Increased Sensitivity of the European Medicines Agency Algorithm for Classification of Childhood Granulomatosis with Polyangiitis

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ABSTRACT. ***Objective.*** Granulomatosis with polyangiitis (Wegener's; GPA) and other antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are rare in childhood and are sometimes difficult to discriminate. We compared use of adult-derived classification schemes for GPA against validated pediatric criteria in the ARChiVe (A Registry for Childhood Vasculitis e-entry) cohort, a Childhood Arthritis and Rheumatology Research Alliance initiative.

Methods. Time-of-diagnosis data for children with physician (MD) diagnosis of AAV and unclassified vasculitis (UCV) from 33 US/Canadian centers were analyzed. The European Medicines Agency (EMA) classification algorithm and European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) and American College of Rheumatology (ACR) criteria for GPA were applied to all patients. Sensitivity and specificity were calculated (MD-diagnosis as reference).

Results. MD-diagnoses for 155 children were 100 GPA, 25 microscopic polyangiitis (MPA), 6 ANCA-positive pauciimmune glomerulonephritis, 3 Churg-Strauss syndrome, and 21 UCV. Of these, 114 had GPA as defined by EMA, 98 by EULAR/PRINTO/PRES, and 87 by ACR. Fourteen patients were identified as GPA by EULAR/PRINTO/PRES but not by ACR; 3 were identified as GPA by ACR but not EULAR/PRINTO/PRES. Using the EMA algorithm, 135 (87%) children were classifiable. The sensitivity of the EMA algorithm, the EULAR/PRINTO/PRES, and ACR criteria for classifying GPA was 90%, 77%, and 69%, respectively, with specificities of 56%, 62%, and 67%. The relatively poor sensitivity of the 2 criteria related to their inability to discriminate patients with MPA.

Conclusion. EULAR/PRINTO/PRES was more sensitive than ACR criteria in classifying pediatric GPA. Neither classification system has criteria for MPA; therefore usefulness in discriminating patients in ARChiVe was limited. Even when using the most sensitive EMA algorithm, many children remained unclassified. (First Release May 15 2012; J Rheumatol 2012;39:1687–97; doi:10.3899/jrheum.111352)

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of primary systemic vasculitides predominantly affecting small to medium-size blood vessels. Disease subtypes under the rubric of AAV include Wegener granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and renal-limited pauciimmune glomerulonephritis[1]. A recent consensus of the American College of Rheumatology (ACR), the American Society of Nephrology, and the European League Against Rheumatism (EULAR) recommended a nomenclature change such that WG now be described as granulomatosis with polyangiitis (GPA)[2]; we will use that term in this report.

Although there is overlap in the clinical, laboratory, and histopathologic features among the AAV entities, pathophysiological differences underscore the need to distinguish between them as a means to obtain accurate assessment of epidemiologic data, prognostic implications, and disease-specific therapeutic guidelines. In the evolution of classification schemes for vasculitis, the ACR defined and tested criteria for GPA and CSS, but MPA criteria were not defined[3]. Subsequently the Chapel Hill Consensuses Conference (CHCC) provided specific definitions for GPA, MPA, and CSS but no classification criteria[4]. As a consequence of there being no criteria for MPA, pediatric and adult cases classified as GPA by ACR criteria may be concurrently described as having MPA using the CHCC definition[5]. Recognizing these limitations for adult patients, the European Medicines Agency (EMA) endorsed a classification algorithm[6] that incorporates ACR criteria and CHCC definitions, and additionally the Lanham criteria for CSS[7] and the presence or absence of ANCA. The system has been tested and validated in adults as a means to classify patients with a mutually exclusive diagnosis [CSS, GPA, MPA, or polyarteritis nodosa (PAN)] and to minimize the number of unclassified patients[6]. None of these schemes was developed or tested in children.

Many childhood vasculitides remain unclassifiable using adult criteria[8,9] and in 2005, the vasculitis working group of the Paediatric Rheumatology European Society (PRES) with the support of the EULAR adapted and modified the ACR criteria in proposing new classification criteria for pediatric vasculitides[10]. Validated in 2008, the EULAR, Paediatric Rheumatology International Trials Organisation (PRINTO), and PRES (EULAR/PRINTO/PRES) criteria reported improved specificity and sensitivity of classification definitions of childhood GPA over the original ACR criteria[11]. Unfortunately, due to the limited number of cases of the less frequent forms of AAV in their population (as with the ACR criteria), classification criteria were not developed for MPA[11]; this is one of the well-recognized limitations of the ACR criteria[12] that has been inherited by the adapted pediatric criteria. To classify children with AAV into mutually exclusive categories therefore remains challenging, although it has been suggested[11] that the EMA algorithm[6] could be applied to children.

