# Applicability of the 2006 European League Against Rheumatism (EULAR) criteria for the classification of Henoch-Schönlein purpura. An analysis based on 766 patients with cutaneous vasculitis

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*Received on September 8, 2014; accepted in revised form on December 1, 2014.*

*Clin Exp Rheumatol 2015; 33 (Suppl. 89): S44-S47.*



**Key words:** purpura, classification, criteria.

*Funding: this study was supported by a grant from the "Fondo de Investigaciones Sanitarias" PI12/00193 (Spain). It was also partially supported by RETICS Programs, RD08/0075 (RIER) and RD12/0009/0013 from the "Instituto de Salud Carlos III" (ISCIII), Spain.*

*Competing interests: none declared.*

**ABSTRACT**

**Objective.** *In 2006 the European League Against Rheumatism (EULAR) proposed new classification criteria for Henoch-Schönlein purpura (HSP). We aimed to establish the applicability of these criteria in patients with primary cutaneous vasculitis (CV). We also compared these criteria with previously established classification criteria for HSP.*

**Methods.** *A series of 766 (346 women/420 men; mean age 34 years) consecutive unselected patients with CV was assessed. One hundred and twenty-four of them with secondary CV or with CV associated with other well defined entities were excluded from the analysis. The 2006 EULAR criteria for HSP were tested in the remaining 642 patients with primary CV. Two sets of criteria for HSP were used for comparisons: a) the 1990 American College of Rheumatology (ACR-1990), and b) the ACR modified criteria proposed by Michel et al. in 1992 (Michel-1992).*

**Results.** *451 (70.2%) of 642 patients were classified as having HSP according to the EULAR-2006 criteria, 405 (63.1%) using the ACR-1990 criteria, and 392 (61.1%) by the Michel-1992 criteria. However, only 336 patients (52.3%) met at the same time the EULAR-2006 and the ACR-1990 criteria, and only 229 patients (35.7%) fulfilled both the EULAR-2006 and Michel-1992 criteria. It is noteworthy that only 276 (43%) patients met the three set of criteria. Children fulfilled all the sets of criteria more commonly than adults (215 [66.6%] of 323 vs. 61 [19%] of 319, respectively; p<0.0001).*

**Conclusion.** *According to our results, the EULAR-2006 criteria show low concordance with previous sets of classification criteria used for HSP.*

## Introduction

Henoch-Schönlein purpura (HSP) is a systemic vasculitis characterised by the involvement of the skin, joints, gastrointestinal tract and kidneys (1-4). Palpable purpura reflecting an underlying "cutaneous vasculitis" (CV) is its main clinical feature (5-7). Although a skin biopsy is the cornerstone for the diagnosis of CV, in the clinical practice, it is not routinely performed in HSP patients, especially in children (8). Diagnosis and classification of vasculitis remained for decades as an important challenge for clinicians and investigators. In the case of HSP, many different diagnostic and classification criteria have been proposed, although none of them has been universally accepted (9-14). In 1990, the American College of Rheumatology (ACR-1990) proposed a set of classification criteria for seven types of primary vasculitis, including HSP and hypersensitivity vasculitis (HV) as two different entities (15). Regrettably, based on the ACR-1990 criteria, many patients with HSP and HV were misclassified (16). Thus, two years later, using the same ACR 1990 database of patients, Michel *et al.* proposed new criteria to differentiate HSP from HV (10). Moreover, in 2006, the Paediatric Rheumatology European Society (PReS), the ACR and European Society of Paediatric Nephrology (ESPN) and the European League Against Rheumatism (EULAR) developed and proposed a new endorsed consensus criteria for classification of HSP in pediatric age (EULAR-2006) (12). These criteria were revised in 2008 and published again in 2010 (13). All these three sets of criteria (Table I) supported the claim that histological data may not always be feasible and

