Published in final edited form as:

Arthritis Care Res (Hoboken). 2017 September ; 69(9): 1377–1383. doi:10.1002/acr.23142.

Variation in treatment of children hospitalized with antineutrophil cytoplasmic antibody-associated vasculitis in the United States

Karen E. James, MD,

Division of Rheumatology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA

Rui Xiao, PhD,

Department of Biostatistics, Children's Hospital of Philadelphia and Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Peter A. Merkel, MD MPH, and

Division of Rheumatology, Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia PA

Pamela F. Weiss, MD MSCE

Division of Rheumatology and Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, Department of Pediatrics and Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Abstract

Objective—There are few reports on treatment of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in children. This study characterizes the use of cyclophosphamide, rituximab, and plasma exchange in children hospitalized with AAV in the United States.

Methods—We conducted a retrospective cohort study of children hospitalized with AAV from 2004-2014 utilizing an administrative and billing database from 47 tertiary care pediatric hospitals. All patients had an ICD-9-CM discharge code of 446.4 and 1 charge for glucocorticoids. Treatment receipt was determined using billing data. Mixed effects logistic regression evaluated factors associated with the likelihood of receipt of each of the three treatments.

Results—During the 11 year study period there were 1290 admissions for 393 children. Median age at index admission was 14.6 years and 61% were female. Sixteen percent and 17% of children required dialysis or mechanical ventilation, respectively. The median length of stay was 9 days. Fifty-seven percent, 21%, and 10% of children received cyclophosphamide, rituximab, or both, respectively. Twenty-two percent received plasma exchange. Mechanical ventilation was associated with receipt of cyclophosphamide and plasma exchange, but not rituximab. There was

Reprint Requests and correspondence should be sent to: Karen James, University of Utah Department of Pediatrics, Division of Rheumatology, 81 N. Mario Capecchi Drive, Salt Lake City, UT 84113, Phone: 801-587-1684, Fax: 801-213-7777, karen.e.james@hsc.utah.edu.

Other Financial Interests:

The other authors report no financial interests

an increasing trend in use of rituximab over time during the study period ($p<0.05$), and a decreasing trend in use of cyclophosphamide ($p<0.05$). Treatment use varied significantly between hospitals, especially for plasma exchange.

Conclusion—The treatment of children with severe AAV is shifting from cyclophosphamide to rituximab and their need for dialysis, mechanical ventilation, and prolonged hospitalization remains common. Use of plasma exchange is highly variable.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of rare diseases characterized by blood vessel inflammation, multi-organ system involvement, and life-threatening morbidities. Treatment for AAV in children is based on physician experience and data from studies done in adults as there are no pediatric-based clinical trials. (1) Historically, high-dose glucocorticoids in combination with cyclophosphamide has been the main form of therapy for induction of remission. However, cyclophosphamide is associated with serious morbidities including infection, hemorrhagic cystitis, infertility, and malignancy.(2-4) Recently, rituximab and plasma exchange have been studied in adults as alternatives and adjunctive treatments, with potentially less long-term morbidity.(2, 5-7) While rituximab use is rising in pediatric patients with autoimmune diseases, use of rituximab has not been studied in children with AAV (8). It is unclear to what extent these recent studies in adult literature have affected the practice of providers caring for children with AAV.

Studies on AAV and its treatment in children have been largely limited by the rarity of the disease, with individual centers frequently seeing only a handful of patients over a decade. Administrative databases provide a unique way to identify a large cohort of children with AAV, in addition to procedures and treatments they may have received. This study utilized an inpatient administrative database to describe the treatments and factors associated with the use of various treatments in children hospitalized with AAV across the United States.

PATIENTS & METHODS

This is a retrospective cohort study of children in the United States hospitalized with AAV. This study was reviewed and determined to be exempt by the Children's Hospital of Philadelphia Internal Review Board, as it was determined to be non-human subjects research.

Data source

Subjects were obtained from the Pediatric Health Information System (PHIS) from 1/1/2004-12/31/2014. PHIS is an administrative billing database of 47 tertiary care children's hospitals across the United States. These hospitals are affiliated with the Children's Hospital Association (Overland Park, KS). Data in PHIS consist of de-identified and encrypted data from inpatient visits. Data available in PHIS include: Level I data-encrypted patient identifiers (trackable across multiple hospitalizations), demographics, admission and discharge dates; and level 2 data-diagnostic and procedure codes, pharmacy,

supply, laboratory, imaging and clinical service financial and utilization codes along with day of service. Data in PHIS undergoes rigorous quality checks prior to entry into the database, and if it does not meet the error threshold, is rejected for correction prior to resubmission.

