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Comparing Presenting Clinical Features in 48 Children With Microscopic Polyangiitis to 183 Children Who Have Granulomatosis With Polyangiitis (Wegener's)

An ARChiVe Cohort Study

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Objective. **To uniquely classify children with microscopic polyangiitis (MPA), to describe their demographic characteristics, presenting clinical features, and initial treatments in comparison to patients with granulomatosis with polyangiitis (Wegener's) (GPA).**

Methods. **The European Medicines Agency (EMA) classification algorithm was applied by computation to categorical data from patients recruited to the ARChiVe (A Registry for Childhood Vasculitis: e-entry) cohort, with the data censored to November 2015. The EMA algorithm was used to uniquely distinguish children with MPA from children with GPA, whose diagnoses had been classified according to both adult- and pediatric-specific criteria. Descriptive statistics were used for comparisons.**

Results. **In total, 231 of 440 patients (64% female) fulfilled the classification criteria for either MPA (n = 48) or GPA (n = 183). The median time to diagnosis was 1.6 months in the MPA group and 2.1 months in the GPA group (ranging to 39 and 73 months, respectively). Patients with MPA were significantly younger than those**

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with GPA (median age 11 years versus 14 years). Constitutional features were equally common between the groups. In patients with MPA compared to those with GPA, pulmonary manifestations were less frequent (44% versus 74%) and less severe (primarily, hemorrhage, requirement for supplemental oxygen, and pulmonary failure). Renal pathologic features were frequently found in both groups (75% of patients with MPA versus 83% of patients with GPA) but tended toward greater severity in those with MPA (primarily, nephrotic-range proteinuria, requirement for dialysis, and end-stage renal disease). Airway/eye involvement was absent among patients with MPA, because these GPA-defining features preclude a diagnosis of MPA within the EMA algorithm. Similar proportions of patients with MPA and those with GPA received combination therapy with corticosteroids plus cyclophosphamide (69% and 78%, respectively) or both drugs in combination with plasmapheresis (19% and 22%, respectively). Other treatments administered, ranging in decreasing frequency from 13% to 3%, were rituximab, methotrexate, azathioprine, and mycophenolate mofetil.

***Conclusion*. Younger age at disease onset and, perhaps, both gastrointestinal manifestations and more severe kidney disease seem to characterize the clinical profile in children with MPA compared to those with GPA. Delay in diagnosis suggests that recognition of these systemic vasculitides is suboptimal. Compared with adults, initial treatment regimens in children were comparable, but the complete reversal of female-to-male disease prevalence ratios is a provocative finding.**

Microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (Wegener's) (GPA) are primary systemic vasculitides that predominantly affect small blood vessels, and are collectively grouped under the umbrella term of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) (1,2). The limited literature available suggests that genetic, pathophysiologic, and prognostic differences exist between MPA and GPA, and this may be relevant to continuing biologic discovery and targeted therapy (3). Distinguishing between these diseases is challenging, because their clinical features are overlapping, standardized definitions are lacking, and mutually exclusive classification criteria have yet to be established. In the pediatric population especially, in whom there are only a few reported cases, accurate assessment of disease-specific epidemiologic data, prognostic implications, and biologic discovery has been particularly limited.

The American College of Rheumatology (ACR) has the most commonly used system for classifying vasculitis (referred to as the ACR 1990 Criteria for Vasculitis) (4). However, a pediatric adaptation of these ACR criteria, the European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) 2008 criteria, is reported to have improved specificity and sensitivity for the classification of childhood GPA (5–7). Neither the pediatric disease classification system nor the adult disease classification system has categorical criteria for MPA, and as a result, many patients defined as having MPA might also be concurrently classified as having GPA or polyarteritis nodosa (PAN), depending on how the disease definitions, such as those proposed by the Chapel Hill Consensus Conference (CHCC), are interpreted by individual physicians (2,6,8,9). Many clinical studies and trials have avoided this conundrum by considering GPA and MPA collectively. On the other hand, Watts et al proposed a classification algorithm, which was developed by consensus and subsequently adopted by the European Medicines Agency (EMA), that can classify patients with all types of AAV and PAN into mutually exclusive diagnostic categories (10). Specifically, the EMA algorithm has been adopted as a practical tool for clinical trials and clinical studies of AAV in adult patients (11,12), and was also applied in a previous study by our group, in which pediatric patients with GPA were actively distinguished from those with MPA using this algorithm (6). However, the EMA algorithm has not been adopted for routine clinical practice.

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The multicenter, contemporary inception cohort known as ARChiVe (A Registry for Childhood Vasculitis: e-entry) has previously reported the largest cohort of children with GPA studied to date (5). Conversely, descriptions of childhood MPA remain limited to only a few studies, in which fewer than 26 patients have been assessed and in which the included patients have not always been uniquely classified (13–17).

In the present study, we aimed to describe the presenting features of childhood MPA among the subcohort of AAV patients recruited to ARChiVe who were uniquely classified as having MPA; that is, after application of the EMA algorithm, these children were found to have no features that would be considered surrogate markers of GPA. We also aimed to compare these patients classified as having MPA against a larger accumulated subcohort of patients formally classified as having GPA by either the ACR 1990 Criteria for Vasculitis or the EULAR/PRINTO/PRES 2008 classification criteria, with the goal of identifying variations in clinical phenotype, diagnostic evaluations, and treatment.

PATIENTS AND METHODS

ARChiVe was first launched in March 2007, and at the time of censoring for this study, 45 pediatric rheumatologists at 45 geographically diverse institutions in Canada (n = 6), the US (n = 34), Europe (n = 3), and Asia (n = 2) had contributed patients. Patient eligibility criteria, the Registry data set, and the strategy for establishing the time to diagnosis have been described previously (5). Briefly, eligible patients included those who were diagnosed as having a primary chronic systemic vasculitis by the treating physician (i.e., given an MD diagnosis) after January 1, 2004 and before the age of 18 years. Patient data were collected retrospectively for those diagnosed before March 2007, and prospectively for those diagnosed subsequently, up to November 2015. Specific patient data items for categorical capture included all criteria that are required for formal diagnosis using either the ACR 1990 Criteria for Vasculitis (4) or the EULAR/PRINTO/PRES classification system (7). In addition, other categorical information, which has been described in the CHCC disease definitions (2,8) and is incorporated in the EMA algorithm for classifying AAV subtypes and PAN (6), was included. The diagnosis in patients could then be formally reclassified according to any of these criteria, by computation of the data.

The specific experience of individual physicians in diagnosing and caring for children with chronic vasculitis is limited, as was recognized in a 2005 survey in which the median number of patients with an AAV diagnosed by any rheumatologist in a single year was <1 (18). A recent international survey of 209 pediatric rheumatologists (Cabral DA, et al: unpublished observations) supports these earlier findings, with respondents showing no uniformity in their approach to the subclassification of patients with AAV as having either GPA or MPA. Individuals were classified according to either a single criteria set or varied combinations of criteria, and as a result, 42% met the ACR 1990 Criteria for Vasculitis, 81% met the EULAR/PRINTO/PRES classification criteria, 82% were classified according to a status of seropositivity for proteinase 3–classic ANCAs (PR3-cANCA) (versus myeloperoxidase–perinuclear ANCAs [MPO-pANCA]), 46% met the CHCC disease definitions, and 27% met other informal criteria. One-third of respondents reported that their final diagnosis was often AAV. Thus, not all patients were routinely subclassified as having a diagnosis of either GPA or MPA.

