

PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY CLINICAL GUIDELINES: SYSTEMIC ARTHRITIS

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Introduction

Systemic arthritis is a chronic inflammatory multisystem disease with flares and clinical and laboratory signs of acute inflammation, which represents 10 to 20 %

of JIA patients. This disease affects equally boys and girls, and there is a slight predominance of cases occurring between the first and the fourth year of life, but less marked than in other forms of JIA, such as oligo- or poly-arthritis. It is characterised by daily fever spikes, arthritis and/or polyarthralgias, an evanescent rash, lymphoid organ hypertrophy, and/or serositis. There is a large differential diagnosis including many infectious, malignant and inflammatory diseases. It is an exclusion diagnosis, and typical or specific autoantibodies are not known. The therapy is based on medical measures (antiinflammatory and immunosuppressive drugs), physical therapies, education and if necessary surgical procedures.

Systemic arthritis is a potentially severe disease, which requires highly specialised paediatric care for diagnostic and therapeutic measures.

Definition (according to the ILAR classification of Durban, 1997)

1. Patient younger than 16 years at disease onset with:
2. Arthritis of at least 6 weeks duration of one or more joints, at the same time or after the onset of
3. daily fever spikes for at least two weeks and
4. associated with one or more of the followings:
 - Evanescent, not fixed erythematous rash
 - Generalised lymph node enlargement
 - Hepatomegaly and/or splenomegaly
 - Serositis.

Joint involvement can be oligoarticular or polyarticular and may be absent during the first months of disease, but is obligatory in order to confirm the diagnosis. When arthritis is not present initially, disease onset will be determined as the onset of the systemic signs. Fever spikes and other systemic signs may last for months or even years. A large differential diagnosis needs to be considered because of the similarities between the systemic symptoms and infectious or malignant diseases.

Classification and measurement of disease severity

Systemic onset juvenile arthritis is a distinct entity and the term is used in all three classification systems of juvenile arthritis (ACR, EULAR and ILAR). The severity of the disease is characterised by the amount of generalised inflammatory

reaction and by the activity of joint inflammation. Very different disease courses may be seen. At one end of the scale, there is a monophasic course that resolves after a few months duration without sequelae, and on the other end there are courses with persistent systemic features and/or severe polyarticular destructive arthritis not responding to therapy, leading to severe incapacity or even early death. Serious complications of systemic onset JIA are the macrophage activation syndrome (MAS), also known as hemophagocytic histiocytosis, and, after long-standing active disease, amyloidosis.

Leading symptoms

Systemic arthritis is characterised by:

- Arthritis and polyarthralgias (often with involvement of the neck). Only polyarthralgias may be present during the first months of disease.
- Fever spikes, higher than 39°C, with a once daily, sometimes twice daily pattern, and subsequent returns to normal or even subnormal levels. Fever occurs usually in the late afternoon or in the evening, and patients may have chills during the rise of the temperature.
- Evanescent exanthema, which is usually present on the trunk and proximal extremities, but may occur anywhere on the body. The rash is pale pink (salmon) with a pale center, macular in 90% of patients, and maculopapular in about 10%. It may be pruritic or have an associated Koebner phenomenon or may resemble urticaria. The rash is migratory and is found most often simultaneously to the fever spikes.
- Hepatomegaly, splenomegaly, lymphadenopathy (2/3 of patients).
- Polyserositis (about 25 %)

There is no single pathognomonic diagnostic symptom or sign. Moreover, the diagnosis is often only established later, because the diagnosis requires the presence of arthritis, which may appear during the course of disease.

How to establish the diagnosis

There is no diagnostic tool that can give the definite diagnosis. In the presence of fever and rash the diagnosis is made by exclusion of other diseases such as infections, malignancies, vasculitis, inflammatory bowel disease and connective

tissue disease. Very often making the diagnosis requires waiting for more disease symptoms to emerge, especially arthritis which often evolves weeks (or even months) after onset of fever.

For definite diagnosis of systemic onset JIA (ILAR criteria), other diseases must be excluded and the following symptoms must be present:

- Characteristic high spiking remitting fever of 2 weeks duration (documented on at least 3 consecutive days)
- Arthritis
- And at least one of the following: typical rash, enlargement of liver or spleen, lymphadenopathy, serositis

The purpose of each diagnostic procedure, especially technical, imaging, and invasive and laboratory tests

