ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

Rheumatology Forum

OFFICIAL JOURNAL OF THE POLISH SOCIETY OF RHEUMATOLOGY

ISSN: 2720-3921

e-ISSN: 2720-3913

AOSD vs. sepsis — diagnosis as a challenge to modern medicine and a nightmare for clinicians

Authors: Natalia Leszczyńska, Michał Furtak, Zuzanna Jamrozy, Jan Kurdybacha, Oleksii Kravets, Monika Roszkowska, Martyna Biadasiewicz, Aleksandra Pytlarz, Natalia Lekston, Dorota Piłat, Gabriela Zemanek, Przemysław Kotyla

DOI: 10.5603/rf.103398

Article type: Review paper

Submitted: 2024-11-02

Accepted: 2025-02-13

Published online: 2025-02-25

AOSD *vs.* sepsis — diagnosis as a challenge to modern medicine and a nightmare for clinicians

Short title: AOSD *vs.* sepsis

DOI: 10.5603/rf.103398

Natalia Leszczyńska[1], Michał Furtak[1], Zuzanna Jamrozy[1], Jan Kurdybacha[1], Oleksii Kravets[1], Monika Roszkowska[1], Martyna Biadasiewicz[1], Aleksandra Pytlarz[1], Natalia Lekston[1], Dorota Piłat[1], Gabriela Zemanek[1], Przemysław Kotyla[2]

[1]*Student Scientific Circle at the Department of Internal Medicine, Rheumatology and Clinical Immunology, Faculty of Medical Sciences in Katowice, Medical University of Silesia in Katowice, Poland*

[2]*Department of Internal Medicine, Rheumatology and Clinical Immunology, Faculty of Medical Sciences in Katowice, Medical University of Silesia in Katowice, Poland*

Correspondence address: Natalia Leszczyńska, ul. Książęca 33A/12, 40–725 Katowice, e-mail: s82950@365.sum.edu.pl, tel. 732935762

Abstract

This article reviews the diagnostic options used in the differentiation of two almost identical diseases in terms of clinical presentation, i.e. adult-onset Still's disease (AOSD) and sepsis.

At the initial stage of the diagnostic process, differentiating between these two pathogenetically distinct disease entities is difficult and sometimes impossible. Both AOSD and sepsis are characterised by a turbulent inflammatory response, difficult to control in the early stage of the disease. High fever and serum biomarkers of inflammation do not clearly indicate a specific condition but only make it difficult for clinicians to make a correct diagnosis and apply effective treatment. Over the last dozen or so years, global literature has proposed several solutions, including determining specific serum markers to indicate a higher probability of the occurrence of a specific disease, which may facilitate further diagnostic procedures.

Among the listed biomarkers, it is worth distinguishing those whose concentration in serum is significantly higher in the case of Still's disease. These include ferritin, haem oxygenase 1, lymphocytosis, platelet morphological indices such as PMR — platelet (PLT) to mean platelet volume (MPV) ratio and PPR — platelet anisocytosis index (PDW) and platelets (PLT) to anisocytosis index (PDW) ratio, interleukin 18 (IL-18), neutrophil (n) CD64 index profile and miRNA profile expression. The markers indicative of sepsis should also be considered. Heparin-binding protein, delta neutrophil index, mean platelet volume (MPV) and red cell distribution width (RDW) show higher levels in the cases of sepsis. Correlation of multiple biomarkers and combined determination of ferritin with several parameters such as platelet hematocrit, IL-18 or sCD163 also seem to be helpful.

Currently, there is no single, highly sensitive and specific marker to reliably discriminate between sepsis and adult-onset Still's disease. Some of the discussed markers are presently still only of scientific interest and their use in routine practice may be difficult due to the high cost of determination as well as methodological and technical difficulties. Therefore, it is necessary to further search for potential biomarkers and critically interpret the currently available indicators.