Using a multicenter contemporary inception cohort called ARChiVe (A Registry for Childhood Vasculitis e-entry) involving members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA), we previously reported on clinical manifestations of childhood GPA in patients defined using the ACR criteria[5]. In that report, the performance of EULAR-PRES pediatric classification criteria for GPA, proposed in 2005, was tested in a cohort of children with the diagnosis of any ANCA-associated or unclassified vasculitis. Within this narrow spectrum of related diagnoses the proposed criteria demonstrated minimally improved diagnostic sensitivity and specificity over those of the ACR criteria[5]. In the current report, we examined the utility of the EMA algorithm for classification of childhood GPA among a larger cohort of patients with a similarly narrow spectrum of related diagnoses. We examined the performance of the pediatric criteria after they were subsequently modified and validated as the EULAR/PRINTO/PRES criteria in 2008, in comparison to the performance of the ACR criteria. Additionally, we analyzed the usefulness of these classification system schema in discriminating children with GPA from those with MPA and

assessed how these classification systems aligned with the physicians' diagnoses.

MATERIALS AND METHODS

The ARChiVe cohort. ARChiVe is a contemporary inception cohort of patients that was established as a CARRA initiative involving its members. A list of the ARChiVe network of collaborating centers and investigators is shown in the Appendix. Since the launch of the ARChiVe registry in March 2007, pediatric rheumatologists at 33 CARRA-associated geographically diverse institutions in the United States (n = 29) and Canada (n = 4) have contributed patients. All enrolled patients were followed at participating centers and diagnosed after January 1, 2004, with GPA, MPA, CSS, ANCA-positive glomerulonephritis (ANCA pos GN), and unclassified vasculitis (UCV). All patients were younger than 18 years of age at the time of diagnosis. The diagnosis entered into the database by the treating pediatric rheumatologist at each of the ARChiVe network sites is described in this report as the MD-diagnosis.

Data were collected retrospectively by review of available medical records for patients diagnosed between January 2004 and the launch of ARChiVe in March 2007, and prospectively for patients diagnosed between March 2007 and February 2010. In both instances, data were collected for the period from clinical onset and presentation until 2 months after diagnosis. The ARChiVe Web-based interface has been described elsewhere[5] and incorporates categorical variables including family and medical history, presenting/diagnostic features, physical examination findings, MD-diagnosis, results of testing including laboratory findings, histopathology, diagnostic imaging, bronchoscopy and pulmonary function tests and other clinical investigations, and details of initial therapy. Dataset items in the ARChiVe database included specific items necessary to apply the CHCC definitions for GPA, CSS, and MPA[4], the ACR[13] and EULAR/PRINTO/PRES criteria[11] for GPA, and the EMA classification algorithm[6]. In addition, other common pediatric presenting features considered by consensus to be useful diagnostic features for AAV classification were incorporated into a standardized data collection form.

Data completeness and quality were reviewed at the main coordinating center, ensuring there were no duplicate cases (some institutions collected data on patients whose care was transferred from other medical institutions or who were referred for a second opinion).

GPA (formerly WG) classification criteria. The ACR criteria for the vasculitides[13] were developed in 1990 from a large cohort of mostly adult patients from Canada, Mexico, and the United States (Table 1). The reported sensitivity and specificity for the ACR GPA criteria were 88.2% and 92.0%, respectively. The EULAR/PRINTO/PRES recently published a formal validation of their proposed classification criteria for pediatric vasculitides[11] (Table 1). The sensitivity and specificity of the final 2008 EULAR/PRINTO/PRES classification criteria for childhood GPA were reported as 93.3% and 99.2%, respectively.

The EMA classification algorithm was developed by consensus as a practical tool for use in epidemiologic studies of patients with AAV and PAN and was recently validated in adults[6]. In a sequential manner, the algorithm (Figure 1) applies different criteria, definitions, and surrogate markers, from most specific to least specific, in a stepwise approach. After initially determining whether the patient does not have CSS using the ACR and Lanham criteria[7], it then determines whether the patient has GPA using the ACR criteria, the CHCC definitions, clinical surrogate features of GPA, and presence or absence of ANCA; subsequently, if the patient does not have CSS or GPA, it is then determined whether they have MPA by the presence of CHCC histological features, clinical surrogates for renal vasculitis, and ANCA; finally it determines which patients have PAN by applying the CHCC PAN definition. Application of the EMA algorithm to primarily adult patients with systemic vasculitis from southern Sweden and China has been reported[14,15]. However, the sensitivity and specificity of this approach in recognizing GPA are not known and have not been studied in pediatric populations with AAV.

Statistical analysis. Sociodemographic and clinical characterization of data for pediatric patients with GPA were provided using means with SD and percentages where applicable. GPA classification according to the ACR and EULAR/PRINTO/PRES criteria and the EMA algorithm was performed by computation of data.

