Do Adult Disease Severity Subclassifications Predict Use of Cyclophosphamide in Children with ANCA-associated Vasculitis? An Analysis of ARChiVe Study Treatment Decisions

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ABSTRACT. ***Objective.*** To determine whether adult disease severity subclassification systems for antineutrophil cytoplasmic antibody-associated vasculitis (AAV) are concordant with the decision to treat pediatric patients with cyclophosphamide (CYC).

Methods. We applied the European Vasculitis Study (EUVAS) and Wegener's Granulomatosis Etanercept Trial (WGET) disease severity subclassification systems to pediatric patients with AAV in A Registry for Childhood Vasculitis (ARChiVe). Modifications were made to the EUVAS and WGET systems to enable their application to this cohort of children. Treatment was categorized into 2 groups, "cyclophosphamide" and "no cyclophosphamide." Pearson's chi-square and Kendall's rank correlation coefficient statistical analyses were used to determine the relationship between disease severity subgroup and treatment at the time of diagnosis.

Results. In total, 125 children with AAV were studied. Severity subgroup was associated with treatment group in both the EUVAS (chi-square 45.14, $p < 0.001$, Kendall's tau-b 0.601, $p < 0.001$) and WGET (chi-square 59.33, $p < 0.001$, Kendall's tau-b 0.689, $p < 0.001$) systems; however, 7 children classified by both systems as having less severe disease received CYC, and 6 children classified as having severe disease by both systems did not receive CYC.

Conclusion. In this pediatric AAV cohort, the EUVAS and WGET adult severity subclassification systems had strong correlation with physician choice of treatment. However, a proportion of patients received treatment that was not concordant with their assigned severity subclass. (First Release Aug 1 2012; J Rheumatol 2012;39:2012–20; doi:10.3899/jrheum.120299

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)[1,2,3,4,5] includes granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis (WG)[6], microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and their localized variants, such as pauciimmune necrotizing glomerulonephritis (GN)[7]. Outcomes for these previously fatal diseases improved with the introduction of cyclophosphamide (CYC) therapy[8,9]. CYC, however, is associated with significant short- and longterm toxicities especially when large cumulative doses are used[10,11]. The challenge in the management of AAV, therefore, is to balance the risks of therapy with the risks of undertreating aggressive disease[12,13,14,15,16,17]. For the purpose of clinical trials, the European Vasculitis (EUVAS) Network[18] and the Vasculitis Clinical Research Consortium (VCRC)[19] subclassify or stage patients according to disease severity, and match increasing disease severity with more aggressive therapy[18,20].

Standardized treatment strategies and pediatric-specific severity subclassification systems have not been established for children with AAV. Children treated with CYC may have a greater malignancy risk as a result of their potentially longer remaining lifetime and, in some cases, because of the need for repeated treatment courses. We recently reported that 83% of 65 pediatric patients with GPA in a multicenter cohort were initially treated with cyclophosphamide[21]. It is not known whether the treatment decisions to use CYC versus other agents were based on either formally or informally assigning an estimate of disease severity. The most common "disease-modifying" treatment alternative to CYC in our series and other single-center case series was methotrexate (MTX)[21,22,23].

The primary aims of our study are to review current practices among US and Canadian centers contributing patients with AAV to A Registry for Childhood Vasculitis (ARChiVe) and to determine whether decisions to treat patients with CYC versus other treatments are concordant with assessment of disease severity as defined by either of the 2 established severity subclassification systems used for adult disease.

MATERIALS AND METHODS

ARChiVe was established in collaboration with members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) as a contemporary inception cohort, initially focusing on children with AAV. A list of collaborating centers and investigators in the ARChiVe network is shown in the Appendix. Since inception in March 2007, pediatric rheumatologists at 36 CARRA-associated institutions in the US (n = 32) and Canada (n = 4) have contributed patient data to the registry. For this study, eligible subjects were all children with GPA or MPA who were diagnosed before their eighteenth birthday and after January 1, 2004, and who were being followed at the participating institutions between March 2007 and June 2010. The diagnosis was established by the treating pediatric rheumatologist at each of the ARChiVe network sites and was entered in the database as the "MD diagnosis." Formal diagnostic criteria for GPA or MPA were not specified. Subjects were excluded if there were insufficient data in ARChiVe to determine severity subclassification or treatment group. 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 as applicable.

