

Juvenile Idiopathic Arthritis in Hong Kong and Its Current Management

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Abstract Juvenile idiopathic arthritis is the most common form of childhood arthritis and one of the more common chronic childhood illnesses in the Western countries. This paper is the retrospective surveillance study of this condition in Chinese children receiving treatment in the Paediatric Units of Public Hospitals. The new classification and current management of juvenile idiopathic arthritis is also updated.

Key words Chinese children; Classification; Juvenile idiopathic arthritis; Management review; Surveillance

Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic condition in children in the western countries. It was estimated that between 5 and 18 of every 100,000 children develop JIA each year; the overall prevalence is approximately 30 to 150 per 100,000.¹ To date, there are no reports on the prevalence or incidence of this condition in Chinese population. Therefore, an inter-hospital surveillance study of JIA in Hong Kong was conducted in year 2000. These data come from all Departments of Paediatrics (except one) of the Hospital Authority and this surveillance was endorsed by the Coordinating Committee of Paediatrics of the Hospital Authority.

JIA is not a benign condition as some thought previously. Many long-term follow up studies²⁻⁶ showed that around 33-66% of patients with JIA are still having active disease and their quality of life scores were impaired. The visual

complications of uveitis were also important in determining the long term outcome. In one study, 17% of patients with JIA developed chronic arthritis; 20% of these children were left with impaired vision.⁷ These data indicated that JIA is often associated with severe and long-lasting effects. Poor prognostic indicators for patients with JIA are: active systemic disease at 6 months, patients with polyarticular onset, rheumatoid factor positivity, persistent morning stiffness, tenosynovitis, subcutaneous nodules, or antinuclear antibody. Timely diagnosis and early appropriate aggressive treatment of patients with poor prognostic features are indicated in order to improve quality of life and outcome. The current management of JIA will also be discussed in this article.

Inter-hospital Surveillance of JIA in Hong Kong

Definition of JIA

JIA is defined as presence of arthritis (swelling or effusion, or presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, and increased heat) in one or more joints. The age at onset is less than 16 years old. The duration of arthritis lasts for 6 weeks or longer and other causes of arthritis (e.g. septic arthritis, malignancy) are excluded.

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ILAR Classification of JIA

Chronic arthritis in children represents a heterogeneous group of diseases with unknown etiology. Previously, there are two classification systems for chronic arthritis in childhood by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR). To classify these patients in more well-defined diagnostic categories, a task force of the International League Against Rheumatism (ILAR)^{8,9} proposed a new classification with precise criteria. The ILAR classification and its revision were proposed by an international group of paediatric rheumatologists (including experts from the United States, the United Kingdom, Canada, China, France, Australia, South Africa, Argentina and Mexico) with the aim of achieving as much homogeneity within categories as possible in order to facilitate communication and clinical research and patient care. The ILAR classification is shown in Table 1.

The Inter-hospital Surveillance of JIA in Hong Kong

Study Population and Method

Paediatricians from 12 Departments of Paediatrics of the Hospital Authority filled out a standard surveillance form with attached appendices explaining the diagnostic and classification criteria. This was a retrospective prevalence data collection including patients with JIA up to year 2000. The data were pooled and analyzed by the surveillance coordinator. The analyzed results have been sent back to the reporting representatives for checking and comments.

Results

There were total 125 patients with JIA receiving treatment in the Hospital Authority up to the year of 2000. All except one were Chinese children and the only Caucasian girl with JIA was not included in the present analysis. The individual hospital distribution was shown in the Figure 1. The male to female ratio was 1:0.9. The relative distribution of course subtypes of JIA was shown in Figure 2. The two most common subtypes were rheumatoid factor negative polyarticular (37%) and persistent oligoarticular JIA (24%) respectively. The age of onset was shown in the Figure 3. Most children presented at around 6 and 10 years old.

