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REVIEW ARTICLE

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Proposal for juvenile idiopathic arthritis guidance on diagnosis and treatment for primary care pediatricians and nonpediatric rheumatologists (2007)

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Abstract The Pediatric Standing Committee of the Japan College of Rheumatology, in collaboration with the Pediatric Rheumatology Association of Japan, produced guidance on the diagnosis and treatment for juvenile idiopathic arthritis (JIA) for primary care pediatricians and nonpediatric rheumatologists in Japan. This guidance aims to achieve early diagnosis and treatment for JIA, which is similar to adult rheumatoid arthritis (RA), based on recent progress in rheumatology, and to resolve arthritis at an early stage and improve the prognosis of the affected inflammatory joints. It describes clinical symptoms and laboratory findings characteristic to JIA in order to make early diagnosis and treatment possible, and also serves as a triage of patients who are refractory to the treatment protocol described here and need more aggressive interventions. However, because JIA is a complicated and heterogeneous disease and the optimal treatment approach can be diverse and different patient by patient, these guidelines should be viewed as recommendations and be individualized according to the condition of the patient. Finally, we hope that this guidance will trigger exploration for further information by referring to the textbooks and literature listed at the end of these guidelines.

Key words Juvenile idiopathic arthritis · Guidance · Diagnosis · Treatment · Methotrexate · Corticosteroid

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Introduction

This guidance aims to achieve early diagnosis and treatment for juvenile idiopathic arthritis (JIA), which is similar to adult rheumatoid arthritis (RA), based on recent progress in rheumatology, and to resolve arthritis at an early stage and improve the prognosis of the affected inflammatory joints. This guidance also serves as a triage of patients who are refractory to the treatment protocol described here and need more aggressive interventions.

Because appropriate use of various biologics which have recently been developed for autoimmune diseases requires clinical expertise and experience, it has been requested in Japan that application of these agents for adult RA should be undertaken only by rheumatologists at specialized rheumatology clinics, and patients on these agents should be registered. After pediatric indication of these agents is approved, the same requirements are expected. Primary care pediatricians who are dealing with children with JIA should therefore have close contact with rheumatologists, especially pediatric rheumatologists, for timely introduction of biologics in order to prevent joint destruction and disability as much as possible when their patients are refractory to the treatment protocol described in this guidance. We hope that this document will assist primary care pediatricians and nonpediatric rheumatologists to manage children with JIA in this context.

Primary care pediatricians and nonpediatric rheumatologists would not frequently see children with JIA because JIA is a rare disease. This guidance describes clinical symptoms and laboratory findings characteristic to JIA in order to make early diagnosis and treatment possible. We hope

that this guidance will trigger exploration for further information by referring to the textbooks and literature listed at the end of this article.

Juvenile idiopathic arthritis is a complicated and heterogeneous disease which includes more individual variations than the currently described classifications. The optimal treatment approach can be diverse and different, patient by patient. How to diagnose and treat children with JIA described in this document should therefore be viewed as recommendations and be individualized according to the condition of the patient. This guidance will be revised and updated according to progress in pediatric medicine and rheumatology.

Overview and classification of chronic childhood arthritis

Chronic childhood arthritis is currently classified according to the criteria proposed by the Pediatric Standing Committee of the International League against Rheumatism (ILAR), which was established in 1993, and the World Health Organization (WHO).[1] According to the proposed classification criteria by the ILAR/WHO, chronic childhood arthritis is called Juvenile Idiopathic Arthritis (JIA)[2,3] and is divided into the following seven subtypes (Table 1): (1) systemic arthritis; (2) oligoarthritis (a, persistent form and b, extended form); (3) rheumatoid factor (RF) negative polyarthritis; (4) RF positive polyarthritis; (5) psoriatic arthritis; (6) enthesitis-related arthritis; and (7) others.

Considering the current clinical practice in pediatric rheumatology in Japan, an overview of the proposed classification criteria is summarized as follows. Systemic arthritis is a disease which develops chronic arthritis in conjunction with systemic symptoms such as fever. Oligoarthritis and both RF negative and positive polyarthritis are called "articular type" because joint disease is the main element of the disorders in these subtypes. Psoriatic arthritis and enthesitis-related arthritis are kinds of "symptomatic arthritis" with underlying diseases (psoriasis and enthesitis, respectively). Juvenile ankylosing spondylitis, which presents with central arthritis associated with HLA-B27, and arthritis associated with inflammatory bowel disease, such as Crohn's disease and ulcerative colitis, are excluded from the classification and are regarded as other diseases in this guidance.

