Juvenile Idiopathic Arthritis: Towards Improving Clinical Care

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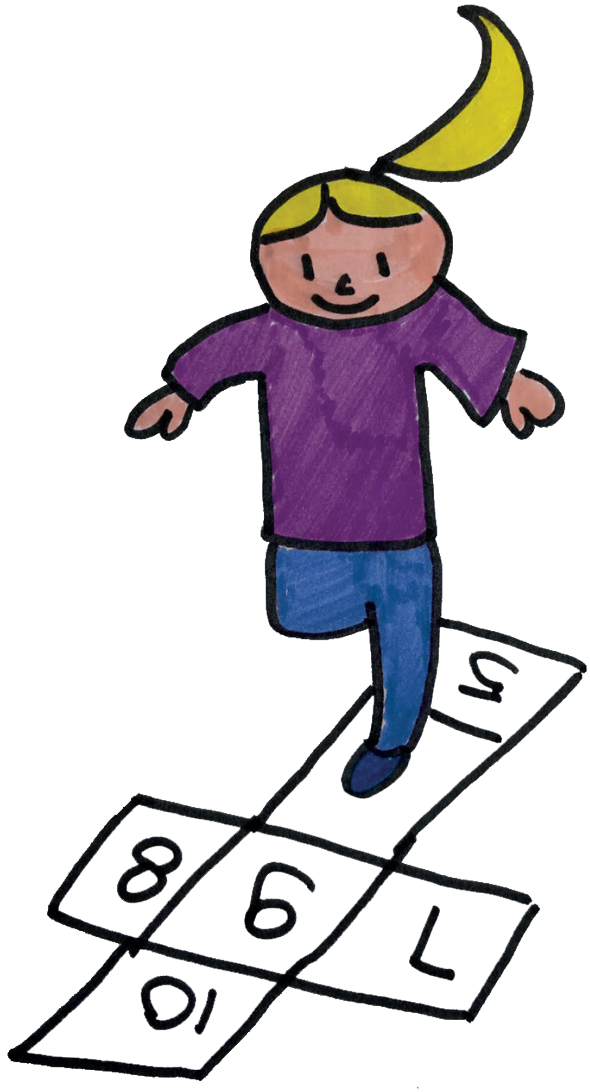
PART ONE

PATHOGENESIS of Juvenile Idiopathic Arthritis



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Oligoarticular and Polyarticular Juvenile Idiopathic Arthritis

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INTRODUCTION

When a child under the age of 16 years has arthritis with a duration exceeding 6 weeks the diagnosis of juvenile idiopathic arthritis (JIA) is probable. Other diseases need to be excluded, especially in the absence of commonly found serological factors such as antinuclear antibodies (ANAs). JIA is a heterogeneous group of diseases and only the category with immunoglobulin M (IgM) rheumatoid factor (RF) is thought to be equivalent to adult rheumatoid arthritis (RA).

In the past, several names have been given to chronic arthritis in childhood such as juvenile RA and juvenile chronic arthritis. Since an International League of Associations for Rheumatology work force (last revised in 2007) proposed the name juvenile idiopathic arthritis, this name has been adopted, both in Europe and the United States. Seven categories of JIA are recognized, as shown in Table 1.1[1].

Table 2.1 | Categories of Juvenile Idiopathic Arthritis (ILAR Classification)

Systemic
Polyarticular RF-negative
Polyarticular RF-positive
Oligoarticular
- Persistent
- Extended
Psoriatic arthritis
Enteritis-related arthritis
Undifferentiated arthritis
- Fits no other category
- Fits more than one category

This classification is currently being questioned. New classification schemes are suggested to incorporate ANA status, age of onset, and symmetry of arthritis[2] but cytokines, genetics, and gene expression profiles might be promising fields to include in future classification[3-8].

Usually children with JIA are first seen by an orthopedic surgeon or a pediatrician and referred to a pediatric rheumatologist in a later stage[9].

As damage to the joints can be prevented by early and adequate medical therapy, permanent postacademic education on the subject of rheumatic diseases in childhood is mandatory in order to obtain early referral of children with a suspicion of inflammatory arthritis.

Having (a child with) JIA creates a considerable burden for the child, the family, friends, and school[10] and interventions have been developed to reduce the impact of the disease[11]. The importance of adequate patient and parent information and education is emphasized[12].

Definitions

Oligoarticular JIA is defined as arthritis in one to four joints during the first 6 months with exclusion of

- psoriasis, diagnosed by a dermatologist in at least one first or second grade family member;
- Human leukocyte antigen-B27 (HLA-B27) associated disease in at least one first or second grade family member;
- Presence of RF;
- Arthritis in a boy older than 8 years and HLA-B27 positive;
- Systemic JIA.

In children with persistent oligoarticular JIA the number of joints involved remains four or less throughout the course of the disease. In extended oligoarticular JIA the arthritis shows extension to polyarthritis after the first 6 months.

IgM RF negative polyarticular JIA is defined as arthritis in five or more joints during the first 6 months with negative tests for IgM RF and exclusion of systemic JIA.

IgM RF positive polyarticular JIA is defined as arthritis in five or more joints during the first 6 months and presence of the IgM RF on two occasions with an interval of 3 months with the exclusion of systemic JIA.

PREVALENCE/EPIDEMIOLOGY

Joint pain, joint swelling, and morning stiffness are not uncommon in childhood. However, only a minority of children with these symptoms, suggestive of arthritis, are diagnosed with JIA by objective criteria and thorough physical examination performed by an experienced (pediatric) rheumatologist. The exact incidence and prevalence of JIA is unknown. Studies on these topics have shown different results, influenced by the different populations that have been studied as well as ethnicity and environmental factors[13, 14]. Also seasonal variation has been described, even in the month of birth[15]. The incidence probably varies from 11 to 35 per 100,000 in the population[16].

Using the American College of Rheumatology criteria, the prevalence of JIA also shows a considerable variability ranging from 15 to 150 per 100,000[13]. Several studies on the prevalence of JIA have suggested that these figures might underestimate the true prevalence. Close examination of the children under study and restriction to those who are at risk will probably lead to a considerably increase in the prevalence of JIA. A trend toward increasing incidence of JIA is observed, unclear whether due to greater awareness or a real increase in patients[14].

Although JIA can be divided into different categories with different peak incidences of age, it is obvious that despite these differences, generally more girls than boys develop JIA except for the systemic onset type.

ETIOLOGY AND PATHOGENESIS

JIA probably has a multifactorial etiology[17]. Genetic predisposition, environmental influences, provoking infections, hormonal factors, and vulnerability in childhood are involved in the development of JIA[18]. The genetic predisposition includes multiple genes that are related to immunity and inflammation.

Genetic Predisposition

HLA class I and class II alleles are both associated with an increased risk to develop JIA. The last decade's research in this field has expanded. It is estimated that genetical factors account for 13% of the risk in JIA[19]. Early-onset oligoarticular JIA in girls is related to the class I antigen HLA-A2. Persistent and extended oligoarticular JIA are associated with class II antigens HLA-DRB108 and HLA-DRB111, DQA104, DQA105, and DQB104. Enthesitis-related JIA is associated with HLA-B27 (class I) and the class II antigens HLA-DRB101 and HLA-DQA10101. Systemic-onset JIA is related to HLA-DRB111. HLA DR4 is associated with RF-positive disease, like in adult disease[20].The genetical associations of JIA were recently reviewed by Cobb[21]. Non-HLA immune regulatory genes are also involved, and the list has expanded in the last years to include PTPN22[22] STAT4[23], TRAF-C5[24], TNF308a, 4q27[25], DNAM-1[26], and VTCN1[27], although not all of them have been independently replicated yet.

The genetic predisposition also includes genes that are related to cytokine production[28]. Nowadays, JIA is thought to be triggered by an initial adaptive immune response toward an unknown autoantigen. Right after this event, almost all cells of the immune system start to be involved. T-lymphocytes, cytokine production, immune complexes (ICs), and immunodysregulation all lead to inflammation of the joint.

Cytokines that are involved in the pathogenesis of nonsystemic JIA are tumor necrosis factor (TNF)-a, IL-1, IL-2, IL-4, IL-6, IL-7, IL-18, and IL2R[29, 30]. Concentrations of these cytokines are increased, both in plasma and in the synovial fluid. IL-1a and IL-1ß are both particularly involved in oligoarticular and polyarticular JIA and related to disease activity. Increase of IL-1a has been detected in plasma and increase of IL-ß in synovial fluid. Soluble TNF-a is also increased in plasma as well as synovial fluid in the more restricted disease types of oligoarticular disease. IL-4 is more prominent in the synovium[31]. IL-17 can induce production of IL-6, MMP-1 and -3, and IL-8 at the synovium, which all can lead to joint damage[32].

During phases of clinical remission, cytokines do not return to a normal healthy-control situation but reflect a condition of compensated inflammation[33].

Bacterial infections not only can cause reactive arthritis, but are also involved in the development of JIA. In children with JIA humoral as well as cellular immune responses against bacterial heat shock proteins (HSPs) have been described. These HSPs are highly conserved proteins of bacterial origin and have been demonstrated in plasma and synovial fluid of JIA patients. T-lymphocyte responses to HSP-60 were demonstrated before remission of JIA and it thus has been speculated that induction of immunotolerance to specific T-cells might be beneficial for JIA patients, and nasal administration of HSP-60 might be used as future immunotherapy[34, 35]. In 2011 HSP-60 serum concentrations were found to be predictive for disease flare[36].

Complement activation is also involved in the pathogenesis of JIA. Complement components of both the classical pathway (C4) and the alternative pathway (Bb) showed increased levels and correlated with disease activity[37, 38]. Mannose-binding lectin (MBL) is a major component of the lectin route of complement activation. An increased frequency of mutations in exon 1 of the MBL2 gene has been demonstrated in RA and JIA patients, indicating a possible role of MBL deficiency in the pathogenesis of JIA[39, 40]. The possible role of infection in JIA has also been demonstrated by increased incidence of chronic arthritis in patients with hypogammaglobulinemia, IgA deficiency, and C2 deficiency[41].

