Diagnosing and managing juvenile arthritis

Early and aggressive therapy, predominantly outpatient based, enables most children and adolescents with juvenile idiopathic arthritis to participate fully in childhood activities with the minimum of pain, if not being totally pain-free.

JANE E. MUNRO
MB BS

ROGER C. ALLEN
MB BS, FRACP

Dr Munro is an Advanced Trainee in Paediatric Rheumatology and Fellow in General Paediatrics, and Dr Allen is Head of Paediatric Rheumatology, Department of General Paediatrics, Royal Children's Hospital, Melbourne, Vic.

Juvenile idiopathic arthritis (JIA) is an inflammatory arthritis of at least six weeks' duration presenting in a child under 16 years of age. Estimates predict that at least 5000 children are affected in Australia at any one time. While this means GPs may care for a child with juvenile arthritis only infrequently, it is important to be aware of important mimics of JIA, to have an approach for diagnosing and managing this serious, chronic disease and to know when to refer patients. This article outlines an approach to the management of children and adolescents with juvenile arthritis.

Misconceptions

Several misconceptions exist regarding the rheumatic diseases of childhood, and juvenile arthritis in particular. JIA is more common than generally recognised, with a prevalence of between one and four cases per 1000 children,[1] which suggests that a number of children are either undiagnosed or misdiagnosed. Persistent joint swelling is abnormal in children and should not be diagnosed as nonspecific joint pains or recurrent musculoskeletal 'sprains'. Also, while previously thought to be a fairly innocuous disease in many children, recent research has revealed that JIA is not benign but carries the potential for longer term inflammatory activity and complications, as well as a lasting impact on quality of life.

The past two decades have seen a radical overhaul in the approach to the management of adult rheumatoid arthritis. Similarly, juvenile arthritis is now managed very differently, with aggressive targeted therapies being the mainstay of the treatment algorithm. Rapidly increasing numbers of international collaborative research projects have led to significant advances in classification and the development of several new and effective therapies.

Classification

JIA represents a heterogenous group of autoimmune disorders of unknown aetiology. No infectious agent has been identified as causative but

IN SUMMARY

- **A multidisciplinary approach is optimal for the management of children and adolescents with juvenile idiopathic arthritis.**
- **Commence therapy with NSAIDs. However, the early introduction of more aggressive therapeutic options is often required.**
- **Manage pain and sleep disturbances.**
- **Look for growth abnormalities, pubertal delay and disease- and treatment-related complications.**
- **Arrange regular ophthalmology review.**
- **Refer earlier rather than later, and to a paediatric rheumatologist if there is one in the local area or to a rheumatologist or paediatrician experienced in the condition.**

there is increasing evidence for a likely genetic predisposition (familial JIA is, however, rare).

The nomenclature and subsequent classification system of JIA is confusing for medical practitioners, let alone patients and their families. For practical purposes, the three traditional categories of oligoarticular, polyarticular and systemic JIA are still used. Other names for JIA include juvenile rheumatoid arthritis and juvenile chronic arthritis. A patient's JIA is classified on the basis of how the disease behaves in the first six months from onset of symptoms rather than the signs and symptoms at initial presentation.[2] The complete seven-subtype classification is outlined in Table 1.

Diagnosis and investigations

The first step in the management of a patient with suspected JIA is to confirm the diagnosis. Most acute nonseptic arthritis is not JIA; however, if septic arthritis is suspected then it must be excluded by joint aspiration and culture.

The diagnosis of JIA is predominantly clinical but also relies on the recognition and exclusion of mimickers of JIA. Identifiable causes of persistent joint pain and/or swelling include systemic lupus erythematosus, acute lymphoblastic leukaemia and inflammatory bowel disease. A guide to history taking and examination of a child presenting with joint symptoms is given in the box on page 21, and examples of the clinical presentation are shown in Figures 1 to 3.

There are no specific diagnostic tests for JIA but various investigations may be useful (see Table 2).

Management

The general principles for the treatment of JIA are to:

- minimise joint destruction
- maximise function
- treat pain
- manage complications of the disease and therapies
- ensure optimal growth, development and activities.

