Editorial

Scoring Adult Onset Still's Disease

Adult-onset Still's disease (AOSD) is a systemic inflammatory disease of uncertain etiology. Patients with AOSD develop a combination of several disease manifestations. Some of these disease manifestations are arthritis, fever, leukocytosis, and evanescent rash. But, in parallel, various systemic manifestations such as splenomegaly and pneumonitis, among others, may occur.

The diagnosis of AOSD is problematic, because no single diagnostic test or characteristic histopathology exists. Patients sometimes suffer from delays in diagnosis including protracted efforts to exclude occult infection or neoplasm because AOSD is a rare diagnosis, and differential diagnoses must be excluded. The clinician should consider AOSD in the evaluation of undiagnosed fever of unknown origin, particularly if present in association with rheumatic complaints[1].

More than 99% of patients with AOSD manifest with fever > 39°C at some time during the course of their disease[2]. Most common is a high-spiking, once per day fever. Low-grade or atypical fever patterns are sometimes encountered in older patients (> 35 yrs). Febrile spikes are often accompanied by exacerbation of other systemic manifestations[1].

As the clinical presentation of AOSD varies and the spectrum of differential diagnoses is broad, unambiguous diagnostic criteria are needed. Several sets of classification criteria have been developed from retrospectively analyzed data[3,4,5,6,7,8,9,10] (see also Table 1), which points to the difficulty of identifying unambiguous criteria.

Almost all criteria include major symptoms of fever, leukocytosis, rash, and arthritis or arthralgia. All scores are split into major and minor criteria. Only the classification score of Crispin, *et al*[4] provides a scoring method for every single symptom. Since the score of Yamaguchi, *et al*[10] is the most sensitive (93.5%)[11], it is most often used for classification in patient cohorts.

An accurate diagnostic procedure requires consideration and exclusion of differential diagnoses. The clinical manifestations and laboratory features of AOSD and septic disease can be similar, e.g., serositis, arthritis, skin manifestations. Treatment of these 2 diseases, however, is different: Septic disease on one hand may be treated employing antibiotic or other antiinfective agents, while AOSD requires immunosuppressive agents. Immunosuppression in a septic patient may be counterproductive as initial treatment; similarly, antiinfective treatment of an AOSD patient may delay immunosuppression. Thus, differentiating these 2 diseases is important.

Besides the above mentioned AOSD classification and diagnostic criteria, Pouchot, *et al* published an activity score with a sensitivity of 92% and a specificity of 93% for discriminating active and non-active AOSD[12]. And, in this issue of *The Journal*, Rau, *et al*[13] used the same Pouchot score[12] in a changed version, adding arthritis and serum ferritin > 3000 μg/l as new factors instead of abdominal pain and splenomegaly. The other factors of the Pouchot score comprised fever, evanescent rash, pharyngitis, myalgia, pleuritis, pericarditis, pneumonia, lymphadenopathy, hepatomegaly or elevated liver enzymes, and leukocyte count > 15,000/μl. Each of these factors is scored as 1 point. A score > 4 is considered to indicate active disease.

Rau, *et al* pursued the question of whether the modified Pouchot score or serological assessment of cytokines, e.g., interleukin 6 (IL-6) and IL-8, could discriminate between acute and chronic AOSD and septic patients. The authors conclude that clinical scoring employing this modified Pouchot score distinguished between sepsis and chronic and acute AOSD. Cytokine levels, in contrast, were less helpful.

Their study deals with an important clinical question: Is the presentation of fever, high leukocyte count, high C-reactive protein level, and various organ involvement the manifestation of a septic disease or an autoimmune disease? The question becomes more important if the organ manifestations comprise arthritis and skin, in which case the clinician should question whether the disease may rather be AOSD or septic disease. As mentioned, this is of special importance due to the different treatment strategies. However, none of the 12 septic patients assessed by Rau, *et al* had evanescent rash or arthritis. Moreover, the presence of ferritin > 3000 μg/l appears to discriminate between most septic and AOSD patients. Fautrel, *et al* demonstrated that positive ferritin is more frequently found in patients with AOSD[14]. Consequently, larger trials comprising patients with AOSD and patients with sepsis and evanescent rash or septic arthritis are needed to identify good discriminating scores for these diseases.

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Table 1. Comparison of different scores for adult-onset Still's disease.

Manifestation	Goldman 1980[7]	Cush 1987[2]	Calabro 1986[3]	Reginato 1987[9]	Kahn 1991[8]	Yamaguchi 1992[10]	Fautrel 2001[14]	Crispin 2005[4*]
Fever	XX	XX	XX	XX	XX	XX	XX	XX
Serological factors								
Leukocytosis	XX	X	X	XX	XX	XX	XX	18
Liver dysfunction				X		XX		
Negative ANA	XX	XX	XX		XX	X		
Negative RF	XX	XX	XX			X		
Ferritin							XX	
Organ manifestations								
Rash	X	X	XX	XX	XX	XX	XX	5
Arthralgia/arthritis	XX	XX	XX	XX	XX	XX	XX	10
Sore throat/pharyngitis				X	X	X	XX	7
Pleuritis/pericarditis	X	X		X	X			
Splenomegaly	X	X	X	X				5
Lymphadenopathy		X	X	X		X		
Hepatomegaly		X		X				
Organ involvement				X				
Myalgia			XX		X			
Similar episode in childhood					XX			
Positive diagnosis	5 major, > 1 minor	3 major, 2 minor	4 major, 2 minor	4 major, or fever + arthritis + 1 major + 1 minor	4 major or 3 major + 2 minor	5 positive criteria, 2 major	4 major or 3 major + 2 minor	≥ 30 points

* Criteria display different values. XX: major criteria; X: minor criteria; ANA: antinuclear antibodies; RF: rheumatoid factor.

Finally, identifying or developing scores that can definitely discriminate septic disease from AOSD may be important. Further, finding an easy to assess clinical disease activity score (e.g., comparable to EULAR/American College of Rheumatology criteria) that can be used during followup of patients may help in conducting clinical trials in AOSD. We think that these questions, tackled by the publication of Rau, *et al*, are important and hope that an easy to use, unambiguous score may be developed in the future.

RUEDIGER B. MUELLER, MD,
Department of Rheumatology,
Kantonsspital St. Gallen,
Rorschacherstr. 95,
9007 St. Gallen, Switzerland;
AHMED SHERIFF, PhD,
Department of Nephrology,
Charité-Virchow Klinikum,
Augustenburger Platz 1,
13353 Berlin, Germany

Address correspondence to Dr. Sheriff. E-mail: Ahmed.Sheriff@charite.de

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