Therefore, for the present study, in which we sought to distinguish children with MPA from those with GPA, we did not use physician diagnoses or physician classifications, since there are no standardized diagnostic criteria and there was no uniform approach among the physicians from the 45 contributing sites, whose experience with AAVs varies. To systematically ensure uniformity, all patients with complete data who were enrolled in ARChiVe up to November 2015 were selected to be uniformly reclassified if they had the following submitting physician's diagnoses: GPA, limited GPA, MPA, ANCA-positive pauci-immune glomerulonephritis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA), PAN, or unclassified small vessel or medium vessel vasculitis. Selected patients were reclassified by computation of categorical variables as follows. Patients considered as having GPA were classified according to the ACR 1990 Criteria for Vasculitis or the EULAR/PRINTO/PRES 2008 classification criteria, which also allowed comparison against similarly defined cohorts of patients with GPA in other studies of pediatric and adult subjects. Patients considered as having MPA were classified according to the EMA algorithm.

As described previously (6,10), the EMA algorithm applies, in a sequential, stepwise manner, different classification criteria, disease definitions, and disease-specific surrogate markers from the CHCC to distinguish patients with individual AAV subtypes and PAN (Figure 1). Beginning with the most specific criteria, the algorithm initially determines whether a diagnosis of EGPA can be ruled out, using either the ACR criteria for EGPA or the Lanham criteria (19,20). Thereafter, the EMA algorithm determines whether a patient has GPA according to the ACR 1990 Criteria for Vasculitis or the EULAR/PRINTO/PRES 2008 classification criteria (using a pediatric modification of the algorithm). These patients classified as having GPA were included in the present study.

In the next step, the EMA algorithm assigns the classification of GPA to additional patients using the CHCC definitions, clinical surrogate features of GPA, and presence or absence of ANCAs. We arbitrarily chose to exclude this group of patients from the present study, describing them as having unclassifiable AAV, because such patients were not included in the cohorts of GPA patients in other comparator groups referred to herein.

Subsequently, the EMA algorithm determines whether a patient has MPA according to the presence of defining histologic features (CHCC definitions), clinical surrogates for renal vasculitis, and ANCAs. Patients determined to have no overlapping features of GPA are classified as having MPA, and these patients were included in the present study. In the final step of the EMA algorithm, patients are evaluated to determine whether they fulfill the CHCC definition of PAN, and these patients were excluded from the present study.

Basic demographic characteristics, clinical features, diagnostic data, and information on treatment usage at baseline were primarily extracted for patients who were uniquely classified as having either MPA or GPA.

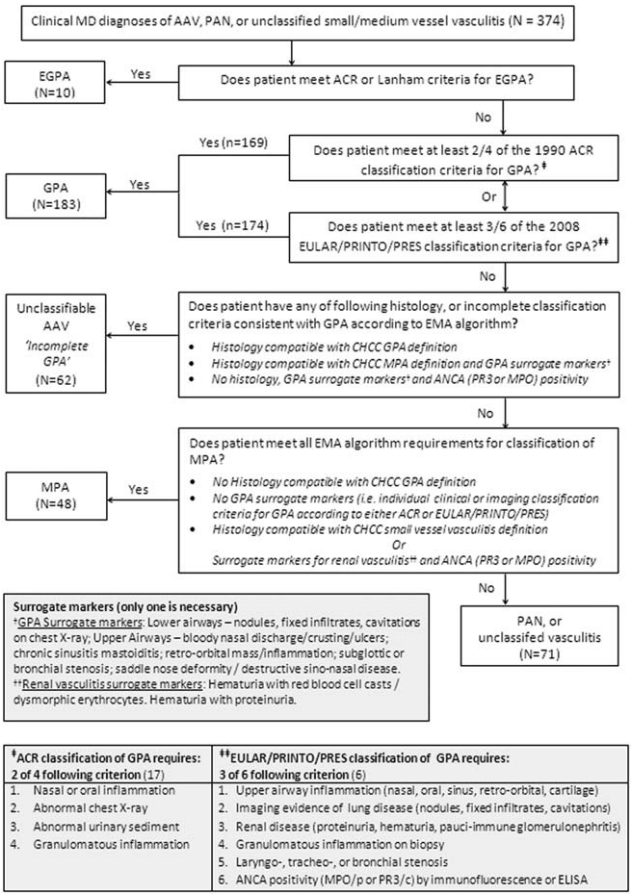

Figure 1. Formal classification of granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) assigned among an ARChiVe (A Registry for Childhood Vasculitis: e-entry) cohort of 374 children with a physician's (clinical MD) diagnosis of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV), polyarteritis nodosa (PAN), or unclassified small vessel or medium vessel vasculitis. Classification of GPA was performed according to either the American College of Rheumatology (ACR) 1990 Criteria for Vasculitis or the European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) 2008 classification criteria. Classification of MPA was done according to the European Medicines Agency (EMA) classification algorithm for classifying AAV and PAN. EGPA = eosinophilic granulomatosis with polyangiitis (Churg-Strauss); CHCC = Chapel Hill Consensus Conference; PR3 = proteinase 3; MPO = myeloperoxidase; ELISA = enzyme-linked immunosorbent assay.

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of British Columbia (21). Written informed consent was obtained from each participant, and the study protocol was approved by the ethics committee at each participating hospital (see Appendix A for institutions and members of the ARChiVe Investigators Network).

Descriptive statistics were generated using Stata (version 13.1; StataCorp). Comparisons were made using chi-square or Fisher's exact tests for categorical variables, and Student's *t*-tests or Mann-Whitney U tests for continuous variables.

RESULTS

Classification. During the study period, among the 440 children enrolled in the ARChiVe cohort, 374 patients with an initial clinical diagnosis (MD diagnosis) of GPA or limited GPA (n = 224), MPA (n = 48), ANCA-positive pauci-immune glomerulonephritis (n = 16), PAN (n = 40), EGPA (n = 10), or unclassified small vessel vasculitis (n = 36) were selected for formal diagnostic reclassification by computation of the data. A total of 231 patients fulfilled the criteria for either MPA (n = 48) or GPA (n = 183) and were included in the present study (Table 1). Patients designated as having unclassifiable AAV (n = 62) or those with PAN or other unclassifiable vasculitis (n = 71) were excluded. Sixty-five of the 183 patients with GPA have been described previously (21). No patients could be concurrently classified as having both MPA and GPA.