Remarks

The above figure may be well below the actual prevalence of JIA due to the following reasons: (i) Children

with arthritis may be treated by bone setters or alternative medicine practitioners; (ii) Data from general practitioners and private hospitals were not available; (iii) There were no special clinics for children with rheumatological diseases in most hospitals and hence the registry was probably incomplete; (iv) Adult-age JIA patients were not included. In order to improve the data quality, it is worthwhile to form a study group for paediatric rheumatology among paediatricians from both public and private sectors to enhance disease surveillance so that continuous prospective surveillance may contribute data for more accurate estimation of disease prevalence and incidence.

Current Management of JIA

Multi-disciplinary Approach

The aims of treatment are to control pain and preserve range of motion, muscle strength, and function; to manage systemic complications; to facilitate normal nutrition, growth, and physical and psychological development. Therefore it is ideal to involve a multi-disciplinary team consisting of paediatric rheumatologist, nurse specialist, social worker, physical therapist, occupational therapist, orthopaedic surgeon and psychologist. Simply suppressing the inflammation by medical therapy alone is inadequate to achieve the above aims. Some children develop disabling joint deformities because of soft tissue contractures as a consequence of painful and swollen joints rather than inflammatory cartilage damage due to synovitis. The roles of physiotherapy and occupational therapy are never over-emphasized. Therapeutic options include stretching, strengthening, gait retraining, serial casting, orthotics, and other devices to help activities of daily living. Consultation with dentist or dietitian is sought when indicated. Regular ophthalmic consultation is mandatory. Orthopaedic surgeon also plays an important part for those with more severe JIA. Surgical treatment includes synovectomy, soft tissue release, osteotomy and arthrodesis. Leg length discrepancy may occur and epiphyseodesis may be required to correct this.

Treatment Algorithms

The treatment algorithms 1 to 3 serve to provide an overall view of treatment options and were modified from British Paediatric Rheumatology Group Management Guidelines.¹⁰ Because of the heterogeneous nature of JIA and its severity in adulthood, in order to minimize long term damage, the aim of treatment should be prompt,

Table 1 ILAR Classification criteria for the idiopathic arthritis of childhood¹⁶

Disease (Onset type)	Disease (Course subtype)	Criteria	Exclusions
Systemic Arthritis		<p><i>Definite:</i></p> <ol style="list-style-type: none"> 1. Quotidian fever for at least 2 weeks 2. Evanescent, non-fixed erythematous rash 3. Arthritis <p><i>Probable:</i></p> <p>In the absence of arthritis, 1 and 2 (above) plus any two of:</p> <ol style="list-style-type: none"> 1. General lymph node enlargement 2. Hepatomegaly or splenomegaly 3. Serositis 	NOMID ^a Periodic syndromes ^b Drug hypersensitivity
Polyarthritis RF-		Arthritis of ≥ 5 joints during the first 6 months of disease	Positive RF ^c
Polyarthritis RF+		<ol style="list-style-type: none"> 1. Arthritis of ≥ 5 joints during the first 6 months of disease 2. Positive RF on at least two occasion 3 months apart 	Psoriasis
Oligoarthritis	Persistent Oligoarthritis	Arthritis of 1-4 joints during the onset or course of the disease	Psoriasis Positive RF
	Extended Oligoarthritis	<ol style="list-style-type: none"> 1. Arthritis of 1-4 joints during the first 6 months of disease 2. Arthritis of ≥ 5 joints after the first 6 months of disease 	Psoriasis Positive RF
Enthesitis - related arthritis		<p>Arthritis and enthesitis or,</p> <p>Arthritis or enthesitis with at least two of:</p> <ol style="list-style-type: none"> 1. Sacroiliac joint tenderness and/or inflammatory spinal pain 2. Presence of HLA B27 3. Family history in at least one first- or second-degree relative of medically confirmed HLA B-27-associated disease 4. Anterior uveitis that is usually associated with pain, redness or photophobia 5. Onset of arthritis in a boy after 8 years of age 	Psoriasis confirmed by a dermatologist in at least one first- or second-degree relative Presence of systemic arthritis
Psoriatic arthritis		<p>Arthritis and psoriasis or,</p> <p>Arthritis and at least two of:</p> <ol style="list-style-type: none"> 1. Dactylitis 2. Nail pitting or onycholysis 3. Family history of psoriasis in a first-degree relative 	Positive RF
Other		Arthritis for ≥ 6 months and does not fit into any of the above categories or fits into more than 1 category	