For subjects diagnosed between January 2004 and the launch of ARChiVe in March 2007, data were collected by review of available medical records. For subjects diagnosed between March 2007 and June 2010, data were collected prospectively. In all cases, data collected pertain to the period from clinical onset and presentation until 2 months after diagnosis. ARChiVe uses a Web-based interface for entry of the following data: MD diagnosis; date of symptom onset; demographic data; family and medical history; presenting/diagnostic features; physical examination findings; results of laboratory testing (including ANCA specificities); results of diagnostic imaging or other procedures such as biopsies, bronchoscopy, and pulmonary function tests; and initial therapy detailing the use of oral prednisone doses in mg/kg/day (i.e., low < 0.5, medium 0.5–1.5, and high > 1.5) and intravenous (IV) corticosteroids, CYC (oral or IV), other disease-modifying drugs, biologic therapies, other concurrently used medications (anticoagulants, antihypertensives), and other interventions such as the need for dialysis, plasmapheresis, or ventilatory assistance. Additional collected data items are described in a previous report[21].

Definitions. We modified definitions used in the EUVAS (Table 1A, 1B) and the VCRC WG Etanercept Trial (WGET; Table 2A, 2B)[18,19] disease severity subclassification systems to enable their application to children and to allow use of categorical data. The refractory subgroup in EUVAS and treatment-refractory subgroup in WGET were not used because we studied initial presentation, and refractoriness can only be determined later in the course of the disease. Because certain criteria of both EUVAS and WGET are not explicitly defined, they are inherently susceptible to differing interpretations. To use categorically collected data as criteria in this

Table 1A. The EUVAS clinical subgroupings of ANCA-associated vasculitis based on extent and severity of disease.

Subgroup	Organ Involvement	Constitutional Symptoms*	ANCA Status
Localized	Upper and/or lower respiratory tract	No	±
Early systemic	Any except renal or imminent vital organ failure†	Yes	Usually +
Generalized	Renal with serum creatinine level < 500 μmol/l and/or other imminent vital organ failure†	Yes	+
Severe renal	Renal with serum creatinine level > 500 μmol/l	Yes	+
Refractory	Progressive disease despite therapy with corticosteroids and cyclophosphamide	Yes	±

* Fever, night sweats, weight loss, malaise, and fatigue. † Includes progressive lung, eye, nervous system, or gastrointestinal vasculitis. EUVAS: European Vasculitis Study; ANCA: antineutrophil cytoplasmic antibody.

Table 1B. The Modified EUVAS clinical subgroupings of AAV based on extent and severity of disease.

Subgroup	Organ Involvement	Constitutional Symptoms*	ANCA Status
Localized	Upper and/or lower respiratory tract	No	±
Early systemic	Any except renal** or imminent vital organ failure†	Yes	Usually +
Generalized	Renal not requiring dialysis and/or other imminent vital organ failure†	Yes	+
Severe renal	Renal requiring dialysis	Yes	+

* Fever, night sweats, weight loss, malaise, and fatigue. ** Children with isolated proteinuria < 1 g/m^2/day were not excluded from the early systemic group. † Defined as alveolar hemorrhage, respiratory failure, mesenteric ischemia, scleritis, retinal hemorrhage, meningitis, stroke, cranial nerve palsy, sensory peripheral neuropathy, and mononeuritis multiplex. EUVAS: European Vasculitis Study; ANCA: antineutrophil cytoplasmic antibody.

context, it was necessary to interpret any inexplicit criterion *a priori* to enable their systematic application to this cohort of patients. The following interpretations and modifications to the criteria were made.

