Occurrence and aetiology of gastrointestinal perforation in patients with vasculitis

V.L. Kronzer[1], D.P. Larson[2], C.S. Crowson[3,4], K.J. Warrington[4], S.R. Ytterberg[4], A. Makol[4], M.J. Koster[4]

[1]Department of Internal Medicine, [2]Department of Anatomic and Clinical Pathology, Mayo Clinic, [3]Department of Health Sciences Research, [4]Division of Rheumatology, Mayo Clinic, Rochester, MN, USA.

Vanessa L. Kronzer, MD, MSCI
Daniel P. Larson, MD
Cynthia S. Crowson, PhD
Kenneth J. Warrington, MD
Steven R. Ytterberg, MD
Ashima Makol, MBBS
Matthew J. Koster, MD

Please address correspondence to:
Dr Vanessa L. Kronzer,
200 First Street SW,
Rochester, MN 55905, USA.
E-mail: kronzer.vanessa@mayo.edu

Received on July 11, 2018; accepted in revised form on September 10, 2018.

Clin Exp Rheumatol 2019; 37 (Suppl. 117): S32-S39.

Key words: vasculitis, Churg-Strauss syndrome, granulomatosis with polyangiitis, polyarteritis nodosa, intestinal perforation, glucocorticoids

Funding: this work was supported by the National Institute of Health's Clinical and Translational Science Awards program [grant no. UL1 TR002377].

Competing interests: none declared.

ABSTRACT

Objective. *This study aimed to characterise the presenting features and outcomes of patients with vasculitis and gastrointestinal perforation.*

Methods. *Using a retrospective cohort design, this study included 20 cases with verified vasculitis and gastrointestinal perforation at Mayo Clinic, Rochester, USA, between 1998 and 2017.*

Results. *Four of the twenty cases experienced vasculitis-induced perforation. Cases with perforations due to vasculitic involvement had more small bowel involvement, longer duration of abdominal pain prior to perforation (41 days vs. 0 days, p=0.005), and a higher proportion of active tobacco use (75% vs. 7%, p=0.01) compared to the cases with non-vasculitis perforation. A majority (88%) of the non-vasculitis perforations were associated with glucocorticoid use. The median cumulative glucocorticoid dose prior to perforation in patients with additional, non-vasculitic risk factors for perforation was 4,320 mg prednisone and was 22,170 mg for those without additional risk factors. Mortality rates for the whole cohort were higher than the general population (standardised mortality ratio: 2.19, 95% confidence interval 1.05–4.02). The cases with vasculitis-induced perforation tended to have increased number of surgeries and length of stay compared to the non-vasculitis cases; however, those differences failed to reach statistical significance.*

Conclusion. *Small bowel location and longer abdominal pain duration may help distinguish vasculitis-induced bowel perforation from other aetiologies. Overall mortality in patients with vasculitis and bowel perforation is increased, highlighting the importance of prompt diagnosis and management.*

Introduction

Vasculitis is characterised by the inflammation of blood vessels. Systemic vasculitides of small and medium vessels, including granulomatosis with polyangiitis (GPA), eosinophilic GPA (EGPA), microscopic polyangiitis (MPA), and polyarteritis nodosa (PAN) can affect many organ systems, including the gastrointestinal tract (1). One of the most feared complications is gastrointestinal perforation, not only because of its devastating gastrointestinal consequences, but also because of its association with poor vasculitis outcomes (2, 3).

Decision-making in these scenarios is critical because of the high associated mortality, yet it is difficult for two reasons. First, gastrointestinal perforation may result not only from vasculitis but also from the therapies used to treat it, including glucocorticoids (4-6). Second, while the treatment for vasculitis-induced perforation is increased immunosuppression, the most prudent response for glucocorticoid-induced perforation and promotion of wound healing is glucocorticoid reduction or cessation. Gastrointestinal perforation in patients with history of vasculitis therefore represents a diagnostic and therapeutic dilemma.

Despite this important and challenging dilemma, existing literature exploring gastrointestinal perforation in patients with small- and medium-sized vasculitis is limited mostly to case reports. A few population-based cohorts describe the gastrointestinal involvement of systemic vasculitides, especially PAN (2, 3, 7-10). However, none of these focus on gastrointestinal perforation in particular. Indeed, the largest report contains nine patients with vasculitis and gastrointestinal perforation, but the majority of those patients had hepatitis B-associated PAN, which now ac-

counts for a small fraction of vasculitis. Furthermore, prior studies provided limited details on the individual cases (3). Thus, clinicians need more data on patients with vasculitis and gastrointestinal perforation in order to make more informed decisions in these high-stakes clinical scenarios.

To address this gap, this study first aimed to describe the presenting features, treatment, and outcomes of gastrointestinal perforation among patients with PAN, EGPA, GPA, or MPA at a large, single institution. Second, it aimed to compare the features of vasculitis-induced perforation with non-vasculitis-induced perforations to aid clinicians in diagnostic and therapeutic decision-making.