Keywords: AOSD; sepsis; differential diagnosis; biomarkers

Introduction

Adult-onset Still's disease (AOSD), due to the rapid development of modern diagnostic methods, is an increasingly recognised condition [1]; however, the correct diagnosis of that disease entity is still quite challenging for clinicians. In the 1970s, the disease was described by E.G. Bywaters [1]. The disease, unlike juvenile idiopathic arthritis, occurs in patients over the age of 16. It is characterised by, inter alia, joint pain, fever above 39°C, unresponsive to antibiotic therapy, a salmon-coloured maculopapular rash and leucocytosis with predominant neutrophilia [1–3]. The 1992 Yamaguchi classification criteria are indispensable in its diagnosis (Tab. 1). These relate to clinical features, laboratory tests and exclusion factors. Considering other diseases, such as lymphomas, polyarteritis nodosa or sarcoidosis, the clinical course of which may be similar to Still's disease, the application of the classification criteria helps to distinguish AOSD from other disease entities [1]. Similar symptoms are also found in sepsis, which involves the haematopoietic system and other vital organs and body systems, which is why sepsis remains a diagnostic challenge for modern medicine. A systemic

infection such as sepsis manifests itself by, among other things, a body temperature above 38°C or below 36°C, tachycardia, leukocytosis and elevated inflammatory parameters [4]. It is important to mention the different way of treatment of Still's disease and sepsis, which is crucial for the patient's health. In AOSD, glucocorticosteroids and biological drugs are the treatment of choice, whereas in sepsis, antimicrobial therapy is the key solution [1, 4]. In recent years, the differential diagnosis of Still's disease and sepsis has focused primarily on finding appropriate biomarkers that provide a solid basis for their differentiation [2]. In diagnostic procedures, it is sometimes proposed to determine such indicators as ferritin concentration, interleukin 18 (IL-18) or platelet count, but none of those parameters is routinely and commonly used [3]. The diagnostic value of single differentiating parameters is limited, therefore a correlation of two or more biomarkers is preferred [2]. This review article illustrates the importance of precise diagnosis, as failure to differentiate between AOSD and sepsis results in delayed diagnosis and, consequently, in inappropriate or delayed treatment and a life-threatening condition for the patient [2].

Table 1. Yamaguchi classification criteria of adult-onset Still's disease (AOSD)

Major criteria	Fever > 39°C lasting one week or longer Joint pain lasting two weeks or longer Typical macular or maculopapular salmon-coloured rash (transient, often accompanying fever) Leukocytosis ≥ 10000/µmol, granulocytosis ≥ 80%
Minor criteria	Sore throat Lymphadenopathy Hepatomegaly or splenomegaly Elevated aminotransferase and/or lactate dehydrogenase levels Negative test results for rheumatoid factor (IgM class) and antinuclear antibodies (by immunofluorescence)
Exclusions	Infections, including sepsis and Epstein-Barr virus infection Neoplastic diseases (lymphomas) Inflammatory diseases (nodular arteritis)
Diagnosis	At least five criteria, including two major criteria and at least three minor criteria, no exclusion criteria

The article was prepared based on a review of the literature available in the PubMed and Scopus databases using a combination of keywords: AOSD, adult-onset Still's disease, sepsis, bloodstream infection, clinical manifestations, differential diagnosis, biomarkers, platelet, ferritin, interleukin, treatment. The review covered the period from 2001 to 2023.

Pathogenesis of AOSD

The aetiopathogenesis of AOSD is still unknown. However, factors such as an imbalance in innate and acquired immunity or increased levels of pro-inflammatory cytokines contribute to disease progression [5, 6]. The starting point of the pro-inflammatory cascade is likely to be specific danger signals, such as pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). The danger signals are transmitted to macrophages and neutrophils via Toll-like receptors (TLRs), which then activate inflammasomes, including NACHT, LRR and PYD domain-containing protein 3 (NLRP3), which then leads to caspase activation and overproduction of active IL-1β [7–11]. This step appears to be crucial in the pathogenesis of AOSD, leading to intense activation of immune cells and overproduction of several pro-inflammatory cytokines, including IL-6, IL-8, IL-17, IL-18 and tumor necrosis factor (TNF) [7–11]. Additionally, several other factors actively contribute to a heightened inflammatory response, which is often referred to as a “burst” or “storm” of cytokines [10, 12]. Apart from IL-1, which triggers retrograde activation of macrophages and neutrophils, various alarmins, such as S100 proteins and advanced glycation end products (AGEs) are involved in that process [8, 10, 11, 13–16]. In addition to amplifying mechanisms, deficiency or dysfunction of regulatory and anti-inflammatory mechanisms, including deficiency of regulatory T cells or natural killer (NK) cells, insufficient production of IL-10, deficiency in the clearance of lipid mediators or production of soluble AGE receptors (sRAGE) and other resolution associated molecular patterns (RAMPs), are important factors in the pathogenesis of autoinflammatory diseases [11, 17–20]. Moreover, genetic background appears to be an important factor in the pathogenesis of AOSD. Previous studies have shown a correlation between genetic susceptibility and polymorphism of the human leukocyte antigens (HLA), including HLA-Bw35, -B17, -B18, -B35, -DR2, -DR4, -DR5, -DQ1, -DRw6, -DRB1 and -DQB1 [6, 21]. Although many HLA alleles have been associated with disease predisposition, a trigger factor still needs to occur to start the chain reaction of inflammation. Some of the