EUVAS modifications. "Imminent vital organ failure" is defined by EUVAS as "progressive lung, eye, nervous system or gastrointestinal vasculitis." In our study, "imminent vital organ failure" was defined operationally as the presence of any of the "major manifestations" of the modified Birmingham Vasculitis Activity Score for WG (BVAS/WG): alveolar hemorrhage, respiratory failure, mesenteric ischemia, scleritis, retinal hemorrhage, meningitis, stroke, cranial nerve palsy, sensory peripheral neuropathy, and mononeuritis multiplex[24,25]. Children who had isolated proteinuria < 1 g/m^2/day were not excluded from the early systemic group. Serum creatinine levels differentiating generalized (< 500 μmol/l) and severe renal (≥ 500 μmol/l) groups did not reflect reference standards for pediatric patients. We chose to categorize patients with serum creatinine levels above normal values for age as generalized, and patients requiring dialysis as severe renal.

WGET modifications. Although WGET classification (Table 2A) is proposed for application in WG, we decided to investigate its application across the broader diagnostic spectrum of pediatric AAV. Modifications and operational definitions of WGET terms in this study are listed in Table 2B. The WGET descriptor of O_2 saturation in room air of < 92% was thus defined as a requirement for supplemental oxygen. Any child with elevated serum creatinine above normal values for age was excluded from the limited disease group. The WGET definition of limited disease specifies that the patient has no red blood cell casts in the urine. We also excluded patients with hematuria from this group because we assumed a potential wide variation in laboratory ability to report casts across the 36 different centers. "Major" clinical manifestations as defined by BVAS/WG were deemed "organ threatening."

For descriptive purposes, treatment was categorized as (1) aggressive, if it included CYC; (2) moderate, if it included a disease-modifying agent other than CYC; and (3) limited, if it included corticosteroids with or without nonsteroidal antiinflammatory drugs (NSAID), hydroxychloroquine, and/or trimethoprim-sulfamethoxazole.

Analysis

Association between disease severity and treatment. For the purposes of comparing severity subclassifications against treatments, moderate and limited treatment categories (2 and 3) were combined into 1 group, referred to as "no cyclophosphamide." WGET disease severity subgroups were compared against the 2 treatment groups "cyclophosphamide" and "no cyclophosphamide." For EUVAS, the 4 severity subgroups were divided into 2 groups, (1) localized/early systemic and (2) generalized/severe renal, and compared against the 2 treatment groups. The rationale for dividing the subgroups was based on adult AAV recommendations to use CYC for generalized or organ-threatening disease, but to consider alternatives such as MTX for less severe disease (i.e., localized or early systemic disease)[26].

Coding of patients into disease severity subgroups and treatment groups was done by KM and checked by DC. Severity subgroups were compared using Pearson's chi-square and Kendall's tau-b rank correlation coefficient against the "cyclophosphamide" and "no cyclophosphamide" treatment categories using SPSS version 20 (SPSS, Chicago, IL, USA). Kendall's tau-b is a nonparametric measure of association based on the number of concordances in paired observations, beyond that expected by chance. Tau-b values of 0.3 to 0.5 were interpreted as fair, 0.6 to 0.8 as strong, and > 0.8 as very strong[27].

RESULTS

Patients. During the study period, 125 ARChiVe patients were described by MD diagnosis as having GPA (n = 100) or MPA (n = 25). All were eligible for inclusion. The median age at diagnosis was 14 years (range 4–17 yrs). Eighty-four (67.2%) of these patients were female.

Disease severity subclassification and treatment groups. Using the modified EUVAS criteria, 6 patients (4.8%) were classified as localized, 18 (14.4%) as early systemic, 82 (65.6%) as generalized, and 19 (15.2%) as severe renal. Using the modified WGET criteria, 27 (21.6%) were classified as limited and 98 (78.4%) as severe. In total, 7 patients

Table 2A. The Wegener's Granulomatosis Etanercept Trial (WGET): definitions.

