Juvenile idiopathic arthritis: in adolescence and beyond

Juvenile idiopathic arthritis differs markedly from adult rheumatoid arthritis. It encompasses all childhood arthritis of unknown cause, representing a group of diseases with a wide variety of clinical manifestations and outcomes. Many patients will suffer active disease and complications into adulthood.

Juvenile idiopathic arthritis is a heterogeneous group of conditions encompassing any arthritis of unknown origin occurring in a patient under 16 years persistent for more than 6 weeks (Petty et al, 2004). In the UK, between 10 000 and 15 000 children suffer from arthritis (Southwood, 2010) and many will have persistent disease into late adolescence and adulthood. The incidence is approximately 1 in 10 000 and prevalence 1 in 1000. Juvenile idiopathic arthritis is characterized by joint inflammation, which may cause joint damage and disability, and could adversely affect development and growth. There are a range of systemic manifestations and complications. Advances in understanding of the pathogenesis of juvenile idiopathic arthritis as well as medical treatment over the last 10 years have significantly improved prognosis. Remission is often achievable but, as yet, there is no cure.

This review describes the clinical subtypes of juvenile idiopathic arthritis with particular reference to prognosis in adolescence and beyond. Advances in medical treatment as well as potential complications and emergencies relevant to hospital medicine are also discussed.

Table 1. Juvenile idiopathic arthritis subtypes according to the International League of Associations for Rheumatology criteria

Category	Criteria
Systemic arthritis	Arthritis in one or more joints with or preceded by fever (at least 2 weeks duration and daily for at least 3 days) plus one or more of: evanescent erythematous rash, hepatomegaly, splenomegaly, serositis, lymphadenopathy
Oligoarthritis	Arthritis affecting one to four joints in the first 6 months of disease
	Persistent: affects no more than four joints throughout disease course
	Extended: affects more than four joints after first 6 months
Polyarthritis (RF -ve)	Arthritis affecting five or more joints in the first 6 months of disease with negative RF test
Polyarthritis (RF +ve)	Arthritis affecting five or more joints in the first 6 months of disease with positive RF (two tests at least 3 months apart)
Psoriatic arthritis	Arthritis and psoriasis or arthritis and two of: dactylitis, nail pitting or onycholysis, psoriasis in a first-degree relative
Enthesitis-related arthritis	Arthritis and enthesitis or arthritis or enthesitis and two of sacroiliac joint tenderness or inflammatory lumbosacral pain (or both), HLA B27 positive, onset of arthritis in a male over 6 years old, acute anterior uveitis, history of HLA B27-associated disease (ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis in inflammatory bowel disease, reactive arthritis, acute anterior uveitis) in first degree relative
Undifferentiated arthritis	Arthritis that fulfils criteria in no specific category or fulfils criteria for more than one category

RF = rheumatoid factor. From Petty et al (2004)

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Definition

The lack of an internationally accepted classification system until recently has lead to confusion and hampered research in this field. Two sets of classification criteria were previously recognized. The American College of Rheumatology used 'juvenile rheumatoid arthritis' which had three different subtypes: polyarticular, pauciarticular and systemic. The European League Against Rheumatism criteria for 'juvenile chronic arthritis' had six subtypes: polyarticular, pauciarticular, juvenile rheumatoid arthritis (polyarticular with positive rheumatoid factor), systemic, juvenile ankylosing spondylitis and juvenile psoriatic arthritis. Although both were widely used, significant confusion arose from the different use of the term 'juvenile rheumatoid arthritis', so neither was universally accepted.

The International League of Associations for Rheumatology sought to unify these criteria under the new name of juvenile idiopathic arthritis, identifying clinically homogeneous sub-groups of disease (Petty et al, 2004). Juvenile idiopathic arthritis is defined as arthritis of unknown aetiology, lasting at least 6 weeks, occurring before a child's 16th birthday. The seven subtypes of juvenile idiopathic arthritis (*Table 1*) are described below. The clinical manifestations, age of onset and disease course differ significantly between subtypes, and determine prognosis in late adolescence and adulthood.

