Clinical Manifestations but not Cytokine Profiles Differentiate Adult-onset Still's Disease and Sepsis

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ABSTRACT. ***Objective.*** To analyze clinical manifestations, serum ferritin, and serum cytokine levels in patients with adult-onset Still's disease (AOSD) or bacterial sepsis and to evaluate their potential use for differential diagnosis.

Methods. Twenty-two consecutive patients with the first flare of AOSD and 6 patients with an established diagnosis of AOSD under immunosuppressive therapy were compared with 14 patients with bacterial sepsis. Clinical manifestations were scored in a Pouchot AOSD activity score including elevated serum ferritin levels to obtain a modified Pouchot score. Serum cytokine profiles were analyzed from each patient.

Results. The scores of clinical manifestations using a modified Pouchot activity score were significantly higher in patients with active untreated AOSD (mean 5.60 ± 1.93) compared with patients with chronic AOSD (mean 1.16 ± 0.98; $p < 0.001$) and patients with sepsis (mean 2.38 ± 1.19; $p < 0.001$). A modified Pouchot score ≥ 4 shows a sensitivity of 92% and a specificity of 93% for active AOSD. Serum cytokine levels of interleukin 1ß (IL-1ß), IL-6, IL-8, IL-10, IL-12, IL-18, interferon-γ, tumor necrosis factor-α, and calprotectin were elevated in acute AOSD and sepsis. Significant differences were detected only in patients with sepsis who had higher levels of IL-6 and IL-8. The overlap of the 2 groups limits the use of cytokines for differential diagnosis in individual patients.

Conclusion. A modified Pouchot AOSD activity score including elevated serum ferritin levels was more useful to confirm the diagnosis of AOSD compared to patients with sepsis. Elevated serum cytokines correlate with inflammation but are of limited use to differentiate between active AOSD and bacterial sepsis. (J Rheumatol First Release September 1 2010; doi:10.3899/jrheum.100247)

Key Indexing Terms:

ADULT-ONSET STILL'S DISEASE	SEPSIS	INTERLEUKIN 1ß
INTERLEUKIN 6	INTERLEUKIN 8	CALPROTECTIN

An immediate diagnosis of patients presenting with systemic inflammatory disorders is still a great challenge in clinical practice. Differentiation between microbial infections and sepsis and rheumatic diseases such as adult-onset Still's disease (AOSD) remains especially difficult in many cases. AOSD is a rare, systemic inflammatory disorder of unknown origin occurring with spiking fever, evanescent rash, arthralgia or arthritis, sore throat, lymphadenopathy, hepatosplenomegaly, and myalgia[1,2]. In the acute phase, all organ systems can be affected and can present as pleuritis, pericarditis, acute respiratory distress syndrome, acute renal failure, acute liver failure, thrombotic thrombocytopenic purpura, or aseptic meningoencephalitis[2,3]. Laboratory tests show a strong inflammatory reaction associated with leukocytosis, anemia, increased levels of acute-phase reactants in serum, hyperferritinemia, and elevated hepatic enzymes[2,3,4]. Patients with AOSD can present with single or recurrent inflammatory attacks or with a persistent inflammatory reaction[5]. Recent studies have investigated cytokine signatures in patients with AOSD. Elevated interleukin 18 (IL-18) levels were found in acute and chronic AOSD and some studies proposed IL-18 as a diagnostic marker and indicator of disease severity[6,7,8,9]. IL-18 is produced by activated monocytes and is considered to orchestrate a type 1 T helper cell (Th1) response in patients with AOSD[6]. Further, activated monocytes secrete IL-6, IL-8, and tumor necrosis factor-α (TNF-α)[10,11] and Th1 cells secrete interferon-γ (IFN-γ), IL-2, and TNF-α[6,8], confirming the role of monocytes and Th1 cells in the pathogenesis of AOSD.

Patients with systemic microbial infections and sepsis present with distinct patterns in the ways that organs are affected[12]. Laboratory tests show nonspecific inflammation, and therapeutic decisions are based on clinical and laboratory findings with limited accuracy[13]. Recent studies investigated cytokine profiles including those of IL-1ß, IL-6, IL-8, IL-10, TNF-α, and procalcitonin to identify patients with

microbial sepsis. Elevated levels of IL-1ß, IL-6, TNF-α, and IL-10 have been described in several studies[14,15]. Serum levels of IL-8 and IL-18 were also elevated in patients with sepsis[14,16,17]. Therefore, neither inflammatory measurements nor organ dysfunction, nor the use of single biomarkers alone, can sufficiently differentiate between microbial sepsis and an autoinflammatory condition imitating sepsis. Some studies suggested procalcitonin as a biomarker for infections with gram-negative bacteria[18,19], but procalcitonin was also elevated in patients with AOSD[20], Wegener's granulomatosis[21], Behcet's disease[22], and Kawasaki disease[23] in the absence of an infection.