Demographics. Collectively, patients with either GPA or MPA were primarily white (55%) and female (64%), and 90% (208 patients) were ANCA positive. Children with MPA were significantly younger at the time of disease onset than those with GPA (median difference in age 3 years; $P = 0.004$). The interval between symptom

Table 1. Characteristics of the ARChiVe study participants classified as having MPA or GPA*

Characteristic	Patients with MPA (n = 48)	Patients with GPA (n = 183)
Female, no. (%)	35 (73)	113 (62)
Ethnicity, no. (%)		
Asian	1 (2)	5 (3)
Black	0 (0)	4 (2)
Hispanic	6 (13)†	6 (3)
White	20 (42)†	107 (59)
Other/unknown	21 (44)	61 (33)
Age at diagnosis, years		
Mean ± SD	11.2 ± 4.5‡	13.4 ± 3.2
Median (range)	12 (1–18)‡	14 (2–18)
Age at onset, years		
Mean ± SD	10.8 ± 4.7‡	12.9 ± 3.3
Median (range)	11 (1–18)‡	14 (2–18)
Time to diagnosis, months		
Mean ± SD	5.6 ± 9.6	5.5 ± 10.6
Median (range)	1.6 (0–39)	2.1 (0–73)
Physician diagnosis (preclassification), no. (%)		
MPA or isolated MPA	16 (33)	20 (11)
GPA or limited GPA	10 (21)	153 (84)
ANCA-positive pauci-immune GN	7 (15)	2 (1)
PAN	6 (13)	0 (0)
Not classified	9 (19)	8 (4)

* ARChiVe = A Registry for Childhood Vasculitis: e-entry; MPA = microscopic polyangiitis; ANCA = antineutrophil cytoplasmic antibody; GN = glomerulonephritis; PAN = polyarteritis nodosa.
† $P < 0.05$ versus patients with granulomatosis with polyangiitis (Wegener's) (GPA).
‡ $P < 0.01$ versus patients with GPA.

onset and diagnosis (time to diagnosis) varied widely both between and within groups. For patients with MPA, the median time to diagnosis was 1.6 months, while for GPA patients, the median time to diagnosis was 2.1 months. Demographic characteristics, the interval of time to diagnosis, and the initial MD diagnosis (prior to formal reclassification) are presented in Table 1.

Presenting clinical features. *Overview of system involvement.* Among patients with MPA, the systems involved in a majority of patients, in order of decreasing frequency, were constitutional (85%), renal (75%), gastrointestinal (58%), musculoskeletal (52%), and cutaneous (52%). Among patients with GPA, the systems involved in a majority of patients were constitutional (88%), renal (83%), pulmonary (74%), upper airways/ear, nose, and throat (ENT) (70%), and musculoskeletal (65%). The difference in the frequency of pulmonary involvement in patients with GPA (74%) compared to patients with MPA (44%) was statistically significant ($P < 0.0001$). The difference in frequency of upper airway involvement between the 2 groups is not surprising, since, in the EMA algorithm, specific ENT characteristics (as described below) are considered surrogate markers of GPA. Their presence in patients who otherwise do not completely fulfill the classification criteria for GPA precludes a unique diagnosis of MPA (Figure 1). In our study, such patients are designated as having unclassifiable AAV. The frequencies of specific clinical features in the cohort with unclassifiable AAV are summarized in Table 2 (together with the GPA and MPA cohorts). Details on other basic characteristics are available upon request from the corresponding author. Individual organ–specific clinical features, laboratory and imaging findings, and histopathologic features in the 2 cohorts with GPA or MPA are described below and summarized in Table 2.

Renal. The frequency and types of renal involvement were similar between patients with MPA and patients with GPA. Both cohorts exhibited common manifestations of proteinuria, microscopic hematuria, and/or red blood cell casts, an abnormal protein-to-creatinine ratio, and impaired creatinine clearance. The serum creatinine level was more often moderately to severely elevated (>30% of the age-adjusted upper limit of normal) among patients with MPA (48% versus 34% of patients with GPA; $P = 0.06$), but this was not a statistically significant difference. Rates of nephrotic-range proteinuria, renal failure requiring dialysis, or end-stage renal disease were similarly low between the 2 groups, but all 3 renal features tended to be more frequent among patients with MPA than among those with GPA.

Renal biopsy samples were obtained from 32 patients with MPA and 108 patients with GPA. Among these patients, histopathologic findings were consistent with a diagnosis of pauci-immune and/or necrotizing glomerulonephritis in 30 (94%) of the patients with MPA and 101 (94%) of the patients with GPA. Furthermore, the findings on renal biopsy were consistent with a diagnosis of vasculitis in 24 patients with MPA (75%) and 74 patients with GPA (69%).

Pulmonary. Pulmonary involvement was overall more frequent among patients with GPA compared to patients with MPA, and individual symptomatic features, such as chronic cough, alveolar hemorrhage, and massive hemoptysis, were also significantly more frequent among patients with GPA. Other pulmonary features, such as a requirement for supplemental oxygen and respiratory failure, also tended to be more frequent among patients with GPA, but this was not statistically significantly different from that in patients with MPA.

Pulmonary imaging was performed in 92% of patients with GPA and 81% of patients with MPA. Results of the imaging revealed pulmonary abnormalities in 89% of patients with GPA and 39% of patients with MPA. The presence of nodules, fixed pulmonary infiltrates, and/or cavitations, described as surrogate features of GPA in the EMA algorithm (see Figure 1), excluded a diagnosis of MPA, and therefore these 3 features were found only in the patients with GPA, at frequencies of 54%, 36%, and 21%, respectively (Table 2). Of note, among the 62 patients considered to have unclassifiable AAV, only 5 patients (8%) had at least 1 of these 3 surrogate pulmonary imaging findings (Table 2). Pleural effusions were found both in patients with MPA (10%) and in patients with GPA (16%), and other findings, such as fibrosis, septal thickening, and pneumothoraces, were identified in fewer than 10% of images from either group.

Of the 31 patients with GPA in whom a lung biopsy was performed, 24 (77%) had biopsy findings that confirmed the presence of vasculitis (48%) or that were consistent with features of vasculitis (29%). Granulomatous inflammation was identified in 4 patients, and 7 had no evidence of vasculitis. In the 3 (and only) patients with MPA who underwent lung biopsy, the histopathologic findings confirmed the presence of vasculitis in 2 of the patients, and the findings were consistent with features of vasculitis in 1 patient. No granulomas were seen in any biopsy sample.