Table 1. Comparison of the American College of Rheumatology (ACR)[13] and revised European League Against Rheumatism (EULAR)/Paediatric Rheumatology International Trials Organisation (PRINTO)/Paediatric Rheumatology European Society (PRES)[11] classification criteria for granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis). Numbers describe patients in the ARChiVe cohort of 155 patients with ANCA-associated vasculitis who fulfilled criteria for GPA according to ACR or EULAR/PRINTO/PRES and patients meeting any individual criterion within these 2 subgroups.

	n
1990 ACR classification criteria	
A patient has GPA when 2 of the following 4 criteria are present:	87
Nasal or oral inflammation: Ulcers or purulent or bloody nasal discharge	56
Abnormal chest radiograph: Nodules, fixed infiltrates, or cavities	70
Abnormal urinary sediment: Microhematuria or red blood cell casts	68
Granulomatous inflammation on biopsy: Intra/peri/extravascular	17
2008 EULAR/PRINTO/PRES classification criteria	
A patient has GPA when 3 of the following 6 criteria are present:	98
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	80
Pulmonary involvement: Abnormal chest radiograph or chest computed tomography scan showing nodules, cavities, or fixed infiltrates	72
Renal involvement: Proteinuria, hematuria or red blood cell casts in the urinary sediment; or necrotizing pauciimmune glomerulonephritis	79
Laryngo-tracheobronchial involvement: Subglottic, tracheal, or bronchial stenosis	20
Granulomatous inflammation on biopsy: Intra/peri/extravascular	17
ANCA positivity: MPO/p or PR3/c ANCA	94

ANCA: antineutrophil cytoplasmic antibody; MPO/p: myeloperoxidase and/or perinuclear; PR3/c: proteinase 3 and/or cytoplasmic.

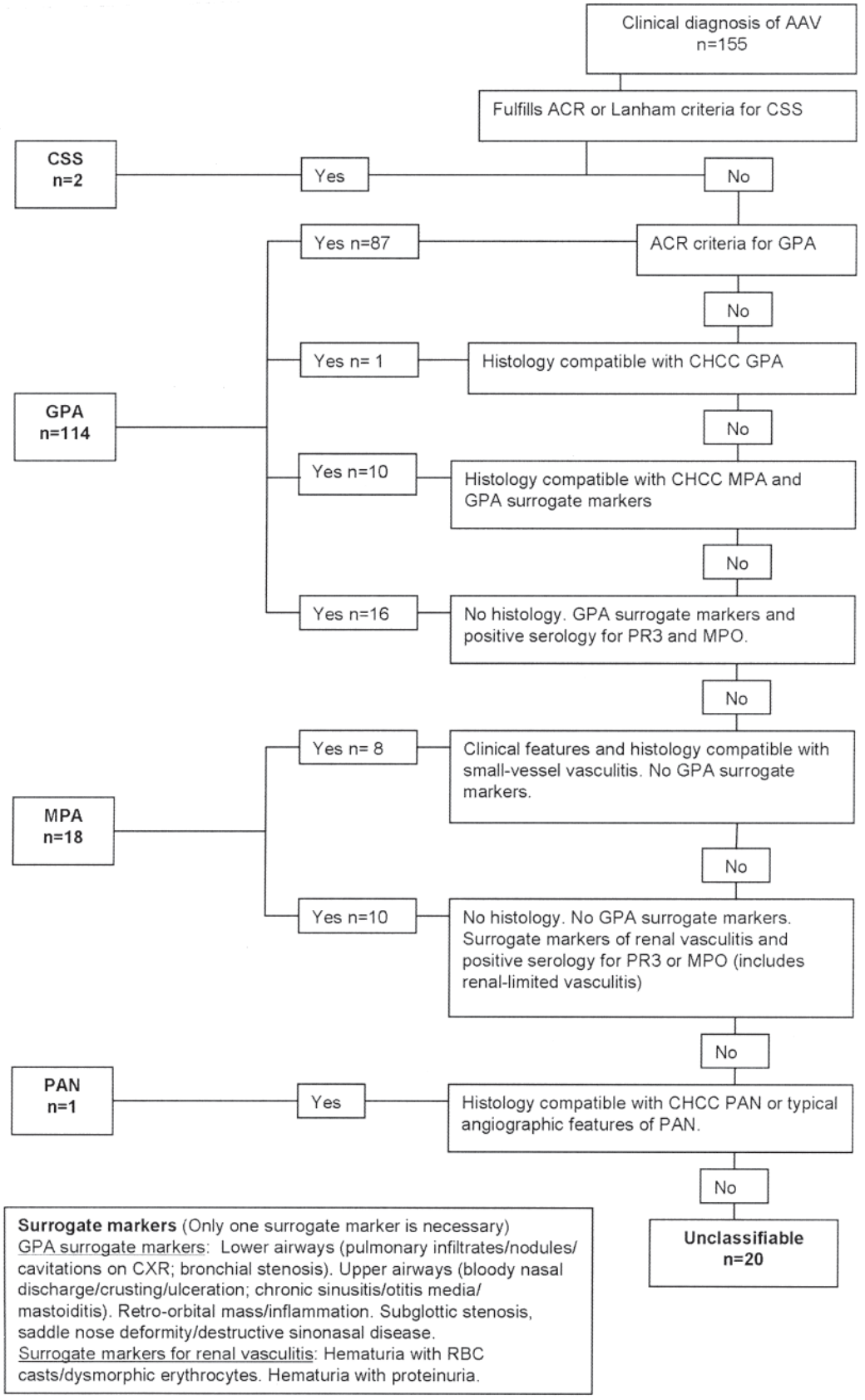

Figure 1. The classification assigned among the cohort of 155 patients in A Registry for Children with Vasculitis e-entry (ARChiVe), according to the European Medicines Agency (EMA) classification algorithm[6]. AAV: antineutrophil cytoplasmic antibody-associated vasculitides; ACR: American College of Rheumatology; CSS: Churg-Strauss syndrome; GPA: Granulomatosis with polyangiitis; CHCC: Chapel Hill Consensuses Conference; MPA: microscopic polyangiitis; PR3: proteinase 3; MPO: myeloperoxidase; PAN: polyarteritis nodosa.