Calprotectin is produced by macrophages and neutrophils and is also known as a heterodimer of the myeloid-related proteins (MRP)-8 and MRP-14[24,25]. Calprotectin belongs to the S100 protein family and is also referred to as S100 A8/A9. Increased serum calprotectin levels have been found in rheumatoid arthritis (RA)[26], Crohn's disease[27], and multiple sclerosis[28]. In patients with juvenile idiopathic arthritis, calprotectin has been suggested as a marker for disease activity[26]. Recent *in vitro* and *in vivo* studies have shown that calprotectin might be involved in dysregulation of cardiac contractility in systemic inflammatory disease[29], indicating that calprotectin could be an indicator or mediator of multiorgan failure associated with sepsis.

We investigated cytokine profiles in patients with AOSD and sepsis to identify crucial mediators in the pathomechanism and to identify biomarkers that could be used for the differential diagnosis.

MATERIALS AND METHODS

Patients and healthy controls. Twenty-eight patients with AOSD were treated at the university hospital of Heidelberg between 2006 and 2008. All patients fulfilled the AOSD classification criteria by Yamaguchi, *et al*[30]. Serum samples from 18 patients with AOSD were available for cytokine analysis. The results were separately analyzed in patients with acute untreated disease (aAOSD; n = 12) and with chronic disease activity (cAOSD; n = 6) according to clinical measurements and elevated serum C-reactive protein (CRP) levels. AOSD activity was assessed by a modified Pouchot score as published, with 1 modification[3]. Recently, serum ferritin was proposed as a marker of disease activity[31] and the Fautrel classification criteria of AOSD included glycosylated ferritin[32]. Therefore, we included serum ferritin to obtain a modified Pouchot score[3] comprising 12 disease manifestations: fever, evanescent rashes, sore throat, arthritis, myalgia, pleuritis, pericarditis, pneumonitis, lymphadenopathy, hepatomegaly or abnormal liver function tests, elevated leukocyte count > 15,000/μl, and serum ferritin > 3000 μg/l.

The sepsis group consisted of 14 patients with systemic microbial infection who were treated at the intensive care units at the university hospital in Heidelberg. All patients in the sepsis group met the sepsis definition criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference in 1991[33]. Blood samples were collected during the first 3 days of hospitalization.

Seven healthy blood donors were included in this study as a control group. All patients gave written informed consent. Acquisition and storage of serum samples was approved by the local ethics committee at the University of Heidelberg.

Cytokine assessment. Serum samples were collected between 9 AM and 11 AM to minimize diurnal variations of serum cytokines. Samples were processed within 1 hour and serum aliquots were stored at –70°C. FlowCytomix Multiplex (Bender MedSystems, Vienna, Austria) was used for detection of serum levels of IL-1ß, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-18, IFN-α, IFN-γ, TNF-α, and TNF-ß, according to the manufacturer's instructions. A commercial ELISA test was used for the measurement of calprotectin (PromoCell, Heidelberg, Germany).

Statistical methods. The Wilcoxon signed-rank test was employed for comparison of serum cytokine levels. The correlation coefficient was obtained by nonparametric Spearman's rank correlation test. P values < 0.05 were considered statistically significant.

RESULTS

Clinical characteristics. Clinical data were available from 15 male and 13 female patients with AOSD with a mean age (± SD) at disease onset of 32.2 ± 16.0 years. Patients with AOSD presented with daily high spiking fever (n = 26), arthritis/arthralgia (n = 27), evanescent rash (n = 16), elevated leukocyte count (n = 22), pharyngitis (n = 9), splenomegaly (n = 6), and elevated liver enzymes (n = 14) at disease onset. All 28 patients with AOSD received pulses of systemic glucocorticosteroids. In addition, some patients were treated with methotrexate (n = 20), leflunomide (n = 4), azathioprine (n = 2), cyclophosphamide (n = 1), and sulfasalazine (n = 1). Patients with chronic AOSD were treated with the biologics anakinra (n = 7), infliximab (n = 4), adalimumab (n = 3), and etanercept (n = 2) during the course of the disease. The clinical manifestations of all 28 patients with AOSD at the time of blood draw are shown in Table 1. The modified Pouchot activity score[3] was significantly higher in patients with aAOSD (mean = 5.60 ± 1.93) compared with patients with cAOSD (mean = 1.16 ± 0.98; p < 0.001) and patients with sepsis (mean = 2.38 ± 1.19; p < 0.001; Table 1), confirming that the modified Pouchot activity score is a useful clinical tool for differentiation between acute and chronic courses of AOSD and sepsis.