Study population

Inclusion criteria: patients were included if they were between the ages of 2-18, and were admitted at a hospital participating in PHIS between June 1, 2004 and December 31, 2014 with a primary or secondary discharge diagnosis ICD-9-CM code of 446.4 (AAV). The index admission was the first admission during the inclusion period with the diagnosis code of 446.4 or a readmission with this code not occurring within 6 months of a prior admission for this same diagnosis. There was only one index admission per subject. The code 446.4 specifically refers to granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and may also be more generically used for AAV. There is no ICD-9-CM code for microscopic polyangiitis (MPA) or renal limited AAV that is specific to those diseases exclusively. Given the extreme rarity of EGPA in the pediatric population, there is not likely a significant portion of patients with EGPA. Therefore, the population represents mainly patients with GPA, but will capture some patients with MPA and renal-limited AAV.

Exclusion Criteria: Exclusions were as follows: 1) index admissions during which glucocorticoids were not administered, since glucocorticoids are a mainstay of treatment for active disease, and 2) receipt of renal transplantation during the index admission, as this would indicate long-standing, non-active disease. The criteria were designed to enrich for patients with new diagnoses and new relapses of disease (which are treated similarly), rather than patients with ongoing disease activity. Receipt of glucocorticoid was chosen to select for patients admitted with active disease since glucocorticoids are a mainstay of treatment for active disease.

Medication use

Medication usage was determined using pharmacy billing data and clinical transaction classification (CTC) codes. CTC codes are codes created specifically for PHIS to have a standardized code to which charges are mapped to. Any billable aspect of the hospitalization, including laboratory tests, imaging, nursing care, respiratory therapy, physician consultations, medications, supplies, and procedures can be mapped to a CTC code. Glucocorticoid use was defined as a code for oral or intravenous administration of beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone. Oral and intravenous cyclophosphamide use was pooled. Receipt of plasma exchange was determined based on the presence of at least one CTC code for plasma exchange (355011) or one ICD-9-CM procedure code for plasma exchange (99.71). (9)

Statistical analysis

All analyses were done using the index admission, unless otherwise noted. Standard descriptive statistics including range, mean and standard deviation for normally distributed

variables or median and interquartile range for non-normally distributed variables were used, as appropriate. Trends in medication use over time were graphically displayed using simple linear regression for cyclophosphamide and plasma exchange, and polynomial regression with a quadratic term for rituximab for the best fit.

Mixed effects logistic regression was used to determine factors associated with the likelihood of receipt of each treatment. This model accounts for the fact that patients were clustered within hospitals by including hospital-specific random effects. Separate models were fitted for cyclophosphamide, rituximab, and plasma exchange. Other variables that were evaluated as fixed effects for each model include year of admission, age, sex, dialysis, mechanical ventilation and receipt of other immunomodulatory treatments. Exposure to dialysis and mechanical ventilation were considered positive for each model only if they occurred prior to initiation of therapy of interest. Concomitant immunomodulatory treatments for each model were considered regardless of timing in relation to the treatment of interest. Backwards selection was used to determine the final models with year of admission, dialysis (yes/no), and mechanical ventilation (yes/no) being forced into the final models. The likelihood ratio tests were used as model selection criteria.

To examine the treatment variation by hospital, only hospitals with at least 5 cases of AAV and that contributed data for at least 10 years of the study were included. All analyses were performed using Stata version 13.1 (Statacorp, TX).

RESULTS

Five hundred twenty-three patients were discharged with a code for AAV across 43 hospitals during the study time period. One-hundred-thirty patients were excluded for the following reasons (not mutually exclusive): No glucocorticoids during first AAV admission (n=92); age older than 18 at first AAV admission (n=29); age less than 2 at first AAV admission (n=3); transplant during first AAV admission (n=6). Three-hundred-ninety-three patients fulfilled study criteria. Demographics and characteristics of the cohort are shown in Table 1. The cohort had a median age of 14.6 years and a slight female predominance (61%). Fifteen percent (n=60) and 17% (n=67) required dialysis and mechanical ventilation, respectively, with 5% (n=20) requiring both interventions, and 27% (n=107) needing one or the other intervention. Thirty-six percent (n=140) required care in an intensive care unit. The median duration of stay for the first admission for all patients was 9 days (IQR 4, 15). The median duration of stay for patients receiving dialysis and/or mechanical ventilation was 19 days (IQR 13, 31), while the median length of stay for patients not receiving either was 6 days (IQR 3, 10). Sixty percent of children had at least one readmission. Median time to first all-cause readmission was 55 days (IQR: 12, 165). Five patients died during the index admission.

