with anakinra, an IL-1 inhibitor, with globally good tolerance, either alone or with high-dose steroid therapy (49–53). Recent data from a comprehensive literature review (25), a meta-analysis (54) and an Italian cohort of 140 AOSD patients (55) suggest that anakinra, but also canakinumab and rilonacept, are globally well tolerated, although more data are needed. Tocilizumab, a humanized anti-IL6 receptor monoclonal antibody, was also reported to be efficacious in RHL complicating AOSD (56–60). However, one should keep in mind that tocilizumab may mask the appearance of RHL during the course of AOSD (31,61). Indeed, the appearance of leukopenia and/or elevated liver enzymes can be mistaken for a side effect of tocilizumab, and a decrease in ESR and lower ferritin levels may be erroneously interpreted as response to treatment but in reality may signify the beginning of RHL.

In case of insufficient response, switching or combining with etoposide or cyclosporine A may be an effective option (11).

Other drugs have been proposed, with hazardous efficacy but frequent and often serious toxicity: methotrexate, mycofenolate mofetil, intravenous immunoglobulins (IVIG), and plasma exchange. Data from the literature concerning TNF inhibitors are scarce and contradictory, and for most authors, have no place in the treatment of RHL, because they might be ineffective or even harmful (11). There are several cases of macrophage activation syndrome following the use of etanercept for AOSD (11,62).

3.2 Blood coagulation disorders

Disseminated intravascular coagulation (DIC) and thrombotic microangiopathy (TMA) are life-threatening hemostasis disorders sometimes observed in AOSD. They are classical

complications of cytolytic hepatitis or RHL, although they can occur apart from them. They can be responsible for severe multi-organ dysfunction and are thus associated with significant morbidity and mortality.

3.2.1 Disseminated intravascular coagulation

DIC involves abnormal, excessive generation of thrombin and fibrin in the circulating blood via uninhibited activation of the coagulation cascade and the fibrinolytic pathway. Therefore, it may cause both bleeding and thromboses (63).

Recently, a Japanese epidemiological study estimated an incidence of 4.9% of DIC during the course of AOSD (64), but earlier studies reported an incidence of 1% to 3% (9,14,65). This increase might be due to the more sensitive diagnostic criteria used by Sakata et al., who also reported a 16% mortality rate in their series (64). DIC can often occur in addition to RHL or acute hepatitis (2,11,66) and lead to multi-organ failure: acute respiratory distress syndrome (ARDS) (67,68), pleural effusion (69), myocarditis (53,70), pulmonary embolism, gastrointestinal bleeding, and central nervous system involvement (71) have been reported. Severe, rapidly evolving DIC is diagnosed by demonstrating thrombocytopenia, elevated prothrombin time and activated thromboplastin time, increased levels of plasma D-dimer (or serum fibrin degradation products), and decreasing plasma fibrinogen level (63) **(Table 4)**.

DIC is a medical emergency, and the patient should be closely monitored in an intensive care unit.

- Supportive measures include replacement of platelets, coagulation factors (in fresh frozen plasma), and fibrinogen (in cryoprecipitate) to control severe bleeding (63). Heparin is used as therapy (or prophylaxis) in patients with slowly evolving DIC who have (or are at risk of) venous thromboembolism (63).
- Specific treatments should be decided in multidisciplinary rounds and include high-dose corticosteroids and immunomodulators. High-dose intravenous methylprednisolone pulse therapy, usually followed by high-dose oral corticosteroid therapy, remains the first-line therapy (15). Corticosteroids should be combined with IL-1 or IL-6 inhibitors (72,73) or cyclosporine (74). As for RHL and owing to recent improved knowledge of the AOSD pathophysiology described previously, many authors suggest that IL-1 inhibitors should be used first, and several reports have shown that anakinra was efficacious in that indication (72,75,76) and in cases refractory to cyclosporine A (53). IL-6 inhibition was also found

effective in a patient with AOSD complicated by DIC that was refractory to glucocorticoid and cyclosporine: tocilizumab led to a rapid response, symptomatic improvement and corticosteroid sparing (73).

4.2.3 Thrombotic microangiopathy

TMA, also called thrombotic thrombocytopenic purpura (TTP) or Moschcowitz syndrome, is an acute, fulminant disorder characterized by thrombocytopenia and microangiopathic (i.e., mechanical) hemolytic anemia and is invariably associated with substantial morbidity and mortality (11,77,78). Loose strands of platelets and fibrin are deposited in multiple small vessels and damage passing platelets and red blood cells, thus causing significant thrombocytopenia and anemia. Platelets are also consumed within multiple small thrombi. The brain, heart, gastrointestinal tract and kidneys are particularly likely to be affected (77). A predisposing factor in many patients is congenital or acquired deficiency of the plasma enzyme ADAMTS13, which cleaves von Willebrand factor (VWF) and thus eliminates abnormally large VWF multimers that can cause platelet thrombi (77).

The diagnosis should be made as early as possible, because lack of treatment results in a mortality rate of about 90%, but even with treatment, the mortality rate can be as high as 20% (11). An early sign that should raise the index of suspicion for TMA is development of acute vision impairment, because blurred vision related to Purtscher-like retinopathy often precedes the appearance of TMA (78). Other manifestations of ischemia develop with varying severity in multiple organs: weakness, confusion, seizures or coma, abdominal pain, nausea, vomiting, diarrhea, cutaneous gangrene and arrhythmias caused by myocardial damage (78). Diagnosis requires demonstrating characteristic laboratory test abnormalities, thrombocytopenia and mechanical hemolytic anemia, evidenced by schistocytes — or schizocytes — on the hemogram, that cannot be explained otherwise (i.e., excluding other causes, mainly with a negative direct antiglobulin test and negative HIV serology) **(Table 4)**. Testing for ADAMTS13 should be done at diagnosis, because its activity and inhibition have been found to be important predictors of disease outcome and of risk of relapse in overall TMA (79).

The association of AOSD with TMA is rare, and to our knowledge, fewer than 30 cases have been reported in the English literature (78,80–83). In most cases, TMA occurred during an AOSD flare, and AOSD treatment was associated with TMA resolution, which argues for a

pathophysiological link between AOSD and TMA (78). Multiple mechanisms may be involved in the TMA pathogenesis (decrease of ADAMTS-13 activity, complement regulatory protein dysfunction, or direct endothelial toxicity due to infections by Shiga toxin-producing microorganisms) but remain unclear in AOSD-associated TMA. Decreased ADAMTS-13 activity related to autoantibodies has been reported during AOSD (84,85), and the antiangiogenic and inhibitory effect of high plasmatic levels of IL-18 on vascular endothelial growth factor has been hypothesized (78). TMA seems more common in African Americans than other races and ethnicities (85).

- Supportive treatment in an intensive care unit is central, and the gold standard remains the combination of plasma exchange and corticosteroids because of the efficacy in randomized controlled trials of overall thrombotic thrombocytopenic purpura (11). Additional options could be considered in refractory or relapsing cases, after a decision of multidisciplinary rounds: IVIG, cyclophosphamide, azathioprine, cyclosporine A, rituximab (11,78). The efficacy of aspirin and vincristine is uncertain because most reports are retrospective and associated with plasma exchange. Hemodialysis is often necessary, and splenectomy might be proposed as a last resort.
- AOSD treatment comes afterward. Reports of AOSD-related TMA treated with biologics are rare. El Karaoui et al. reported the efficacy of an IL-1 inhibitor (anakinra) in treating an AOSD-related TMA resistant to plasma exchange, hemodialysis and corticosteroids (78), and Sumida et al. described a case of multi-drug resistance successfully treated with an IL-6 inhibitor (tocilizumab) (80).

3.3 Fulminant hepatitis

Liver abnormalities are frequent, mainly a mild to moderate increase in aminotransferase activity, which occurs in 43% to 76% of patients; hepatomegaly has been found in 45% of patients (3). However, cases of fulminant and fatal hepatitis have been reported (86,87), so hepatic impairment is one of the most dangerous life-threatening complications of AOSD that should be known and always screened by the physician.

