Improving outcome assessment in pediatric vasculitis

Reliable assessment of a chronic multisystem disease is a prerequisite for its optimal management as well as for conducting collaborative studies. The core set of outcome measures has been identified for the assessment of small vessel vasculitis in adults. Chronic systemic vasculitides in childhood are rare, but severe conditions that urgently need systematic evaluation. This is only possible when pediatric-specific disease classification has been completed and appropriate instruments developed. Previous work on disease assessment in other pediatric rheumatic diseases and adult vasculitis has formed a background for the development of pediatric vasculitis measures of disease activity and damage. The Paediatric Vasculitis Activity Score, derived from the adults' Birmingham Vasculitis Activity Score version 3, has been preliminarily validated. The Paediatric Vasculitis Damage Index based on the adult Vasculitis Damage Index is a tool that is under development. Patient-reported outcome assessment in vasculitis needs to be further explored.

KEYWORDS: children ■ disease activity ■ disease damage ■ health-related quality of life ■ outcome ■ systemic vasculitis

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Background

A name game

For non-native English speakers it is often difficult to correctly translate 'disease outcome' to their own languages. Among frequently used substitutions, terms such as 'disease course', 'prognosis' or 'response to treatment' are used in the context of a description of disease outcome, although their meaning only partly captures that of an 'outcome'. This linguistic difficulty reflects what health professionals, regardless their country of origin, know by heart: disease outcome is an extremely complex entity where objective, both quantifiable and qualitative features combine with subjective perception and interpretation. To add to the complexity, all of those measures can be evaluated by health professionals as well as patients and/or caregivers.

Terminology definitions

For the purpose of clinical trials, outcome terminology has been better specified. An outcome domain can be defined as a relatively broad aspect of the effect of illness on a child. Multiple measurable variables can be identified within this domain while several outcome domains may form a composite or global outcome. In this setting, an outcome measure is a tool (scale, scoring system, questionnaire and so on) used for measuring an outcome [1].

This review summarizes the state-of-the-art of pediatric vasculitis outcome assessment on the background of other pediatric rheumatic diseases as well as adult vasculitis assessments and outlines the future developments in the area.

Pediatric vasculitis

General considerations

Systemic vasculitis (SV) belongs to the most challenging conditions in pediatric rheumatology practice. The spectrum of primary vasculitides affecting children, as well as their clinical presentations, differ from that of adults. The annual incidence of Henoch–Schönlein purpura, the most common primary systemic vasculitis in children, has been estimated at 20.4 new cases in 100,000 patients younger than 18 years. The second most frequent, Kawasaki disease, is an exclusively pediatric condition with an annual incidence in patients younger than 5 years of 5.5/100,000. On the other hand, chronic primary systemic vasculitides are extremely rare in childhood, with a combined estimated annual incidence of 0.24/100,000 children [2]. The North American survey among pediatric rheumatologists has demonstrated very low exposure to these diseases, with only approximately two to five patients seen by an individual physician over 1 year [3]. This contrasts with the overall annual incidence of 1.13/100,000 for one single primary systemic vasculitis in adults, granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis) [4]. On top of the epidemiological difference, the distribution of organ

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involvement appears to differ in children with GPA, who seem to have a higher prevalence of upper airway involvement, which was recognized in as many as 86% of children [5]. In childhood polyarteritis nodosa (PAN), the systemic subtype was identified in 57% of patients, with the cutaneous subtype being the second most common (30%) and microscopic polyangiitis (8%) and hepatitis B-related PAN (5%) the least frequent ones [6]. In adults, classic PAN was reported less commonly than microscopic polyangiitis [7].