Treatments during the index hospitalization are shown in table 2. Cyclophosphamide and rituximab were used in 56% (n=222) and 21% (n=83) of index admissions, respectively. Patients started cyclophosphamide and rituximab a median of 4 days (IQR 2, 7) and 5 days (IQR 3, 9) respectively, after admission. Rituximab was not used in any hospital prior to 2005. Thirty-three percent (n=128) of patients did not receive cyclophosphamide or

rituximab. Of the patients who did not receive cyclophosphamide or rituximab, the most commonly used immunosuppressant medications were methotrexate, azathioprine, and mycophenolate mofetil. The median time to initiation for methotrexate, azathioprine, and mycophenolate mofetil was 2 days (IQR 0,9), 1 day (IQR 0,1), and 1 day (IQR 1,1) respectively.

Twenty-one percent (n=84) of patients received plasma exchange during their first hospitalization, 95% (n=80) of whom received it in combination with cyclophosphamide and/or rituximab. Plasma exchange was initiated a median of 3 days after admission (IQR 1, 6). Twelve of 84 (14%) patients receiving plasma exchange started on the first day of hospitalization. The median number of cycles of plasma exchange was 6 (IQR 4, 7). Of the 31 patients who received rituximab and plasma exchange, 7 (23%) received rituximab 1-9 days before their last cycle of plasma exchange, 5 (16%) on the same day as their last cycle of plasma exchange, and 19 (61%), after their last cycle of plasma exchange. Of the 71 patients who received cyclophosphamide and plasma exchange, 56 (79%) received their first dose of cyclophosphamide before their last plasma exchange cycle, 15 (21%) received their first dose on the same day or after their last cycle of plasma exchange.

Figure 1 shows the variation in each treatment over time. Use of cyclophosphamide significantly decreased over time ($p=0.05$), while use of rituximab during the index hospitalization increased significantly over time ($p<0.01$). There was a non-statistically significant trend towards increased use in plasma exchange over time ($p=0.06$).

The factors associated with the receipt of each of the 3 treatments are shown in Table 3. Year of admission, concomitant cyclophosphamide, concomitant rituximab, use of dialysis, and need for mechanical ventilation were significantly associated with receipt of plasma exchange. Year, plasma exchange, and mechanical ventilation were associated with receipt of cyclophosphamide. Use of rituximab was negatively associated with receipt of cyclophosphamide. Year and use of plasma exchange were significantly associated with receipt of rituximab. Variability in the unadjusted use of cyclophosphamide, rituximab, and plasma exchange across hospitals is shown in figures 2a-c. All hospitals used cyclophosphamide, but rituximab and plasma exchange were not utilized at every hospital during the period of study. While use of cyclophosphamide and plasma exchange varied regardless of the hospital size, rituximab use was more frequent in hospitals with a higher volume of AAV patients.

DISCUSSION

This study reports characteristics of the initial hospitalization and initial treatments for children discharged with a diagnosis of AAV and is the largest cohort of pediatric AAV reported to date. Our results highlight that the need for dialysis and mechanical ventilation is common among children hospitalized with AAV, and that disease requiring these interventions is associated with prolonged hospitalization. Five children died. Our results demonstrating significant morbidity at diagnosis are in accordance with previously reported smaller cohorts. (10, 11) Most children received cyclophosphamide and/or rituximab during their index hospitalization. Use of plasma exchange was variable, and some of the hospitals

with the highest AAV patient load rarely used plasma exchange for their patients. Over time, the use of cyclophosphamide decreased, while use of plasma exchange and rituximab increased. There was variability seen in hospital use of all 3 medications, however rituximab use appeared to be more closely related to the volume of patients with AAV seen at a given hospital.