- Thorough clinical examination to find hints for the diagnosis (for example the rash is often overlooked)
- Rule out infections by taking cultures of all available body fluids and searching for microorganisms by other techniques (PCR, serologic tests)
- Rule out leukemia by assessing blood smears and eventually bone marrow aspiration (before treatment with steroids); evaluate for signs of systemic inflammation such as anaemia, leucocytosis, thrombocytosis; be aware of signs for early MAS
- Perform chest X-ray to evaluate for serositis or, rarely, interstitial lung disease, as well as to assess for the presence of generalized infections (disseminated tuberculosis), Hodgkin's disease, sarcoidosis
- Bone scintigraphy may be helpful to exclude osteomyelitis or tumours
- Abdominal ultrasound to detect or document enlargement of liver and spleen, exclude tumours
- ECG to exclude myocarditis and evaluate for pericarditis; echocardiography to exclude endocarditis or aneurysms and find pericarditis and, where appropriate, to assess myocardial function.
- Laboratory tests to find signs of generalised inflammatory reaction (high ESR and CRP), to exclude organ involvement that might be a hint for septicaemia, connective tissue disease, MAS

- Autoantibodies are usually not found in systemic arthritis but are performed to rule out other autoimmune diseases such as connective tissue diseases, if required.

List of usual technical, imaging or laboratory procedures

The type of diagnostic procedures to be performed will depend on clinical presentation and the subsequent list is neither mandatory nor complete.

Tests to assess inflammatory activity:

Complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, ferritin, and iron.

Tests and procedures to assess organ involvement:

Blood chemistry, X-ray assessments, joint sonography, CT, MRI, echocardiography, electrocardiography, lung function test, diagnostic taps of pleural/pericardial fluid or joints if indicated, with microbiologic and other examination of these fluids.

Tests indicated for the differential diagnosis:

Immunoglobulins, urinalysis, blood culture, serologic tests for infectious agents, autoantibody determination, complement (C3, C4), bone marrow aspiration, abdominal sonography, bone scintigraphy, lung function assessment, biopsies, radiological diagnostic methods if required.

Tests and procedures used during the follow-up:

CBC, ESR, CRP, blood chemistry controls as required for the treatment used, and urinalysis. In case of diagnostic uncertainty, the tests for organ involvement or for other diseases in the differential diagnosis may have to be repeated.

Evaluation of individual diagnostic procedures

All diagnostic procedures may add to the correct evaluation of the patient, but do not permit a diagnosis in the absence of astute assessment of the complete clinical picture. The normal values for each test are set by the laboratory. Additional tests may be required according to initial results and follow-up.

For the control and evaluation of a child's disease course and of any organ changes, e.g., the possible development of amyloidosis, a close monitoring of clinical

and laboratory data as well as imaging is necessary. The early recognition or prevention of amyloidosis has an important influence on the prognosis.

Which diseases have to be excluded?

A large differential diagnosis has to be considered depending on the clinical presentation, including in particular:

-*Infectious diseases* (severe bacterial infections, viral infections including EBV and CMV.)

-*Malignancies* (leukaemia, lymphoma, generalized neuroblastoma, histiocytosis)

-*Chronic inflammatory diseases* (inflammatory bowel disease, sarcoidosis, Behçet's disease)

-*Other rheumatic diseases* (SLE, JDM, Kawasaki disease, other vasculitides, acute rheumatic fever)

-*Periodic fever syndromes* (FMF, TRAPS, HIDS, CINCA)

-*Miscellaneous diseases and syndromes* (immune deficiency, Castleman's disease)

Which procedures allow the diagnosis?

The diagnosis is a clinical one. Other diagnoses need to be excluded by the history, physical examination and the necessary laboratory, imaging and other procedures.

Which diagnostic procedures are not required?

Diagnostic and therapeutic strategies may need to be modified individually and according to the disease course of each child. As the diagnosis of systemic juvenile idiopathic arthritis is made by exclusion, extensive diagnostics may be necessary to exclude diseases with similar clinical symptoms and systemic involvement.

Therefore, it is not usually justified to criticize a diagnostic procedure as not required or indicated in retrospect. Arthroscopy or other surgical procedure are only needed in very special cases.

Indication that should perform these diagnostic procedures?

If systemic juvenile idiopathic arthritis is considered clinically, further assessment and the final diagnosis should be made by or with the help of a pediatric

rheumatologist. Additional consultations may be needed by other subspecialists including a pediatric hematologist, nephrologist, cardiologist, infectious disease specialist, radiologist, and by the orthopedic surgeon when deemed necessary.

Treatment

The treatment should be chosen depending of the type of presentation and the course of the disease. The aim of the treatment is to control the systemic and the joint inflammation and to limit the complications, as well as the damage to the musculoskeletal apparatus. The treatment usually consists of pharmacotherapy (NSAID, corticosteroids and other drugs), education and physical and occupational therapy. The treatment has to be supervised by a pediatric rheumatologist. Interdisciplinary management may be necessary for organ involvement.

Causative therapy

Since the etiology of the disease is not known, no specific treatment or cure is available.