The pathophysiology of liver involvement is not known. Cytokine production and sustained macrophage activation have been implicated to play a role in AOSD-related cytolytic hepatitis (3,5). Several cases of autoimmune hepatitis complicating AOSD have been reported

(88–90). Liver biopsy, if performed, reveals non-specific portal infiltrates of lymphocytes, plasma cells and polymorphonuclear cells (2). Hepatocytic lesions or massive necrosis has been described in fulminant hepatitis with rapidly progressive hepatic insufficiency (2).

Cytolytic hepatitis with hepatic failure might be a spontaneous complication of the disease, but some authors also mentioned that aspirin, non-steroidal anti-inflammatory drugs or methotrexate might also contribute to liver damage in AOSD (2,11). Thus, clinicians should closely monitor liver function from the onset of the disease and particularly after prescription of potentially hepatotoxic drugs. Self-medication should be avoided.

Patients with acute hepatitis can present no symptoms (incidental discovery on monitoring liver blood tests) or a protean clinical picture that might associate one or more of the following signs or symptoms: right abdominal pain, hepatomegaly, loss of appetite, jaundice, digestive disorders, hemorrhagic syndrome or encephalopathy (11).

Once acute hepatitis is diagnosed, the physician should keep in mind that this is a medical emergency:

- Severity should be assessed by prothrombin time and liver function tests, and a triggering factor such as RHL, DIC and/or TMA should always be sought and treated simultaneously (2).
- A differential diagnosis, such as viral hepatitis (which may trigger AOSD (91) or be reactivated by immunosuppressive treatments) or DRESS syndrome (92), should be ruled out.
- All potentially hepatotoxic drugs (acetaminophen in particular) should be stopped.
- Patients with acute hepatic failure should ideally receive care in a specialized intensive care unit and provided supportive treatment, along with high-dose corticosteroids, potentially combined with immunosuppressive or immunomodulatory treatment. Cyclosporine (93,94), anakinra (95), and tocilizumab (96) have been found efficacious. However, tocilizumab-induced hepatic injury has also been reported (97). Liver transplantation might be necessary in a few exceptional cases (86,87).

3.4 Cardiac complications

Each cardiac complication requires a close monitoring and treatment of the underlying

AOSD.

3.4.1 Pericarditis and cardiac tamponade

Pericarditis is commonly described (16%) in most published series and is sometimes serious, with potential evolution toward tamponade (3). As in other SAIDs and sJIA, recurrent pericarditis is possible (98).

- High-dose corticosteroids are usually efficacious, but relapse with treatment tapering is common (2,3,99,100). Thus, many authors suggest systematically combining high-dose corticosteroids with one or several immunosuppressors (mainly cyclosporine A). However, the presence of a serositis (pleuritis or pericarditis) might be a red flag in AOSD because it would be associated with a disease course more resistant to conventional therapy with corticosteroids and immunosuppressive agents (101). Hence, the current trend would be to more rapidly use a biologic in those patients. Treatment with anakinra and tocilizumab has been successful (101,102). However, anti-TNF agents do not seem efficacious in this indication, although isolated reports of favorable evolution under these therapies have been described (101).

3.4.2 Myocarditis

Myocarditis is a more rarely reported complication. The exact prevalence is difficult to define, but in a retrospective series, Gerfaud-Valentin et al. reported 4 cases of myocarditis in 57 patients, estimating a prevalence of 7% in that series (103). From a comprehensive literature review, the authors collected 20 additional cases of myocarditis-complicated AOSD and compared the characteristics of those 20 patients with those of AOSD patients without myocarditis. Myocarditis occurred early (during the first year of the disease course in 80% of cases) and was present at AOSD onset in 54% of cases. Patients with myocarditis-complicated AOSD were younger (mean age at myocarditis onset 29 years [range, 16-57]) and more frequently male (75%). Pericarditis was often associated. Although potentially life-threatening, myocarditis during AOSD seems to have a good prognosis (only one death occurred in the previous series), and responds positively to steroids and other inflammatory drugs.

- In the Gerfaud-Valentin et al. series, steroids alone were effective in 50% of patients with myocarditis. IVIG, methotrexate, and TNF-α blockers were also prescribed and often found effective, as was anakinra. Cases associated with DIC (104) or RHL have been reported, with good response to anakinra in the latter (53).

3.4.3 Endocarditis

Exceptional cases of endocarditis complicating the AOSD course have been reported (105,106).

3.4 Pulmonary arterial hypertension

Pulmonary hypertension (PH) is a severe, rare lung disease characterized by high blood pressure in the pulmonary arteries, which can lead to potential right heart failure. According to the World Health Organization (WHO), PH is defined by a mean pulmonary artery pressure ≥ 25 mmHg at rest, measured during right heart catheterization (107,108) **(Table 5)**. The WHO clinical classification of PH is intended to categorize multiple clinical conditions into five groups according to their similar clinical presentation, pathological findings, hemodynamic characteristics and treatment strategies (108) **(Table 5 and Supplementary Table 2)**. The term pulmonary arterial hypertension (PAH) refers to a subpopulation of patients with PH characterized hemodynamically by the presence of pre-capillary PH including an end-expiratory pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 3 Wood Units. It is highly associated with connective tissue disease (CTD), mainly systemic sclerosis and systemic lupus erythematosus (109). In contrast, post-capillary PH is defined by a PAWP >15 mm Hg and is mainly found in left-heart diseases.

PAH is a very rare complication of AOSD, but its prevalence is probably under-estimated because only symptomatic case reports have been documented (11). To our knowledge, 15 cases have been reported (110–123). Age of onset ranged from 18 to 41 years old. A female predominance was reported (14 females to 1 male). Onset from PAH ranged from 0 to 108 months after AOSD diagnosis, with a median of 24 months. PAH may be a life-threatening complication, because death was reported in about 40% of these cases. However, authors may have preferentially published fatal cases, therefore introducing a bias in the prognosis (113). The key symptom is dyspnea, which is often progressive, but more acute onset has been reported (112). Fatigue, dizziness, syncope and chest pain are also possible. Ultimately, clinical signs of right heart failure and syncope may appear and are predictors of the poorest outcome (107,108). ARDS has been described (116). The electrocardiogram might show signs of right atrium hypertrophy. Echocardiography is useful for estimating left ventricle ejection fraction (differential diagnosis), potential enlargement of the right ventricle and atrium, searching for an associated pericardial effusion. Furthermore, PH will be highly suspected with

elevated systolic pulmonary artery pressure (SPAP) > 35 mmHg on the echocardiogram. However, formal diagnosis of PH is hemodynamic and requires right heart catheterization (107,108) **(Table 5)**. High-resolution CT is helpful for etiologic and differential diagnosis, especially searching for thromboembolic disease and interstitial involvement (116). Although diffusion capacity can be normal in PAH, most patients have decreased diffusing capacity of the lungs for carbon monoxide (DLCO). An abnormal low DLCO, defined as <45% of predicted, is associated with poor outcome (108). Importantly, associated RHL should always be searched (117).

The exact pathophysiology of PAH during AOSD remains unknown. However, it is now widely accepted that altered immune mechanisms play a significant role in idiopathic PAH (iPAH) and CTD-associated PAH (CTD-PAH), by recruiting inflammatory cells, remodeling the pulmonary vasculature, and promoting autoimmune responses (109). Furthermore, levels of IL-1β, IL-6, IL-18 and TNF-α (i.e., the usual suspects participating in the AOSD "cytokine storm") are also increased in iPAH and CTD-PAH. Pulmonary microangiopathy, especially with TMA, could also participate in the pathogenesis of PAH with AOSD, as well as veno-occlusive disease and formation of microthrombi (113,116,120). Further studies are needed to properly characterize the pathogenesis in order to clarify PAH during the AOSD course in the PH WHO clinical classification system. Similarities with iPAH and CTD-PAH could lead to classification of AOSD PAH as group 1, although the association of PH with interstitial pneumonia during AOSD has been reported, so determining the appropriate classification (group 1 or 3) is challenging (117).