This study encompasses a time period during which many advances in optimizing the treatment of AAV in adults were reported. In 2010, 2 landmark studies were published showing rituximab was non-inferior to cyclophosphamide for induction of remission of severe AAV. (12, 13) Since that time, additional studies have demonstrated the efficacy of rituximab not only for inducing remission (including refractory or relapsing disease), but also for maintaining remission. (14) Our study demonstrates a gradual decline in the use of cyclophosphamide, a gradual increase in the use of plasma exchange, and an exponential increase in the utilization of rituximab, indicating that data from the adult studies has clearly influenced treatment paradigms in children. There was a sharp increase in use of rituximab in 2011 following the landmark adult studies. (12, 13) Interestingly, this increase occurred in hospitals with the highest AAV case volume, and was not driven by markers of severe disease (receipt of dialysis or mechanical ventilation). This finding suggests that while rituximab use is increasing, it is more likely to be used in hospitals that see more patients with AAV and whose physicians may therefore have more experience and comfort with using this treatment for AAV or similar conditions. As expected, receipt of cyclophosphamide and plasma exchange were associated with markers of more severe disease (dialysis and mechanical ventilation), suggesting these treatments are less influenced by the hospital case volume.

Plasma exchange was rarely used in the absence of cyclophosphamide or rituximab in this cohort, consistent with its role as an adjunctive treatment, rather than a stand-alone treatment for AAV. In 2007, the MEPEX trial showed that in adult patients with severe renal involvement adjunctive plasma exchange increased the rate of renal function recovery in comparison to adjunctive pulse methylprednisolone. (15) The long-term follow-up to this study was not as supportive of plasma exchange, with no difference in dialysis free survival. (7) This clinical equipoise has led to the ongoing PEXIVAS trial looking to better determine the efficacy of plasma exchange. (16) The variability seen in use of plasma exchange at different hospitals may be related to differences in the case mix, however each of the included hospitals is a major tertiary care and referral center in a metropolitan area. The variability in use of plasma exchange could also reflect clinical equipoise regarding its utility, paralleling the reports of published studies.

The primary advantage of using a large administrative database is capture of a large cohort of pediatric AAV patients. The results of our study, however, should be considered in the context of several limitations. First, the administrative nature of this database requires us to identify patients based on diagnosis codes. The code used for identification of subjects 446.4 refers specifically to GPA and EGPA, but not specifically to MPA or renal limited AAV, although those patients may receive the code as well. Patients with MPA may also be coded under the code for polyarteritis nodosa, and patients with renal limited disease may be coded for under various codes for glomerulonephritis. These codes were not included due to their

lack of specificity for AAV. Therefore, this population is likely enriched for patients with GPA, and may not include all patients with MPA or renal-limited disease. The population also includes both new diagnoses and relapses, and therefore the median time to initiation of medications may be somewhat shorter than that for newly diagnosed patients. Second, the administrative nature limits determination of specific organ involvement and clinical indications for treatment. To partially address this limitation, we used mechanical ventilation and dialysis as surrogate markers for the severe disease manifestations of renal failure and respiratory failure. Third, this study is limited to children who require hospitalization. In our clinical experience, however, the vast majority of diagnoses of AAV in children are made during hospitalization. By limiting our analysis to hospitalized patients, we focused our investigation on the most severe spectrum of disease. These severe presentations are those most likely to require the induction therapies studied herein. Lastly, information in this database is limited to hospitalization; there is no outpatient or follow-up data other than readmission. Given the uniqueness of the data presented in this study and the relatively large size of the cohort for a rare pediatric disease, we believe this information is a highly valuable contribution to the existing literature.

These results highlight existing variability in the use of cyclophosphamide, rituximab, and plasma exchange for children hospitalized with AAV. Multiple studies have shown that variability in care negatively impacts important clinical outcomes. (17-19) Our results show that children with AAV are ill at presentation, more than one quarter require ventilator or dialysis support, morbidity is high, and readmissions are common. There is a vital need for pediatric-specific studies to evaluate the effectiveness and efficacy of cyclophosphamide, rituximab, and plasma exchange in this population. Ultimately, this information will guide the creation of pediatric-specific guidelines to improve morbidity and mortality in children.

Acknowledgments

Funding Support: Karen James received support from NIH T32 grant 5T32HD064567 and the Rheumatology Research Foundation/Amgen Fellowship Training Award. Pamela Weiss is supported by NIH grant K23-AR059749.

Dr. Merkel has current or has had recent financial support for research, consultation, and/or educational activities from the following sources:

Consulting: Actelion, Alexion, Bristol Myers Squibb, ChemoCentryx, Genzyme/Sanofi, GlaxoSmithKline, Genentech/Roche

Research Support: Actelion, Bristol Myers Squibb, Celgene, ChemoCentryx, Genentech/Roche, GlaxoSmithKline.