clinical manifestations of AOSD, such as fever, lymphadenitis or increased liver enzymes, resemble viral or bacterial infection, suggesting that infection may initiate the inflammatory response in the course of AOSD. Reported infectious aetiological agents include adenovirus, human immunodeficiency virus (HIV), mycoplasma pneumoniae, parvovirus B19, Epstein-Barr virus (EBV), rubella virus, measles morbillivirus (MeV), hepatitis virus, influenza virus, rubella, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in late 2019 [6, 22, 23].

Clinical picture of AOSD

Fever is the most common clinical symptom in patients with AOSD, occurring almost daily during the active phase of the disease. The onset is sudden, with temperature often exceeding ≥ 39°C, rising in the afternoon or early evening. In addition, the fever may resolve spontaneously. In some cases, it may be the only clinical manifestation of AOSD and therefore constitutes an important diagnostic issue when assessing a fever of unknown aetiology. Joint pain is the second most common symptom in Still's disease, occurring both with and without fever. All joints of the body are affected. In the initial stages, joint involvement is usually mild and transient. Then, the joint pain gradually progresses to chronic arthritis. Commonly described symptoms of the disease include a salmon-pink colour transient skin rash accompanied by fever. AOSD may also manifest itself with other non-specific symptoms, including pharyngitis, myalgia, lymphadenopathy, hepatomegaly, splenomegaly, pleuritis and pericarditis [11, 24–26].

Concerning the clinical course, AOSD can be divided into three classic patterns: self-limiting (lasts < 1 year), recurrent (recurrence of symptoms may be frequent) and chronic (symptoms persist continuously for a year). Approximately 19–44% of AOSD patients demonstrate a self-limiting pattern with a one-off occurrence of clinical symptoms. Patients have only one symptomatic episode and full resolution of symptoms is achieved after a few weeks or months. Approximately 10–41% of patients experience a multiple pattern, where several discrete relapses of systemic or joint symptoms occur, with periods of remission between episodes. Moreover, approximately 35–67% of patients have a chronic disease with a high incidence of joint symptoms, usually involving the wrists, knees and ankles, which may lead to erosive arthritis [10, 11, 24, 25]. There are rare but life-threatening complications of AOSD, such as macrophage activation syndrome (MAS), diffuse alveolar haemorrhage, thrombotic thrombocytopenic purpura (TTP), pulmonary hypertension and meningitis, which should be

recognised as early as possible and treated promptly to reduce the progression of complications and mortality [24, 27].

Both the clinical picture and laboratory markers of Still's disease may resemble sepsis, which significantly complicates appropriate and early diagnosis. Despite the low prevalence of that disease entity, patients with AOSD are often misdiagnosed and treated inappropriately. Therefore, it is important to increase the diagnostic precision of AOSD, especially to quickly distinguish it from sepsis. Due to the lack of specific disease markers, there is a need to determine a more detailed procedure for the differential diagnosis of AOSD and sepsis [28].

Differential diagnosis of AOSD and sepsis

Early diagnostic differentiation of sepsis and systemic autoinflammatory diseases such as AOSD is a significant challenge in clinical practice. Several biomarkers have been proposed to distinguish between these two disease entities at an early stage of progression.

Haem oxygenase 1 is a 32,000 Da microsomal enzyme that breaks down haem to carbon monoxide, ferrous ions and biliverdin. It is produced by. e.g., monocytes and macrophages [29]. Ferritin is an intracellular protein that belongs to the acute phase proteins alongside C-reactive proteins (CRP), haptoglobin or ceruloplasmin. It is responsible for the storage of iron in the liver, which is then used in the synthesis of haemoglobin [29].

Both markers are valuable diagnostic tools in the recognition of Still's disease. Concentrations of both ferritin and haem oxygenase-1 are significantly higher in patients in the active phase of the disease compared to the control group of healthy individuals and those in the remission stage of the disease. Furthermore, these markers can also be used as indicators of disease relapse in patients with short remission times. This allows the conclusion that both ferritin and haem oxygenase-1 can be referred to as biomarkers of AOSD and could be included in the Yamaguchi criteria, as their elevated levels indicate Still's disease with high probability [29].