Upper airways. Upper airway disease was a predominant presenting clinical feature among patients with GPA (70%). The virtual absence of upper airway features among patients with MPA is not surprising. Specifically, having any nasal/sinus involvement or tracheal/subglottic stenosis qualifies a patient as having 1 of the specific EULAR/PRINTO/PRES criteria for the classification of GPA (presence of 3 of 6 criteria required) (7). If patients

Table 2. Presenting clinical features of the ARChiVe study participants classified as having MPA, GPA, or unclassified AAV*

Clinical feature	Patients with MPA (n = 48)	Patients with GPA (n = 183)	Patients with unclassifiable AAV (n = 62)
Constitutional/general	41 (85)	160 (88)	39 (63)
Malaise, fatigue	37 (77)	152 (83)	33 (53)
Fever	25 (52)	97 (53)	22 (35)
Weight loss	15 (31)	80 (44)	10 (16)
Renal	36 (75)	151 (83)	24 (39)
Hypertension (age-adjusted)	16 (33)	39 (21)	8 (13)
Clinically "nephrotic" with edema	11 (23)†	20 (11)	2 (3)
Renal failure requiring dialysis	12 (25)†	24 (13)	4 (6)
End-stage renal disease	5 (10)	12 (7)	2 (3)
Impaired creatinine clearance (decreased by >25% of the LLN) or abnormal protein:creatinine ratio	28 (58)	99 (54)	6 (10)
Proteinuria	33 (69)	132 (72)	20 (32)
Hematuria >1+ or ≥10 RBCs/hpf or red cell casts	29 (60)	132 (72)	19 (31)
Biopsy-proven glomerulonephritis	30 (94) of 32	101 (94) of 108	17 (27)
Pulmonary	21 (44)‡	136 (74)	37 (60)
Chronic cough	11 (23)‡	99 (54)	18 (29)
Wheeze or expiratory dyspnea	2 (4)	15 (8)	5 (8)
Alveolar hemorrhage/massive hemoptysis	7 (15)‡	76 (42)	9 (15)
Pleurisy	4 (8)	25 (14)	3 (5)
Supplemental oxygen requirement	6 (13)	40 (22)	5 (8)
Respiratory failure	2 (4)	22 (12)	4 (6)
Imaging findings			
Nodules	0 (0)	97 (54)	3 (4)
Fixed pulmonary infiltrates	0 (0)	64 (36)	4 (6)
Cavitations	0 (0)	38 (21)	3 (5)
Ear, nose, and throat	0 (0)	128 (70)	24 (39)
Septal perforation or nasal collapse	0 (0)	15 (8)	3 (5)
Recurrent nasal bloody discharge/crusting/obstruction/ulcer	0 (0)	98 (53)	6 (10)
Chronic or recurrent sinusitis	0 (0)	71 (39)	5 (8)
Conductive or sensorineural hearing loss	0 (0)	19 (10)	3 (5)
Otitis/mastoiditis	0 (0)	31 (17)	5 (8)
Subglottic involvement	0 (0)	19 (10)	6 (10)
Oral ulcers/granulomata	2 (4)	27 (15)	3 (5)
Eyes	15 (31)	78 (43)	19 (31)
Conjunctivitis	3 (6)	21 (11)	3 (5)
Nonspecific red eye	1 (2)	19 (10)	6 (10)
Episcleritis	2 (4)	15 (8)	4 (6)
Proptosis or retroorbital mass	0 (0)	3 (2)	7 (11)
Retinal exudates, hemorrhages, aneurysms, or vessel thrombosis	1 (2)	0 (0)	0 (0)
Cutaneous	25 (52)	86 (47)	20 (32)
Palpable purpura/petechial rash	15 (31)	49 (27)	8 (13)
Gastrointestinal	28 (58)§	66 (36)	18 (29)
Nonspecific abdominal pain	18 (38)†	41 (22)	11 (18)
Chronic nausea	16 (33)‡	22 (12)	7 (11)
Musculoskeletal	25 (52)	118 (65)	25 (40)
Arthralgia or confirmed arthritis	20 (42)	112 (61)	24 (39)
Myalgia, muscle weakness, or confirmed myositis	9 (19)	24 (14)	4 (7)
Nervous system	10 (21)	36 (20)	15 (24)
Headache	6 (13)	20 (11)	9 (15)
Dizziness	2 (4)	12 (7)	5 (8)
Cardiovascular	3 (6)	10 (5)	2 (3)
Venous thrombosis	0 (0)	3 (2)	2 (3)

* Values are the number (%) of patients. ARChiVe = A Registry for Childhood Vasculitis: e-entry; MPA = microscopic polyangiitis; AAV = antineutrophil cytoplasmic antibody–associated vasculitis; LLN = lower limit of normal; RBCs = red blood cells; hpf = high-power field.
† $P < 0.05$ versus patients with granulomatosis with polyangiitis (Wegener's) (GPA).
‡ $P < 0.001$ versus patients with GPA.
§ $P < 0.01$ versus patients with GPA.

with these characteristic ENT features do not completely fulfill the classification criteria for GPA, these so-called surrogate markers of GPA, according to the EMA algorithm, still relegate the patient to a diagnosis of GPA, albeit the diagnosis may be considered to be incomplete. These patients are therefore precluded from a diagnosis of MPA; for the purposes of our study, these patients are described as having unclassifiable AAV (Figure 1). Among the 62 patients considered to have unclassifiable AAV, 24 (39%) had upper airway (ENT) pathologic features (Table 2).

Among the patients with GPA included in the study, the most commonly reported upper airway abnormalities were chronic recurrent nasal symptoms (53%) and recurrent or chronic sinusitis (39%) (Table 2). Oral ulcers (15%), subglottic or tracheal stenosis/inflammation (10%), hearing loss (10%), and tissue damage from septal perforations or nasal collapse (8%) occurred less frequently than other upper airway manifestations.

Sinus imaging was performed on 123 patients with GPA and 11 patients with MPA. There were no sinus abnormalities identified among the patients with MPA. Among the patients with GPA, the specifically characterized sinus abnormalities were abnormal fluid levels or opacities (53%), bone destruction (6%), mass effect (5%), and other unspecified abnormalities (31%). The results of paranasal sinus imaging or upper airway biopsy performed in 36 patients with GPA confirmed the presence of vasculitis in 8 patients (22%), were consistent with a diagnosis of vasculitis in 13 patients (36%), and showed no evidence of vasculitis in 15 patients (42%).

Other systems. Gastrointestinal symptoms were significantly more frequent in patients with MPA (58%) than in patients with GPA (36%). Chronic nausea was specifically more frequent in patients with MPA (33% of patients with MPA versus 12% of patients with GPA; $P < 0.04$). Nonspecific abdominal pain was relatively common in both groups (38% of patients with MPA versus 22% of patients with GPA). Severe gastrointestinal features of persistent diarrhea, bleeding, or ischemic abdominal pain were each found in fewer than 5% of patients in either group.

Skin involvement was reported in 48% of all patients, and most frequently included palpable purpura and/or petechial rash, in 31% of patients with MPA and 27% of patients with GPA. Other skin findings, found in fewer than 10% of patients in either group, included subcutaneous nodules (6% of patients with MPA versus 8% of patients with GPA), infarctions (6% of patients with MPA versus 3% of patients with GPA), livido (2% of patients with MPA versus 1% of patients with GPA), Raynaud's phenomenon (0% of patients with MPA versus 3% of patients with GPA), and subcutaneous swelling (4% of patients with MPA versus 3% of patients with GPA). Features of mucous membrane or eye involvement, which were reported in 40% of all patients, included red and/or painful eye conditions attributable to conjunctivitis, episcleritis, or another nonspecific condition. Three patients with GPA had proptosis with retroorbital mass, and 1 patient with MPA had retinal exudates/hemorrhages/aneurysms/vessel thrombosis. Relatively few patients with either MPA (4%) or GPA (15%) presented with oral ulcers.

