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PEER REVIEWED FEATURE
2 CPD POINTS

Juvenile idiopathic arthritis

Early recognition improves outcomes

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With the availability of highly efficacious treatments for juvenile idiopathic arthritis, including biologic therapies, outcomes have improved and full disease remission is now the aim. Early diagnosis allows early aggressive treatment and is crucial for the best outcomes.

Key points

- **Juvenile idiopathic arthritis (JIA) is the most common rheumatological disease of childhood, affecting one per 1000 children.**
- **Presentation may be subtle and diagnostic delay, often for many months, is common.**
- **Excellent treatment options are now available for children with JIA, including biologic therapies, which have revolutionised outcomes.**
- **The therapeutic focus has shifted to early aggressive treatment, with minimal tolerance for any disease activity.**
- **Many children with JIA are immunosuppressed and require regular blood test monitoring, avoidance of live vaccines and vigilance for infection, especially varicella.**
- **The outlook for children with JIA and their families is now bright, with therapeutic goals aiming for normal physical and psychosocial functioning.**

Musculoskeletal pain is a common symptom in childhood and is usually benign and self-resolving. Recognising rare but treatable causes, including inflammatory, malignant and infectious aetiologies, remains a constant challenge. Juvenile idiopathic arthritis (JIA) is the most common inflammatory arthritis of childhood. It affects approximately one in 1000 children, although this figure varies with ethnicity, and Australian studies have found a prevalence as high as one in 250.[1,2] JIA is often unrecognised, and long diagnostic delays are common.[3] As our treatment paradigm shifts towards early aggressive treatment, timely recognition and referral of affected children have become even more important.

JIA is not yet curable, although disease remission can often be achieved with modern therapy. In the past, management was directed at suppressing overt disease activity and controlling symptoms of JIA. However, standards of care are now far more ambitious and target the suppression of even low levels of inflammation and subclinical disease.[4,5] Nonetheless, diagnostic delay remains a major barrier to good outcomes; median time from symptom onset to specialist paediatric rheumatology assessment approaches six months.[3]

WHAT IS JUVENILE IDIOPATHIC ARTHRITIS?

JIA is a heterogenous disease that is defined as:

- arthritis of more than six weeks' duration

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TABLE. SUBTYPES OF JUVENILE IDIOPATHIC ARTHRITIS AND THEIR COMMON CLINICAL FEATURES

Subtype	Typical phenotype	Percentage of all JIA cases	Sex
Oligoarticular	• Up to four affected joints in the first six months of disease • Usually large joints (knee, ankle, wrist) • Strong association with eye disease	40 to 50%	F>M
Polyarticular – RF negative	• More than four affected joints at the time of diagnosis • Symmetrical	25%	F>M
Polyarticular – RF positive	• Subtype that overlaps most closely with adult rheumatoid arthritis • Typically occurs in teenaged girls, tends to persist into adulthood	5%	F>M
Enthesitis-related arthritis	• Axial and weight-bearing joints most commonly involved, including sacroiliac joints • May have enthesitis • Commonly HLA-B27 positive	5 to 10%	M>F
Psoriatic arthritis	• Psoriasis in the patient or a first-degree relative, or typical psoriatic nail changes (pitting, ridging, onycholysis) or dactylitis	5 to 10%	F>M
Systemic onset (Still's disease)	• Arthritis and systemic features, especially fever and rash • May have associated hepatosplenomegaly and lymphadenopathy • Can be life-threatening	5 to 10%	F=M
Undifferentiated	• Does not meet criteria for other subtypes	10%	

ABBREVIATIONS: F = female; JIA= juvenile idiopathic arthritis; M = male; RF = rheumatoid factor.

- with onset before the 16th birthday
- where no other cause is identified.

There are seven distinct subtypes of JIA (see the Table). Subtyping is based on:

- the number of affected joints at presentation
- serological results – presence of antinuclear antibodies (ANA), rheumatoid factor and human leucocyte antigen B27 (HLA-B27)
- family history (spondyloarthropathy, psoriasis)
- associated features.