Serum samples were available from 18 of 28 patients with AOSD in our AOSD cohort. Twelve previously untreated patients with a flare and with elevated inflammatory measurements (CRP > 20 mg/l) were considered as aAOSD. Six patients with long-lasting disease received therapy with 1 or more immunosuppressive drugs. These patients had normal inflammatory measurements (CRP < 5 mg/l) and were considered as having cAOSD.

Fourteen patients with bacterial sepsis were chosen as a control group because of similar clinical symptoms. Six female and 8 male patients with a mean age (± SD) of 60.9 ± 16.8 years and serum CRP levels > 75 mg/l were included in our study. Eight patients with sepsis had pneumonia or were immunocompromised because of hematologic malignancies (n = 4). Three patients acquired sepsis after autologous blood stem cell transplant and were included after engraftment of blood stem cells. Six of 14 patients died during hospitalization. Serum samples from all 14 patients with sepsis and from 7 healthy blood donors (5 men, 2 women, mean age 55.1 ± 8.4 yrs) were acquired and cytokine profiles were analyzed.
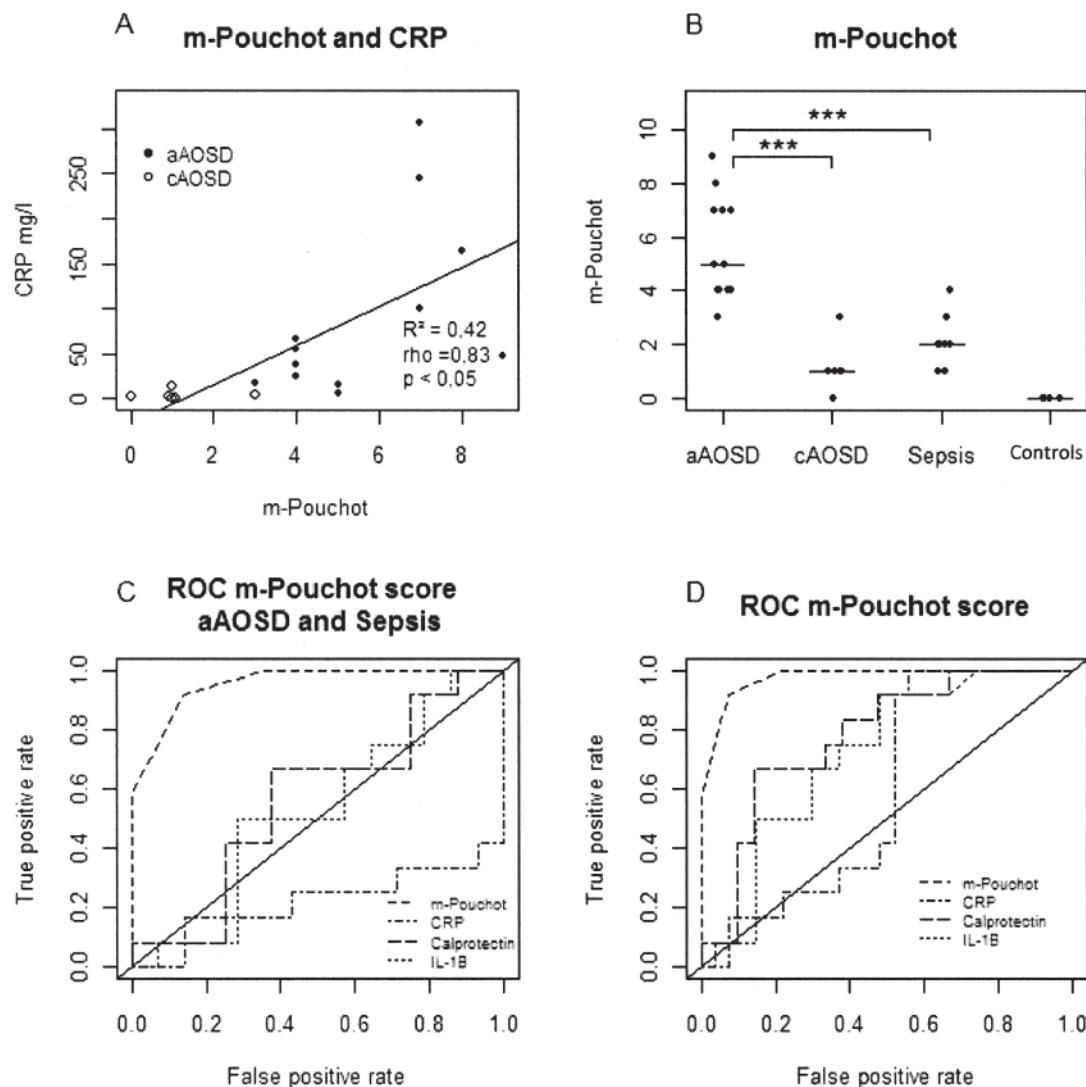
Figure 1. The modified Pouchot adult-onset Still's disease (AOSD) activity score correlates with C-reactive protein (CRP) levels in patients with acute or chronic AOSD (A) and differentiates active disease (aAOSD), inactive chronic disease (cAOSD), and patients with sepsis (B). Receiver-operation characteristic (ROC) curves for the modified Pouchot score and serum markers in patients with active AOSD and bacterial sepsis (C) and in all patients and blood donors (D) show a good discrimination of the modified Pouchot score but limited sensitivity and specificity of serum markers for the differential diagnosis between AOSD and sepsis. ***p < 0.001.

