EDITOR'S CHOICE

EULAR/PRINTO/PRES criteria for Henoch–Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria

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ABSTRACT

Objectives To validate the previously proposed classification criteria for Henoch–Schönlein purpura (HSP), childhood polyarteritis nodosa (c-PAN), c-Wegener granulomatosis (c-WG) and c-Takayasu arteritis (c-TA).

Methods Step 1: retrospective/prospective web-data collection for children with HSP, c-PAN, c-WG and c-TA with age at diagnosis ≤18 years. Step 2: blinded classification by consensus panel of a representative sample of 280 cases. Step 3: statistical (sensitivity, specificity, area under the curve and κ-agreement) and nominal group technique consensus evaluations.

Results 827 patients with HSP, 150 with c-PAN, 60 with c-WG, 87 with c-TA and 52 with c-other were compared with each other. A patient was classified as HSP in the presence of purpura or petechiae (mandatory) with lower limb predominance plus one of four criteria: (1) abdominal pain; (2) histopathology (IgA); (3) arthritis or arthralgia; (4) renal involvement. Classification of c-PAN required a systemic inflammatory disease with evidence of necrotising vasculitis OR angiographic abnormalities of medium-/small-sized arteries (mandatory criterion) plus one of five criteria: (1) skin involvement; (2) myalgia/muscle tenderness; (3) hypertension; (4) peripheral neuropathy; (5) renal involvement. Classification of c-WG required three of six criteria: (1) histopathological evidence of granulomatous inflammation; (2) upper airway involvement; (3) laryngo-tracheo-bronchial involvement; (4) pulmonary involvement (x-ray/CT); (5) antineutrophilic cytoplasmic antibody positivity; (6) renal involvement. Classification of c-TA required typical angiographic abnormalities of the aorta or its main branches and pulmonary arteries (mandatory criterion) plus one of five criteria: (1) pulse deficit or claudication; (2) blood pressure discrepancy in any limb; (3) bruits; (4) hypertension; (5) elevated acute phase reactant.

Conclusion European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society propose validated classification criteria for HSP, c-PAN, c-WG and c-TA with high sensitivity/specificity.

INTRODUCTION

In 1990 the American College of Rheumatology (ACR) proposed classification criteria for patients with vasculitides[1–5] by analysing 807 adults patients with different form of vasculitis: 85 with Henoch–Schönlein purpura (HSP), 118 with polyarteritis nodosa (PAN), 85 with Wegener granulomatosis (WG), 63 with Takayasu arteritis (TA) and 456 with other vasculitides (Churg–Strauss, hypersensitivity, giant cell arteritis and other unspecified forms).[6] Patients with each specific vasculitis were compared with all the remaining diseases grouped into a single control category.

The ACR criteria for HSP (sensitivity 87.1%, specificity 87.7%) require the presence of at least two of the following: (1) age ≤20 years at disease onset; (2) palpable purpura; (3) acute abdominal pain; (4) biopsy showing granulocytes in the walls of small arterioles/venules.[1]

The ACR criteria for PAN (sensitivity 82.2%, specificity 86.6%) require at least three of the 10 following criteria: (1) granulocyte or mixed leucocyte infiltrate in an arterial wall on biopsy; (2) arteriographic abnormalities; (3) livedo reticularis; (4) myalgia; (5) diastolic blood pressure (BP) >90 mm Hg; (6) mono- or polyneuropathy; (7) elevated blood urea nitrogen or creatinine; (8) testicular pain/tenderness; (9) hepatitis B reactants; (10) weight loss >4 kg.[3 5]

The ACR criteria for WG (sensitivity 88.2%, specificity 92%) require at least two of the following: (1) abnormal urinary sediment (red cell casts or >5 red blood cells per high power field);

(2) abnormal findings on chest radiograph (nodules, cavities or fixed infiltrates); (3) oral ulcers or nasal discharge; (4) granulomatous inflammation on biopsy.[4]

Finally, the ACR criteria for TA (sensitivity of 91%, specificity 98%) require the presence of at least three of the following: (1) arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal, upper or lower extremities; (2) decreased brachial artery pulse; (3) claudication of an extremity; (4) systolic BP >10 mm Hg difference in systolic BP between arms; (5) a bruit over subclavian arteries or the aorta; (6) age at disease onset ≤40 years.[2] The ACR criteria were derived by comparing 63 patients with adult TA with 744 controls with other vasculitides.

In 2005 the vasculitis working group of the Paediatric Rheumatology European Society (PRES) proposed new classification criteria for paediatric vasculitides, endorsed by the European League Against Rheumatism (EULAR).[7] However, these proposed modifications were mainly based on a literature review and a consensus-based process and were not formally validated. Thanks to support from EULAR, the Paediatric Rheumatology International Trials Organisation (PRINTO)[8] and PRES, a formal statistical validation process, with a large-scale, web-based data collection, was undertaken. The project culminated finally at the 2008 Ankara Consensus Conference which had, as its primary objective, the validation of the aforementioned EULAR-endorsed criteria for paediatric vasculitides.