JIA is distinct from rheumatoid arthritis, and hence the term 'juvenile rheumatoid arthritis' is no longer used. The classification system has changed over time and continues to be debated, particularly as our knowledge of genetic and serological disease markers grows.[6]

The aetiology of JIA is, by definition, unknown. It is an autoimmune disease and is known to cluster in families with other autoimmune conditions, including rheumatoid arthritis and type 1 diabetes mellitus.[7] Like many other autoimmune diseases, JIA is over-represented in children of European heritage.[8] JIA has a complex genetic basis; it is now clear that both HLA and non-HLA gene associations play a role in its development, and susceptibility genes shared with other autoimmune conditions have been identified.[9,10] Nevertheless, although sibling sets with the disease are well recognised, most siblings of children with JIA will not be affected.[11]

WHAT ARE THE COMPLICATIONS?

Complications of JIA may be articular or extra-articular. Inflammatory eye disease – anterior uveitis – is common, affecting up to 30% of children with JIA (Figure 1).[12] Prevalence of eye disease varies significantly with disease subtype, with the highest risk in ANA-positive girls with oligoarticular disease who are younger than six years. As eye disease is mostly asymptomatic, all children with JIA should have routine ophthalmology reviews with slit lamp examination at regular intervals. The risk of eye disease is greatest in the first few years after diagnosis. Complications of inflammatory eye

1. THE GP'S ROLE IN MANAGEMENT OF PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

Recognise early and refer to a paediatric rheumatologist
Current Australian guidelines dictate that a child with suspected juvenile idiopathic arthritis (JIA) should be seen by a specialty service within four weeks of referral, or 10 weeks of symptom onset.[5]

Commence NSAIDs for symptomatic relief while awaiting rheumatology review
Avoid corticosteroids as they can confuse the diagnosis (including masking malignancy). Naproxen and ibuprofen are available in liquid formulations, and piroxicam in a soluble form, for children who cannot tolerate tablets.

Ensure immunisations are up to date
Ensure all immunisations are up to date, with the exception of live vaccines (varicella, measles-mumps-rubella), which must be avoided in children who are systemically immunosuppressed, such as those taking methotrexate. Encourage annual influenza vaccination.

Perform regular blood tests
Most children receiving systemic immunosuppressants require blood tests every three months to monitor for cytopenia and abnormalities of liver function. Any abnormalities should be discussed with the treating specialist.

Ensure regular eye examinations are undertaken
As JIA-associated eye disease is mostly asymptomatic, all children with JIA should have routine ophthalmology reviews with slit lamp examination at regular intervals. These are usually arranged by the rheumatology team, but the GP may be of help in identifying local ophthalmology services.

Notify the rheumatology team when an immunosuppressed child has a significant exposure to varicella–zoster virus
Zoster immunoglobulin may be necessary. Significant exposure is defined as a household contact with varicella or herpes zoster, or being in direct face-to-face contact with a person with varicella or herpes zoster for at least five minutes, or being in the same room for at least one hour.[19]

Be vigilant to possible infection, including with unusual organisms
Children receiving immunosuppression who develop an infection may deteriorate quickly. Those receiving biologic therapy often cannot mount a febrile response, so the absence of fever is not necessarily reassuring.

Manage contraception
Manage contraception in females of childbearing age taking potentially teratogenic medications.

Maximise bone health
Encourage good calcium intake and weight-bearing exercise and monitor vitamin D levels.

Provide emotional support and mental health surveillance
Mental health disorders, including anxiety and depression, are common comorbidities in patients with JIA, who may require appropriate mental health referral.[20]

disease include cataracts, glaucoma and reduced visual acuity. In the prebiologic era, blindness occurred in 10% of patients, and visual impairment in many more.[12]

Other complications of JIA may be disease or treatment related. Long-term uncontrolled joint inflammation can cause joint erosions (especially in patients who are positive for rheumatoid factor), flexion contractures and muscle wasting.[13,14] Joint hyperaemia around the growth plates can cause overgrowth in the affected limb, with consequent limb length discrepancy. Poor disease control and long-term systemic corticosteroid use can cause growth retardation and short stature. Chronic inflammation, reduced mobility and corticosteroid use may contribute to reduced bone mineral density and a risk of pathological fracture. Systemic-onset JIA can be complicated by macrophage activation syndrome, a form of widespread uncontrolled systemic inflammation that can lead to multiorgan failure or even death.