Materials and methods

Study design and population

This retrospective cohort study received approval from the Mayo Clinic Institutional Review Board (17-010669) and complies with the Declaration of Helsinki. Potential cases came from an electronic database query of patients seen at the Mayo Clinic in Rochester, Minnesota, USA, from January 1, 1998 to December 31, 2017. Search criteria for vasculitis included International Classification of Diseases Ninth Revision (ICD-9) or Tenth Revision (ICD-10) codes for PAN, GPA, MPA, EGPA, arteritis not otherwise specified (NOS), or vasculitis NOS. This search yielded 23,868 patients with at least one diagnosis code for vasculitis. Eligible patients further needed at least one ICD-9 or ICD-10 code for perforation in the oesophagus, stomach, duodenum, gallbladder, small bowel, appendix, large bowel, or rectum, which left 128 unique patients.

Based on manual chart review, nineteen patients met criteria for inclusion by having documented evidence of vasculitis and confirmed gastrointestinal perforation. A previously reported cohort of PAN patients by the study authors provided one additional case (8), yielding 20 total cases. These cases fell into three groups based on clinical, histological, and radiographic data. The "vasculitis-induced (VI)" group consisted of cases where vasculitis caused perforation. The "active vasculitis, non-vasculitis induced (AV-non-VI)" group consisted of cases where active vasculitis was present at the time of perforation but was not considered the direct cause. The "inactive vasculitis, non-vasculitis-induced (IV-non-VI)" group consisted of cases with a known history of vasculitis that was inactive at the time of perforation and was not considered the cause.

Measures

All data for this study came from manual chart review. To ensure consistency and quality of data collection, we performed data extraction using the Research Electronic Data Capture (REDCap) system. We calculated the Charlson Comorbidity Index (CCI) (11) for each patient using a tool designed for chart review (12). The Five Factors Score (FFS) (2) and Birmingham Vasculitis Activity Score (BVAS, version 3) (13) quantified disease activity at the time of diagnosis and again at perforation. Cumulative prednisone dose before perforation came from adding the total glucocorticoid dose (in prednisone equivalents) starting from the most recent steroid-free interval. We categorised the treatment decision at the time of perforation using the definitions outlined by Mukhtyar *et al*. (13). These included major escalation, continue at a major level, minor escalation, continue at a minor level, reduction of treatment, and no treatment.

Statistical analysis

We used proportions and chi-square tests for categorical variables, and medians and Mann-Whitney U-tests for continuous variables. Calculations excluded missing data. We calculated median follow-up time using the reverse Kaplan-Meier method (14). Survival analyses used the Kaplan-Meier method, with death as the primary endpoint, and date of most recent patient contact in the chart as the time of censorship. Observed and expected survival were compared using the log-rank test, where expected survival for persons of the same age, sex and calendar year was estimated using United States white population lifetables. The ratio of observed number of deaths to the expected number, the standardised mortality ratio (SMR), was estimated. Ninety-five percent confidence intervals (CI) were computed for the SMR assuming that the expected rates are fixed and the observed number of deaths follows a Poisson distribution. Quasi-Poisson regression models were used to examine differences between the groups in rates of recurrent perforation, glucocorticoid discontinuation, immunosuppression reduction, and relapse, with adjustment for overdispersion. This manuscript follows guidelines for reporting clinical case series (15). Statistical analyses were performed using SAS v. 9.4 (SAS Institute Inc., Cary, NC) and R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Over the twenty-year time period, 20 total patients with small or medium-vessel vasculitis experienced bowel perforation (Table I). Three had EGPA, 11 GPA, three MPA, and three PAN. None of the cases of PAN were associated with Hepatitis B virus. Of the twenty cases, four experienced perforations directly from vasculitis (the "VI" group) based on clinical (case no. 12, 14, 15, and 16), angiographic (case no. 14, Fig. 1A), and histological (case no. 15 and 16, Fig. 1B and 1C) findings. Nine cases had active vasculitis but with a non-vasculitis cause of perforation (the "AV-non-VI" group). Finally, seven cases had history of vasculitis that was not active at the time of perforation, which was deemed to be due to non-vasculitis aetiology (the "IV-non-VI" group). Perforations spanned the entire GI tract from oesophagus to distal sigmoid colon. However, those attributed to vasculitis ranged only from small bowel to cecum (Table I).

Characteristics

In addition to bowel location, a few other characteristics differed among the VI, AV-non-VI, and IV-non-VI groups (Table II). Tobacco use was most prevalent in the VI group (p=0.04). In particular, active tobacco use was present in 75% of vasculitis-induced bowel perforation, compared to only

Table I. Location and aetiology of gastrointestinal perforation among patients with history of vasculitis.

