Paediatric and adolescent rheumatic diseases: measures of disease activity

ABSTRACT

Juvenile idiopathic arthritis, juvenile systemic lupus erythematosus and juvenile dermatomyositis are rare, chronic, multi-systemic rheumatic disorders that can be associated with significant morbidity, not only during childhood, but lifelong.

Dedicated disease activity and damage assessment tools are essential to guide clinical management and perform multicentre clinical trials to ensure the best possible care and outcome for children with rheumatic diseases using an evidence-based, treat-to-target approach. This article summarizes the outcome measures most commonly used in paediatric rheumatology.

In recent years more and more evidence showed that a treat-to-target approach conveys better outcomes than routine clinical care. Therefore, several international collaborations have joined forces to create and validate dedicated assessment tools specifically designed for children with rheumatic diseases. These will help investigators perform large international studies, and thus improve daily clinical practice with an evidence-based, unanimous management and therapeutic approach.

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis is arthritis of unknown aetiology that begins before the age of 16 years and persists for a minimum of 6 weeks. It is an umbrella term that includes seven heterogeneous subtypes defined by the International League Against Rheumatism (Petty et al, 2004) and is the most common rheumatic disease in childhood, affecting approximately 1 in 1000 children in the UK (Symmons et al, 1996). Juvenile idiopathic arthritis is characterized by chronic synovial inflammation that may cause joint damage. About 15% of children with juvenile idiopathic arthritis also develop chronic anterior uveitis which, if not promptly recognized and treated, may also cause severe damage, including cataract and visual loss (Holland et al, 2009). Only about 5% of children with juvenile idiopathic arthritis have similar clinical characteristics to those of adult rheumatoid arthritis, including positive rheumatoid factor antibody, but the remaining population has a very different disease, especially in terms of response to medications and clinical outcome.

Several outcome measures have been developed and validated for use in the paediatric population to help paediatric and adolescent rheumatologists monitor disease activity, and also to evaluate the response to treatment and occurrence of damage.

Achieving and maintaining clinical remission is essential to ensure a better long-term outcome and to prevent damage. The Wallace criteria are used to define inactive disease in oligoarticular (persistent and extended), polyarticular (rheumatoid factor positive and negative) and systemic juvenile idiopathic arthritis (Wallace et al, 2011). These are:

- No joints with active arthritis
- No fever, rash, serositis, splenomegaly or generalized lymphadenopathy as a result of juvenile idiopathic arthritis
- No active uveitis
- Erythrocyte sedimentation rate or C-reactive protein level within normal limits
- Best possible physician's global assessment of disease activity score.

When the criteria for inactive disease are met for a minimum of 6 consecutive months while the patient is receiving anti-rheumatic medications the patient is classified as being in the state of clinical remission on medication; when the same criteria are met for 12 consecutive months after the patient has discontinued all anti-rheumatic medications, the patient is classified as being in the state of clinical remission without medications.

Minimal disease activity was defined in 2008 as the presence of a physician's global rating of disease activity ≤3.4, a parent's global rating of wellbeing ≤2.5 and a swollen joint count ≤1 in polyarthritis, and as a physician's global assessment of disease activity ≤2.5 and a swollen joint count = 0 in oligoarthritis (Magni-Manzoni et al, 2008).

More recent studies have also suggested that paediatric disease activity scores should continue to be used in adult patients with juvenile idiopathic arthritis, because scoring systems such as DAS28 might underestimate the disease activity in this cohort (Wu et al, 2016).

The most important tools used in juvenile idiopathic arthritis in daily clinical practice are summarized in *Table 1*.

Juvenile systemic lupus erythematosus

Systemic lupus erythematosus is a multi-organ autoimmune disease characterized by dysregulated

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Table 1. Outcome measures used in juvenile idiopathic arthritis