Routine laboratory test results. Twelve patients with aAOSD had anemia with Hb (mean ± SD) of 10.8 ± 2.1 g/dl, elevated leukocyte count 20,700 ± 5,100/μl, normal thrombocyte count, and elevated CRP levels of 102.8 ± 98.4 mg/l. Seven of 12 patients with aAOSD had elevated serum ferritin levels > 3000 μg/l, mean 10,327.7 ± 17,039.3 μg/l, at the time of the blood draw. Liver enzymes were elevated [glutamate pyruvate transaminase (GPT) 260.7 ± 433.4 U/l, glutamate oxalacetate transaminase (GOT) 632.4 ± 1136.8 U/l, lactate dehydrogenase (LDH) 563.2 ± 515.8 U/l] in 8 patients with aAOSD and 2 patients with cAOSD. CRP levels were 4.4 ± 4.8 mg/l in 6 patients with cAOSD.

An additional 10 patients with aAOSD but without avail-able serum samples were included in this cohort and were analyzed from a clinical perspective and routine laboratory findings. During the acute phase of their disease, these patients with aAOSD had anemia with Hb 11.4 ± 1.8 g/dl, leukocyte counts of 14,330 ± 5,600/μl, normal thrombocyte counts, CRP levels of 123.6 ± 104.1 mg/l, and serum ferritin levels of 4,606.0 ± 12,396.7 μg/l. Liver enzymes were elevated in 6 of 10 patients with aAOSD (GPT 150.0 ± 330.9 U/l, GOT 223.7 ± 698.7 U/l, LDH 392.1 ± 402.9 U/l).

All 14 patients with sepsis had elevated CRP levels (157.2 ± 127.0 mg/l), anemia (Hb 9.6 ± 1.4 g/dl), and thrombocytopenia (103,400 ± 69,300/μl). Eight of 14 patients with sepsis had elevated leukocyte counts > 13,000/μl, and

Table 1. Clinical conditions of patients with adult-onset Still's disease (AOSD).

Clinical Conditions	Acute AOSD, n = 22	Chronic AOSD n = 6	Sepsis, n = 14
Fever	20	2	12
Evanescent rash	10	0	0
Pharyngitis	4	2	0
Arthritis	20	3	0
Myalgia	10	3	0
Pleuritis	7	0	2
Pericarditis	5	0	0
Pneumonitis	4	0	8
Lymphadenopathy	3	1	1
Hepatomegaly or elevated liver enzymes	11	0	2
Leukocyte count > 15,000/μl	14	0	5
Ferritin > 3000 μg/l	19	1	1
Mean (SD)	5.56 (1.67)	1.17 (0.98)	2.36 (0.93)
Median	5.00	1.00	2.00
p		< 0.001	
p			< 0.001

5 patients with sepsis were leukopenic with < 4000/μl. Although leukopenia was not associated with low cytokine levels, patients with sepsis < 1500 leukocytes/μl were excluded from our study. Healthy donors had normal laboratory results.