A majority of patients in each group presented with nonspecific musculoskeletal symptoms (52% of patients with MPA and 65% of patients with GPA). Among all patients, neurologic involvement was relatively uncommon, with the more common features being seizures (8% of patients with MPA and 3% of patients with GPA) and the nonspecific symptoms of headache (13% of patients with MPA and 11% of patients with GPA) and dizziness (4% of patients with MPA and 7% of patients with GPA). Severe neurologic features, such as peripheral neuropathy, weakness, or stroke, were reported in fewer than 3% of all patients. Cardiovascular manifestations, primarily venous thromboses, were recorded in only 3 patients, all of whom had GPA.

Other laboratory features. The majority of all patients presented with elevated markers of inflammation and hematologic abnormalities. Marked elevation in the erythrocyte sedimentation rate (>50 mm/hour) was typical in both groups (65% of patients with MPA and 70% of patients with GPA), while elevation in the levels of C-reactive protein was more frequently observed in patients with GPA (85%) than in those with MPA (65%; $P < 0.01$). One-half of the patients with GPA had elevated levels of both total white blood cells and neutrophils, compared to one-third of the patients with MPA. Eosinophil levels were normal in most patients. More than 80% of all patients had anemia, and approximately one-third had elevated platelet counts. Levels of the Von Willebrand antigen (tested in only 10 patients with MPA and 59 patients with GPA) were frequently elevated in both groups (60% and 69% of patients, respectively). Increased antistreptolysin O titers were observed more frequently among the patients with MPA tested (39% of patients with MPA versus 13% of patients with GPA; $P = 0.006$). There was little evidence of other infectious causes or concurrent diseases, such as tuberculosis or hepatitis B or C.

MPO-ANCA and/or pANCA were more frequent in patients with MPA (55%) than in those with GPA (26%) ($P < 0.01$), whereas PR3-ANCA and/or cANCA were more common in patients with GPA (67%) compared to patients with MPA (17%; $P < 0.01$). In all, 26%

Table 3. Initial treatments administered to the ARChiVe study participants classified as having MPA or GPA*

Medication use	Patients with MPA (n = 48)	Patients with GPA (n = 183)
Corticosteroids	44 (92)	179 (98)
Corticosteroids plus cyclophosphamide	33 (69)	142 (78)
DMARDs collectively†	44 (92)	173 (95)
Cyclophosphamide (oral or IV)	33 (69)	142 (78)
Methotrexate (oral or subcutaneous)	4 (8)	20 (11)
Mycophenolate mofetil	4 (8)	2 (1)
Azathioprine	4 (8)	2 (1)
Rituximab	5 (10)	23 (13)
Intravenous immunoglobulin	2 (4)	10 (5)
Plasmapheresis	9 (19)	40 (22)
Trimethoprim sulfamethoxazole	10 (21)‡	90 (49)
Other adjuvant medications	41 (85)	135 (74)
Antihypertensives with or without ACE inhibitors	26 (54)§	68 (38)

* Values are the number (%) of patients. ARChiVe = A Registry for Childhood Vasculitis: e-entry; MPA = microscopic polyangiitis; IV = intravenous; ACE = angiotensin-converting enzyme.
† Disease-modifying antirheumatic drugs (DMARDs) include cyclophosphamide, methotrexate, mycophenolate mofetil, and azathioprine.
‡ $P < 0.001$ versus patients with granulomatosis with polyangiitis (Wegener's) (GPA).
§ $P < 0.05$ versus patients with GPA.

of patients with MPA and 5% of patients with GPA tested negative for ANCAs, whether tested by immunofluorescence or by enzyme-linked immunosorbent assay. Three patients did not undergo ANCA testing.

Initial therapies. The initial immunosuppressive therapies administered to children with GPA and children with MPA were very similar (Table 3). Nearly all of the patients received corticosteroids (97%), and this was usually combined with another immunosuppressive drug. Most patients (76%) were treated with cyclophosphamide (69% of patients with MPA and 78% of patients with GPA), while 11% received other conventional disease-modifying antirheumatic drugs (DMARDs), which included methotrexate, mycophenolate mofetil, or azathioprine (25% of patients with MPA and 13% of patients with GPA), and 12% of patients were taking rituximab (10% of patients with MPA and 13% of patients with GPA), either singly or in combination with another DMARD. In total, 6% of patients did not receive any of the listed DMARDs or rituximab. Furthermore, 21% of all patients received plasmapheresis. A significantly smaller proportion of patients with MPA (21%) compared to those with GPA (49%) received trimethoprim, either for upper respiratory infection or *Pneumocystis jiroveci* pneumonia prophylaxis ($P = 0.0005$). Antihypertensive agents and/or angiotensin-converting enzyme inhibitors were administered to 41% of all patients.

Patients with unclassifiable AAV. The 62 patients designated as having unclassifiable AAV were predominantly female (76%). Among these patients, the MD diagnosis was GPA (55%), MPA (13%), ANCA-associated pauci-immune glomerulonephritis (6%), PAN (5%), or unclassified AAV (21%). A majority of these patients had constitutional features of disease (63%) and pulmonary histopathologic features (60%). Other systems involved, in decreasing frequency, were musculoskeletal (40%), renal (39%), upper airways/ENT (39%), cutaneous (32%), and gastrointestinal (29%) (Table 2). The results of testing for ANCAs, among the 59 patients with unclassifiable AAV who were tested, were as follows: 36% with PR3-ANCA and/or cANCA, 32% with MPO-ANCA and/or pANCA, and 32% negative for ANCAs (details available upon request from the corresponding author).

DISCUSSION

Our study involved the largest cohort of pediatric patients with AAV described to date, albeit excluding patients with EGPA. The relative ratio of patients with GPA to patients with MPA from contributing centers was 4:1, and this likely reflects a predominantly white population of Northern European origin, in contrast to previously studied populations from Japan and China (22,23) and perhaps Southern Europe (24), where MPA was more common than GPA. The subcohort of 183 patients with GPA in the current study is the largest reported cohort of pediatric patients with that disease, and includes 65 patients previously recruited to the ARChiVe cohort up to November 2008 (5). The subcohort of 48 pediatric patients with MPA is larger than the 5 largest previous pediatric case series that contained retrospective data on patients with MPA from Turkey

(n = 26), Japan (n = 21), Serbia (n = 7), Beijing, China (n = 19), and Guangzhou, China (n = 16) (13–17). The earliest of these studies, from Turkey (14), described 26 children with PAN, among whom 24 might now be considered to have MPA if diagnosed according to contemporary definitions. In the subsequent studies, patients with MPA were distinguished from those with GPA according to different disease definitions or descriptions that have evolved over time. In the studies from Serbia (15) and Beijing (17), the diagnosis of MPA, as distinguished from GPA, was ultimately determined by the presence of MPO-ANCA or pANCA. In using the EMA algorithm (10), the present study is the only one to define patients as having MPA in a way that is mutually exclusive of the diagnosis of GPA, EGPA, or PAN.