Juvenile idiopathic arthritis

The incidence of JIA in Japan is 10 to 15 per 100 000 children, which is almost the same as that in Europe and the

Table 1. Diagnosis/Classification criteria of juvenile idiopathic arthritis (ILAR/WHO classification)

Systemic arthritis	***1. Systemic arthritis***
	Arthritis with remittent fever for more than 2 weeks and one of the following symptoms: (1) Evanescent erythematous rash (2) Generalized lymph node enlargement (3) Hepatomegaly or splenomegaly (4) Serositis
Articular arthritis	***2. Oligoarthritis***
	Arthritis affecting 1 to 4 joints during the first 6 months of disease. Two subcategories are recognized: (a) Persistent oligoarthritis: affects no more than 4 joints throughout the disease course (b) Extended oligoarthritis: affects accumulative total of 5 joints or more after the first 6 months of disease
	3. Polyarthritis (RF negative)
	Arthritis affecting 5 or more joints within the first 6 months of disease; tests for RF are negative
	4. Polyarthritis (RF positive)
	Arthritis affecting 5 or more joints within the first 6 months of disease, associated with positive RF tests on 2 occasions at least 3 months apart
Symptomatic arthritis	***5. Psoriatic arthritis***
	Either of the following: (1) Arthritis and psoriasis, or (2) Arthritis and at least 2 of: (a) dactylitis (b) nail abnormalities (c) family history of psoriasis in a first-degree relative
	6. Enthesitis-related arthritis
	Either of the following: (1) Arthritis and enthesitis (2) Arthritis and enthesitis with at least 2 of: (a) sacroiliac joint tenderness and/or inflammatory spinal pain (b) presence of HLA-B27 (c) family history in at least one first or second degree relative of HLA-B27 associated disease (d) Anterior uveitis that is usually associated with pain, redness, or photophobia (e) Onset of arthritis in a boy after 8 years of age
	7. Others
	Children with arthritis of unknown cause that persists for at least 6 weeks

ILAR, International League against Rheumatism; WHO, World Health Organization; RF, rheumatoid factor

United States. However, the incidence by the subtypes is different among regions. Specifically, systemic arthritis accounts for approximately 20% of JIA in Japan but only for approximately 10% in Europe and the United States. With regard to the articular type JIA, the incidence of polyarthritis is higher in Japan, while the incidence of oligoarthritis is higher in Europe and the United States.[4,5]

Because systemic arthritis is different from articular arthritis in terms of the clinical course as well as treatment approach,[6] they are described separately in this document.

Systemic arthritis (systemic juvenile idiopathic arthritis: s-JIA)

Definition

Arthritis with remittent fever for more than 2 weeks and one of the following symptoms:

(1) evanescent erythematous rash,
(2) generalized lymph node enlargement,
(3) hepatomegaly or splenomegaly,
(4) serositis

Patients with psoriasis or a history of psoriasis in the patient or family are excluded.

Diagnosis

(1) Symptoms and laboratory findings
   a. Remittent fever, rheumatoid rash, and arthritis are major clinical presentations in s-JIA. s-JIA is often associated with pleurisy, pericarditis, and/or hepatosplenomegaly.
   b. Hematological changes include a significant increase of leukocytes, of which neutrophils account for 80%–90% with no left shift. Thrombocytosis and progression of anemia are also observed.
   c. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A protein are elevated. IgG level also increases if the inflammation lasts for several months.
   d. Ferritin is also elevated in many cases.[7] If ferritin is significantly elevated, extra caution should be exercised because it can be one of the signs for development of macrophage activation syndrome.
   e. It has been suggested that IL-6/IL6R play a central role in the pathogenesis of s-JIA.[8,9]
(2) Diagnostic process
   a. Diagnosis of s-JIA may be challenging early in the course of the disease. The possibilities of various other diseases should be thoroughly reviewed, especially when the patient has neither arthritis nor a typical rash. There is no laboratory finding specific to s-JIA. It is important to inquire about the disease history and the family history in detail.
   b. It is a hallmark in the diagnosis of s-JIA to recognize rheumatoid rash and arthritis coincident with remittent fever and pyrexia. In addition, it is essential to understand the clinical conditions of arthritic diseases in detail (examination of a total of 70 joints of the extremities and jaw as well as joints of the cervical vertebra). Subsequently, a differential diagnosis is performed.
   c. Inflammatory status is evaluated by blood tests (ESR and CRP). In addition, it is important to closely monitor changes in laboratory values indicating a transition to macrophage activation syndrome and to take action immediately if the transition occurs.

Differential diagnosis (Table 2)

(1) Infection: acute infection, bacteremia and sepsis, infectious mononucleosis, erythema infectiosum
(2) Allergic reaction to infection: virus-associated hemophagocytic syndrome
(3) Inflammatory bowel disease: Crohn's disease, ulcerative colitis
(4) Other rheumatic disease: vasculitis syndrome (especially Takayasu arteritis, nodosa, and Kawasaki disease), systemic lupus erythematosus, juvenile dermatomyositis
(5) Tumorous disease, malignant tumor: leukemia, Castleman's disease, myofibroblastoma
(6) Autoinflammatory syndrome: chronic infantile neurological, cutaneous, and articular (CINCA) syndrome/neonatal-onset multisystem inflammatory disease (NOMID), hyper IgD syndrome, familial Mediterra-

