

Clinical course and outcomes of childhood-onset granulomatosis with polyangiitis

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ABSTRACT

Objective. To characterise the clinical course and outcomes of a cohort of children with granulomatosis with polyangiitis (GPA).

Methods. Retrospective cohort study of children diagnosed with GPA in a tertiary care facility from 2000-2014. All subjects met the American College of Rheumatology 1990 criteria for GPA or the 2008 European League against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society criteria for GPA. Predictors of readmission were determined using univariate logistic regression. Kaplan-Meier analysis was used to demonstrate the relapse-free survival probability in follow-up.

Results. Twenty-eight children (median age 14.7 years) were diagnosed during the study period. At presentation 14 (50%), 5 (18%), and 4 (14%) children required intensive care unit care, ventilator support, and dialysis, respectively. One-third of the children in our cohort had gastrointestinal involvement, one-quarter of whom were previously diagnosed with inflammatory bowel disease. Two-thirds of children were readmitted. Renal failure and infections accounted for most readmissions. Twenty-three (85%) patients achieved remission, however, 11 subsequently flared (median time to flare 21.5 months). Haematuria at diagnosis was significantly associated with readmission (OR 6.25). At a median follow-up of 3.3 years (range 5 months to 6 years) 10 (37%) children had chronic kidney disease (> stage 2) and none of the children died.

Conclusion. Children with GPA frequently have severe disease presentations including significant renal, respiratory and gastrointestinal involvement. While most children with GPA achieve remission, nearly half have subsequent relapses.

Introduction

Granulomatosis with polyangiitis (GPA) is the most common anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) of childhood and up to 3.3% of cases of GPA have an onset prior to age 20 years (1, 2). GPA is a potentially life-threatening condition, and while treatments have greatly improved survival, they also have substantial side effects including infection, infertility, and malignancy (3). Despite the severity of disease, however, there is a paucity of paediatric-focused studies, particularly regarding outcomes related to both the disease and its treatments. Most of the data on paediatric GPA is based on small, single-centre case series. These studies have shown several key differences in paediatric versus adult-onset disease including a female predominance and higher prevalence of renal and pulmonary involvement at presentation (4-8). Some studies suggest more frequent subglottic stenosis in children over the course of their disease, however this finding has not been consistent (4, 5, 9, 10).

Paediatric providers make treatment decisions based largely on data from adult patients, without knowing if the prognosis or response to treatment is different in children. This study aimed to characterise the presenting symptoms, treatments, and disease course of a cohort of children with GPA treated at a tertiary care facility.

Materials and methods

The protocol for the conduct of this study was approved by The Children's Hospital of Philadelphia (CHOP) Committee for the Protection of Human Subjects.

We performed a retrospective chart review of all patients, ages 2-18 years, evaluated in our tertiary care paediatric rheumatology practice between the

years of 2000-2014 who were given the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 446.4 (GPA) and met criteria for GPA. Primary long-term management of AAV was by rheumatology (n=20), or nephrology (n=7). Only patients with a new diagnosis were included for analysis. All subjects met at least one of the following criteria for GPA during their disease course: the American College of Rheumatology 1990 Classification Criteria or the 2008 European League against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society Criteria for Wegener Granulomatosis (11, 12). Patients with a pre-existing non-autoimmune condition (sickle cell disease, congenital cyanotic heart disease, and congenital renal disease) that can cause clinical manifestations similar to GPA were excluded.

Patient demographics and clinical course were abstracted from the medical record (paper or electronic). Study data were recorded in REDCap electronic data capture tools hosted at the Children's Hospital of Philadelphia (13).

Clinical factors

For this study, the initial diagnostic period was defined as the first 6 weeks from presentation. The presentation was defined as the start date of the visit at which AAV was first considered, and confirmatory testing and/or disease specific treatments were initiated. Haematuria was defined as greater than 10 red blood cells per high-power field (14). Proteinuria was defined as greater than 1+ or 100 mg/dL of protein by dipstick testing (14, 15). Abnormal renal function was defined as a rise in creatinine >30% from baseline, or an estimated glomerular filtration rate (GFR) of <90 ml/minute/1.73 meter², not attributable to other causes including drug toxicity or dehydration (14, 15). All GFR's were calculated using the revised Schwartz formula (16).