^a Neonatal onset multi-system inflammatory disease^b Including familial Mediterranean fever, hyper-IgD syndrome, FAPA (fever, aphthous ulceration, pharyngitis, adenopathy)^c RF=Rheumatoid factor

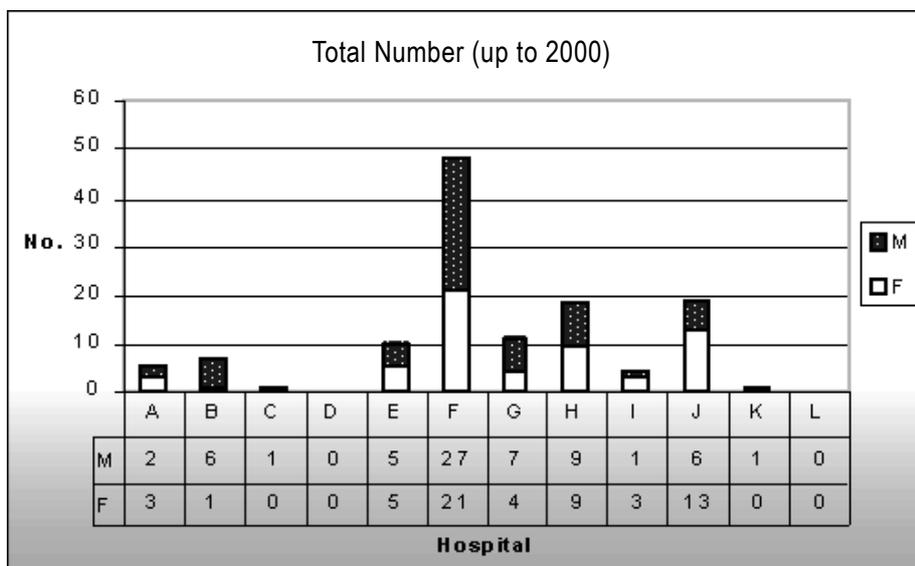


Figure 1 Prevalence of patients with JIA in 2000.

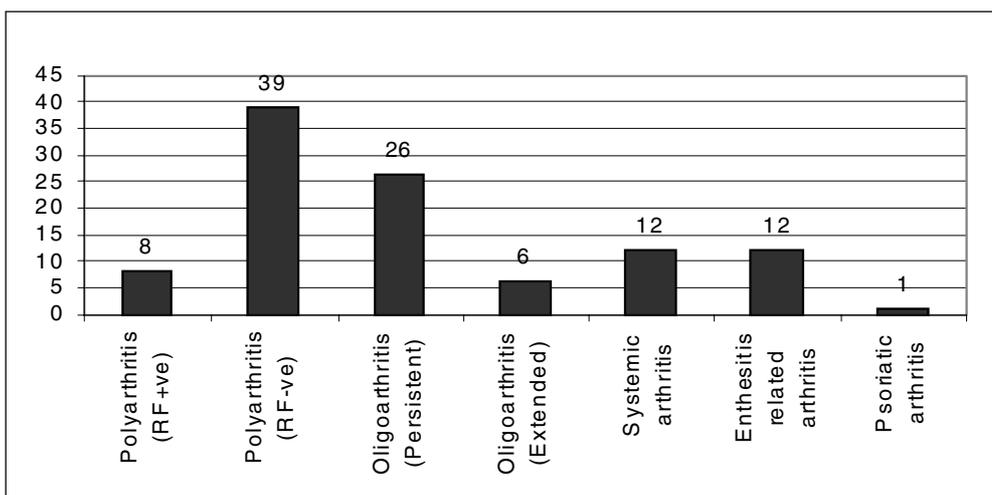


Figure 2 Course type distribution (ILAR classification).

consistent and complete (or very nearly complete) suppression of the inflammation while avoiding chronic corticosteroid therapy. That means the need of early aggressive use of one or more disease modifying anti-rheumatic drugs (DMARDs) in certain patients.