Table 2. Differential diagnosis of systemic juvenile idiopathic arthritis

Infections
Typical bacterial infections (including sepsis), viral infections (e.g. EBV, CMV, parvovirus), and uncommon infections (e.g. tuberculosis, Q fever, cat-scratch disease)
Malignancy such as childhood leukemia
Orthopedic joint diseases, traumatic arthritis
Cytokine-producing tumor
Castleman's disease, myofibroblastoma
Autoinflammatory syndrome
Familial Mediterranean fever, hyper IgO syndrome, TRAPS, CINCA/NOMID syndrome, juvenile sarcoidosis
Other rheumatic diseases
Takayasu arteritis, polyarteritis nodosa, Kawasaki disease, mixed connective tissue disease, Sjögren's syndrome, Behçet's disease

EBV, Epstein–Barr virus; CMV, cytomegalovirus; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; CINCA, chronic infantile neurological, cutaneous, and articular syndrome; NOMID, neonatal-onset multisystem inflammatory disease; hyper IgD syndrome, familial Mediterranean fever, TNF receptor associated periodic syndrome (TRAPS)

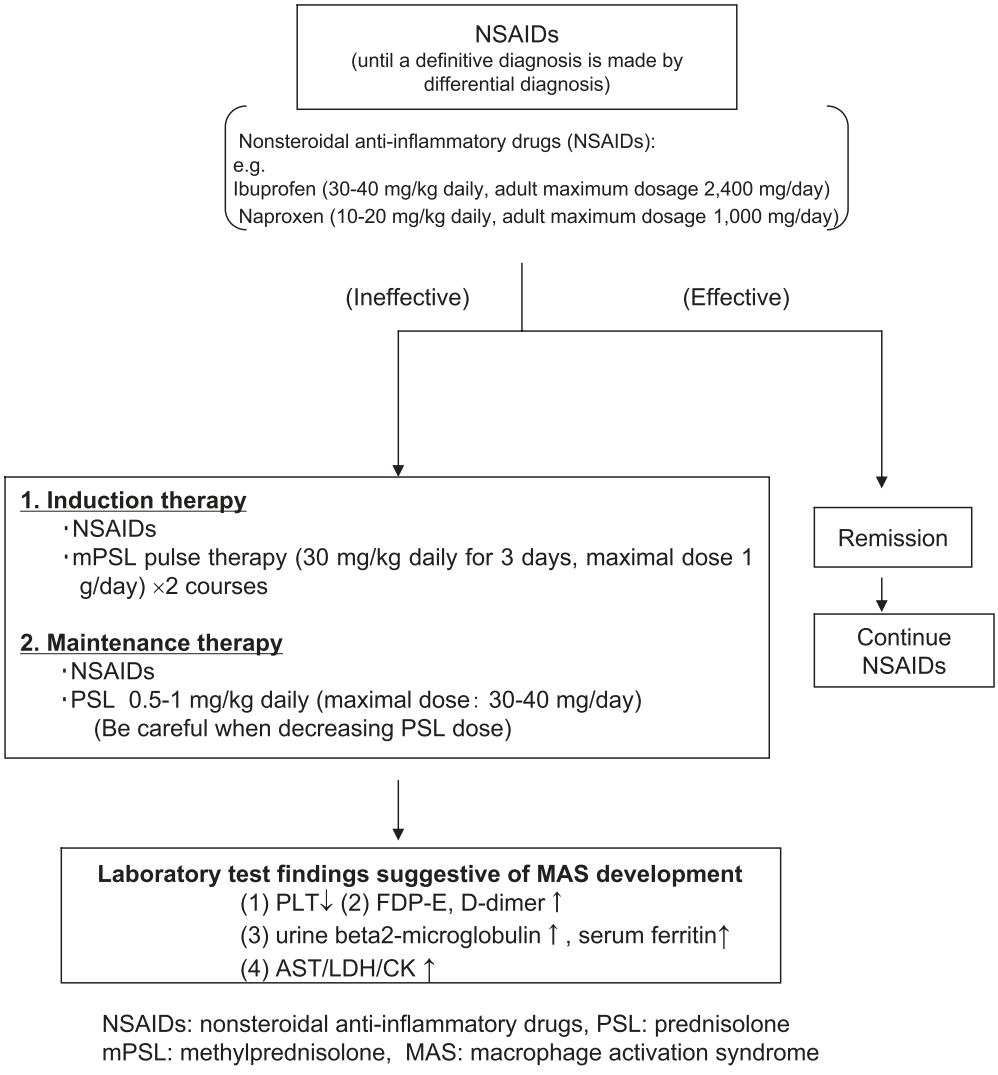


Fig. 1. Treatment flowchart for systemic juvenile idiopathic arthritis

NSAIDs: nonsteroidal anti-inflammatory drugs, PSL: prednisolone
mPSL: methylprednisolone, MAS: macrophage activation syndrome

Consult with pediatric rheumatologists about use of biologics etc. if the patient fails to respond to the treatments above for at least 3 months.**
(**Reference: http://www.ryumachi-jp.com/authori/promeibo.html)

nean fever, tumor necrosis factor (TNF) receptor associated periodic syndrome (TRAPS)

Treatment (Fig. 1)

(1) Nonsteroidal anti-inflammatory drugs (NSAIDs)[3,10]
Ibuprofen: Brufen (Kaken Pharmaceutical, Tokyo, Japan), 30–40 mg/kg daily (adult maximum dosage 2400 mg/day)
Naproxen: Naixan (Tanabe Seiyaku, Osaka, Japan), 10–20 mg/kg daily (adult maximum dosage 1000 mg/day) etc.