REFERENCES

1. Twilt M, Benseler S. Childhood antineutrophil cytoplasmic antibodies associated vasculitides. *Current opinion in rheumatology*. 2014; 26(1):50–5. [PubMed: 24247117]
2. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Annals of the rheumatic diseases*. 2009; 68(3):310–7. [PubMed: 18413444]
3. Moorthy AV, Chesney RW, Segar WE, Groshong T. Wegener granulomatosis in childhood: prolonged survival following cytotoxic therapy. *The Journal of pediatrics*. 1977; 91(4):616–8. [PubMed: 908985]

4. Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nolle B, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. *Arthritis and rheumatism*. 2000; 43(5):1021–32. [PubMed: 10817555]
5. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *The New England journal of medicine*. 2013; 369(5):417–27. [PubMed: 23902481]
6. Walsh M, Catapano F, Szpirt W, Thorlund K, Bruchfeld A, Guillevin L, et al. Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2011; 57(4): 566–74. [PubMed: 21194817]
7. Walsh M, Casian A, Flossmann O, Westman K, Hoglund P, Pusey C, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. *Kidney Int*. 2013; 84(2):397–402. [PubMed: 23615499]
8. Tzaribachev N, Koetter I, Kuemmerle-Deschner JB, Schedel J. Rituximab for the treatment of refractory pediatric autoimmune diseases: a case series. *Cases journal*. 2009; 2:6609. [PubMed: 20184679]
9. Weiss PF, Klink AJ, Friedman DF, Feudtner C. Pediatric therapeutic plasma exchange indications and patterns of use in us children's hospitals. *Journal of clinical apheresis*. 2012; 27(6):287–94. [PubMed: 22811262]
10. Cabral DA, Uribe AG, Benseler S, O'Neil KM, Hashkes PJ, Higgins G, et al. Classification, presentation, and initial treatment of Wegener's granulomatosis in childhood. *Arthritis and rheumatism*. 2009; 60(11):3413–24. [PubMed: 19877069]
11. Akikusa JD, Schneider R, Harvey EA, Hebert D, Thorner PS, Laxer RM, et al. Clinical features and outcome of pediatric Wegener's granulomatosis. *Arthritis and rheumatism*. 2007; 57(5):837–44. [PubMed: 17530684]
12. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *The New England journal of medicine*. 2010; 363(3):221–32. [PubMed: 20647199]
13. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *The New England journal of medicine*. 2010; 363(3):211–20. [PubMed: 20647198]
14. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *The New England journal of medicine*. 2014; 371(19):1771–80. [PubMed: 25372085]
15. Jayne DRW, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis. *Journal of the American Society of Nephrology*. 2007; 18(7):2180–8. [PubMed: 17582159]
16. Walsh M, Merkel PA, Peh CA, Szpirt W, Guillevin L, Pusey CD, et al. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. *Trials*. 2013; 14:73. [PubMed: 23497590]
17. Florin TA, Byczkowski T, Ruddy RM, Zorc JJ, Test M, Shah SS. Variation in the management of infants hospitalized for bronchiolitis persists after the 2006 American Academy of Pediatrics bronchiolitis guidelines. *The Journal of pediatrics*. 2014; 165(4):786–92. e1. [PubMed: 25015578]
18. Todd J, Bertoch D, Dolan S. Use of a large national database for comparative evaluation of the effect of a bronchiolitis/viral pneumonia clinical care guideline on patient outcome and resource utilization. *Archives of pediatrics & adolescent medicine*. 2002; 156(11):1086–90. [PubMed: 12413334]
19. Norton SP, Pusic MV, Taha F, Heathcote S, Carleton BC. Effect of a clinical pathway on the hospitalisation rates of children with asthma: a prospective study. *Archives of disease in childhood*. 2007; 92(1):60–6. [PubMed: 16905562]

Significance and Innovation

- This study is the largest cohort to evaluate pediatric onset AAV.
- Use of cyclophosphamide, rituximab, and plasma exchange for induction in hospitalized patients with childhood-onset AAV varies across the United States.
- Treatment with cyclophosphamide for induction in children is still common, although its use is slowly declining, while use of rituximab is increasing.