Outcomes

Remission was defined as at least one month with no evidence of active vasculitis using patient-reported symptoms,

clinical exam or laboratory studies (normal c-reactive protein, and no casts on urinalysis), and treatment with less than 10 mg of prednisone daily in children >40 kg or <0.25 mg/kg in children <40 kg. There is a lack of consensus on the definition of remission for GPA, with some studies defining remission as the absence of active disease for varying periods of time, regardless of treatment, while others require cessation of glucocorticoids (17). Since many children were maintained on low-dose glucocorticoids for extended periods as part of their maintenance regimen, we chose our primary outcome of remission to include low-dose glucocorticoids. Ten milligrams of prednisone or less was considered low-dose (or equivalent dose of other glucocorticoids), in alignment with the dose chosen for the secondary outcome of remission on low-dose prednisone in the RAVE trial. (18) As a secondary outcome, we looked at glucocorticoid-free remission, defined as at least one month with no evidence of active vasculitis using patient-reported symptoms, clinical exam or laboratory studies (normal c-reactive protein, and no casts on urinalysis) on no glucocorticoids. Date of remission was defined as the first visit at which a child met the definition of remission. Disease relapse was defined as new or worsening clinical features of vasculitis requiring an escalation of therapy after being on previously stable doses of medications, after achieving remission. Relapse date was approximated using patient-reported duration of symptoms at the first visit after symptom onset. In cases where no clear date was provided, the date of the relapse was computed as the halfway point between the visit at which the relapse was documented and the previous visit. The highest chronic kidney disease stage during follow-up was noted, using the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease in children and adolescents (19).

Analysis

Demographics and clinical variables were summarised using count and percentage or median and interquartile

range, as appropriate. A Kaplan-Meier curve was used to demonstrate the relapse-free survival probability after achieving remission over the period of follow-up. Univariate logistic regression was used to test for the association of clinical variables at presentation (haematuria, proteinuria, positive cytoplasmic ANCA test (cANCA), positive perinuclear ANCA test (pANCA), hospitalisation at presentation, dialysis at presentation, and mechanical ventilation at presentation) with readmission after the diagnostic period, and with relapse after remission. Statistical significance was $p < 0.05$. All data analysis was performed using Stata 13.1 (Stata Corp, College Station, TX).

Results

Subjects

Forty-five patients with the ICD-9-CM diagnosis code of 446.4 were evaluated during the study period. Seventeen subjects were excluded for the following reasons: 1) concomitant diagnosis of sickle cell disease (n=1), 2) pre-existing diagnosis at first visit (n=6), 3) failure to fulfill classification criteria for GPA (n=3), 4) Evaluated with concern for AAV, but given other diagnosis (n=7). Twenty-eight patients were included in subsequent analyses. The median age at presentation was 14.7 years (IQR: 12.5, 16.3) and 61% were female. Twenty-one (75%), 1 (4%), and 6 (21%) were Caucasian, Black, or Asian, respectively. The median duration of symptoms prior to presentation was 1.5 months (IQR 0.8, 6.4). Long-term follow-up was available on 27 (96%) patients. Median duration of follow-up was 3.2 years (IQR 1.8, 4.3 years, range 2 months to 10.6 years). The median age at last follow-up was 18.4 years (IQR 15.8, 19.6).

Presentation

Twenty-five (89%) patients required hospitalisation at presentation, 14 (56%) of whom required intensive care unit level care. Nine (36%) were sent to the intensive care unit for respiratory failure or impending respiratory failure, 2 for haemodynamic instability (one after a gastrointestinal bleed), 1 for hyperkalaemia requiring urgent dialysis, 1 for a severe drug reaction,

and 1 for monitoring following a lung biopsy. Five (18%) required mechanical ventilatory support, and 4 required dialysis during the initial diagnostic period. Of the 25 hospitalised patients, the median duration of hospitalisation was 16 days (IQR 7, 27).

