

# Juvenile Idiopathic Arthritis: Most Common Rheumatic Disorder in Children- An Overview

S A RAHMAN

### Summary:

*Juvenile Idiopathic Arthritis (JIA) is the most common form of chronic arthritis in children and an important cause of both the short term and long term morbidities. JIA is the new terminology proposed by the International League of Associations of Rheumatologists (ILAR). Three separate systems are used currently to classify chronic arthritis in children. These are American College of Rheumatology (ACR) classification, The European League against Rheumatism (EULAR) classification and ILAR classification. The diagnosis of JIA remains a clinical one, and is essentially one of exclusion in addition to suspicion and recognition of patterns. There is no*

*single test for the diagnosis of JIA. The treatment of JIA is rapidly changing. Aims of good management of JIA include: controlling pain and inflammation, preserving function and promoting normal growth and development. Remarkable advances have been made in the management of JIA with the advent of new modalities of treatment. Effective management of JIA needs a multidisciplinary team approach. Even after effective management, about one-third of JIA patients continue to manifest their disease activity into adulthood with serious morbidity and disabilities.*

*(J Bangladesh Coll Phys Surg 2009; 27: 91-98)*

### Introduction:

Juvenile idiopathic arthritis (JIA) is an umbrella term referring to a group of disorders characterized by chronic arthritis<sup>1</sup>. JIA is the most common chronic rheumatic illness in children and is a significant cause of both the short and long term morbidity and disability<sup>1,2</sup>. Arthritis may be present in children in a number of conditions including infection, systemic diseases, and malignancies and as a part of autoimmune disease. But the prototype of childhood arthritis is JIA.

JIA is a clinical diagnosis made in a child less than 16 years of age with arthritis (defined as swelling or limitation of motion of the joint accompanied by heat, pain or redness) for at least 6 weeks duration with other identifiable causes of arthritis excluded<sup>1</sup>.

The prevalence of JIA ranges from 8 to 150 per 100,000 children with an annual incidence of 1 to 22 per 100,000<sup>3,4</sup>. Many factors contribute to the discrepancies between reported prevalence and incidence of JIA. Studies based truly in the community reported the highest prevalence and incidence<sup>5</sup>.

---

**Address of correspondence:** Shahana A Rahman FCPS, M.Med. Ed., Professor of Paediatrics, Bangabandhu Sheikh Mujib Medical University

**Received:** 6 February, 2008

**Accepted:** 22 January, 2009

Twice as many girls as boys develop JIA. Among children with poly-articular onset, girls outnumber boys by a ratio of about 3:1. In striking contrast, systemic onset occurs with equal frequency in boys and girls. No race or geographical region is immune to JIA.

### Classification of JIA:

The classification of juvenile arthritis is an evolving process which has not yet achieved its ultimate goal. The ultimate goal of classification is delineation of biologically distinct disease groups with prediction of outcome and responses to treatment<sup>2</sup>. It has been problematic for decades. The heterogeneity of these diseases was discussed by Diamont-Berger and Still in 1891 and 1896<sup>6</sup>. They recognised that many children with chronic arthritis had a disease that was unlike adult rheumatoid arthritis. However, subsequent workers have differed as to whether childhood arthritis should be grouped with adult rheumatoid arthritis or with spondylo-arthropathies.

In the 1970s, two sets of criteria were proposed to classify chronic arthritis in childhood:

1. Developed and tested by a committee of American College of Rheumatology (ACR) and the definitive Juvenile rheumatoid arthritis (JRA) criteria were published<sup>7</sup>.
2. European League Against Rheumatism (EULAR)

proposed Juvenile chronic arthritis (JCA) and its criteria for diagnosis<sup>8</sup>.