Term	Definition
Limited disease	A patient who meets the modified American College of Rheumatology criteria for a diagnosis of Wegener's granulomatosis (WG) but who does not have disease that poses an immediate threat to either a critical individual organ or to the patient's life. Specifically, this means: 1. Patient has no red blood cell casts in the urine. 2. Serum creatinine must be ≤ 1.4 mg/dl and there must be no evidence of a rise in serum creatinine > 25% above the patient's baseline. 3. Pulmonary involvement must be circumscribed, such that the room air pO_2 is > 70 mm Hg or the room air O_2 saturation by pulse oximetry is > 92%. No disease may exist within any other critical organ (e.g., gastrointestinal tract, eyes, central nervous system) that, without the immediate institution of maximal therapy (i.e., pulse methylprednisolone and daily cyclophosphamide), threatens the function of that organ and/or the patient's life.
Severe disease	Any patient with WG whose disease is not classifiable as limited has, by definition, severe disease.
Treatment-refractory	A patient with a history of immunosuppressive therapy (glucocorticoids and/or a cytotoxic agent) prior to the initiation of treatment for the WG activity that made the patient eligible for WGET.

Table 2B. The modified Wegener's Granulomatosis Etanercept Trial: definitions.

Term	Definition
Limited disease	A patient who does not have disease that poses an immediate threat to either a critical individual organ or to the patient's life. Specifically, this means: 1. Patient has no red blood cells in the urine. 2. Serum creatinine is normal. 3. Pulmonary involvement must be circumscribed, such that supplemental oxygen therapy is not required. No disease may exist within any other critical organ (e.g., gastrointestinal tract, eyes, central nervous system) that, without the immediate institution of maximal therapy (i.e., pulse methylprednisolone and daily cyclophosphamide), threatens the function of that organ and/or the patient's life.
Severe disease	Any patient with WG whose disease is not classifiable as limited has, by definition, severe disease.

(5.6%) received limited treatment, 19 moderate treatment (15.2%), and 99 (79.2%) aggressive treatment. Three patients received rituximab and 19 received plasma exchange therapy. All patients who received either rituximab or plasma exchange therapy also received CYC and therefore were classified as having received aggressive treatment. The distribution of patients in each severity subgroup receiving each treatment is shown in Figure 1 for modified EUVAS and in Figure 2 for modified WGET. Dividing the 4 EUVAS subgroups resulted in 24 patients (19.2%) in the localized/early systemic subgroup and 101 patients (80.8%) in the generalized/severe renal subgroup.

Association between disease severity and treatment. Overall, 99 children (79.2%) received CYC as part of their initial treatment and 26 children (20.8%) did not. Severity subgroup was associated with use of CYC in both the EUVAS (chi-square 45.14, $p < 0.001$, Kendall's tau-b 0.601, 95% CI 0.423–0.764, $p < 0.001$) and WGET (chi-square 59.33, $p < 0.001$, Kendall's tau-b 0.689, 95% CI 0.515–0.837, $p < 0.001$) systems. When the WGET criteria were applied only to patients with GPA (n = 100), the association between disease severity and treatment was similar as compared to when the criteria were applied to all patients (chi-square 49.75, $p < 0.001$, Kendall's tau-b 0.705, 95% CI 0.510–0.861, $p < 0.001$).