Nomenclature

Life- or organ-threatening, chronic systemic vasculitides are often associated with substantial morbidity and mortality. Until recently, collaborative studies were not possible due to the lack of consensus in childhood vasculitis classification. Both the Paediatric Rheumatology European Society Vasculitis Working Group and the North American Childhood Arthritis and Rheumatology Research Alliance Vasculitis Committee set their long-term aims in vasculitis research. Establishing common language in terms of disease definitions was considered the number one priority, and therefore childhood-specific disease classification was the first task to accomplish. Based on the international expert group consensus in 2005, classification of pediatric vasculitis was proposed by Özen *et al.* [8]. Box 1 presents established pediatric vasculitis classification with some terminology amendments based on the 2012 update on vasculitis nomenclature [9]. Validation of the proposed criteria has been subsequently completed for Henoch–Schönlein purpura, childhood PAN, childhood Takayasu arteritis and childhood GPA (Wegener's) [10,11].

Principles of disease assessment

General overview

Disease assessment forms an inevitable part of a chronic patient follow-up. The etiopathological complexity and heterogeneous, multiorgan nature of vasculitis diminish the applicability of simple laboratory or imaging measures for disease assessment. Moreover, the rarity of chronic vasculitides underlines the importance of well-defined and reproducible methods to be used in both clinical practice and in collaborative studies by physicians with varying degree of clinical experience.

In a broad sense, the assessment of a chronic systemic inflammatory condition should cover all of its potential aspects. It could be divided into multiple categories characterizing the involvement of individual organs and systems, as well as overall health and functioning. Ideally, disease assessment should allow the evaluation of disease extent and severity at a given time point and thus aid therapeutic decisions in order to minimize long-term disease sequelae and to establish the prognosis. To further complicate the situation, clinical manifestations caused by the underlying inflammatory process and its structural and functional consequences should be distinguished from the treatment adverse effects and comorbidities.

To fulfill these requirements, pathological features need to not only be detected and adequately recorded, but also evaluated in terms of their etiology (related or unrelated to the underlying inflammation), severity (organ- or life-threatening potential) and reversibility/ability to improve with anti-inflammatory treatment. Moreover, the nature of described changes combines structural (e.g., retinal damage) and functional (e.g., visual loss) components with variable potential for subjective and objective evaluations.

Main principles

An international Vasculitis Working Group has been formed under an umbrella of the wider rheumatology initiative aimed to improve outcome measurement in rheumatology, Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) [12,13]. It has identified the key components of the core set of outcome measures (composite outcome) in small vessel vasculitis: disease activity, disease damage, mortality and health-related quality of life complemented by patient-reported outcomes. These four domains have been identified with corresponding validated outcome instruments for each of them (Table 1). Additional domains were also considered for which no validated tools currently exist: biomarkers, imaging, participation and functional assessment [14,15].

The disease activity domain captures reversible features of acute morbidity caused by the underlying inflammation. Therapeutic decision-making is directly related to this measure. Its quantification enables response to treatment, remission and relapse to be further defined [15]. The disease activity instrument should list and rate pathological features directly caused by active vasculitis using clear definitions to avoid misinterpretation of clinical data.

On the other hand, irreversible consequences of previous active disease or long-term sequleae of drug adverse effects and comorbidities form

the basis of the disease damage domain. Damage accumulated during the vasculitis course represents an important part of the long-term disease burden for the patient. From the physician's perspective, it reflects the overall treatment efficacy in terms of the risk–benefit evaluation as it encompasses both the consequences of uncontrolled vasculitis as well as drug toxicities. Careful distinction between disease damage and activity is enormously important in deciding which clinical manifestations may respond to immunosuppressive therapy in order to prevent overtreatment [16].

Patient perception of the disease may significantly differ from that of medical professionals and its components are not fully captured by traditional disease assessment methods [17,18]. Physical function in terms of the degree of disability and psychosocial functioning including educational and vocational aspects are, therefore, additional important components of the patient-reported outcome domain as expressed by the measure of health-related quality of life (HRQL).

Box 1. Classification of childhood vasculitis.