To compare the ACR and EULAR/PRINTO/PRES classification criteria for GPA, all patients in the registry with any physician-assigned diagnosis (GPA, MPA, CSS, ANCA-pos GN, or UCV) were analyzed. The MD-diagnosis of patients was used as the reference standard to assess the sensitivity, specificity, and predictive values of the ACR, EULAR/PRINTO/PRES, and EMA in diagnosing GPA. All data were processed using Stata v. 10.1 for Windows (StataCorp LP, College Station, TX, USA).

The study protocol was approved by the local research ethics board at each participating center. Informed consent for participation was obtained from parents and informed consent or assent was obtained from patients for both retrospective and prospective recruitment as applicable.

RESULTS

During the study period, 155 pediatric patients (105 female; 67.7%) were recruited in the ARChiVe cohort. Data were collected prospectively for over half these patients (89 children; 57%). MD-diagnoses of the patients in the cohort were 100 GPA, 25 MPA, 6 ANCA-pos GN, and 3 CSS. In the remaining 21 patients (13.5%) the MD-diagnosis was UCV.

Application of the EMA algorithm to the ARChiVe cohort. After applying the EMA algorithm to the cohort of 155 patients, 2 children were classified as CSS (Figure 1). Of the 114 children considered to have GPA based on this algorithm, 87 fulfilled the ACR criteria for GPA; 1 patient showed extravascular granulomatous inflammation on an upper-airway biopsy, meeting the CHCC GPA definition; 10 patients met the CHCC definition of MPA but had GPA clinical surrogate markers; and finally, 16 patients without histological criteria for GPA or MPA (or no biopsy done) had GPA clinical surrogate markers plus positive ANCA serology. GPA clinical surrogate markers among patients in the last 2 categories were nasal involvement (n = 6), nasal septal ulceration or destructive disease (n = 3), chronic sinusitis/otitis/mastoiditis (n = 17), sinusitis with nasal septal ulceration or destructive disease (n = 1), subglottic stenosis (n = 6), pulmonary involvement (n = 6), and retroorbital mass (n = 3); there were 10 patients with GPA as per the EMA algorithm with more than 1 GPA clinical surrogate marker. Eighteen patients were classified as having MPA and 1 as having PAN. Twenty patients (12.9%) were unclassifiable after application of the EMA algorithm (Figure 1), 13 of whom were also diagnosed with UCV by MD-diagnosis. The remaining 8 out of 21 patients with UCV by MD-diagnosis were assigned diagnoses of GPA (n = 4), MPA (n = 3), and PAN (n = 1) by the EMA algorithm.

GPA classification using the ACR, EULAR/PRINTO/PRES, and EMA classification schemes in the ARChiVe cohort. Application of the ACR and EULAR/PRINTO/PRES criteria (Table 1) and the EMA algorithm (Figure 1 and details above) to the 155-patient cohort classified, respectively, 87, 98, and 114 patients as having GPA. Overall, the EMA classification algorithm showed the highest sensitivity for classifying GPA (90.0%), followed by EULAR/PRINTO/PRES criteria (77.0%) and then ACR criteria (69.0%; Table 2). Specificities for classifying GPA were slightly lower for the EMA algorithm (56.4%) than for both the EULAR/PRINTO/PRES and ACR criteria (61.8% and 67.3%, respectively; Table 2). Level of kappa agreement (coefficient κ and CI) between MD-diagnosis and the different classification schema were for EMA algorithm κ = 0.49 (95% CI 0.33–0.65), for EULAR/PRINTO/PRES criteria κ = 0.39 (95% CI 0.22–0.55), and for ACR criteria κ = 0.34 (95% CI 0.19–0.50; Table 2).

Figure 2 shows Venn diagrams comparing the EULAR/PRINTO/PRES, ACR, and EMA algorithm with each other; Figure 2d compares the EMA algorithm, the most sensitive of these classification schemes, with the MD-diagnosis. There were 17 patients classified as GPA by either EULAR/PRINTO/PRES or ACR criteria but not both (Figure 2a). In

Table 2. Discriminant validity of the American College of Rheumatology (ACR)[13], the European League Against Rheumatism (EULAR)/Paediatric Rheumatology International Trials Organisation (PRINTO)/Paediatric Rheumatology European Society (PRES) classification criteria[11], and European Medicines Agency (EMA) classification algorithm[6] for granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis) as applied to children in the ARChiVe cohort compared to reported sensitivity and specificity of PRES cohort (MD diagnosis or consensus classification as reference standard).