Early diagnosis and initiation of a disease-specific treatment algorithm is essential, because it might improve survival in these patients (11).

- The patients should be closely monitored and referred to a PH reference centre and multidisciplinary rounds to define the appropriate therapeutic strategy (108). This strategy should combine vasodilator and immunosuppressive therapy.
- Besides calcium channel blockers, endothelin receptor antagonists, phosphodiesterase-5 inhibitors (and other guanylate cyclase stimulators), and prostacyclin analogues are advanced vasodilator therapies that have been found to improve pulmonary hemodynamics and functional status in patients with iPAH and CTD-PAH (107,108).

- High-dose steroids associated with various immunomodulating agents — methotrexate, azathioprine, cyclophosphamide, cyclosporine, and rituximab — have been found efficacious (116). Recent data on the central role of IL-1 and IL-6 led to the use of specific blocking agents. Anakinra was efficacious (in combination with vasodilators and corticosteroids, and either azathioprine or cyclosporine) in two case reports (one case also had RHL) (110,117). Failure was reported in one patient (121), and 3 patients (one died) showed worsening after its introduction (114,118,123). However, with the critical and unstable nature of this complication, drawing robust conclusions about the specific anakinra role in these unfavorable evolutions is difficult. Only one case of PAH improvement after tocilizumab has been reported (114). Cyclosporine combined with sildenafil resulted in clinical and hemodynamic improvement with long-term survival 15 years after an initial presentation of AOSD (121).

3.5 Pulmonary complications

3.5.1 Pleuritis

Pleuritis is the most frequent lung involvement; it was mentioned in 10% to 50% of the main retrospective AOSD series (3).

3.5.2 Interstitial lung disease

The number of cases reported in the literature of interstitial lung disease (ILD)-associated AOSD is small, and to our knowledge, only about 30 cases have been reported in the English literature. Recently, Gerfaud-Valentin et al. reported 3 cases out of 57 in a retrospective cohort and then reviewed all available literature cases, estimating that a specific ILD may occur in about 5% of AOSD cases (124). ILD in AOSD can be divided into two major categories: one with ARDS, which occurs in 40% of patients, and another without ARDS (60%).

In the Gerfaud-Valentin et al. study, ARDS occurred only in the systemic pattern of the disease and was an early complication of AOSD, because it mainly occurred within the first year after diagnosis (124). It was severe in most cases, and the complications associated with AOSD were frequent (67% experienced at least one complication, mainly SIRS, multiple organ failure and DIC). Finally, the occurrence of ARDS should suggest an associated RHL, because it was responsible for all AOSD+ILD-associated deaths in this study.

Non-ARDS ILD in AOSD occurred mainly during systemic AOSD, although it was also rarely reported during AOSD chronic joint involvement but at any time during the course of the disease. The most frequent respiratory symptoms in patients with non-ARDS ILD were cough, dyspnea and chest pain.

The main high-resolution CT patterns were non-specific interstitial, pneumonia, organizing pneumonia, and unclassified ILD. Pulmonary function tests were occasionally performed, but when done they showed restrictive lung function or isolated decreased DLCO; occasionally, pulmonary function tests revealed an obstructive pattern. Similarly, bronchoalveolar lavage (BAL) analyses were rarely available, and the differential cell count usually had a neutrophilic profile, non-specific for ILD-associated AOSD.

For ILD occurring during AOSD, other differential diagnoses should be ruled out, mainly infections (sputum culture, BAL fluid analysis, blood culture, serology, antibiotic treatment failure), cardiogenic causes (brain natriuretic peptide dosage, transthoracic ultrasonography), connective tissue and other systemic diseases (immunology), toxic or iatrogenic causes (with special attention to methotrexate and tobacco) (124). Physicians should also be cautious to rule out cancer, because AOSD-like paraneoplastic syndromes have been described (125).

In most of non-ARDS AOSD-associated ILD cases, corticosteroids are efficient and the outcome is favorable. Hence, corticosteroids should be considered the first-line treatment, and data from Gerfaud-Valentin et al. do not support the systematic combination with DMARDs such as methotrexate, cyclosporine A, cyclophosphamide or IVIG (124). Most cases of ARDS AOSD-associated ILD also responded well to corticosteroids as first-line treatment. However, in case of corticosteroid failure, physicians should systematically search for an underlying RHL and/or other systemic complications such as SIRS, multiorgan failure, DIC and/or TMA. Identifying these entities should be a key element in ARDS control, because this speeds switching the treatment to biological agents (potentially combined with cyclosporine or etoposide in case of RHL) (124). In a recent case series, 3 of 7 patients with RHL in AOSD had lung involvement. Two received anakinra, with a favorable outcome (126).

3.5.3. Aseptic empyema and diffuse alveolar hemorrhage

Finally, other rarer pulmonary complications of AOSD such as aseptic empyema and diffuse alveolar hemorrhage have been anecdotally reported (127,128). Both complications responded well to high-dose corticosteroid therapy.

3.8 Amyloid A (AA) amyloidosis

As in other SAIDs, AA amyloidosis is becoming extremely rare but remains possible in cases of chronic uncontrolled inflammation and in long-standing refractory chronic articular AOSD. The main fear is renal impairment, although digestive localization has been reported (7,129–132). Early diagnosis and treatment are essential, although no strategy is clearly codified. The combination of prednisone, colchicine and cyclophosphamide could be efficacious (131).

4. Conclusion

Although its prognosis is generally favorable in Western countries, AOSD is a rare SAID that may be infrequently associated with significant morbidity and life-threatening manifestations. In the literature, deaths were due to overwhelming infections, ARDS, or multiple organ failure during RHL, DIC, TMA or involvement of the central nervous system (3). Clinicians should be aware of those complications, because early recognition and prompt management in a monitored setting can significantly decrease morbidity and mortality (11). Treatment of life-threatening complications should include both supportive measures and immunomodulatory drugs to control the underlying systemic inflammation.

5. Expert Commentary:

Progress in pathogenesis knowledge of AOSD led most authors to consider the disease as an SAID. Indeed, AOSD shares several features with auto-inflammatory diseases: clinical manifestations (fever, skin involvement, serositis and arthritis), absence of autoantibodies and/or auto-antigen–specific T cells (the hypothesis of an autoimmune disorder in AOSD is very unlikely), and a striking clinical response to IL-blocking strategies (especially IL-1β) (3). Likewise, AOSD treatment has considerably progressed over the past decade, and a remission is possible in a large number of patients. Nevertheless, serious complications remain possible, before or during treatment.

The key question for the physician managing AOSD complications is to define whether the latter are related to an overwhelming underlying AOSD disease, uncontrolled despite the treatment, or to a triggering factor, mainly an infection and especially a viral reactivation, potentially favored by the treatment, or to a direct adverse event of the drug. As for AOSD diagnosis, which implies first ruling out a large list of differential diagnoses, the etiologic diagnosis with a complication requires a cautious and exhaustive assessment. As an example, DRESS syndrome can mimic multi-organ failure over the AOSD course (92). Of note, viral reactivation (of EBV, CMV, human herpes virus-6 or -7) and a CD8+ T-lymphocyte dysfunction has also been described in this syndrome (133).

Owing to the rarity of the disease and the absence of a randomized controlled trial, treatment decisions continue to be based on empiric data and expert opinion. High-dose corticosteroids, along with supportive measures, remain the first-line treatment for all serious and life-threatening complications, because their effects are wide and quite constant in an emergency context. In case of insufficient response (or from the outset if the clinical picture is severe), combination with a biological agent (IL-1 or IL-6 inhibitor) becomes the preferred option. Considering the central position of inflammasome and caspase pathway activation in SAID pathogenesis **(Figure 1)**, our expert perception is that IL-1 inhibitors are of great interest and should perhaps be prioritized, because IL-1 (and IL-18) act upstream of IL-6 in the inflammatory cytokine cascade (5). Another argument for trying IL-1 inhibitors first is their short half-life, so they are easier to use (once daily), and can be stopped in case of ineffectiveness or side effects. The future will probably help to define whether an actual difference in effectiveness exists between IL-1 and IL-6 inhibitors but also among IL-1 inhibitors. Whether all of the latter have the same efficacy and safety is still unclear, because anakinra and rilonacept (not available in Europe) neutralize both IL-1α and IL-1β activity, whereas canakinumab is specific only for IL-1β (25). Canakinumab, whose use is easy for patients because of only monthly injections — versus daily for anakinra — due to its long half-life, is probably not optimal in emergency situations (in addition to its extremely high cost).