In the 1990s a third classification had been proposed by the paediatric task force of the International League of Associations for Rheumatology (ILAR)<sup>9</sup>. The ILAR classification and its revision were proposed by an international group of paediatric rheumatologists in Santiago and Durban with the aim of achieving as much homogeneity within categories as possible<sup>2,10</sup>. This was necessary because the terms JCA and JRA were not inter-changeable as their subgroups were different<sup>2</sup>. None of the classification system is perfect: some patients fulfill criteria for more than one subtype, whereas others are difficult to classify into any specific subgroups. In the ILAR system, these patients are classified as "other"<sup>1</sup>. All of these three schemata are shown in Table I and II.

**Table-I**

*Summary of classification of chronic arthritis in children<sup>1</sup>*

ACR (1977) JRA	EULAR (1978) JCA	ILAR (1997) JIA
Systemic	Systemic	Systemic
Polyarticular	Polyarticular	Polyarticular RF negative
	JRA	Polyarticular RF positive
Pauciarticular	Pauciarticular	Oligoarticular
		persistent
		extended
	Juvenile psoriatic	Psoriatic arthritis
	Juvenile ankylosing	Enthesitis-related arthritis
	spondylitis	Others

**Table-II**

*Summary of the differences among the three classification systems<sup>1</sup>*

	ACR	EULAR	ILAR
Onset types	3	6	7
Age of onset	<16 years	<16 years	<16 years
Duration of arthritis	>6 weeks	>3 months	>6 weeks
Includes JAS, JpSA	No	Yes	Yes
Includes IBD	No	Yes	Yes
Includes course	No	No	Yes

#### **Actio-pathogenesis:**

Although the causes of JIA still remain unclear, it seems to have a complex genetic background

involving the effects of multiple genes related to immunity and inflammation<sup>11</sup>. Some hypotheses are there like, arthritis may be triggered by psychological stress, abnormal hormone levels, trauma or infection is a genetically pre-disposed individual. Certain HLA class I and class II alleles are associated with an increased risk of JIA<sup>12</sup>. Other genes conferring risk include cytokine production-regulating genes.

There is evidence of immune- dysregulation in JIA. Complement activation and consumption promote inflammation. Increasing serum levels of immune-complexes are found with active disease. Anti-nuclear antibodies (ANA) are found in approximately 40% of patients with JIA<sup>13</sup>. Approximately 5% to 10% patients are Rheumatoid factor (RF) positive<sup>11</sup>

The T lymphocyte-mediated immune response is involved in chronic inflammation and these are the pre-dominant mononuclear cells in the synovial fluid. Elevated serum levels of IL-6 IL 2R and soluble tumour necrosis factor (TNF) receptor correlate with inflammatory parameters in JIA patients<sup>14</sup>. Earliest change is swelling and congestion of the synovial membrane and the underlying connective tissues, which become infiltrated with lymphocytes, plasma cells and macrophages<sup>15</sup>. The synovitis is characterized by villous hypertrophy and hyperplasia with hyperaemia and oedema of sub-synovial tissue. Pannus formation occurs in advanced or uncontrolled diseases and result in progressive erosion of articular cartilage and adjacent bones<sup>16</sup>. Later on fibrosis or bony ankylosis may occur.

#### **Clinical Presentation:**

The ILAR classification of JIA includes seven subtypes. In order of frequency, the disease subtypes are oligoarticular JIA (50-60%), Polyarticular JIA (30-35%), systemic onset (10%-20%), psoriatic arthritis (2-15%) and Enthesitis related arthritis (1-7%)<sup>1</sup>. The subtypes are classified depending on the clinical features during the first 6 months of disease. Important clinical features other than arthritis include: presence of enthesitis, dactylitis, inflammatory lumbo-sacral pain, sacroilitis, psoriasis, nail pitting, fever, rash and serositis<sup>1</sup>.

#### **Oligoarticular JIA (OJIA)**

It is diagnosed in patients with arthritis in fewer than five joints during the first 6 months of disease.

Usually there is involvement of large joints of the lower limbs such as knees and ankles. Oligo-articular patients, especially ANA positive girls, are at higher risk of developing uveitis, which is usually their most serious problem<sup>1</sup>.

Arthritis that remains confined to four or less joints is designated as persistent oligo-articular JIA. A child who develops active arthritis of five or more joints after the first 6 months of disease is considered to have extended oligo-articular JIA. Extended disease confers a worse prognosis<sup>17</sup>.