Discriminant Validity	ARChiVe Cohort			PRES Cohort		
	EMA Algorithm	ACR Criteria	EULAR/PRINTO/PRES Criteria	EMA Algorithm	ACR Criteria	EULAR/PRINTO/PRES Criteria
Sensitivity, %	90.0	69.0	77.0	NR	83.0	93.3
Specificity, %	56.4	67.2	61.8	NR	98.0	99.2
Overall accuracy, %	73.2	68.1	69.4	NR	90.5	96.3
κ coefficient (95% CI)	0.49 (0.33–0.65)	0.34 (0.19–0.50)	0.38 (0.22–0.55)	NR	0.77 (NR)	0.90 (0.84–0.97)
LR positive	2.1	2.1	2.0	NR	NR	NR
LR negative	0.2	0.5	0.4	NR	NR	NR
PPV, %	78.9	79.3	78.6	NR	NR	NR
NPV, %	75.6	54.4	59.6	NR	NR	NR

NR: not reported; LR: likelihood ratio for a positive/negative result; PPV: positive predictive value; NPV: negative predictive value.

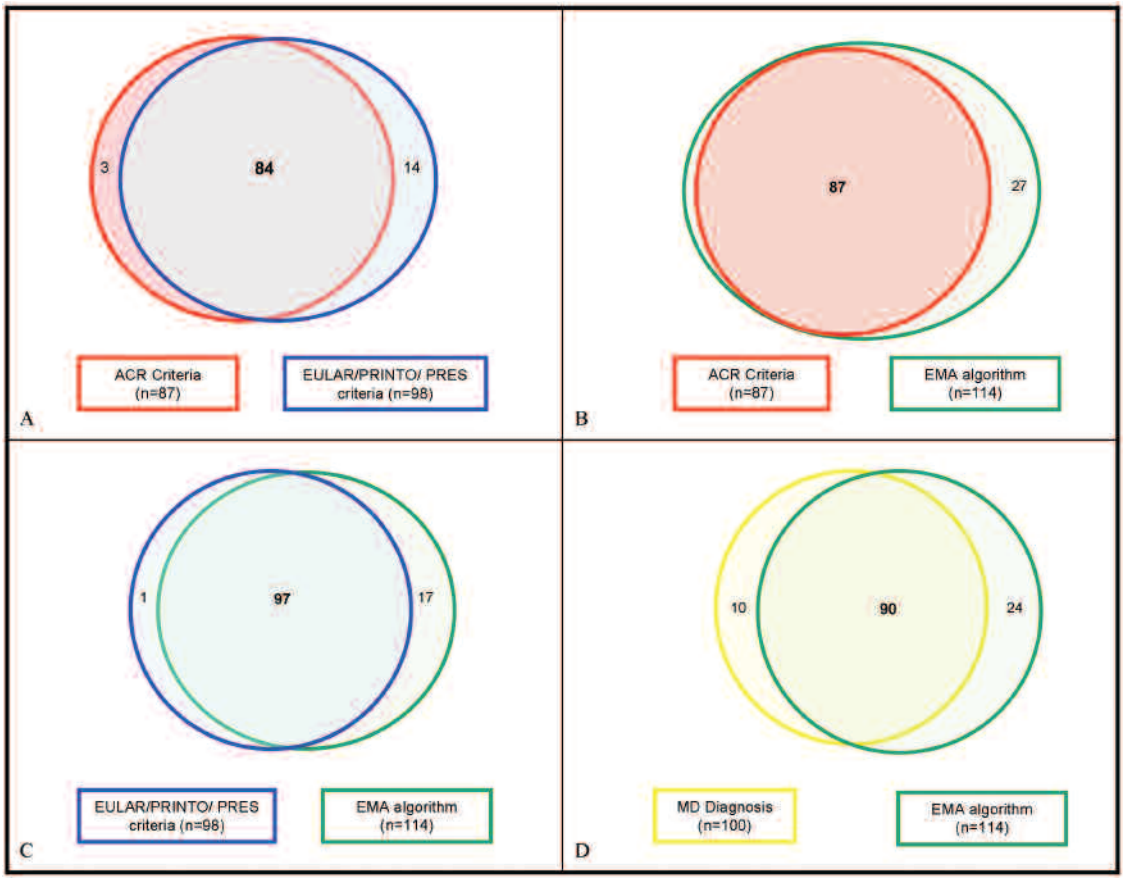

Figure 2. Venn diagrams show patients defined in different ways as having granulomatosis with polyangiitis (GPA) among the 155 patients in ARChiVe. Patients with an MD-diagnosis of GPA are shown in yellow (n = 100), those fulfilling criteria of the American College of Rheumatology (ACR)[13] in red (n = 87), those fulfilling criteria of the EULAR/PRINTO/PRES[11] in blue (n = 98), and those classified according to the European Medicines Agency (EMA) algorithm[6] in green (n = 114). Panel (a): 84 patients were identified as GPA by both EULAR/PRINTO/PRES and ACR criteria; 14 were identified as GPA only by EULAR/PRINTO/PRES and 3 only by ACR. Panel (b): 87 patients were identified as GPA by both EMA algorithm and ACR criteria; 27 patients were classified as GPA only by EMA algorithm. Panel (c): 97 patients were identified as GPA by both EMA algorithm and EULAR/PRINTO/PRES criteria; 17 were identified as GPA only by EMA algorithm and 1 only by EULAR/PRINTO/PRES criteria. Panel (d): 90 patients were identified as GPA by both MD-diagnosis and the EMA algorithm; 24 were identified as GPA only by EMA algorithm and 10 only by MD-diagnosis. EULAR/PRINTO/PRES: European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society.

the 14 identified as GPA by EULAR/PRINTO/PRES but not ACR criteria, features that enabled classification were the presence of sinus involvement, ANCA positivity, subglottic-tracheal-endobronchial stenosis, and significant proteinuria. Conversely, of the 3 patients with GPA classified by ACR but not EULAR/PRINTO/PRES, 2 patients presented with nasal-sinus involvement and granulomatous vasculitis on biopsy, and 1 patient had lung and renal involvement; all 3 had negative ANCA serology (Figure 3). The EMA algorithm classified as GPA all patients identified as GPA by ACR criteria, plus an additional 27 patients (Figure 2b). The EMA algorithm classified as GPA all but 1 patient identified by EULAR/PRINTO/PRES criteria as GPA plus an additional 17 patients (Figure 2c).