The use of TNF inhibitors is disappointing, because most patients achieve only partial remission and the retention rates are lower than with IL-1 and IL-6 inhibitors (134). They are currently regarded as third-line drugs, preferentially in patients with chronic arthritis. Cyclosporine A and etoposide remain of interest, especially with RHL. Plasma exchange may

be useful for TMA. Methotrexate might prevent articular complications, but no data support its use in life-threatening complications. Although their efficacy has been sometimes reported in systemic manifestations, other conventional drugs (such as IVIG, cyclophosphamide, azathioprine or mycophenolate mofetil) have a limited place because of their potential toxicity and hazardous efficacy. Rituximab does not seem a logical option, regarding the current knowledge of pathogenesis, and the absence of autoantibodies in AOSD. Indeed, its effectiveness was reported in isolated reports, but it was almost always combined with other drugs.

AOSD remains a complex and probably heterogeneous disease. Its complications are always difficult to forecast, so such patients must be cared for in reference centers for rare diseases, which are now connected internationally within the European Reference Network for European Network on Rare Immunodeficiency, auToinflammatory and Autoimmune diseases (ERN RITA, http://rita.ern-net.eu/)

6. Five-year view

There is a crucial need for better understanding of AOSD pathogenesis and probably for its disentanglement in several more specific entities in terms of mechanisms, clinical expression or evolution. Prospective disease-specific cohorts and international collaborative registries are thus required to:

- better stratify the different phenotypes;

- define the clinical relevance of several biomarkers for diagnosis, disease evolution prediction, disease activity assessment, prediction of flares and prognosis that have been recently identified (such as S100 proteins or soluble CD163) (135);

- and to better assess the risk of complications as well as better understand and characterize them. Indeed, the weight of each cytokine inside the “cytokine storm” does not seem the same and that an imbalance in the distinct cytokine pathways may be responsible for the pathogenesis of the different phenotypes. Hence, systemic phenotypes have been reported to present higher plasma levels of IL-1β and IL-18, whereas a dominant IL-6 cytokine profile pattern has been found in patients with chronic articular disease (6,136,137). Furthermore, blocking a selective cytokine may induce a greater imbalance within the cytokine storm, which could be responsible for some complications observed under IL-inhibitor treatment. Thus, it has been hypothesized that RHL under IL-1 or IL-6 inhibitor therapy could be related to excess

IL-18 level (30). Hence, a map of the cytokine profile of each complication of AOSD is needed to drive the targeted therapy choices and develop more robust treatment sequences or algorithms.

The future will probably point to the place of IL-18 blockade because a recombinant human IL-18 binding protein (IL-18BP or Tadekinig alpha) is currently under investigation. This drug was tested in healthy volunteers, psoriasis and rheumatoid arthritis patients in phase I studies and demonstrated good safety and tolerability profile with only mild adverse events at the injection site. Because of the postulated role of IL-18 in the pathogenesis of AOSD, investigating the effects of Tadekinig alpha in this condition was a logical step. Recently, a first open-label, dose-finding phase 2 study in AOSD involving multiple centers in Europe was designed to capture safety information as the primary outcome. Tadekinig alfa appears to have a favorable safety profile and is associated with early signs of efficacy in patients with AOSD (138). This new drug could be of great importance, considering the central role of IL-18 in the pathogenesis of severe life-threatening complications such as RHL or acute hepatitis (5,12,139).

Better understanding of the AOSD pathogenesis and the contribution of translation research would probably help to define new treatment targets and lead to the development of new therapies. Modulation of IFN-γ and IL-17 pathways will probably be explored in the near future (3,5).

Key issues

- The prognosis of AOSD is triple: vital (related to the severity of the visceral complications and multi-organ failure), functional (mainly linked with the potential articular destruction) and iatrogenic (mainly corticosteroid-induced complications and infections).
- The key question with a complication is to define whether it is related to uncontrolled AOSD itself or to an environmental triggering factor, such as an infection — either de novo or a reactivation — potentially favored by the treatment.
- RHL is the most frequent life-threatening complication of AOSD. It is a medical emergency that should be suspected with one or more cytopenias, normal (or normalized) ESR and hypofibrinogenemia. It can be associated with DIC and TMA.

- Liver involvement is frequent during AOSD but can be serious with acute cytolitic hepatitis. Liver function tests should be closely monitored, especially with methotrexate or NSAID prescription and auto-medication avoided.
- Other life-threatening complications include pulmonary and cardiac complications. All can all lead to multi-organ dysfunction, SIRS and death, and therefore require supportive measures.
- High-dose corticosteroids remain the first-line treatment for all life-threatening complications. This initial treatment needs to be rapidly complemented by more specific AOSD treatments such as IL-1 or IL-6 inhibitors. Targeting the inflammasome pathway, hence IL-1β, seems more specific regarding the AOSD pathogenesis and should be prioritized. Trials with an IL-18BP are ongoing and seem promising.

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References:

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Bywaters EG. Still's disease in the adult. Ann Rheum Dis 1971;30(2):121-133.
2. Fautrel B. Adult-onset Still disease. Best Pract Res Clin Rheumatol. 2008; 22(5):773-92.
3. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. Autoimmun Rev. 2014; 13(7):708-22.
*** This article reviews the recent progresses in adult-onset Still's disease pathogenesis, and the main clinical and biological features of the disease.**

4. Jamilloux Y, Gerfaud-Valentin M, Martinon F, Belot A, Henry T, Sève P. Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart. Immunol Res. 2015 Feb;61(1-2):53-62.
5. Maria ATJ, Le Quellec A, Jorgensen C, Touitou I, Rivière S, Guilpain P. Adult onset Still's disease (AOSD) in the era of biologic therapies: Dichotomous view for cytokine and clinical expressions. Autoimmun Rev. 2014 Nov;13(11): 1149-59.
*** This article reviews the different cytokine profiles that have been described in adult-onset Still's disease.**

6. Inoue N, Shimizu M, Tsunoda S, Kawano M, Matsumura M, Yachie A. Cytokine profile in adult-onset Still's disease: Comparison with systemic juvenile idiopathic arthritis. Clin Immunol. 2016 Aug;169:8-13.
*** Different cytokine profiles have been observed in the different clinical phenotypes of the systemic form of juvenile idiopathic arthritis.**

7. Uppal SS, Al-Mutairi M, Hayat S, et al. Ten years of clinical experience with adult onset Still's disease: is the outcome improving? Clin Rheumatol 2007;26:1055–60.
8. Pouchot J, Sampalis JS, Beaudet F et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. Medicine (Baltimore) 1991; 70: 118–136.
9. Gerfaud-Valentin M, Maucort-Boulch D, Hot A, Iwaz J, Ninet J, Durieu I et al. Adult-onset Stil disease: manifestations, treatments, outcome, and prognostic factors in 57 patients. Medicine (Baltimore) 2014; 93(2):91-9.
10. Priori R, Colafrancesco S, Picarelli G, et al. Adult-onset Still's disease: not always so good. Clin Exp Rheumatol. 2012 Jan-Feb;30(1):142; author reply 143. Epub 2012 Mar 7.
11. Efthimiou P, Kavadath S, Mehta B. Life-threatening complications of adult-onset Still's disease. Clin Rheumatol. 2014;33(3):305-14.
*** Comprehensive review of the literature summarizing the current pathogenesis knowledge, diagnostic features and therapeutic strategy for hemophagocytic lymphohistiocytosis.**

12. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haemophagocytic syndrome. Lancet. 2014 Apr 26;383(9927):1503-1516. doi:10.1016/S0140-6736(13)61048-X.