Medications

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are the first line therapy for all types of JIA. Naproxen is effective in management of joint inflammation

in a dose of 15-20 mg/kg/day in two divided doses. It is available as a suspension. Other NSAIDs include ibuprofen (35 mg/kg/day in 4 divided doses), tolmetin (25-30 mg/kg/day in 3 doses) and diclofenac (3-5 mg/kg/day in 4 doses). Other NSAIDs have specific indications but are not officially approved for use in children. Celecoxib and rofecoxib are COX-2 (cyclooxygenase-2) inhibitors that are less likely to induce peptic ulcer disease. Indomethacin (1-2 mg/kg/day in 3 doses with maximum dose of 125 mg/day) may be useful in more severe inflammatory joint disease.

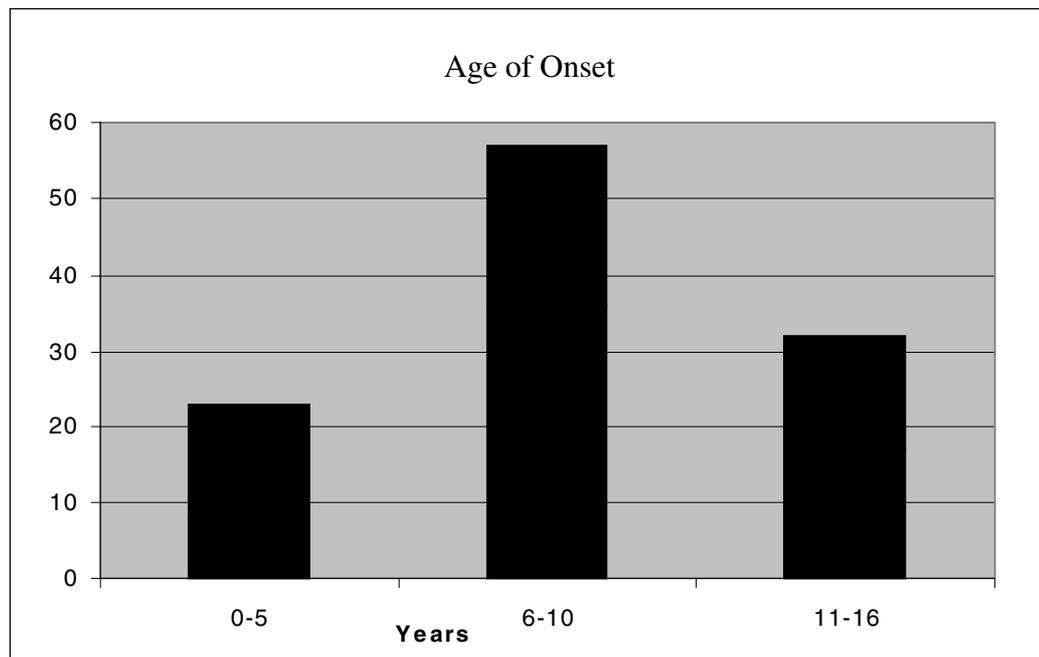


Figure 3 Relative distribution of age of onset.

Methotrexate

Methotrexate (MTX) continues to be the main disease modifying anti-rheumatic drug (DMARD) for JIA. The starting dose is 10-15 mg/m²/week by either oral or subcutaneous (sc) or intramuscular route.¹¹⁻¹³ The maximum dose is approximately 1 mg/kg/week (usually not exceeding 30-40 mg/week).^{10,14} Intramuscular or subcutaneous route can be used when higher doses are indicated and there are uncertainties about oral absorption. It has been used to treat JIA for more than 10 years.^{12,15-17} Between 60% to 80% of JIA patients experience some clinical improvement after treatment with MTX. Some uncontrolled studies also suggest that MTX slows radiographic progression in JIA.¹⁸ The most common adverse effects are gastrointestinal symptoms (~13%) and mouth sores. Supplementation with folic acid 1 mg/day may help alleviate these side effects without diminution of its clinical effectiveness. Principal toxicities are directed at the bone marrow, liver and lung. According to ACR guideline, complete blood count, white blood cell differential and platelets counts, creatinine and serum liver enzymes levels should be monitored monthly for first 6 months and 1-2 monthly thereafter. Teenagers are advised for total abstinence of alcohol if they are taking methotrexate.