The EMA algorithm was most sensitive at classifying GPA patients, identifying all but 1 patient classified by the other 2 schemes; we therefore compared it against MD-diagnosis (Figure 2d) and described the patients where diagnosis/classification differed for GPA. Of the 24 patients classified as having GPA by the EMA algorithm and not by their treating physician, 17 were given an MD-diagnosis of MPA. Twelve of these 17 patients had positive results for both anti-myeloperoxidase (MPO) antibody and perinuclear ANCA (pANCA) serology, while 1 patient had positive MPO antibody and 1 had positive pANCA only; 2 had proteinase 3 (PR3) antibody [none was cytoplasmic ANCA (cANCA)-positive] and 1 had negative ANCA serology. Three patients had MD-diagnosis of ANCA pos GN, 1 of whom, in addition to an abnormal urinalysis/urinary sediment and positive ANCA, had nasal/sinus inflammation. All 4 who were assigned the MD-diagnosis of

Patients meeting only EULAR/PRINTO/PRES criteria for GPA (n=14)															ACR versus *EULAR/PRINTO/PRES*	Patients meeting only ACR criteria for GPA (n=3)		
7	10	10	11	13	13	14	14	15	16	16	16	17	17			12	12	15
pA/m	-/m	pA/m	pA/m	cA/pr	-/pr	cA/pr	cA/pr	pA/m	cA/pr	cA/pr	pA/m	-/-	cA/pr			-/-	-/-	-/-
✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		Age			
					•			•		•					1 Nasal or oral inflammation	•	•	
✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		*1 Nasal or sinus inflammation*	✓	✓	
				•		•							✓		2 Abnormal CXR		•	
				✓		✓							✓		*2 Abnormal CXR or CT scan*		✓	
•		•	•			•			•		•				3 Abnormal urine sediment		•	
✓		✓	✓			✓			✓	✓	✓	✓	✓		*3 Abnormal urine sediment or necrotizing pauci-immune glomerulonephritis*			✓
	•														4 Granulomatous inflammation on biopsy	•	•	
	✓														*4 Granulomatous inflammation on biopsy*	✓	✓	
					✓	✓		✓		✓	✓	✓			*5 Subglottic, tracheal or bronchial stenosis*			
✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		*6 ANCA positive Immunofluorescence/ELISA*			

Figure 3. Seventeen patients from ARChiVe fulfilled either ACR[13] (shown in normal typeface; n = 3) or EULAR/PRINTO/PRES[11] (italic typeface; n = 14) classification criteria for granulomatosis with polyangiitis (GPA), but not both criteria. Columns represent individual patients, horizontal lines show presence of the components of the criteria set in each patient. A complete description of both sets of criteria is given in Table 1. •: indicates ACR criteria. √: indicates EULAR/PRINTO/PRES criteria. CXR: chest radiograph; CT: computed tomography; ANCA: antineutrophil cytoplasmic antibody; cA: cytoplasmic ANCA; pA: perinuclear ANCA; m: positive myeloperoxidase antibody; pr: positive proteinase 3 antibody; –: negative ANCA; EULAR/PRINTO/PRES: European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society; ACR: American College of Rheumatology.

UCV had abnormalities on pulmonary imaging, and 3 of them had abnormal urinalysis/urinary sediment; of these 4 patients 1 had positive cANCA (PR3 antibody-positive), 1 had positive pANCA (PR3/MPO antibody-negative), and 2 had no detectable ANCA.