An outline of the overall treatment of JIA is shown in the flowchart on page 23.[4] This algorithm is more detailed than is usually necessary in the general practice treatment of patients with JIA (and indeed some treatments are not even allowed to be used by general paediatricians). It is preferable that the more difficult cases should only be managed by clinicians with specialist training in paediatric rheumatology.

Diagnosing and managing juvenile arthritis

Juvenile idiopathic arthritis is not the generally benign disease it was traditionally considered to be. Early and aggressive targeted therapy is now the mainstay of treatment and has, together with ongoing follow up and the development of new pharmacotherapies, greatly improved the outlook for children and adolescents with the condition.

Pharmacotherapy

The general approach to pharmacotherapy for JIA is to treat aggressively early in the disease process to prevent long term joint damage while balancing the risks of medications. We tell our

patients and their families that we have the next 80 or so years of the child's life in mind and plan to keep their joints in as good a working order as possible so that they can run around after their grandchildren. The days of accepting ongoing disease activity, particularly synovitis, without an escalation in therapy are gone. While there is no cure for JIA, the aims of treating the child with JIA are the induction of remission and control of the disease.

The major advances in treatments for JIA include the use of intra-articular corticosteroids, early initiation of methotrexate as a disease modifying agent and the development of multidisciplinary teams with outcomes-based research to guide therapy. The most recent advance has been the introduction of 'biologic agents' to the available pharmaceutical options for the treatment of patients with refractory JIA.

Nonsteroidal anti-inflammatory drugs

Traditional NSAIDs remain the therapy used at disease presentation for most subgroups of JIA (Table 3). Analgesia, relief of stiffness and anti-inflammatory action are the main indications for their use. In children there are few indications for the use of COX-2-specific inhibitors as gastrointestinal risk factors are uncommon.

While NSAIDs remain the recommended option for children with JIA, there are few options available on the PBS for younger children requiring a liquid suspension form. The COX-2-specific inhibitor rofecoxib was an option, but this has now been withdrawn internationally. Ibuprofen requires dosing three times per day and is cost-prohibitive as the suspension form is not on the PBS but sold over-the-counter. At present, naproxen syrup is being supplied in Australia but it is only available, unsubsidised, under the Special Access Scheme (SAS) requiring individual patient application to the Therapeutics Goods Administration. The dispersible form of piroxicam (Feldene-D Tablets, GenRx Piroxicam Dispersible Tablets, Mobilis D Tablets, Pirohexal-D) is currently the only relatively straightforward preparation for children unable to swallow tablets or capsules.

The use of aspirin is not recommended because of the risk of Reye's syndrome and its predisposition to causing toxicity because of its pharmacokinetics.

Table 1. Classification of JIA[2]

Type of JIA	Comments
Oligoarthritis	Affects four or fewer joints during first six months; commonest form; many cases remit in adolescence
- persistent oligoarthritis	- affects no more than four joints throughout disease course
- extended oligoarthritis	- affects more than four joints after six months; often persists into adulthood
Polyarthritis RF-negative*	Affects five or more joints during first six months; may remit in later childhood
Polyarthritis RF-positive	Affects five or more joints during first six months; especially prevalent in older females; often destructive; behaves similar to adult rheumatoid arthritis
Systemic arthritis	Fever, rash +/- multisystem involvement; least common form; about 50% of cases remit in two to three years; may be life threatening
Enthesitis-related arthritis	Peripheral arthritis more common than spine involvement in childhood; entheseal involvement may present first; typically HLA B27-positive
Psoriatic arthritis	Oligo- or polyarthritis; spectrum of severity often independent of rash
Unclassified	Features not consistent with any subtype or consistent with multiple subtypes

Abbreviation. RF = rheumatoid factor.