Disease features at presentation are shown in Table I. Eight patients (29%) had limited disease without renal involvement. There were no patients with subglottic stenosis or uveitis at diagnosis. Twenty-three patients (82%) had pulmonary symptoms at presentation, all of whom had had abnormalities on chest imaging. Two children were followed for 39 and 90 months for presumed idiopathic pulmonary haemorrhage with recurrent pulmonary haemorrhage and haemoptysis before the diagnosis of AAV was established. Twenty patients (71%) had renal involvement, manifested most commonly as haematuria. Six (21%) children had a GFR of less than 25 ml/minute/1.73 meter². Five of these children had renal biopsies. The four patients requiring dialysis had biopsies with partial to global sclerosis in the majority of glomeruli. The fifth patient, who had recovery of renal function, had diffuse, pauci-immune, necrotising, crescentic glomerulonephritis, without sclerosis.

Eight children (28%) had gastrointestinal involvement at presentation, 75% of whom had haematochezia (Table II). Three children developed haematochezia within a few days of GPA presentation. Three children had gastrointestinal symptoms, including abdominal pain, diarrhoea, and haematochezia as their primary symptoms 5 months to 6 years before developing definitive symptoms of GPA. Two patients carried a prior diagnosis of inflammatory bowel disease (indeterminate type and Crohn disease) for 7 and 74 months respectively prior to diagnosis.

Induction therapy

All patients received glucocorticoids. Six (21%) patients received rituximab and 20 (71%) patients received cyclophosphamide. Of those who received rituximab, 5 (18%) received rituximab plus cyclophosphamide, and 1 (4%) received rituximab plus methotrexate.

All patients, except 1, who received cyclophosphamide or rituximab received pulse methylprednisolone (30 mg/kg with a maximum of 1 gram, daily), for 3-5 days. Rituximab was not used prior to 2006 at our institution. Indications for the 20 patients receiving cyclophosphamide were as follows: 1) alveolar haemorrhage without renal failure (n=8), 2) alveolar haemorrhage with dialysis-dependent renal failure (n=3), 3) renal failure with eGFR <50 mg/dl without alveolar haemorrhage with dialysis (n=1), 4) renal failure with eGFR <50 mg/dl without alveolar haemorrhage or dialysis (n=4), 5) cavitory pulmonary lesions (n=3), and 6) stroke (n=1). Other non-glucocorticoid immunosuppressive medications used for induction therapy included the following: methotrexate (n=6) and infliximab (n=1). The patient who received infliximab carried a previous diagnosis of inflammatory bowel disease. Infliximab was started shortly before her GPA diagnosis, prior to the results of increased malignancy in the Wegener's Granulomatosis Etanercept Trial, and continued due to clinical response. (20) Ten patients (36%) received plasma exchange in combination with cyclophosphamide with or without rituximab for a median of 7.5 cycles (IQR 6, 9) for alveolar hemorrhage (n=8) and/or elevated creatinine with concern for progressive renal involvement (n=6). Twenty-two patients (79%) received trimethoprim-sulfamethoxazole, 13 (46%) of which were used as part of the glucocorticoid-sparing regimen (not for prophylaxis against *Pneumocystis jirovecii* [carinii] pneumonia).

Outcomes

Outcomes of patients at last follow-up are shown in Table III. None of the 4 patients receiving dialysis at presentation recovered renal function; 3 children underwent renal transplantation and one child continued to receive dialysis until the last recorded visit 5 months after diagnosis. None of the remaining patients required initiation of renal replacement therapy after the initial diagnostic period. Of the 6 patients who received plasma exchange for acute kidney injury, 3 had partial to full recovery of renal

Table I. Disease features present at diagnosis^a for 28 children with granulomatosis with polyangiitis.