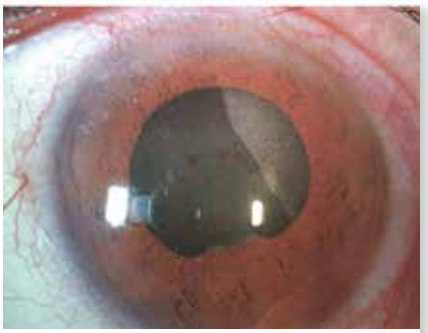

Figure 1. Irregularly shaped pupil in a child with juvenile idiopathic arthritis (JIA), caused by posterior synechiae, a complication of anterior uveitis where the iris adheres to the anterior surface of the lens. This can disrupt flow of the vitreous humour from the posterior to anterior chambers of the eye, increasing intraocular pressure. Routine ophthalmology screening is important for children with JIA.

WHY IS EARLY RECOGNITION AND TREATMENT IMPORTANT?

Outcomes in JIA have improved dramatically over the past decade. We are now firmly in the era of biologics – monoclonal antibodies that target the specific cytokines that drive arthritis. With the availability of these highly efficacious agents, treatment standards have become more ambitious, with minimal tolerance of any inflammation. Management now aims for full disease

2. PRESENTATIONS SUGGESTING INFLAMMATORY ARTHRITIS IN CHILDREN

- Morning stiffness or new reluctance to get out of bed
- Joint swelling
- Joint (not bone) pain
- Pain and stiffness that improve with physical activity
- Limp, especially morning limp
- Deterioration in functioning (e.g. handwriting, gross motor skills, ability to keep up with peers)

remission with minimal medication side effects and no long-term articular damage.[14] Many children now achieve these goals, either on or, when in true remission, off therapy.

Evidence is mounting in support of early aggressive treatment of children with JIA. This is not merely to interrupt joint damage; there is growing evidence that 'switching off' inflammation early and definitively may improve treatment response and prognosis throughout the disease course.[15,16] This parallels the approach to adult rheumatoid arthritis, where a treat-to-target strategy involving early aggressive treatment to capitalise on a perceived 'window of opportunity', has become the international standard.[17,18]

DIAGNOSIS AND MANAGEMENT

The GP's role in the diagnosis and management of patients with JIA is summarised in Box 1.[5,19,20]

How do I recognise and investigate JIA?

Diagnosis of JIA is mainly clinical. The history may reveal typical inflammatory symptoms (Box 2). Children with systemic-onset JIA may have prominent fevers and rashes in addition to their joint symptoms, but the presence of these features warrants consideration of malignant and infectious causes.

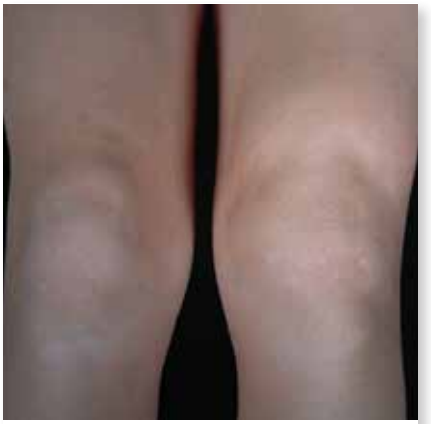

Figure 2. Left-sided knee effusion in a child with juvenile idiopathic arthritis, showing fullness, especially medially and superiorly, and loss of concavity in surface anatomy compared with the unaffected side.

Joint examination in children can be difficult, especially in younger children who have more subcutaneous fat and hence less-defined surface anatomy. Features suggestive of arthritis include:

- effusion (Figure 2)
- warmth
- tenderness along the joint line
- reduced range of movement
- pain at extremes of movement ('stress pain').

Differences in presentation between JIA subtypes can be dramatic. For example, oligoarticular disease frequently presents with monoarticular knee arthritis in a child who appears relatively untroubled, whereas polyarticular or systemic disease may manifest as debilitating pain, profoundly reduced functioning and inability to attend school.

Investigation is useful in confirming the diagnosis and excluding potential causes other than JIA. The differential diagnosis of musculoskeletal pain in children is outlined in Box 3. Ultrasound examination is helpful when the presence of effusion and synovitis is not clear on examination alone. Radiography has a role in excluding trauma and bony pathology but is not a necessary baseline investigation if the diagnosis is otherwise clear.[21] Similarly, MRI is needed only when other causes need to be excluded.