### **Polyarticular JIA**

Patients with arthritis of five or more joints in the first six months of disease are diagnosed as polyarticular JIA. This subtype again includes children with RF negative disease (20%-30% of JIA patients) and RF positive disease (5%-10% of JIA patients)<sup>11</sup>. Common age of onset in this category is one to five years. Older teenage girls with polyarticular diseases often have a positive rheumatoid factor<sup>18</sup>. In polyarticular disease, usually small joints of the hands are involved symmetrically and large joints of both upper and lower limbs may also be affected. Chronic uveitis develops less frequently than in oligo-articular disease.

### **Systemic onset JIA (SOJIA)**

SOJIA is the only subtype of JIA without a strong age, gender or HLA association<sup>1</sup>. At onset extra-articular manifestations including rash, fever, lymphadenopathy, hepato-splenomegaly and serositis predominate. The diagnosis remains a challenge in the absence of arthritis which may evolve over time. About 10 percent patients may not develop arthritis for many months. Children with SOJIA typically have 2 weeks of high-spiking fever, classically with two peaks daily (double quotidian). During episodes of fever, chills are common, and the child appears very toxic, but when a febrile, child appears well.

With the characteristic quotidian fever with an evanescent rash and other extra-articular manifestations, diagnosis of probable SOJIA may be made, with confirmation of the diagnosis when persistent arthritis develops<sup>19</sup>. The arthritis associated with systemic onset JIA is usually polyarticular,

affecting both small and large joints. Asymmetric, oligoarthritis is less common.

### **Enthesitis related arthritis (ERA)**

Enthesitis related arthritis is much more common in boys than in girls. It is most common in boys older than 8 years of age<sup>20</sup>. Patient with juvenile ankylosing spondylitis and arthritis associated with inflammatory bowel diseases are included in the ERA subtype. The hallmarks of the disease are pain, stiffness and eventual loss of mobility of the back. Peripheral arthritis usually affecting few joints of the lower extremity precedes axial involvement and arthritis of the sacro-iliac joints may take years to develop.

Extra-articular manifestations include anterior uveitis, aortic insufficiency, aortitis, muscle weakness and low grade fever. Acute uveitis is common, often unilateral and recurrent. It may present as a red, photophobic eye<sup>1</sup>.

### **Psoriatic Arthritis**

Juvenile psoriatic arthritis is sometimes quite difficult to diagnose. The pattern of arthritis may be variable: asymmetric large joint involvement and the small joints of the hand and feet<sup>21</sup>. Interphalangeal joints and the tendon sheath are often inflamed, resulting in the diffuse swelling of the digit known as "sausage digit". Arthritis may develop many years before the skin rash. Other than rash, extra-articular manifestations include nail changes (pitting, onycholysis, and oil-drop sign) and anterior uveitis.

### **Diagnosis of JIA:**

The diagnosis of JIA is a clinical one made after identifiable causes of arthritis are excluded by a careful history and examinations along with appropriate radiographs and laboratory tests<sup>1</sup>. Important clinical features like systemic illness, preceding infection, duration of fever, rash, bleeding, injury and character of the arthritis help to differentiate JIA from other causes of arthritis<sup>1</sup>. The differential diagnosis of arthritis includes: reactive arthritis, inflammatory diseases, septic arthritis, acute rheumatic fever, multi-system diseases like SLE, malignancy and trauma. A number of laboratory tests and imaging studies are required to exclude all the differential diagnosis and to confirm the diagnosis of JIA<sup>6</sup>.

**Laboratory findings:**

Complete blood count is by far the most important investigation, which classically shows: lower haemoglobin, neutrophilic leukocytosis, thrombocytosis and high ESR<sup>16</sup>. ESR and C - reactive protein (CRP) are always high in children with SOJIA and polyarticular disease, but is often normal in oligo arthritis and ERA<sup>1,6</sup>.