Low glycated ferritin concentrations may also indicate Still's disease in the presence of atypical pulmonary involvement, indicative of infectious disease. The normal glycated ferritin level is between 50 and 80%. In three patients with pulmonary symptoms, its levels were 11, 6 and 12%, respectively, which shows that it may also be an auxiliary diagnostic marker [30].

Heparin-binding protein (HBP) seems to be a promising marker in the differential diagnosis of AOSD and sepsis. It is produced by neutrophils in response to a developing infection in the

body. Relevant to the issue addressed in the article are the different HBP concentrations in both active and inactive forms of AOSD. A higher concentration of HBP is observed in the case of sepsis. Additionally, its level — like that of CRP or procalcitonin — increases in the case of inflammation. This indicates the high diagnostic value of the protein in the case of inflammatory diseases, as well as the disease entities under consideration [31].

The delta neutrophil index (DNI) may be another helpful marker for diagnosis. This is the ratio of immature neutrophils to the total number of neutrophils in the peripheral circulation. That parameter is calculated automatically. Based on the research, its concentration is slightly lower in patients with AOSD than in those with sepsis. Studies indicate that DNI may be a helpful indicator in the early stages of the disease. DNI enables the prognosis of sepsis probably better than other parameters, such as WBC or CRP. It is a disease-specific indicator [32].

Mean platelet volume (MPV) is a typical indicator of inflammation in the body. Its value is routinely given in peripheral blood smear test reports. While preparing the paper, it was noticed that the MPV value was lower in patients with AOSD than in the group of patients with sepsis. The diagnostic value increases with the simultaneous determination of ferritin levels. Their simultaneous measurement (MPV/ferritin) may indicate a specific disease entity. Low MPV and high ferritin are a typical picture of AOSD. In addition, the price of MPV determination is low, thus its every-time measurement seems reasonable [33, 34].

Red cell distribution width (RDW) is another helpful indicator in differentiating between sepsis and Still's disease in the early phase of the occurrence. It is usually used in the diagnosis of anaemia. This is because the automatic measurement method allows differences in red blood cell size to be determined. It was observed that in the case of sepsis, the RDW value is higher than in the case of Still's disease, and in both of these groups - higher than in the healthy control group. In contrast, haemoglobin and haematocrit values did not differ between the two groups, and RDW was inversely proportional to them. In turn, no significant correlations were found between RDW values and CRP, ferritin or WBC [35].

It is presumed that the RDW value may reflect precise changes in inflammation within a narrow spectrum and within a short time after hospitalisation. Furthermore, it is worth remembering that this is a cheap marker to implement. However, it should not be determined as a stand-alone parameter, but only as a supplement to ferritin concentration tests, the value of which is significantly higher in patients with AOSD [35].

Other parameters worth paying attention to are platelet haematocrit and lymphocytosis. The number of lymphocytes is significantly higher in patients with AOSD compared to those diagnosed with sepsis. These parameters should be considered together with ferritin. The relatively low cost also argues in favour of their determination each time. The simultaneous determination of PCT, lymphocytes and ferritin shows significant diagnostic value in differentiating AOSD from sepsis [36]. At the same time, platelet haematocrit is a parameter in the case of which many shortcomings have been found. The way in which retrospective data are measured and analysed does not fully reflect the true value of that parameter [37].

A helpful indicator for differentiating AOSD from sepsis is the PPR — platelet anisocytosis index (PDW) and platelets (PLT) to anisocytosis index (PDW) ratio. Its diagnostic value increases when determined in combination with ferritin. In both AOSD and sepsis patients, the PPR value is increased compared to the control group. A higher PPR value is noticed in patients with AOSD compared to those diagnosed with sepsis. PPR — like ferritin — is easy to determine, which further proves its significant diagnostic value [38]. However, the situation is different in the case of PDW (platelet anisocytosis index), which is higher in patients with sepsis [38].

Another helpful platelet parameter to distinguish between sepsis and Still's disease may turn out to be PMR — platelet count (PLT) to mean platelet volume (MPV). The PMR value is significantly higher in patients with AOSD compared to those with sepsis. It is a marker that, as one of several possible markers described above, can be determined together with ferritin to distinguish between Still's disease and sepsis. It can also be determined on its own, the cost of which is low. The parameters (PLT and MPV) required for PMR are not challenging to diagnose [28].