If JIA is suspected then a useful baseline blood panel includes a full blood count and film (to exclude other diagnoses, including leukaemia) and measurement of erythrocyte sedimentation rate, C-reactive protein level, ANA and rheumatoid factor, as well as HLA-B27 testing in boys aged over 8 years (the highest risk group for enthesitis-related arthritis). Levels of inflammatory markers are often but not invariably elevated in children with JIA.

3. DIFFERENTIAL DIAGNOSIS OF MUSCULOSKELETAL PAIN IN CHILDREN

Differential diagnosis of arthritis

- Septic arthritis, including tuberculosis
- Postinfectious arthritis – poststreptococcal, reactive arthritis
- Osteomyelitis with sympathetic effusion
- Malignancy, especially leukaemia
- Other inflammatory disorder (e.g. juvenile lupus, juvenile dermatomyositis, inflammatory bowel disease, sarcoidosis)
- Acute rheumatic fever
- Vasculitis – Kawasaki disease, polyarteritis nodosa
- Haemarthrosis, including haemophilia
- Structural joint changes – slipped epiphysis, Perthes' disease, trauma

Differential diagnosis of arthralgia

- Benign nocturnal limb pain
- Acute rheumatic fever
- Trauma or injury
- Chondromalacia patellae
- Osgood–Schlatter disease
- Complex regional pain syndrome
- Tumour – benign or malignant (including leukaemia)
- Hypermobility
- Structural joint changes – slipped epiphysis, Perthes' disease, trauma

Who should be referred?

Referral to a paediatric rheumatologist should be considered for any child with persistent musculoskeletal symptoms or symptoms consistent with JIA, especially joint pain, swelling and stiffness. Specifying the presence of any clinical, laboratory or radiological evidence of inflammatory disease will assist in triaging the referral as urgent.

How is JIA treated?

Treatment of patients with JIA depends on the disease subtype and number of joints involved, as well as the presence of comorbidities such as eye disease.

NSAIDs

Anti-inflammatory drugs are a useful first-line therapy and should be prescribed while patients await initial specialist review. NSAIDs are generally well tolerated, provide good symptomatic relief and – unlike corticosteroids – will not cloud the diagnosis or mask malignancy. Children with JIA often find greater relief from taking NSAIDs regularly rather than on an as-needed basis.

Intra-articular corticosteroids

Intra-articular corticosteroid injections (IAS) have an important role in the management of children with JIA. Joint injections are safe, effective and well tolerated, and treatment response is rapid, generally within 48 hours.[22] In children with oligoarticular disease, IAS may serve as definitive therapy, obviating the need for systemic agents altogether. In children whose disease takes a polyarticular course, IAS can be useful as bridging therapy while awaiting a response to disease-modifying antirheumatic drugs (DMARDs), or to 'mop up' occasional residual joint inflammation that persists after an otherwise good response to systemic therapy. IAS is performed under general anaesthesia in younger children, whereas nitrous oxide sedation is often adequate in older children.

Systemic corticosteroids are used occasionally for short-term symptomatic relief or in severe refractory disease.

Disease-modifying antirheumatic drugs

DMARDs are widely used for the treatment of children with polyarticular disease and those with oligoarticular JIA refractory to joint injections and NSAIDs. The most commonly used agent is methotrexate, given once weekly by mouth or subcutaneous injection.[9] Methotrexate has been used in the management of patients with JIA for decades and remains a useful first-line therapy.

Common side effects of methotrexate include nausea and vomiting, mouth ulcers and malaise. Folic acid is given to counteract these side effects, but they can be sufficiently debilitating to warrant cessation of therapy. As methotrexate may be associated with cytopenia and liver dysfunction, patients should have regular blood tests while taking this drug, usually three monthly but more often during the introductory phase.

Leflunomide, sulfasalazine and hydroxychloroquine are also used in the treatment of patients with JIA, especially those who do not tolerate methotrexate.

Biologic therapy

Biological DMARDs (bDMARDs or biologics) are targeted therapies that have been engineered to block the key cytokines in arthritis development. They consist of monoclonal antibodies and fusion proteins, administered subcutaneously or intravenously, which act on tumour necrosis factor, interleukin-6 or other crucial cytokines.