ID	Location	Age	Sex	Type	BVAS	Likely aetiology
8	oesophagus	58	M	GPA	7	ulceration from PEG bumper in setting of GCs
10	oesophagus	58	F	GPA	26	traumatic intubation in the setting of GCs
11	stomach	75	F	GPA	6	GCs in setting of peptic ulcer disease
9	stomach	75	M	EGPA	0	SMA syndrome causing gastric dilation and ischaemic ulcers
18	ant. pylorus	87	M	GPA	0	GCs without GI ppx plus Helicobacter pylori
3	duodenum	85	M	MPA	0	ischaemia from an MI in setting of pre-existing ulcer and GC use
5	duodenum	80	F	GPA	0	GCs without GI ppx
6	duodenum	76	F	MPA	19	GCs without GI ppx plus trauma from clipping bleeding ulcers
15	jejunum/ileum	31	M	EGPA	10	vasculitis
14	terminal ileum	31	F	PAN	4	vasculitis
16	small bowel	72	F	PAN	-	vasculitis
13	caecum	63	M	GPA	0	trauma during colonoscopy for colonic pseudoobstruction
12	caecum/asc. colon	56	M	MPA	44	vasculitis
19	transverse colon	70	M	GPA	0	GCs in the setting of diverticulosis
1	sigmoid colon	72	M	GPA	45	GCs in the setting of diverticulosis
2	sigmoid colon	51	M	GPA	3	GCs in the setting of diverticulitis
4	sigmoid colon	55	M	EGPA	0	GCs, diverticulitis, and non-vasculitic hypoxemic respiratory failure
7	sigmoid colon	74	F	GPA	21	clostridium difficile colitis and GCs in setting of diverticulosis
20	sigmoid colon	72	F	GPA	18	GCs in setting of diverticulosis and recent ischaemic colitis from CAD
17	distal sig. colon	72	F	PAN	4	GCs in context of active diverticulitis and CMV colitis

Ant: anterior; Asc: ascending; BVAS: Birmingham Vasculitis Activity Score; CMV: cytomegalovirus; EGPA: eosinophilic granulomatosis with polyangiitis; GC: glucocorticoid; GI: gastrointestinal; GPA: granulomatosis with polyangiitis; MI: myocardial infarction; MPA: microscopic polyangiitis; PAN: polyarteritis nodosa; PEG: percutaneous endoscopic gastrostomy; ppx: prophylaxis; SMA: superior mesenteric artery.

7% of the non-vasculitis perforations (p=0.002). Patients with vasculitis-induced bowel perforation had a median of 41 days (range 11–56 days) of abdominal pain before the perforation occurred, which was significantly longer than patients with non-vasculitis perforation (p=0.005). Overall, laboratory parameters were similar among groups. Although diverticulosis was present in all of the large bowel perforations, it was only known prior to perforation in three of the eight non-vasculitis colon perforations.

Glucocorticoid use

All but one of the cases (no. 16) were on prednisone at the time of perforation, and glucocorticoids were implicated as a potential contributor in fourteen out of the sixteen non-vasculitis perforations (Table I). The median cumulative glucocorticoid dose prior to colon perforation in patients with at least one risk factor for perforation such as clostridium difficile infection, cytomegalovirus infection, ischaemia, trauma, or lack of prophylaxis (gastric and duodenal perforation), was 4.320 mg. In contrast, the median cumulative glucocorticoid dose prior to perforations in patients without such risk factors was 22,170 mg. A smaller cumulative dose of prednisone (approximately 1,500 mg) was necessary for perforation to occur in the colon, compared to approximately 4,000 mg for the other bowel locations.

Twelve cases received pulse dose glucocorticoids in the 12 weeks prior to perforation (Table II). Five patients in the IV-non-VI group received pulse glucocorticoids, one (case no. 4) empirically during hypoxemic respiratory failure, one (case no. 9) for initial concern of active EGPA, and three (cases