Modified Pouchot scores. Modified Pouchot scores and CRP levels showed a significant correlation in patients with aAOSD and cAOSD (R^2 = 0.42, rho = 0.83, p < 0.05; Figure 1A). The variation of the modified Pouchot score in individual patients shows a minimal overlap of both groups (Figure 1B). Therefore, a modified Pouchot score ≥ 4 can be used as a discrimination threshold for patients with active AOSD and bacterial sepsis. Receiver-operation characteristic (ROC) curves indicate that the modified Pouchot score has a high sensitivity and specificity for the diagnosis of active AOSD and for the differential diagnosis between active AOSD or sepsis (Figure 1C). In addition, ROC curves of the modified Pouchot score also indicate a high sensitivity and specificity for active AOSD compared with chronic-inactive AOSD and sepsis (Figure 1D). A modified Pouchot score cutoff value ≥ 4 predicted the correct diagnosis with good sensitivity (92%), specificity (93%), a negative predictive value of 96%, a positive predictive value of 85%, and an area under the ROC curve of 0.98 (Table 2). Other serum markers including IL-6, IL-8, IL-10, IL-12p70, IL-18, TNF-α, and IFN-γ show even lower sensitivities and specificities (data not shown) and are not useful for differentiation between active AOSD and sepsis.

Serum cytokine profiles in patients with AOSD and sepsis. Serum samples were available from 18 patients with AOSD (12 aAOSD, 6 cAOSD), 14 patients with sepsis, and 7 healthy blood donors. IL-1ß (Figure 2A) and IL-8 (Figure 2C) were detected in almost all sera, but IL-6 (Figure 2B) and IL-10 (Figure 2D) were barely detectable in healthy donors. IL-1ß, IL-6, and IL-10 levels were up to 10 pg/ml and IL-8 levels up to 230 pg/ml in healthy donors and patients with cAOSD (Figure 2).

Serum cytokine levels for IL-1ß, IL-6, IL-8, and IL-10 were elevated in patients with aAOSD and sepsis but not in patients with cAOSD or healthy donors (Figure 2 A–D). Concentrations of IL-1ß were detected up to ~1000 pg/ml, and IL-6, IL-8, and IL-10 were detected up to 11,647 pg/ml. The highest levels of IL-6 and IL-8 were detected in patients with sepsis (Figure 2). Also, medians of IL-6 and IL-8 were significantly higher in patients with sepsis compared to patients with aAOSD (Figure 2B, 2C; p < 0.01).

Table 2. Sensitivity, specificity, predictive values, and area under the receiver-operation characteristic curve (AUC ROC) for modified Pouchot score and serologic measurements.

Factor	Cutoff Value	Sensitivity, %	Specificity, %	NPV, %	PPV, %	AUC ROC
Modified Pouchot score	≥ 4	92	93	96	85	0.98
CRP	15.6 mg/l	92	48	93	44	0.59
IL-1ß	10.9 pg/ml	92	52	93	46	0.72
IL-6	7.2 pg/ml	83	48	87	42	0.56
IL-8	40.6 pg/ml	75	41	79	36	0.44
Calprotectin	3.6 ng/ml	83	62	87	56	0.77