Corticosteroids

Intra-articular therapy

Aspiration of joints and intra-articular injection of long acting corticosteroids (such as triamcinolone acetonide [Kenacort-A] or triamcinolone hexacetonide [Aristopan; a SAS drug]) has become a safe and effective mainstay of therapy in children for oligoarticular JIA, and for polyarticular JIA in combination with other therapy. Such treatment reduces long term joint complications such as leg length discrepancy and flexion deformities.[5] The duration of response is the main variable but remission can be for 12 months or more, particularly in younger children. A dramatic reduction in synovial inflammation and symptoms is usually evident within one to three days.

Only those doctors experienced in the technique should perform joint injection. Procedural pain management and sedation should be individualised, and general anaesthesia is usually indicated for injection of difficult to access joints or multiple joints in children under 8 years of age. The use of ultrasound guidance or image intensification may be appropriate for some joints (for example, hip or subtalar joints).

History and examination in a child with suspected JIA

History taking

- Is the onset acute or insidious?
- What is the timing of symptoms? Generally early morning stiffness equates to an inflammatory condition and post-activity pain to a mechanical condition.
- What is the duration of illness? If longer than six weeks, reactive or postviral arthritis is less likely.
- Are there any intercurrent infections? Postviral infections are probably the commonest cause of transient arthritis.
- What recent medications have been taken? For example, cefaclor can cause a serum sickness-like reaction that includes joint pain.
- What is the most symptomatic site? Joint, muscle, adjacent bone or a more diffuse area?
- Are there any extra-articular symptoms? These can give clues for differential diagnoses.
- Is there interruption of normal physical activities and interests?
- What is the level of functioning? For example, school, sleep, family and peer relationships, and potential stress experiences.
- Is there any family history for other inflammatory types of arthritis, particularly the spondyloarthropathies, autoimmune disorders and pain syndromes (e.g. fibromyalgia or other potential pain models)?

Examination

- Observe the child as he or she moves about the room, watch him or her undress and be opportunistic when examining.
- Is the child unwell or well?
- Assess growth parameters.
- Examine all joints, not only the site of the presenting complaint, as there may be inflammation without symptoms in JIA.
- Localise the site of maximal discomfort. For example, is it the joint capsule, adjacent bone or muscle belly, tendon or ligament attachments?
- Examine for signs of both systemic diseases with an articular component and extra-articular features of JIA. Assess skin, eyes, abdomen, nails and lymph nodes.

Musculoskeletal assessment

- Joint: signs of inflammation such as swelling or tenderness, the range of movement and deformity.
- Entheses: bone attachment sites of ligaments/tendons. For example, the Achilles tendon.
- The tendon sheaths of fingers and toes. For example, dactylitis in psoriasis.
- Gait: antalgic, limp, Trendelenberg's sign.
- Muscle tenderness, muscle wasting or weakness. For example, inability to toe or crouch walk.
- Patellar tracking pattern. Does the patella move vertically on walking?
- Shoe sole and heel wearing pattern.
- Leg length measurement.
- Spinal flexion, including Schober test (the measurement of the lumbosacral range should increase by at least 6 cm on maximal flexion; the starting range is between the lumbosacral junction and a point 10 cm above).

Oral and parenteral corticosteroids

There is a role for systemic corticosteroids (as oral or IV 'pulse' therapy) in the treatment of systemic JIA, particularly at initiation of therapy or during flares of disease. They are given orally (prednisone [Panafcort, Predsone, Sone]; prednisolone [Panafcortelone, Predsolone, Solone, Predmix Oral Liquid, Redipred Oral Liquid]) or intravenously (IV 'pulse' therapy; methylprednisolone sodium succinate [Solu-Medrol]). Corticosteroid therapy also has a role in polyarticular disease, such as when waiting for disease-modifying antirheumatic drugs (DMARDs) to become efficacious. Ongoing concerns regarding the potential toxicities of corticosteroids remain the driving force behind minimising their use (and dosage) and weaning as soon as possible.

Disease-modifying antirheumatic drugs

Referral to a paediatric rheumatologist, rheumatologist or paediatrician with experience in managing JIA is recommended before commencing a DMARD.