Epub 2013 Nov 27.
13. Kim HA, Sung JM, Suh CH. Therapeutic responses and prognosis in adult-onset Still's disease. Rheumatol Int 2012;32:1291-8.
14. Colina M, Zucchini W, Ciancio G, Orzincolo C, Trotta F, Govoni M. The evolution of adult-onset Still disease: an observational and comparative study in a cohort of 76 Italian patients. Semin Arthritis Rheum. 2011 Oct;41(2):279-85.
15. Franchini S, Dagna L, Salvo F, et al. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. Arthritis Rheum. 2010 Aug;62(8):2530-5. doi:10.1002/art.27532.
16. Ruscitti P, Cipriani P, Masedu F, Iacono D, Ciccia F, Liakouli V, et al. Adult-onset Still's disease: evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. BMC Med. 2016 Dec;14(1):194.
17. Masui-Ito A, Okamoto R, Ikejiri K, et al. Tocilizumab for uncontrollable systemic inflammatory response syndrome complicating adult-onset Still disease: Case report and review of literature. Medicine (Baltimore). 2017;96(29):e7596. doi:10.1097/MD.0000000000007596.
18. Singh S, Samant R, Joshi VR. Adult onset Still's disease: a study of 14 cases. Clin Rheumatol. 2008 Jan;27(1):35-9. Epub 2007 Aug 15.
19. Fukaya S, Yasuda S, Hashimoto T, et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. Rheumatology (Oxford). 2008 Nov;47(11):1686-91. doi: 10.1093/rheumatology/ken342. Epub 2008 Sep 9.
20. Arlet JB, Le TH, Marinho A, et al. Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literature. Ann Rheum Dis. 2006 Dec;65(12):1596-601. Epub 2006 Mar 15.
21. Dhote R, Simon J, Papo T, et al. Reactive hemophagocytic syndrome in adult systemic disease: report of twenty-six cases and literature review. Arthritis Rheum. 2003 Oct 15;49(5):633-9.
22. Hot A, Toh ML, Coppéré B, et al. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features and long-term outcome: a case-control study of 8 patients. Medicine (Baltimore). 2010 Jan;89(1):37-46. doi: 10.1097/MD.0b013e3181caf100.
23. Behrens EM, Beukelman T, Paessler M, et al. Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. J Rheumatol 2007;34(5):1133–1138, PubMed PMID: 17343315. Epub 2007/03/09.
24. Bleesing J, Prada A, Siegel DM, Villanueva J, Olson J, Ilowite NT, et al. The diagnostic significance of soluble CD163 and soluble interleukin-2 receptor alpha-chain in macrophage activation syndrome and untreated new-onset juvenile idiopathic arthritis. Arthritis Rheum. 2007;56(3):965-71.
25. Junge G, Mason J, Feist E. Adult onset Still's disease—The evidence that anti-interleukin-1 treatment is effective and well-tolerated (a comprehensive literature review). Semin Arthritis Rheum. 2017 Oct;47(2):295-302.doi:10.1016/j.semarthrit.2017.06.006. Epub 2017 Jun 23.
****Comprehensive literature review of the efficacy and tolerance of IL-1 inhibitors in adult-onset Still's disease.**

26. Banse C, Vittecoq O, Benhamou Y, et al. Reactive macrophage activation syndrome possibly triggered by canakinumab in a patient with adult-onset Still's disease.Joint Bone Spine. 2013 Dec;80(6):653-5. doi: 10.1016/j.jbspin.2013.04.011. Epub 2013 Jun 7.
27. Cifaldi L, Prencipe G, Caiello I. Inhibition of natural killer cell cytotoxicity by interleukin-6: implications for the pathogenesis of macrophage activation syndrome.Arthritis

Rheumatol. 2015 Nov;67(11):3037-46.doi:10.1002/art.39295.
28. Weiss ES, Girard-Guyonvarc'h C, Holzinger D, et al. Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome. Blood. 2018 Jan 11. pii: blood 2017-12-820852. doi: 10.1182/blood-2017-12-820852. [Epub ahead of print].
*** This work, along with reference 26, highlights the central role of interleukin 18 in the pathogenesis of reactive hemophagocytic lymphohistiocytosis (macrophage activation syndrome).**

29. Girard-Guyonvarc'h C, Palomo J, Martin P, et al. Unopposed IL-18 signaling leads to severe TLR9-induced macrophage activation syndrome in mice. Blood. 2018 Jan 2. pii: blood-2017-06-789552. doi: 10.1182/blood-2017-06-789552. [Epub ahead of print].
*** This work, along with reference 25, highlights the central role of interleukin 18 in the pathogenesis of reactive hemophagocytic lymphohistiocytosis (macrophage activation syndrome).**

30. Lieben L. Autoinflammatory diseases: Free IL-18 causes macrophage activation syndrome. Nat Rev Rheumatol. 2018 Feb 1. doi: 10.1038/nrrheum.2018.11. [Epub ahead of print].
31. Deroux A, Andry F, Bouillet L. [Macrophage activation syndrome secondary to tocilizumab: Myth or reality?]. [Article in French]Rev Med Interne. 2016 Aug;37(8):564-6.doi:10.1016/j.revmed.2015.10.348. Epub 2016 Mar 9.
32. Yokota S, Itoh Y, Morio T, et al. Macrophage Activation Syndrome in Patients with Systemic Juvenile Idiopathic Arthritis under Treatment with Tocilizumab. J Rheumatol. 2015 Apr;42(4):712-22. doi: 10.3899/jrheum.140288. Epub 2015 Feb 15.
33. Agnihotri A, Ruff A, Gotterer L, et al. Adult Onset Still's Disease Associated with Mycoplasma pneumoniae Infection and Hemophagocytic Lymphohistiocytosis. Case Rep Med. 2016;2016:2071815. Epub 2016 Oct 26.
34. Prendki V, Stirnemann J, Lemoine M, et al. Prevalence and clinical signifi cance of Küpff er cell hyperplasia with hemophagocytosis in liver biopsies. Am J Surg Pathol 2011; 35: 337–45.
35. Gupta A, Weitzman S, Abdelhaleem M. The role of hemophagocytosis in bone marrow aspirates in the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2008; 50: 192–94.
36. Emmenegger U, Schaer DJ, Larroche C, et al. Haemophagocytic syndromes in adults: current concepts and challenges ahead. Swiss Med Wkly 2005; 135: 299–314.
37. Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–31.
38. Ravelli A, Magni-Manzoni S, Pistorio A, et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr 2005;146:598–604.
39. Fardet L, Coppo P, Kettaneh A, et al. Low glycosylated ferritin, a good marker for the diagnosis of hemophagocytic syndrome. Arthritis Rheum 2008;58:1521–7.
40. Imashuku S. Differential diagnosis of hemophagocytic syndrome: underlying disorders and selection of the most effective treatment. Int J Hematol 1997;66:135–51.
41. Wong KF, Chan JK. Reactive hemophagocytic syndrome: a clinicopathologic study of 40 patients in an Oriental population. Am J Med 1992;93:177–80.
42. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a