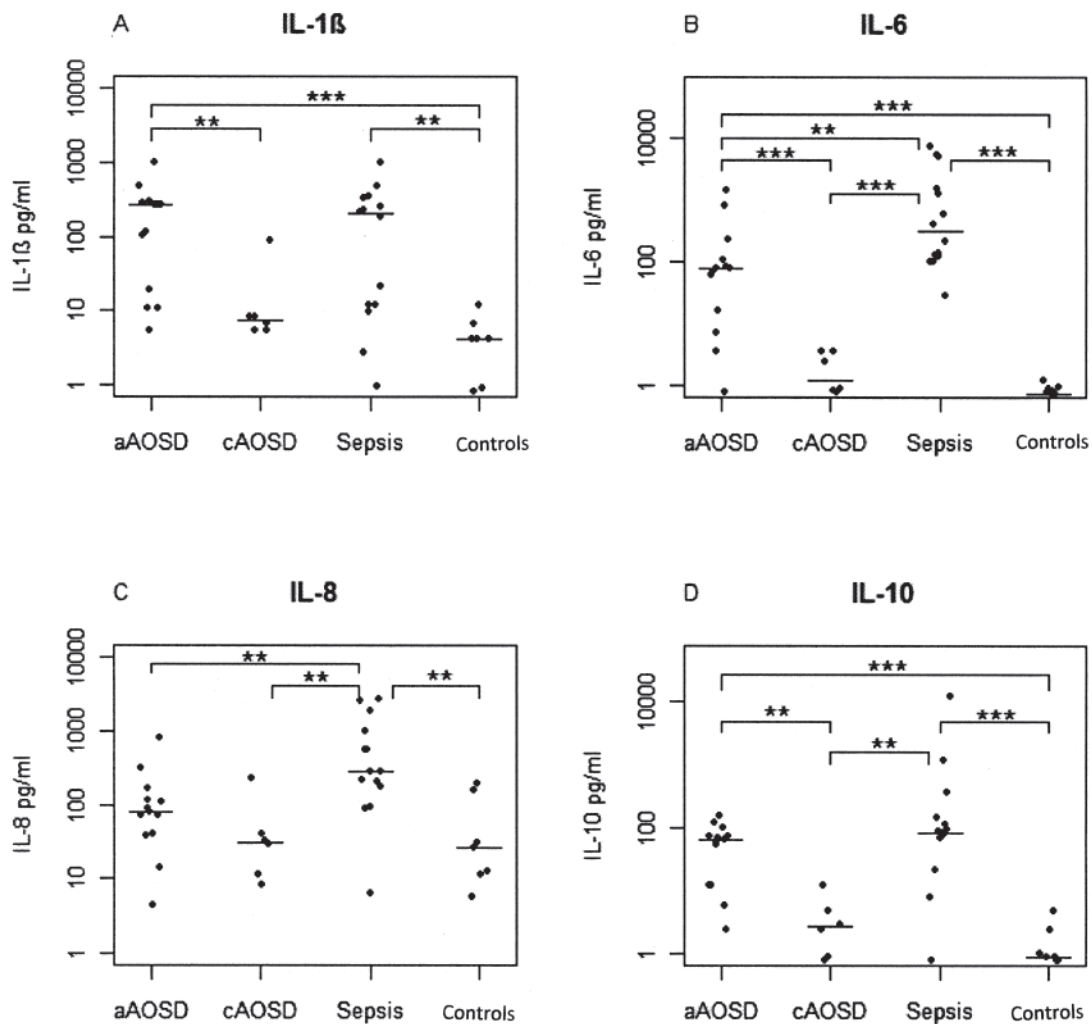NPV: negative predictive value; PPV: positive predictive value; CRP: C-reactive protein; IL: interleukin.

Figure 2. Serum levels of interleukin (IL)-1ß, IL-6 (B), IL-8 (C), and IL-10 (D) in patients with active adult-onset Still's disease (aAOSD; n = 12), chronic disease activity (cAOSD; n = 6), sepsis (n = 14), and in controls (n = 7). Medians are shown as horizontal lines. Statistical analyses were performed using a Mann-Whitney U test. **$p < 0.01$, ***$p < 0.001$.

Our data indicated that patients with sepsis could be differentiated from patients with aAOSD by higher levels of IL-6 and IL-8. However, although differences were statistically significant, we observed a broad overlap of cytokine levels in single patients (Figures 2B, 2C), compromising the usefulness of these cytokines in individual patients.

The monocyte-derived cytokines IL-12p70 (Figure 3A), TNF-α (Figure 3C), and calprotectin (Figure 3D), and the Th1 lymphocyte-derived IFN-γ (Figure 3B) showed a similar distribution with high serum levels in patients with aAOSD and sepsis and moderate or low levels in patients with cAOSD and healthy donors. Calprotectin was detected in sera at concentrations between 500 and 9000 pg/ml (Figure 3D). Significantly elevated calprotectin levels were detected in patients with aAOSD and sepsis with no significant difference between the 2 groups (Figure 3D).

We did not detect any significant differences of these cytokines between patients with aAOSD and patients with sepsis.

The highest concentrations of the monokine IL-18 were detected up to ~200,000 pg/ml in individual patients with aAOSD but also in patients with sepsis (data not shown). However, because of the broad range of IL-18 levels in all groups of patients, we did not find significant differences between patients with active AOSD and those with sepsis (data not shown).