Predominantly large-vessel vasculitis
- Childhood Takayasu arteritis

Predominantly medium-sized vessel vasculitis
- Childhood polyarteritis nodosa
- Cutaneous polyarteritis
- Kawasaki disease

Predominantly small-vessel vasculitis
- Granulomatous
  - Childhood granulomatosis with polyangiitis (Wegener´s)
  - Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)
- Nongranulomatous
  - Henoch–Schönlein purpura
  - Microscopic polyangiitis
  - Isolated cutaneous leucocytoclastic vasculitis
  - Hypocomplementemic urticarial vasculitis

Other vasculitides
- Behçet´s disease
- Vasculitis secondary to infection (including Hepatitus B-associated polyarteritis nodosa), malignancies and drugs, including hypersensitivity vasculitis
- Vasculitis associated with connective tissue diseases
- Isolated vasculitis of the CNS
- Cogan syndrome
- Unclassified

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Disease outcome measures in systemic pediatric rheumatic diseases

Since reduction of inflammation is the main therapeutic target in rheumatic diseases, disease activity has been considered the main treatment response measure. Its complex character has led international expert groups to the development of core sets of disease activity variables that have become universally recognized and used for standardized comparison of patient cohorts as well as for monitoring individual patient disease course in juvenile idiopathic arthritis, juvenile systemic lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM) [19]. All of them cover several components of disease activity: physician and patient/parent global assessments, functional ability/HRQL measure and disease-specific measure [20–23].

While global physician and patient/parent assessments are performed using the visual analog scale, functional ability is captured by the internationally validated tool Childhood Health Assessment Questionnaire (CHAQ) [24–26].

Global disease activity tools have been chosen as the most relevant disease-specific activity instruments for both JSLE and JDM, accompanied by additional measures reflecting specific organ involvement: renal (in JSLE) and muscle (in JDM). In JSLE, global disease activity tools used in adult disease have been applied [27]. The Disease Activity Score, Myositis Disease Activity Assessment Tool and Childhood Myositis Assessment Scale have been used in children with JDM [28,29]. Moreover, therapeutic response has been defined for various levels of improvement and definitions of inactive disease, remission and relapse have been proposed [30–34].

A corresponding core set of measures including parent/patient/physician assessments, functional and disease-specific tools have been chosen for the damage assessment in JDM and JSLE [21–23]. Among the disease-specific global damage instruments, the Myositis Damage Index has been validated in JDM and pediatric modification of the Systemic Lupus International Collaborating Clinics/ACR Damage Index has been proposed [35,36].

HRQL can be captured by generic tools used in pediatric disease such as the Child Health Questionnaire or the Pediatric Quality of Life Inventory [24,37]. Recently, a disease-specific tool has been developed to assess HRQL in JSLE: the Simple Measure of the Impact of Lupus Erythematosus in Youngsters [38].

Chronic primary systemic vasculitis: disease assessment

General perspective

Simultaneous to the ongoing disease classification efforts, the Paediatric Vasculitis Outcome (PVO) Group was formed in 2004 and, in

Table 1. OMERACT core set of outcome measures for clinical trials in ANCA-associated vasculitis.

Domain	Validated instrument
Disease activity	BVAS, BVAS/WG, BVASv.3
Damage assessment	VDI
Patient-reported outcome	SF-36
Mortality	Death

BVAS: Birmingham Vasculitis Activity Score; BVASv.3: BVAS version 3; BVAS/WG: BVAS for Wegener's granulomatosis; SF-36: Medical Outcome Sudy Short-Form 36 Survey; VDI: Vasculitis Damage Index. Adapted with permission from [15].

collaboration with the EUVAS experts, started to define pediatric tools for vasculitis assessment. At the time, tools for the assessment of disease activity and damage in adult vasculitis were widely accepted: the Birmingham Vasculitis Activity Score (BVAS) and its modifications, and the Vasculitis Damage Index (VDI) [39,40]. Psychometric properties of these instruments according to the OMERACT Filter [12] have been recently reviewed [15]. They have been used in many vasculitis trials [41–47] and have been established as appropriate outcome measures for use in clinical trials of adult ANCA-associated vasculitis. When looking at the similar situation related to the use of adult global disease activity tools for JSLE assessment, the PVO Group felt that it was also appropriate to consider this general approach in childhood vasculitis.