score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014 Sep;66(9):2613-20. doi: 10.1002/art.38690.
43. Hejblum G, Lambotte O, Galicier L, et al. A web-based delphi study for eliciting helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients. PLoS One. 2014 Apr 7;9(4):e94024. doi:10.1371/journal.pone.0094024. eCollection 2014.
44. Jordan MB, Allen CE, Weitzman S, et al. How I treat hemophagocytic lymphohistiocytosis. Blood 2011;118:4041–52.
45. Zhuang JL, Jiang QW, Xu Y, et al. Recombinant activated factor VII in hemophagocytic lymphohistiocytosis with disseminated intravascular coagulation. Chin Med J (Engl) 2011;124: 3189–91.
46. Celkan T, Alhaj S, Civilibal M, et al. Control of bleeding associated with hemophagocytic syndrome in children: an audit of the clinical use of recombinant activated factor VII. Pediatr Hematol Oncol 2007; 24: 117–21.
47. Wang S, Degar BA, Zieske A, et al. Hemophagocytosis exacerbated by G-CSF/GM-CSF treatment in a patient with myelodysplasia. Am J Hematol 2004; 77: 391–96.
48. Quesnel B, Catteau B, Aznar V, et al. Successful treatment of juvenile rheumatoid arthritis associated haemophagocytic syndrome by cyclosporin A with transient exacerbation by conventional-dose G-CSF. Br J Haematol 1997;97: 508–10.
49. Bruck N, Suttorp M, Kabus M, et al. Rapid and sustained remission of systemic juvenile idiopathic arthritis-associated macrophage activation syndrome through treatment with anakinra and corticosteroids. J Clin Rheumatol. 2011; 17(1):23–27, PubMed PMID: 21169853. Epub 2010/12/21.
50. Kelly A, Ramanan AV. A case of macrophage activation syndrome successfully treated with anakinra. Nat Clin Pract Rheumatol. 2008; 4(11):615–620, PubMed PMID: 18825135. Epub 2008/10/01.
51. Pamuk ON, Pamuk GE, Usta U, et al. Hemophagocytic syndrome in one patient with adult-onset Still's disease. Presentation with febrile neutropenia. Clin Rheumatol. 2007; 26(5):797–800, PubMed PMID: 16550302. Epub 2006/03/22.
52. Record JL, Beukelman T, Cron RQ. Combination therapy of abatacept and anakinra in children with refractory systemic juvenile idiopathic arthritis: a retrospective case series. J Rheumatol. 2011;38(1): 180–181, PubMed PMID: 21196588. Epub 2011/01/05.
53. Parisi F, Paglionico A, Varriano V, et al. Refractory adult-onset Still disease complicated by macrophage activation syndrome and acute myocarditis: A case report treated with high doses (8 mg/kg/d) of anakinra. Medicine (Baltimore). 2017 Jun;96(24):e6656. doi:10.1097/MD.0000000000006656.
54. Hong D, Yang Z, Han S, et al. Interleukin 1 inhibition with anakinra in adult-onset Still disease: a meta-analysis of its efficacy and safety. Drug Des Devel Ther. 2014 Nov 25;8:2345-57. doi:10.2147/DDDT.S73428.
55. Colafrancesco S, Priori R, Valesini G, et al. Response to Interleukin-1 Inhibitors in 140 Italian Patients with Adult-Onset Still's Disease: A Multicentre Retrospective Observational Study. Front Pharmacol. 2017 Jun 13;8:369. doi:10.3389/fphar.2017.00369.
56. Watanabe E, Sugawara H, Yamashita T, et al. Successful Tocilizumab Therapy for Macrophage Activation Syndrome Associated with Adult-Onset Still's Disease: A Case-Based Review. Case Rep Med. 2016;2016:5656320. doi: 10.1155/2016/5656320. Epub 2016 Sep 5.
*** This paper reviews the majority of case-reports that have described successful tocilizumab theraphy for reactive hemophagocytic lymphohistiocytosis.**

57. de Boysson H, Février J, Nicolle A, et al. Tocilizumab in the treatment of the adult-onset Still's disease: current clinical evidence.Clin Rheumatol. 2013 Jan;32(1):141-

7.doi:10.1007/s10067-012-2105-2. Epub 2012 Oct 30.
58. Komiya Y, Takenaka K, Nagasaka K. Successful treatment of glucocorticoid and cyclosporine refractory adult-onset Still's disease complicated with hemophagocytic syndrome with plasma exchange therapy and tocilizumab: a case report. Nihon Rinsho Meneki Gakkai Kaishi. 2013;36(6):478-83.
59. Savage E, Wazir T, Drake M, et al. Fulminant myocarditis and macrophage activation syndrome secondary to adult-onset Still's disease successfully treated with tocilizumab. Rheumatology (Oxford).2014Jul;53(7):1352-3.doi:10.1093/rheumatology/keu019. Epub 2014 Mar 7.
60. Kobayashi D, Ito S, Murasawa A, et al.Two cases of adult-onset Still's disease treated with tocilizumab that achieved tocilizumab-free remission.Intern Med. 2015;54(20):2675-9.doi:10.2169/internalmedicine.54.4935. Epub 2015 Oct 15.
61. Shimizu M, Nakagishi Y, Kasai K, et al. Tocilizumab masks the clinical symptoms of systemic juvenile idiopathic arthritis-associated macrophage activation syndrome: the diagnostic significance of interleukin-18 and interleukin-6. Cytokine. 2012 May;58(2):287-94. doi:10.1016/j.cyto.2012.02.006. Epub 2012 Mar 6.
62. Stern A, Riley R, Buckley L. Worsening of macrophage activation syndrome in a patient with adult onset Still's disease after initiation of etanercept therapy. J Clin Rheumatol. 2001; 7(4):252–256, PubMed PMID: 17039144. Epub 2006/10/14.
63. Moake JL. Hypercoagulable states. Adv Intern Med. 1990;35:235-47.
64. Sakata N, Shimizu S, Hirano F, et al. Epidemiological study of adult- onset Still's disease using a Japanese administrative database. Rheumatol Int. 2016 Oct;36(10):1399-405. doi:10.1007/s00296-016-3546-8. Epub 2016 Aug 9.
65. Wouters JM, van de Putte LB. Adult-onset Still's disease;clinical and laboratory features, treatment and progress of 45 cases. Q J Med.1986 Nov;61(235):1055-65.
66. Mimura T, Shimodaira M, Kibata M, et al. Adult-onset Still's disease with disseminated intravascular coagulation and hemophagocytic syndrome: a case report.BMC Res Notes. 2014 Dec 22;7:940. doi: 10.1186/1756-0500-7-940.
67. Shinohara T, Hidaka T, Matsuki Y, et al. Calcinosis cutis and intestinal pseudoobstruction in a patient with adult onset Still's disease associated with recurrent relapses of disordered coagulopathy.Intern Med. 1999Jun;38(6):516-20.
68. Yokoyama M, Suwa A, Shinozawa T, et al. A case of adult onset Still's disease complicated with adult respiratory distress syndrome and disseminated intravascular coagulation. Nihon Rinsho Men'eki Gakkai kaishi=Japanese journal of clinical immunology 18(2):207–214, PubMed PMID: 7553055. Epub 1995/04/01.
69. Yamashita S, Furukawa NE, Matsunaga T, et al. Extremely High Serum Ferritin: An Instrumental Marker of Masquerading Adult-Onset Still's Disease with Hemophagocytic Syndrome. Am J Case Rep. 2017 Dec6;18:1296-1301.
70. Colina M, Govoni M, Trotta F. Fatal myocarditis in adult-onset Still disease with diffuse intravascular coagulation. Rheumatol Int. 2009 Sep;29(11):1355-7. doi: 10.1007/s00296-008-0813-3. Epub 2008 Dec 2.
71. Namas R, Nannapaneni N, Venkatram M, et al. An Unusual Case of Adult-Onset Still's Disease with Hemophagocytic Syndrome, Necrotic Leukoencephalopathy and Disseminated Intravascular Coagulation. Case Rep Rheumatol. 2014;2014:128623. doi: 10.1155/2014/128623.
72. Lenert A, Yao Q.Macrophage activation syndrome complicating adult onset Still's disease: A single center case series and comparison with literature. Semin Arthritis Rheum. 2016 Jun;45(6):711-6. doi: 10.1016/j.semarthrit.2015.11.002. Epub 2015 Nov 10.
73. Matsumoto K, Nagashima T, Takatori S, et al. Glucocorticoid and cyclosporine refractory adult onset Still's disease successfully treated with tocilizumab. Clin Rheumatol.