Urine analysis should be done to exclude the possibilities of infection and SLE. Antinuclear antibody (ANA) is found in approximately 40% of all children with oligo articular or polyarticular JIA<sup>13</sup>. But this is always negative in systemic onset diseases. Rheumatoid factor (RF) is found in 5% to 8% cases of polyarticular JIA especially in older girls. RF positivity is usually associated with poor overall prognosis and eventual functional disability<sup>6</sup>. Anti-cyclic citrullinated peptide (Anti-CCP) antibody is a good serological marker for early rheumatoid arthritis which is highly specific for the disease<sup>22</sup>.

**Imaging studies:**

Radiographs of the affected joints give information about soft tissue swelling, decreased bone density, joint space narrowing, joint erosion, deformity and fracture<sup>15</sup>. Ultrasonography is often the best way of identifying intra articular fluid, particularly in joints such as shoulder and hip, where it is difficult to identify clinically<sup>6</sup>. Magnetic resonance imaging (MRI) provides very detailed and sensitive information of both structure and physiology of cartilage, bone and other loco-motor tissue<sup>16</sup>.

**Management of JIA**

Management of JIA is rapidly changing as the need for more effective treatment is regularly documented by different studies<sup>23</sup>. Objectives of the management of JIA are:

- Controlling pain and inflammation
- Preserving function
- Promoting normal growth
- Overall development and well being.

There are no therapies till date that have been demonstrated to achieve these results consistently. Treatment of JIA is even more challenging as because the aetiology of JIA is unknown, and the mechanisms of action of commonly used drugs are not clearly

known. During past decades, a major transformation had occurred in the treatment of rheumatoid arthritis in terms of approach, termed the therapeutic pyramid, where conservative management was done with non-steroidal anti-inflammatory drugs (NSAIDs) for several years; disease modifying anti-rheumatic drugs (DMARDs) were withheld until clear evidence of erosions was seen<sup>24</sup>. This form of treatment had been replaced by early initiation of DMARDs and combination DMARDs therapy in patients with the potential for progressive disease. The idea of early intervention with DMARDs had been validated by several randomized trials<sup>25, 26</sup>.

This paradigm shift is the result of unsatisfactory outcomes with the pyramid approach, and an increased awareness of the cost, lost productivity, morbidity and decreased life expectancy associated with JIA<sup>24</sup>.

**Non steroidal anti-inflammatory drugs (NSAIDs):**

First-line therapy of JIA includes NSAIDs. In addition, long-acting intra-articular corticosteroid injections are safe and effective and may have beneficial effects on growth as well<sup>27</sup>. NSAIDs control pain and inflammation and are usually given to all types of JIA for 4 to 8 weeks before starting treatment with a DMARD (Fig-1).