Assessment of vasculitis disease activity

Disease activity has been recognized as a central domain within the core set of outcome measures for clinical trials in adults [14,15,48]. Designed by consensus of a multispecialty group of vasculitis experts, the BVAS has been validated as a comprehensive multisystem tool for the standard assessment of systemic vasculitis disease activity. The BVAS version 3 (BVASv.3) has been the latest validated version of the tool [49].

A modified version of BVAS had been used in several observational studies in children [50–52]. The performance of BVAS has recently been assessed in pediatric patients from North American and European Vasculitis registries [53,54]. Despite the preliminary evidence of the relevance of this approach in children, the need for a pediatric-specific tool has been recognized as children differ in clinical manifestations as well as comorbidities [8]. Furthermore, adult reference ranges are not always applicable in children. Simultaneously, compatibility of the pediatric tool with BVAS was considered essential as it would allow long-term follow-up of patients beyond their childhood as well as including pediatric patients in trials.

Two main types of BVAS modifications were employed during the development of a Paediatric Vasculitis Activity Score (PVAS): addition of new items and redefinition of existing items [55]. Data-driven generation of new items was based on the analysis of the presenting clinical features of the three defined chronic systemic vasculitides (childhood PAN, childhood Takayasu arteritis and childhood GPA) in 116 pediatric patients enrolled in the Paediatric Rheumatology European Society/Paediatric Rheumatology International Trials Organisation vasculitis registry. Eight clinical features of active vasculitis other than the existing 56 BVAS v.3 items were identified in at least 20% of the patients and were added to the PVAS. Modified nominal group technique was then applied to reach consensus on new item definitions and their weighting as well as redefinition of 22 original BVAS items. **Figure 1 & Supplementary Table 1** (see online at: www.futuremedicine.com/doi/suppl/10.2217/ijr.14.2) show the current version of the PVAS tool and its glossary of terms with the scoring system. Importantly, the maximum score assigned to each of the nine organ categories has remained unchanged from the BVASv.3.

The PVAS scoring sheet simply records the presence or absence of each item, which must be attributable to active vasculitis after exclusion of other causes, such as infection or damage caused by previous active disease or its treatment. It reflects the need for immunosupressive therapy and is based on the intention to treat the patient. For the purpose of scoring, active disease is defined by the presence of a feature that has been new or worse within the last 4 weeks or in case of longer persistence of that feature it must have been present for less than 3 months. Every item has an assigned score in the 'new/worse' and 'persistent' scale, weighted according to severity **(Supplementary Table 1)**. The total score on all nine organ systems gives an indication of the disease activity of each patient at the time of scoring. As in BVASv.3, the new/worse scale has a maximum score of 63, while the persistent scale has a maximum overall score of 33. Although any single active disease item can be either new/worse or persistent, presence of just one new or worse disease feature is sufficient to shift the scores of all other persistently active disease features into the new/worse scale. This is simply to reflect the fact that in practical terms if the patient has a flare of the disease

Paediatric Vasculitis Activity Score

◯ Tick 'Active' box only if abnormality due to active vasculitis is newly present or worse over the last 4 weeks or persists for less than 3 months. After that, if ALL items are persistent and represent smouldering/low grade/grumbling disease, and there are no new/worse features, please tick the box at the bottom right corner. At the very first assessment all active items are considered as active/worse. If there are no abnormalities in a system, please tick the 'None' box. For items present longer than 3 months refer to the Paediatric Vasculitis Damage Index (PVDI) to score damage.