Furthermore, MBL deficiency might lead to defective clearance of ICs and apoptotic cells, as seen in individuals with C1q deficiency. Partial C4 deficiency has also been linked to JIA[42]. Recently the alternative pathway was suspected to be involved in oligoarticular JIA[43].

Circulating immune complexes (CICs) have been demonstrated in JIA. These CICs have been detected in plasma and synovial fluid and revealed complement activation as well as

cytokine secretion potential. The CICs correlated with disease activity and systemic features of JIA[37]. The activating capacity of CICs is related to their size. Although often undetectable in plasma of JIA patients, IgM RF is bound to the ICs and concentration of this RF is related to disease activity[44]. Membrane-attack complex bound to CICs correlated significantly with erythrocyte sedimentation rate (ESR), further supporting the notion of complement-mediated tissue injury that is triggered by IC-mediated classical pathway activation[45].

The T-lymphocyte-mediated immune response is important in chronic inflammation. T-lymphocytes are the most prominent mononuclear cells in synovial fluid. The T-lymphocytes can be differentiated in CD4 (helper/inducer) and CD8 (suppressor/cytotoxic) cells with different functional abilities.

An impaired thymic function, reflected by a decrease in CD4+ T-cells, was described in oligoarticular and polyarticular JIA[46]. Recently the same phenomenon of premature aging was observed for CD8+ T-cells in JIA patients[47].

The results of different studies on the possible pathogenetic role of CD4+ and CD8+ T-lymphocytes have been inconsistent[18]. Increased CD8+ T-lymphocytes have been demonstrated in systemic and polyarticular JIA; however, other studies showed decreased CD8+ T-lymphocytes, especially in systemic disease[48].

Regulatory T-cells (T-regs) first described by Sakaguchi[49] are increasingly thought to play a role in the pathogenesis of (the remitting course of) JIA[50]. These cells are characterized by expression of FOXP3, a transcriptional factor, necessary for the control of inflammation. Recently a review on the emerging role of the T-regs was published[51].

Co-expression of CD25 and FOXP3 in combination with a hypomethylated region within the FOXP3 gene, called the Treg-specific demethylated region, is considered the hallmark of stable T-regs. Recently it was discovered that environment-specific breakdown in FOXP3 stability may threaten the abrogation of inflammation in JIA[51].

Natural (thymic derived) and adaptive T-regs exist, but cannot be discerned as of this writing[51]. It seems that T-regs are heterogeneous and can differ in function. T-regs can be divided by HLA expression (DR+ and DR-)and by cellular markers (naive or memory). In oligoarticular JIA, at the site of inflammation T-regs of the activated memory phenotype are present.

Th17 cells, a subset of the CD4+ effector T-cells producing IL-17, are also present at the site of inflammation[52] and have a reciprocal relation to T-regs[53]. Both need TGF-beta for induction and the T-regs and Th17 cells need to be balanced in a healthy-state situation. T-regs even seem to be able to convert into Th17 cells under certain circumstances[54].

In 2004 it was discovered that in JIA the numbers of T-regs are in fact paradoxically increased in the inflamed joint[55]. Serum Treg numbers, on the other hand, are normal or decreased in O-JIA. In SF of persistent oligoarticular JIA patients the numbers of T-regs are higher than in SF of extended to-be JIA patients. It is hypothesized that the balance between T-regs and Th17 cells is crucial in JIA and that they behave in a reciprocal relationship at the site of inflammation[56].

Possibly T-regs are dysfunctional in JIA? Studies suggest that the T-regs function well (are potent suppressors of inflammation) when taken out of the synovium, suggesting a role for the microenvironment affecting the T-regs in their function.

Dendritic Cells

Dendritic cells (DCs) are antigen-presenting cells, necessary for T-cell activation. Evidence for their suspected role in the initiation and perpetuation of inflammation is scarce. Increased numbers of DC in synovial fluid have been described in oligoarticular and polyarticular JIA[57]. B-cell concentration is normal in oligoarticular and polyarticular JIA, however generally increased in patients with systemic JIA. Total levels of IgG might be elevated and a diversity of autoantibodies can be detected in sera of JIA patients.

Like IgM rheumatoid-factor JIA, anticyclic citrullinated peptide (CCP) is associated with erosive disease[58]. The pathogenesis of JIA is also influenced by psychological factors. Dysregulation of the autonomic nervous system is related to impaired immunologic response and possible development of autoimmune disease[59].

Gene Expression Profiling

Gene expression profiling, also known as transcriptomics, measures the expression level of mRNAs (transcripts) in a cell population at a certain time. In oligoarticular JIA, gene expression profiling on synovial fluid could help predict patients with an extended disease phenotype[60]. In polyarticular JIA, recently it was shown that gene expression was linked to therapeutic outcome at 6 months[61]. Furthermore, in polyarticular JIA, remission could be genomically characterized and differed markedly between methotrexate (MTX) and MTX/etanercept-induced remission. At the therapeutic level, gene expression profiles were studied before and after MTX administration to analyze differentially expressed

genes. A gene was identified that could contribute to genetic variability in MTX response[6, 62, 63]. Clinical remission on medication and clinical remission reflect states of balanced homeostasis between pro-and anti-inflammatory since gene expression profiling differed between healthy controls and the aforementioned categories[33].

Myeloid-Related Protein 8/14 (S100A8/A9), S100A12

These calcium-binding proteins produced by activated neutrophils and monocytes are present in the serum of patients with both oligoarticular and polyarticular JIA, next to their extreme elevation in active systemic JIA. These danger signals increase before clinical flare is obvious and therefore have predictive value. The serum concentrations of S100A8/A9 and S100A12 are related to the amount of inflammation[64, 65]. Levels to predict disease flares have been determined and an ELISA is commercially available[66].

Clinical Manifestations

When taking a history of (parents of) children with JIA pain is usually not a major symptom at onset[67], but the parents of young children may have noticed a regression in the motor phase of their child[68]. An asymmetric pattern is especially alarming. Swelling of the knee or ankle is often noticed by chance when parents are undressing or bathing the child. Other signs at onset can be behavioural problems, limping, or refusal to walk. In older children, especially in those with (IgM RF positive) polyarticular JIA, pain can be a presenting symptom. General malaise, low-grade fever, and fatigue can be present in severely affected children, mostly in those with polyarticular JIA. Morning stiffness and stiffness after spending prolonged time in the same position are common. The onset of JIA may be acute but usually is insidious.

At physical examination the general condition of the child should be noticed. They may look anemic and, when suffering from systemic features, ill and in pain. Length and weight should be measured regularly as general growth impairment points at active disease and this may be aggravated by prolonged use of glucocorticoids, which is, in the biological era, becoming less common. In children with IgM RF-positive polyarticular JIA rheumatoid nodules at the extensor surface of the elbows or at the lateral sides of the feet can be found.

Asymmetrical diffuse edema of hands or lower leg and ankle in a sock-like form can be found in some children with polyarticular JIA[69]. This lymphedema is usually non-pitting and not painful.

In children with JIA who develop chronic anterior uveitis (CAU) before the onset of arthritis secondary changes in the eyes can be noticed, irregular pupils that do not respond properly

to light may reflect the presence of synechia. Calcifications of the cornea may be present in the form of band keratopathy.

Signs of arthritis are local swelling, increased temperature, pain elicited by movement, and limitation of motion. Local discoloration is very unusual except over the small joints in the hands and feet[70], and when present over a knee or ankle should be a reason for reconsideration of the JIA diagnosis.

Establishing arthritis can be difficult, especially in young children with baby fat. An observation by an experienced child physiotherapist and/or the use of ultrasound or MRI with gadolinium enhancement can be helpful[71]. In children with oligoarticular JIA asymmetric swelling of large joints like the knee, ankle, and elbow are most frequent, while in children with polyarticular JIA symmetric involvement of the small joints of the hands and feet is more common. In children with IgM RF swelling around the styloid processus of the ulnar can be prominent. Several complications may develop in children with oligoarticular and polyarticular JIA.

Impaired growth and delay of puberty may be the result of disease activity[72] and the (currently outdated) chronic use of glucocorticoids aggravates the impairment of linear growth. Muscle atrophy and leg length discrepancy by accelerated local growth are findings in longstanding asymmetric arthritis[73]. Decreased bone mineral content can be observed in a quarter of children with early onset JIA[74]. Osteopenia can be detected in adolescents with early onset JIA[75].

Cardiac manifestations are rare but may be the cause of significant morbidity, especially valvular disease in RF-positive polyarticular JIA[76]. Parenchymal lung disease is an infrequent finding, but pulmonary function is impaired in some children with JIA[77].

Temporomandibular involvement is common in children with oligoarticular and polyarticular JIA[78, 79]. Because of the high prevalence and discrepancy between clinical signs and presence of arthritis in the temporomandibular joint, regular orthodontic evaluation and orthopantomograms are recommended to enable early intervention[78]. Involvement of the temporomandibular joints may lead to impaired opening of the mouth and retrognatia.

Chronic Anterior Uveitis (CAU) is reported in up to 10-20%[80, 81] of patients with JIA, and is the main secondary disease in JIA. It is associated with the presence of ANA. All children with JIA need to be screened with regular intervals (see Table 1.2) as this type of uveitis is asymptomatic until complications develop. The classic presentation of CAU is an anterior,

nongranulomatous, uni-or bilateral uveitis. Slit-lamp examination is necessary to detect the inflammatory cells in the anterior chamber of the eye. It is therefore essential that all children with JIA are seen by an ophthalmologist at regular intervals.

Early detection and treatment of CAU is of major importance to avoid sight-threatening complications including band keratopathy, synechia, cataract, glaucoma, macular edema, decreased vision, phthisis bulbi, and blindness[82]. Young age of onset (arthritis and uveitis), active uveitis at the time of onset of arthritis, and high uveitis activity at the time of diagnosis is associated with a higher risk of sight-threatening complications. The recommended frequency is listed in Table 1.2.