Ten patients with MD-diagnosis of GPA were not classified as GPA by the EMA algorithm (Figure 2d), although 1 of them (Figure 2c) was classified by EULAR/PRINTO/PRES as GPA. Five of the remaining 9 patients were classified as MPA by EMA: 3 had histology compatible with CHCC MPA and positive ANCA, without surrogate markers of GPA or renal vasculitis, and 2 patients had surrogate markers for renal vasculitis and a positive ANCA. The 4 remaining patients were diagnosed by EMA with UCV: 3 of these had GPA surrogate markers but had no measured ANCA, and 1 had a positive ANCA with no GPA surrogate markers.

DISCUSSION

Classification of childhood AAV remains a significant challenge. Overlapping clinical manifestations, the lack of appropriate "gold standard" definitions, the need for invasive testing modalities for diagnosis, and the relative rarity of these illnesses (particularly those other than GPA) have limited the development of classification criteria with high sensitivity and specificity. Not surprisingly, this has resulted in the generation of several classification systems, none of which has been entirely satisfactory, particularly in children[12,16]. In this work, we used data from the largest cohort of childhood AAV assembled to date to compare the performance of the EMA algorithm, the recently validated EULAR/PRINTO/PRES, and the ACR criteria for classification of childhood GPA among children with AAV and UCV, and assessed how these different classification schemes relate to the MD-diagnosis.

Using the diagnosis provided by the treating physician as the reference standard, the EMA algorithm had the highest sensitivity, followed by the EULAR/PRINTO/PRES and ACR criteria, and the relative specificities were in the reverse order. The positive predictive values for all schemes were very similar, while the negative predictive value of the EMA algorithm was highest and overall had the highest diagnostic accuracy (Table 2). In this large cohort of patients with childhood AAV, the EMA algorithm appeared to have superior performance.

The intent of the EULAR/PRINTO/PRES classification criteria was to enable classification of more patients to GPA by incorporating criteria that were more characteristic of childhood disease. These new criteria for GPA were built upon previous ACR criteria and therefore it is reassuring that when tested in this cohort, overall, more patients were classifiable as GPA. Notwithstanding, because of the more rigorous requirement for 3 criteria in EULAR/PRINTO/PRES criteria, 3 patients classified by ACR as having GPA (Figure 2a) did not fulfill the new pediatric criteria.

One limitation of both the EULAR/PRINTO/PRES and ACR classification schemes is the absence of criteria for MPA[11,13]. Because lungs and kidneys are the major organs involved in both GPA and MPA, differentiation may be difficult. The EMA algorithm, by explicitly including the CHCC definitions[4], permits assignment of a diagnosis of MPA. Our cohort included 25 children (16%) with an MD-diagnosis of MPA, and this may partially explain the superior performance of the EMA algorithm. Because of the inclusion of criteria/characteristics in addition to the ACR (i.e., surrogate markers of GPA and renal vasculitis, and presence or absence of ANCA), it was not surprising that more patients in our cohort were identified as having GPA by EMA as compared to the other 2 classification schemes.

Classification of a patient (ideally to a very specific category) is not the same as diagnosis. Through the process of formulating a diagnosis, a physician needs to consider a complex set of clinical features, and by using information beyond the limited traditional criteria required for classification it is more sensitive. Classification, in its requirement for limited and specific criteria, defines more phenotypically homogeneous groups of patients that are generally more suitable for clinical trials and basic research. However, for rare diseases such as the AAV, even the most experienced physician specialists might have seen only a few patients[17] and so (and perhaps inappropriately)[18] they might place more reliance on classification criteria in making a clinical diagnosis. Unfortunately, in this regard, the classification criteria and definitions for the individual AAV are limited, especially with respect to MPA. The EMA algorithm attempts to address these limitations, and in its systematic application of multiple criteria and diagnostic characteristics to define a patient as having GPA, it is arguably more akin to a physician making a diagnosis.

Although in this study the concordance with MD-diagnosis of GPA is highest for the EMA algorithm compared with the other classification schemes (see Table 2 and κ agreement) there remains significant disparity. Of the 24 patients diagnosed with GPA by the EMA algorithm but not by the physician, the majority (77%) were given an MD-diagnosis of MPA. Our results suggest that the type of ANCA (i.e., pANCA with specificity for MPO vs cANCA with specificity for PR3) might have been inappropriately used by physicians as the characteristic distinguishing whether a patient has, respectively, MPA versus GPA. The EMA algorithm, on the other hand, does not use ANCA specificity to distinguish between GPA and MPA; rather, the presence of ANCA (whatever specificity) helps define GPA or MPA as distinct from PAN. Nine patients were classified as GPA by MD-diagnosis but not by EMA (or any other criteria); these patients did not have any unifying unique feature that led to the MD-diagnosis.

This difference between MD-diagnosis and EMA classification arguably relates to the consistent hierarchical and systematic application of criteria used in the EMA algorithm. In contrast, in making a diagnosis, individual physicians might systematically evaluate, include, and weigh different clinical features dependent on their overall clinical experience and

their knowledge of evolving classification systems, etc. The consequent differing diagnostic pathways may lead to different, albeit related, diagnoses compared to other physicians or compared to the EMA algorithm.