With this second paper we describe the final classification criteria for each of the four vasculitides analysed (HSP, c-TA, c-PAN and c-WG) while the general methodology and overall demographic and clinical characterisation are reported in the accompanying paper.[9]

PATIENTS AND METHODS

The methodology used is described in detail in the accompanying introduction and methods paper.[9] In brief, after obtaining consent from parent(s)/child and ethics committee approval as appropriate, 97 PRINTO/PRES institutions in 36 countries, enrolled children with vasculitides, into a three-step retrospective/prospective study.

Step 1: Web-based data collection

Children with age at diagnosis ≤18 years, diagnosed by their treating physician, as HSP, c-PAN, c-WG, c-TA or other c-primary systemic vasculitis (c-other) were included. Data collected included demographic, diagnosis, signs/symptoms (glossary provided) before/or at the date of diagnosis and at least 3 months after, laboratory, histopathological and imaging reports.

Step 2: Classification by consensus panel

Using three Delphi technique[10] web-rounds, a subgroup of 280 cases were classified (blinded to original diagnosis by the treating physician), by a panel of 11 paediatric rheumatologists/nephrologists into HSP, c-PAN, c-WG, c-TA or c-other. The main purpose of the classification exercise was to evaluate the κ level of agreement[11 12] with 95% CI between the consensus panel classification and the attending physician diagnosis.

Step 3: Statistical and consensus evaluations

A nominal group technique[10] consensus conference was convened in Ankara in October 2008 to discuss the statistical performance (frequency, sensitivity, specificity, area under the curve (AUC) and κ) of clinical/laboratory findings (criteria) and of 56 HSP, 29 c-PAN, 62 c-WG and 25 c-TA definitions. For the purposes of the statistical analysis all cases of specific vasculitis (eg, HSP classified by the consensus panel or diagnosed by the treating physician) were compared with the control group represented by the remaining cases of childhood vasculitides (eg, c-PAN, c-WG, c-TA, c-other).

RESULTS

Of the 1398 children enrolled, 860 (62%) were diagnosed by the treating physician as HSP, 172 (12%) as c-PAN, 67 (5%) as c-WG, 99 (7%) as c-TA and 200 (14%) as c-other.

Henoch–Schönlein purpura

Step 1: Web-based data collection

From the 860/1398 (62%) children with HSP available in the database, 29 patients were excluded from the analysis for the following reasons: 16 patients because they were diagnosed with infantile haemorrhagic oedema/Finkelstein purpura (all aged <1 year), seven because of other co-morbid conditions and six for missing data.

Step 2: Classification by consensus panel

Sixty patients (22 difficult cases and 38 randomly selected) were blinded for the referring centre diagnosis and classified by the consensus panel: 56 were confirmed as HSP while four were excluded (in three patients consensus not achieved and one was unclassifiable). The κ-agreement between the consensus panel and treating physician was 0.96 (95% CI 0.84 to 1), therefore justifying the inclusion of all 827 patients with HSP in the next step.

Step 3: Statistical and consensus evaluations

The 827/1183 (70%) patients with HSP (771 diagnosed by the treating physician and 56 by the consensus panel) were included in the final analysis and compared with the remaining 356 patients with another form of vasculitides who were used as a control group (c-PAN 150, c-WG 60, c-TA 87, c-other 59 patients).

All patients had purpura (lower limb predominance or diffuse combined) while the characteristic palpable purpura, commonly in crops, with lower limb predominance was seen in 89% of the patients with HSP and in 15% of those with c-PAN and c-WG. Diffuse abdominal pain was present in 60% of children with HSP, arthritis/arthralgia in 78%, proteinuria/haematuria combined in 33%. IgA deposition was observed in 83/827 (10%) of the HSP cases but only 125 patients (89 HSP and 36 controls) had biopsies available. There were no other signs and symptoms, laboratory/biopsy/imaging reports that were more frequently seen in patients with HSP than in the other vasculitides (see accompanying paper[9] for further details and online supplementary figure 1A web).

Figure 1A shows the sensitivities/specificities of patients with HSP versus the other c-vasculitides. Purpura with lower limb predominance and IgA deposition had both sensitivities/specificities >80%; vessel wall granulocytes (ACR criterion) had a low specificity (26%). Abdominal pain had sensitivities/specificities >60%, arthritis/arthralgia was sensitive (78%) but less specific and proteinuria/haematuria was specific (70%) but less sensitive.

Table 1 provides a glossary of definitions, sensitivity/specificity/AUC for each HSP criterion and the final EULAR/PRINTO/PRES definition. The sensitivities/specificities/AUC and κ-agreement (between the consensus panel and specific definition) of the final HSP EULAR/PRINTO/PRES classification definition was 100%/87%/93.5%, respectively, with an almost perfect κ-agreement of 0.90 (95% CI 0.84 to 0.96) compared with 100%/69% of the preliminary EULAR HSP proposal. The sensitivity/specificity of the original HSP