**Table I.** Comparison of the three set of criteria used in the present study for HSP classification.

| ACR-1990 (9,15) | | Michel *et al*. 1992 (10) | EULAR-2006 (12,13) |
|---|---|---|---|
| *Criterion definition* | | | |
| HSP | HV | HSP or HV | HSP |
| 1. Age ≤20 years: Onset of the first symptoms at the age of 20 or less. | 1. Age > 16 years: e Onset of the first symptoms at the age of 16 or more | 1. Age at onset ≤20 years: Development of first symptoms at age 20 or less. | 1. Purpura: (commonly palpable and in crops) or petechiae, with lower limb predominance, not related to thrombocytopenia. |
| 2. Palpable purpura: Slightly elevated purpuric rash over one or more areas of the skin not related to thrombocytopenia. | 2. Palpable purpura: Slightly elevated purpuric rash over one or more areas of the skin not related to thrombocytopenia. | 2. Palpable purpura: Slightly elevated purpuric rash over one or more areas of the skin not related to thrombocytopenia. | 2. Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusceptions and gastrointestinal bleeding. |
| 3. Skin biopsy: Granulocytes inside arteriolar or venular wall. | 3. Skin biopsy: Granulocytes in a periarteriolar, extraarteriolar or venular location. | 3. Gastrointestinal bleeding: Gastrointestinal bleeding, including melena, haematochezia or positive test for occult blood in the stool. | 3. Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit |
| 4. Bowel angina: Diffuse abdominal pain that worsens with meals. | 4. Maculo-papular rash: Raised plates of various sizes. | 4. Bowel angina: Diffuse abdominal pain worse after meals or bowel ischaemia usually including bloody diarrhoea. | 4. Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion. Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion. |
| | 5. Drugs at onset: Presence of medication that may cause the syndrome. | 5. No medications: Absence of any medications at onset of disease which may have been a precipitating factor. | 5. Proteinuria >0.3 g/24h or > 30mmol/mg of urine albumin/creatinine ratio on a spot morning sample. Haematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or ≥2+ on dipstick. |
| | | 6. Haematuria: Gross haematuria or microhaematuria. | |
| *Classification criteria* | | | |
| The presence of any 2 or more criteria classifies the patient as HSP with a sensitivity of 87.1% and a specificity of 87.7%. | The presence of 3 or more criteria classifies the patient as HV with a sensitivity of 71% and a specificity of 83.9%. | The presence of any 3 or more criteria yields a correct classification of HSP in 87.1% of cases. The presence of 2 or less criteria yields a correct classification of HV in 74.2% of cases. | Presence of purpura or petechiae (mandatory) with lower limb predominance* not related with thrombocytopenia and at least one of the other criteria. Sensitivity 100%, specificity 87%. (*For purpura with atypical distribution a demonstration of an IgA deposit in a biopsy is required.) |

supported the use of a combination set of clinical, laboratory and pathological findings to make a diagnosis of HSP.

To the best of our knowledge, the EULAR-2006 criteria have not been externally validated in an unselected series of patients with CV. Therefore, our aim was *i)* to establish the applicability of these criteria in patients with primary CV, and *ii)* to compare these criteria with those proposed by the ACR (ACR-1990) and Michel *et al*. For this purpose we took advantage of a large series of unselected patients with CV from a single tertiary-care referral centre.

## Patients and methods

We performed a retrospective study of unselected patients diagnosed as having CV at a teaching tertiary-care hospital in Santander (Northern Spain), from January 1976 to December 2011. The diagnosis of CV was based on either *i)* a skin biopsy showing histological findings of vasculitis (neutrophilic infiltration, leukocytoclasia, fibrinoid necrosis or erythrocyte extravasation into the vessel wall) or *ii)* the presence of typical non-thrombocytopenic palpable purpura.

Data were retrieved from the clinical charts according to a predefined protocol and then stored in a computerised file. To minimise entry error, all data were double checked and reviewed for diagnosis confirmation.

A series of 766 (346 women/420 men; mean age 34 years) consecutive unselected patients with CV was initially assessed. One hundred and twenty-four of them with secondary CV or with CV associated to other well defined entities were excluded from the analysis. Thus, CV associated with connective tissue diseases (n=35), bacterial infections (n=27), malignancies (n=16), essential mixed cryoglobulinaemia (n=13), granulomatosis with polyangiitis (Wegener's granulomatosis) (n=3), eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (n=3), urticarial vasculitis (n=21) and polyarteritis nodosa (n=7) were not included in the assessment of the classification criteria. One patient with urticarial vasculitis was associated with an underlying malignancy and was included in both categories.

The remaining 642 patients with primary CV were classified as having HSP using the ACR-1990 criteria and also in

accordance with Michel *et al*. criteria and the EULAR-2006 criteria.

For this purpose, patients were classified according to the ACR-1990 methodology and criteria. A comparative study using the ACR-1990 classification criteria (9, 15), Michel *et al*. criteria (10) and the EULAR-2006 criteria was performed (12, 13). We analysed the overall group and also the subgroup of adults (with age at diagnosis >20 years) and children (age ≤20 years) separately. This cut-off point was chosen to be consistent with the EULAR 2006.