(2) Corticosteroid
a. Oral prednisolone: 1 mg/kg per day
If treatment with higher dose is necessary, methylprednisolone pulse therapy described below should be considered.
b. Methylprednisolone pulse therapy followed by oral prednisolone as a maintenance therapy (Fig. 2)[11]
- Methylprednisolone pulse therapy:
30 mg/kg per day (a maximum of 1000 mg/day) for 3 consecutive days × 2 courses
- Maintenance therapy (oral prednisolone):
0.7 to 1.0 mg/kg per day (a maximum of 30 to 40 mg/day)

Note: Methylprednisolone pulse therapy must be applied with anticoagulation using heparin (continuous i.v. of 100 units/kg over 24 h).
c. Reduction of oral corticosteroid should be gradual. Treating physicians should be careful on the amount of dose to be reduced. Alternate-day administration should not be used.

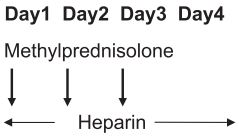
(3) Immunosuppressive agents such as cyclosporine and/or methotrexate may be added.

1. Pre-treatment screening:

   1) Screening for infections
   2) Ophthalmologic examination: intraocular pressure, cataract

2. Protocol

   1) Drug and dose: Solu-medrol 30 mg/kg (max. 1,000 mg/body)
   2) Administration method
      a) Solu-medrol + 5% glucose solution 100 mL: i.v. infusion over 2 hours (i.v. infusion over 4 hours if the patient has a medical history of hypertension or if his/her cardiac function is compromised)
      b) Always add anticoagulants
         Continuous i.v. infusion of heparin 100 units/kg over 24 hours (mixed injection)



3. Cautions

   1) Hypertension
      Blood pressure should be measured every 30 minutes from the beginning to the completion of the infusions

   2) Blood test (Pre-infusion, Post-infusion)
      CBC, blood biochemistry (BUN, Cr, Na, K, Cl, Ca, blood glucose, CRP), urinalysis

Fig. 2. Treatment protocol: methylprednisolone pulse therapy

Note 1: Cyclosporine may enhance the effect of the corticosteroid by suppressing multidrug-resistant gene product (P-glycoprotein).[12]
Note 2: Although methotrexate is expected to be effective for articular symptoms associated with s-JIA, it is generally less beneficial than in other subtypes of JIA.[13]

Advanced treatment: treatment using biologic response modifiers under supervision of specialists

(1) Biologic response modifiers used to treat rheumatic diseases include anti-TNF-α inhibitors (infliximab: anti-TNF-α monoclonal antibody, etanercept: soluble TNF-α receptor fusion protein), interleukin (IL)-1 receptor antagonist (anakinra), anti-IL-6 receptor monoclonal antibody (tocilizumab) and others.[14]
(2) Because these agents are known to suppress inflammation related to inflammatory diseases as well as infections, adverse events associated with infections are frequently reported. In addition, it should be kept in mind that their effect on organs unrelated to immune function, carcinogenicity, and development of autoimmune disease is largely unknown.
(3) Anti-TNF-α inhibitors appear to be less beneficial in s-JIA than in other subtypes of JIA. Case reports indicated that treatment with IL-1 receptor antagonist was effective in s-JIA.[15] It was confirmed in a randomized, double-blind clinical trial performed in Japan that anti-IL-6 receptor monoclonal antibody was effective in treating patients with s-JIA.[16]

Macrophage activation syndrome

(1) It has been reported that sudden death occurs at an incidence of approximately 11% in the clinical course of s-JIA and is caused by a transition to macrophage activation syndrome (MAS) or cardiac/hepatic/renal failure due to amyloidosis, which is often seen in patients with long-term disease.
(2) Although pathological cause of MAS is unknown, viral infections and use of some drugs including NSAIDs seem to be involved with the event. Clinical conditions of MAS include prolonged high fever, decrease in white blood cells and platelets, progression of apoptosis and necrosis of multiple organs/cells, vascular endothelial activation responsible for the coagulopathy, progression of disseminated intravascular coagulation, and development of multi-organ failure with poor prognosis.
(3) Excessive activation of pro-inflammatory cytokines such as IL-6/IL-6R, interferon (IFN)-γ, IL-1β, TNF-α, IL-8, etc. was observed in MAS.[17]
(4) If MAS is suspected based on clinical signs, or blood/urine/bone marrow examinations, the treating physicians should immediately consult with specialists or refer the patients to a specialist hospital.