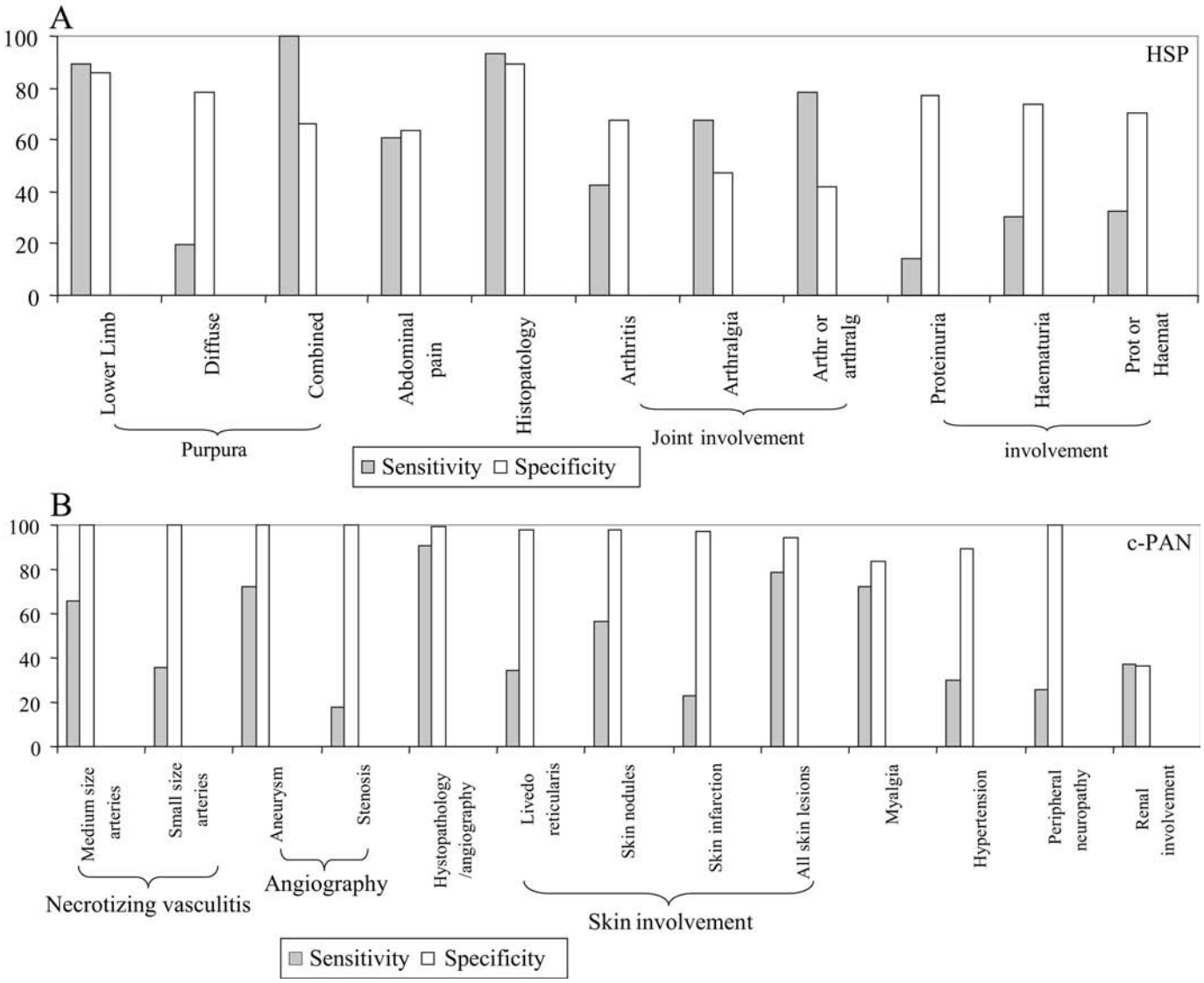

Figure 1 (A) Sensitivity and specificity values seen in the 827 patients with HSP versus the other forms of childhood vasculitides (c-PAN 150, c-WG 60, c-TA 87). (B) Sensitivity and specificity values seen in the 150 patients with c-PAN versus the other forms of childhood vasculitides (HSP 827, c-WG 60, c-TA 87). c-PAN, childhood polyarteritis nodosa; c-TA, c-Takayasu arteritis; c-WG, Wegener granulomatosis; HSP, Henoch–Schönlein purpura.

ACR criteria were 100%/2%/51% (κ=0.04), which rose to 100%/75%/87.5% (κ=0.81) when the age criterion (≤20 years) was not considered.

Childhood polyarteritis nodosa

Step 1: Web-based data collection

A total of 172/1398 (12%) children with c-PAN were available in the database.

Step 2: Classification of difficult cases by consensus panel

Sixty patients (37 difficult cases and 23 randomly selected) were blinded for the referring centre diagnosis and classified by the consensus panel: 38 as c-PAN while 22 were excluded (more than one reason possible: one because of hepatitis B association, two because of incomplete data, 12 because consensus was not achieved and 10 because they were unclassifiable). The κ-agreement between the consensus panel and treating physician was 0.73 (95% CI 0.62 to 0.84), therefore justifying the inclusion of all 150 patients with c-PAN into the next step. The 45 patients with cutaneous PAN and 14 with microscopic polyangiitis were also excluded from the analysis.

Step 3: Statistical and consensus evaluations

The 150/1124 (13%) patients with c-PAN (112 diagnosed by the treating physician and 38 by the consensus panel) were included in the final analysis and compared with the remaining 974 patients (HSP 827, c-WG 60, 87 c-TA).