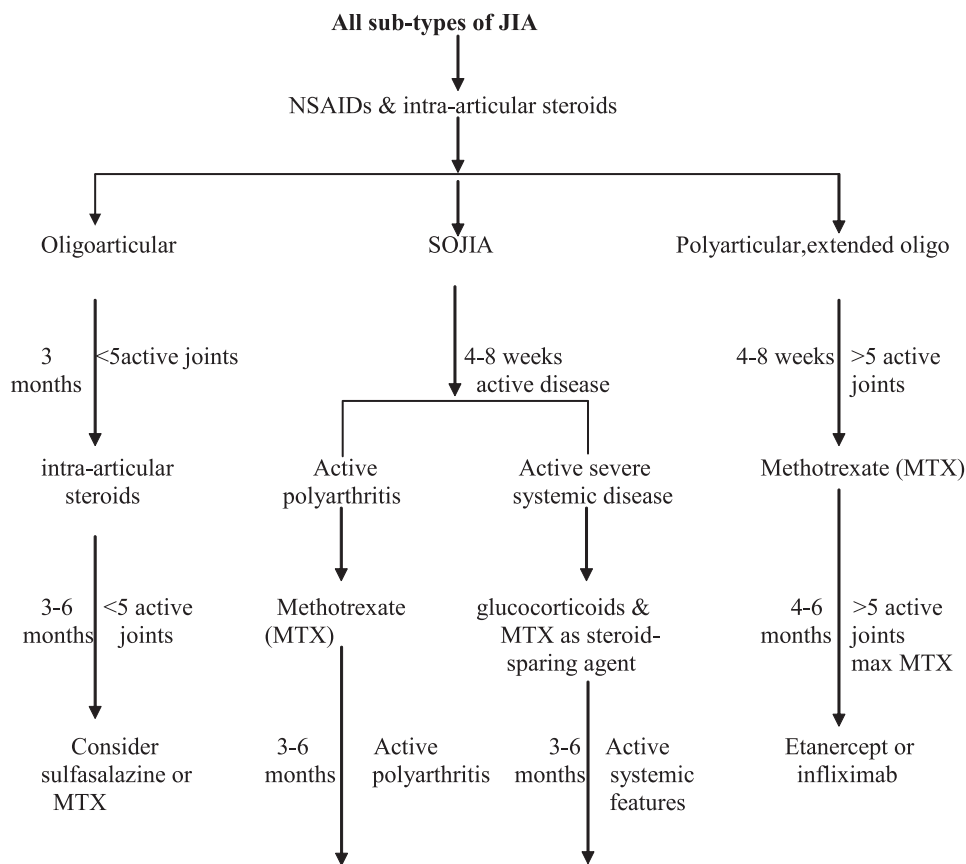
Commonly used NSAIDs are aspirin, naproxen, ibuprofen, diclofenac and indomethacin<sup>18</sup>. Till now, there is no clear-cut consensus on the optimal NSAIDs for patients with JIA. Many clinicians choose NSAIDs on the basis of considerations, such as dosing schedule, patient preference or medication taste<sup>27</sup>. But most physicians use naproxen as a first choice in the majority of cases<sup>16</sup>.

**Disease-Modifying Anti-rheumatic Drugs (DMARDs):**

The term "Disease-modifying antirheumatic drugs" (DMARDs) is limited to agents that retard radiologic progression of the disease<sup>27</sup>. These drugs include methotrexate, hydroxychloroquine, sulphasalazine, gold salts, leflunamide, cyclosporine, cyclophosphamide and azathioprine<sup>28</sup>.

**Methotrexate (MTX)**

The introduction of MTX few decades ago redefined the treatment algorithm for JIA and MTX became the



Consider anakinra or enbrel or infliximab or thalidomide or IL-6 MRS

**Fig.-1:** Suggested treatment algorithm for JIA1

gold standard of therapy<sup>28,29</sup>. Methotrexate has proven to be an effective, safe and reliable option for treatment in all forms of JIA<sup>28-31</sup>. It has a major advantage that it can be administered as once weekly dose. Single weekly doses of MTX found to be effective in children with 0.3 – 1.0 mg/Kg/week (10-30 mg/m<sup>2</sup>). These doses are much higher than weekly doses usually given to adult patients<sup>23</sup>. Sub-cutaneous use of MTX increases the bioavailability and efficacy. Supplementation with folic acid lessens the gastrointestinal and muco-cutaneous side effects without altering the therapeutic effect of MTX<sup>32</sup>.

Liver enzymes and a complete blood count should be monitored every 1 to 2 months, although serious, irreversible liver disease is rare in children<sup>1</sup>. There is no doubt that MTX is currently the most useful drug for the treatment of JIA. But there is nothing to guide the clinical decision making regarding the duration of

MTX treatment after remission is achieved<sup>33</sup>. Some authors did not find any influence on remission after prolonged MTX treatment<sup>34</sup>.

**Sulfasalazine**

Sulfasalazine is an effective drug suppressing the disease activity of JIA patients<sup>23</sup>. However, drug toxicity is a problem. Headache, rash, elevated liver enzymes, leucopenia, hypoinmuno-globulinaemia and gastrointestinal problems are common side effects of Sulfasalazine.