Cohen's kappa (κ) coefficient was used to assess inter-criteria agreement between both EULAR-2006 and ACR-1990 or Michel *et al*. criteria, The statistical analysis was conducted using the STATISTICA software package (Statsoft Inc. Tulsa, OK, USA).

## Results

Figure 1 shows the flow chart of the study, including the classification of CV patients according to the ACR-1990 criteria (9, 15), and those proposed by Michel *et al*. (10) and the EULAR-2006 (12, 13).

Overall, 451 (70.2%) of 642 patients were classified as having HSP according to the EULAR-2006 criteria, 405 (63.1%) using the ACR-1990 criteria, and 392 (61.1%) by the Michel-1992 criteria. However, only 336 patients (52.3%) met at the same time the EULAR-2006 and the ACR-1990 criteria, and only 229 patients (35.7%) fulfilled both the EULAR-2006 and Michel *et al*. criteria.

Figure 2 shows the distribution of patients according to the above-mentioned set of criteria for HSP in adults and in children. It is noteworthy that only 276 (43%) patients met the three set of criteria. The number of patients that fulfilled all the three sets of criteria was significantly higher in the group of children than in the group of adults (215/323 [66.6%] *vs*. 61/319 [19%]; $p<0.0001$).

The results of the inter-criteria agreement analysis were as follow: ACR-1990 *vs*. EULAR-2006 (Adults: κ=0.31; $p=0.05$; Children: κ=0.23; $p=0.07$; Adults & Children: κ=0.36; $p=0.04$); Michel *et al*. *vs*. EULAR-2006 (Adults: κ=0.33; $p=0.05$; Children: κ=0.24; $p=0.06$; Adults & Children κ=0.38; $p=0.04$). In a further step we reassessed the data using 16 years as the cut-off point for age instead of 20 years. However, the results were essentially the same as those found using as a cut-off 20 years (data not shown).

## Discussion

Our study highlights the heterogeneity of criteria for the classification of HSP and the need for a unification and implementation of a well-defined set of diagnostic criteria focused on the daily clinical practice. Despite attempts made by the ACR group of experts to characterise and classify different types of vasculitides, due to the lack of specific symptoms or diagnostic schemes, systemic vasculitides remain to be a challenge for clinicians. In this regard, it is important to emphasise that the ACR-1990 criteria were originally designed as a classification method, but not as a diagnostic tool. This fact was emphasised by Rao *et al*. who pointed out that in some cases individuals without systemic vasculitis may fulfill one or more ACR-1990 classification criteria (17).

We have found that approximately 60% of our patients with CV fulfilled the ACR-1990 criteria for HSP. Similar results were observed when the criteria proposed by Michel *et al*. were applied. In this regard, we feel that the criteria put forward by Michel *et al*. may be more useful in the clinical practice, because they are focused on the typical features of the disease, such as abdominal manifestations (gastrointestinal bleeding and bowel angina) and renal involvement manifested by haematuria, and, of note, a skin biopsy is not mandatory for their application. However, these criteria were not specifically designed for HSP diagnosis, but for differentiating this entity from HV, a disorder usually confined to the skin, which is included nowadays in the "Single organ cutaneous small-vessel vasculitis"