Small- or medium-sized artery necrotising vasculitis was documented in 28 (19%) and 52 (35%) patients, respectively (small or medium in 67 patients, 45%). Angiographic abnormalities were present in 64 patients (43%), with 14 (9%) having stenoses of medium/small arteries and 57 (38%) aneurysms. The presence of necrotising vasculitis or angiographic abnormalities was seen in 116 (77%) of the patients. Among the others signs/symptoms the most common was myalgia reported by 108 (72%) patients. The second clinical characteristic was skin involvement observed in 104 (69%) patients with c-PAN versus 18 (30%) with c-WG; 51 (34%) with livedo reticularis, 84 (56%) with skin nodules, 19 (13%) with superficial skin infarction

Table 1 Final EULAR/PRINTO/PRES HSP criteria (with glossary) and classification definition (sample 973)

Criterion	Glossary	Sensitivity (%)	Specificity (%)	AUC (%)
Purpura (mandatory criterion)	Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, * not related to thrombocytopenia	89	86	87.5
1. Abdominal pain	Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding	61	64	62.2
2. Histopathology	Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit	93	89	91.1
3. Arthritis or arthralgias	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	78	42	59.9
4. Renal involvement	Proteinuria >0.3 g/24 h or >30 mmol/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	33	70	51.4
HSP EULAR/PRINTO/PRES Ankara 2008 classification definition: κ 0.90 (95% CI 0.84 to 0.96)	Purpura or petechiae (mandatory) with lower limb predominance* and at least one of the four following criteria: Abdominal pain Histopathology Arthritis or arthralgia Renal involvement	100	87	93.5

*For purpura with atypical distribution a demonstration of an IgA deposit in a biopsy is required.
AUC, area under the curve; EULAR, European League Against Rheumatism; HSP, Henoch–Schönlein purpura; PRES, Paediatric Rheumatology European Society, PRINTO, Paediatric Rheumatology International Trials Organisation.

and 16 (11%) with deep skin infarction. Hypertension was documented in 44 (29%) patients with c-PAN and in 55 (63%) with c-TA. Peripheral neuropathy (mono- or polyneuropathy) in 39 (26%) and renal involvement (proteinuria, haematuria or red blood cell casts) in 44 (29%). Finally, testicular pain or tenderness was present in 15/75 male children (20%) and signs/symptoms suggesting vasculitis of any other major organ system (pulmonary, gastrointestinal, cardiovascular, or central nervous system) were reported in 113 (75%). There were no other signs and symptoms that were more frequently observed in patients with c-PAN than in the other vasculitides (see accompanying paper[9] for further details and online supplementary figure 1B).

Figure 1B shows the sensitivities/specificities of patients with c-PAN versus the other c-vasculitides. Specificity was >99.5% for the mandatory criteria with sensitivity being higher for aneurysm (72%), followed by medium-, small-size artery necrotising vasculitis and stenoses. Sensitivity/specificity for histopathological changes or angiographic abnormalities combined were 90.6%/99.6% in this population. Specificity of the remaining signs/symptoms were>80% with the exception of renal involvement (37%), while sensitivity was >70% only for skin involvement and myalgia.

Table 2 provides a glossary of definitions, sensitivity/specificity/AUC for each c-PAN criterion and the final EULAR/PRINTO/PRES definition. The sensitivities/specificities/AUC and κ-agreement (between the consensus panel and specific definition) of the final EULAR/PRINTO/PRES c-PAN classification definition was 89.6%/99.6%/94.6%, respectively, with an almost perfect κ-agreement of 0.92 (95% CI 0.86 to 0.98) compared with 86.3%/99.6%/93% of the preliminary EULAR c-PAN proposal. The sensitivity/specificity for the original adult PAN ACR criteria were 94.7%/95.2%/95% (κ=0.77) in this paediatric population.

Childhood Wegener granulomatosis

Step 1: Web-based data collection

A total 0f 67/1398 (5%) children with c-WG were available in the database.

Step 2: Classification of difficult cases by consensus panel

Sixty patients (19 difficult cases and 41 randomly selected) were blinded for the referring centre diagnosis and classified by the consensus panel: 51 were confirmed as c-WG (plus one was originally diagnosed as c-PAN and one as another form of c-vasculitis) while nine were excluded (multiple reasons possible: one because age at onset >18 years, one because of other co-morbid conditions, five because consensus was not achieved and four because they were classified as c-other). The κ-agreement between consensus panel and treating physician was 0.88 (95% CI 0.76 to 0.99), therefore justifying the inclusion of all 60 patients with c-WG in the next step.

Step 3: Statistical and consensus evaluations

The 60/1183 (5%) patients with c-WG (seven diagnosed by the treating physician and 53 by the consensus panel) were included in the final analysis and compared with the remaining 1123 patients (HSP 827, c-PAN 150, c-TA 87, c-other 59 patients).

Granulomatous inflammation lesions were present in 27/50 patients (54%) (13 in the upper airways, seven kidney, four orbital mass, three others). More than 70% of the patients had upper airway involvement (either nasal discharge or septum perforation or sinus inflammation), chest x-ray or CT signs (47/60 patients, 78%), versus <10% in the other vasculitides. Immunofluorescence antineutrophilic cytoplasmic antibody (ANCA) was positive in 47 (78%) patients, MPO/pANCA in 14 (23%) and PR3/cANCA in 38 (63%) (any ANCA positivity in 54, 90%) while the frequency of any ANCA positivity was 11% in c-PAN and <5% in the other vasculitides. Renal involvement was observed in 39 (65%) of the patients with 24 (40%) patients having necrotising pauci-immune glomerulonephritis. There were no other signs and symptoms, laboratory/biopsy/imaging reports that were more frequently observed in patients with c-WG than in the other vasculitides (see accompanying paper[9] for further details and online supplementary figure 2A).