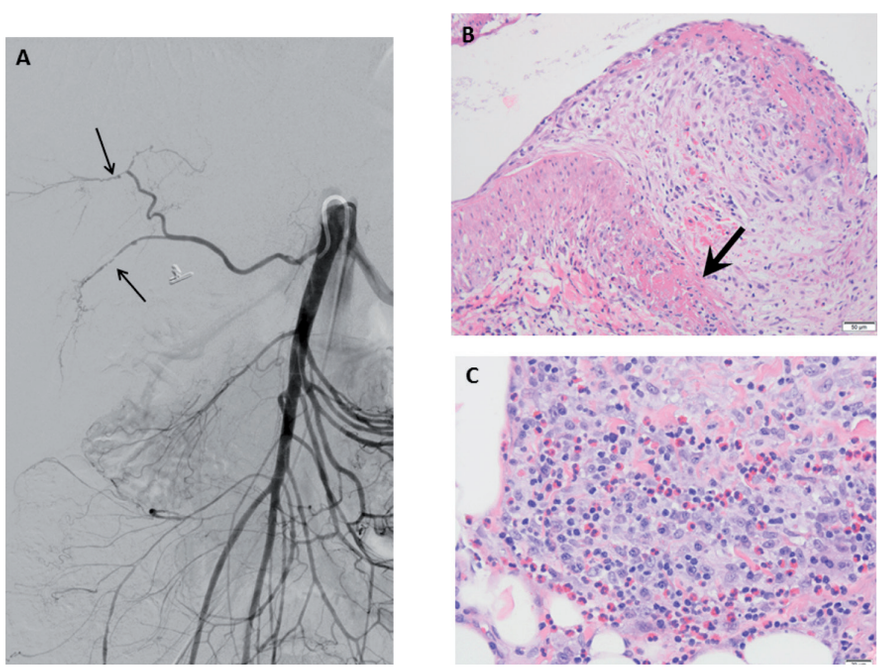

Fig. 1. Angiographic and histologic evidence of vasculitis-induced bowel perforation.
A: Conventional mesenteric angiogram of patient with polyarteritis nodosa (case no.14) demonstrating beaded narrowing and microaneurysms (thin arrows) of the right colic branch of the superior mesenteric artery. **B**: Pathology from small intestine (case no.15) showing a muscular artery with active vasculitis characterised by fibrinoid necrosis (thick arrow); **C**: inflammation with numerous eosinophils.

Table II. Characteristics of the study population by perforation type.

Characteristic	Number (%) or Median (IQR)			*p*-value
	Vasculitis-induced (n=4)	AV-non-VI (n=9)	IV-non-VI (n=7)	
Age (years)	44 (31,64)	72 (58,74)	75 (63,85)	0.07
Male sex	2 (50)	3 (33)	6 (85)	0.11
Vasculitis type				0.11
EGPA	1 (25)	0 (0)	2 (29)	
GPA	0 (0)	7 (78)	4 (57)	
MPA	1 (25)	1 (11)	1 (14)	
PAN	2 (50)	1 (11)	0 (0)	
Body Mass Index	26 (20,29)	24 (22,26)	21 (18,37)	0.82
Charlson Comorbidity Index	2 (2,3)	6 (4,7)	6 (5,9)	0.02
Tobacco use				0.04
Never	0 (0)	3 (33)	2 (28)	
Previous	1 (25)	4 (44)	5 (71)	
Current	3 (75)	1 (11)	0 (0)	
Alcohol use	1 (25)	3 (33)	5 (71)	0.29
NSAID use prior to perforation	1 (25)	3 (33)	0 (0)	0.25
GI prophylaxis at perforation	3 (75)	5 (56)	3 (43)	0.59
Diverticular disease known prior	1 (25)	4 (44)	2 (29)	0.72
Clostridium difficile	0 (0)	2 (22)	0 (0)	0.26
Days of preceding abdominal pain	41 (11,56)	1 (0,2)	0 (0,0)	0.007
Years from vasculitis onset	0.4 (0.2,6)	2 (1,3)	6 (0.3,11)	0.53
Years from vasculitis diagnosis	0.2 (0.1,5)	2 (0.2,2)	5 (0.2,11)	0.43
BVAS at diagnosis	25 (17,36)	19 (18,25)	22 (17,29)	0.80
FFS at diagnosis	2.5 (1.5,3.5)	2 (1,2)	1 (1,2)	0.40
BVAS at perforation	19 (7,36)	18 (6,21)	0	0.59
Pulse steroids within 12 weeks	2 (50)	5 (55)	5 (71)	0.73
Prednisone dose at perf (mg)	55 (25,70)	60 (50,60)	30 (10,40)	0.14
Cum. prednisone prior (g)	9 (4,12)	4 (4,11)	8 (4,22)	0.83
Cum. days of GC prior to perforation	54 (15,349)	84 (23,297)	102 (3,1902)	0.73
Haemoglobin, gm/dL	13 (8,14)	10 (9,13)	10 (8,12)	0.62
Eosinophils, x10^9/L	0 (0,0.4)	0 (0,0)	0 (0,0)	1.00
White blood cells, x10^9/L	12 (2,19)	12 (8,19)	10 (7,17)	0.92
Platelets, x10^9/L	316 (35,457)	229 (120,239)	194 (111,294)	0.75
ESR, mm/hr	15 (5,147)	43 (27,98)	17 (14,29)	0.24
CRP, mg/L	246 (229,372)	182 (132,189)	22 (3,41)	0.09
Creatinine, mg/dL	1.5 (0.8,1.7)	1.4 (1.2,2.5)	1.5 (0.9,2.4)	0.84
Lactate, mmol/L	1.9 (1.4,2.3)	1.9 (0.9,2.9)	1.0 (0.8,1.4)	0.44
INR	1.6 (1.3,1.6)	1.1 (1.0,1.1)	1.3 (1.1,1.4)	0.03

BVAS: Birmingham Vasculitis Activity Score; CRP: C reactive protein; EGPA: eosinophilic granulomatosis with polyangiitis; ESR: erythrocyte sedimentation rate; FFS: Five Factors Score; g: grams; GI: gastrointestinal; GPA: granulomatosis with polyangiitis; IQR: interquartile range; mg: milligrams; MPA: microscopic polyangiitis; NSAID: non-steroidal anti-inflammatory drug; PAN: polyarteritis nodosa; SD: standard deviation.

no. 5, 13, 18) for previously active vasculitis several weeks prior that had subsequently resolved by the time of perforation. The median number of days between steroid pulse and perforation date was somewhat higher among the IV-non-VI (54 days), than the AV-non-VI (10 days) and VI (11 days) groups, but this difference did not reach statistical significance (p=0.42).