Generally patients with JIA are divided into high-and low-risk groups depending on known risk factors for uveitis. Risk factors are young age of onset, female gender, and oligoarticular onset of JIA. Onset of arthritis usually precedes the onset of uveitis, but uveitis may also start first. The risk of developing uveitis is the highest shortly after onset of arthritis and decreases gradually after the first year[83].

DIAGNOSTIC INVESTIGATIONS

In all children with chronic arthritis a full blood count is indicated. In most children with oligoarticular JIA normal hemoglobin levels are found. In some children with oligoarticular JIA with high disease activity and in children with polyarthritis moderate normocytic, hypochromic anemia can be present characteristic of the chronic anemia of inflammation[84]. Anemia and raised platelet count are associated with a less favorable prognosis.

In a child with other systemic features like fever, skin rash, and lymph node enlargement other diagnosis like systemic JIA, other autoimmune diseases (such as systemic lupus erythematosus, SLE), or malignancy should be considered.

The leukocyte count usually is normal. In children with active disease leukocytosis may be present. During treatment with sulfasalazine or MTX a low leukocyte count may represent drug-induced bone marrow suppression. In a child with possible JIA a low leukocyte count could be the key to another diagnosis; for example, SLE or leukemia. Platelets are within the normal range in most children with oligoarticular and polyarticular JIA, but may be raised in children with high disease activity.

Table 2.2 | Recommended frequency of Ophthalmological Investigation in Children With Persistent or Extended Oligoarticular Juvenile Idiopathic Arthritis According to the American Academy of Paediatrics (1993)

Subtype of Arthritis	Onset of Arthritis (Years of Age)	
	< 7 years[a]	≥ 7 years[b]
Persistent oligoarticular		
+ANA	H[c]	M
– ANA	M	M
Extended oligoarticular		
+ANA	H[c]	M
– ANA	M	M

H: high risk = every 3-4 months ophthalmological investigation.
M: medium risk = every 6 months ophthalmological investigation.
L: Low risk = every 12 months ophthalmological investigation (all other patients with JIA).
[a] All patients are regarded low risk 7 years from onset of arthritis; ophthalmological investigation yearly.
[b] All patients are regarded low risk 4 years from onset of arthritis; ophthalmological investigation yearly.
[c] All patients are regarded medium risk 4 years from onset of arthritis.

The acute phase reactants (ESR, C-reactive protein (CRP) levels) can be normal in children with JIA, but may be raised at onset of the disease and during exacerbations[85]. Blood chemistry is usually not abnormal at onset of JIA. The level of serum urea can increase during the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Liver function tests need to be carefully followed during the use of SSZ and MTX. In the diagnostic phase, broad screening for infectious causes of arthritis is indicated as a variety of microorganisms may induce arthritis (see differential diagnosis).The onset of JIA and its exacerbations are frequently preceded by infections[86]. In children with active (poly)arthritis, a raised IgG can be present. In children with oligoarticular JIA the IgA may be low or even absent. During treatment with sulfasalazine the level of IgA may decrease[87].

ANAs are found in about 75% of children with oligoarticular JIA and in 50% of children with polyarticular JIA[8, 88]. Their presence is strongly associated with the risk of developing CAU but does not seem to be associated with the severity of the uveitis[81]. A positive ANA is rare in children, but can be a temporary false-positive finding in infections (streptococci, viral). Antibodies to dsDNA are usually not found. When they are detected the child could have SLE. Antibodies to extractable nuclear antigens (anti-ENA) are rarely present; anti-ENA may indicate other autoimmune diseases such as mixed connective tissue disease (MCTD).

Tests for the IgM RF are less frequently positive in children with JIA than in adults with RA. In 5-10% of children with JIA, IgM RF can be detected during the course of the disease.

Their presence is associated with onset of disease in girls around 13 years of age with clinical signs as in RA, progressive disease, and early erosions. Anti-CCP antibodies can be detected in the sera of patients with JIA but almost exclusively in the subset of children with IgM RF-positive disease[58].

Serum complement levels usually are within the normal ranges, but may be elevated at onset and during exacerbations of the illness.
Analysis of the synovial fluid may provide valuable information in the diagnostic phase of a child with monoarthritis. The number of leukocytes reflects the severity of inflammation. A low leukocyte count (<2x 10^9) is unlikely in infectious arthritis and suggests a mechanical disorder of the joint. Gram preparation and culture are indispensable to rule out infection. Polymerase chain reaction (PCR) for Borrelia burgdorferi and Mycobacterium tuberculosis are available.

In children with oligoarticular and polyarticular JIA the synovial fluid is yellow with decreased viscosity. The white cell count is usually around 20,000 x 10^9/L with predominantly polymorphonuclear neutrophils and mononuclear cells.
In a child with a chronic monoarthritis without circulating ANA, a synovial biopsy can be necessary to exclude local abnormalities of the synovial membrane when MRI findings are insufficient to make a diagnosis. In children with JIA the histological finding is an aspecific chronic inflammation. For the follow-up of radiological damage by JIA plain X-rays can be used. But in the changing era with early initiation of highly effective therapies there is a need for more sophisticated imaging modalities, more sensitive in detecting pre-erosive changes. Ultrasound and MRI are suitable to serve that purpose, but have not been validated yet[88-90]. The growing skeleton gives rise to numerous physiological changes over time which need to be taken into account during ultrasound and MRI examinations. There is an urgent need for normal values regarding ultrasound and MRI in healthy children. Up to the time of this writing, the exact value of MRI and ultrasound in detecting disease activity in JIA needs to be determined.

Ultrasound can be a useful tool, but is not validated yet for detection of synovitis[89]. Subclinical synovitis on ultrasound is present in 3% of JIA patients in clinical remission. Subclinical synovial abnormalities are not related with early flare, in contrast with RA patients[90].

Pediatric scoring systems for MRI have been developed and are validated[91-93]. Recently a study showed that MRI is a promising biomarker in measuring therapeutic response[94]. Evidence-based points regarding the role of imaging in JIA are summarized and have been published[71].

At plain X-rays, at onset of the disease, usually only soft tissue swelling and periarticular osteoporosis can be detected. During the course of disease various radiological abnormalities may develop[95]. Ossification centers can develop earlier by increase of blood flow in the involved extremity, resulting in overgrowth but eventually premature closing of the epiphysis may lead to stunting of bone growth. Loss of cartilage can be reflected by narrowing of the joint space. Development of erosions in an early stage can be present in children with IgM RF polyarticular JIA. A radiological scoring system for children with JIA has been developed[96].

DIFFERENTIAL DIAGNOSIS

Joint complaints are relatively frequent in childhood, but usually self-limiting and seldom require referral to a hospital. For a correct differential diagnosis, a clear difference must be made between myalgia, arthralgia, arthritis, and possible involvement of the bones.

Infectious arthritis as well as reactive arthritis often have an acute onset and will recover with or without medication within approximately 6 weeks. Duration of arthritis of more than 6 weeks is called chronic arthritis. The most frequent cause of chronic arthritis in childhood is JIA. Not only infection or inflammatory diseases can cause complaints of the joints; other possibilities include traumatic, metabolic, hematological, malignant, and even psychogenic causes[97].

Infectious or bacterial arthritis is an acute illness, also called septic arthritis[98]. The child with septic arthritis is often very ill with high fever, and refuses to use the involved joint. One of the most important characteristics is extreme pain. Bacteria can enter the joint either by hematological spread or directly by penetration of the skin. Physical examination should include inspection of the skin to detect a porte d'entrée, which might lead to identification of the microorganism. Most frequently involved microorganisms are Staphylococci and Streptococci. When bacterial arthritis is suspected, puncture of the joint to obtain synovial fluid should be performed for analysis on leukocyte count and bacterial culture. In recent years the occurrence of Kingella kingae as a pathogenic microorganism is increasingly recognized in cases of septic arthritis. This Gram-negative bacterium is the number one causative organism of septic arthritis in the age group 6-36 months[99, 100]. It is recommended to have a high index of suspicion in young children presenting with joint inflammation, especially in cases of mildly elevated inflammatory markers[101]. PCR techniques for detection of K. kingae are therefore advocated. K. kingae is generally susceptible to the main antibiotics used in children with osteoarticular infections. The clinical course after

treatment initiation is benign. It should be taken into account that osteomyelitis in the vicinity of a joint may give a clinical picture similar to that of infectious arthritis without yielding a positive culture of the synovial fluid[102]. Another microorganism that can cause arthritis is B. burgdorferi[103]. Lyme arthritis is often preceded by erythema migrans, myalgia, and arthralgia, which can be followed by recurrent as well as chronic arthritis[104]. Only in the minority of the patients is a tick bite remembered. After the erythema migrans, arthritis can develop even after months, often starting in one or both knees in episodes. Chronic arthritis occurs in approximately 20% of patients with Lyme arthritis, most frequent as monoarthritis of the knee. Diagnostic tests include PCR of synovial fluid and serology. The presence of anti-Borrelia IgG antibodies is not definite proof of Lyme arthritis because 5% of the adult population have positive IgG antibodies due to asymptomatic infection in the past. Anti-Borrelia IgM antibodies turn positive after approximately 6 weeks and are present for months, whereas IgG antibodies can be detected for years. Lyme arthritis eventually has a relatively good prognosis with complete recovery but a substantial proportion of patients need more than one course of antibiotics and/or additional treatment with NSAIDs, disease-modifying antirheumatic drugs (DMARDs), intra-articular steroids, or even synovectomy[105].

Arthritis can also develop after viral infections such as parvovirus, rubella, and hepatitis B, as well as viruses of the herpes group, adenoviruses, and para-myxoviruses[106]. Most of these viral infections will lead to reactive arthritis, and detection of the virus in the synovial fluid is often negative. Viral arthritis generally completely resolves within 6 weeks although chronic duration is possible. Arthritis can develop even after vaccination. Clinical presentation, viral exanthema, and duration of the arthritis are helpful in the diagnosis of possible viral arthritis.