Disease features	AAV n (%)
ANCA-positivity	27 (96)
cANCA ^b	15 (54)
pANCA ^c	10 (36)
aANCA ^d	2 (7)
anti-PR3 ^e	13 (52)
anti-MPO ^f	6 (23)
Systemic symptoms	22 (79)
Fever	17 (61)
Fatigue/malaise	21 (75)
Weight loss	7 (25)
Otorhinolaryngeal	26 (93)
Sinus disease	19 (68)
Nasal inflammation ^g	19 (68)
Saddle nose	1 (4)
Mastoiditis	5 (18)
Hearing loss	2 (7)
Joint symptoms	17 (61)
Arthralgias	17 (61)
Arthritis	6 (21)
Pulmonary disease	23 (82)
Cough	16 (57)
Haemoptysis	12 (43)
Infiltrate or nodules on imaging	23 (82)
Pleuritis	7 (25)
Respiratory failure ^h	4 (14)
Renal disease	20 (71)
Haematuria ⁱ	19 (68)
Proteinuria ^j	16 (57)
Abnormal renal function ^k	14 (50)
Eye disease	6 (21)
Proptosis	1 (4)
Keratitis	2 (7)
Conjunctivitis	5 (18)
Episcleritis	2 (7)
GI involvement	8 (29)
Diarrhoea	7 (25)
Bloody stool	6 (21)
Skin	11 (33)
Purpura/petechiae	5 (18)
Oral ulcers	9 (32)
Genital ulcers	1 (4)
Neurologic	1 (4)
CNS infarct	1 (4)
Other	
Venous thrombosis	3 (11)
Multiple splenic infarcts	1 (4)
Non-infectious aortic vegetation	1 (4)

^aIncludes symptoms leading up to and 6 weeks after diagnosis; ^bcytoplasmic anti-neutrophil antibody; ^cperinuclear anti-neutrophil antibody; ^datypical anti-neutrophil antibody; ^eresults only available for 25 patients; ^fresults only available for 26 patients; ^gnasal inflammation defined as discharge, crusting, epistaxis or ulceration; ^hrespiratory failure defined by need for mechanical ventilation; ⁱhaematuria defined as >10 RBC per HPF; ^jProteinuria defined as >1+ or 100 mg/dL of protein; ^kAbnormal renal function defined as rise in creatinine >30% from baseline, or GFR according to modified Schwartz formula.

Table II. Gastrointestinal involvement at presentation.

Age (years) /sex	GI diagnosis	GI symptoms at presentation	ANCA IF/ELISA	Imaging/Endoscopy	Biopsy
16.9/ M	None	Weight loss, haematochezia, severe acute lower GI bleed	cANCA/ PR3+	None	None
16.8/ F	Crohn's disease	Abdominal pain, diarrhoea, intermittent haematochezia	pANCA/ PR3+	Capsule endoscopy: ileal ulcerations and erythema, normal appearing colon	No inflammation of colon (while on infliximab)
14.8/ F	None	Weight loss, diarrhoea, haematochezia	pANCA/ PR3+	UGI/SBFT: gastroesophageal reflux, otherwise normal	None
7.6/ M	None	Non-bloody diarrhoea	pANCA/ MPO+	None	None
10.8/ M	IBD (unspecified), Primary sclerosing cholangitis	Abdominal pain, diarrhoea, haematochezia	cANCA/ NA	CT abdomen & pelvis: thickening of ascending colon with pericolonic adenopathy	None at diagnosis, 4 months prior showed mild active colitis with mild chronic change
16.7/ F	None	Abdominal pain, grossly bloody stool	cANCA/ NA	Colonoscopy: multiple deep rectal ulcers	Fragments of normal colon and active ulcer bed without evidence of chronicity
18.3/ M	None	Abdominal pain, grossly bloody stool	pANCA/ negative	Colonoscopy: patchy erythema. Tagged white blood cell scan: increased colonic uptake	None
13.3/ F	None	Non-bloody diarrhoea	cANCA/ negative	None	None

GI: gastrointestinal; ANCA: anti-neutrophil cytoplasmic antibody; ELISA: enzyme-linked immunosorbent assay; M: male; F: female; IBD: inflammatory bowel disease; UGI/SBFT: upper GI with small bowel follow-through; NA: not available.