Treatment and outcomes

In this study, the treating provider determined immunosuppressive treatment prior to and after the perforation. Four cases underwent major escalation of therapy, five continued at a major level, six continued at a minor level, and five underwent reduction in treatment. There was no discernable difference in number of surgeries, repeat perforation, vasculitis relapse, duration of glucocorticoid therapy or immunosuppression, or death among those four treatment groups (Table III). Although there was no standard approach to management of patients with vasculitis-induced bowel perforation, all four received either cyclophosphamide or rituximab and underwent surgery.

Median follow-up after perforation for the entire cohort was 3.5 years, and ten patients died during follow-up. The overall five-year survival was 53% (95% CI 32% to 88%, Fig. 2A). The expected number of deaths was 4.6, so the observed mortality rate was 2.19 times expected for similar adults from the United States (95% CI 1.05 to 4.02). In comparing the individual groups, there were five deaths compared with 4.2 expected in the IV-non-VI group (SMR: 1.19, 95% CI 0.39 to 2.79, Fig. 2B), and five deaths compared with 0.4 expected in the AV-non-VI group (SMR: 13.1, 95% CI 4.3 to 30.6, Fig. 2C). In the VI group, there were no deaths during the limited follow-up, precluding estimation of the SMR.

Outcomes were similar among groups, though the VI group tended to have more surgeries related to perforation and longer hospital stay after perforation, while the AV-non-VI group had the highest rate of relapse (Table IV). Repeat perforation occurred in only two cases (no. 4 and 18), both of whom belonged to the IV-non-VI group.

Discussion

This study identified several salient features associated with vasculitis-induced bowel perforation including small bowel location and longer abdominal pain duration. It also established the concept of a potential cumulative steroid perforation threshold that clinicians should strive to avoid. Finally, overall mortality was increased, highlighting the importance of a high index of suspicion and prompt management.

Currently, the diagnosis of vasculitis-induced bowel perforation rests on clinical, histological, and angiographic evidence. However, these parameters either separately or combined can at times be unclear and inconclusive. Indeed, histological evidence of vasculitis was present in only half of the cases with vasculitis-induced bowel perforation in this study. While many of the published case reports have histology consistent with vasculitis, the larger studies show a similarly low proportion of vasculitis on histology ranging from

Table III. Treatment decisions and outcomes by group.

ID	Group	Type	Prior Treatment	Treatment Decision	Subsequent treatment	no. of Surg	no. of Rlpse	Stopped GC	Stopped Immuno	Died	F/U (yrs)
12	VI	MPA	Pulse GC, RTX, PLEX	Continue at major level	continued pulse GC, PLEX, and RTX; surgery	3	0	No	Yes	No	0.1
14	VI	PAN	GC, MMF	Major escalation	loop ileostomy; pulse GC, MMF changed to CYC	5	0	Yes	Yes	No	1.1
15	VI	EGPA	GC, mepolizumab	Major escalation	Bowel pulse GC; bowel resection; re-dosed mepolizumab then changed to CYC 6 days later	2	0	No	Yes	No	0.3
16	VI	PAN	None	Major escalation	bowel resection; CYC and pulse GC 16 days later	1	0	No	No	No	0.1
1	AV-non-VI	GPA	GC, MTX	Reduction of treatment	colectomy; decreased GC, stopped MTX	2	0	Yes	N/A	No	3.5
2	AV-non-VI	GPA	GC, MMF	Continue at major level	sigmoidectomy; continued GC and MMF	2	2	Yes	Yes	No	15.9
6	AV-non-VI	MPA	GC, CYC	Continue at major level	surgery; continued GC, paused CYC x2 days	1	0	Yes	Yes	No	0.5
7	AV-non-VI	GPA	GC	Continue at minor level	surgery; continued GC	1	0	No	N/A	Yes	0.1
8	AV-non-VI	GPA	Pulse GC	Reduction of treatment	surgery; reduced GC	1	1	Yes	N/A	Yes	1.2
10	AV-non-VI	GPA	GC	Major escalation	bowel rest; pulse GC, RTX, PLEX	0	1	Yes	Yes	No	0.6
11	AV-non-VI	GPA	GC, RTX	Reduction of treatment	reduced GC, continued RTX; surgery five days later	1	0	No	No	Yes	0.2
17	AV-non-VI	PAN	GC	Continue at minor level	colostomy; continued GC	1	0	No	N/A	Yes	0.1
20	AV-non-VI	GPA	GC, CYC	Reduction of treatment	bowel rest then sigmoidectomy; reduced GC, stopped CYC	1	1	No	Yes	Yes	1.4
3	IV-non-VI	MPA	GC	Continue at minor level	bowel rest; continued GC	0	0	No	N/A	Yes	0.9
4	IV-non-VI	EGPA	GC	Continue at minor level	surgery; continued GC	1	0	Yes	N/A	Yes	8.4
5	IV-non-VI	GPA	GC, CYC	Continue at major level	laparoscopic repair; increased GC, held CYC x3 days then resumed	1	0	Yes	No	No	7.7
9	IV-non-VI	EGPA	MTX	Reduction of treatment	partial resection; held MTX	1	0		No	Yes	0.0
13	IV-non-VI	GPA	GC	Continue at minor level	cecal resection; continued GC	2	0	No	N/A	No	0.1
18	IV-non-VI	GPA	GC	Continue at minor level	surgery with Graham patch; continued GC	1	0	Yes	Yes	Yes	11.5
19	IV-non-VI	GPA	GC, MMF, cyclosporine	Continue at major level	hemicolectomy; continued GC and cyclosporine*	1	0	No	Yes	Yes	9.6