The miRNA profile (miR-142-5p, miR-101-3p, miR-29a-3p, miR-29c-3p and miR-141-3p) is also an interesting marker. miRNAs are single-stranded molecules, the length of which is from 21 to 23 nucleotides. They do not encode genetic information but are responsible for regulating translation and modulating messenger RNA, thereby ensuring gene expression. In patients with AOSD, the expression of the miRNA profile is significantly higher than in patients diagnosed with sepsis. Moreover, the level of miRNA also correlates with the activity of Still's disease. In the case of miR-101-3, the level increases similarly to other markers of inflammation, i.e. IL-6 or TNF-α [39].

IL-18 is a pro-inflammatory cytokine belonging to the IL-1 family. It is produced by, e.g., monocytes and macrophages. Most possibly, it is responsible for the activation of Th1 lymphocytes, which play a key role in the production of interleukins [IL-2, interferon gamma (INF-γ), TNF-α] in patients with AOSD [40]. FGF-2, in turn, is a fibroblast growth factor responsible for, e.g., embryogenesis, cell growth, healing processes but also tumour growth and development [41]. As studies have shown, relatively high levels of IL-18 are observed in AOSD patients compared to sepsis patients. IL-18 levels correlate positively with FGF-2, which is also a useful marker for differentiating AOSD and sepsis [40, 41].

Another diagnostically relevant marker may be the neutrophil (n) CD64 index profile. nCD64 is a high-affinity receptor for IgG, localised on neutrophils. That receptor is helpful in the diagnosis of sepsis, as its expression on neutrophils increases after contact with inflammatory cytokines or IFN-γ. A higher expression of nCD64 is observed in patients with Still's disease — compared to those diagnosed with sepsis. It should be mentioned that there is a positive correlation between nCD64 and procalcitonin or CRP [42].

sCD163 is a serum marker, the role of which in the diagnosis may be of great importance since its concentration is linked to ferritin produced by macrophages. The concentration of that marker is higher in people with active Still's disease, whereas no significant difference in sCD163 concentration was observed in patients with AOSD and sepsis. This means that the marker should not be used to differentiate between AOSD and sepsis, but only for active or inactive Still's disease. However, a positive correlation between sCD163 and ferritin levels was observed in patients with AOSD, which ultimately allows, thanks to the use of the second marker, to differentiate between AOSD and sepsis. In a study from 2014, the concentration of sCD163 in the lymph nodes of patients was detected using the ELISA method, which enabled the scientists to draw the above conclusions [43].

Below, there is a comparison of the described diagnostic markers and a determination of their usefulness in the differential diagnosis of AOSD and sepsis based on a review of the literature (Tab. 2).

Table 2. Biomarkers and their relevance in the differential diagnosis of Adult-onset Still's disease (AOSD) and sepsis

Biomarker	**Diagnostic significance**
Ferritin	Further studies are needed to include the biomarker in the

	Yamaguchi criteria
Glycated ferritin	Further studies are needed to determine the diagnostic utility
Haem oxygenase 1 (HO-1)	Further studies are needed to include the biomarker in the Yamaguchi criteria
Heparin-binding protein	Useful for diagnosis
Delta neutrophil index (DNI)	Useful for diagnosis in the early disease stage, complementary to ferritin
Mean platelet volume (MPV)	Useful for diagnosis, complementary to ferritin
PMR — platelet count (PLT) to mean platelet volume (MPV) ration	Useful for diagnosis as a single or complementary biomarker
PPR — platelet anisocytosis index (PDW) and platelets (PLT) to anisocytosis index ratio	Useful for diagnosis, correlation of PPR and ferritin
Platelet haematocrit (PLT)	Useful for diagnosis, complementary to ferritin
Red cell distribution width (RDW)	Useful for diagnosis in the early disease stage
Lymphocytes	Useful for diagnosis
Non-coding RNA molecules	Further studies are needed to determine the diagnostic utility
Interleukin 18 (IL-18)	Useful for diagnosis, correlation of IL-18 and ferritin Useful for diagnosis, correlation of IL-18 and FGF-2
sCD163	Useful for diagnosis, positive correlation with ferritin
nCD64	Useful for diagnosis

Conclusions

To sum up, this review shows that the determination of the described biomarkers in serum can be used in diagnosis for the early differentiation of AOSD and sepsis. Additionally, the determination of these parameters may be useful in monitoring the progress of Still's disease. Higher concentrations of ferritin, haem oxygenase 1, lymphocytes, some platelet parameters and interleukin-18 strongly support the diagnosis of AOSD, whereas an increase in heparin-

binding protein or an elevated delta neutrophil index suggest the occurrence of sepsis. Nevertheless, further studies are necessary to confirm the findings and justify their application in clinical practice.