	None	Active		None	Active
1. General	◯		**6. Cardiovascular**	◯	
Myalgia		◯	Loss of pulses		◯
Arthralgia or arthritis		◯	Bruits over accessible arteries		◯
Fever ≥38.0°C		◯	Blood pressure discrepancy		◯
Weight loss ≥5% body weight		◯	Caudication of extremities		◯
2. Cutaneous			Ischemic cardiac pain		◯
Polymorphous exanthema	◯		Cardiomyopathy		◯
Livedo		◯	Congestive cardiac failure		◯
Panniculitis		◯	Valvular heart disease		◯
Purpura		◯	Pericarditis		◯
Skin nodules		◯	**7. Abdominal**	◯	
Infarct (nail edge lesion, splinter hemorrhage)		◯	Abdominal pain		◯
Ulcer (full-thickness necrosis)		◯	Peritonitis		◯
Gangrene (extensive necrosis)		◯	Blood in stools or bloody diarrhoea		◯
Other skin vasculitis (specify below)		◯	Bowel ischemia		◯
3. Mucous membranes/eyes	◯		**8. Renal**	◯	
Mouth ulcers/granulomata		◯	Hypertension >95th centile (for height)		◯
Genital ulcers		◯	Proteinuria >0.3 g/24 h; >20 mg/mmol creatinine		◯
Adnexal inflammation		◯	Hematuria ≥2+ or 5 rbc/hpf or red cell casts		◯
Significant proptosis		◯	GFR 50–80 ml/min/1.73 m^2		◯
Red eye (epi)scleritis		◯	GFR 15–49 ml/min/1.73 m^2		◯
Red eye conjunctivitis/blepharitis/keratitis		◯	GFR <15 ml/min/1.73 m^2		◯
Uveitis		◯	Rise in creatinine >10% or creatinine clearance (GFR) fall >25%		◯
Blurred vision		◯			
Sudden visual loss		◯	**9. Nervous system**	◯	
Retinal vasculitis/retinal vessel thrombosis/retinal exudates/hemorrhages		◯	Headache		◯
			Meningitis/encephalitis		◯
4. Ear, nose and throat	◯		Organic confusion/cognitive dysfunction		◯
Nasal discharge/crusts/ulcers/granuloma		◯	Seizures (not hypertensive)		◯
Paranasal sinus involvement		◯	Stroke		◯
Subglottic stenosis/hoarseness/stridor		◯	Cord lesion		◯
Conductive hearing loss		◯	Cranial nerve palsy		◯
Sensorineural hearing loss		◯	Sensory peripheral neuropathy		◯
5. Chest	◯		Motor mononeuritis multiplex		◯
Wheeze or expiratory dyspnea		◯	**10. Other**	◯	
Endobronchial/endotracheal involvement		◯			
Nodules or cavities		◯			
Pleural effusion/pleurisy		◯	Persistent disease only		◯
Infiltrate		◯	Tick here if there is no new/worse abnormality present in ANY of the systems above and all active items represent persistently active disease		☐
Massive hemoptysis/alveolar hemorrhage		◯			
Respiratory failure		◯			

Figure 1. Paediatric Vasculitis Activity Score.
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it usually requires treatment. It is possible for patients to simultaneously have some symptoms that are resolving and others that are deteriorating. This would indicate poor disease control and a more intensive therapy would probably be introduced. On the other hand, if all active vasculitis features have been persistently present for longer than 4 weeks and less than 3 months and represent low-grade, grumbling disease activity, then a persistent disease score would apply.

Several important additional rules for standard disease activity assessment have been adopted from the adult vasculitis assessment instructions [101]. These include the first scoring of a new patient and the need for a specialist opinion in the assessment of some disease features, for example, ocular or ear, nose and throat (ENT) manifestations. In case of the first disease evaluation, usually at the time of diagnosis and always prior to the initiation of immunosuppressive treatment, all vasculitis manifestations are scored as new/worse, regardless of their prior duration.

The PVAS has undergone its preliminary prospective validation across the spectrum of pediatric patients with various forms of vasculitis. In terms of the OMERACT filter for outcome measures in rheumatology, it appears to be a feasible tool with face, content and convergent validity and is reproducible and sensitive to change in patient clinical status [55].

Assessment of vasculitis disease damage

Defining disease damage and distinguishing it from disease activity is of enormous importance to the clinical care of patients with vasculitis as it helps to identify which disease manifestations do not require more immunosuppression. Since damage prevention is one of the main purposes of the treatment of active inflammatory disease, its reliable assessment may be the most important measure in evaluating patients with vasculitis [56].