Table III. Outcomes at last evaluation for children with granulomatosis with polyangiitis*.

	n (%)
Median duration of follow-up (IQR)	3.3 (2.9,6.4)
Chronic kidney disease (stage 2 or higher) [^]	9 (33)
Renal transplant	3 (11)
Chronic hypertension	10 (37)
Nasal bridge collapse	1 (4)
Permanent hearing loss	1 (4)
Subglottic stenosis	1 (4)
Avascular necrosis	3 (11)

*Follow-up information available for 27/28 patients. [^]based on highest stage during follow-up.

function and did not require dialysis. One patient had persistent hearing loss, present since diagnosis. There were no new cases of nasal bridge collapse. One patient developed subglottic stenosis. Twenty-three children (85%) achieved remission on low-dose glucocorticoids in combination with glucocorticoid sparing agents and 16 children (59%) achieved glucocorticoid-free remission at least once. Median time to reach remission on low-dose glucocorticoids was 7.6 months (IQR 4.2, 15.2), and

to glucocorticoid-free remission was 14.4 months (IQR 9.9, 24). Three of the 4 patients who did not achieve remission on low-dose glucocorticoids had less than 5 months of follow-up. Initial glucocorticoid sparing maintenance regimens for the 23 patients achieving remission were as follows: Methotrexate (n=12, 51.8%) Azathioprine (n=7, 25.9%), mycophenolate mofetil (n=3, 11.1%), and trimethoprim-sulfamethoxazole alone (n=2, 7.4%).

Of the 23 patients who reached remission on low-dose glucocorticoids, 11 (48%) had one or more disease relapses with a median relapse-free survival of 21.5 months after achieving remission on low-dose glucocorticoids. The time to first relapse following remission on low-dose glucocorticoids is shown in Figure 1. Seven (33%) disease relapses required hospitalisation. The median number of relapses per child was 2 (IQR 1, 3). None of the factors measured at presentation were significantly associated with having a relapse.

Eighteen (67%) children required hospitalisation, all cause, after the initial diagnostic period, with 13 (48%) having more than 1 readmission. The

median time to readmission was 4.7 months (IQR: 3.2, 18.4) and the median number of readmissions was 2 (IQR: 2, 5). Overall, there were 69 readmissions for 18 children. The most common reasons for readmission were infections (n=22, 32%) and active vasculitis, (n=17, 25%). Among the 34 hospitalisations for patients who did not require dialysis, the most common causes for readmission were active vasculitis (n=17, 50%), and infection (n=10, 29%). Other causes for readmission included need for medication infusion (n=4, 11%), gastritis (n=1, 3%), chest pain (n=1, 3%), and severe headache after rituximab infusion (n=1, 3%). The 4 patients on dialysis were all readmitted and accounted for more than half of the total readmissions, (n=35/69, 51%). Fourteen (40%) admissions for those children receiving dialysis were related to transplant rejection or renal failure, 12 (34%) were for infections, 4 (11%) were for renal transplantation, 3 (9%) were for hypertensive urgency, 1 (3%) for evaluation of abdominal pain, and 1 (3%) for a dialysis catheter malfunction. The patients requiring dialysis had no readmissions for active vasculitis.

Table IV shows the results of the univariate analysis for readmission. In univariate analysis, haematuria at diagnosis was the only factor significantly associated with readmission (OR: 6.3; 95% CI: 1.0, 38.1). There was a trend towards increased odds of readmission with proteinuria (OR: 5.2; 95% CI: 0.9, 29.3, $p=0.06$) and decreased odds with a positive test for cytoplasmic ANCA by immunofluorescence (OR: 0.2; 95% CI 0.0, 1.1, $p=0.07$).