Author contributions

Manuscript concept: P.K.; Methodology: N.L., M.F., Z.J., J.K., O.K., M.R., M.B., A.P., N.L., D.P., G.Z., P.K.; Visualization: N.L., M.F., Z.J., J.K., O.K., M.R., M.B., A.P., N.L., D.P., Gabriela Zemanek; Tables 1 and 2: N.L., M.F., Z.J. Manuscript writing: N.L. (20%), M.F. (20%), Z.J. (10%), J.K. (10%), O.K. (5%), M.R. (5%), M.B. (5%), A.P. (5%), N.L. (5%), D.P. (5%), G.Z. (5%), P.K. (5%); Critical review: N.L., M.F., Z.J., J.K., O.K., M.R., M.B., A.P., N.L., D.P., G.Z., P.K.

Conflict of interest

Authors declare no conflict of interest.

Funding

None declared.

References

1. Samborski W, Sikorska D. Choroba Stilla dorosłych. Stany nagłe w reumatologii, tom II. In: Kotyla P. ed. Stany nagłe w wybranych chorobach reumatycznych. VM Media Group, Gdańsk 2021.
2. Zhou D, Xie J, Wang J, et al. Establishment of a differential diagnosis method and an online prediction platform for AOSD and sepsis based on gradient boosting decision trees algorithm. Arthritis Res Ther. 2023; 25(1): 220, doi: 10.1186/s13075-023-03207-3, indexed in Pubmed: 37974244.
3. Yin S, Luo F, Xie J, et al. Identification of discriminatory factors and construction of nomograms for differentiating AOSD and sepsis. Clin Rheumatol. 2024; 43(1): 569–578, doi: 10.1007/s10067-023-06824-0, indexed in Pubmed: 38063950.
4. Levy MM, Fink MP, Marshall JC, et al. International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003; 29(4): 530–538, doi: 10.1007/s00134-003-1662-x, indexed in Pubmed: 12664219.

5. Sfriso P, Bindoli S, Galozzi P. Adult-Onset Still's Disease: Molecular Pathophysiology and Therapeutic Advances. Drugs. 2018; 78(12): 1187–1195, doi: 10.1007/s40265-018-0956-9, indexed in Pubmed: 30069732.
6. Macovei LA, Burlui A, Bratoiu I, et al. Adult-Onset Still's Disease-A Complex Disease, a Challenging Treatment. Int J Mol Sci. 2022; 23(21), doi: 10.3390/ijms232112810, indexed in Pubmed: 36361602.
7. Church LD, Cook GP, McDermott MF. Primer: inflammasomes and interleukin 1beta in inflammatory disorders. Nat Clin Pract Rheumatol. 2008; 4(1): 34–42, doi: 10.1038/ncprheum0681, indexed in Pubmed: 18172447.
8. Jamilloux Y, Gerfaud-Valentin M, Martinon F, et al. Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart. Immunol Res. 2015; 61(1-2): 53–62, doi: 10.1007/s12026-014-8561-9, indexed in Pubmed: 25388963.
9. Mellins ED, Macaubas C, Grom AA. Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions. Nat Rev Rheumatol. 2011; 7(7): 416–426, doi: 10.1038/nrrheum.2011.68, indexed in Pubmed: 21647204.
10. Mitrovic S, Fautrel B. New Markers for Adult-Onset Still's Disease. Joint Bone Spine. 2018; 85(3): 285–293, doi: 10.1016/j.jbspin.2017.05.011, indexed in Pubmed: 28529117.
11. Feist E, Mitrovic S, Fautrel B. Mechanisms, biomarkers and targets for adult-onset Still's disease. Nat Rev Rheumatol. 2018; 14(10): 603–618, doi: 10.1038/s41584-018-0081-x, indexed in Pubmed: 30218025.
12. Fautrel B. Adult-onset Still disease. Best Pract Res Clin Rheumatol. 2008; 22(5): 773–792, doi: 10.1016/j.berh.2008.08.006, indexed in Pubmed: 19028363.
13. Wittkowski H, Frosch M, Wulffraat N, et al. S100A12 is a novel molecular marker differentiating systemic-onset juvenile idiopathic arthritis from other causes of fever of unknown origin. Arthritis Rheum. 2008; 58(12): 3924–3931, doi: 10.1002/art.24137, indexed in Pubmed: 19035478.
14. Foell D, Roth J. Proinflammatory S100 proteins in arthritis and autoimmune disease. Arthritis Rheum. 2004; 50(12): 3762–3771, doi: 10.1002/art.20631, indexed in Pubmed: 15593206.
15. Foell D, Wittkowski H, Hammerschmidt I, et al. Monitoring neutrophil activation in juvenile rheumatoid arthritis by S100A12 serum concentrations. Arthritis Rheum. 2004; 50(4): 1286–1295, doi: 10.1002/art.20125, indexed in Pubmed: 15077313.