The VDI is an inventory of 64 items of damage grouped into 11 organ systems selected by expert consensus to represent forms of damage occurring in adult patients with systemic vasculitis [40]. Damage is defined as the presence of irreversible features ('scars') arbitrarily defined as any item present for more than 3 months at any time since the onset of vasculitis that develop as a consequence of the initial disease or its treatment. Therefore, the VDI score can only increase or remain stable as all previously recorded items are carried on during the follow-up. The damage items are often the direct result of previous disease activity, but may occur from treatment or other comorbidity if this occurs after the onset of vasculitis.

There is no generally accepted and validated tool to assess disease damage in children with vasculitis. As part of pediatric vasculitis assessment efforts driven by the PVO Group that has developed the PVAS, development of a systematic pediatric vasculitis damage tool started in 2008. As for the disease activity assessment, the PVO Group has agreed to accept the general principles of adult disease damage evaluation via pediatric adaptation of the VDI, which has been validated and widely accepted for use in adult vasculitis trials [15,40].

During the process of the pediatric adaptation of the VDI, several rounds of PVO Group discussions with the help of other pediatric specialists (from ophthalmology, ENT, respiratory medicine, cardiology and so on) and paper case evaluations (derived from the existing VDI training cases) have resulted in minor changes in disease item grouping and the addition and redefinition of some VDI disease items that were felt to be pediatric appropriate. The latest version of the Paediatric Vasculitis Damage Index (PVDI) contains 72 items grouped into ten systems: musculoskeletal, skin/mucous membranes, ocular, ENT, chest, cardiovascular, abdominal, renal, nervous system and other. Similar to the VDI, it is accompanied by a detailed PVDI glossary explaining the meaning of individual damage items relevant to the pediatric age group. As an addition to the damage score, the one-page PVDI form contains a separate assessment of school absence defined by the mean number of missed days per month since the previous disease evaluation.

Specific attention has been paid to the concept of potential reversibility of those damage items that do not represent true physical scars (such as tissue loss or vertebral collapse). This question has been addressed by an OMERACT Vasculitis Working Group and reflected in proceedings from their meetings [16]. Pediatric damage items such as delayed puberty or failure to thrive do fulfill the definition of damage by their duration and psychosocial impact, but may eventually completely subside without long-term sequelae. In order to incorporate this concept in the pediatric tool, while retaining its compatibility with the VDI, the PVDI allows scoring each item under the column 'present' or 'no longer present'. Every scored item always

receives only one point (regardless of the evaluation of its current presence or absence) and if the no longer present box is ticked, the item must have fulfilled the condition of its previous duration of at least 3 months.

The PVDI has yet to undergo the validation process to establish its OMERACT Filter properties of truth, discrimination and feasibility. In the future, it will also have to remain a dynamically changing tool reflecting new information gathered through the upcoming pediatric vasculitis trials, as well as the continuous developments in the field of adult vasculitis damage assessment.

Training in the use of vasculitis assessment tools

In rare diseases such as chronic systemic vasculitides, reliability and reproducibility of disease assessments are crucial for the successful conduct of clinical trials. The EUVAS Group experience showed that even in clinicians who were experienced in the management of vasculitis patients, the consensus between observers for assessing BVAS and VDI was very poor, while the training of investigators led to a dramatic improvement. Therefore, structured training in the application of vasculitis activity and damage concepts and in the practical use of the tools has become an essential part of systematic disease evaluation in adult vasculitis clinical trials [49, 57,58,101].

Considering the even more prominent rarity of chronic vasculitis in the pediatric population and consequent relative lack of pediatricians' expertise in this area, such training is vitally important for pediatric specialists and should be provided to all investigators participating in collaborative vasculitis projects.

The training program for pediatric vasculitis assessment has recently been introduced. The training manual covers the theoretical background of disease activity and damage concepts followed by detailed explanation of the correct use of the PVAS and PVDI assessments with example paper cases scoring exercise.