Disease activity scores	Juvenile arthritis disease activity score (Consolaro et al, 2009)	First composite disease score for juvenile idiopathic arthritis including:	■ Physician's global assessment of disease activity (0–10 VAS) ■ Parent global assessment of wellbeing (0–10 VAS) ■ Erythrocyte sedimentation rate (normalized to a 0–10 scale) ■ Count of joints with active disease ■ Three versions developed based on number of active joints considered 10, 27 or 71
	Juvenile Spondyloarthritis Disease Activity (Weiss et al, 2014)	Composite disease score specific for enthesitis-related arthritis including:	■ Active joint count, tender enthesis count, clinical sacroiliitis, morning stiffness, back mobility ■ Parent/child assessment of pain ■ Uveitis ■ Inflammatory markers ■ Score 0–8 (8=greater disease activity)
	Child/parent global assessment of overall wellbeing	■ Parent or patient global evaluation on a 0–10 VAS	
	ACR Pedi30, 50, 70 paediatric measures of improvement criteria (Giannini et al, 1997)	Response is defined as 30%, 50%, 70% improvement from baseline in three of the six following variables, with no more than one remaining variable worsening by >30%:	■ Global assessment of disease activity (0–10 VAS) ■ Parent/patient assessment of overall wellbeing (0–10 VAS) ■ Functional ability ■ Number of joints with active arthritis ■ Number of joints with limited range of movement ■ Erythrocyte sedimentation rate
Function and health-related quality of life	Childhood health assessment questionnaire	Composite questionnaire with score 0 to 3 (3=highest disability):	■ Physical functioning in 30 items divided into eight domains (dressing, arising, eating, walking, hygiene, reach, grip, activities) ■ Pain VAS 0–10 ■ Overall wellbeing VAS 0–10
	Juvenile arthritis multidimensional assessment report (Filocamo et al, 2011)	Completed by parent/child it includes:	■ Assessment of physical function 15 items ■ Pain, level of disease activity and overall wellbeing VAS 0–10 ■ Presence of joint pain or swelling ■ Assessment of morning stiffness (present or absent) ■ Assessment of extra-articular symptoms (fever and rash) (present or absent) ■ Rating of disease status and disease course ■ Medications and eventual side effects ■ Report of school or work problems ■ Health-related quality of life assessment with a 10-item scale
Damage	Juvenile arthritis damage index (Viola et al, 2005)	Physician evaluation of	■ Articular damage (maximum total score 72) ■ Extra-articular damage (maximum total score 17)

VAS=visual analogue scale where 0 is best/normal

autoantibody production involving both the innate and adaptive immune systems. It has an overall incidence of 4.9 per 100 000 people in the UK and a prevalence of 72.8 per 100 000 people in the UK with a 6–10-fold female predominance. In about 10–20% of patients disease onset is before the age of 18 years (juvenile systemic lupus erythematosus) and in this population the disease is generally more severe than in adult-onset disease, requiring more immunosuppressive medications and with higher risk of long-term damage and morbidity (Mina et al, 2010). Increasing evidence shows that monogenic causes are especially common in young children with disease onset before 5 years of age and that they can have a particularly severe disease, with a higher frequency of lupus nephritis and CNS involvement (Hiraki and Silverman, 2017).

The diagnosis of systemic lupus erythematosus and juvenile systemic lupus erythematosus is based on four out of the 11 American College of Rheumatology criteria (Hochberg, 1997):

Table 2. Outcome measures used in juvenile systemic lupus erythematosus

Disease activity scores	Systemic Lupus Erythematosus Disease Activity Score (SLEDAI) (Bombardier et al, 1992)	Weighted scale with range from 0 to 105 (105 = highest disease activity) which includes:	■ 16 clinical findings ■ 8 laboratory tests ■ A score above 8 highlights moderate disease activity
	Physician global assessment of disease severity	Clinical evaluation of disease severity on a visual analogue scale 0–10	
	Child/parent global assessment of overall wellbeing	Parent or patient global evaluation on a visual analogue scale 0–10	
	Inactive disease status (Mina et al, 2012)	■ Absence of clinical signs and symptoms caused by juvenile systemic lupus erythematosus ■ Presence of two or more of the following symptoms is permitted: mild fatigue, arthralgia, myalgia, headache ■ Normal urinary sediment and blood tests, especially full blood count, C3 and transaminase ■ Positive or normal results for the following blood tests is allowed: antinuclear antibodies, C4, stable antiphospholipid syndrome and erythrocyte sedimentation rate ≤2 times normal value	
	PRINTO criteria from improvement (Ruperto et al, 2011)	At least 50% improvement from baseline in any two among the following five core set measures, with no more than one of the remaining, worsening by more than 30%:	■ Physician global assessment ■ Child/parent global assessment of overall wellbeing ■ Child health questionnaire or Paediatric Rheumatology Quality of Life Scale ■ SLEDAI, Systemic Lupus Activity Measures or European Consensus Lupus Activity Measurement ■ 24-hour proteinuria
Damage score	Systemic Lupus Collaboration Clinics/American College of Rheumatology Damage Index (Gladman et al, 1996)	It measures the presence of irreversible damage since juvenile systemic lupus erythematosus onset defined as presence of any item for at least 6 months	■ 41-item score, maximal damage = 41 ■ 12 different domains: ocular, renal, neuropsychiatric, pulmonary, cardiovascular, skin, peripheral vascular, gastrointestinal, musculoskeletal, premature gonadal failure, diabetes mellitus, and malignancy

C3, C4= complement component 3,4.

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Non-erosive arthritis
6. Pleuritis or pericarditis
7. Renal disorder
8. Neurological disorder
9. Haematological disorder
10. Immunological disorder
11. Positive antinuclear antibody.

The most important tools used in patients with juvenile systemic lupus erythematosus in daily clinical practice are summarized in *Table 2*.