2009 Apr;28(4):485-7. doi:10.1007/s10067-009-1097-z. Epub 2009 Jan 30.
74. Park JH, Bae JH, Choi YS, el al. Adult-onset Still's disease with disseminated intravascular coagulation and multiple organ dysfunctions dramatically treated with cyclosporine A. J Korean Med Sci. 2004 Feb;19(1):137-41.
75. Kumar A, Kato H. Macrophage Activation Syndrome Associated with Adult-Onset Still's Disease Successfully Treated with Anakinra. Case Rep Rheumatol. 2016;2016:3717392. Epub 2016 Oct 12.
76. Kötter I, Wacker A, Koch S,Anakinra in patients with treatment-resistant adult-onset Still's disease: four case reports with serial cytokine measurements and a review of the literature. Semin Arthritis Rheum. 2007 Dec;37(3):189-97. Epub 2007 Jun 20.
77. Bianchi V, Robles R, Alberio L, et al. Von Willebrand factor-cleaving protease (ADAMTS13) in thrombocytopenic disorders: a severely deficient activity is specific for thrombotic thrombocytopenic purpura. Blood 2002;100: 710–3.
78. El Karoui K, Karras A, Lebrun G, et al. Thrombotic microangiopathy and purtscher-like retinopathy associated with adult-onset Still's disease: a role for glomerular vascular endothelial growth factor? Arthritis Rheum. 2009 Nov 15;61(11):1609-13. doi: 10.1002/art.24826.
79. Zheng XL, Kaufman RM, Goodnough LT, et al. Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. Blood. 2004 Jun 1;103(11):4043-9. Epub 2004 Feb 24.
80. Sumida K, Ubara Y, Hoshino J, et al. Etanercept-refractory adult-onset Still's disease with thrombotic thrombocytopenic purpura successfully treated with tocilizumab. Clin Rheumatol. 2010 Oct;29(10):1191-4.doi:10.1007/s10067-010-1418-2. Epub 2010 Mar 12.
81. Masuyama A, Kobayashi H, Kobayashi Y, et al. A case of adult-onset Still's disease complicated by thrombotic thrombocytopenic purpura with retinal microangiopathy and rapidly fatal cerebral edema. Mod Rheumatol. 2013 Mar;23(2):379-85. doi: 10.1007/s10165-012-0650-9. Epub 2012 May 24.
82. Khobragade AK, Chogle AR, Ram RP, et al. Reversible posterior leukoencephalopathy syndrome in a case of adult onset Still's disease with concurrent thrombotic thrombocytopenic purpura: response to high dose immunoglobulin infusions.J Assoc Physicians India. 2012 Nov;60:59-62.
83. Rawal S, Einbinder Y, Rubin L, et al. Thrombotic microangiopathy in a patient with adult-onset Still's disease.Transfusion. 2014 Nov;54(11):2983-7. doi: 10.1111/trf.12708. Epub 2014 May 20.
84. Hirata S, Okamoto H, Ohta S, Kobashigawa T, Uesato M, Kawaguchi Y, et al. Deficient activity of von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura in the setting of adult-onset Still's disease. Rheumatology (Oxford) 2006;45:1046–7.
85. Gopal M, Cohn CD, McEntire MR, et al. Thrombotic thrombocytopenic purpura and adult onset Still's disease. Am J Med Sci 2009;337:373–6.
86. Dino O, Provenzano G, Giannuoli E, et al. Fulminant hepatic failure in adult onset Still's disease. J Rheumatol. 1996 Apr;23(4):784-5.
87. McFarlane M, Harth M, Wall WJ. Liver transplant in adult Still's disease. J Rheumatol. 1997 Oct;24(10):2038-41.
88. Fujii K, Rokutanda R, Osugi Y, et al. Adult-onset Still's disease complicated by autoimmune hepatitis: successful treatment with infliximab. Intern Med. 2012;51(9):1125-8. Epub 2012 Apr 29.
89. Liu LL, Feng ML, Wang LNJ et al. A case report of successful treatment with plasma exchange for adult-onset Still's disease with autoimmune hepatitis. Clin Apher. 2010;25(2):74-6. doi: 10.1002/jca.20227.

90. Xia LX, Xiao T. An unusual case of autoimmune hepatitis in a patient with adult-onset Still's disease. Clin Rheumatol. 2010 Jan;29(1):95-7. doi:10.1007/s10067-009-1186-z. Epub 2009 May 8.
91. Gambichler T, Paech V, Rotterdam S, et al. Hepatitis B-assocciated adult-onset Still's disease presenting with neutrophilic urticaria. Eur J Med Res. 2003 Dec 9;8(12):527-30.
92. Ben m'rad M, Leclerc-Mercier S, Blanche P, et al. Drug-induced hypersensitivity syndrome: clinical and biologic disease patterns in 24 patients. Medicine (Baltimore). 2009 May;88(3):131-40. doi: 10.1097/MD.0b013e3181a4d1a1.
93. Omagari K, Matsunaga Y, Yamashita H, et al. Successful treatment with cyclosporin in adult-onset Still disease manifesting as acute hepatitis with marked hyperferritinemia. Am J Med Sci. 2003 Sep;326(3):148-51.
94. Sahutoglu T, Kara E, Dogan IO, et al. Acute Severe Hepatitis and Hemophagocytosis in Adult Onset Still's Disease. Arch Iran Med. 2015 Oct;18(10):724-8. doi: 0151810/AIM.0014.
95. Mylona E, Golfinopoulou S, Samarkos M, et al. Acute hepatitis in adult Still's disease during corticosteroid treatment successfully treated with anakinra. Clin Rheumatol. 2008 May;27(5):659-61. Epub 2007 Dec 20.
96. Kishida D, Okuda Y, Onishi M, et al. Successful tocilizumab treatment in a patient with adult-onset Still's disease complicated by chronic active hepatitis B and amyloid A amyloidosis. Mod Rheumatol. 2011 Apr;21(2):215-8. doi:10.1007/s10165-010-0365-8. Epub 2010 Oct 8.
97. Drepper M, Rubbia-Brandt L, Spahr L. Tocilizumab-Induced Acute Liver Injury in Adult Onset Still's Disease. Case Reports Hepatol. 2013;2013:964828. doi:10.1155/2013/964828. Epub 2013 Jul 15.
98. Hintenberger R, Falkinger A, Danninger K, et al. Cardiovascular disease in patients with autoinflammatory syndromes. Rheumatol Int. 2018 Jan;38(1):37-50. doi: 10.1007/s00296-017-3854-7. Epub 2017 Nov 1.
99. Buss SJ, Wolf D, Mereles D, et al. A rare case of reversible constrictive pericarditis with severe pericardial thickening in a patient with adult onset Stil's disease. Int j Cardiol. 2010 Oct8;144(2):e23-5. doi: 10.1016/j.ijcard.2008.12.079. Epub 2009 Jan 30.
100. Bilska A, Willnska E, Sztumowicz M, et al. Reccurent effusive pericarditis in the course of adult-onset Still's disease--case reports of two patients. Pneumonol Alergol Pol. 2011;79(3):215-21.
101. Dall'Ara F, Frassi M, Tincani A, et al. A retrospective study of patients with adult-onset Still's disease: is pericarditis a possible predictor for biological disease-modifying anti-rheumatic drugs need? Clin Rheumatol. 2016;35(8)/2117-2123. doi:10.1007/s10067-015-3164-y. Epub 2016 Jan 12.
102. Kawaguchi H, Tsuboi H, Yagishita M, et al. A case of severe adult-onset Still's disease with constrictive pericarditis and pleuritis that was successfully treated with tocilizumab in addition to corticosteroids and cyclosporin A. Intern Med. 2017 Dec 21. doi: 10.2169/internalmedicine.9809-17. [Epub ahead of print].
103. Gerfaud-Valentin M, Sève P, Iwaz J, et al. Myocarditis in adult-onset still disease. Medicine (Baltimore). 2014;93(17):280-9. doi: 10.1097/MD.0000000000000112.
*** This retrospective study reviews the different cases and features of myocarditis in adult-onset Still's disease described in the literature.**