Methotrexate

Methotrexate (Ledertrexate, Methoblastin, Methotrexate Injection and Tablets [DBL], Methotrexate Injection) is the first line DMARD treatment for JIA, and is given once weekly, orally or subcutaneously. The full immunosuppressant effect of the drug may not be seen, however, for two to three months. The most common side effects are nausea and occasionally mouth ulcers; these can be minimised with folic acid supplementation. The long term risks from methotrexate in children and adolescents are minimal compared with

Table 2. Investigations in a child with suspected JIA

Often useful

- Full blood examination
- Erythrocyte sedimentation rate and/or C-reactive protein*
- Synovial fluid culture (only if sepsis is considered)
- Antinuclear antibodies (ANAs)†
- Imaging – plain X-ray‡, bone scan and ultrasound
- Diagnostic aspirate – worthwhile if sepsis or haemarthrosis is considered; differentiates inflammatory from mechanical causes but will not necessarily differentiate between causes of inflammatory arthritides
- Specific bacterial/viral studies – for example, antistrepsolysin O titre (ASOT; for group A streptococci), antiDNase B (for nongroup A streptococci), *Yersinia* and parvovirus serology, if the clinical picture is suggestive

Occasionally useful

- Rheumatoid factor – in polyarticular patients or older children, or if the pattern of disease appears unusual
- Ferritin – useful if very elevated in systemic JIA
- Genetic marker – HLA B27 in an apparent spondyloarthropathy (almost 9% of the Caucasian population are positive)

Not useful

Serum uric acid

* Normal inflammatory markers do not exclude the diagnosis.
† Beware of over-interpretation as up to 20% of normal children may have a low positive ANA.
‡ Early in an arthritis, plain films usually give no more information than a careful examination. They may be useful in difficult sites such as the hip, or if there is a long history of arthritis.[3]

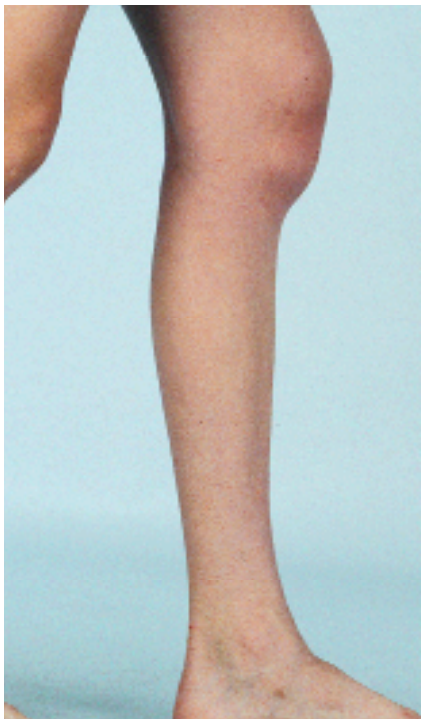


Figure 1. Synovitis of the knee with a large effusion in the suprapatellar pouch.

those in adults. Monitoring every two to three months for liver or haematological complications is recommended .

Once commenced, methotrexate is usually continued for a minimum of one to two years and weaned slowly when complete disease control is achieved.[6] Ongoing review, with a high index of suspicion, is needed for early detection of any relapse .

Other DMARDs, including biological therapies

Other drugs with disease modifying properties include leflunomide (Arabloc, Arava), hydroxychloroquine (Plaquenil), sulfasalazine (Pyralin EN, Salazopyrin) and cyclosporin (Cicloral, Cysporin, Neoral, Sandimmun). Patients on these medications require monitoring for side effects.