Symptomatic treatment

Fever: acetaminophen, NSAID (e.g., indomethacin), physical measures

Drug treatment

NSAID:

naproxen (15 mg/kg/d), bid

ibuprofen (40 mg/kg/d), tid

diclofenac (2-3 mg/kg/d), bid

indomethacin (2-3 mg/kg/d), bid or tid

Steroids:

Prednisone: oral, initially 1-2 mg/kg, qd to qid, with gradual reduction after response to treatment (decrease to < 0.2 mg/kg/d as soon as possible).

Methylprednisolone: intravenous pulses of 500 or 1000 mg/1.73 m² (20-30 mg/kg) for 3 consecutive days; may be repeated weekly to monthly.

Intraarticular steroid injection

Remissive drugs: (during phases of systemic involvement, these drugs may have an increased rate of side effects.)

Usual drugs *Methotrexate:* 10-25 mg/m²/week, weekly dose

Oral or s.c. application (the higher doses should be given parenteral),

Optional: folic acid (5 mg/week or 1 mg daily) (however, folic acid might reduce the therapeutic effect of methotrexate)

CBC and transaminases to be assessed during treatment

Azathioprine: 2-3 mg/kg/d, daily dose

CBC and transaminases to be assessed during treatment

Cyclosporine A: 3-5 mg/kg/d (trough level below 150 µg/ml),

CBC, transaminases, creatinine and urinalysis to be assessed during treatment

Blood pressure monitoring

Uric acid and serum lipid control

Etanercept: 0.4 mg/kg s.c. twice weekly

For persisting arthritis, combination therapy of above mentioned drugs may be tried

Special drugs: Intravenous immunoglobulins (controversial)

Leflunomide (under investigation for pediatric patients)

Infliximab, adalimumab (under investigation for pediatric patients)

Thalidomide (under investigation), anti IL-6 (under investigation)

Cyclophosphamide pulse therapy (in conjunction with steroid pulse therapy)

In case of treatment resistance or atypical disease course, re-evaluate patient to assess for infection, macrophage activation syndrome (MAS) and other inflammatory diseases such as vasculitides.

Interventional treatment

Autologous bone marrow transplantation may be considered as a treatment of last resort in persistently active disease and after failure of several combinations of therapies including high dose methotrexate and treatment with etanercept.

Surgical procedures

Patients with long-standing joint involvement should be assessed together with a specialized pediatric orthopedic surgeon. Surgical procedures will be considered as treatment for impending or detected damage to the osteoarticular apparatus (soft tissue surgery correcting tendons and ligaments in rare cases, joint prosthesis, if possible not before final growth is reached). Particular attention should be given to the cervical spine and radiological procedures performed if there is a risk of atlanto-dental subluxation with consecutive spinal cord injury. In case of untreatable localized arthritis, synovectomy may be considered. The anesthetist should be advised of the risk related to temporomandibular and/or cervical arthritis (difficult intubation, risk of quadraplegia).

Rehabilitation

Rehabilitation represents a key issue in case of long-standing joint involvement: intensive physical therapy, occupational therapy, cryotherapy, use of weight supporting aids, functional or supportive splinting. All these measures should enhance optimal participation in daily life activities, school, extracurricular activities, sports including physical education and active leisure time. Rehabilitation will also include psychological support for the patient and the family including early school and career advice to enable adequate education and integration.

Prevention, education, treatment of secondary diseases

Early referral to a center specialized in pediatric rheumatology is essential, since these patients need experienced medical care with regular clinical and laboratory assessments. Patient education programs are useful for this chronic disease in order to improve patient's and parents' adherence to treatment and the quality of life for the patient and his family.

Secondary disease may be due to systemic arthritis itself or due to the treatment. Macrophage activation syndrome (MAS) may complicate systemic arthritis, and should be treated early with methylprednisolone, prednisone and cyclosporine. Long-standing chronic inflammation recalcitrant to treatment may induce amyloidosis. Treatment of amyloidosis is with methotrexate and anti-TNF-agents. Only if acute phase response cannot be controlled by these measures should chlorambucil may be tried. Chlorambucil bears the risk of secondary leukemia.

The main risk of immunosuppressive therapy is infection, which should always be considered in the differential diagnosis of fever. For osteoporosis (consequence of disease and/or steroid therapy), calcium and vitamin D supplementation should be used, and bisphosphonates may be indicated (still under investigation in children). Physical exercise is likely to favor bone mineralization and should be proposed depending on joint involvement. Growth retardation (consequence of disease and/or steroid therapy) may be treated with growth hormone supplementation, but placebo controlled data about long-term benefit are missing. Furthermore, there are reports that growth hormone therapy may induce MAS.