The biologic therapies have revolutionised JIA management, with treatment targets becoming more ambitious and outcomes improving accordingly. In general, the biologics are well tolerated. However, as they are new medications, long-term safety data are limited; some links to demyelination and malignancy, especially lymphoma, have been reported.

Biologic agents available on the PBS for the treatment of patients with JIA in Australia include etanercept, adalimumab and tocilizumab. Choice of agent depends on disease characteristics, comorbidities (including uveitis) and previous agent response. Biologic therapies remain extremely expensive, and supply is tightly controlled by the PBS.

Treatments for eye disease

Treatment of patients with eye disease parallels general JIA treatment – corticosteroids (usually topical eye drops), DMARDs (especially methotrexate) and biologic agents.

Vigilance for infections

As JIA is an autoimmune condition, many of the therapies used in its treatment are immunosuppressive. Children on DMARDs or biologic agents are at higher risk of all infections, but particular attention should be paid to varicella and tuberculosis. Significant varicella exposure warrants discussion with the specialist team for consideration of zoster immunoglobulin. Given the potential for disseminated infection, tuberculosis screening is routine before the commencement of any biologic. Opportunistic infections, including those caused by unusual organisms, should be considered in any unwell child on biologic agents, and the treating team should be notified in the case of suspected infection. Children who are immunosuppressed, especially those receiving biologic therapies, may not develop a fever even in the context of severe bacterial infection. Consequently, absence of fever is not necessarily a reassuring finding.

Other treatments

Standards of care in JIA now specifically address quality of life and psychological and functional outcomes of this disease. The involvement of a multidisciplinary team, including nurse educators, physiotherapists and occupational therapists, provided through a specialist paediatric rheumatology service, is now considered desirable in achieving these outcomes.[5,23]

Use of complementary therapy is common among patients with JIA, especially dietary manipulation and supplements.[24] It is important to ensure that these therapies do not interact with standard medications or otherwise compromise the child's overall health and nutrition.

WHAT IS THE FUTURE FOR JUVENILE IDIOPATHIC ARTHRITIS?

The development of disease biomarkers, including protein, cellular or genetic markers of disease activity and treatment response, is a growing area of interest in JIA, but as yet none have been validated for clinical use. In the future, disease biomarkers may be able to predict disease trajectory and allow targeted personalised therapy choices, based on the likelihood of response in any given individual.

The role of imaging – especially ultrasound and MRI – in monitoring disease activity and attainment of remission continues to evolve, particularly as we strive to eradicate all inflammation, not just that which is clinically apparent.[25,26] New biologics continue to be developed with the aim of achieving and maintaining rapid disease remission in all children with JIA.[27] As our therapies and investigative modalities improve, the development of validated health outcome measures to assess subtle disease activity and response to treatment continues.[28]

CONCLUSION

Outcomes for patients with JIA have improved dramatically in recent years but still depend on early recognition and referral to a paediatric rheumatology service. Diagnostic delays are common as presentations are often subtle. In this era of biologic therapies, the therapeutic focus has shifted to early aggressive treatment and the elimination of even low levels of inflammation. Monitoring for disease complications, including inflammatory eye disease, is crucial to maintaining normal function. The outlook for children with JIA and their families is now bright, with therapeutic goals aiming for normal physical and psychosocial functioning. MT

COMPETING INTERESTS: None.