Triage of patients to pediatric rheumatologists

(1) A definitive diagnosis of s-JIA is difficult to make and requires expertise in pediatric rheumatology. Inappropriate treatments during the early disease often result in development of MAS. Management of patients with suspected s-JIA should therefore be shared with specialists. Treatments for patients with s-JIA should be initiated and followed up under the supervision of specialists until the inflammatory status becomes stable.
(2) The treating physicians should also consult with specialists when:
   a. Unable to reduce the steroid dose
   b. Signs and symptoms related to development of MAS are detected
   c. Patient's clinical conditions necessitate more advanced treatments

Articular juvenile idiopathic arthritis (Table 1)

Articular JIA corresponds to oligoarthritis and both RF negative and positive polyarthritis in the ILAR/WHO classification. Joint disease is the most prominent feature in articular JIA. Bone and cartilage are destroyed and disrupted within 1 or 2 years after the onset of the disease. Prompt diagnosis and early appropriate treatment are therefore essential.

Definition

(1) Oligoarthritis
Arthritis affecting 1 to 4 joints during the first 6 months of disease. Two subcategories are recognized:
   a. Persistent oligoarthritis: affects no more than 4 joints throughout the disease course.
   b. Extended oligoarthritis: affects a cumulative total of 5 joints or more after the first 6 months of disease.

(2) Polyarthritis (rheumatoid factor negative)
Arthritis affecting 5 or more joints during the first 6 months of disease; tests for RF are negative.

(3) Polyarthritis (rheumatoid factor positive)
Arthritis affecting 5 or more joints during the first 6 months of disease, associated with positive RF tests on 2 occasions at least 3 months apart.

Clinical findings

Joint diseases in articular JIA are clearly identified by physical examination as symmetrical arthritides. Articular symptoms such as pain, swelling, heat, and limitation of motion are often exacerbated from early morning to noon. Plain X-ray cannot identify abnormal joint findings at the early stage of the disease, but contrast-enhanced MRI reveals synovial proliferation in the joints.

(1) Oligoarthritis
Patients in this subtype rarely show extra-articular manifestation. The prognosis of joint disease is relatively good. In patients with positive ANA, attention should be paid to chronic arthritis as well as chronic uveitis.[18] Arthritis in this subtype often becomes apparent in the lower limbs, especially the knees and ankles, but rarely in the hip joints. It is difficult to confirm a diagnosis of this subtype if arthritis is asymmetric, in which case a thorough checkup is required.
   a. Persistent oligoarthritis: arthritis affecting no more than 4 joints throughout the disease course. This subtype represents the original concept of oligoarthritis.
   b. Extended oligoarthritis: arthritis affecting a cumulative total of 5 joints or more after the first 6 months of disease. RF positive case is included.

(2) Polyarthritis
Arthritis that affects 5 or more joints during the first 6 months of disease is defined as polyarthritis. Polyarthritis is further categorized as RF positive and negative. The arthritis in this subtype is often insidious with progressive involvement of additional joints and tends to be symmetric. In many cases, it involves the large joints of the limbs (the knees, ankles, elbows, and wrists). Arthritis in the cervical spine and temporomandibular joints is one of the characteristics associated with this subtype. Small-joint disease of the hands or feet may occur in some cases. Patients in this subtype exhibit the most variable clinical presentation. The differential diagnosis should be thoroughly reviewed to confirm the diagnosis.
This subtype is more frequently seen in girls who are older than 10 years to adolescence, and resembles adult rheumatoid arthritis. Because the majority of patients with this subtype are HLA-DR4 positive with rheumatoid nodules, the joint disease can lead to erosive joint destruction. In RF negative cases, affected joints are relatively fewer. Small-joint disease of the hands or feet and formation of rheumatoid nodule are uncommon.
Patients with polyarthritis develop systemic symptoms including prolonged fever (usually low grade), hepatosplenomegaly, lymphadenopathy, and anorexia/weight loss more commonly than those with oligoarthritis.

Diagnosis

(1) Clinical course and diagnostic process
   a. The patients usually present with the chief complaints of persistent arthralgia/joint swelling, especially intense joint pain from the early morning to noon. Morning stiffness, persistent low-grade fever, and anorexia/weight loss are also frequently recognized. Sometimes patients with polyarthritis may develop high fever, in which case a differential diagnosis from s-JIA will be required.
   b. During physical examination, it is important to confirm the presence of arthritis and clinically recognize the details of arthritis (examination of a total of 70 joints of the extremities and jaw as well as joints of the cervical vertebra).
   c. The following laboratory examinations should be conducted:
      (i) Inflammatory findings (ESR, CRP, and serum amyloid A protein, etc.),
      (ii) Biomarkers for articular disease (MMP-3, hyaluronic acid, FDP-E fraction)
      (iii) Confirmation of the disease type (rheumatoid factor, antinuclear antibodies)
   Note: Measurement of anti-CCP antibodies recently has been recommended as a disease marker. There are many reports on the utility of this marker for the diagnosis and the prediction of prognosis.[19,20]
   d. Generally, no abnormal findings are noted in the affected joint by plain X-rays during a few months after the disease onset, which, however, does not prove the absence of the disease. Joint space narrowing and erosions can develop if the arthritis is prolonged.
   e. Contrast-enhanced MRI can identify retention of joint fluid and proliferative synovitis in the affected joint.
   f. All findings in clinical and laboratory examinations and contrast-enhanced MRI should be fully taken into account to make a differential diagnosis.