**Leflunomide**

Leflunomide, an immunosuppressive agent, is approved for the treatment of adult rheumatoid arthritis and is currently being studied for use in JIA. Preliminary published results show that its efficacy is similar to that of MTX<sup>34</sup>.

**Corticosteroids**

**Intra-articular therapy:** Intra-articular injection of corticosteroids in the treatment of JIA is well-established for mono or oligoarthritis, or alternatively as an adjunct in treating polyarticular disease<sup>28</sup>. Intra-articular therapy can effectively treat joint inflammation locally, for long periods of time, with excellent and rapid resolution of synovitis.

**Parenteral corticosteroids:** Parenteral high-dose corticosteroids used intermittently in 'pulse fashion' is a useful and very effective adjunct to therapy in SOJIA or severe polyarticular JIA<sup>35</sup>. It is also thought to minimize the cumulative steroid toxicity of continuous daily oral steroids.

**Oral corticosteroids:** The general approach to oral corticosteroid use is to avoid them if possible, and if required, to use the minimum dose. Commonest use of oral corticosteroid is while awaiting the desired effect of DMARDs therapy, and once effective, steroids should be weaned rapidly<sup>28</sup>.

**Biological agents:**

The biologics (etanercept, infliximab, adalimumab, anakinra, abatacept and rituximab) have been demonstrated to be effective in treating inflammatory arthritis<sup>23</sup>. Their use in children poses special problems, including the increased risk of infections, possibilities of later malignancies or possible development of de-myelinating disease. The cases of re-activated tuberculosis have been particularly difficult.

An important issue with anti-TNF (Etanercept, infliximab and Adalimumab), anti IL-1 (Anakinra) and the B-cell depletor (rituximab) is how and when to discontinue these powerful and effective treatments.

**Autologous stem cell transplantation:**

A number of studies have reported the use of autologous stem cell transplantation in very severe forms of JIA, resistant to all forms of treatment<sup>36</sup>. Encouraging results, including complete and long lasting remission induction have been reported.

**Other issues in the management:**

At present, remarkable advances in the treatment of JIA have been made with the advent of new

DMARDs, and biologic therapy. Physical and occupational therapies are important adjuncts to medication because they help to maintain and improve range of motions, muscle strengths, and skills for activities of daily living. Splints may be used to prevent contractures or work to improve range of motion. Arthroplasty might be needed for patients with severe deformities<sup>1</sup>. So, effective management of JIA requires a multidisciplinary team approach.

Nutritional impairment is common in children with JIA. Growth may be affected by decreased total calorie intake, by active disease itself or by medication side-effects<sup>28</sup>. Localized disturbances in growth, such as leg-length discrepancy or jaw growth abnormalities may also occur. Delayed puberty is quite common in JIA patients. Attention to growth parameters including pubertal status is important.

Children with JIA are at increased risk for osteopenia and osteoporosis<sup>1</sup>. Low bone mineral density (BMD) has been associated with severe disease; younger age, lower body mass index, and lean body mass, decreased intake of calcium and vitamin D, and decreased physical activities. Appropriate calorie and calcium intake along with physical activities should be encouraged<sup>1,28</sup>.

Uveitis remains as an important complication in some JIA patients. Regular screening of all children is needed for early detection and management of uveitis and prevention of blindness<sup>28</sup>. Attention to the psychological well-being of the patient with JIA is essential in the setting of this chronic painful and disabling condition. Early discussion with the patient when they reach early adolescence, along with their family is very important regarding the process of transition to adult health care services<sup>37</sup>.

Counseling the family is most important for effective management of this chronic illness. The parents and if appropriate the child must be educated about the present state of knowledge of JIA, its outcome, and therapy. An optimistic attitude must be maintained<sup>6</sup>.

**Monitoring of progress:**

Disease progress should be determined by a range of factors or outcome measures. These are critical objective parameters both for therapeutic trials and

for day-to-day practice to judge whether or not the patient has improved. These variables are now used in a combined fashion as a standardized outcome measures<sup>38</sup>.