We compared the performance of EULAR/PRINTO/PRES and ACR criteria for GPA as described for patients in the PRES cohort[11] against their performance when applied to patients in the ARChiVe cohort in this study. In both cohorts, the sensitivity of the EULAR/PRINTO/PRES criteria was clearly better than the ACR criteria, resulting in more patients being classified with GPA; however, the overall sensitivity of either set of criteria was relatively poor when tested against MD-diagnosis in the ARChiVe cohort. The best explanation for this disparity relates to the differences in the populations tested. In the PRES cohort of 1183 patients, there were 60 with GPA who were included among patients with very different clinical types of the vasculitis; notably, 827 patients (69% of cohort) had Henoch-Schönlein purpura (HSP) and only 14 patients (1.2% of cohort) had MPA. On the other hand, in the ARChiVe cohort of 155 patients, 100 had GPA and were included among patients with clinically similar types of vasculitis, and notably, 25 patients (16% of cohort) had MPA. The limitations of classification systems that do not incorporate specific criteria for MPA are thus evident. We note the extraordinary but not surprising high κ agreement (κ = 0.9) in the PRES cohort achieved for classifying GPA by the EULAR/PRINTO/PRES criteria[11]. In that study, the "agreement" was between diagnosis (confirmed by a group of experts) and classification (developed by the same group of experts). We also note (as with ARChiVe) agreement was similarly less (κ = 0.77) for the ACR criteria (Table 2).

Some may argue that there is little necessity to separate GPA and MPA, given their current grouping in clinical trials, for example[19], and the increasing acceptance of the term AAV. However, we believe that the distinction is an important one, and that the current grouping of AAV is largely one of convenience, related to our current inability to distinguish GPA and MPA reliably and the need for patient numbers in clinical trials. It is likely that the pathogenesis of these forms of systemic vasculitis is different, demonstrated by the different antigenic targets for the ANCA predominating in each (PR3 vs MPO), different pathology (granulomas vs no granulomas), and different lung disease (nodular or cavitating disease vs capillaritis). The EMA algorithm and most recently the application of artificial neural networks[20] represent promising efforts to accurately classify patients with vasculitis into nonoverlapping categories (i.e., GPA or MPA). In the future, it is possible that a better understanding of these differences will lead to better and more specific therapies for these diseases.

The limitations of our study can be summarized as follows. First, the lack of an appropriate gold standard for the diagnosis of GPA limits the evaluation of all classification criteria. Our use of MD-diagnosis as a reference standard, as provided by certified pediatric rheumatologists at 33 centers, was comparable to the reference standard used in the pediatric criteria validation study[11]. In that validation trial patient diagnoses were provided by physician members of PRES who have varied formal specialty training in pediatric rheumatology; diagnosis by "expert consensus" was sought on a large minority of the patients, especially when the submitted diagnosis was questionable. Consensus was then based upon evaluation of a limited set of sometimes incomplete categorical "registry" data. The resulting set of diagnoses was used as the reference standard in that study. Neither this reference standard nor the MD-diagnosis reference standard used in the current study qualifies as a "gold standard," but each was the most practicable reference for comparative studies. Second, the majority of patients in our cohort have GPA, while the other patients in the cohort against whom they were compared (apart from a few with UCV) had related and clinically similar diseases defined under the rubric of AAV. Although this has highlighted the discriminatory difficulties of classification within the AAV subset of vasculitides, it would be useful to replicate these results in a cohort where the spectrum of vasculitis is better represented. A similar criticism could be made of the pediatric criteria validation study, where two-thirds of the patients had HSP and only rare patients had MPA. Third, the ARChiVe database currently includes only data entry at a single timepoint. Longitudinal data would allow additional certainty about the diagnosis, and provide important information about outcomes.

We evaluated 2 major classification systems (EULAR/PRINTO/PRES and ACR criteria) and the EMA algorithm for vasculitis in classifying childhood AAV, using the largest cohort of patients with childhood AAV assembled to date. When using physician diagnosis as the reference standard, the EMA algorithm had the highest sensitivity and diagnostic accuracy for GPA, although its specificity was lower than the ACR criteria. While the EULAR/PRINTO/PRES classification for vasculitis in children is an improvement on the ACR criteria, it lacks discrimination when patients with MPA are included among the cohort of patients to be studied. We have shown that the EMA algorithm is a useful tool to study and uniquely diagnose children with either GPA or MPA. Arguably, in the absence of an alternative, the EMA classification algorithm could also be used by physicians for diagnosis when their experience of patients with AAV is limited. The remaining appreciable number of pediatric patients with vasculitis who continue to be unclassifiable should be a subject of future research and a concern for all classification systems. Understanding why some patients are classified differently by their physicians will assist in the development of more accurate classification systems. ARChiVe is well positioned to continue collecting the prospective data that will contribute to this effort.

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APPENDIX

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