Figure 2A shows the sensitivities/specificities of patients with c-WG versus the other c-vasculitides. Sensitivities/specificities were >75% for upper airway involvement, pulmonary

Table 2 Final EULAR/PRINTO/PRES c-PAN criteria (with glossary) and classification definition (sample 1099)

Criterion	Glossary	Sensitivity (%)	Specificity (%)	AUC (%)
	A systemic inflammatory disease characterised by:			
Histopathology	Evidence of necrotising vasculitis in medium or small sized arteries	84.8	99.7	92.3
Angiographic abnormalities	Angiography showing aneurysm, stenoses or occlusion of a medium or small sized artery, not due to fibromuscular dysplasia, or other non-inflammatory causes. Conventional angiography is the preferred imaging modality.	81.0	99.9	90.5
	(Histopathology or angiography are mandatory criterion)	90.6	99.6	95.1
1. Skin involvement	Livedo reticularis: purplish reticular pattern usually irregularly distributed around subcutaneous fat lobules, often more prominent with cooling Skin nodules: tender subcutaneous nodules Superficial skin infarctions: superficial skin ulcers (involving skin and superficial subcutaneous tissue) or other minor ischaemic changes (nailbed infarctions, splint haemorrhages, digital pulp necrosis) Deep skin infarctions: deep skin ulcers (involving deep subcutaneous tissue and underlying structures), digital phalanx or other peripheral tissue (nose and ear tips) necrosis/gangrene	78.8	94.3	86.6
2. Myalgia or muscle tenderness	Muscle pain or tenderness	72.5	83.6	78.1
3. Hypertension	Systolic/diastolic blood pressure greater than 95th centile for height	29.7	89	59.4
4. Peripheral neuropathy	Sensory peripheral neuropathy: neuropathy resulting in glove or stocking distribution of sensory loss Motor mononeuritis multiplex Neuritis of named peripheral nerve, only scored if motor involvement	26.0	99.8	62.9
5. Renal involvement	Proteinuria >0.3 g/24 h or >30 mmol/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 Impaired renal function: measured or calculated GFR (Schwartz formula) <50% normal	37.3	36.7	37
c-PAN EULAR/PRINTO/PRES Ankara 2008 classification definition: κ 0.92 (95% CI 0.86 to 0.98)	Histopathology or angiographic abnormalities (mandatory) plus one of the five following criteria: Skin involvement Myalgia/muscle tenderness Hypertension Peripheral neuropathy Renal involvement	89.6	99.6	94.6

AUC, area under the curve; c-PAN, childhood polyarteritis nodosa; EULAR, European League Against Rheumatism; GFR, glomerular filtration rate; PRES, Paediatric Rheumatology European Society, PRINTO, Paediatric Rheumatology International Trials Organisation.

involvement on chest x-ray or CT and ANCA (sensitivities/specificities immunofluorescence 84%/91%, MPO 26%/94%, PR3 69%/96%).

Table 3 provides the glossary of definitions, sensitivity/specificity/AUC for each c-WG criterion and the final EULAR/PRINTO/PRES definition. The sensitivities/specificities of the final 2009 EULAR/PRINTO/PRES classification definition were 93.3%/99.2%/96.3%, respectively, with an almost perfect κ-agreement of 0.90 (95% CI 0.84 to 0.97) compared with 88%/100%/94% for the preliminary EULAR c-WG proposal. The sensitivities/specificities of the original adult WG ACR criteria were 83%/98%/90.5% (κ=0.77) in this paediatric population.

Childhood Takayasu arteritis

Step 1: Web-based data collection

A total of 99/1398 (7%) children with c-TA were available in the database.

Step 2: Classification of difficult cases by consensus panel

Sixty patients (10 difficult cases and 50 randomly selected) were blinded for the referring centre diagnosis and classified by the consensus panel: 48 as c-TA while 12 were excluded (multiple reasons possible: two because age at onset was >18 years, one because of incomplete data, nine because consensus was not achieved and three because they were unclassifiable). The κ-agreement between consensus panel and treating physician was 0.84 (95% CI 0.73 to 0.96) therefore justifying the inclusion of all 87 patients with c-TA in the next step.

Step 3: Statistical and consensus evaluations

The 87/1183 (7%) patients with c-TA (39 diagnosed by the treating physician and 48 by the consensus panel) were included in the final analysis and compared with the remaining 1096 patients with other form of vasculitides (HSP 827, c-PAN 150, c-WG 60, other forms 59 patients).

All 87 patients had angiographic abnormalities (100%) (for three patients stenoses were documented by MRI or CT), of whom 74 (85%) had stenoses and 43 (49%) aneurysms. Decreased peripheral artery pulse(s) were observed in 62 (71%) and claudication of extremities in 33 (38%) (either signs in 65 patients, 75%). Discrepancy of four limb BP >10 mm Hg, bruits over aorta and/or its major branches were reported in 54 (62%) and 50 (57%) patients, respectively. Also, hypertension was present in 55 (63%) children as compared with the 44 (29%) patients with c-PAN and six (10%) with WG. Abnormal acute phase reactants (erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)) were observed, at the time of diagnosis, in 76 (87%), similar to c-PAN and c-WG. There were no other signs and symptoms that were more frequently observed in patients with c-TA than in the other vasculitides (see accompanying paper[9] for further details and online supplementary figure 2B).