Biologic agents are potent new drugs that target inflammatory cytokines involved in the disease pathogenesis in JIA. Etanercept (Enbrel) is the most widely

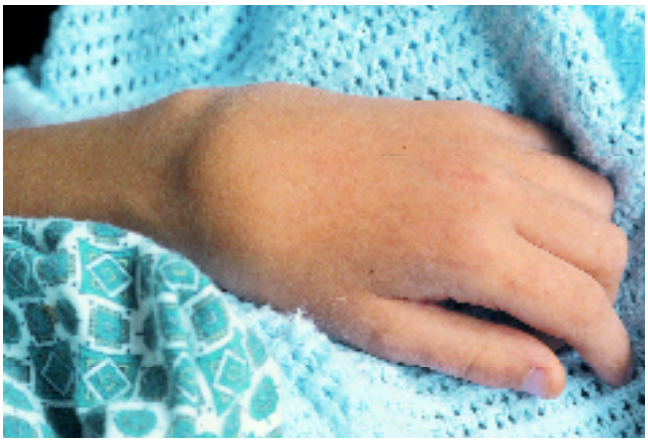


Figure 2. Dorsal sheath swelling over the wrist.

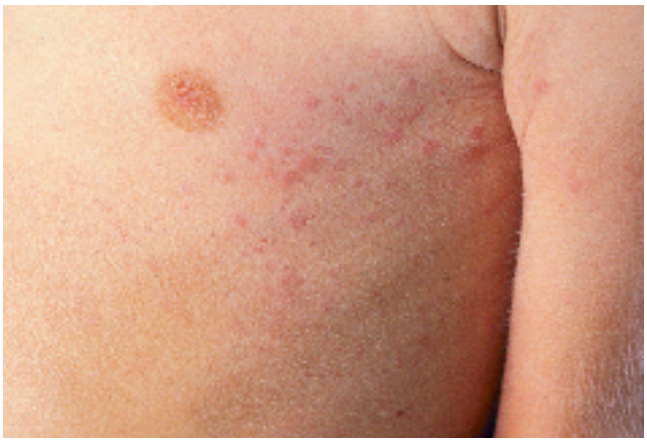
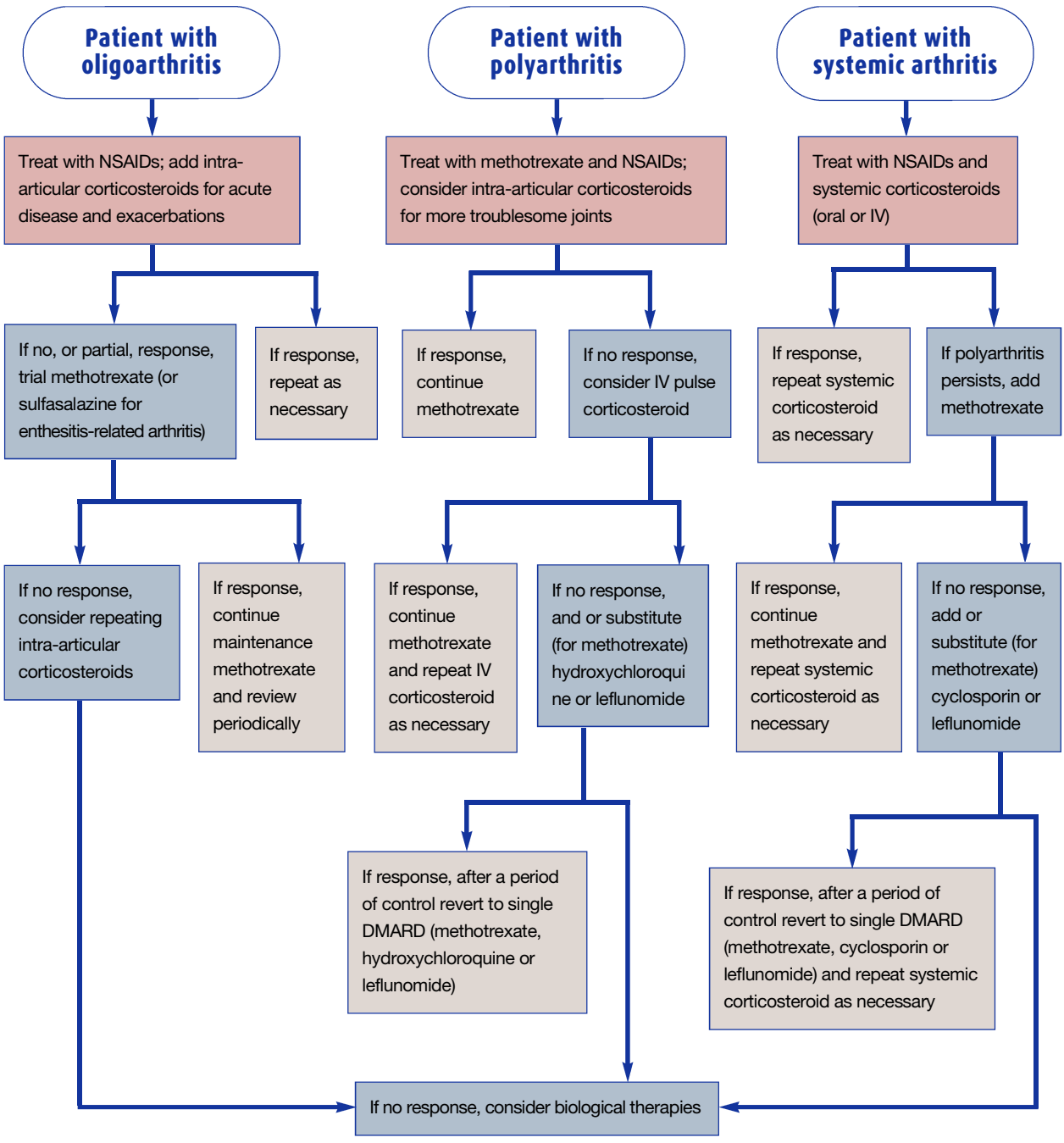