Corticosteroids

a) Systemic Corticosteroids

Systemic corticosteroids are avoided when possible, but will sometimes be used for disease exacerbations. It should be instituted only with a well-considered therapeutic plan and a clear set of clinical objectives. Important complications with chronic steroid therapy include growth retardation, osteoporosis, osteonecrosis, Cushingoid syndrome and immunosuppression. The high frequency of significant side effects and lack of evidence of altering the natural history of articular manifestations strongly weigh against routine use in JIA.

Intravenous pulse corticosteroid¹⁹⁻²¹ is sometimes indicated in treatment of serious and unresponsive disease. It can be given as 10-30 mg/kg/day for 3 days with maximum dose 1000 mg/day. The patient should be hospitalized for close cardiovascular monitoring (because of potential complications of hypertension and cardiac arrhythmia) during infusion and for a short time thereafter. Electrolyte and fluid balance should also be monitored.

b) Intra-articular Corticosteroids

Intra-articular corticosteroids are effective in managing

inflammation in a child with monoarticular or oligoarticular arthritis. It is sometimes indicated in treatment of particular symptomatic joints in a child with polyarticular arthritis. Triamcinolone hexacetonide are given in a dose of about 1 mg/kg body weight for large joints and about half that dose for smaller joints.²² It is effective in correcting joint contractions and deformities and it may be the only therapy needed in patients with oligoarticular JIA, obviating the need for prolonged oral medications. It has been shown by magnetic resonance imaging studies that intra-articular steroid therapy resulted in significant suppression of inflammation and pannus formation without evidence of toxic effects on cartilage.²³

Biologic Agents

Etanercept (Enbrel) is a genetically engineered fusion protein, composed of tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. Etanercept binds tumor necrosis factor (TNF) and blocks its interaction with cell surface receptors. TNF plays an important role in the inflammatory processes of rheumatoid arthritis (RA) and the resulting joint pathology. A randomized double-blind study showed treatment with etanercept leads to significant improvement in patients with active polyarticular juvenile rheumatoid arthritis.²⁴ It is approved by FDA for use in reducing signs and symptoms of moderately to severely active polyarticular JIA that is refractory to one or more DMARDs. Etanercept is well tolerated by paediatric patients. Short term safety and tolerability appear to be excellent. Significant theoretic concern exists over the development of secondary infections, malignancies, or other autoimmune diseases and demyelinating diseases such as multiple sclerosis.

Infliximab is a chimeric monoclonal antibody that binds to human tumor necrosis factor alpha (TNF-alpha) receptor sites, thereby interfering with endogenous TNF-alpha activity. However, there are no formal trials of infliximab (Remicade) conducted in children.

However, these two agents are prohibitively expensive and they are not available in Hong Kong yet. It is hoped that children with refractory JIA in Hong Kong can benefit from these new agents when they are available locally and the price goes down to reasonable level.

Transplantation

Despite the emergence of new therapeutic agents which appear to be more effective in treating JIA, there surely will still be some patients who remain resistant to medical therapies. Autologous stem-cell transplantation (ASCT)

may be the final alternative therapy for this group of patients. Reports of good response of children with JIA to ASCT have been published.^{25,26} A comprehensive review of the international experience with ASCT to treat JIA reported 5 mortalities among 36 children treated.²⁷ We have also performed autologous stem cell transplantation for a 10-year-old girl with refractory JIA in 2001. After transplantation, all medications were able to be stopped and she remained in full remission in terms of symptoms, joint inflammation and laboratory inflammatory markers during 12 months follow-up period. At present, this treatment should be considered experimental and should be only reserved for those patients who have most severe disease unresponsive to standard treatment.