Aetiology

Juvenile idiopathic arthritis is a multifactorial autoimmune disease with environmental and genetic factors playing a role in aetiology. Both HLA class I (including HLA A2 and HLA B27) and HLA class II (including HLA DRB1 and HLA DP) have associations with juvenile idiopathic arthritis but the strength of association differs between disease

subtypes and ethnic background. Other non-HLA genes have been studied but only a few associations could be confirmed (including protein tyrosine phosphatase and macrophage inhibitory factor) (Prakken et al, 2011).

Differential diagnosis

Juvenile idiopathic arthritis is characterized by joint inflammation which manifests as joint pain and swelling, morning stiffness and reduced mobility. The most important differential diagnoses in a child presenting with arthritis include infection (septic arthritis, osteomyelitis or reactive arthritis), neoplasm (in particular leukaemia and neuroblastoma), and other autoimmune diseases including systemic lupus erythematosus and vasculitis. A more comprehensive list is given in *Table 2*.

Subtypes of juvenile idiopathic arthritis

Systemic arthritis

This affects approximately 1 in 100 000 children or up to 10% of those with juvenile idiopathic arthritis and is the most severe form of the disease. The most common age of onset is between 1 and 5 years but it occurs throughout childhood into adult years. It is equally common in males and females. The arthritis affects multiple joints and may be mild and remitting or severe, progressive and destructive. Other symptoms may precede the arthritis by several weeks or months. Patients have daily spiking fevers (1–3 per day) which persist for at least 2 weeks associated with a salmon pink, macular evanescent rash which may be urticarial or pruritic. Serositis, hepatosplenomegaly and lymphadenopathy may be major features and precede arthritis. Patients can be severely unwell and require hospitalization.

There is no one diagnostic test. Investigations may show anaemia with raised white blood cells, platelets and inflammatory markers. Liver function tests may be abnormal and ferritin can be at least ten times the normal level. Systemic arthritis may be difficult to diagnose and infection and neoplasm must be excluded as the presentation may be similar.

The milder cases (around 50%) resolve within a few years without permanent joint damage. In the others, the disease is severe with joint damage and other complications including growth failure and osteoporosis.

Oligoarthritis

This is the most frequent form of juvenile idiopathic arthritis, affecting up to 50% (1 in 15 000 children), commonly occurring in early childhood (1–5 years) and in girls. The arthritis is usually asymmetrical affecting up to four joints in the first 6 months. It usually affects the large lower limb joints, especially the knees and ankles, but also elbows and wrists. After this, oligoarthritis subdivides into persistent disease which continues to affect four or fewer joints and extended disease which involves multiple joints. Extended oligoarthritis occurs in around a quarter of patients who then follow an identical disease course to polyarticular juvenile idiopathic arthritis.

Failure to control joint inflammation may result in deformities and leg length discrepancies requiring surgical correction. Patients who are antinuclear antibody (ANA) positive (up to 75%) have a significant risk (approximately 25%) of chronic anterior uveitis in childhood.

Those following a persistent disease course have a good prognosis and around 75% go into remission in late childhood. Those with extended oligoarthritis are much more likely to have active disease in adulthood. Uveitis rarely occurs in adolescence or adulthood but the sequelae of earlier eye disease may be seen and require treatment.

Polyarthritis (rheumatoid factor negative)

Affecting 20–30% of all those with juvenile idiopathic arthritis (1 in 25 000 children) and more commonly girls, polyarthritis can be symmetrical or asymmetrical. Both large and small joints are affected, most commonly knee, wrist, ankle, hip and elbow. The cervical spine and temporomandibular joints (causing micrognathia) may