Juvenile dermatomyositis

Juvenile dermatomyositis is a rare systemic autoimmune disease characterized by a vasculopathy that primarily affects muscles and skin, but may involve the lung, bowel, heart and other organs (Feldman et al, 2008). Juvenile dermatomyositis is the most common inflammatory myopathy of childhood, affecting 1.9 cases per million children in the UK (Symmons et al, 1995). The most common clinical findings are proximal muscle weakness, which in severe cases can also include nasopharyngeal muscles, and typical skin rash affecting the eyelids, face and extensor surface of the upper and lower limbs.

The diagnosis of juvenile dermatomyositis is based on the Bohan and Peter criteria (Bohan and Peter, 1975a,b):

- Typical dermatomyositis skin rash
- Symmetrical proximal muscular weakness
- Serum elevation of skeletal muscles enzymes
- Abnormal electromyography suggestive of myopathy changes
- Abnormal muscle biopsy suggestive of inflammatory myositis.

In paediatrics muscular electrophysiology is now less often performed; magnetic resonance imaging is preferred because it is less invasive and provides more accurate information.

In children juvenile dermatomyositis can present with clinical or laboratory characteristics of other autoimmune diseases, especially scleroderma and lupus, but is never a paraneoplastic manifestation, which is frequently the case with adult-onset dermatomyositis. There are many outcome tools to assess this complex disorder, some are also used to evaluate patients with adult onset dermatomyositis such as the Manual Muscle Testing of 8 groups (Rider et al, 2010) and the Myositis Damage Score (Isenberg et al, 2004). The outcome tools specifically developed and validated in children and are summarized in *Table 3*.

Quality of life

In terms of quality of life, one of the most commonly used questionnaire in paediatric rheumatology is the child health questionnaire. This was originally developed in the United States of America in 1996. It is a generic tool administered to both parents and child, designed to capture in 14 domains the physical, emotional and social components of health status in children aged 5–18 years, and provides a physical and psychosocial summary score. As a generic questionnaire it can be used across different childhood conditions, and it has also been validated for use in juvenile idiopathic arthritis, juvenile systemic lupus erythematosus and juvenile dermatomyositis (Landgraf et al, 1998).

Another frequently used outcome measure is the childhood health assessment questionnaire. This is a quantitative measure of physical function which has been validated in children with different rheumatic disorders. It is commonly used in clinical practice and research, especially for patients with juvenile idiopathic arthritis, juvenile systemic lupus erythematosus and juvenile dermatomyositis. The childhood health assessment questionnaire is divided into disability and discomfort indices which assess function in eight areas (score 0–3), pain intensity and overall wellbeing respectively (Singh et al, 1994).

Last, but more important, serial monitoring of height and weight, Tanner puberty stage and menses for girls are essential outcome measures to evaluate long-term damage in children with chronic diseases. These can frequently be impaired if the disease is not well controlled or by the treatment received, especially corticosteroids, but also tend to improve, especially in young children, once the disease is under control and corticosteroid therapy is stopped or reduced.

Conclusions

In recent years, an intense international effort has been made to develop and validate outcome measures specifically for children and young people with rheumatic disorders. The use of quantitative measures increases the reliability of patient follow up and the comparison of different patient populations to enable multicentre international research studies, which are vital for rare diseases. Furthermore, as our understanding of the pathogenesis of these diseases keeps improving, new or updated classification criteria and outcome measures will become essential. These tools will also need to be harmonized with the assessments used in young adult and adult age to ensure a smooth transition to adult care. **BJHM**

Conflict of interest: none.

KEY POINTS

- Outcome measures provide a standardized assessment of disease activity, ensuring accurate follow up and improving prognosis for patients with chronic diseases.
- Paediatric onset rheumatic disorders are different from those of adult onset and required specific designed and validated tools.
- It is crucial to harmonize assessment tools used in paediatric, adolescent and adult rheumatic diseases to ensure a careful and safe follow up.

Table 3. Disease activity scores used in juvenile dermatomyositis

Childhood Myositis Assessment (Huber et al, 2004)	■ 14-item score with range from 0 to 52 (52 = normal muscle strength) ■ It specifically evaluates muscle strength and endurance	
Disease Activity Score (Bode et al, 2003)	■ 19-item score with a range of 0–20 (20 = most severe disease activity) ■ The tool assesses muscle and cutaneous manifestations ■ It is also possible to report the Disease Activity Score skin score (range 0–9) and the Disease Activity Score muscle score (range 0–11) separately	
Physician global assessment of disease severity	Clinical evaluation of disease severity on a visual analogue scale 0–10	
Child/parent global assessment of overall wellbeing	Parent/patient global evaluation on a visual analogue scale 0–10	
PRINTO inactive disease status (Lazarevic et al, 2013)	At least three of four conditions to be met:	■ Creatinine kinase ≤150 U/litre ■ Childhood Myositis Assessment ≥48 ■ Manual muscle testing 8 ≥78 ■ Physician global assessment of overall disease activity ≤0.2

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