Figure 2B shows the sensitivities/specificities of patients with c-TA versus the other c-vasculitides. Stenoses had higher sensitivities/specificities (85%/100%) than aneurysms (49%/99.9%) (stenoses or aneurysm 100%/99.9%). The other four features showed a specificity of ≥90%, while sensitivity was >70% only for pulse deficit/claudication. Sensitivities/specificities of abnormal acute phase reactants (ESR<20 or CRP elevated) were 95%/14%.

Table 4 provides a glossary of definitions, sensitivity/specificity/AUC for each c-TA criterion and the final EULAR/PRINTO/PRES definition. The sensitivity/specificity/AUC of the final EULAR/PRINTO/PRES classification definition was 100%/99.9%/99.95%, respectively, with an almost perfect κ-agreement of 0.99 (95% CI 0.93 to 1) compared with 94.3%/99.9%/97.1% of the preliminary EULAR c-TA proposal. The sensitivities/specificities for the original adult TA ACR criteria were 85.1%/99.6%/92.4% (κ=0.89) in this paediatric population with a decrease in sensitivity if the age criterion (<40 years) was removed.

Further results on sensitivities, specificities, AUC and κ-agreement

In order to control for potential skewing of data we repeated the analysis with a random sample of 120 patients with HPS instead of the full 827 sample. Sensitivities, specificities, AUC and κ-agreement of the final classification criteria, as well as of the individual criterion for HSP, c-PAN, c-WG and c-TA did not change when a random sample of 120 patients with HSP was used instead of the full 827 HSP sample (data not shown).

DISCUSSION

The diagnosis of classic HSP is commonly made by paediatricians. However, validated classification criteria did not exist. This is crucial for future collaborative studies, which require standardised criteria. While there are some similarities between the original ACR criteria and the new criteria (eg, purpura and abdominal pain), some changes were also considered. The ACR criteria required biopsy showing granulocytes in the walls of arterioles or venules; however, this criterion had a very low