Table 2. Differential diagnosis of joint pain in children

Infective	Septic arthritis
	Reactive arthritis (viral or bacterial cause)
	Osteomyelitis
Inflammatory	Juvenile idiopathic arthritis
	Other autoimmune rheumatic disease or vasculitis including: systemic lupus erythematosus, dermatomyositis, sarcoid, Henoch–Schonlein purpura, Kawasaki, polyarteritis nodosa
	Chronic recurrent multifocal osteomyelitis
	Periodic fever syndromes
	Associated with other chronic disease: inflammatory bowel disease, cystic fibrosis, immunodeficiency, Down's syndrome, Turner's syndrome
Neoplastic	Leukaemia
	Neuroblastoma
Mechanical	Trauma
	Hypermobility
	Chondromalacia patellae (anterior knee pain)
	Slipped femoral epiphyses
	Perthes' disease
	Osgood–Schlatter's disease
	Scheurmann's disease
Endocrine and metabolic	Vitamin D deficiency
	Hypo- or hyperthyroidism
	Diabetes mellitus
Genetic	Collagen disease
	Mucopolysaccharidosis
	Skeletal dysplasias
	Haemophilia
Miscellaneous	Chronic pain syndromes

be involved early. The arthritis may be progressive and destructive, persisting into adulthood, although around a third, especially those with less severe disease, will go into remission in late childhood or adulthood. Those who are ANA positive (around 50%) have a similar risk of uveitis to those with oligoarticular juvenile idiopathic arthritis.

Polyarthritis (rheumatoid factor positive)

This is more unusual (less than 1 in 100 000 children) and is clinically identical to adult onset seropositive rheumatoid arthritis. It is a symmetrical deforming polyarthritis, more common in girls with onset usually in the teenage years. The most common joints affected are: hands, wrists, knees and feet with progression to most joints unless treated. The disease does not remit in adulthood and is associated with rheumatoid nodules, lung disease and vasculitis as in adults.

Psoriatic arthritis

This is also unusual (less than 1 in 100 000) and similar to the adult form of the disease, with equal incidence in males and females. It may mimic oligoarticular or polyarticular juvenile idiopathic arthritis. Psoriasis can occur years after the onset of arthritis but there may be a family history. In addition to progressive arthritis, dactylitis and enthesitis are characteristic. Disease persists into adulthood.

Enthesitis-related arthritis

This accounts for 10–14% of all cases of juvenile idiopathic arthritis with 75–85% having HLA B27. Occurring mainly in boys in late childhood and adolescence, it may be similar to adult ankylosing spondylitis but there are significant differences, in particular asymmetrical lower limb large joint arthropathy is typical at onset. Enthesitis is also common, especially around the patella, Achilles tendon and plantar fascia. Sacroiliac and spinal inflammation occurs 2–3 years after onset (earlier in some) in over half of all patients and may be associated with severe hip arthritis. There may be two distinct phenotypes of enthesitis-related arthritis: those with early spinal inflammation often associated with hip arthritis and those with predominantly peripheral arthritis and enthesitis who never develop spinal inflammation (Fisher et al, 2012).

Enthesitis-related arthritis is unlikely to remit in adulthood but those with more peripheral disease have a higher chance of remission. It is associated with extra-articular manifestations including acute anterior uveitis (in contrast to the chronic uveitis associated with juvenile idiopathic arthritis) and inflammatory bowel disease.

Treatment

As with all chronic childhood diseases, juvenile idiopathic arthritis should be managed by a multidisciplinary team. In adolescence, management is particularly challenging because of problems with adherence, and experimentation with alcohol may lead to problems with medication, especially methotrexate. A significant number of patients with juvenile idiopathic arthritis are sexually active before 18 years of age (Packham and Hall, 2002c), so counselling with regard to medication and risk to pregnancy (especially methotrexate) and sexually transmitted infections is important.

Transition of care to adult services can be difficult for both the patient and his/her parents. There can be significant differences in the provision of care, including reduced access to the multidisciplinary team. Lack of preparation for such differences may lead to reduced compliance and risk of disease flare. Effective transition results in improved disease control and adherence to appointments (McDonagh, 2007). Adolescent and young adult clinics aid smooth transition to adult services.

Drug treatment in juvenile idiopathic arthritis (*Table 3*) has been revolutionized in recent years by use of biologic therapies. The aim is to control inflammation quickly, reducing joint damage and deformity and achieving remission if possible. Significant advances in randomized clinical trial data have made this possible, aided by the formation of two large international research networks (Paediatric Rheumatology Collaborative Study Group and Paediatric Rheumatology International Trial Organisation). However, most trials are carried out in patients with polyarticular or oligoarticular juvenile idiopathic arthritis, with a few specific to systemic juvenile idiopathic arthritis. Clinical trials in other subtypes are lacking.