#### Outcome of JIA:

Traditionally, the teaching regarding the prognosis of JIA was over optimistic, such that most children 'grow out of it'. Realistically, and depending on types, JIA is not a benign disease. Once remission has been achieved, nearly 50% of the patients may have relapse at any time. Nearly one-third of patients have their disease activity into adulthood. Among them many live with considerable limitations of daily activities<sup>28</sup>. In general longer disease duration, poly-articular disease and systemic onset JIA have worst prognosis. Oligo-articular JIA is known to be as the most benign<sup>1</sup>. The mortality rate based on reports from the United States and Canada is reported as 0.29/100 patients. Most deaths occurred in patients with Systemic onset JIA<sup>39</sup>.

#### Conclusion:

In spite of new insights into aetiology and considerable advances in the management, JIA remains an important cause of chronic pain and disability in children. Recognition of the need to treat this disease early, effectively and aggressively have resulted in increasingly better disease control and achievement of inactive disease in greater number of children. It is expected that these approaches will result in better quality of life allowing children with JIA to become adults leading normal or near normal lives.

#### References:

- Jennifer EW, Norwan TI. Juvenile Idiopathic Arthritis. *Pediatr Clin N Am* 2005; 52: 413-442.
- Hofer M, Southwood T R. Classification of childhood arthritis. *Best Pract Res Clin Rheumatol* 2002; 16: 379-396.
- Gare BA. Juvenile arthritis- who gets it, where and when? A review of current data on incidence and prevalence. *Clin Exp Rheumatol* 1999; 17: 367-74.
- Prieur AM, Le Gall E, Karman F. Epidemiologic survey of Juvenile chronic arthritis in France: comparison of data obtained from two different regions. *Clin Exp Rheumatol* 1987; 5: 217-23.
- Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis: why does it vary so much? *J Rheumatol* 2002; 29: 1520-30.
- Cassidy JT, Petty RE. Juvenile Rheumatoid Arthritis. In: Cassidy JT, Petty RE, editors. *Text book of Pediatric Rheumatology*. 4th ed. Philadelphia: W.B.Saunders Company; 2001; p. 218-321.
- Brewer E J Jr, Bass J, Baum J. Current proposed revision of JRA criteria. *Arthritis Rheum* 1977; 20 (Suppl): 195-99.
- European League Against Rheumatism. *EULAR Bulletin No. 4: Nomenclature and Classification of Arthritis in Children*. Basel; National Zeitung AG, 1977.
- Fink CW. Proposal for the development of classification criteria for idiopathic arthritides of childhood. *J Rheumatol* 1995; 22:1566-69.
- Petty RE, Stouthwood TR, Baum J. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban 1997. *J Rheumatol* 1998; 25: 1991-94.
- Lang BA, Shore A. A review of current concepts on the pathogenesis of juvenile rheumatoid arthritis. *J Rheumatol* 1990; 17: 1-15.
- Thomson W, Barrett JH, Donn R. Juvenile idiopathic arthritis classified by the ILAR criteria: HLA associations in UK patients. *Rheumatology* 2002; 41: 1183-89.
- Petty RE, Cassidy JT, Sullivan DB. Clinical correlates of antinuclear antibodies in juvenile rheumatoid arthritis. *J Pediatr* 1973; 83: 386-89.
- Mangee H, Kenzian H, Gallistl S. Serum cytokines in juvenile rheumatoid arthritis. *Arthritis Rheum* 1995; 2: 211-20.
- Doherty M, Lanyon P, Ralston SH. Musculoskeletal Disorders. In: Boon Na, Colledge NR, Walker BR, Hunter JAA, editors. *Davidson's Principles and Practice of Medicine*. 20th ed. London: Churchill Livingstone; 2006: p. 1065 -1144.
- Miller ML, Cassidy JT. Juvenile Rheumatoid Arthritis. In: Kleigman RM, Behrman RE, Jenson HB, Stanton BF, editors. *Nelson Text book of Pediatrics*. 18th ed. Philadelphia: W B Saunders; 2007: p.1001- 1010.
- Minden K, Niewerth M, Listing J. Long-term outcome in patients with juvenile idiopathic arthritis. *Arthritis Rheum* 2002; 46: 2392-401.
- Sawhney S, Woo P. Diagnosis and management of Juvenile Idiopathic Arthritis: Current status. *Indian pediatrics* 2001; 38: 1083-1090.
- Schaller JG. Juvenile rheumatoid arthritis. *Pediatr Rev* 1980; 2 (6): 163-74.
- Burgos-Vargas R, Petty RE. Juvenile ankylosing spondylitis. *Rheum Dis Clin North Am* 1992; 18: 123-42
- Shore A, Ansell BM. Juvenile psoriatic arthritis – an analysis of 60 cases. *J Pediatr* 1982; 100: 529-35.
- Vossenaar ER, Venrooij WVJ. Anti-CCP antibodies, a highly specific marker for rheumatoid arthritis. *Clin and App Immun Rev* 2004; 4: 239-262.