*Maintenance immunosuppression for prior renal transplant for end-stage renal disease secondary to GPA.
AV: active vasculitis; CYC: cyclophosphamide; EGPA: eosinophilic granulomatosis with polyangiitis; F/U: follow-up; GPA: granulomatosis with polyangiitis; GC: glucocorticoid; immuno: immunosuppression; IV: inactive vasculitis; MMF: mycophenolate mofetil; MPA: microscopic polyangiitis; MT: methotrexate; PAN: polyarteritis nodosa; PLEX: plasma exchange, rlpse: relapse; RTX: rituximab; surg: surgery; VI: vasculitis-induced; yrs: years.

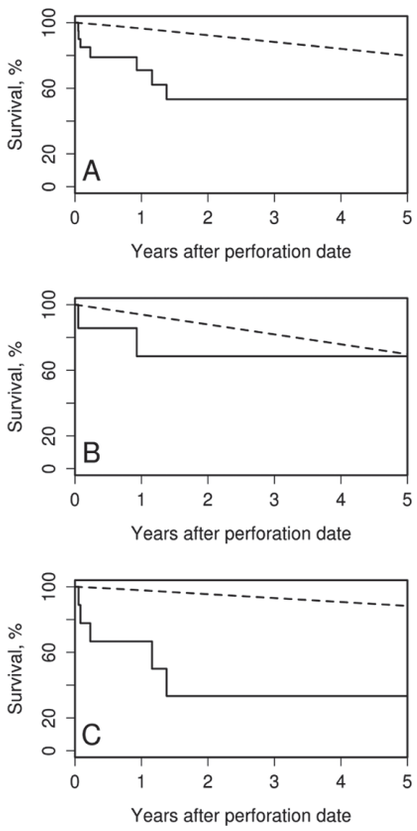

Fig. 2. Survival of patients with vasculitis and bowel perforation.
Survival of the vasculitis and bowel perforation cohort (solid line) compared to expected (dotted line) for (**A**) the entire cohort (n=20), (**B**) patients without active vasculitis at the time of perforation (n=7), and (**C**) patients with active vasculitis that was not the cause of perforation (n=9).

Table IV. Outcomes by perforation type.

Outcome	Median (IQR) or Number (rate per 100 py)			*p*-value
	Vasculitis-induced (n=4)	AV-non-VI (n=9)	IV-non-VI (n=7)	
Number of surgeries for perforation	2.5 (1.5,4)	1 (1,1)	1 (1,1)	0.06
Length of stay after perforation (days)	34 (25,75)	29 (21,36)	11 (5,34)	0.13
Recurrent perforation	0 (0)	0 (0)	2 (11)	0.84
Glucocorticoid discontinuation	1 (69)	5 (68)	3 (26)	0.80
Immunosuppression reduction	3 (504)	4 (198)	2 (12)	0.08
Number of relapses	0 (0)	4 (21)	0 (0)	0.007

AV: active vasculitis; IQR: interquartile range; IV: inactive vasculitis; py: person years; VI: vasculitis-induced.

43–75%. Storesund *et al*. note three out of seven (16), Levine *et al*. six out of eight (7), Pagnoux 18 out of 36 (3), and Eriksson two out of four (9). Vasculitis-related bowel resection may lack histological evidence of vasculitis for two reasons. First, if the vasculitis occurred proximally causing mesenteric thrombosis and distal bowel ischaemia, the resection specimen might only demonstrate patchy ischaemia, necrosis, or thrombosis. Second, a predominately necrotic specimen cannot be evaluated for vasculitis because viable tissue is absent. Given the low sensitivity of histology, a high index of suspicion is essential. Interestingly, three of the four cases in this report that occurred after 2014 were attributed to vasculitis. This recent clustering might represent coincidence, or alternatively, it might suggest higher awareness of vasculitis.