DISCUSSION
Patients with AOSD exhibit a combination of several disease manifestations. An accurate diagnostic procedure requires consideration and exclusion of differential diagnoses and recognition of typical clinical and laboratory findings of AOSD. The clinical and laboratory features of bacterial sepsis can be similar to those of active AOSD. Our
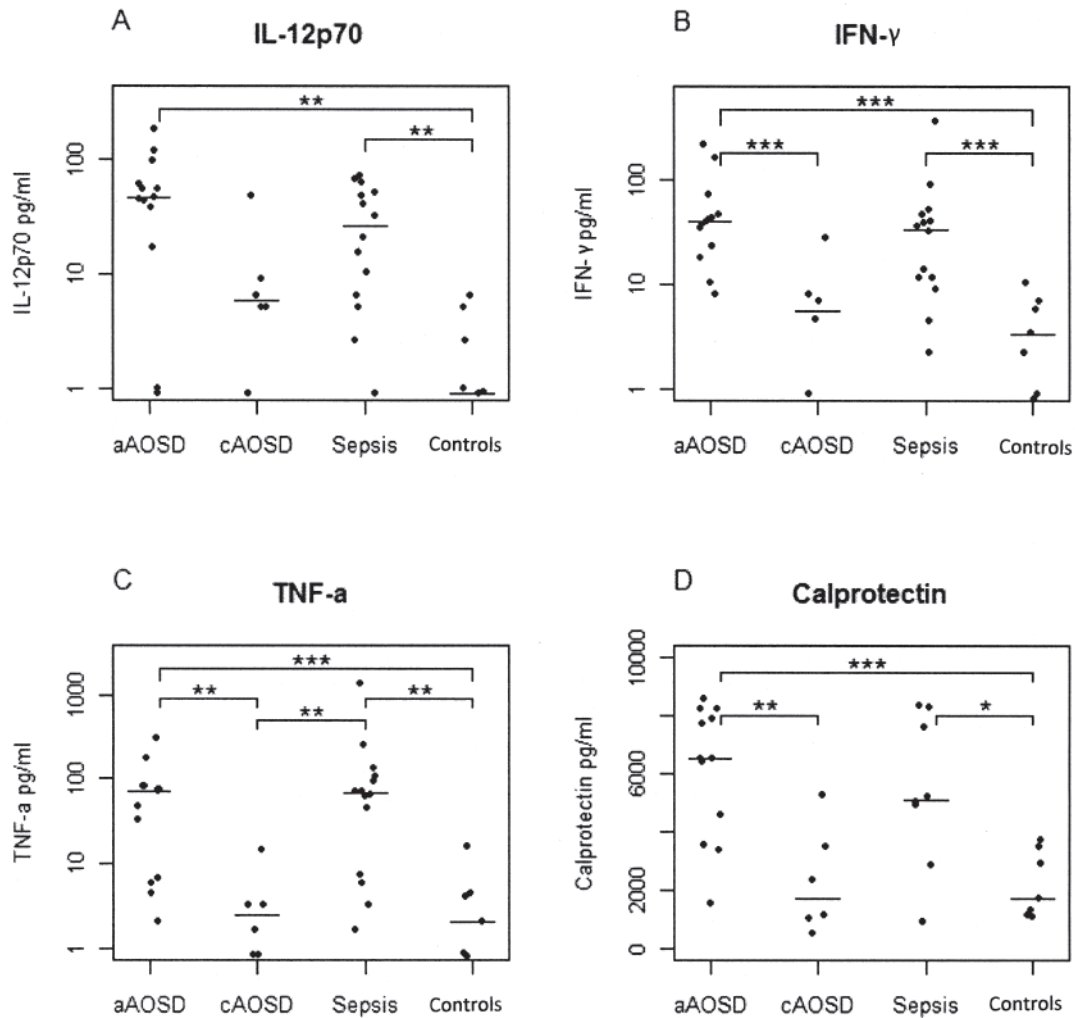
Figure 3. Serum levels of IL-12p70 (A), interferon-γ (IFN-γ) (B), tumor necrosis factor-α (TNF-α) (C), and calprotectin (D) in patients with aAOSD, cAOSD, sepsis, and controls. Medians are shown as horizontal lines. Statistical analyses were performed using the Mann-Whitney U test. *p < 0.05, **p < 0.01, ***p < 0.001.

results show that a modified Pouchot score combines information about clinical symptoms and laboratory results and shows a minimal overlap in individual patients. Therefore, a modified Pouchot score can differentiate between AOSD and bacterial sepsis. A modified Pouchot cutoff score ≥ 4 shows a sensitivity of 92% and a specificity of 93% for the diagnosis of AOSD.