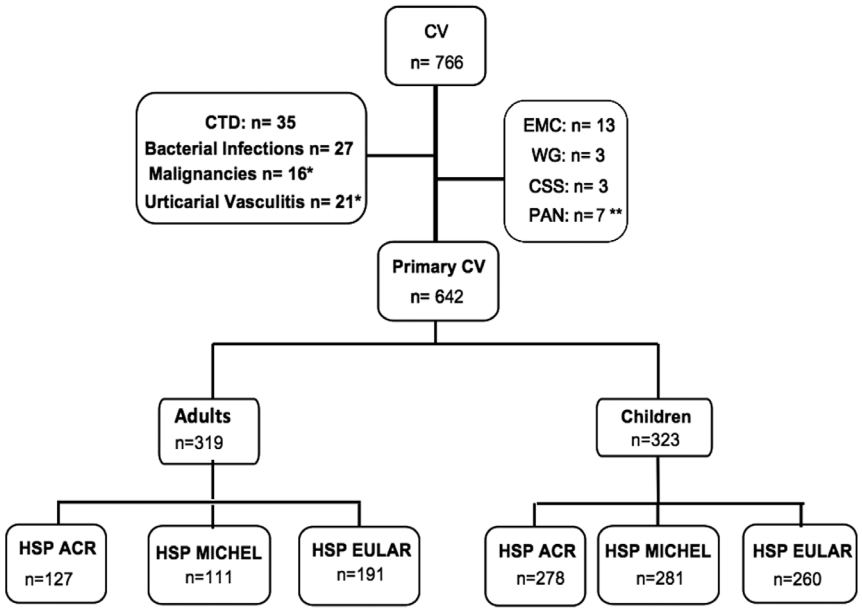


**Fig. 1.** Flow chart of the study.
CV: Cutaneous vasculitis;
CTD: Connective Tissue Diseases;
EMC: Essential Mixed Cryoglobulianemia;
WG: Wegener Granulomatosis;
CSS: Churg-Strauss Syndrome;
PAN: Panarteritis nodosa;
ACR: American College of Rheumatology;
HSP: Henoch-Schönlein Purpura;
HV: Hypersensitivity Vasculitis;
NC: Not Classified.
*A patient with urticarial vasculitis was related to an underlying malignancy and was included in both groups.
**Four patients with microscopic polyangiitis were included in the group of panarteritis nodosa according to the ACR-1990 criteria.

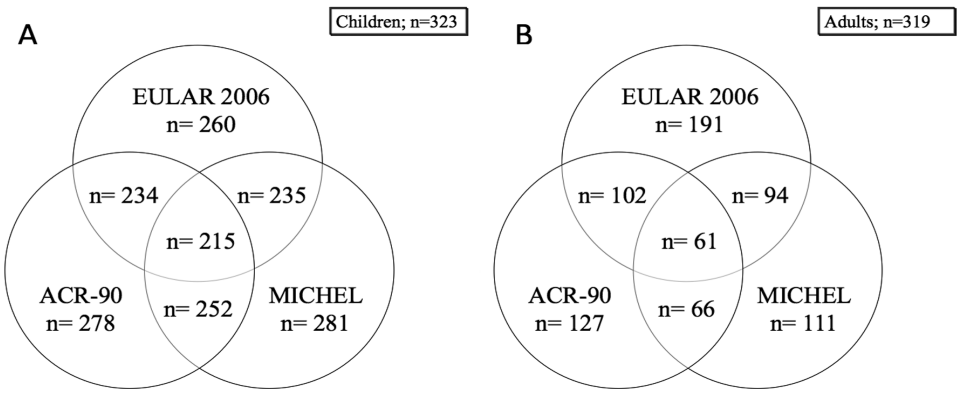


**Fig. 2.** Classification of 642 patients (Box A children and Box B adults) with primary Cutaneous vasculitis (CV) – Henoch-Schönlein purpura (HSP) according to the three set of criteria analysed. The figures inside the rings represent the number of patients.

group, according to the 2012 Revised International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (14).

Since HSP is the most frequent paediatric CV, in an attempt to develop a new set of criteria for the classification of childhood vasculitis, the PReS with the endorsement of the EULAR published in 2006 new criteria for HSP based on a Delphi consensus (12, 13). The criterion of age was removed, and the experts reached consensus to define HSP if there was purpura or petechiae not related to thrombocytopenia with lower limb predominance (mandatory criterion), and at least one of the following four manifestations: abdominal pain, arthritis or arthralgia, renal involvement (haematuria and/or proteinuria), and leukocytoclastic vasculitis with predominant IgA deposit in the skin or kidney.

Following the EULAR-2006 criteria, we classified a higher number of patients as having HSP (70.2%) than using the ACR-1990 or the Michel *et al*. criteria. This may be due to the exclusion of age as a criterion. In fact, in our series, some patients older than 20 years that did not fulfill the other set of criteria were classified as HSP when the EULAR-2006 classification criteria were applied. Thus, 191 of 319 adult patients with CV (59.8%) where classified as HSP following EULAR-2006 criteria. In this sense, we feel that the EULAR-2006 criteria may be useful for HSP classification in patients with CV regardless of age. Nevertheless, only 52.3% of our patients met the ACR-1990 and the EULAR-2006 classification criteria at the same time. The number of patients who fulfilled the EULAR-2006 and the Michel *et al*. criteria at the same time was even lower. In addition, only 19% of adults and 66.6% of children fulfilled all the three set criteria, reflecting the heterogeneity of diagnostic criteria for HSP.

In conclusion, according to our results, the ACR-1990 criteria, the criteria proposed by Michel *et al*. and the EULAR-2006 criteria for HSP show low concordance and their use separately has a limited value for the classification of patients with primary CV. Further efforts are needed to better define HSP in adults and children. In this regard, new criteria based on prospective studies encompassing large number of patients may help to classify patients with systemic vasculitis. It is also applicable to the complex group of disorders presenting with CV.

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