A variety of other criteria and definitions used by pediatric rheumatologists for subclassifying patients as having MPA or GPA were identified in an international survey completed by a majority of physicians who contributed patients to the ARChiVe cohort. These results, describing a nonuniform approach to disease classification, are provided in Patients and Methods as a rationale for our decision to systematically reclassify our patient cohort. Of note, among the 62 patients designated as having unclassifiable AAV, the ratio of the assigned MD diagnosis of GPA to that of MPA, a ratio of 4:1, was similar to that in the present study. Moreover, the predominance of female patients was similar to that in both the GPA cohort and the MPA cohort. Generally, patients in the cohort with unclassifiable AAV had more limited disease and had fewer systems involved, and therefore were arguably less likely to fulfill the formal classification criteria. The frequencies of patients with PR3-ANCA and/or cANCA (36%), those with MPO-ANCA and/or pANCA (32%), and those negative for ANCAs (32%) were evenly distributed in patients with unclassifiable AAV, and therefore the ANCA status was not indicative of this group being more likely to have either GPA or MPA.

The discrepancy in frequency of patients formally classified as having MPA according to the EMA algorithm, when compared to those who were given an MD diagnosis of MPA, was evaluated and discussed in depth in our earlier study in which a smaller cohort of patients recruited to the ARChiVe cohort was assessed (6). Several patients who were classified formally as having GPA were given the MD diagnosis of MPA, seemingly on the basis of the type of ANCA (i.e., pANCA with specificity for MPO).

The mean age at disease onset in patients with MPA in our study (mean age 10.8 years) falls within the range of ages (mean ages 9–12 years) from other pediatric series (13–17). The marked predominance of female patients in our study, a reported frequency of 73%, was also characteristic of that in other case series, in which frequencies of up to 90% have been described; only the Turkish case series (14) had a lower frequency of female patients, at 53%. This is in complete contrast to studies of adult patients, in which a predominance of male patients with MPA has been described, ranging from 55% to 60% (12,25,26). Notably, the 2 more recent of these 3 studies used an algorithmic classification of GPA (12,25).

The frequencies of involvement of different organ systems (and specific presenting clinical features) in our MPA cohort are listed in Table 2. The frequencies of the more commonly involved systems fell within the wide range of frequencies described in other pediatric case series (13–17). The frequency of general constitutional symptoms (85%) was in the low end of the ranges reported. Renal disease, present in 75% of the patients in the present study, was also in the low end of the range of frequencies, and is in contrast to that reported previously from Departments of Nephrology, in which renal disease has been reported to be present in 100% of patients (13–17). Skin manifestations, predominantly palpable purpura or petechiae, occurred in a majority of our patients (52%) and was consistent with the reported frequencies (15–100%) in other studies (13–17); it should be noted that the 100% frequency of skin manifestations that was reported in the Serbian study was observed in a cohort of only 7 patients.

In spite of the fact that the EMA algorithm characteristically precludes a diagnosis of MPA among patients with selected lung features on imaging, pulmonary involvement, which was identified in a minority of our patients (44%), was in the middle range of frequencies that have been reported previously (15–62%) (13–17). Gastrointestinal involvement occurred in a little more than one-half of our patients, with nonspecific abdominal pain and chronic nausea representing the primary manifestations and gastrointestinal bleeding occurring in only 1 patient. Gastrointestinal involvement was not typically characterized in other case series, but when it was described, it occurred in 15–55% of patients (4,13,15–17). Nervous system involvement was infrequent; notably, peripheral neuropathy was not reported, a finding that was similar to that in other pediatric and adult case series of patients in whom a diagnosis of PAN was actively excluded (13,15–17).

The subcohort of 183 patients with GPA was triple in size compared to the 2 previous largest pediatric case series of 56 patients from the PRINTO database (27) and 65 patients from our earlier report on the ARChiVe cohort (5). In the earlier ARChiVe report, patients were classified as having GPA according to the ACR 1990 Criteria for Vasculitis; however, since that time, pediatric-specific

criteria have become available, and patients in both the PRINTO study and in the present study were classified according to the EULAR/PRINTO/PRES criteria (7). Despite the difference in population pools and classification criteria, the results of this much larger series overall support the findings of the previous studies. The preponderance of females and white patients was similar in all 3 studies. The median age at disease onset of 14 years (median diagnostic delay of 2.1 months) in this study was slightly older than that reported for patients in the PRINTO registry, in which the median age at disease onset was 11.7 years (median diagnostic delay of 4.2 months).

In comparing the current study with our earlier report on the ARChiVe cohort, the frequencies of organ system involvement among patients with GPA were very similar, although among patients in the present study, cutaneous findings were more frequent (47% versus 35%). Both venous thrombosis (3 patients) and periorbital masses (3 patients) were only observed among patients in this later and larger cohort.

With regard to presenting clinical features, the following features were less frequent in the current ARChiVe cohort than in patients from the PRINTO registry: ENT findings (70% versus 91%), eye findings (12% versus 35%), and the presence of fixed lung infiltrates (36% versus 47%). In contrast, the following features were more frequent in the ARChiVe cohort than in the PRINTO registry: renal disease defined by hematuria and/or casts (72% versus 63%), gastrointestinal findings (36% versus 16%), the presence of hemoptysis/alveolar hemorrhage (42% versus 25%), and pulmonary nodules (54% versus 30%).

In spite of the slight variations in frequencies of clinical features, our findings overall support the conclusions of the PRINTO registry report, in that when compared to the adult case series (using the same comparator groups as used in that report [28–30]), adult patients showed lower frequencies of constitutional, respiratory, and renal involvement, and a higher frequency of conductive hearing loss. Unlike the PRINTO series, we did not demonstrate a higher frequency of ENT findings in our pediatric cohort when compared to adults. In contrast to the findings in adult patients, so-called limited or localized GPA, as defined by the absence of kidney disease, occurred in a minority of children at diagnosis and at presentation. This apparent difference might reflect the known difficulties in formally classifying children as having GPA when they only have single-organ involvement (for example, subglottic stenosis, chronic sinusitis, episcleritis, or retroorbital mass) at presentation. Indeed, such patients are more frequently designated as having unclassifiable AAV (incomplete GPA), as was found in the cohort of 62 patients in the present study, in whom the time to diagnosis (diagnostic delay) was also longer than that in either patients with GPA or patients with MPA.

In the absence of any formal classification criteria for MPA, we have applied a modified pediatric EMA algorithm and used categorical data provided by the contributing physicians to uniquely classify patients as having MPA (i.e., without overlapping features of GPA). Using this strategy, we were able to overcome the potentially differing diagnostic/classification principles used by the variety of pediatric rheumatologists at the 45 diverse institutions that have contributed patients to ARChiVe.