(2) Differential diagnosis
   a. Oligoarthritis
   Septic arthritis, trauma (intra-articular hematoma), juvenile ankylosing spondylitis, juvenile

Table 3. Differential diagnosis of the articular juvenile idiopathic arthritis

Infections
Typical bacterial infections (including sepsis), uncommon infections (tuberculosis, Lyme disease etc.), reactive arthritis, viral arthritis
Enthesitis
Blood dyscrasias (Sickle cell anemia, childhood leukemia, neuroblastoma)
Other rheumatic diseases
Systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease, scleroderma, Schönlein–Henoch purpura, etc.
Hereditary diseases
Turner's syndrome, Marfan syndrome, Ehlers–Danlos syndrome
Inflammatory bowel disease
Autoinflammatory syndrome
Familial Mediterranean fever, hyper IgO syndrome, TRAPS, CINCA/NOMID syndrome, juvenile sarcoidosis
Orthopedic joint diseases, traumatic arthritis

psoriatic arthritis, juvenile sarcoidosis, Schönlein–Henoch purpura, hematological disorders (hemophilia, leukemia, malignant tumor), structural disorders (discoid meniscus, osteochondritis dissecans, etc.)

b. Polyarthritis (Table 3)
The differential diagnoses include septic arthritis, the majority of which are monoarthritis, viral arthritis, Lyme disease, arthralgia/arthritis associated with other rheumatic diseases (e.g., systemic lupus erythematosus, mixed connective tissue disease, Sjögren's syndrome, inflammatory bowel disease, juvenile ankylosing spondylitis, juvenile psoriatic arthritis, Behçet's disease, Schönlein-Henoch purpura, etc.), orthopedic diseases (especially the cruciate ligaments injury), childhood leukemia, etc.
"Growing pains" often encountered in outpatient clinics are characterized by pains in the knee joints and/or ankle joints perceived from the evening through the night. In this case, no inflammatory findings are noted by joint examination.

Treatment (Fig. 3)

(1) Treatment until a definite diagnosis is made
a. Nonsteroidal anti-inflammatory drugs (NSAIDs):
e.g. Ibuprofen (Brufen, 30–40 mg/kg per day, adult maximum dosage 2400 mg/day)
Naproxen (Naixan, 10–20 mg/kg per day, adult maximum dosage 1000 mg/day)
(i) Treatment with NSAIDs results in pain relief and in some cases improves arthritis. However, inflammatory markers such as CRP and ESR are usually unchanged. If inflammatory markers show abnormal values even when pain relief is achieved by the treatment, the treating physician should consider that inflammation is still active and that advanced therapies are necessary. If NSAIDs show some efficacy, the treatment should be continued.
(ii) Patients who are refractory to NSAIDs are defined as follows:
persistent inflammatory conditions such as arthralgia and joint swelling that do not subside during the first 2 to 3 weeks of NSAIDs treatment, and/or failure to normalize ESR and CRP during the first 2 to 3 weeks of NSAIDs treatment.

b. Low-dose methotrexate pulse therapy[21,22]
For NSAIDs refractory cases, low-dose methotrexate pulse therapy should be introduced as early as possible.
- Use of methotrexate – overview
(i) Methotrexate is the most commonly selected drug for NSAIDs refractory cases because of its significant anti-inflammatory effect with acceptable safety profile. Use of methotrexate is internationally accepted as one of the standard treatments.[21,23]
(ii) Methotrexate is a folic acid antagonist showing anti-inflammatory activity on chronic arthritis with an unknown mechanism of action.
(iii) The most concerning toxicities associated with methotrexate are myelosuppression, hepatic fibrosis, and pulmonary fibrosis. However, hepatic fibrosis is scarcely observed with a weekly dosage regimen used for arthritis. Methotrexate induced pneumonitis is also extremely rare, which has been confirmed by long-term follow-up of many children treated with methotrexate.
(iv) The pharmacokinetic profile of methotrexate is unique; renal excretion is faster in children compared with that in adults. Weekly subcutaneous injection or oral administration of 10 to 15 mg/m^2 is therefore a preferred dosage regimen for pediatric population in Europe and the United States.[24]
(v) In Japan, the maximum weekly dose recommended for adult RA is 8 mg.[25] The optimal pediatric dose by oral route seems to be 10 mg/m^2 per week (approximately up to 0.3 mg/kg).[3]
(vi) Usually oral methotrexate is administered as a single dose in the morning once a week or as a divided dose every 12 h for 2 doses. Patient compliance can be increased if patients are instructed to take the drug on the same day every week.