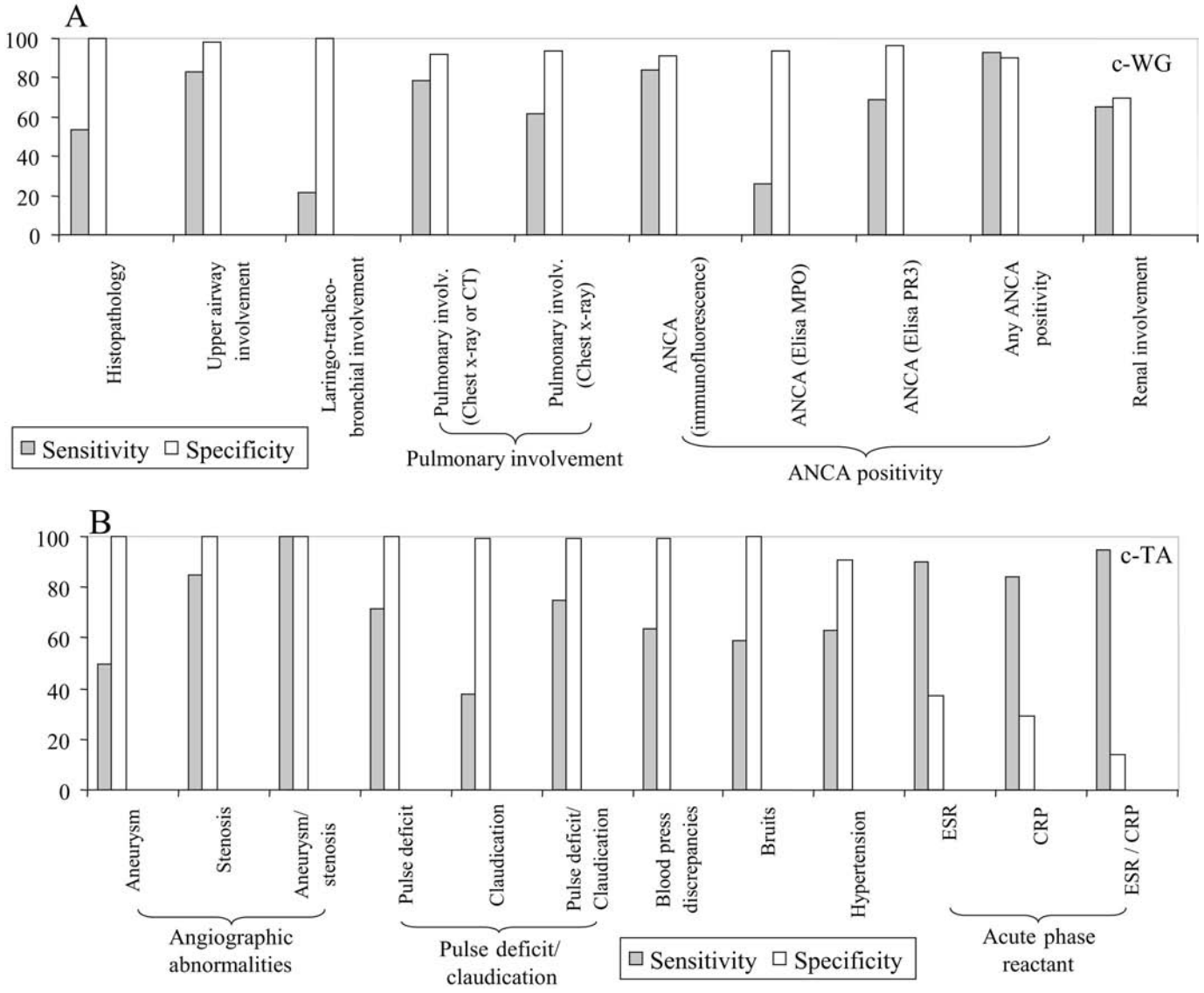

Figure 2 (A) Sensitivity and specificity values seen in the 60 patients with c-WG versus the other forms of childhood vasculitides (HSP 827, c-PAN 150, c-TA 87). (B) Sensitivity and specificity values seen in the 87 patients with c-TA versus the other forms of childhood vasculitides (HSP 827, c-PAN 150, c-WG 60). ANCA, antineutrophilic cytoplasmic antibody; c-PAN, childhood polyarteritis nodosa; CRP, C-reactive protein; c-TA, c-Takayasu arteritis; c-WG, Wegener granulomatosis; ESR, erythrocyte sedimentation rate; HSP, Henoch–Schönlein purpura.

Table 3 Final EULAR/PRINTO/PRES c-WG criteria (with glossary) and classification definition (sample 939)

Criterion	Glossary	Sensitivity (%)	Specificity (%)	AUC (%)
1. Histopathology	Granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area	54	99.6	76.8
2. Upper airway involvement	Chronic purulent or bloody nasal discharge or recurrent epistaxis/crusts/ granulomata Nasal septum perforation or saddle nose deformity Chronic or recurrent sinus inflammation	83	99	91
3. Laryngo-tracheo-bronchial involvement	Subglottic, tracheal or bronchial stenoses	22	99.8	60.7
4. Pulmonary involvement	Chest x-ray or CT showing the presence of nodules, cavities or fixed infiltrates	78	92	85.2
5. ANCA	ANCA positivity by immunofluorescence or by ELISA (MPO/p or PR3/c ANCA)	93	90	91.7
6. Renal involvement	Proteinuria >0.3 g/24 h or >30 mmol/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 Necrotising pauci-immune glomerulonephritis	65	69.6	67.3
c-WG EULAR/PRINTO/PRES Ankara 2008 classification definition: κ 0.90 (95% CI 0.84 to 0.97)	At least three of the six following criteria: Histopathology Upper airway involvement Laryngo-tracheo-bronchial stenoses Pulmonary involvement ANCA positivity Renal involvement	93.3	99.2	96.3

ANCA, antineutrophilic cytoplasmic antibody; AUC, area under the curve; c-WG, c-Wegener granulomatosis; EULAR, European League Against Rheumatism; PRES, Paediatric Rheumatology European Society, PRINTO, Paediatric Rheumatology International Trials Organisation.

specificity in this paediatric population. On the other hand, although biopsies were rarely done, the presence of IgA in the biopsy was very specific. Thus the consensus panel chose histopathology showing typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit for all doubtful cases such as for purpura with atypical characteristics or distribution. Other differences were related to the inclusion of joint involvement that is more common and with higher sensitivity in children than in the patients of the ACR paper.[1] Renal involvement was also considered worth including to underline the importance of prospective monitoring for haematuria/proteinuria when HSP evolves to severe renal damage. The final HSP definition had greater sensitivity than the preliminary 2005 EULAR-endorsed criteria,[7] with a substantial κ-agreement with the blinded evaluation of difficult cases by the consensus panel. Although the sensitivity and specificity of the ACR was >87% in the subjects analysed in the original paper,[1] the specificity dropped dramatically in our sample because all patients had, by inclusion criteria, an age <18 years; indeed, the specificity rose to 75% when the age criterion was removed.

For the diagnosis of c-PAN, histopathological and angiographic findings are crucial and for this reason this combined criterion was already mandatory in the 2005 EULAR/PRES[7] criteria. During the discussion there was a specific concern about the imaging modalities to be used in children owing to the recent advances in these techniques. Although conventional angiogram remains the current 'gold standard', it is an invasive technique especially in young children where the problem of radiation should also be considered. The group is aware that imaging modalities are advancing rapidly. Future studies may establish a place for non-invasive angiographic techniques. The major change to the original 2005 EULAR/PRES-endorsed c-PAN criteria was the removal of the criteria for the signs and symptoms for vasculitis in specific organ systems and testicular pain or tendernes; this change led to an increase of the sensitivity and to a simplification of the final criteria. A special challenge in the classification of PAN is the lack of consensus on the borders of cutaneous PAN, which constitutes a large group in paediatric practice.[13] We have not included in the analysis microscopic polyangiitis and cutaneous c-PAN since data related to these two subgroups of the disease were few and since they were empirically defined in the 2005 EULAR/PRES criteria.