23. Wallace CA. Current management of juvenile idiopathic arthritis. *Best Practice & Research Clinical Rheumatology* 2006; 20: 279-300.
24. Lee DM, Weinblatt ME. Rheumatoid arthritis. *Lancet* 2001; 358: 903-10.
25. Van der Heide A, Jacobs JW, Bijlsma JW. The effectiveness of early treatment with "Second line" anti rheumatic drugs: a randomized, controlled trial. *Ann Intern Med* 1996; 124: 699-707.
26. Egsmose C, Lund B, Borg G. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year follow up of a prospective double blind placebo controlled study. *J Rheumatol* 1995; 22: 2208-13.
27. Ilowite NT. Current Treatment of Juvenile Rheumatoid Arthritis. *Pediatrics* 2002; 109: 109-115.
28. Munro JE, Murray KJ. Advances in paediatric rheumatology: Beyond NSAIDs and joint replacement. *J. Paediatr Child Health* 2004; 40: 161-169.
29. Ramanan AV, Whitworth P, Baildam EM. Use of methotrexate in juvenile idiopathic arthritis. *Arch Dis Child* 2002; 88: 197-200.
30. Bharadwaj A, Aggarwal A, Misra R. Methotrexate in Juvenile Rheumatoid Arthritis: Randomized placebo controlled study. *J Indian Rheumatol Assoc* 2003; 11: 30-34.
31. Wallace CA. The use of Methotrexate in childhood rheumatic diseases. *Arthritis & Rheum* 1998; 41: 381-391.
32. Hunt PG, Rose CD, Mc Ilvain- Simpson G. The effects of daily intake of folic acid on the efficacy of Methotrexate therapy in children with juvenile rheumatoid arthritis: A controlled study. *J Rheumatol* 1997; 24: 2230-2.
33. Foell D, Frosch M, Wiesch ASZ, Vogl T, Sorg C, Roth J. Methotrexate treatment in juvenile idiopathic arthritis: When is the right time to stop? *Annals Rheum. Dis* 2004; 63: 206-208.
34. Silverman E, Mouy R, Spiegel L. Durability of efficacy, safety and tolerability of leflunomide or Methotrexate over 48 weeks of treatment in pediatric patients with juvenile rheumatoid arthritis. *Arthritis Rheum* 2004; 50; S 90.
35. Adebajo AO, Hall MA. The use of intravenous pulsed methyl prednisolone in the treatment of systemic onset juvenile chronic arthritis. *Br J Rheumatol* 1998; 37: 1240-2.
36. Weederburn LR, Abinun M, Palmer P, Foster HE. Autologous haematopoietic stem cell transplantation in juvenile idiopathic arthritis. *Arch. Dis. Child* 2003; 88: 201-5.
37. Mc Donagh JE, Southwood TR, Ryder CA. Bridging the gap in rheumatology. *Ann. Rheum. Dis.* 2000; 59: 86-93.
38. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997; 40: 1202-1209.
39. Wallace CA, Levinson JE. Juvenile rheumatoid arthritis: outcome and treatment for the 1990's. *Rheum Dis Clin North Am* 1991; 17: 891-904.