Despite these strong associations, 7 patients classified in the EUVAS localized/early systemic group (29%) and in the WGET limited disease group (26%) received CYC (the same 7 patients in both classifications). The disease manifestations of these patients are shown in Table 3. All 7 had ear, nose, and throat (ENT) involvement, including chronic sinusitis (n = 6), nasal disease (n = 5), subglottic stenosis (n = 4), and chronic otitis media and/or mastoiditis (n = 1). Other features of the 7 patients included constitutional

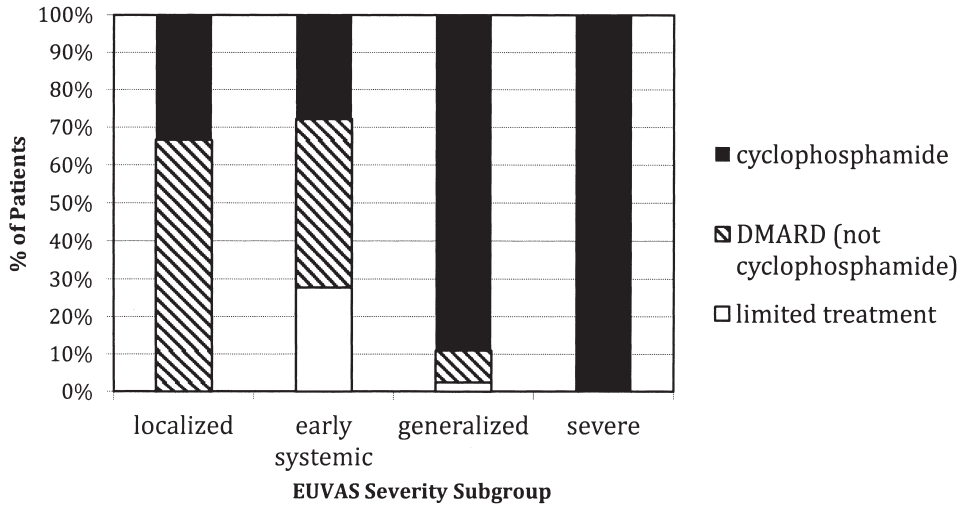

Figure 1. Treatment categories of children with antineutrophil cytoplasmic antibody-associated vasculitis according to European Vasculitis Study (EUVAS) severity subgroup. DMARD: disease-modifying antirheumatic drug.

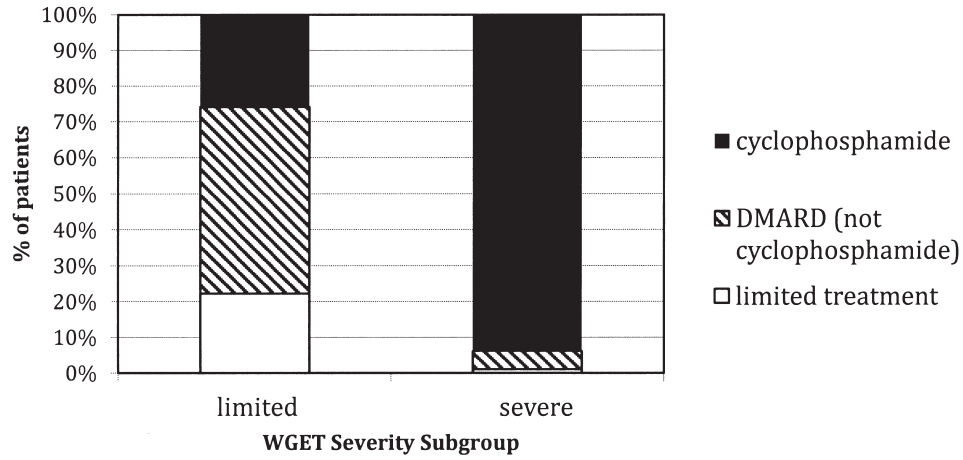

Figure 2. Treatment categories of children with antineutrophil cytoplasmic antibody-associated vasculitis according to Wegener's Granulomatosis Etanercept Trial (WGET) severity subgroup. DMARD: disease-modifying antirheumatic drug.

symptoms (n = 5), respiratory symptoms including cough and/or shortness of breath without signs of pulmonary hemorrhage (n = 4), rash (n = 3), isolated proteinuria < 1 g/m^2/day, and arthritis (n = 2).