A. Change in proportion of use of cyclophosphamide over time

B. Change in proportion of use of rituximab over time

C. Change in proportion of use of plasma exchange over time

Figure 1. Change in use of treatments for children with ANCA-associated vasculitis from 2004-2014

Each dot represents the raw proportion of patients in each year receiving a) cyclophosphamide, b) rituximab, c) plasma exchange. The lines represent the best fit line (1a. and 1.c) and the quadratic best fit (1.b)

A. Percent of patients with AAV at each hospital receiving cyclophosphamide

B. Percent of patients with AAV at each hospital receiving rituximab

C. Percent of patients with AAV at each hospital receiving plasma exchange

Figure 2. Variation in treatment of children with ANCA-associated vasculitis across hospitals
Percent of children with ANCA-associated vasculitis (AAV) at each hospital who received a. cyclophosphamide, b. rituximab, and c) plasma exchange during their index admission. Only hospitals with at least 5 cases of AAV and who contributed data for at least 10 of the 11 years of the study are included.

Table 1
Characteristics of the study cohort of patients with ANCA-associated vasculitis

Patient Characteristics	Median (IQR)
Total number of patients	393
Female, N (%)	238 (61%)
Age (years)	14.6 (12, 16.1)
<u>First admission (n=393)</u>	
Duration of stay, days	9 (4, 15)
Dialysis, N (%)	60 (15%)
Mechanical ventilation, N (%)	67 (17%)
<u>Readmissions (n=897):</u>	
Number of patients with readmission	236 (60%)
Number of readmissions	2 (1, 3)
Time to first readmission (days)	55 (12, 165)
Duration first readmission (days)	3 (2, 6)

ANCA = antineutrophil cytoplasmic antibody; IQR = inter-quartile range

Table 2
Treatments of children during first hospitalization for ANCA-associated vasculitis

	Without plasma exchange N=309 N (%)	With plasma exchange N=84 N (%)	Total N=393
Cyclophosphamide	133 (43%)	49 (58%)	182 (46%)
Rituximab	34 (11%)	9 (11%)	43 (11%)
Cyclophosphamide and rituximab	18 (6%)	22 (26%)	40 (10%)
Other immunosuppressive medications (not mutually exclusive, N=128) *			
Glucocorticoids alone	75(19%)	4 (5%)	79 (20%)
Methotrexate	19 (6%)	0	19 (5%)
Azathioprine	11 (4%)	0	11 (3%)
Mycophenolate	10 (3%)	0	10 (3%)
Intravenous immunoglobulin	10 (3%)	0	10 (3%)
Tacrolimus	5 (1%)	0	5 (1%)
Cyclosporine	3 (1%)	0	3 (1%)
Anti-tumor necrosis factor	2 (1%)	0	2 (1%)

* Without cyclophosphamide or rituximab.

Table 3

Factors associated with receipt of plasma exchange, cyclophosphamide, and rituximab among children hospitalized with ANCA-associated vasculitis

	Odds ratio	95% Confidence Interval	P value
Receipt of cyclophosphamide			
Plasma exchange *	8.19	3.79, 17.71	<0.001
Rituximab *	0.52	0.27, 0.98	0.042
Dialysis #	0.59	0.25, 1.41	0.235
Ventilator #	2.88	1.29, 6.46	0.010
Year	0.91	0.84, 0.99	0.031
Receipt of rituximab			
Age (years)	1.10	0.98, 1.23	0.102
Plasma exchange *	3.83	1.60, 9.13	0.003
Cyclophosphamide	0.55	0.27, 1.09	0.085
Hospital AAV volume ^	1.79	0.93, 3.42	0.080
Dialysis #	0.62	0.23, 1.66	0.343
Ventilator #	1.52	0.64, 3.59	0.339
Year	0.71	1.27, 1.62	0.202
Square transformation of year **	1.05	0.41, 1.20	0.011
Receipt of plasma exchange			
Cyclophosphamide * use	9.30	4.20, 20.59	<0.001
Rituximab * use	3.10	1.45, 6.64	0.004
Dialysis #	2.73	1.12, 6.65	0.027
Ventilator #	3.42	1.54, 7.63	<0.003
Year	1.22	1.07, 1.38	0.002

Multivariate mixed effects logistic regression. Hospital was treated as a random effect within each model, and is not shown.

* Receipt at any point during hospitalization.

Receipt prior to exposure of interest.

^ Average case volume per hospital.

** A quadratic term for year was used in the rituximab model.