Mycoplasma pneumonia is another microorganism that can cause arthritis as well as spondylarthropathy in children[107]. Important symptoms include fever, cough, headache, and myalgia. Approximately 30% of the children with M. pneumonia infection will develop arthritis.

Reactive arthritis can develop after viral infections, Neisseria meningococci infection, as well as gastroenteritis by Salmonella, Shigellla, Campylobacter, or Yersinia[108]. Reiter's syndrome is an example of reactive arthritis, associated with HLA-B27, characterized by the triad of arthritis, conjunctivitis, and urethritis[109]. Acute rheumatic fever (ARF) is caused by Group A beta-hemolytic Streptococci (GABHS)[110]. It develops approximately 3 weeks after the GABHS infection, characterized by angina, high fever, illness, and headache. A sore throat is not always present. Arthritis is present in 80% of the patients, often with acute onset, painful polyarticular, migrating from one joint to another, and preferentially involving

the large joints of the lower extremities[111]. The diagnosis of ARF is made according to the Jones criteria[112]. Carditis with possible heart failure is an important complication of ARF that occurs in 50% of patients. Mitralis valve and aorta valve stenosis can develop[113]. Other complications include Sydenham's chorea, subcutaneous noduli, erythema marginatum, and (cutaneous) vasculitis[114]. When carditis is present, prophylactic antibiotic therapy (penicillin) is indicated according to the American Heart Association[115].

Reactive arthritis can develop after an infection with Streptococci without fulfilling the Jones criteria[116, 117]. This arthritis is often less severe and not migrating, but with a longer duration. Other Streptococci species in addition to GABHS can cause this form of arthritis[118]. Diagnostic tests include bacterial culture of the throat, nose, and/or ears, as well as antistreptolysin-O-antibody titer and anti-Dnase-B[119, 120]. Polyarthritis can be the first clinical sign of other autoimmune diseases like SLE, juvenile dermatomyositis, scleroderma, Sjögren syndrome, MCTD, and systemic vasculitis. Apart from arthralgia, arthritis, and myalgia, these autoimmune diseases are characterized by organ involvement and positive autoantibodies. Hemophilia and sickle cell disease are both hematological disorders with possible involvement of the joint. Vaso-occlusive episodes can be very painful and difficult to distinguish from arthritis[121]. Malignancies like leukemia, lymphoma, Hodgkin disease, osteosarcoma, Ewing sarcoma, as well as neuroblastoma can lead to bone pain, arthralgia, and/or swelling of joints. Nocturnal bone and joint pain is one of the most characteristic clinical signs for malignancy. Differentiation between systemic JIA and malignancy can be difficult when general malaise, fever, anemia, and leukocytosis are present[67, 102, 122-126].

Another group of diseases that can present with arthritis, as well as arthralgia or myalgia, is the rare group of periodic fever syndromes like familial Mediterranean fever; hyper IgD syndrome; TNF receptor-1 associated periodic syndrome; Muckle-Wells syndrome; and periodic fever, aphtous stomatitis, pharyngitis, and adenitis[127]. These genetic diseases are also known as auto-inflammatory disorders. Other possible causes of arthritis and arthralgia in childhood include coxitis fugax, Perthes disease, epiphysiolysis, Osgood-Schlatter disease, chondromalacia, hypermobility syndromes, and trauma[128].

TREATMENT

The treatment of children with JIA is mostly medical but physiotherapy and other non-pharmacological therapies are also of importance in some patients. Nowadays, children are less frequently referred to a rehabilitation center where therapies can be organized in a multidisciplinary way. In the last two decades an expanding spectrum of effective drugs has

become available[129]. The arrival of biologicals has made a significant difference initially to children who were refractory to previously used anti-rheumatic drugs. But as time progressed biologicals were prescribed earlier to JIA patients[130]. Nowadays the biggest challenges are to select the right JIA patients for treatment with biologicals[131] and to choose the optimal moment to apply them. Furthermore, a concern is how to deal with biosimilars in the treatment of patients with JIA. Long-term safety is guarded by the use of international databases.

Outcome Measures

To measure efficacy of medical treatment a definition of improvement[132] has been developed using a core set of outcome variables and a definition of remission (clinically inactive disease, CID) is available[133]. Definitions have followed for clinical remission on (CID on 6 months therapy) and off medication (CID for more than 12 months off therapy)[134]. More recently the juvenile arthritis disease activity score (JADAS) was developed[135], including cut-off values[136] summarized in table 1.3.

Increasing evidence[137, 138] advocates the early initiation of therapy depending on mild, moderate, or severe disease clinical characteristics. Several guidelines for children with oligoarticular and polyarticular JIA are available and summarized in the paper by Hinze et al[88,87]. Illustrative algorithms for children with oligoarticular and polyarticular JIA can be found in the paper by Beukelman[139].

Drugs Used in Children With JIA

NSAIDs are effective in suppressing fever and signs of inflammation such as pain and stiffness. Naproxen, ibuprofen, and indomethacine are frequently used. Pseudoporhyria can occur with the propionacid derivatives like naproxen and ibuprofen and induce scarring of sun-exposed areas. Indomethacine can cause headache and malaise in some children.

As DMARDs hydroxychloroquine, sulfasalazine, MTX, and leflunomide are used. Regular blood checks are advised, especially liver function tests. Retinopathy can occur as an adverse reaction to hydroxychloroquine accumulation. Ophthalmological follow-up is advised every 6 months. Sulfasalazine is effective and safe in children with oligoarticular and polyarticular JIA, but not well tolerated in about one-third of children[140]. Sulfasalazine may induce or worsen low levels of IgA[87]. Nowadays sulfasalazine is mainly reserved for the category of JIA with enthesitis[139]. MTX has gained the position of gold standard for RA and is also very effective in JIA patients[141, 142] as monotherapy, but also in combination therapy with a biological[143-145]. It is administered once a week as tablets or subcutaneous injection. The use of folic acid can decrease nausea, malaise, and mucosal ulcerations[146].

Table 2.3 | Definitions of Disease Status an Juvenile Arthritis Disease Activity Score Cut-off Values

Clinical Condition	Cut-off Value
Clinical remission	1
Minimal disease activity	Oligo 2 Poly 3.8
Acceptable symptom state	Oligo 3 Poly 4.3
Low disease activity	One or no active joints, normal ESR of C-reactive protein, physician global assessment of overall disease activity score < 3 (0-10), patients/parent GA of overall well-being score < 2 (0-10)

In some children anti-emetics are necessary to alleviate the weekly misery of MTX. During high-dose treatment with MTX, vaccination with live attenuated viruses should be avoided. Further advice on vaccinations in JIA patients is summarized in the European League Against Rheumatism recommendations by Heijstek et al[147]. Leflunomide is tolerated well by most children with slightly less efficacy as MTX[148]. The use of systemic glucocorticoids should be restricted to life-threatening complications. In some children low-to-medium doses glucocorticoids are used to bridge the interval between start and moment of effectiveness of DMARDs. Glucocorticoids are mainly used as intra-articular injection with good results[149] and no short-term adverse effects on the cartilage. Leakage to the system may induce secondary Cushing syndrome[150]. Triamcinolonhexacetonide has shown to be superior to triamcinolonacetonide judged by the duration of remission[151]. The biologicals have extended the therapeutic arsenal for children with therapy-resistant JIA. To hamper TNF-a both soluble receptors (etanercept) as blocking antibodies (infliximab, adalimumab) are available, but for the use in children only etanercept and adalimumab are registered. The child has to fail on sufficiently high-dose MTX or show unacceptable side effects. About 75% of children with longstanding, resistant, polyarticular course JIA respond to etanercept in a blinded randomized controlled trial[152]. The clinical improvement lasts for over 2 years in the majority of patients[153] without significant adverse events[154]. Since 2008 abatacept, a CTLA4/IgG fusion protein-inhibiting T-cell activation by co-stimulation blocking, was added to the spectrum of therapeutics. In the original withdrawal trial[155] significantly more flares occurred in the placebo group compared to the abatacept group. It has to be noted that during the initial open-label period approximately 25% did not respond to abatacept, comparable to nonresponse rates as observed in TNF-a blockers. Tocilizumab is a humanized, monoclonal, IL-6-receptor antibody, inhibiting IL-6-mediated signaling. Recently the efficacy of tocilizumab in polyarticular course JIA was noted[156]; likewise, in a withdrawal trial design with significantly more flares in the placebo group compared to the tocilizumab group. Tocilizumab for polyarticular course JIA is dosed in 4-week intervals compared to 2-week intervals in systemic JIA. The GO-KIDS trial of golimumab

(a human monoclonal antibody that binds both to soluble and transmembrane TNF-a) in polyarticular course JIA has not met its primary and secondary end-points[157], therefore previously preventing golimumab from registration for JIA.

FUTURE

In the near future the development of other anticytokine-directed strategies (certolizumab, ustekinumab, tofacitinib)[158] holds great promise for the treatment of children with resistant JIA although the concerns about infections and long-term consequences remain[159].

Concerns of Infectious Complications During (Biological) Treatment

Large cohort studies in JIA patients have not revealed increasing numbers of severe infections, requiring hospital admission due to biological treatment[160]. Having JIA without DMARD treatment increased the changes on these complications twofold, which remained twofold with the use of MTX or biologicals irrespective of MTX. Swart et al. reported that additional biologicals increased the chances to severe adverse events and infections compared to MTX only[161].

Concerns of Opportunistic Infections During (Biological) Treatment

Opportunistic infections are rare in JIA patients. In almost 14,000 person-years of follow-up a few cases of coccidioides (occurring while not on biological treatment) and Salmonella were mentioned, as well as 32 cases of herpes zoster[164]. An increased incidence rate of herpes zoster in JIA patients on etanercept was confirmed by Nimmrich et al[162].

Concerns of Development of Other Autoimmune Diseases

Under the use of diverse biologicals, cases of other autoimmune diseases like demyelinating disease, inflammatory bowel disease, or the new development of autoantibodies have been documented, which is summarized in the manuscript by Swart et al[159].