While both GPA and MPA are included among the spectrum of differential diagnoses for pulmonary/renal syndromes, only a minority (44%) of patients with MPA presented with any respiratory features. Patients with GPA also tended to have more frequent and more severe pulmonary manifestations (i.e., hemorrhage, requirement for supplemental oxygen, or pulmonary failure) compared to patients with MPA. In patients with MPA, the age at disease onset was younger, and although the frequency of renal disease was similar to that in patients with GPA, it tended to be more severe in phenotype. Gastrointestinal manifestations also occurred more frequently in patients with MPA. Among the patients with GPA, however, 75% presented with lower respiratory tract manifestations, and the disease was associated with ANCAs directed against the PR3 antigen. The presence of other surrogate markers of GPA (including upper respiratory tract manifestations of nasal and sinus involvement), as incorporated in the EMA algorithm, precluded the diagnosis of MPA. Similarly, the less frequent, but relatively specific, manifestations of tracheal and subglottic stenosis or inflammatory eye disease were found only in patients with GPA.

When comparing specific clinical manifestations in patients with MPA and patients with GPA in our cohort, features that were more prevalent among patients with MPA included nephrotic-range proteinuria with edema, renal failure requiring dialysis, and chronic nausea. While we found that 75% of patients with MPA in our cohort had renal disease, previous reports (predominantly from Departments of Nephrology) have described renal manifestations in 100% of patients with MPA (13–17). The frequency of nephrotic syndrome in our cohort (23%) was similar to that in 2 case series from China (30%) (16) and Serbia (29%) (15). A requirement for dialysis for renal failure, around the time of diagnosis, was only described in the Serbian study (15), and occurred in 29% of patients, similar to the frequency of 25% in the present study. Gastrointestinal involvement (specifically, chronic nausea) was seen in one-half of the patients with MPA compared to one-third of the patients with GPA, a finding that is somewhat unique to our study; its relevance remains

unclear. That being stated, it seems plausible that chronic nausea, in particular, may also reflect more severe renal disease in patients with MPA.

Prompt identification of AAV followed by initiation of appropriate immunosuppressive treatment is crucial to preventing adverse outcomes. Several studies of adult patients have identified the level of kidney function at presentation and, in particular, whether dialysis is required, as independent risk factors for mortality in patients with AAV (31,32). We demonstrated wide variations in the time to diagnosis. Thus, we speculate that variations in the rate of onset and severity of prodromal symptoms may delay disease recognition in some patients. In addition, because of its rarity, primary health care might not always consider AAV among the diagnostic possibilities in pediatric patients.

Both MPA and GPA are rare, yet potentially devastating, systemic vasculitides that affect the small and medium-sized arteries in multiple organ systems. In the absence of definitive diagnostic tests, classification criteria are an essential tool for characterizing and comparing patients with overlapping clinical phenotypes across studies. Although in this comparative description of patients with MPA and patients with GPA, the number of patients classified as having MPA was relatively small, the findings are consistent with those in previously described smaller cohorts. Nevertheless, our limited conclusions should be viewed with caution. Our study has allowed us to delineate differences between MPA and GPA, notably, an earlier age at disease onset and perhaps more severe renal disease presentation in children with MPA. The marked predominance of female patients in the pediatric MPA cohort, compared to the predominance of male patients in similarly classified adult cohorts, invokes a cautionary note against making broad generalizations about the similarities between adult and pediatric vasculitis.

International collaborations in childhood vasculitis have led to the development and validation of classification criteria for childhood vasculitis, have advanced our understanding of the clinical phenotype at presentation of childhood AAV, and have improved our ability to capture disease activity and determine treatment choices (33). Ongoing biomarker-driven studies may complement systems for subclassifying patients with AAV, and will further shape our understanding of these diseases. Several challenges remain with regard to evaluating the safety and efficacy of current treatment strategies, which have been largely derived from studies of adults, and assessing the long-term morbidity in children with AAV.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Cabral had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Cabral, Muscal, Eberhard, Higgins, Moorthy, Morishita, Nielsen, O'Neil.

Acquisition of data. Cabral, Canter, Muscal, Nanda, Wahezi, Spalding, Twilt, Benseler, Campillo, Charuvanij, Dancey, Eberhard, Elder, Hersh, Higgins, Huber, Khubchandani, Kim, Klein-Gitelman, Kostik, Lawson, Lee, McCurdy, Moorthy, Nielsen, O'Neil, Reiff, Ristic, Robinson, Shenoi, Toth, Van Mater, Wagner-Weiner, Weiss, White, Yeung.

Analysis and interpretation of data. Cabral, Canter, Muscal, Spalding, Twilt, Benseler, Lubieniecka, Moorthy, Morishita, Nielsen, Sarmiento.

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APPENDIX A: MEMBERS OF THE ARChiVe INVESTIGATORS NETWORK

The coordinating center of the ARChiVe Investigators Network was British Columbia Children's Hospital (Vancouver, British Columbia, Canada), with the following members: David A. Cabral (Study Principal Investigator), Angelyne Sarmiento and Qun Yang (Study Coordinators), Victor Espinosa (IT Manager), Joanna Lubieniecki (Statistician), and Jaime Guzman, Kristin Houghton, Kimberly Morishita, Ross Petty, and Lori Tucker (Site Investigators). Other participating centers and members are as follows: Akron Children's Hospital (Akron, OH): Mary B. Toth (Site Principal Investigator); Alberta Children's Hospital (University of Calgary, Calgary, Alberta, Canada): Susanne Benseler (Site Principal Investigator), Marinka Twilt (Site Investigator); Alder Hey Children's