Prognosis

Outcome studies have previously shown high levels of functional limitation in patients with juvenile idiopathic arthritis at long-term follow up, but early use of intra-articular steroid, methotrexate and biologic therapy have improved prognosis significantly and up to date outcome studies should reflect this. Data currently available are mostly based on patients treated 10–30 years ago, well before the frequent and early use of biologics.

Table 4 shows outcome studies for childhood arthritis published in the last 10 years. There are few studies and little consistency between the data reported. Comparisons between studies are made more difficult because of the different classification criteria used, as well as the major differences in study design and patient selection.

Predictors of persistent disease identified in a study by Flatø et al (2003) included young age at disease onset, female sex, extensive symmetrical disease, prolonged elevation of erythrocyte sedimentation rate, positive rheumatoid factor and the presence of HLA DRB1*08, HLA DRB1*01 and the combination of HLA B27 and HLA DRB1*08. In addition, patients with juvenile idiopathic arthritis had greater disability, more bodily pain, poorer general health and higher unemployment than controls from the general population.

Overall, only those with persistent oligoarticular juvenile idiopathic arthritis have a good chance of remission in adolescence and adulthood. Many patients continue to have active disease or sequelae from previous

disease well into adult life (Minden, 2009). However, up to date studies are needed in light of advances in therapy, as a marked improvement in function and levels of disability should be evident.

Complications relevant to hospital medicine

Medication side effects and infection risk

Table 3 lists side effects of individual medications. The most important adverse event with disease-modifying

Table 3. Drug treatment in juvenile idiopathic arthritis

Category	Drug	Indications	Evidence	Complications or side effects
Non-steroidal anti-inflammatory drug	Ibuprofen, diclofenac, naproxen and others	Symptomatic relief of pain and fever can be used while diagnosis is being confirmed	Multiple randomized controlled trials, no effect on disease course	Gastrointestinal upset, abnormal liver function tests
Corticosteroids	Triamcinalone hexacetonide	Intra-articular injection for active disease in single or small number of joints	Randomized double blind trial showed 85% joints still in remission after 1 year (Zulian et al, 2004)	Increased pain for 24–72 hours post-injection, rarely joint infection, skin atrophy and depigmentation at injection site
	Prednisolone or methylprednisolone	Oral or intravenous systemic use for uncontrolled inflammation in multiple joints or disease flare or while waiting for other drugs to take effect	Randomized open label trial of methylprednisolone 'mini-pulses' (Picco et al, 1996)	Long-term use avoided if possible: multiple side effects including osteoporosis, growth retardation, weight gain (and body image issues), diabetes
DMARD	Methotrexate (oral or subcutaneous) (in general given with folic acid)	Arthritis in multiple joints or persistent disease in a few joints despite intra-articular steroid (takes up to 3 months to work)	Randomized double blind clinical trial (Giannini et al, 1992), 'non-responder' rate may be as high as 30%, higher with some subtypes especially systemic juvenile idiopathic arthritis (Pain and McCann, 2009)	Nausea and vomiting, particularly in adolescence, abnormal liver function tests, cytopenias, opportunistic infections
	Sulfasalazine	As for methotrexate	In general lower response rate (44%; van Rossum et al, 1998) and more adverse effects than with methotrexate	Gastrointestinal side effects, rash, myelosuppression
	Leflunomide	As for methotrexate	Randomized double blind trial (Silverman et al, 2005), response rate 68%, clinical experience limited	Gastrointestinal side effects, especially diarrhoea, headache, rash, abnormal liver function tests
Biologic therapy: anti-TNF drugs	Etanercept	Active juvenile idiopathic arthritis despite DMARD treatment	Randomized controlled trial (Lovell et al, 2000), 74% response rate	Opportunistic infections (especially tuberculosis), injection site reaction, sepsis, (very rarely: lupus-like illness, neuropsychiatric complications, demyelination), unknown long-term safety
	Adalimumab	As for etanercept	Randomized controlled trial (Lovell et al, 2008)	As for etanercept
	Infliximab	As for etanercept but not licenced	Randomized controlled trial (Ruperto et al, 2007)	As for etanercept and infusion reactions (secondary to human anti-chimeric antibodies)
Biologic therapy: others	Abatacept (T cell co-stimulation modulator)	Active juvenile idiopathic arthritis despite DMARD and anti-TNF therapy	Randomized controlled trial (Ruperto et al, 2008)	Infusion reaction, opportunistic infection, sepsis, unknown long-term effects
	Tocilizumab (IL-6 receptor antibody)	Active systemic juvenile idiopathic arthritis previously treated with DMARD and anti-TNF therapy	Randomized controlled trial (Yokota et al, 2008), trial currently ongoing in polyarticular juvenile idiopathic arthritis	Infusion reaction, abnormal liver function tests, cytopenias, raised serum cholesterol, reduces signs but increases risk of infection, unknown long-term effects
	Anakinra (IL-1 receptor antagonist)	Active systemic juvenile idiopathic arthritis previously treated with DMARD	Randomized controlled trial (Quartier et al, 2011)	Injection site reaction, opportunistic infection, sepsis, rash, unknown long-term effects
	Canakinumab (human IL-1β receptor antibody)	Active systemic juvenile idiopathic arthritis, clinical trials only	No randomized controlled trials yet, use in clinical trials	Injection site reaction, opportunistic infection, sepsis, rash, unknown long-term effects
	Rituximab (chimeric anti-CD20 antibody causing B cell depletion)	Active rheumatoid factor positive polyarticular juvenile idiopathic arthritis despite DMARD and anti-TNF treatment (as per adult rheumatoid arthritis)	No randomized controlled trials yet	Infusion reaction, opportunistic infection, unknown long-term effects