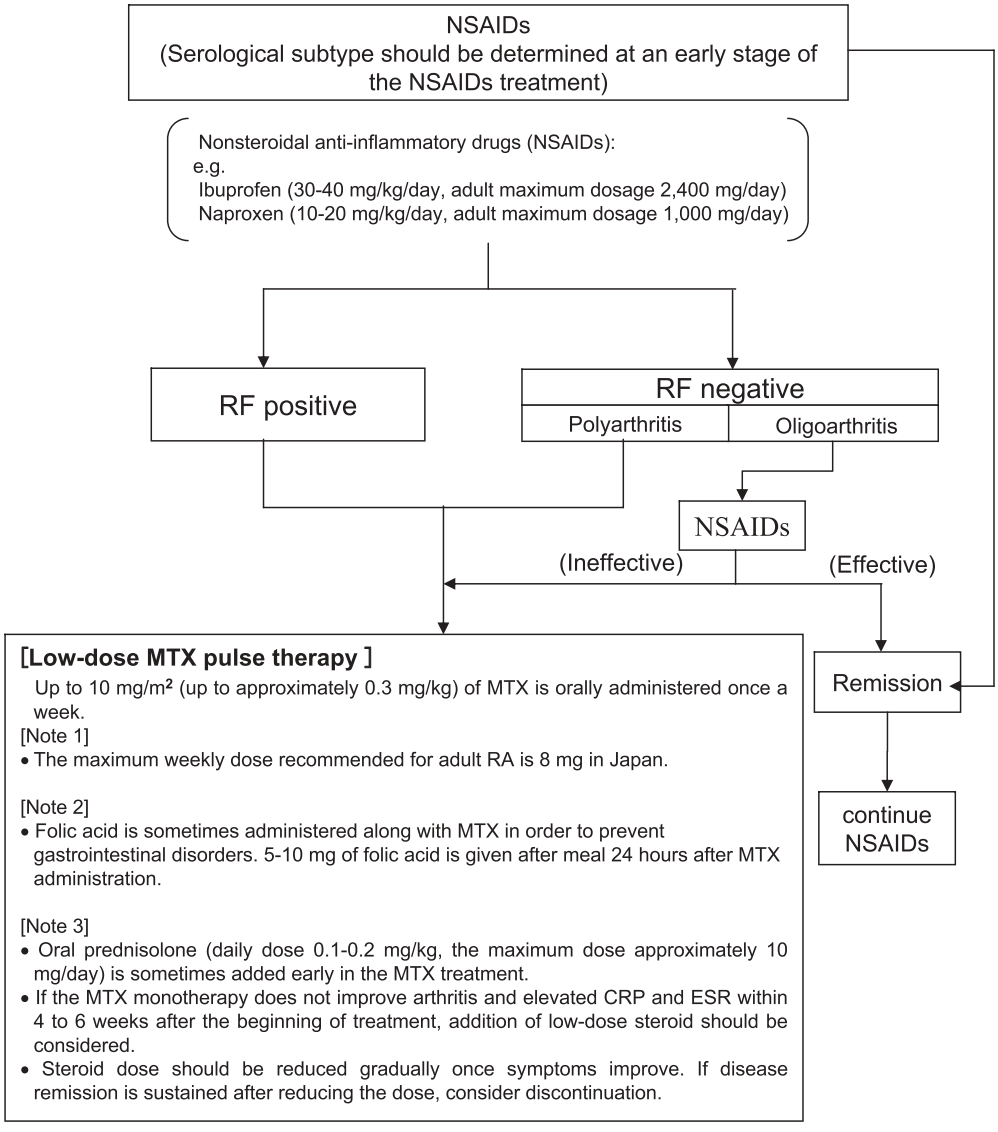


Fig. 3. Treatment flowchart for articular juvenile idiopathic arthritis

NSAIDs: nonsteroidal anti-inflammatory drugs, RF: rheumatoid factor
MTX: methotrexate, PSL: prednisolone

Consult with pediatric rheumatologists about use of biologics etc. if the patient fails to respond to the treatments above.**
(**Reference：http://www.ryumachi-jp.com/authori/promeibo.html)

(vii) The following oral dosage forms are available for methotrexate in Japan:
Rheumatrex (Wyeth, Tokyo, Japan; 2 mg per capsule)
Metolate (Santen Pharmaceutical, Osaka, Japan; 2 mg per tablet)
Methotrexate (Wyeth; 2.5 mg per tablet)

(viii) Folic acid is sometimes administered along with methotrexate. If folic acid supplementation is prescribed, 5 to 10 mg of folic acid is given after a meal once a week 24 h after the methotrexate administration.

(ix) Some patients may develop nausea from 6 to 12 h after taking methotrexate orally. Antiemetics [e.g., Domperidone (Nauzelin, Kyowa Hakko, Tokyo, Japan)] can be effective against the nausea.