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REFERENCES

1. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine 2014; 81: 112-117.
2. Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken) 2011; 63: 465-482.
3. Foster HE, Eltringham MS, Kay LJ, Friswell M, Abinun M, Myers A. Delay in access to appropriate care for children presenting with musculoskeletal symptoms and ultimately diagnosed with juvenile idiopathic arthritis. Arthritis Rheum 2007; 57: 921-927.
4. Vastert S, Prakken B. Update on research and clinical translation on specific clinical areas: from bench to bedside: how insight in immune pathogenesis can lead to precision medicine of severe juvenile idiopathic arthritis. Baillieres Best Pract Res Clin Rheumatol 2014; 28: 229-246.
5. Munro J, Murray K, Boros C, et al. Australian Paediatric Rheumatology Group standards of care for the management of juvenile idiopathic arthritis. J Paediatr Child Health 2014; 50: 663-666.
6. Martini A. It is time to rethink juvenile idiopathic arthritis classification and nomenclature. Ann Rheum Dis 2012; 71: 1437-1439.
7. Pohjankoski H, Kautiainen H, Kotaniemi K, Korppi M, Savolainen A. Diabetes, coeliac disease, multiple sclerosis and chronic arthritis in first-degree relatives of patients with juvenile idiopathic arthritis. Acta Paediatr 2012; 101: 767-771.
8. Saurenmann RK, Rose JB, Tyrrell P, et al. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. Arthritis Rheum 2007; 56: 1974-1984.
9. Prince FH, Otten MH, van Suijlekom-Smit LW. Diagnosis and management of juvenile idiopathic arthritis. BMJ 2010; 341: c6434.
10. Hinks A, Ke X, Barton A, et al; UK Rheumatoid Arthritis Genetics Consortium; British Society of Paediatric and Adolescent Rheumatology Study Group. Association of the IL2RA/CD25 gene with juvenile idiopathic arthritis. Arthritis Rheum 2009; 60: 251-257.
11. Moroldo MB, Chaudhari M, Shear E, Thompson SD, Glass DN, Giannini EH. Juvenile rheumatoid arthritis affected sibpairs: extent of clinical phenotype concordance. Arthritis Rheum 2004; 50: 1928-1934.
12. Petty RE, Smith JR, Rosenbaum JT. Arthritis and uveitis in children. A pediatric rheumatology perspective. Am J Ophthalmol 2003; 135: 879-884.
13. Flato B, Lien G, Smerdel A, et al. Prognostic factors in juvenile rheumatoid arthritis: a case-control study revealing early predictors and outcome after 14.9 years. J Rheumatol 2003; 30: 386-393.
14. Gowdie PJ, Tse SM. Juvenile idiopathic arthritis. Pediatr Clin North Am 2012; 59: 301-327.
15. Albers HM, Wessels JA, van der Straaten RJ, et al. Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. Arthritis Rheum 2009; 61: 46-51.
16. Magnani A, Pistorio A, Magni-Manzoni S, et al. Achievement of a state of inactive disease at least once in the first 5 years predicts better outcome of patients with polyarticular juvenile idiopathic arthritis. J Rheumatol 2009; 36: 628-634.
17. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010; 69: 631-637.
18. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology 2004; 43: 906-914.
19. Australian Government Department of Health and Ageing Australian Technical Advisory Group on Immunisation, NHMRC. Australian immunisation handbook. 10th ed (updated January 2014). Canberra: Commonwealth of Australia; 2013.
20. Bomba M, Meini A, Molinaro A, et al. Body experiences, emotional competence, and psychosocial functioning in juvenile idiopathic arthritis. Rheumatol Int 2013; 33: 2045-2052.
21. Rouster-Stevens KA, Ardoin SP, Cooper AM, et al. Choosing wisely: the American College of Rheumatology's top 5 for pediatric rheumatology. Arthritis Care Res 2014; 66: 649-657.
22. Bloom BJ, Alario AJ, Miller LC. Intra-articular corticosteroid therapy for juvenile idiopathic arthritis: report of an experiential cohort and literature review. Rheumatol Int 2011; 31: 749-756.
23. Davies K, Cleary G, Foster H, Hutchinson E, Baildam E, British Society of Paediatric and Adolescent Rheumatology. BSPAR standards of care for children and young people with juvenile idiopathic arthritis. Rheumatology (Oxford) 2010; 49: 1406-1408.
24. April KT, Feldman DE, Zunzunegui MV, Descarreaux M, Malleson P, Duffy CM. Longitudinal analysis of complementary and alternative health care use in children with juvenile idiopathic arthritis. Complement Ther Med 2009; 17: 208-215
25. Magni-Manzoni S, Malattia C, Lanni S, Ravelli A. Advances and challenges in imaging in juvenile idiopathic arthritis. Nat Rev Rheumatol 2012; 8: 329-336.
26. Sheybani EF, Khanna G, White AJ, Demertzis JL. Imaging of juvenile idiopathic arthritis: a multimodality approach. Radiographics 2013; 33: 1253-1273.
27. Kessler EA, Becker ML. Therapeutic advancements in juvenile idiopathic arthritis. Baillieres Best Pract Res Clin Rheumatol 2014; 28: 293-313.
28. Luca NJ, Feldman BM. Health outcomes of pediatric rheumatic diseases. Baillieres Best Pract Res Clin Rheumatol 2014; 28: 331-350.