Discussion

This cohort study demonstrates that children with GPA have a significant burden of disease, both at presentation and throughout the disease course. Ninety percent of children required hospitalisation at the time of diagnosis with half requiring intensive care unit level care, and 18% requiring the support of a ventilator. Renal, pulmonary, otorhinolaryngeal, and systemic manifestations were common at presentation and had a similar prevalence to prior reports, as was the lower prevalence of c-ANCA positivity compared to adult populations (4-8, 10). Gastrointestinal manifestations were common in this cohort and frequently preceded the diagnosis of GPA. The effects of early-onset morbidities including end-stage renal disease, hearing loss, and saddle nose deformity were sustained throughout the follow-up period. Most children were able to achieve remission at least once, however relapses were common and primarily managed in the outpatient setting. Complications of renal failure and infections accounted for most readmissions. Haematuria at diagnosis was associated with increased odds for readmission, with a trend towards increased odds with proteinuria, suggesting patients with renal involvement are more likely to be readmitted. There was a non-significant trend towards decreased odds for readmission in patients who were cANCA positive.

Several results from this study warrant further discussion. First, gastrointestinal manifestations of GPA may be under-recognised in children with GPA. Previous studies in children report frequencies of gastrointestinal manifestations from 12-42% (4, 6-10).

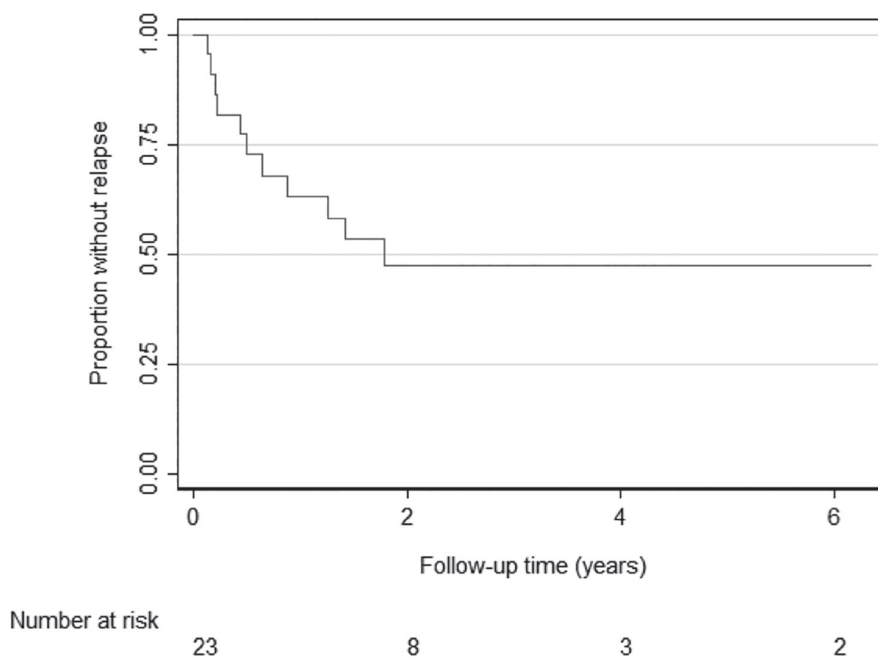


Fig. 1. Relapse-free survival in children with granulomatosis with polyangiitis. Kaplan-Meier relapse-free survival after first remission is shown for the 23 children who achieved remission during follow-up. Relapse was defined as new or worsening clinical features of vasculitis requiring an escalation of therapy after being on stable doses of medications.

Table IV. Factors at presentation associated with readmission.

Covariate	Odds ratio	95% confidence Interval	p -value
Haematuria	6.25	1.03, 38.08	0.05
Proteinuria	5.2	0.92, 29.26	0.06
+ cytoplasmic ANCA	0.18	0.03, 1.14	0.069
+ perinuclear ANCA	2.8	0.45, 17.38	0.27
Hospitalised	4.86	0.38, 62.63	0.23
Dialysis	-	-	-
Mechanical Ventilation	2.29	0.22, 24.14	0.49

Results of univariate regression are shown. Odds ratios and confidence intervals were not available for dialysis due to complete collinearity between dialysis and readmission.