DMARD = disease-modifying anti-rheumatic drug; TNF = tumour necrosis factor

anti-rheumatic drugs and biologic therapy is bacterial or viral infection with serious manifestations and opportunistic infection, in particular tuberculosis with anti-tumour necrosis factor treatment. Varicella infection can be more severe in patients on disease-modifying anti-rheumatic drugs or biologic therapy and may require hospitalization. Treatment should be stopped if a patient has active infection but restarted as soon as safe to prevent disease flare.

Signs of severe infection may be masked in these patients, so a high index of suspicion and low threshold for antibiotics or antivirals is imperative, after relevant cultures and investigations. In patients treated with tocilizumab, the C-reactive protein response is impaired even in the presence of severe sepsis but erythrocyte sedimentation rate is usually elevated as expected.

Annual influenza vaccination is recommended, as well as pneumococcal vaccination (single dose). Live vaccines should be avoided but inactivated vaccines are safe. Patients should also be screened (according to local guidelines) for previous tuberculosis infection before starting biologic therapy.

Growth failure

Generalized growth failure is seen with severe juvenile idiopathic arthritis where disease has remained active for a prolonged period. This is thought to be the result of premature epiphyseal closure and may be worsened by corticosteroid treatment. Biologic therapies have reduced the risk of this significantly and have even been shown to increase growth velocity in children with juvenile idiopathic arthritis (Pain and McCann, 2009). Growth hormone treatment may also be beneficial. However, short stature is common in those who had already reached adulthood before these therapies were introduced or who have not responded adequately to treatment. This is significant in 41% of patients with systemic juvenile idiopathic arthritis and 11% with polyarticular juvenile idiopathic arthritis (Minden, 2009). Localized growth defects may also occur, affecting the jaw (micrognathia), fingers, toes and limbs. Bony overgrowth, particularly around the knee joint, causes leg length discrepancies. The detrimental effect on body image in the adolescent patient is significant.

Osteoporosis

During the time when peak bone mass is attained in childhood and adolescence, high levels of disease activity, immobilization and treatment with corticosteroids all contribute to the high prevalence of low bone mass in patients with juvenile idiopathic arthritis. Even with remission, adults do not achieve completely normal bone density (Brabnikova Maresova, 2011). This increases fracture risk both in childhood and throughout adult life.