Some patients classified as having generalized or severe disease did not receive CYC. Using the modified EUVAS criteria, 9 of 101 patients (8.9%) with generalized/severe renal disease did not receive CYC (Table 4). Treatments received by these patients included corticosteroids in 8, MTX in 6, trimethoprim-sulfamethoxazole in 4, and azathioprine in 1. The disease features that excluded these patients from being classified as having localized/early systemic disease included hematuria in 5 and hemoptysis/alveolar hemorrhage in 5, including 1 with respiratory failure. Other features included constitutional symptoms in 7 patients, upper airway disease in 5, arthritis in 3, seizures in 1, and rash in 1. Using the modified WGET criteria, 6 out of 98 patients (6.1%) classified as having severe disease did not receive CYC. These 6 patients were all included among the 9 patients described above. No consistent pattern was seen in erythrocyte sedimentation rates or ANCA pattern to suggest an explanation for the use or non-use of CYC in the patients listed in Tables 3 and 4.

DISCUSSION

Because of its extreme rarity, there have been no large pediatric outcomes studies, no pediatric-specific severity subclassification systems, and no standardized treatment strate-

Table 3. Disease manifestations in children with ANCA-associated vasculitis classified as having less severe disease who received cyclophosphamide.

Age, yrs	Sex	Diagnosis	Disease Manifestations	Concomitant Treatment
17	F	GPA	Subglottic stenosis, proteinuria*	CS, TMP-SMX
14	M	GPA	Subglottic stenosis, sinusitis, nasal disease, otitis media, cough	CS
14	M	GPA	Malaise, weight loss, sinusitis, nasal disease	CS
16	F	GPA	Malaise, weight loss, fever, subglottic stenosis, sinusitis, nasal disease, purpura, dacrocystitis, shortness of breath, proteinuria, arthralgias	CS
16	F	GPA	Malaise, weight loss, sinusitis, nodular rash, oral ulcers, arthritis	CS
9	F	GPA	Malaise, fever, subglottic stenosis, sinusitis, nasal disease, shortness of breath, cough, proteinuria	CS
7	F	GPA	Malaise, weight loss, fever, sinusitis, nasal disease, purpura, nodular rash, cough nonspecific abdominal pain, arthritis	CS

* Proteinuria in all cases was < 1 g/m^2/day. CS: corticosteroids; TMP-SMX: trimethoprim-sulfamethoxazole; ANCA: antineutrophil cytoplasmic antibody; GPA: granulomatosis with polyangiitis.

Table 4. Disease manifestations in children with ANCA-associated vasculitis classified as having severe disease by the modified EUVAS severity subclassification system who did not receive cyclophosphamide.

Age, yrs	Sex	Diagnosis	Disease Manifestations	Concomitant Treatment
12	F	GPA	Sinusitis, conductive hearing loss, hematuria, proteinuria, arthralgias	CS, TMP-SMX, MTX
15	F	GPA	Purpura, livedo reticularis, hematuria, proteinuria, arthritis	CS, MTX
16	F	GPA	Malaise, subglottic stenosis, cough, wheeze, hematuria, proteinuria	CS
10*	M	GPA	Malaise, sinusitis, conductive hearing loss, oral ulcers, hemoptysis/alveolar hemorrhage, cough, shortness of breath, seizures, hepatomegaly, arthralgias	TMP-SMX, MTX
17*	M	MPA	Malaise, elevated creatinine†, hematuria, proteinuria, hypertension, nonspecific abdominal pain	CS, AZA
14*	M	GPA	Malaise, weight loss, fever, hemoptysis/alveolar hemorrhage, cough, shortness of breath, pleurisy	CS, MTX
16*	F	GPA	Malaise, weight loss, sinusitis, nasal ulcers, hemoptysis/alveolar hemorrhage, cough, pleurisy, hematuria, proteinuria, nonspecific abdominal pain, arthralgia	CS, TMP-SMX, MTX
18*	F	MPA	Malaise, hemoptysis/alveolar hemorrhage, respiratory failure, shortness of breath, cough, arthritis	CS
16*	F	GPA	Malaise, weight loss, fever, subglottic stenosis, sinusitis, nasal disease, otitis media, hemoptysis/alveolar hemorrhage, cough, shortness of breath, arthritis	CS, TMP-SMX, MTX