Concerns on Malignancies During Biological Treatment

In 2008 a black-box warning on the use of biologicals in children with JIA was warranted by the FDA. To know the background rate of malignancy in JIA, it is essential to address this issue. Studies on this topic are scarce and difficult due to relative small sample sizes[163, 164]. Beukelman demonstrated no increase in malignancies due to use of TNF inhibitors, but in general a small increased rate of incident malignancy in JIA was noted[165]. Large registries are highly needed to gather information on this topic and initiatives to do so are evident both in the United States and Europe[159, 166]. Autologous stem cell transplantation was

used as an experimental treatment in children with therapy refractory polyarticular and systemic JIA[167] with significant mortality. In recent years less children were candidates for this procedure as a consequence of high effectiveness of biologicals. Complications are less common due to better treatment strategies, therefore diminishing the need for treatment of complications. The experimental use of recombinant human growth hormone restores linear growth and improves body composition in children with glucocorticoid-induced impaired growth and severe osteoporosis[168, 169].

The treatment of uveitis consists of topical and systemic drugs

Treatment recommendations for JIA-associated uveitis are summarized in a recent guideline[170]. Topical glucocorticoids are the first choice of treatment and sometimes are combined with mydriatic agents. Subtenon injections of steroids can be used. A large group of patients with uveitis need systemic treatment to achieve adequate disease control. Systemic glucocorticoids are effective, but the use should be minimized because of the harmful effects on bone and growth. Systemic glucocorticoids may also contribute to cataract formation and glaucoma. Intravenous pulses of glucocorticoids (30 mg/kg per dose with a maximum of 1g) may be effective at lower risk of side effects. MTX and cyclosporin A can be effective and glucocorticoid sparing, but reports about the use of immunosuppressive drugs are scarce[171]. Other agents that are reported to have some effect in smaller series are mycophenol mofetil, intravenous immunoglobulins, and anti-TNF-a drugs, especially adalimumab. Immunomodulatory therapy started early in the course of uveitis is associated with better visual acuity[172]. Several cases of a flare of uveitis or de novo development of uveitis are reported during the use of etanercept[154, 173, 174].

The use of abatacept in severe therapy refractory uveitis did not lead to sustained benefit in 21 patients[175].

PROGNOSIS

Literature on the outcome of JIA in the prebiological era described ongoing arthritis in almost half of the patients with polyarticular JIA after 10 years[176]. In addition, oligoarticular-onset JIA was shown to be a severe disease with frequent complications[177]. In 2003 Fantini et al. reported that 75% of their patients with a minimum follow-up of 10 years never reached remission[178]. The course of the disease and outcome depend on the category of JIA and the presence of IgM RF or ANA[179, 180]. Patients with ANA-positive JIA seem to constitute a homogeneous subgroup[181] and ocular complications determine visual prognosis in this subgroup[82, 172]. The prognosis of IgM-RF polyarticular JIA can be compared with that of RA in

adults. After introduction of the biologicals, outcome has improved due to earlier initiation of therapy and efficacy of TNF blockers and other biologicals reflected by almost 80% of JIA patients reaching an active joint count of 0 after 2 years in the ReACCh-Out cohort[182], although flares still frequently occur[183]. At this moment JIA remains a chronic disease with considerable psychosocial impact that often extends into adulthood[184], although outcome has improved over the years[185-187].

REFERENCES

1. Petty, R.E., *Growing pains: the ILAR classification of juvenile idiopathic arthritis.* J Rheumatol, 2001. 28(5): p. 927-8.
2. Martini, A., *It is time to rethink juvenile idiopathic arthritis classification and nomenclature.* Ann. Rheum. Dis, 2012. 71(9): p. 1437-1439.
3. Barnes, M.G., et al., *Subtype-specific peripheral blood gene expression profiles in recent-onset juvenile idiopathic arthritis.* Arthritis Rheum, 2009. 60(7): p. 2102-2112.
4. Griffin, T.A., et al., *Gene expression signatures in polyarticular juvenile idiopathic arthritis demonstrate disease heterogeneity and offer a molecular classification of disease subsets.* Arthritis Rheum, 2009. 60(7): p. 2113-2123.
5. Ravelli, A., et al., *Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis.* Arthritis Rheum, 2011. 63(1): p. 267-275.
6. Thompson, S.D., et al., *Heterogeneity in juvenile idiopathic arthritis: impact of molecular profiling based on DNA polymorphism and gene expression patterns.* Arthritis Rheum, 2010. 62(9): p. 2611-2615.
7. Eng, S.W., et al., *The biologic basis of clinical heterogeneity in juvenile idiopathic arthritis.* Arthritis Rheumatol, 2014. 66(12): p. 3463-3475.
8. van den Broek, T., et al., *Cytokine profiling at disease onset: support for classification of young antinuclear antibody-positive patients as a separate category of juvenile idiopathic arthritis.* Ann. Rheum. Dis, 2015. 74(2): p. 470-472.
9. Cuesta, I.A., et al., *Subspecialty referrals for pauciarticular juvenile rheumatoid arthritis.* Arch. Pediatr. Adolesc. Med, 2000. 154(2): p. 122-125.
10. Stinson, J.N., et al., *Jointly managing arthritis: information needs of children with juvenile idiopathic arthritis (JIA) and their parents.* J. Child Health Care, 2012. 16(2): p. 124-140.
11. Akikusa, J.D. and R.C. Allen, *Reducing the impact of rheumatic diseases in childhood.* Best. Pract. Res. Clin. Rheumatol, 2002. 16(3): p. 333-345.
12. Len, C.A., M.e.S. VB, and M.T. Terreri, *Importance of adherence in the outcome of juvenile idiopathic arthritis.* Curr. Rheumatol. Rep, 2014. 16(4): p. 410.
13. Thierry, S., et al., *Prevalence and incidence of juvenile idiopathic arthritis: a systematic review.* Joint Bone Spine, 2014. 81(2): p. 112-117.
14. Oberle, E.J., J.G. Harris, and J.W. Verbsky, *Polyarticular juvenile idiopathic arthritis - epidemiology and management approaches.* Clin. Epidemiol, 2014. 6: p. 379-393.
15. Berkun, Y., et al., *Seasonality of birth of patients with juvenile idiopathic arthritis.* Clin. Exp. Rheumatol, 2015. 33(1): p. 122-126.
16. Berkun, Y. and S. Padeh, *Environmental factors and the geoepidemiology of juvenile idiopathic arthritis.* Autoimmun. Rev, 2010. 9(5): p. A319-A324.
17. Prakken, B., S. Albani, and A. Martini, *Juvenile idiopathic arthritis.* Lancet, 2011. 377(9783): p. 2138-2149.
18. Macaubas, C., et al., *Oligoarticular and polyarticular JIA: epidemiology and pathogenesis.* Nat. Rev. Rheumatol, 2009. 5(11): p. 616-626.
19. Hinks, A., et al., *Dense genotyping of immune-related disease regions identifies 14 new susceptibility loci for juvenile idiopathic arthritis.* Nat. Genet, 2013. 45(6): p. 664-669.
20. Thomson, W., et al., *Juvenile idiopathic arthritis classified by the ILAR criteria: HLA associations in UK patients.* Rheumatology. (Oxford), 2002. 41(10): p. 1183-1189.
21. Cobb, J.E., A. Hinks, and W. Thomson, *The genetics of juvenile idiopathic arthritis: current understanding and future prospects.* Rheumatology. (Oxford), 2014. 53(4): p. 592-599.

22. Hinks, A., et al., *Association between the PTPN22 gene and rheumatoid arthritis and juvenile idiopathic arthritis in a UK population: further support that PTPN22 is an autoimmunity gene.* Arthritis Rheum, 2005. 52(6): p. 1694-1699.

23. Ellis, J.A., et al., *Independent replication analysis of genetic loci with previous evidence of association with juvenile idiopathic arthritis.* Pediatr. Rheumatol. Online. J, 2013. 11(1): p. 12.

24. Albers, H.M., et al., *The TRAF1/C5 region is a risk factor for polyarthritis in juvenile idiopathic arthritis.* Ann. Rheum. Dis, 2008. 67(11): p. 1578-1580.

25. Albers, H.M., et al., *Association of the autoimmunity locus 4q27 with juvenile idiopathic arthritis.* Arthritis Rheum, 2009. 60(3): p. 901-904.

26. Reinards, T.H., et al., *CD226 (DNAM-1) is associated with susceptibility to juvenile idiopathic arthritis.* Ann. Rheum. Dis, 2014.

27. Albers, H.M., et al., *Genetic variation in VTCN1 (B7-H4) is associated with course of disease in juvenile idiopathic arthritis.* Ann. Rheum. Dis, 2014. 73(6): p. 1198-1201.

28. Moncrieffe, H., S. Prahalad, and S.D. Thompson, *Genetics of juvenile idiopathic arthritis: new tools bring new approaches.* Curr. Opin. Rheumatol, 2014. 26(5): p. 579-584.

29. Mangge, H., S. Gallistl, and K. Schauenstein, *Long-term follow-up of cytokines and soluble cytokine receptors in peripheral blood of patients with juvenile rheumatoid arthritis.* J. Interferon Cytokine Res, 1999. 19(9): p. 1005-1010.

30. de, J.W., et al., *Blood and synovial fluid cytokine signatures in patients with juvenile idiopathic arthritis: a cross-sectional study.* Ann. Rheum. Dis, 2007. 66(5): p. 589-598.

31. Murray, K.J., et al., *Contrasting cytokine profiles in the synovium of different forms of juvenile rheumatoid arthritis and juvenile spondyloarthropathy: prominence of interleukin 4 in restricted disease.* J. Rheumatol, 1998. 25(7): p. 1388-1398.