104. Colina M, Govoni M, Trotta F. Fatal myocarditis in adult-onset Still disease with diffuse intravascular coagulation. Rheumatol Int. 2009;29:1355–1357.
105. Ertugrul BM, Uyar G, Ozturk B, Sakarya S. A rare presentation of endocarditis in

adult-onset Still's disease in diagnosis of fever of unknown origin. J Rheumatol. 2012 Jan;39(1):198-9. doi:10.38899/jrheum.110935.
106. Garcia-Porrua C, Gonzalez-Juanatey C, Gonzalez-Gay MA. Endocarditis in adult onset Still's disease: a 12 month followup. J Rheumatol. 2001 Sep;28(9):2141-2.
107. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation. 2009 Apr 28;119(16):2250-94. doi:10.1161/CIRCULATIONAHA.109.192230. Epub 2009 Mar 30.
**** This American expert consensus sets the diagnostic and therapeutic guidelines for pulmonary hypertension, along with the European guidelines (reference 108).**

108. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2015; 46:903-975. doi:10.1183/13993003.01032-2015.
**** This European expert consensus sets the diagnostic and therapeutic guidelines for pulmonary hypertension, along with the American guidelines (reference 107).**

109. Huertas A, Perros F, Tu L, et al. Immune dysregulation and endothelialdysfunction in pulmonary arterial hypertension: a complex interplay. Circulation. 2014;129:1332–40.
110. Campos M and Schiopu E. Pulmonary arterial hypertension in adult-onset Still's disease: rapid response to Anakinra. Case Rep Rheumatol 2012; 2012: 537613.
111. Chen CH, Chen HA, Wang HP, et al. Pulmonary arterial hypertension in autoimmune diseases: an analysis of 19 cases from a medical center in northern Taiwan. J Microbiol Immunol Infect 2006; 39: 162–168.
112. de Siqueira M, Rodrigues R and Kormann APM. Adult-onset Still's disease and pulmonary arterial hypertension. Respiratory Medicine CME 2009; 2: 70–72.
113. Guilleminault L, Laurent S, Foucher A, et al. Pulmonary arterial hypertension in adult onset Still's disease: a case report of a severe complication. BMC Pulm Med. 2016 May 10;16(1):72. doi:10.1186/s12890-016-0237-x.
114. Kadavath S, Zapantis E, Zolty R, et al. A novel therapeutic approach in pulmonary arterial hypertension as a complication of adult-onset Still's disease: targeting IL-6. Int J Rheum Dis 2014; 17: 336–340.
115. Khattri S and Barland P. Pulmonary hypertension in a patient with adult-onset Still disease: a rare entity or an overlooked complication? J Muscoskel Med 2011: 388.
116. Lowther GH, Chertoff J, Cope J, et al. Pulmonary arterial hypertension and acute respiratory distress syndrome in a patient with adult-onset stills disease. Pulm Circ. 2017 Oct-Dec;7(4):797-802. doi:10.1177/2045893217712710.
117. Mehta MV, Manson DK, Horn EM, et al. An atypical presentation of adult-onset Still's disease complicated by pulmonary hypertension and macrophage activation syndrome treated with immunosuppression: a case-based review of the literature. Pulm Circ. 2016 Mar;6(1):136-42. doi: 10.1086/685112.
118. Mubashir E, Ahmed MM, Hayat S, et al. Pulmonary hypertension in a patient with adult-onset Stills disease. Clin Rheumatol 2007; 26: 1359–1361.
119. Padilla-Ibarra J, Sanchez-Ortiz A, Sandoval-Castro C, et al. Rituximab treatment for pulmonary arterial hypertension in adult-onset Still's disease. Clin Exp Rheumatol 2013; 31:657–658.

120. Thakare M, Habibi S, Agrawal S, et al. Pulmonary arterial hypertension complicating adult-onset Still's disease. Clin Rheumatol 2013; 32: S1–2.
121. Weatherald J, Lategan J, Helmersen D. Pulmonary arterial hypertension secondary to adult-onset Still's disease: Response to cyclosporine and sildenafil over 15 years of follow-up. Respir Med Case Rep. 2016 Jun 20;19:27-30. doi: 10.1016/j.rmcr.2016.06.007. eCollection 2016.
122. Zen A, Yamashita N, Ueda M, et al. [A case of adult Still's disease with pulmonary hypertension]. Ryumachi 1990; 30:45–52.
123. Robillard N, Wistaff R, Lamarre-Cliche M, et al. Still out of breath? J Med Cases. 2013;4:240-4.
124. Gerfaud-Valentin M, Cottin V, Jamilloux Y, et al. Parenchymal lung involvement in adult-onset Still disease: A STROBE-compliant case series and literature review. Medicine (Baltimore). 2016 Jul;95(30):e4258. doi:10.1097/MD.0000000000004258.
*** This retrospective study reviews the different cases and features of lung involvement in adult-onset Still's disease described in the literature.**

125. Wu N, Li Q, Gu CX, et al. Paraneoplastic syndrome mimicking adult-onset Still's disease caused by advanced lung cancer: a case report. BMC Cancer. 2011 Nov 16;11:487. doi:10.1186/1471-2407-11-487.
126. Lenert A, Yao Q. Macrophage activation syndrome complicating adult onset Still's disease: A single center case series and comparison with literature.Semin Arthritis Rheum. 2016 Jun;45(6):711-6. doi:10.1016/j.semarthrit.2015.11.002. Epub 2015 Nov 10.
127. Mattiuzzo M, Del FornoM, Branca B, et al. Bilateral empyema caused by adult-onset Still's disease. Respir Int Rev Thorac Dis 2001;68:88–90.
128. Sari I, Birlik M, Binicier O, et al. A case of adult-onset Still's disease complicated with diffuse alveolar hemorrhage. J Korean Med Sci 2009;24:155–7.
129. Ben Ghorbel I, Khanfir M, Houman MH. Amyloidosis in adult onset Still's disease. Rev Med Interne 2004;25:675–7.
130. Ishii T, Sasaki T, Muryoi T, et al. Systemic amyloidosis in a patient with adult onset Still's disease. Intern Med jan. 1993;32(1):50–2.
131. Oh YB, Bae SC, Jung JH, et al. Secondary renal amyloidosis in adult onset Still's disease: case report and review of the literature. Korean J Intern Med 2000;15:131–4.
132. Rivera F, Gil CM, Gil MT, et al. Vascular renal AA amyloidosis in adult Still's disease. Nephrol Dial Transplant 1997;12:1714–6.
133. Picard D, Janela B, Descamps V, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response.Sci Transl Med. 2010 Aug 25;2(46):46ra62. doi: 10.1126/scitranslmed.3001116.
134. Fautrel B, Sibilia J, Mariette X et al. Tumour necrosis factor alpha blocking agents in refractory adult Still's disease: an observational study of 20 cases. Annals of the Rheumatic Diseases 2005; 64: 262–266.
135. Mitrovic S, Fautrel B. New Markers for Adult-Onset Still's Disease. Joint Bone Spine. 2017 May 18. pii: S1297-319X(17)30102-1. doi: 10.1016/j.jbspin.2017.05.011. [Epub ahead of print].
*** This article reviews the new biomarkers that have emerged over the past years.**

136. Chen DY, Lan JL, Lin FJ, Hsieh TY. Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset Still's disease. J Rheumatol 2004;31(11):2189-98.

137. Choi JH, Suh CH, Lee YM, Suh YJ, Lee SK, Kim SS, et al. Serum cytokine profiles in patients with adult onset Still's disease. J Rheumatol. 2003;30(11):2422-7.
138. Gabay C, Fautrel B, Rech J, et al. Open-label, multicentre, dose-escalating phase II clinical trial on the safety and efficacy of tadekinig alfa (IL-18BP) in adult-onset Still's disease. Ann Rheum Dis. 2018 Feb 22. pii: annrheumdis-2017-212608. doi: 10.1136/annrheumdis-2017-212608. [Epub ahead of print].
**** This is the first clinical trial to provide data on the safety and efficacy of an IL-18 inhibitor, Tadekinig alpha, in adult-onset Still's disease.**

139. Priori R, Barone F, Alessandri C, Colafrancesco S, McInness IB, Pitzalis C, et al. Markedly increased IL-18 liver expression in adult-onset Still's disease-related hepatitis. Rheumatology (Oxford). 2011;50(4):776-80.
*** This work highlights the central role of interleukin 18 in the pathogenesis of hepatitis in adult-onset Still's disease**.