Future perspective

Introduction of the pediatric modifications of vasculitis assessment tools will now enable systematic accumulation of reliable and reproducible clinical data on larger cohorts of children through upcoming pediatric vasculitis international collaborative studies and therapeutic trials. It is to be expected that both the PVAS and PVDI will undergo multiple refinements where disease items may be deleted as well as added in the data-driven process. Weighting of the PVAS items may change from their adult BVAS counterparts and introduction of the weighting system to the PVDI may follow the currently ongoing process of improving adult vasculitis damage assessment [14–16,59].

The concept of irreversibility of damage items will be re-examined and predictive value of disease assessment components tested [16]. This should allow disease status to be better defined in terms of various degrees of disease activity and severity, definitions of inactive disease, remission and relapse. It is also possible that current generic vasculitis assessment tools that have been originally developed to fit mainly adult small vessel vasculitides will not prove sufficiently sensitive across the whole spectrum of pediatric vasculitis and more disease-specific modifications will be needed especially for large vessel vasculitis assessment [60]. As future research will probably bring more reliable biomarkers of various aspects of vasculitis, clinical assessment tools will have to show their potential to correlate with these objectively quantifiable measures.

The domain of patient-reported outcome and HRQL is of essential importance in the chronic disease assessment as it brings a real-life perspective from the patient and his/her family, which may substantially differ from that of the healthcare professionals [17]. In pediatric care, the situation is even more complex. It is expected that parents or caregivers will provide adequate information about their offspring's wellbeing, but this may not be true as shown by discordance even in a relatively simple functional assessment such as CHAQ [61]. Therefore, variants of HRQL instruments should be applied to address both parents and the child in an age-appropriate manner. At the moment, the CHAQ and Child Health Questionnaire are the most commonly used physical and psychosocial functioning assessment tools that have been internationally validated in children and used in multiple clinical studies in pediatric rheumatic diseases [19,20,30–33]. Their performance in pediatric vasculitis is yet to be established. The Simple Measure of the Impact of Lupus Erythematosus in Youngsters tool that has been originally developed for HRQL assessment in JSLE [38] has been modified for a more generic use and its validation in systemic vasculitis is ongoing. Comprehensive outcome assessment in children should also cover aspects of schooling and higher education, peer relationships and adolescent issues. Patient and parent input

will be needed to refine the method of patient-reported outcome and HRQL assessment in pediatric disease.

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Executive summary

Terminology

- Disease outcome is a broad aspect of the effect of illness on a patient.

Pediatric vasculitis

- Chronic primary vasculitides in children are rare diseases that are potentially organ or life threatening.
- Recently validated classification of childhood vasculitis has enabled collaborative research in the area.

Disease assessment

- Disease features should be systematically recorded and evaluated in terms of etiology (vasculitic or not), severity and reversibility.
- The core-set of adult vasculitis outcome measures contains four domains: disease activity, disease damage, mortality and health-related quality of life (HRQL).

Disease outcome measures in systemic pediatric rheumatic diseases

- The core sets of disease activity and damage measures in juvenile systemic lupus erythematosus and juvenile dermatomyositis contain physician and patient/parent global assessments, disease-specific instruments and measure of functional ability and HRQL.

Chronic primary systemic vasculitis: disease assessment

- Disease activity captures reversible features of active vasculitis that are likely to respond to immunosuppression.
- Disease damage reflects irreversible consequences of previous active disease or long-term sequleae of drug adverse effects and comorbidities.
- Validated tools are available for adult vasculitis assessment: the Birmingham Vasculitis Activity Score and its modifications and Vasculitis Damage Index.
- The Paediatric Vasculitis Activity Score has been developed and the Paediatric Vasculitis Damage Index proposed for use in childhood disease.
- Training in the use of vasculitis assessment tools has become an essential part of systematic disease evaluation in vasculitis clinical trials.

Future perspective

- With upcoming collaborative research activities in pediatric vasculitis, disease assessment will remain a dynamic process open to data-driven revisions.
- The Paediatric Vasculitis Damage Index will reflect changes to the adult vasculitis damage instrument and will be refined during the validation process.
- Validation of existing measures of HRQL in childhood vasculitis and possible development of new tools is needed.

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- ▪ of interest
- ▪▪ of considerable interest

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