We investigated whether serum cytokine levels can contribute to the differential diagnosis between AOSD and bacterial sepsis. A plethora of studies investigated cytokine profiles in patients with AOSD[6,7,8,9,10,11] and bacterial infection[12,13,14,15,16,17,18,19], but to our knowledge this is the first study that directly compares serum cytokines in patients with active AOSD or bacterial sepsis. Elevated monocyte-derived cytokines such as IL-6, IL-8, IL-18, and TNF-α[6,7,8,9,10,11] and Th1-derived cytokines such as IFN-γ indicated that activated monocytes and activated Th1 cells probably have a crucial role in the pathogenesis of AOSD. However, similar results were also reported in patients with bacterial sepsis[12,14,15,16,17,18,19]. These results were confirmed by our data. Significantly higher levels of IL-6 and IL-8 were detected in sera from patients with sepsis compared to active AOSD. However, because of the broad overlap of the 2 groups, these cytokines are of limited use for the differential diagnosis in clinical practice. Other cytokines did not show significant differences between patients with AOSD and patients with sepsis.

Activated monocytes secrete IL-1ß, IL-6, IL-8, IL-18, and TNF-α. Synthesis of IL-1 and IL-18 requires activation of Toll-like receptors and nuclear factor-κB as well as activation of intracellular Nod-like receptors and subsequent interaction of an adaptor-mediated multiprotein complex called the inflammasome. The inflammasome activates caspase-1, which cleaves inactive proleukines into biologically

active IL-1 and IL-18, which could be secreted by monocytes[34]. IL-1ß is the principal pyrogenic cytokine[34] that might be responsible for the daily spiking fever in patients with aAOSD. Intrinsic overstimulation of IL-1ß production is associated with autoinflammatory syndromes, which show similar clinical signs during a flare compared with patients with AOSD or sepsis. Significantly elevated levels of IL-1ß were also detected in patients with active disease, which is consistent with previous reports in patients with aAOSD[34] or sepsis[14,35]. Because large numbers of IL-1ß receptors are abundant in all tissues, unbound IL-1ß has a very short lifetime *in vivo*[34], indicating that we probably detect only a small amount of total IL-1ß. An intrinsic overproduction of IL-1ß can be reduced with drugs such as anakinra, rilonacept, or canakinumab. However, these biologic drugs probably enhance immunosuppression in patients with sepsis, which might cause death. Therefore, a rapid and reliable differentiation between AOSD and sepsis is mandatory before the initiation of anti-IL-1ß targeted therapy.

Calprotectin is another biomarker that is produced by activated monocytes. Good correlations between calprotectin and CRP and other acute-phase reactants were reported recently in patients with juvenile idiopathic arthritis[26], polymyalgia rheumatica[36], and RA[37]. Our data show that patients with aAOSD have significantly higher serum calprotectin levels than patients with cAOSD, but calprotectin levels cannot differentiate between microbial and intrinsic inflammation.

Previous studies suggested that hypoglycosylated serum ferritin (below 20% of total serum ferritin) could help to differentiate AOSD from other inflammatory conditions[38]. However, the same report showed that hypoglycosylated serum ferritin can also be detected in patients who are non-AOSD but have bacterial infections or systemic disease[38], indicating overlapping conditions. In addition, glycosylated serum ferritin tests were not routinely available in many institutions. Another recent report suggested the use of procalcitonin to differentiate between autoinflammatory disease activity and bacterial infection in patients with AOSD[39]. However, our experience with procalcitonin indicated a limited specificity of procalcitonin for bacterial infections in patients with autoimmune or autoinflammatory diseases. Therefore, procalcitonin was not determined routinely in our institution.

Some limitations of our study are the low number of patients and the restriction to 13 cytokines. Cytokines such as IL-1ß, IL-6, and TNF-α are known to exhibit diurnal variations. In addition, detection of cytokines can be compromised by soluble cytokine receptors and a short half-life *in vivo*[40,41]. To minimize these effects, we standardized our sample preparation procedure as indicated, but we cannot fully exclude these variations from our study.

Our data show that the modified Pouchot score compris-

ing typical clinical signs and laboratory findings can differentiate between patients with AOSD and patients with bacterial sepsis. Serum cytokines are elevated in both conditions and are of limited use to differentiate between AOSD and bacterial sepsis.

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