32. Agarwal, S., R. Misra, and A. Aggarwal, *Interleukin 17 levels are increased in juvenile idiopathic arthritis synovial fluid and induce synovial fibroblasts to produce proinflammatory cytokines and matrix metalloproteinases.* J. Rheumatol, 2008. 35(3): p. 515-519.

33. Knowlton, N., et al., *The meaning of clinical remission in polyarticular juvenile idiopathic arthritis: gene expression profiling in peripheral blood mononuclear cells identifies distinct disease states.* Arthritis Rheum, 2009. 60(3): p. 892-900.

34. van, E.W., R. van der Zee, and B. Prakken, *Heat-shock proteins induce T-cell regulation of chronic inflammation.* Nat. Rev. Immunol, 2005. 5(4): p. 318-330.

35. Albani, S. and B. Prakken, *T cell epitope-specific immune therapy for rheumatic diseases.* Arthritis Rheum, 2006. 54(1): p. 19-25.

36. Wu, C.T., et al., *Serum heat shock protein 60 can predict remission of flare-up in juvenile idiopathic arthritis.* Clin. Rheumatol, 2011. 30(7): p. 959-965.

37. Jarvis, J.N., et al., *Immune complex size and complement regulate cytokine production by peripheral blood mononuclear cells.* Clin. Immunol, 1999. 93(3): p. 274-282.

38. Aggarwal, A., et al., *Evidence for activation of the alternate complement pathway in patients with juvenile rheumatoid arthritis.* Rheumatology. (Oxford), 2000. 39(2): p. 189-192.

39. Gergely, P., Jr., et al., *Structural polymorphisms in the mannose-binding lectin gene are associated with juvenile idiopathic arthritis.* J. Rheumatol, 2009. 36(4): p. 843-847.

40. Dolman, K.M., et al., *Mannose-binding lectin deficiency is associated with early onset of polyarticular juvenile rheumatoid arthritis: a cohort study.* Arthritis Res. Ther, 2008. 10(2): p. R32.

41. Davies, K., et al., *Juvenile idiopathic polyarticular arthritis and IgA deficiency in the 22q11 deletion syndrome.* J. Rheumatol, 2001. 28(10): p. 2326-2334.

42. Gilliam, B.E., A.E. Wolff, and T.L. Moore, *Partial C4 deficiency in juvenile idiopathic arthritis patients.* J. Clin. Rheumatol, 2007. 13(5): p. 256-260.

43. Brunner, J., et al., *Analysis of the classical, alternative, and mannose binding lectin pathway of the complement system in the pathogenesis of oligoarticular juvenile idiopathic arthritis.* Rheumatol. Int, 2012. 32(6): p. 1815-1818.
44. Jarvis, J.N., T. Pousak, and M. Krenz, *Detection of IgM rheumatoid factors by enzyme-linked immunosorbent assay in children with juvenile rheumatoid arthritis: correlation with articular disease and laboratory abnormalities.* Pediatrics, 1992. 90(6): p. 945-949.
45. Gilliam, B.E., et al., *Significance of complement components C1q and C4 bound to circulating immune complexes in juvenile idiopathic arthritis: support for classical complement pathway activation.* Clin. Exp. Rheumatol, 2011. 29(6): p. 1049-1056.
46. Prelog, M., et al., *Premature aging of the immune system in children with juvenile idiopathic arthritis.* Arthritis Rheum, 2008. 58(7): p. 2153-2162.
47. Dvergsten, J.A., et al., *Premature cell senescence and T cell receptor-independent activation of CD8+ T cells in juvenile idiopathic arthritis.* Arthritis Rheum, 2013. 65(8): p. 2201-2210.
48. Gattorno, M., et al., *Synovial fluid T cell clones from oligoarticular juvenile arthritis patients display a prevalent Th1/Th0-type pattern of cytokine secretion irrespective of immunophenotype.* Clin. Exp. Immunol, 1997. 109(1): p. 4-11.
49. Sakaguchi, S., *Naturally arising CD4+ regulatory t cells for immunologic self-tolerance and negative control of immune responses.* Annu. Rev. Immunol, 2004. 22: p. 531-562.
50. Mijnheer, G., B.J. Prakken, and W.F. van, *The effect of autoimmune arthritis treatment strategies on regulatory T-cell dynamics.* Curr. Opin. Rheumatol, 2013. 25(2): p. 260-267.
51. Pesenacker, A.M. and L.R. Wedderburn, *T regulatory cells in childhood arthritis--novel insights.* Expert. Rev. Mol. Med, 2013. 15: p. e13.
52. Harrington, L.E., et al., *Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages.* Nat. Immunol, 2005. 6(11): p. 1123-1132.
53. Nistala, K., et al., *Interleukin-17-producing T cells are enriched in the joints of children with arthritis, but have a reciprocal relationship to regulatory T cell numbers.* Arthritis Rheum, 2008. 58(3): p. 875-887.
54. Nistala, K., et al., *Th17 plasticity in human autoimmune arthritis is driven by the inflammatory environment.* Proc. Natl. Acad. Sci. U. S. A, 2010. 107(33): p. 14751-14756.
55. De Kleer, I.M., et al., *CD4+CD25bright regulatory T cells actively regulate inflammation in the joints of patients with the remitting form of juvenile idiopathic arthritis.* J. Immunol, 2004. 172(10): p. 6435-6443.
56. Nistala, K. and L.R. Wedderburn, *Th17 and regulatory T cells: rebalancing pro- and anti-inflammatory forces in autoimmune arthritis.* Rheumatology. (Oxford), 2009. 48(6): p. 602-606.
57. Smolewska, E., et al., *Distribution and clinical significance of blood dendritic cells in children with juvenile idiopathic arthritis.* Ann. Rheum. Dis, 2008. 67(6): p. 762-768.
58. van, R.M., et al., *Anti-cyclic citrullinated peptide (anti-CCP) antibodies in children with juvenile idiopathic arthritis.* J. Rheumatol, 2003. 30(4): p. 825-828.
59. Kuis, W., et al., *The autonomic nervous system and the immune system in juvenile rheumatoid arthritis.* Brain Behav. Immun, 1996. 10(4): p. 387-398.
60. Hunter, P.J., et al., *Biologic predictors of extension of oligoarticular juvenile idiopathic arthritis as determined from synovial fluid cellular composition and gene expression.* Arthritis Rheum, 2010. 62(3): p. 896-907.
61. Jiang, K., et al., *Whole blood gene expression profiling predicts therapeutic response at six months in patients with polyarticular juvenile idiopathic arthritis.* Arthritis Rheumatol, 2014. 66(5): p. 1363-1371.
62. Moncrieffe, H., et al., *Generation of novel pharmacogenomic candidates in response to methotrexate in juvenile idiopathic arthritis: correlation between gene expression and genotype.* Pharmacogenet. Genomics, 2010. 20(11): p. 665-676.
63. Albers, H.M., et al., *Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis.* Arthritis Rheum, 2009. 61(1): p. 46-51.

64. Foell, D., et al., *Monitoring neutrophil activation in juvenile rheumatoid arthritis by S100A12 serum concentrations.* Arthritis Rheum, 2004. 50(4): p. 1286-1295.

65. Schulze zur, W.A., et al., *Myeloid related proteins MRP8/MRP14 may predict disease flares in juvenile idiopathic arthritis.* Clin. Exp. Rheumatol, 2004. 22(3): p. 368-373.

66. Rothmund, F., et al., *Validation of relapse risk biomarkers for routine use in patients with juvenile idiopathic arthritis.* Arthritis Care Res. (Hoboken.), 2014. 66(6): p. 949-955.

67. McGhee, J.L., et al., *Identifying children with chronic arthritis based on chief complaints: absence of predictive value for musculoskeletal pain as an indicator of rheumatic disease in children.* Pediatrics, 2002. 110(2 Pt 1): p. 354-359.

68. Ansell, B.M., *Rheumatic disease mimics in childhood.* Curr. Opin. Rheumatol, 2000. 12(5): p. 445-447.

69. Bardare, M., et al., *Idiopathic limb edema in children with chronic arthritis: a multicenter report of 12 cases.* J. Rheumatol, 1997. 24(2): p. 384-388.

70. Gedalia, A., H. Gewanter, and J. Baum, *Dark skin discoloration of finger joints in juvenile arthritis.* J. Rheumatol, 1989. 16(6): p. 797-799.

71. Colebatch-Bourn, A.N., et al., *EULAR-PReS points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice.* Ann Rheum Dis, 2015. 74(11): p. 1946-57.

72. Saha, M.T., et al., *Growth of prepubertal children with juvenile chronic arthritis.* Acta Paediatr, 1999. 88(7): p. 724-728.

73. Vostrejs, M. and J.R. Hollister, *Muscle atrophy and leg length discrepancies in pauciarticular juvenile rheumatoid arthritis.* Am. J. Dis. Child, 1988. 142(3): p. 343-345.

74. Lien, G., et al., *A two-year prospective controlled study of bone mass and bone turnover in children with early juvenile idiopathic arthritis.* Arthritis Rheum, 2005. 52(3): p. 833-840.

75. Lien, G., et al., *Frequency of osteopenia in adolescents with early-onset juvenile idiopathic arthritis: a long-term outcome study of one hundred five patients.* Arthritis Rheum, 2003. 48(8): p. 2214-2223.

76. Bultink, I.E., et al., *Severe aortic regurgitation in RF positive polyarticular JIA.* Ann. Rheum. Dis, 2002. 61(3): p. 282-283.

77. Knook, L.M., et al., *Lung function abnormalities and respiratory muscle weakness in children with juvenile chronic arthritis.* Eur. Respir. J, 1999. 14(3): p. 529-533.

78. Twilt, M., et al., *Temporomandibular involvement in juvenile idiopathic arthritis.* J. Rheumatol, 2004. 31(7): p. 1418-1422.

79. te Veldhuis, E.C., A.H. te Veldhuis, and M.J. Koudstaal, *Treatment management of children with juvenile idiopathic arthritis with temporomandibular joint involvement: a systematic review.* Oral Surg. Oral Med. Oral Pathol. Oral Radiol, 2014. 117(5): p. 581-589.