NHS Foundation Trust Hospital (Liverpool, UK): Michael Beresford (Site Principal Investigator), Eileen Baildam (Site Co-Principal Investigator); Ann & Robert H. Lurie Children's Hospital of Chicago (Chicago, IL): Marisa Klein-Gitelman (Site Principal Investigator), Michael Miller and Megan Curran (Site Investigators); Birmingham Children's Hospital NHS Foundation Trust (Birmingham, UK): Taunton Southwood (Site Principal Investigator); Breach Candy Hospital (Mumbai, India): Raju Khubchandani (Site Principal Investigator); Children's Hospital at Montefiore (New York, NY): Norman T. Ilowite (Site Principal Investigator), Dawn M. Wahezi (Site Investigator); Children's Hospital of Boston: Susan Kim (Site Principal Investigator), Fatma Dedeoglu, Robert Fuhlbrigge, Melissa Hazen, Mary Beth Son, and Robert Sundel (Site Investigators); Children's Hospital, Los Angeles (Los Angeles, CA): Andreas Reiff (Site Principal Investigator), Diane Brown, Katherine Marzan, Anusha Ramanathan, and Bracha Shaham (Site Investigators); Children's Hospital of Eastern Ontario (Ottawa, Ontario, Canada): Ciaran Duffy (Site Principal Investigator); Children's Hospital of Michigan (Detroit, MI): Matthew Adams (Site Principal Investigator), Rudolf Valentini (Site Investigator); Children's Hospital of Pittsburgh (Pittsburgh, PA): Margalit Rosenkranz (Site Principal Investigator), Daniel Kietz, Elaine Cassidy, and Kathryn Torok (Site Investigators); Children's Mercy Hospital (Kansas City, MO): Mara Becker (Site Principal Investigator); Children's National Medical Center (Washington, DC): Lawrence K. Jung (Site Principal Investigator); Cleveland Clinic Foundation (Cleveland, OH): Steven Spalding (Site Principal Investigator), Andrew Zeft (Site Investigator); Cohen Children's Medical Center of New York (New Hyde Park, NY): Anne Eberhard (Site Principal Investigator), Bett Gottlieb and Cagri Toruner (Site Investigators); Comer Children's Hospital (Chicago, IL): Linda Wagner-Weiner (Site Principal Investigator), Karen Onel, Charles Spencer, Deidre De Ranieri, and Melissa Tesher (Site Investigators); Morgan Stanley Children's Hospital of New York—Presbyterian (New York, NY): Andrew Eichenfield (Site Investigator), Lisa Imundo (Site Investigator); Duke Children's Hospital and Health Center (Duke University Medical Center, Durham, NC): Heather Van Mater (Site Principal Investigator), C. Egla Rabinovich, Laura Schanberg, and Jeffery Dvergsten (Site Investigators); Great North Children's Hospital (Newcastle, UK): Mark Friswell (Site Principal Investigator); Hospital for Sick Children (Toronto, Ontario, Canada): Rae Yeung (Site Principal Investigator), Brian Feldman, Deborah Levy, Earl D. Silverman, Ronald Laxer, and Rayfel Schneider (Site Investigators); Hospital Sant Joan de Deu Barcelona (Barcelona, Spain): Jordi Anton (Site Principal Investigator); IWK Health Centre and Dalhousie University (Halifax, Nova Scotia, Canada): Adam M. Huber (Site Principal Investigator), Bianca A. Lang, Suzanne Ramsey, and Elizabeth Stringer (Site Investigators); Janeway Children's Health and Rehabilitation Centre (St. John's, Newfoundland, Canada): Paul Dancey (Site Principal Investigator); Joseph M. Sanzari Children's Hospital (Hackensack University Medical Center, Hackensack, NJ): Suzanne C. Li (Site Principal Investigator), Kathleen Haines, Yukiko Kimura, Ginger Janow, and Jennifer Weiss (Site Investigators); Leeds Children's Hospital (Leeds, UK): Mark Wood (Site Principal Investigator); Mayo Eugenio Litta Children's Hospital (Mayo Clinic, Rochester, MN): Thomas Mason (Site Principal Investigator), Ann Reed (Site Investigator); Medical College of Georgia (Augusta, GA): Rita Jerath (Site Principal Investigator); Meyer Children's Hospital (Florence, Italy): Rolando Cimaz (Site Principal Investigator); Monroe Carell Jr. Children's Hospital at Vanderbilt (Nashville, TN): Thomas B. Graham (Site Principal Investigator), Amy Woodward and Donna Hummel (Site Investigators); Mother and Child Health Care Institute of Serbia (Belgrade, Serbia): Goran Ristic (Site Principal Investigator); Nationwide Children's Hospital (Columbus, OH): Gloria C. Higgins (Site Principal Investigator); Nuffield Orthopaedic Centre (University of Oxford, Oxford, UK): Raashid Luqmani (Site Principal Investigator); Phoenix Children's Hospital (Phoenix, AZ): Kaleo Ede (Site Principal Investigator), Michael Shishov (Site Investigator); Randall Children's Hospital at Legacy Emmanuel (Portland, OR): Daniel J. Kingsbury (Site Principal Investigator), Victoria Cartwright and Andrew Lasky (Site Investigators); Rigshospitalet (Copenhagen, Denmark): Susan Nielsen (Site Principal Investigator); Riley Children's Hospital (Indianapolis, IN): Kathleen O'Neil (Site Principal Investigator), Peter Chira, Susan Ballinger, Stacey Tarvin, and Michael Blakley (Site Investigators); Royal Hospital for Children (Glasgow, UK): Neil Martin (Site Principal Investigator); Royal Manchester Children's Hospital (Manchester, UK): Janet McDonagh (Site Principal Investigator); Rutgers-Robert Wood Johnson Medical School (New Brunswick, NJ): Lakshmi Nandini Moorthy (Site Principal Investigator), Alexis Boneparth (Site Investigator); Saint Louis Children's Hospital (Washington University School of Medicine, St. Louis, MO): Kevin Baszis (Site Principal Investigator), Andrew White (Site Investigator); Saint-Petersburg State Pediatric Medical University (St. Petersburg, Russia): Mikhail Kostik (Site Principal Investigator); Seattle Children's Hospital (Seattle, WA): Susan Shenoi (Site Principal Investigator), Kabita Nanda, Anne Stevens, Alexandra Aminoff, and Carol Wallace (Site Investigators); Sheffield Children's NHS Foundation Trust (Sheffield, UK): Anne-Marie McMahon (Site Principal Investigator); Siriraj Hospital (Mahidol University, Bangkok, Thailand): Sirirat Charuvanij (Site Principal Investigator); Stanford Children's Health (Stanford University School of Medicine, Stanford, CA): Tzielan Lee (Site Principal Investigator), Imelda Balboni, Michal Cidon, Jennifer Frankovich, Dana Gerstbacher, Joyce J. Hsu, and Christy Sandborg (Site Investigators); Southampton General Hospital (Southampton, UK): Alice Leahy (Site Principal Investigator); Texas Children's Hospital (Baylor College of Medicine, Houston, TX): Eyal Muscal (Site Principal Investigator), Barry L. Myones (Site Investigator); The Montreal Children's Hospital (McGill University Health Centre, Montreal, Quebec, Canada): Sarah Campillo (Site Principal Investigator), Gaëlle Chédeville and Rosie Scuccimarri (Site Investigators); The Hospital for Special Surgery (New York, NY): Thomas Lehman (Site Principal Investigator), Laura Barinstein, Emma MacDermott, and Alexa Adams (Site Investigators); University Children's Hospital Muenster (Muenster, Germany): Dirk Foel (Site Principal Investigator); University Hospitals Case Medical Center (Rainbow Babies and Children's Hospital, Cleveland, OH): Angela Byun Robinson (Site Principal Investigator), Elizabeth B. Brooks (Site Investigator); University of California at Los Angeles: Deborah McCurdy (Site Principal Investigator); University of California at San Francisco: Erica Lawson (Site Principal Investigator); University of Florida (Gainesville, FL): Melissa E. Elder (Site Principal Investigator); University of Louisville School of Medicine (Louisville, KY): Kenneth N. Schikler (Site Principal Investigator); University of Saskatchewan (Saskatoon, Saskatchewan, Canada): Alan Rosenberg (Site Principal Investigator); University of Texas Southwestern (Texas Scottish Rite Hospital, Dallas, TX): Marilynn Punaro (Site Principal Investigator), Lorien Nassi and Virginia Pascual (Site Investigators); University of Salt Lake City (Salt Lake City, UT): Aimee Hersh (Site Principal Investigator), C. J. Inman, Sara Stern, and John Bohnsack (Site Investigators); University of Vermont (Burlington, VT): Leslie Abramson (Site Principal Investigator); Wellington Hospital (Wellington, New Zealand): Arno Ebner (Site Principal Investigator).