16. 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; 8: 369, doi: 10.3389/fphar.2017.00369, indexed in Pubmed: 28659802.
17. Shields AM, Thompson SJ, Panayi GS, et al. Pro-resolution immunological networks: binding immunoglobulin protein and other resolution-associated molecular patterns. Rheumatology (Oxford). 2012; 51(5): 780–788, doi: 10.1093/rheumatology/ker412, indexed in Pubmed: 22190690.
18. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature. 2014; 510(7503): 92–101, doi: 10.1038/nature13479, indexed in Pubmed: 24899309.
19. Hofmann SR, Kubasch AS, Ioannidis C, et al. Altered expression of IL-10 family cytokines in monocytes from CRMO patients result in enhanced IL-1β expression and release. Clin Immunol. 2015; 161(2): 300–307, doi: 10.1016/j.clim.2015.09.013, indexed in Pubmed: 26404542.
20. Chen DY, Chen YM, Lin CC, et al. The potential role of advanced glycation end products (AGEs) and soluble receptors for AGEs (sRAGE) in the pathogenesis of adult-onset still's disease. BMC Musculoskelet Disord. 2015; 16: 111, doi: 10.1186/s12891-015-0569-3, indexed in Pubmed: 25956266.
21. Ma Y, Meng J, Jia J, et al. Current and emerging biological therapy in adult-onset Still's disease. Rheumatology (Oxford). 2021; 60(9): 3986–4000, doi: 10.1093/rheumatology/keab485, indexed in Pubmed: 34117886.
22. Mitrovic S, Fautrel B. Clinical Phenotypes of Adult-Onset Still's Disease: New Insights from Pathophysiology and Literature Findings. J Clin Med. 2021; 10(12), doi: 10.3390/jcm10122633, indexed in Pubmed: 34203779.
23. Kaneko Y. Interluekin-6 inhibitors for the treatment of adult-onset Still's disease. Mod Rheumatol. 2022; 32(1): 12–15, doi: 10.1093/mr/roab004, indexed in Pubmed: 34894252.
24. Rao S, Tsang LSL, Zhao M, et al. Adult-onset Still's disease: A disease at the crossroad of innate immunity and autoimmunity. Front Med (Lausanne). 2022; 9: 881431, doi: 10.3389/fmed.2022.881431, indexed in Pubmed: 36072947.
25. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. J Autoimmun. 2018; 93: 24–36, doi: 10.1016/j.jaut.2018.07.018, indexed in Pubmed: 30077425.