80. *Uveitis in juvenile idiopathic arthritis.* Dtsch. Arztebl. Int, 2015. 112(6): p. 92-100.

81. Foeldvari, I., *Ocular Involvement in Juvenile Idiopathic Arthritis: Classification and Treatment.* Clin. Rev. Allergy Immunol, 2014.

82. de, B.J., N. Wulffraat, and A. Rothova, *Visual loss in uveitis of childhood.* Br. J. Ophthalmol, 2003. 87(7): p. 879-884.

83. Vitale, A.T., E. Graham, and J.H. de Boer, *Juvenile idiopathic arthritis-associated uveitis: clinical features and complications, risk factors for severe course, and visual outcome.* Ocul. Immunol. Inflamm, 2013. 21(6): p. 478-485.

84. Bertero, M.T. and F. Caligaris-Cappio, *Anemia of chronic disorders in systemic autoimmune diseases.* Haematologica, 1997. 82(3): p. 375-381.

85. Giannini, E.H. and E.J. Brewer, *Poor correlation between the erythrocyte sedimentation rate and clinical activity in juvenile rheumatoid arthritis.* Clin. Rheumatol, 1987. 6(2): p. 197-201.

86. Pugh, M.T., T.R. Southwood, and J.S. Gaston, *The role of infection in juvenile chronic arthritis.* Br. J. Rheumatol, 1993. 32(9): p. 838-844.

87. van Rossum, M.A., et al., *Effects of sulfasalazine treatment on serum immunoglobulin levels in children with juvenile chronic arthritis.* Scand. J. Rheumatol, 2001. 30(1): p. 25-30.
88. Hinze, C., F. Gohar, and D. Foell, *Management of juvenile idiopathic arthritis: hitting the target.* Nat. Rev. Rheumatol, 2015.
89. Collado, P., et al., *Is ultrasound a validated imaging tool for the diagnosis and management of synovitis in juvenile idiopathic arthritis? A systematic literature review.* Arthritis Care Res. (Hoboken.), 2012. 64(7): p. 1011-1019.
90. Magni-Manzoni, S., et al., *Ultrasound-detected synovial abnormalities are frequent in clinically inactive juvenile idiopathic arthritis, but do not predict a flare of synovitis.* Ann. Rheum. Dis, 2013. 72(2): p. 223-228.
91. Nusman, C.M., et al., *Contrast-enhanced MRI of the knee in children unaffected by clinical arthritis compared to clinically active juvenile idiopathic arthritis patients.* Eur. Radiol, 2015.
92. Malattia, C., et al., *Development and preliminary validation of a paediatric-targeted MRI scoring system for the assessment of disease activity and damage in juvenile idiopathic arthritis.* Ann. Rheum. Dis, 2011. 70(3): p. 440-446.
93. Hemke, R., et al., *Reliability and responsiveness of the Juvenile Arthritis MRI Scoring (JAMRIS) system for the knee.* Eur. Radiol, 2013. 23(4): p. 1075-1083.
94. Malattia, C., et al., *MRI versus conventional measures of disease activity and structural damage in evaluating treatment efficacy in juvenile idiopathic arthritis.* Ann. Rheum. Dis, 2013. 72(3): p. 363-368.
95. van Rossum, M.A., et al., *Radiologic features in juvenile idiopathic arthritis: a first step in the development of a standardized assessment method.* Arthritis Rheum, 2003. 48(2): p. 507-515.
96. van Rossum, M.A., et al., *Development of a standardized method of assessment of radiographs and radiographic change in juvenile idiopathic arthritis: introduction of the Dijkstra composite score.* Arthritis Rheum, 2005. 52(9): p. 2865-2872.
97. Malleson, P.N., *Management of childhood arthritis. Part 1: Acute arthritis.* Arch. Dis. Child, 1997. 76(5): p. 460-462.
98. Ross, J.J., *Septic arthritis.* Infect. Dis. Clin. North Am, 2005. 19(4): p. 799-817.
99. Yagupsky, P., *Kingella kingae: carriage, transmission, and disease.* Clin. Microbiol. Rev, 2015. 28(1): p. 54-79.
100. Williams, N., C. Cooper, and P. Cundy, *Kingella kingae septic arthritis in children: recognising an elusive pathogen.* J. Child Orthop, 2014. 8(1): p. 91-95.
101. Yagupsky, P., et al., *Differentiating Kingella kingae septic arthritis of the hip from transient synovitis in young children.* J. Pediatr, 2014. 165(5): p. 985-989.
102. Frank, G., H.M. Mahoney, and S.C. Eppes, *Musculoskeletal infections in children.* Pediatr. Clin. North Am, 2005. 52(4): p. 1083-106, ix.
103. Shapiro, E.D., *Borrelia burgdorferi (Lyme disease).* Pediatr. Rev, 2014. 35(12): p. 500-509.
104. Oliveira, C.R. and E.D. Shapiro, *Update on persistent symptoms associated with Lyme disease.* Curr. Opin. Pediatr, 2015. 27(1): p. 100-104.
105. Borchers, A.T., et al., *Lyme disease: A rigorous review of diagnostic criteria and treatment.* J. Autoimmun, 2015. 57C: p. 82-115.
106. Calabrese, L.H. and S.J. Naides, *Viral arthritis.* Infect. Dis. Clin. North Am, 2005. 19(4): p. 963-80, x.
107. Harjacek, M., J. Ostojic, and R.O. Djakovic, *Juvenile spondyloarthropathies associated with Mycoplasma pneumoniae infection.* Clin. Rheumatol, 2006. 25(4): p. 470-475.
108. Flores, D., et al., *Reactive arthritis: newer developments.* Rheum. Dis. Clin. North Am, 2003. 29(1): p. 37-59, vi.
109. Toivanen, A. and P. Toivanen, *Reactive arthritis.* Best. Pract. Res. Clin. Rheumatol, 2004. 18(5): p. 689-703.
110. Marijon, E., et al., *Rheumatic heart disease.* Lancet, 2012. 379(9819): p. 953-964.
111. Carapetis, J.R., M. McDonald, and N.J. Wilson, *Acute rheumatic fever.* Lancet, 2005. 366(9480): p. 155-168.
112. Burke, R.J. and C. Chang, *Diagnostic criteria of acute rheumatic fever.* Autoimmun. Rev, 2014. 13(4-5): p. 503-507.

113. Vogel, T., et al., *The heart and pediatric rheumatology.* Rheum. Dis. Clin. North Am, 2014. 40(1): p. 61-85.

114. Tani, L.Y., et al., *Rheumatic Fever in children under 5 years.* Pediatrics, 2004. 114(3): p. 906.

115. Gerber, M.A., et al., *Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics.* Circulation, 2009. 119(11): p. 1541-1551.

116. Uziel, Y., et al., *Post-streptococcal reactive arthritis in children: a distinct entity from acute rheumatic fever.* Pediatr. Rheumatol. Online. J, 2011. 9(1): p. 32.

117. Barash, J., *Rheumatic Fever and post-group a streptococcal arthritis in children.* Curr. Infect. Dis. Rep, 2013. 15(3): p. 263-268.

118. AH, v.d.H.-v.M., *Acute rheumatic fever and poststreptococcal reactive arthritis reconsidered.* Curr. Opin. Rheumatol, 2010. 22(4): p. 437-442.

119. Petersel, D.L. and L.H. Sigal, *Reactive arthritis.* Infect. Dis. Clin. North Am, 2005. 19(4): p. 863-883.

120. Ahmed, S. and E.M. Ayoub, *Poststreptococcal reactive arthritis.* Pediatr. Infect. Dis. J, 2001. 20(11): p. 1081-1082.

121. Avina-Zubieta, J.A., G. Galindo-Rodriguez, and C. Lavalle, *Rheumatic manifestations of hematologic disorders.* Curr. Opin. Rheumatol, 1998. 10(1): p. 86-90.

122. Cabral, D.A. and L.B. Tucker, *Malignancies in children who initially present with rheumatic complaints.* J. Pediatr, 1999. 134(1): p. 53-57.

123. Trapani, S., et al., *Incidence of occult cancer in children presenting with musculoskeletal symptoms: a 10-year survey in a pediatric rheumatology unit.* Semin. Arthritis Rheum, 2000. 29(6): p. 348-359.

124. McGhee, J.L., L.M. Kickingbird, and J.N. Jarvis, *Clinical utility of antinuclear antibody tests in children.* BMC. Pediatr, 2004. 4: p. 13.

125. Goncalves, M., et al., *Diagnosis of malignancies in children with musculoskeletal complaints.* Sao Paulo Med. J, 2005. 123(1): p. 21-23.

126. Zombori, L., et al., *Rheumatic symptoms in childhood leukaemia and lymphoma-a ten-year retrospective study.* Pediatr. Rheumatol. Online. J, 2013. 11: p. 20.

127. Masters, S.L., et al., *Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease (*).* Annu. Rev. Immunol, 2009. 27: p. 621-668.

128. Grahame, R., *Pain, distress and joint hyperlaxity.* Joint Bone Spine, 2000. 67(3): p. 157-163.

129. Stoll, M.L. and R.Q. Cron, *Treatment of juvenile idiopathic arthritis: a revolution in care.* Pediatr. Rheumatol. Online. J, 2014. 12: p. 13.

130. Otten, M.H., et al., *Trends in prescription of biological agents and outcomes of juvenile idiopathic arthritis: results of the Dutch national Arthritis and Biologics in Children Register.* Ann. Rheum. Dis, 2015. 74(7): p. 1379-1386.

131. Zhao, Y. and C. Wallace, *Judicious use of biologicals in juvenile idiopathic arthritis.* Curr. Rheumatol. Rep, 2014. 16(11): p. 454.

132. Giannini, E.H., et al., *Preliminary definition of improvement in juvenile arthritis*

14. Arthritis Rheum, 1997. 40(7): p. 1202-1209.

133. Wallace, C.A., N. Ruperto, and E. Giannini, *Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis.* J. Rheumatol, 2004. 31(11): p. 2290-2294.