Table 4. Outcome studies in childhood arthritis published in last 10 years

Study	Patient number	Follow-up duration	Remission rate	Active disease	Other outcomes
Ostlie et al (2009)	55 (chronic childhood arthritis)	18.3 years after symptom onset	Not stated	Not stated	Physical disability (significant correlation with pain): 38% Psychiatric distress (significant correlation with pain and fatigue): 22% Fatigue in significant number of patients
Foster et al (2003)	82 (juvenile idiopathic arthritis)	21 years disease duration (median age 30 years)	Not stated	39%	Short form-36 scores: significantly worse compared with controls Educational attainment: comparable to local controls Unemployment: three-fold higher than controls
Fantini et al (2003)	683 (juvenile chronic arthritis)	About 10 years	32.8%	Not stated	
Packham and Hall (2002a,b) Packham et al (2002)	246 (juvenile idiopathic arthritis, criteria applied retrospectively)	Average disease duration 28.3 years	Not stated	Clinically: 43.3%, laboratory: 54.4%	Severe disability (health assessment questionnaire > 1.5): 42.9%, mean height shorter than general population, major prosthetic joint replacement: 51.2%, patients still on disease-modifying anti-rheumatic drugs: 36.3%, educational attainment: significantly better than national average, unemployment: >2 x national average, severe pain: 31.9%, workplace discrimination: 25.1%, depression at some point: 21.1%
Minden et al (2002)	215 (juvenile rheumatoid arthritis)	16.5 years median follow up	Persistent oligoarticular: 73%, extended oligoarticular: 12%, systemic: 47%, polyarticular: 30%, enthesitis-related arthritis: 18%	50% (approx.)	Tender or swollen joints: 41%, restricted joints: 54%, local growth disturbances (mostly mild limb length discrepancies): 26%, joint operations (mainly synovectomies): 45%, severe disability (health assessment questionnaire >1): 6.5%, educational attainment: comparable or slightly higher than age-matched population, lower unemployment rate compared to age-matched population, patients still on disease-modifying anti-rheumatic drugs: 26%
Oen et al (2002)	392 (juvenile rheumatoid arthritis)	>5 years after disease onset	Systemic: 37%, pauciarticular: 47%, rheumatoid factor –ve polyarticular: 23%, rheumatoid factor +ve polyarticular: 6%		Joint replacement surgery: 13–57% after 15 years of disease, severe disability (health assessment questionnaire >1.5): 6%, higher unemployment rates

Treatment includes adequate calcium and vitamin D supplementation, especially during corticosteroid treatment. Anti-tumour necrosis factor therapy reduces disease activity and increases bone mass (Simonini et al, 2005). Treatment with bisphosphonates is not recommended until later life because of their long half-life and unknown effect on the maturing skeleton as well as on future fetal development in premenopausal women.

Early joint replacement

It is anticipated that earlier treatment with methotrexate and biologic therapy will reduce the need for joint replacement in children and young adults with juvenile idiopathic arthritis. However, around 25–50% require major surgery including joint replacement at some point (Hashkes and Laxer, 2005). Survival rates of the replacement joint are poor (Malviya et al, 2010), especially if patients have been treated with corticosteroids. This, in addition to surgery at a young age, increases the need for revision surgery and the complications associated with this.

Uveitis

Chronic anterior uveitis occurs in up to a quarter of all patients with juvenile idiopathic arthritis in childhood but is rare in adolescence and adulthood. It occurs in every form of the disease but is most common in those with oligoarticular and rheumatoid factor negative polyarticular juvenile idiopathic arthritis who are ANA positive. There is a risk of flare or even new presentation of uveitis on withdrawal of immunosuppressant treatment for juvenile idiopathic arthritis. Untreated, it can cause significant ocular damage and potentially blindness with cataracts the most common complication. There may be few or no symptoms, so guidelines for screening all patients with juvenile idiopathic arthritis should be followed (*Table 5*). Treatment is with topical corticosteroids and then disease-modifying anti-rheumatic drugs, including methotrexate but also ciclosporin and mycophenolate mofetil, progressing to anti-tumour necrosis factor agents if necessary. The efficacy of etanercept for uveitis has not been proven and studies suggest infliximab and adalimumab are more effective in this group (Pain and McCann, 2009).