† Serum creatinine > 30% above the upper limit of normal for age. * Subjects that were also classified as severe by the modified WGET severity subclassification system. CS: corticosteroids; TMP-SMX: trimethoprim-sulfamethoxazole; MTX: methotrexate; MAP: microscopic polyangiits; GPA: granulomatosis with polyangiitis; AZA: azathioprine.

gies for childhood AAV. It is not known whether treatment strategies based on outcome studies of adult patients or adult-derived disease severity subclassification systems are applicable to children. The establishment of ARChiVe has enabled a network of investigators across North America to collaborate and identify the large cohort of children with AAV studied here. Our study demonstrates that for pediatric patients with AAV there is a substantial concordance between treatment intensity and disease severity as defined by either the modified EUVAS or the WGET criteria. Despite this strong association, there were some patients with less severe disease subtypes who received CYC as part of their initial treatment, and some with severe disease subtypes who received no CYC.

Children with less severe subtypes who received CYC had primarily ENT involvement, constitutional symptoms, and respiratory symptoms that were specifically not associated with pulmonary hemorrhage. In adult trials of AAV, isolated ENT manifestations are typically treated without CYC[13,14,16,17]. A recent study of GPA in children reported a high frequency of upper airway involvement (86% of patients) and similarly suggested that airway progression often occurs despite the use of systemic immunosuppressive therapy[28]. There are a number of possible explanations for the discrepancy between severity subclassification and treatment intensity. First, there is no pediatric-specific evidence supporting the use of less aggressive therapy in patients with milder disease. Several of the large adult AAV studies evaluating less aggressive treatment approaches have only been published within the last decade and therefore the observed discrepancy may reflect the usual cautious delay in adapting newer adult practices to pediatrics. Moreover, physicians in isolated practices who see very few patients may have less opportunity or need to stay current with the adult literature. Second, physicians might believe that children with AAV require more aggressive initial treatment than adults with AAV, because the longterm toxicities associated with chronic inflammation or corticosteroid use are potentially worse for a growing child than an adult. Children with other diseases such as systemic lupus erythematosus (SLE), for

example, have been shown to have more active disease both at onset and over the disease course compared to adult patients with SLE[29,30]. In addition, pediatric-onset SLE has been associated with lower rates of remission and worse outcomes[30,31,32]. Finally, in the absence of any clinical trials or expert consensus guidelines for treating AAV in children, treatment choices reflect physician preference and these may be based on factors other than disease severity.

We also observed a small proportion of children classified as having severe disease who received less aggressive treatment. Patients included in this group had either evidence of pulmonary hemorrhage and/or evidence of renal disease based on abnormal laboratory findings (hematuria, renal casts, abnormal serum creatinine, and/or proteinuria). Both the EUVAS and WGET systems use arguably subjective criteria such as "imminent vital organ failure" or "disease that poses an immediate threat to either a critical individual organ or to the patient's life" to allow placement of patients in the severe disease subgroupings. We were unable to evaluate individual physicians' judgments about imminent organ failure, or threat to the patient's life. We used instead the presence of major items in BVAS/WG to place patients in the severe categories. Thus it is possible that some of the patients we categorized as severe were deemed by their physicians not to have "imminent organ failure" and were treated less aggressively. Reliance on a physician's subjective assessment might be considered a weakness of the existing classification schemes, whether they be used in children or adults. As noted above, we treated hematuria with the same weighting as red blood cell casts, and this may have resulted in some patients being misclassified as having severe disease. We acknowledge the limitations of having to make certain assumptions to enable use of registry data.