134. Wallace, C.A., et al., *American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis.* Arthritis Care Res. (Hoboken.), 2011. 63(7): p. 929-936.

135. Consolaro, A., et al., *Development and validation of a composite disease activity score for juvenile idiopathic arthritis.* Arthritis Rheum, 2009. 61(5): p. 658-666.

136. Consolaro, A., et al., *Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score.* Arthritis Rheum, 2012. 64(7): p. 2366-2374.

137. Wallace, C.A., et al., *Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis.* Arthritis Rheum, 2011.

138. Tynjala, P., et al., *Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial.* Ann. Rheum. Dis, 2011. 70(9): p. 1605-1612.

139. Beukelman, T., 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(4): p. 465-482.

140. van Rossum, M.A., et al., *Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment.* Ann. Rheum. Dis, 2007. 66(11): p. 1518-1524.

141. Giannini, E.H., et al., *Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group.* N Engl J Med, 1992. 326(16): p. 1043-9.

142. Takken, T., J. Van der Net, and P.J. Helders, *Methotrexate for treating juvenile idiopathic arthritis.* Cochrane. Database. Syst. Rev, 2001(4): p. CD003129.

143. Horneff, G., et al., *Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry.* Ann. Rheum. Dis, 2009. 68(4): p. 519-525.

144. Ruperto, N., et al., *Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension.* Ann. Rheum. Dis, 2010. 69(4): p. 718-722.

145. Lovell, D.J., et al., *Adalimumab with or without methotrexate in juvenile rheumatoid arthritis.* N. Engl. J. Med, 2008. 359(8): p. 810-820.

146. Ravelli, A., et al., *Efficacy of folinic acid in reducing methotrexate toxicity in juvenile idiopathic arthritis.* Clin. Exp. Rheumatol, 1999. 17(5): p. 625-627.

147. Heijstek, M.W., et al., *EULAR recommendations for vaccination in paediatric patients with rheumatic diseases.* Ann. Rheum. Dis, 2011. 70(10): p. 1704-1712.

148. Silverman, E., et al., *Leflunomide or methotrexate for juvenile rheumatoid arthritis.* N Engl J Med, 2005. 352(16): p. 1655-66.

149. Eberhard, B.A., et al., *Comparison of the intraarticular effectiveness of triamcinolone hexacetonide and triamcinolone acetonide in treatment of juvenile rheumatoid arthritis.* J. Rheumatol, 2004. 31(12): p. 2507-2512.

150. Gondwe, J.S., et al., *Secondary Cushing's syndrome in children with juvenile idiopathic arthritis following intra-articular triamcinolone acetonide administration.* Rheumatology. (Oxford), 2005. 44(11): p. 1457-1458.

151. Zulian, F., et al., *Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial.* Rheumatology. (Oxford), 2004. 43(10): p. 1288-1291.

152. Lovell, D.J., et al., *Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group.* N. Engl. J. Med, 2000. 342(11): p. 763-769.

153. Lovell, D.J., et al., *Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial.* Arthritis Rheum, 2003. 48(1): p. 218-226.

154. Horneff, G., et al., *The German etanercept registry for treatment of juvenile idiopathic arthritis.* Ann. Rheum. Dis, 2004. 63(12): p. 1638-1644.

155. Ruperto, N., et al., *Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial.* Lancet, 2008. 372(9636): p. 383-391.

156. Brunner, H.I., et al., *Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial.* Ann. Rheum. Dis, 2015. 74(6): p. 1110-1117.

157. Brunner, H.I., et al., *A Multi-Center, Double-Blind, Randomized-Withdrawal Trial of Subcutaneous Golimumab in Pediatric Patients with Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate Therapy: Week 48 Results.* Arthritis & Rheumatology Special Issue: Abstracts from the 2014 Pediatric Rheumatology Symposium Volume 66, Issue Supplement S3, 2014: p. S191-S192.

158. Webb, K. and L.R. Wedderburn, *Advances in the treatment of polyarticular juvenile idiopathic arthritis.* Curr. Opin. Rheumatol, 2015. 27(5): p. 505-510.

159. Swart, J.F., R.S. de, and N.M. Wulffraat, *What are the immunological consequences of long-term use of biological therapies for juvenile idiopathic arthritis?* Arthritis Res. Ther, 2013. 15(3): p. 213.

160. Beukelman, T., et al., *Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment.* Arthritis Rheum, 2012.

161. Swart, J.F., et al., *The Addition of One or More Biologics to Methotrexate in Children with Juvenile Idiopathic Arthritis Increases the Incidence of Infections and Serious Adverse Events. The 5882 Pharmachild Cohort.* Ann Rheum Dis 2015;74:91 doi:10. 1136/annrheumdis-2015-eular. 4397, 2015.

162. Nimmrich, S. and G. Horneff, *Incidence of herpes zoster infections in juvenile idiopathic arthritis patients.* Rheumatol. Int, 2015. 35(3): p. 465-470.

163. Mannion, M.L. and T. Beukelman, *What is the background incidence of malignancy in children with rheumatic disease?* Curr. Rheumatol. Rep, 2013. 15(3): p. 310.

164. Ruperto, N. and A. Martini, *Juvenile idiopathic arthritis and malignancy.* Rheumatology. (Oxford), 2014. 53(6): p. 968-974.

165. Beukelman, T., et al., *Rates of malignancy associated with juvenile idiopathic arthritis and its treatment.* Arthritis Rheum, 2012.

166. Ringold, S., et al., *Novel method to collect medication adverse events in juvenile arthritis: results from the childhood arthritis and rheumatology research alliance enhanced drug safety surveillance project.* Arthritis Care Res. (Hoboken.), 2015. 67(4): p. 529-537.

167. Brinkman, D.M., et al., *Autologous stem cell transplantation in children with severe progressive systemic or polyarticular juvenile idiopathic arthritis: long-term follow-up of a prospective clinical trial.* Arthritis Rheum, 2007. 56(7): p. 2410-2421.

168. Simon, D., et al., *Effects on growth and body composition of growth hormone treatment in children with juvenile idiopathic arthritis requiring steroid therapy.* J Rheumatol, 2003. 30(11): p. 2492-9.

169. Grote, F.K., et al., *Growth hormone treatment in children with rheumatic disease, corticosteroid induced growth retardation, and osteopenia.* Arch Dis Child, 2006. 91(1): p. 56-60.

170. Bou, R., et al., *Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus.* Rheumatol. Int, 2015.

171. Agle, L.M., M. Rosenkranz, and T.J. Lehman, *Novel therapies for the treatment of juvenile rheumatoid arthritis (juvenile idiopathic arthritis).* Expert Opin Investig Drugs, 2003. 12(1): p. 19-28.

172. Yu, E.N., et al., *Outcomes of treatment with immunomodulatory therapy in patients with corticosteroid-resistant juvenile idiopathic arthritis-associated chronic iridocyclitis.* Ocul. Immunol. Inflamm, 2005. 13(5): p. 353-360.

173. Kakkassery, V., S. Mergler, and U. Pleyer, *Anti-TNF-alpha treatment: a possible promoter in endogenous uveitis? observational report on six patients: occurrence of uveitis following etanercept treatment.* Curr Eye Res, 2010. 35(8): p. 751-6.

174. Foeldvari, I., I. Becker, and G. Horneff, *Uveitis events upon Adalimumab, Etanercept and methotrexate in juvenile idiopathic arthritis (JIA) in the BIKER-registry.* Arthritis Care Res. (Hoboken.), 2015.

175. Tappeiner, C., et al., *Abatacept in the Treatment of Severe, Longstanding, and Refractory Uveitis Associated with Juvenile Idiopathic Arthritis.* J. Rheumatol, 2015.

176. Wallace, C.A. and J.E. Levinson, *Juvenile rheumatoid arthritis: outcome and treatment for the 1990s.* Rheum. Dis. Clin. North Am, 1991. 17(4): p. 891-905.

177. Guillaume, S., et al., *Long-term outcome and prognosis in oligoarticular-onset juvenile idiopathic arthritis.* Arthritis Rheum, 2000. 43(8): p. 1858-1865.

178. Fantini, F., et al., *Remission in juvenile chronic arthritis: a cohort study of 683 consecutive cases with a mean 10 year followup.* J. Rheumatol, 2003. 30(3): p. 579-584.

179. Felici, E., et al., *Course of joint disease in patients with antinuclear antibody-positive juvenile idiopathic arthritis.* J. Rheumatol, 2005. 32(9): p. 1805-1810.

180. Wallace, C.A., et al., *Patterns of clinical remission in select categories of juvenile idiopathic arthritis.* Arthritis Rheum, 2005. 52(11): p. 3554-3562.

181. Ravelli, A., et al., *Patients with antinuclear antibody-positive juvenile idiopathic arthritis constitute a homogeneous subgroup irrespective of the course of joint disease.* Arthritis Rheum, 2005. 52(3): p. 826-832.

182. Guzman, J., et al., *The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort.* Ann. Rheum. Dis, 2014.

183. Guzman, J., et al., *The risk and nature of flares in juvenile idiopathic arthritis: results from the ReACCh-Out cohort.* Ann. Rheum. Dis, 2015.

184. Selvaag, A.M., et al., *Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis.* Ann. Rheum. Dis, 2014.

185. Oen, K., et al., *Early outcomes and improvement of patients with juvenile idiopathic arthritis enrolled in a Canadian multicenter inception cohort.* Arthritis Care Res. (Hoboken.), 2010. 62(4): p. 527-536.

186. Anink, J., et al., *Long-term quality of life and functional outcome of patients with juvenile idiopathic arthritis in the biologic era: a longitudinal follow-up study in the Dutch Arthritis and Biologicals in Children Register.* Rheumatology. (Oxford), 2015.

187. Minden, K., et al., *Long-term outcome of patients with JIA treated with etanercept, results of the biologic register JuMBO.* Rheumatology. (Oxford), 2012. 51(8): p. 1407-1415.

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