For c-WG the main differences from the ACR criteria were the addition of chest CT scan results, the inclusion of ANCA positivity and more specific items for upper and lower respiratory involvement. These additions were thought to be important since c-WG has some features such as more frequent subglottic stenoses that differentiate it from the adult form.[14] Very minor changes were made to the original 2005 EULAR/PRES c-WG that includes any detected ANCA (immunofluorescence/MPO/PR3) as a positive finding. Thus, the final EULAR/PRINTO/PRES definition had a slight increase in specificity compared with the preliminary 2005 EULAR-endorsed c-WG criteria.[7] Also, the sensitivity/specificity of the final definition was higher than the original ACR criteria as also reported recently by Cabral *et al*[15] who used, as control group, other ANCA-associated vasculitides. At the Ankara Consensus Conference limited forms of c-WG, such as isolated orbital/retro-orbital disease or limited upper airway involvement, were specifically considered and it was agreed they should be dealt with in the future separately from the more widespread form of the disease. Similarly, it was not possible to formally differentiate c-WG from microscopic polyangiitis and Churg–Strauss syndrome since too few cases were available in the dataset. Thus, at present, the approach suggested by Watts *et al*[16] to differentiate between WG and microscopic polyangiitis could be applied to children since the surrogate markers described in his classification algorithm are also included in their classification.

For c-TA, angiographic findings are crucial in the diagnosis and thus this criterion had already been defined as mandatory in the 2005 EULAR/PRES[7] c-TA criteria. We had also considered more recent imaging modalities, such as CT or MRI, which were not considered at the time the ACR criteria were published. Indeed, arteriographic abnormalities were present

Table 4 Final EULAR/PRINTO/PRES c-TA criteria (with glossary) and classification definition (sample 1056)

Criterion	Glossary	Sensitivity (%)	Specificity (%)	AUC (%)
Angiographic abnormality (mandatory criterion)	Angiography (conventional, CT, or MRI) of the aorta or its main branches and pulmonary arteries showing aneurysm/dilatation, narrowing, occlusion or thickened arterial wall not due to fibromuscular dysplasia, or similar causes; changes usually focal or segmental	100	99.9	99.9
1. Pulse deficit or claudication	Lost/decreased/unequal peripheral artery pulse(s) Claudication: focal muscle pain induced by physical activity	74.7	99.1	86.9
2. Blood pressure (BP) discrepancy	Discrepancy of four limb systolic BP >10 mm Hg difference in any limb.	63.5	99.6	81.6
4. Bruits	Audible murmurs or palpable thrills over large arteries	58.8	99.8	79.3
5. Hypertension	Systolic/diastolic BP greater than 95th centile for height	63.2	90.5	76.8
6. Acute phase reactant	Erythrocite sedimentation rate >20 mm per first hour or CRP any value above normal (according to the local laboratory)	95.0	14.1	54.6
c-TA EULAR/PRINTO/PRES Ankara 2008 classification definition: κ 0.99 (95% CI 0.93 to 1.00)	Angiographic abnormalities of the aorta or its main branches and pulmonary arteries showing aneurysm/dilatation (mandatory criterion) plus one of the five following criteria: Pulse deficit or claudication Four limbs BP discrepancy Bruits Hypertension Acute phase reactant	100	99.9	99.9

AUC, area under the curve; CRP, C-reactive protein; c-TA, c-Takayasu arteritis; EULAR, European League Against Rheumatism; PRES, Paediatric Rheumatology European Society; PRINTO, Paediatric Rheumatology International Trials Organisation.

in 41% of the children and this figure rose to 100% when we considered all imaging modalities. During the consensus discussion special emphasis was placed on the differential diagnosis of non-inflammatory conditions such as fibromuscular dysplasia or mid-aortic syndrome for which future imaging technologies may be of help. Other differences from the ACR were the combination of pulse deficit and claudication, which were both very frequent (75%) and highly specific, the addition of hypertension (more frequent than in the other c-vasculitides) and the removal of the age limit criterion. Moreover, the addition of increased acute phase reactants as an extra criterion, led us to properly classify all cases in which this laboratory sign, associated with angiographic abnormalities, was an important finding before the onset of complications such as hypertension or pulse deficit or claudication. Together, these changes increased the sensitivity to 100% and the κ-agreement reached between the final classification definition and the consensus panel choice was very close to 1. It should be noted that in children, TA is a distinct and unique entity while by contrast in adult disease, relatively younger patients with giant cell arteritis and relatively older patients with TA may cause some difficulty in classification.

The main advantage of the proposed definitions lies in the worldwide data collection that ensures greater variability of the cases examined, as well as in full validation testing that combined both statistics and consensus formation processes. The final EULAR/PRINTO/PRES criteria had an overall better performance for all four diseases, with substantially better specificity for defining the disease. They also all reached a κ-agreement of >0.80 between the final classification definition and the consensus panel. Thus we suggest that, at least in children, they are superior to the previously existing criteria. With these new validated classification criteria we can start planning multicentre studies similar to those carried out by EUVAS, and gathering our expertise and knowledge so that we can serve these children better. It should be emphasised, however, that the proposed definitions are not diagnostic criteria but rather classification criteria.

In conclusion EULAR/PRINTO/PRES propose validated classification criteria for HSP, c-PAN, c-WG and c-TA with high sensitivity/specificity.

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