Figure 3. Systemic rash (Still's rash) over the chest wall.

A treatment algorithm for JIA[4]*



* Early referral is recommended, to a paediatric rheumatologist or rheumatologist or paediatrician with experience in the condition.
Abbreviation. DMARD = disease-modifying antirheumatic drug.

studied biological therapy for children with JIA, and works against tumour necrosis factor (TNF), both suppressing disease activity and preventing joint destruction. It is available for the treatment of severe refractory JIA and is given twice weekly by subcutaneous injection. However, it can only be prescribed under the supervision of a paediatric rheumatologist and there are strict eligibility criteria for its availability on the PBS for children. Both short term and longer term studies have shown impressive results in terms of disease suppression and modification of joint damage.[7]

The other currently available anti-TNF agents, infliximab and adalimumab, have recently been approved for use in adult rheumatoid arthritis but are not yet approved for use in children within Australia.

Physical therapies

Physiotherapy management targets joint position and function, and also treatment of contractures and pain. Occupational therapists have a role in maximising a patient's level of function at home and school, particularly regarding activities of daily living. They also play an important role, along with the treating doctor and local support organisation, in liaising with and educating staff at the patient's school. Both physiotherapists and occupational therapists have key roles in the education and support of patients, families and community physical therapists.

Follow up and monitoring of progress

Ongoing surveillance for disease activity, complications of JIA and complications of treatments is important. Not only the multidisciplinary team but also the family, local medical practitioner, school and other community health practitioners are included in helping to ensure optimal outcomes and holistic management in the child with JIA.

Monitoring of disease progress involves clinical assessment and the use of laboratory indices and measurement tools (Table 4).

Uveitis

Children with JIA can develop eye disease. Chronic uveitis, the most concerning, is generally asymptomatic and can cause significant visual impairment. Regular long term screening (three- to six-monthly initially) by an ophthalmologist experienced in working with small children is essential in preventing blindness and other serious ocular complications of JIA.[8] Screening is required until about 12 years of age.

Growth

JIA can cause growth and pubertal delays as well as local growth or joint complications such as joint contractures or leg length discrepancies. Bone mineral density scans and supplementation with calcium and vitamin D is suggested, particularly for those on longer term corticosteroids.

Development

Developmental delay is uncommon in children with JIA, but many patients may be unable to participate fully in standard age-appropriate activities and may develop behaviours that minimise their independence.

Psychosocial management

JIA is a chronic and painful condition that can have an enormous effect on the psychological wellbeing of both the affected child and his or her family. While many children are resilient in the face of ongoing disease and therapy, the potential impacts this condition can have for patients and their families should be addressed as early as possible.