Importantly, this study showed that small bowel location of perforation and longer duration of abdominal pain might represent useful features for suggesting vasculitis-induced perforation. Vasculitis-induced perforation occurred between the small bowel and the cecum. Perforation in this location also appeared to be specific for vasculitis, as all cases of perforation between the small bowel and caecum resulted from vasculitis except one (case no. 13). Existing literature also suggests that vasculitis commonly involves the small bowel (17), and less commonly involves the colon (18). Interestingly, in four case reports of vasculitis-induced bowel perforation without preceding glucocorticoids (*i.e*. those where glucocorticoids could definitely not have contributed to perforation), three occurred in the small bowel and one in the caecum (19-22), a distribution identical to the cases in the current study.

Duration of abdominal pain prior to perforation was perhaps the most distinguishing feature between patients with vasculitis-induced and non-vasculitis induced perforation. Abdominal pain occurred simultaneously with perforation in the IV-non-VI group and approximately one day prior to perforation in the AV-non-VI group. However, in the VI group, the median duration between onset of abdominal pain and perforation was 41 days. Thus, the number of days of preceding abdominal pain may be a key diagnostic clue to the aetiology of perforation.

Several other characteristics varied amongst the groups. Tobacco use, especially active use, was also associated with vasculitis-induced perforation, though sample size was extremely limited. This finding reiterates the importance of tobacco cessation in all patients with vasculitis, especially those with bowel ischaemia or perforation. CCI was lowest in the VI group and highest in the AV-non-VI and IV-non-VI groups, suggesting a role of older age and higher comorbidity burden in non-vasculitic perforations. Time since vasculitis onset and diagnosis trended lower in the VI group (approximately three months) compared to the AV-non-VI (two years) and IV-non-VI (six years) groups, consistent with a prior observation that bowel manifestations of GPA usually occur within the first two years of disease (16). However, this factor may not be a reliable indicator in distinguishing the aetiology of perforation, as the differences were not significant, and one member of the VI group (case no. 15) had been diagnosed ten years prior to perforation. While the difference in International Normalised Ratio (INR) was statistically significant, it was not clinically significant.

This study provides further granularity regarding steroid use prior to perforations. The concept of glucocorticoid-induced bowel perforation gained greater understanding in the 1960s, with glucocorticoids being thought to thin the mucosal lining of the bowel wall and reduce its antimicrobial defenses, predisposing it to perforation (4, 5). If an outside factor such as critical illness caused both glucocorticoid use and perforation (an effect-effect relationship), then cases without pre-existing glucocorticoid use should also exist. In this study, the only case without pre-existing glucocorticoid use was one of the vasculitis-induced cases. In addition,

repeat perforation occurred in only two patients, who were both in IV-non-VI group. This may have occurred because glucocorticoid-induced thinning of the GI tract is more of a chronic and irreversible change compared to vasculitis, which can be potentially reversible with immunosuppression.

Bowel perforations in this study also appeared to occur above certain cumulative glucocorticoid dose thresholds. For patients with perforation risk factors such as ischaemia, infections, or lack of gastrointestinal mucosal prophylaxis, this threshold was approximately 5,000 mg prednisone. For those without such risk factors it was approximately 20,000 mg. Many of these non-vasculitis perforations occurred in the colon, of which all occurred at sites of colonic diverticula. However, history of diverticulosis was present in only three out of eight. Although colonic perforation is not commonly considered a glucocorticoid-associated adverse event, this study suggests that clinicians may need to pay particular attention to this potential complication. They should reduce cumulative glucocorticoid exposure whenever possible, even in patients without history of diverticulosis.

In this study, treatment before and after perforation varied widely, making conclusions about optimal treatment after perforation elusive. Treatment for glucocorticoid-induced perforation is straightforward and consists of glucocorticoid reduction both to address the underlying cause and promote wound healing. Maintenance treatment for systemic vasculitis is also well-defined (23, 24). However, the timing, intensity, and duration of treatment for vasculitis-induced perforation is less clear, specifically if surgery is required. In the current report, all four cases with perforation resulting from active vasculitis underwent surgery in combination with glucocorticoids and at least one immunosuppressive agent. Prior studies have recommended early surgical intervention (25, 26), which occurred in two out of four cases (no. 14 and 16). Other studies have also suggested increasing immunosuppression to reduce glucocorticoid burden and its associated effects on wound and surgical healing (17, 18, 20). While two cases received additional immunosuppressive agents (cases no. 15 and 16), none received immediate glucocorticoid reduction. In fact, three received pulse glucocorticoids after perforation. Unfortunately, this study was too small to evaluate the relationship between these therapeutic decisions and long-term outcomes.

In general, mortality among patients with vasculitis and bowel perforation was twice that of the general population. This finding is consistent with prior observations that bowel perforation is a serious complication that confers significant morbidity and mortality (2, 3). Mortality in the AV-non-VI group was particularly high. Although mortality could not be calculated in the VI group, the number of surgeries and length of stay trended higher in this subset.

