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Outcome measures of disease activity used for paediatric and adolescent rheumatic diseases

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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 all 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.

The aim of this article is to provide a summary of the outcome measures most commonly used in paediatric rheumatology.

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

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is defined as 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 comprehends seven heterogeneous subtypes defined by the International League Against Rheumatism (ILAR) (Petty et al, 2004) and overall is the most common rheumatic disease in childhood affecting approximately 1 in 1000 children in UK (Symmons et al, 1996). JIA is characterized by chronic synovial inflammation that may cause joint damage. About 15% of children with JIA 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 JIA have similar clinical characteristics to adult rheumatoid arthritis, including positive rheumatoid factor, 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 to be used in the paediatric population to help paediatric and adolescent rheumatologists monitor disease activity, but also evaluate the response to treatment and occurrence of damage.

To achieve and maintain clinical remission it is essential to ensure a better long term outcome and prevent damage. *The Wallace criteria* are used to define inactive disease in oligoarticular (persistent and extended), polyarticular (rheumatoid factor positive and negative), and systemic JIA (Wallace et al 2011):

- No joints with active arthritis;
- No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy due to JIA;
- No active uveitis;
- ESR or CRP level within normal limits;
- Best possible physician's global assessment of disease activity score.

When the criteria for inactive disease are met for a minimal 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*.

The definition of *minimal disease activity* has been defined in 2008 as the presence of a physician's global rating of disease activity ≤3.4, a parent's global rating of well-being ≤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).

The most important tools used in JIA in daily clinical practice are summarised in *Table 1.*

Juvenile systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease characterised by dysregulated autoantibody production involving both innate and adaptive immune system. It has an overall incidence of 4.9 people in UK and prevalence of 72.8 people in UK with a 6-10-fold female predominance. In about 10-20% of patients the disease onset is before the age of 18 year old

(Juvenile SLE or JSLE) and recent studies showed that in this population the disease is generally more severe than the adult-onset, requiring more immunosuppressive medications and with higher risk of long term damage and morbidity (Mina et al 2010). Furthermore increasing evidence showed 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 higher frequency of lupus nephritis and central nervous system involvement (Hiraki et al 2017).

The diagnosis of SLE and JSLE is based on 4 out of the 11 *American College of Rheumatology (ACR) Criteria* (Hochberg, 1997):

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Non-erosive arthritis
6. Pleuritis or Pericarditis
7. Renal disorder
8. Neurologic disorder
9. Hematologic disorder
10. Immunologic disorder
11. Positive ANA

The most important tools used in JSLE patients in daily clinical practice are summarised in *Table 2.*

Juvenile dermatomyositis

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

The diagnosis of JDM is based on the following *Bohan and Peters criteria* (Bohan et al, 1975):

- 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 the recent years in paediatrics it is less common to perform muscular electrophysiology, whilst it is preferred to perform magnetic resonance imaging (MRI), because it is less invasive, and provides more accurate information.

In children JDM can present with clinical or laboratory characteristics of other autoimmune diseases, especially scleroderma and lupus, but is never a paraneoplastic manifestation, as 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 (MMT8) (Rider et al, 2010) and the Myositis Damage Score

(Isenberg et al, 2004), others have been specifically developed and validated in children and are summarized in *Table 3*.

In terms of quality of life, one of the most commonly questionnaire used in paediatric rheumatology is the child health questionnaire (CHQ). The CHQ was originally developed in the United States 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 ages 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 JIA, JSLE and JDM (Landgraf et al, 1998).

Another frequently used outcome measure is the childhood health assessment questionnaire (CHAQ). CHAQ is a quantitative measure of physical function which has been validated in children with different rheumatic disorders and it is commonly used in clinical practice and research especially for patients with JIA, JSLE and JDM. The CHAQ is divided into disability and discomfort indices which assess function in 8 areas (score 0–3) and pain intensity and overall wellbeing, respectively (Sigh et al, 1994).

Lastly, but more importantly, essential outcome measures to evaluate long term damage in children with chronic diseases are serial monitoring of height and weight, Tanner Puberty stage and menses for girls. In fact they can be frequently 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 the past decades, 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 patients follow up and the comparison of different patient populations to enable multi-centre international research studies, which are vital for rare diseases. Furthermore, as our understanding of the pathogenesis of these diseases keeps improving, in the coming years, new or updated classification criteria and outcome measures will become essential. These tools will also need to be harmonized with the assessment made in young adult and adult age to ensure a smooth transition to adult care.

Key points

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

Key words: outcome measures, paediatric rheumatology, juvenile idiopathic arthritis, juvenile systemic lupus erythematosus, juvenile dermatomyositis.