Pain management and sleep quality

Attention to managing pain adequately is important. Local therapies such as heat, cold, massage and splinting can be effective. However, pain relief additional

Table 3. Recommended NSAID and aspirin dosages at presentation of JIA

Drug	Dosage	Form
Indomethacin	0.5 to 1 mg/kg two to three times daily (adult dose 25 to 50 mg)	Tablets
Ibuprofen	10 mg/kg three to four times daily (adult dose 400 to 800 mg)	Tablets or suspension
Naproxen	5 to 10 mg/kg two times daily (adult dose 250 to 500 mg)	Tablets (suspension available only via Special Access Scheme)
Piroxicam	0.2 to 0.4 mg/kg once daily (adult dose 10 to 20 mg)	Tablets (including dispersible)
Diclofenac	1 mg/kg two times daily (adult dose 50 mg)	Tablets
Celecoxib	2 to 4 mg/kg twice daily (adult dose 100 to 200 mg)	Tablets
Meloxicam	0.2 to 0.35 mg/kg once daily (adult dose 7.5 to 15 mg)	Tablets
Aspirin (although use is not recommended)	15 to 25 mg/kg four times daily	Tablets

to the analgesia provided by NSAIDs may need to be prescribed. Paracetamol and codeine are appropriate, and stronger opioids are rarely required. Assessment of sleep quality is often overlooked; adequate pain relief can improve poor sleep quality.

Schooling

Generally, children and adolescents with stable JIA should not need to miss significant amounts of school. However, increased awareness within the school of the potential impact of early morning stiffness, impaired mobility and pain can be helpful for affected students. Suggested modifications include access to laptops, extra sets of schoolbooks (to avoid carrying these to and from school), appropriate height of lockers and minimising stairs and distances between classes. For Year 11 and 12 students, early liaison with the appropriate authorities for arrangements such as special consideration and extra time for examinations may be worthwhile.

Sport and physical activities

Physical activity is encouraged and our approach is to encourage the child, to a degree, to set his or her own limits. Physical education teachers are often unfamiliar with JIA and thus set inappropriate restrictions or misinterpret day-to-day variation in ability as inattention or manipulation on the part of the child; education (e.g. via the Arthritis Foundation) can be very beneficial.

Nutrition

Obesity and undernutrition (particularly in patients with very active disease) can be problems. Early identification and management of these issues is important and referral to a dietician can be useful.

Adolescent issues

Several issues should be addressed with adolescents with JIA – for example, vocational expectation or potential limitation, transition to adult health care services, potential of delayed puberty and possible body image issues, and issues of alcohol use with medication. Engaging adolescents actively in the consultation process (and spending time alone with them during the appointment) can mean they develop more self-sufficiency and feel more involved regarding their chronic illness. Benefits to the patient include improved adherence to therapies and better understanding of their arthritis. The process of transition to adult health care services should ideally be discussed years before the planned transition date.

When to refer

Given the potential for long term morbidity and even mortality from some of the subgroups of JIA, early referral and ongoing follow up, as well as close liaison with local medical practitioners and community health professionals, are required to optimise care for these children. Indications for referral are given in Table 5.

Children with suspected JIA should be referred to a paediatric rheumatologist if possible, or to a rheumatologist or paediatrician with experience in looking after children with JIA. There are now

Table 4. Monitoring of disease progress in JIA

Clinical assessment

- Symptoms of pain, joint swelling, early morning stiffness, sleep disruption
- Signs of synovitis, tenderness, restricted range of movement, fever, muscle wasting and local joint complications (contractures and growth abnormalities)

Laboratory indices

- Full blood examination – anaemia of chronic disease
- Inflammatory markers – erythrocyte sedimentation rate, C-reactive protein

Measurement tools

- Physician Global Assessment
- Patient Global Assessment
- Standardised measures, e.g. the Children's Health Assessment Questionnaire

Table 5. When to refer the child with suspected JIA

- Joint pain or swelling lasting longer than four weeks
- Features suggestive of a systemic arthritis
- Any signs of a chronic arthritis, such as muscle wasting, joint contractures or leg length discrepancy
- If one of the more serious mimics is possible

Note that patients with suspected JIA should be referred to a paediatric rheumatologist or to a rheumatologist or paediatrician with experience in looking after children with JIA.