26. Castañeda S, Vicente EF, González-Gay MA. [Adult-onset Still's disease]. Med Clin (Barc). 2016; 147(5): 217–222, doi: 10.1016/j.medcli.2016.03.034, indexed in Pubmed: 27207239.
27. Efthimiou P, Kadavath S, Mehta B. Life-threatening complications of adult-onset Still's disease. Clin Rheumatol. 2014; 33(3): 305–314, doi: 10.1007/s10067-014-2487-4, indexed in Pubmed: 24435354.
28. Ge S, Ma Y, Xie M, et al. The role of platelet to mean platelet volume ratio in the identification of adult-onset still's disease from sepsis. Clinics (Sao Paulo). 2021; 76: e2307, doi: 10.6061/clinics/2021/e2307, indexed in Pubmed: 33886787.
29. Kirino Y, Kawaguchi Y, Tada Y, et al. Beneficial use of serum ferritin and heme oxygenase-1 as biomarkers in adult-onset Still's disease: A multicenter retrospective study. Mod Rheumatol. 2018; 28(5): 858–864, doi: 10.1080/14397595.2017.1422231, indexed in Pubmed: 29278009.
30. Biron C, Chambellan A, Agard C, et al. Acute respiratory failure revealing adult-onset Still's disease: diagnostic value of low glycosylated ferritin level. Clin Rheumatol. 2006; 25(5): 766–768, doi: 10.1007/s10067-005-0078-0, indexed in Pubmed: 16283419.
31. Tian R, Chen X, Yang C, et al. Serum Heparin-Binding Protein as a Potential Biomarker to Distinguish Adult-Onset Still's Disease From Sepsis. Front Immunol. 2021; 12: 654811, doi: 10.3389/fimmu.2021.654811, indexed in Pubmed: 33868298.
32. Park HJ, Ha YJ, Pyo JY, et al. Delta neutrophil index as an early marker for differential diagnosis of adult-onset Still's disease and sepsis. Yonsei Med J. 2014; 55(3): 753–759, doi: 10.3349/ymj.2014.55.3.753, indexed in Pubmed: 24719144.
33. Luo L, Zhang L, Jiang J, et al. Role of mean platelet volume in differential diagnosis of adult-onset Still's disease and sepsis. Rev Assoc Med Bras (1992). 2021; 67(10): 1443–1447, doi: 10.1590/1806-9282.20210649, indexed in Pubmed: 35018973.
34. Frater JL, Shirai CL. Role of mean platelet volume in differential diagnosis of adult-onset Still's disease and sepsis. Rev Assoc Med Bras (1992). 2022; 68(6): 736–738, doi: 10.1590/1806-9282.20220190, indexed in Pubmed: 35584437.
35. Park HJ, Song J, Park YB, et al. Red blood cell distribution width is useful in discriminating adult onset Still's disease and sepsis within 24 hours after hospitalization. Korean J Intern Med. 2018; 33(6): 1234–1240, doi: 10.3904/kjim.2016.068, indexed in Pubmed: 28838228.

36. Zhang M, Xie M, Wang Y, et al. Combination value of biomarkers in discriminating adult onset Still's disease and sepsis. Wien Klin Wochenschr. 2021; 133(3-4): 118–122, doi: 10.1007/s00508-020-01668-z, indexed in Pubmed: 32430612.
37. Beyan C, Beyan E, Beyan C, et al. Plateletcrit May Not be a Marker for Recurrent Pregnancy Loss. Clin Appl Thromb Hemost. 2015; 21(6): 588–589, doi: 10.1177/1076029615579100, indexed in Pubmed: 25850918.
38. Liu JP, Wang YM, Zhou J. Platelet parameters aid identification of adult-onset still's disease from sepsis. Netherl J Med. 2019; 77(8).
39. Yang CA, Chen PK, Lan JL, et al. Expression signature of inflammation-associated long non-coding RNAs in adult-onset Still's disease. Clin Exp Rheumatol. 2021; 39 Suppl 132(5): 67–74, doi: 10.55563/clinexprheumatol/4jx6zy, indexed in Pubmed: 34524081.
40. Priori R, Colafrancesco S, Alessandri C, et al. Interleukin 18: a biomarker for differential diagnosis between adult-onset Still's disease and sepsis. J Rheumatol. 2014; 41(6): 1118–1123, doi: 10.3899/jrheum.130575, indexed in Pubmed: 24786926.
41. Koga T, Sumiyoshi R, Furukawa K, et al. Interleukin-18 and fibroblast growth factor 2 in combination is a useful diagnostic biomarker to distinguish adult-onset Still's disease from sepsis. Arthritis Res Ther. 2020; 22(1): 108, doi: 10.1186/s13075-020-02200-4, indexed in Pubmed: 32381117.
42. Liu Q, Gao Y, Yang T, et al. nCD64 index as a novel inflammatory indicator for the early prediction of prognosis in infectious and non-infectious inflammatory diseases: An observational study of febrile patients. Front Immunol. 2022; 13: 905060, doi: 10.3389/fimmu.2022.905060, indexed in Pubmed: 35967346.
43. Colafrancesco S, Priori R, Alessandri C, et al. sCD163 in AOSD: a biomarker for macrophage activation related to hyperferritinemia. Immunol Res. 2014; 60(2-3): 177–183, doi: 10.1007/s12026-014-8563-7, indexed in Pubmed: 25388964.