The definitions used for gastrointestinal involvement in these studies varied widely and manifestations were mostly described as abdominal pain or nausea (4, 6-10). In this study, we report that nearly one-third of children had gastrointestinal symptoms at presentation, and the majority of the children with gastrointestinal manifestations had haematochezia. While there are case reports of such symptoms in children with GPA, the frequency of these specific symptoms is unknown. The severity of gastrointestinal involvement may reflect a referral bias, as 3 of the children with ongoing haematochezia were referred to our institute for second opinions due to refractory symptoms, development of multisystem disease, and re-evaluation

of their underlying diagnosis. Studies in adults report gastrointestinal involvement in 5-20% of patients with GPA including transient abdominal pain, cholecystitis, inflammatory ileocolitis, haemorrhage, and bowel perforations that are potentially life-threatening (22, 23). This may be even more common in other forms of AAV, with up to 1/3 of eosinophilic granulomatosis with polyangiitis patients reported to have gastrointestinal involvement (24). There are reports of patients who have concomitant diagnoses of inflammatory bowel disease and GPA or other forms of AAV (25-27). Three patients in our study presented with GPA and symptoms of colitis indistinguishable from those of inflammatory bowel disease. Interest-

ingly, 2 of these 3 patients were initially diagnosed with inflammatory bowel disease and only later were the gastrointestinal problems felt to be more consistent with GPA. These presentations raise the question of whether patients with GPA truly have a separate diagnosis of inflammatory bowel disease, or if these intestinal manifestations are part of a broader disease spectrum. We recommend that a high index of suspicion should be maintained for a diagnosis of GPA or other forms of AAV in children with inflammatory bowel disease who develop extra-intestinal manifestations. Second, morbidity from both the vasculitis and the medications used to treat the disease remain an issue of concern for children with GPA. Children in our cohort were treated with potent immunosuppressive therapy, including combinations of cyclophosphamide, rituximab, glucocorticoids, and plasma exchange. Over the study period, the use of rituximab to treat AAV was adopted, however this drug was generally used in combination with cyclophosphamide rather than as a stand-alone medication. The burden of disease in our cohort was significant and sustained throughout the disease course as evidenced by the patients' frequent repeat hospitalisations, high prevalence of hypertension and chronic kidney disease, saddle nose deformities, and hearing loss. The long-term morbidities are not only disease-related but are also secondary to treatment. Avascular necrosis of the bone occurred in 5 patients, likely secondary to high-dose glucocorticoids. Infection, likely secondary to immunosuppression, was the second highest indication for hospital readmission. These treatments, particularly cyclophosphamide, also have the potential to cause life-altering morbidity such as infertility and malignancy (28). In adults, disease morbidity is associated with poorer health-related quality of life, both during active disease and remission (29, 30). While this has not been directly studied in children with vasculitis, studies have shown that chronic illness in childhood can have lasting effects on children's psychological development, with effects lasting into adulthood (31). Future studies should address the

patient-reported outcomes in children with AAV so that treatments can be optimised for both effective disease control and quality of life.

This study has several limitations to consider including the retrospective design and small sample size. Nonetheless, this study is one of the largest to evaluate the course and outcomes of children with GPA and explores the extent of gastrointestinal involvement in more depth than previous studies. Although this study was performed at a single tertiary care facility, this centre is a regional referral centre and the study population likely represents the full spectrum of disease in children. Additionally, restricting the analysis to patients with a new diagnosis decreased the likelihood of over-representing the most severe patients referred to our centre secondary to complicated and refractory disease course. Notably, outcomes were available to the extent children were followed at our centre and we do not report outcomes after transition to adult care. The median follow-up time was 3.3 years and it will be important for future studies to evaluate more extended outcomes and potentially to compare outcomes in patients with AAV who had onset of disease as children *versus* as adults. Despite these limitations, this is one of the largest studies on the features and disease course in children with GPA, and represents a contemporary cohort that incorporates newer therapies such as rituximab. Additionally, observational cohorts can provide insight into the disease course and treatment response of the full spectrum of patients, whereas randomised control trials tend to select for patients with more severe disease (32).

Morbidity remains high in children with GPA, from both the disease and its treatments. There have been no clinical trials to evaluate the effectiveness of treatments specifically in children, who may have differential responses to treatments in both efficacy and tolerability (18, 33-37). More research on children with AAV is vitally needed to better characterise the effectiveness and risks of treatments in children and to better understand the long-term outcomes for children with this complex disease.

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