Future Directions and Challenges

Juvenile idiopathic arthritis is an important chronic disease affecting a significant population of children but the attention it gets is disproportionately less. To date, this surveillance study is the first of its kind in Chinese children. We believe that the actual prevalence is underestimated due to the reasons stated above. With better awareness of the significance of this condition and the continued efforts of prospective surveillance, it is hoped that more accurate data on prevalence and incidence could be obtained in the future. The new classification scheme for JIA may be a step forward in categorizing patients with JIA, facilitating better communication in research, epidemiology and clinical care.

There have been new and significant advances in the treatment of JIA. Paediatric rheumatologists have become more aggressive in the use of anti-inflammatory medications because of the frequent chronicity and risk of irreversible damage to joints or eyes in children with JIA whose chronic arthritis or uveitis is only partially controlled.

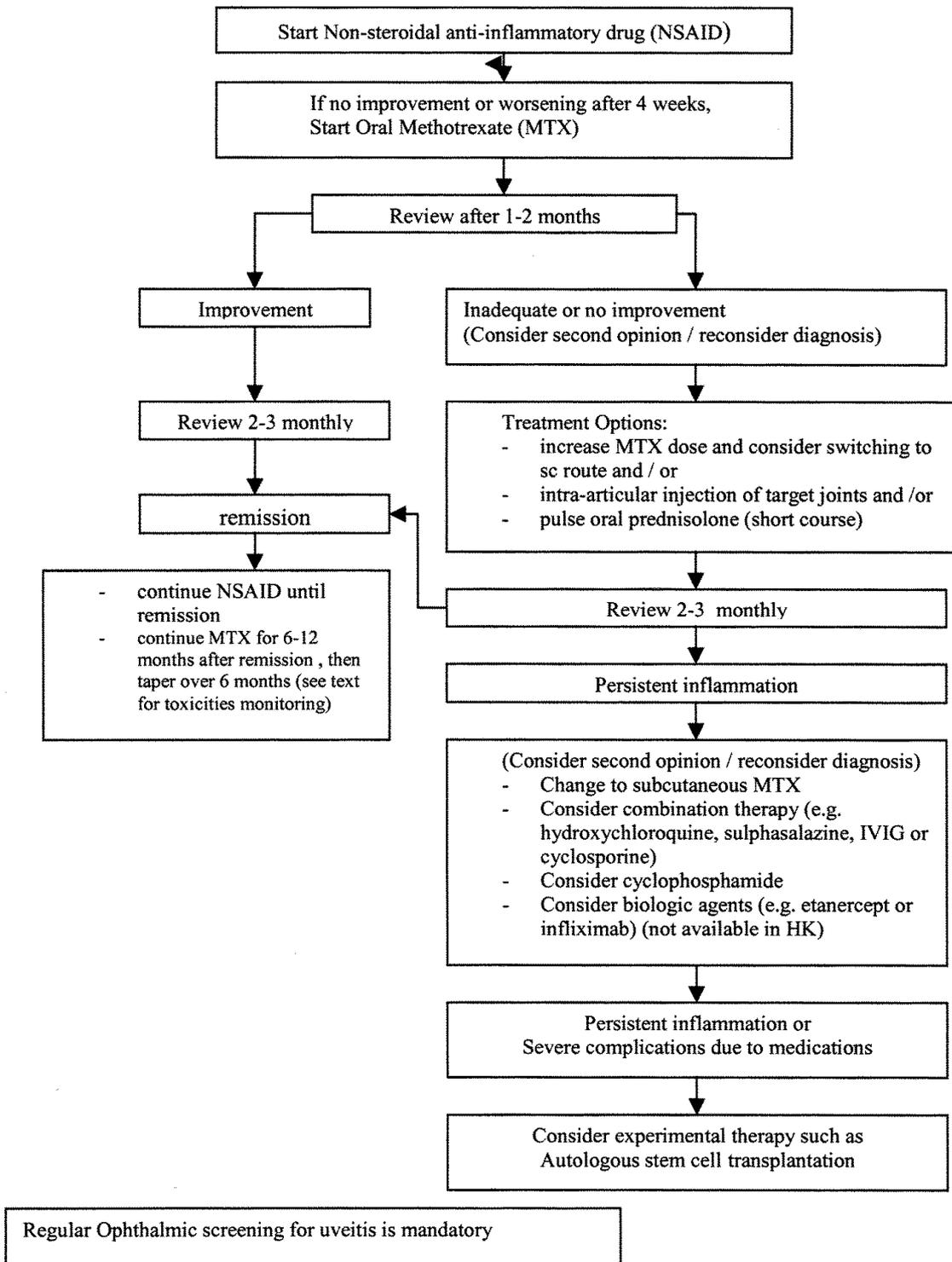
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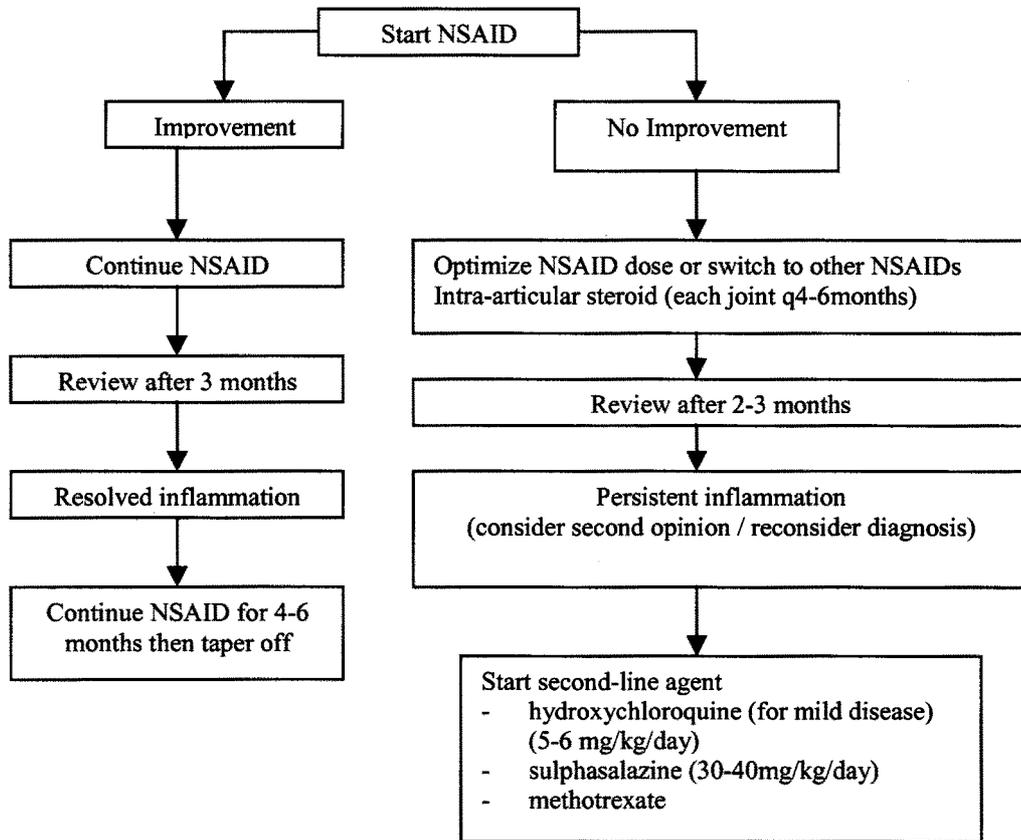
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Medical Treatment Algorithm 1 for Polyarticular JIA



Medical Treatment Algorithm 2 for Oligoarticular JIA



Regular Ophthalmic screening for uveitis is mandatory

Medical Treatment Algorithm 3 for Systemic JIA