Information resources on juvenile arthritis

- Paediatric rheumatologists: contact details available from local paediatric tertiary centres
- The American Juvenile Arthritis Organization (a council of the American Arthritis Foundation) www.arthritis.org/communities/juvenile_arthritis/about_ajao.asp
- Paediatric rheumatology diseases website, a project of the Paediatric Rheumatology International Trials Organisation (PRINTO) and the Paediatric Rheumatology European Society (PRES) www.printo.it/pediatric-rheumatology/
- Arthritis Foundation of Australia. Each State and Territory branch has youth affairs officers who can play vital roles in advocacy and education for families, health professionals and within schools (and may make school visits for the education of staff and students). The Foundation can send out information to families and GPs www.arthritisfoundation.com.au

paediatric rheumatologists in most major cities in Australia. The scope of this subspecialty includes inflammatory rheumatic conditions and noninflammatory musculoskeletal disorders.

Resources

Various resources for GPs, patients and their families and others involved in the care of children with JIA are listed in the box on this page.

Prognosis

JIA is not the generally benign disease it has been considered traditionally to be. At least one-third of patients have disease activity into adulthood and one-third have marked functional disability (variation within subtypes). Recent research has shown that at least 40% of paediatric patients with JIA have active disease 10 years after disease onset.[9] However, with the outlined management approach, most children with JIA can usually regain full activities, attend school, play sport and have pain minimised if not be totally pain-free.

Conclusion

A multidisciplinary approach, predominantly outpatient based, is necessary when managing children and adolescents with JIA. Once the correct diagnosis is recognised, early and aggressive therapy is the mainstay of treatment. The aims of therapy are minimising joint damage, maximising function, treating pain and ensuring optimal growth, development and activities throughout the course of this chronic illness. Ongoing follow up is essential for surveillance of disease activity, complications and treatment side effects. An expanding research base and arsenal of effective pharmacotherapies as well as more health professionals training in this subspecialty in Australasia means the future is looking brighter for children with JIA. MT

References

1. Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis. Why does it vary so much? J Rheumatol 2002; 29: 1520-1530.
2. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998; 25: 1991-1994.
3. Miller ML. Use of imaging in the differential diagnosis of rheumatic diseases in children. Rheum Dis Clin North Am 2002; 28: 483-492.
4. Munro JE, Murray KJ. Advances in paediatric rheumatology: beyond NSAIDs and joint replacement. J Paediatr Child Health 2004; 40: 161-169.
5. Cleary AG, Murphy HD, Davidson JE. Intra-articular corticosteroid injections in juvenile idiopathic arthritis. Arch Dis Child 2003; 88: 192-196.
6. Ramanan AV, Whitworth P, Baildam EM. Use of methotrexate in juvenile idiopathic arthritis. Arch Dis Child 2003; 88: 197-200.
7. Wilkinson N, Jackson G, Gardner-Medwin J. Biologic therapies for juvenile arthritis. Arch Dis Child 2003; 88: 186-191.
8. Petty RE, Smith JR, Rosenbaum JT. Arthritis and uveitis in children. A pediatric rheumatology perspective. Am J Ophthalmol 2003; 135: 879-884.
9. Foster HE, Marshall N, Myers A, Dunkley P, Griffiths I. Outcome in adults with juvenile idiopathic arthritis: a quality of life study. Arthritis Rheum 2003; 48: 767-775.

DECLARATION OF INTEREST: Neither author has any financial links to any drug company committees and the like. The Royal Children's Hospital, Melbourne, has participated in multicentre, company sponsored (Merck Sharp and Dohme, Amgen and Aventis Pharma) drug studies for which Dr Allen has been an investigator.