Table 1. Outcome measures used in Juvenile Idiopathic Arthritic		
Disease Activity Scores	Juvenile arthritis disease activity score (JADAS) (Consolaro et al , 2009)	First composite disease score for JIA including: • physician's global assessment of disease activity (0–10 VAS) • parent global assessment of well-being (0–10 VAS) • ESR (normalised to a 0-10 scale) • count of joints with active disease • 3 versions developed based on number of active joint considered 10, 27 or 71.
	Physician global assessment of disease severity	• Clinical evaluation of disease severity on VAS scale 0-10
	Child/parent global assessment of overall well-being	• Parent or patient global evaluation on a VAS 0-10
	ACR Pedi30, 50, 70 paediatric measures of improvement criteria (Giannini et al, 1997)	Response is defined as 30 %, 50%, 70% improvement from baseline in 3 of 6 following variables, with no more than 1 remaining variable worsening by >30 %: • global assessment of disease activity (0-10 VAS) • parent/patient assessment of overall well-being (0-10 VAS) • functional ability • number of joints with active arthritis • number of joints with limited range of movement • ESR.
Function and HRQoL	Childhood health assessment questionnaire (CHAQ)	Composite questionnaire with score 0 to 3 (3=highest disability): • physical functioning in 30 items divided into 8 domains (dressing, arising, eating, walking, hygiene, reach, grip, activities); • pain VAS 0-10 • overall well-being VAS 0-10
	Juvenile arthritis multidimensional assessment report (JAMAR) (Filocamo et al, 2011)	Completed by parent/child it includes: • assessment of physical function 15 items • pain, level of disease activity and overall well-being VAS 0-10 • presence of joint pain or swelling • assessment of morning stiffness (present/absent) • assessment of extra-articular symptoms (fever and rash) (present/absent); • Rating of disease status and disease course • Medications and eventual side effects • Report of school/work problems • HRQoL assessment with a 10 item scale
Damage	Juvenile arthritis damage index (JADI) (Viola et al, 2005)	Physician evaluation of: • articular damage (JADI-A) • extra-articular damage (JADI-E).

		The maximum total score is 72 for JADI-A and 17 for JADI-E.
VAS=visual analogue scale where 0 is best/normal; ESR =erythrocyte sedimentation rate		

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 VAS scale 0-10
	Child/parent global assessment of overall well-being	• Parent or patient global evaluation on a VAS 0-10
	Inactive disease status (Mina et al, 2012)	• Absence of clinical signs and symptoms due to JSLE • Presence of 2 or less 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/normal following blood tests is allowed: ANA, C4, stable aPL and ESR ≤ 2 times normal value.
	PRINTO criteria from improvement (Ruperto et al, 2011)	At least 50% improvement from baseline in any 2 among the following 5 core set measures, with no more than 1 of the remaining, worsening by more than 30%: • Physician global assessment • Child/parent global assessment of overall well-being • CHQ or PRQL • SLEDAI or SLAM or ECLAM • 24-hour proteinuria
Damage score	Systemic Lupus Collaboration Clinics/American College of Rheumatology Damage Index (SDI) (Gladman et al, 1996)	It measures the presence of irreversible damage since JSLE onset defined as presence of any item for at least 6 months • 41- item score, maximal damage = 41 • 12 different domains divided in ocular, renal, neuropsychiatric, pulmonary, cardiovascular, skin, peripheral vascular, gastrointestinal, musculoskeletal, premature gonadal failure, diabetes mellitus, and malignancy.
ANA= anti nucleus antibodies; C3, C4= complement component 3,4; aPL= anti phospholipid syndrome; PRQL=Paediatric Rheumatology Quality of Life Scale; ECLAM=European Consensus Lupus Activity Measurement; SLAM=Systemic Lupus Activity Measures;		

Table 3. Outcome measures used in Juvenile Dermatomyositis		
Disease Activity Scores	Childhood Myositis Assessment (CMAS) (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 (DAS) (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 DAS skin score (range 0–9) and the DAS muscle score (range 0–11) separately.
	Physician global assessment of disease severity	• Clinical evaluation of disease severity on a VAS scale 0-10
	Child/parent global assessment of overall well-being	• Parent/patient global evaluation on a VAS 0-10
	PRINTO inactive disease status (Lazarevic et al, 2013)	At least three of four conditions to be met: • creatinine kinase (CK) ≤150 U/L • CMAS ≥48, • MMT8 ≥78 • PGA of overall disease activity ≤0.2.
CK= creatine kinase; PGA= Physician global assessment		

Conflict of interest: none.

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