The results of our study should be interpreted with the following caveats. First, for the patients diagnosed between January 2004 and March 2007, the data in ARChiVe were collected retrospectively. Retrospective data may be subject to recall bias or may be incomplete. Data collection, however, was done using a standardized Web-based data entry system that was regularly reviewed centrally for data consistency and to minimize incomplete information. Given the size of the study and constraints of a Web-based dataset, our discussion of patients whose treatment did not correlate with severity subclass was limited to description. As previously discussed, the categorical data submitted for each patient may not reflect the overall clinical impression of the patient as judged by the treating physician. In addition, it may be difficult to determine from registry data when clinical findings represent disease activity or damage. In the future, prospectively collected data and variables defined *a priori* would allow more comprehensive analysis to determine predictors of CYC use or non-use.

Second, not every patient with AAV is necessarily entered into the registry and those that are entered may be selected for in some way. The large number of centers participating in this network, however, makes it less likely that there is a systematic selection of more severe patients at 36 sites, as compared to a single large referral center's cohort. Further, in an earlier ARChiVe study of 65 patients with WG, the patient demographics, clinical features, and treatment modalities for the cohort were similar to those reported in other studies[21].

Third, because of the structure of the dataset, we were not able to determine the relative influence of patient/parent preference on the chosen medical treatments. For example, those patients with severe disease who did not receive CYC initially may have had parents who refused such treatment.

Finally, ARChiVe currently collects only time-of-diagnosis data and does not include followup data. Severity subclassification systems are intended for use at the time of diagnosis or flare to prognosticate and guide therapy. Determining the applicability of adult severity classification schemes for the assessment of flares in childhood AAV will require followup data. Future longitudinal data collection for ARChiVe is planned.

In this cohort of 125 children with AAV, we found that applying modified adult severity subclassification systems, from EUVAS and WGET, resulted in substantial concordance between severity subgroups and physician choice of treatment; however, a proportion of patients received treatment that was not concordant with the severity subclass to which they were assigned. There is a potential role for use of these criteria in pediatric AAV, albeit with some modifications, that will ideally be based on data from longitudinal studies.

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APPENDIX

Collaborators in A Registry for Children with Vasculitis e-entry (ARChiVe) Network:

Coordinating Center: British Columbia Children's Hospital, Vancouver, BC: David A. Cabral (Study Principal Investigator), Angelyne Sarmiento (Study Coordinator), Victor Espinosa (IT Manager, Statistician); Jaime Guzman, Kristin Houghton, Kimberly Morishita, Ross Petty, Lori Tucker, Stuart Turvey (Site Investigators).

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Children's Hospital of Pittsburgh, Pittsburgh, PA: Margalit Rosenkranz (Site Principal Investigator), Raphael Hirsh, Daniel Kietz, Paul Rosen, and Kathryn Torok (Site Investigators). Children's Memorial Hospital, Chicago, IL: Marisa Klein-Gitelman (Site Principal Investigator), Lauren Pachman (Site Investigator). Cincinnati Children's Hospital Medical Center, Cincinnati, OH: Daniel J. Lovell (Site Principal Investigator), Hermine Brunner, Thomas Griffin, and Alexi Grom (Site Investigators). Cleveland Clinic Foundation, Cleveland, OH: Steven Spalding (Site Principal Investigator), Andrew Zeft (Site Investigator), Phil Hashkes (formerly Site Investigator). Columbia University Medical Center, New York, NY: Lisa F. Imundo (Site Principal Investigator), Andrew Eichenfield (Site Investigator). Creighton Medical Center at University of Omaha, Omaha, NE: Lawrence Jung (Site Principal Investigator). 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University of Louisville School of Medicine, Louisville, KY: Kenneth N. Schikler (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 Utah Primary Children's Medical Center, Salt Lake City, UT: Aimee Hersh (Site Principal Investigator), John Bonsack (Site Investigator). University of Vermont, Burlington, VT: Leslie Abramson (Site Principal Investigator).

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