Acute anterior uveitis is a separate condition seen in association with HLA B27 and thus enthesitis-related arthritis. It is painful, causes a red eye and rarely leads to long-term problems. It is treated with topical corticosteroids.

Fertility and birth

There does not seem to be a significant difference between patients with juvenile idiopathic arthritis and the general population in terms of age of menarche and age at first child. There may be an increased rate of menstrual disturbances but spontaneous miscarriage rates are comparable with the general population. However, Packham and Hall (2002c) noted that fewer juvenile idiopathic arthritis patients become pregnant, perhaps because a lower number are in a stable relationship or because of disability. They found infertility in a small proportion as a result of premature ovarian failure and azoospermia, and higher rates of delivery by caesarean section particularly in patients with poor hip abduction and short stature.

The teratogenic effects of drugs such as methotrexate and leflunomide, as well as the unknown effects of others (including biologic treatment), must be taken into account when advising patients about pregnancy.

Macrophage activation syndrome

This is a secondary form of haemophagocytic lymphohistiocytosis and is a serious complication of systemic juvenile idiopathic arthritis, although it can be seen in other subtypes. It has a high mortality if untreated, so early recognition and treatment are essential. Triggers may include the underlying disease process itself, where there are high levels of inflammation but also infections and drugs. Cardinal features include unremitting fever, lymphadenopathy, hepatosplenomegaly, abnormal liver function tests and cytopenias in an acutely unwell patient. Clinical presentation may resemble overwhelming sepsis or a flare of systemic juvenile idiopathic arthritis, so a high index of suspicion is necessary. Further tests that aid diagnosis include high triglycerides and ferritin (often extremely high), low erythrocyte sedimentation rate and fibrinogen (suggesting underlying coagulopathy). An abnormal blood film, falling platelets and abnormal liver function tests (in particular transaminitis) are often seen. There may be neurological, renal, pulmonary and cardiac involvement. Diagnosis is confirmed by bone marrow

Table 5. Screening schedule guidelines for uveitis in juvenile idiopathic arthritis

Initial screening	New patients will be screened as soon as possible and no longer than 6 weeks after referral to ophthalmology		
	Symptomatic patients should be seen within 1 week		
Subsequent screening	2-monthly for 6 months		
	3–4-monthly thereafter until 11–12 years (or see specific schedules for subtypes below)		
	1 year of screening for patients presenting after 11 years of age		
	6 months screening (2-monthly) if immunosuppression stopped then revert to previous schedule		
		Disease onset	Years screening required
Oligoarticular juvenile idiopathic arthritis, psoriatic arthritis, enthesitis-related arthritis onset <11 years		< 3 years	8
		3–4 years	6
		5–8 years	3
		9–10 years	1
Polyarticular juvenile idiopathic arthritis antinuclear antibody +ve onset <10 years		< 6 years	5
		6–9 years	2
Polyarticular juvenile idiopathic arthritis antinuclear antibody –ve onset <7 years		< 7 years	5

From British Society for Paediatric and Adolescent Rheumatology and Royal College of Ophthalmologists (2006)

biopsy showing haemophagocytosis. Urgent treatment is required with intravenous corticosteroids, ciclosporin and occasionally etoposide in those who fail to respond.

Conclusions

For many patients juvenile idiopathic arthritis is a lifelong disease. It is a heterogeneous disease with a variety of clinical manifestations. Differential diagnoses include infection and malignancy. Classification of disease subtype is important as this determines the clinical course, potential complications and prognosis. Advances in treatment have dramatically improved prognosis in recent years but there is no cure and many patients experience active disease or the sequelae of previous disease into adulthood. **BJHM**

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KEY POINTS

- Juvenile idiopathic arthritis is not one disease but a group of heterogeneous conditions.
- Clinical features and prognosis vary depending on subtype.
- The most important differential diagnoses to exclude are infection and neoplasia.
- Treatment includes immunosuppressant medications which make patients more susceptible to severe sepsis and opportunistic infections.
- Macrophage activation syndrome is a life-threatening complication of systemic juvenile idiopathic arthritis requiring urgent diagnosis and treatment.
- Most patients with juvenile idiopathic arthritis do not go into remission in late childhood and will require treatment throughout their adult years.