Note: It is recognized internationally that low-dose methotrexate pulse therapy is the mainstay in treatment for JIA; however, other anti-inflammatory agents are added for early resolution of inflammation in several countries because methotrexate is a slow-acting drug. For this purpose, hydroxychloroquine (not approved in Japan) is added in the United States and sulfasalazine in the United Kingdom to enhance the action of methotrexate.[26] In Japan, oral prednisolone (daily dose 0.1 to 0.2 mg/kg, the initial maximum

dose approximately 15 mg/day, depending on age and clinical conditions) is added. During this therapy, the dose of oral prednisolone is gradually decreased to reach the maintenance dose (0.1 mg/kg per day or 3 to 5 mg/day for school-age or older children) when low-dose methotrexate pulse therapy becomes effective, which takes at least 4 weeks after the beginning of the treatment. There is relatively little concern on the steroid side effects such as growth retardation and osteoporosis if the maintenance dose is in this range or lower. When remission of arthritis is sustained, oral prednisolone should be further reduced gradually and finally discontinued.

c. Other disease-modifying antirheumatic drugs
Parental gold (Shiosol, Shionogi, Osaka, Japan) is sometimes administered to older children who are resistant to the standard therapy, but it may cause interstitial nephritis and agranulocytosis. Oral gold (auranofin; Ridaura, Glaxo Smith Kline, Tokyo, Japan) is not indicated for children because of the possibility of marked gastrointestinal symptoms as well as less beneficial efficacy. Bucillamine (Rimatil, Santen Pharmaceutical) is sometimes used to treat adult RA patients but is not indicated for children because it often induces renal disorders.

Advanced treatment: treatment using biologic response modifiers under supervision of specialists

(1) This guidance aims to help primary care pediatricians manage children with JIA in general practice. Approximately 70%–75% of children with chronic arthritis achieve remissions by treatment with NSAIDs as the first-line and low-dose methotrexate pulse therapy-based combination treatments as the second-line.[27]
(2) However, the remaining 20%–30% of patients need more advanced treatments. The treating physicians should consider whether biologic response modifiers are indicated to treat these non-responders, in cooperation with specialists. It usually takes at least 3 to 6 months to judge the response to the first-line and second-line treatments.[3]
(3) Biologic response modifiers such as infliximab (anti-TNF-α monoclonal antibody, Remicade (Tanabe Seiyaku), being marketed for adult RA[28]), etanercept (soluble TNF-α receptor fusion protein, Enbrel (Wyeth), pediatric clinical trials completed[29]), tocilizumab (humanized anti-IL-6 receptor monoclonal, Actemra (Chugai Pharmaceutical, Tokyo, Japan), pediatric clinical trials completed[30]), etc. are expected to be available for JIA.
(4) Because these biologic response modifiers are monoclonal antibodies or receptor fusion proteins against proinflammatory cytokines and are potent inhibitors for excessive reactions as well as physiological reactions, appropriate use of these agents requires clinical expertise and experience. If these biologic response modifiers are indicated, the primary care pediatricians who are treating children with JIA should consider referring the patients to pediatric rheumatologists or establish close contact with specialists regarding the management.
(5) "Guidance on use of biologic response modifiers for juvenile idiopathic arthritis" is being prepared under the supervision of the Ministry of Health, Labour and Welfare in Japan, in reference to the guidance for the pediatric population in Europe[31] as well as that for adult RA patients in Japan.[32]

Triage of patients to pediatric rheumatologists

The treating physicians should consult with specialists in the following cases:

(1) Lack of response in clinical symptoms including arthritis and laboratory parameters even after 3 months of treatment according to this guidance
(2) Inability to reduce steroid dose or unacceptable side effects associated with steroids even after commencing low-dose methotrexate pulse therapy or combination methotrexate therapy
(3) Unacceptable side effects associated with methotrexate (e.g., severe nausea, liver dysfunction), even if the standard dose of methotrexate is administered

Adverse reactions associated with the treatments

NSAIDs

(1) Aseptic meningitis: Aseptic meningitis should be suspected if severe headache develops within a few hours after NSAIDs administration.
(2) Gastrointestinal ulceration: Gastric ulcer is noted in approximately 15% of geriatric rheumatoid arthritis patients, and because most of these patients are asymptomatic, they are susceptible to gastric perforation. The most common site is the antral lesser curvature of stomach. The incidence of NSAIDs-induced ulcer in children is unknown.
(3) Use of species-specific selective COX-2 inhibitors can minimize the toxicities, which makes long-term treatment with these agents possible.

Methotrexate

(1) Common adverse reactions include nausea, pruritus, rash, and abnormal values in hepatic/renal function tests.
(2) Serious adverse reactions include shock, myelosuppression, serious hepatic/renal function disorder, interstitial pneumonia, skin disorder, pancreatitis, osteoporosis, and infections.

Prednisolone

(1) Adverse reactions associated with high-dose steroids include increased susceptibility to infection, diabetes mellitus, gastric ulcer, steroid psychosis, and moon face/central obesity.
(2) Adverse reactions associated with long-term steroid treatment include adenocortical insufficiency, osteoporosis, hyperlipidemia, hypertension, muscular weakness, myalgia, cataract/glaucoma, and impaired glucose tolerance.

Rehabilitation

Suppressing the inflammation is often not enough to return children to normal functioning whatever their disease types of arthritis. During periods of active inflammation, rehabilitation programs maintaining normal range of motion of the unaffected joints and soft tissue surrounding the joints need to be instituted. Once arthritis improves, physical therapy for the affected joints should be initiated to prevent the joint contracture as soon as possible.

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