Strengths of this study include the fact that it is the first large, single-institution cohort of patients with known ANCA-vasculitis or PAN and gastrointestinal perforation in which both the activity of the vasculitis and the aetiology of the perforation have been compared. Using a cohort derived from the past twenty years, its relatively recent cohort improves its generalisability compared to older cohorts. For example, older studies of bowel perforation and PAN included primarily HBV-induced PAN, which is now less common (3). Another strength is the detailed characterisation of prednisone usage, an associated potential factor in the aetiology of gastrointestinal perforation.

This study also has important limitations. First, its retrospective nature introduces selection bias and referral bias by only including patients at a large, tertiary medical centre for whom vasculitis or bowel perforation was known and charted. Second, only four of the twenty patients had perforation deemed conclusively due to vasculitis. This small sample size limits our ability to make definitive interpretations of these data. For example, while the VI group tended to have worse outcomes, none of the differences were statistically significant. Similarly, due to the small sample size, it is possible the observed significant differences such as the differences in location, pain duration, and tobacco may have been due to chance. Finally, follow-up of the VI group was limited, prohibiting conclusions about treatments or survival. Future studies should use a larger sample size to determine the optimal treatment, which still remains unclear. Separate, larger studies specifically evaluating the threshold for glucocorticoid-induced bowel perforation are also warranted, as high-dose glucocorticoids are commonly used in the management of several diseases.

In conclusion, bowel location and abdominal pain duration may help distinguish glucocorticoid-induced bowel perforation, the more common aetiology, from vasculitis-induced bowel perforation, the more hazardous aetiology.

References

1. ANDERSON E, GAKHAR N, STULL C, CAPLAN L: Gastrointestinal and Hepatic Disease in Vasculitis. *Rheum Dis Clin North Am* 2018; 44: 1-14.
2. GUILLEVIN L, LHOTE F, GAYRAUD M *et al*.: Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine* (Baltimore) 1996; 75: 17-28.
3. PAGNOUX C, MAHR A, COHEN P, GUILLEVIN L: Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. *Medicine* (Baltimore) 2005; 84: 115-128.
4. GLENN F, GRAFE WR, JR: Surgical complications of adrenal steroid therapy. *Ann Surg* 1967; 165: 1023-34.
5. MATOLO NM, GARFINKLE SE, WOLFMAN EF, JR: Intestinal necrosis and perforation in patients receiving immunosuppressive drugs. *Am J Surg* 1976; 132: 753-4.
6. MPOFU S, MPOFU CM, HUTCHINSON D, MAIER AE, DODD SR, MOOTS RJ: Steroids, non-steroidal anti-inflammatory drugs, and sigmoid diverticular abscess perforation in rheumatic conditions. *Ann Rheum Dis* 2004; 63: 588-590.
7. LEVINE SM, HELLMANN DB, STONE JH: Gastrointestinal involvement in polyarteritis nodosa (1986-2000): presentation and outcomes in 24 patients. *Am J Med* 2002; 112: 386-91.
8. ALIBAZ-ONER F, KOSTER MJ, CROWSON CS *et al*.: Clinical spectrum of medium-sized vessel vasculitis. *Arthritis Care Res* (Hoboken) 2017; 69: 884-91.
9. ERIKSSON P, SEGELMARK M, HALLBÖÖK O: Frequency, diagnosis, treatment, and outcome of gastrointestinal disease in granulomatosis with polyangiitis and microscopic polyangiitis. *J Rheumatol* 2018; 45: 529-37.

10. SALVARANI C, CALAMIA KT, CROWSON CS *et al*.: Localized vasculitis of the gastrointestinal tract: a case series. *Rheumatology* (Oxford) 2010; 49: 1326-35.
11. CHARLSON ME, POMPEI P, ALES KL, MACKENZIE CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373-83.
12. CHARLSON ME: Charlson Comorbidity Index: Chart review version. http://www.bgs.org.uk/pdfs/assessment/cci.pdf. Accessed Apr 9, 2018.
13. MUKHTYAR C, LEE R, BROWN D *et al*.: Modification and validation of the Birmingham Vasculitis Activity Score (version 3). 2009; 68: 1827-32.
14. SCHEMPER M, SMITH TL: A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; 17: 343-6.
15. JABS DA: Improving the reporting of clinical case series. *Am J Ophthalmol* 2005; 139: 900-5.
16. STORESUND B, GRAN JT, KOLDINGSNES W: Severe intestinal involvement in Wegener's granulomatosis: report of two cases and review of the literature. *Br J Rheumatol* 1998; 37: 387-90.
17. VENDITTI D, VALERIO B, IELPO B, BUONOMO O, PETRELLA G: Bowel perforations in a patient affected by Churg-Strauss syndrome under high-dose steroid treatment: will alternative drugs reduce risk of surgery? *Rheumatol Int* 2011; 31: 1239-41.
18. GUILLEVIN L, LHOTE F, GALLAIS V *et al*.: Gastrointestinal tract involvement in polyarteritis nodosa and Churg-Strauss syndrome. *Ann Med Interne* (Paris) 1995; 146: 260-7.
19. MELEK M, BEGER B, SIMSEK M, EPCACAN S, KOSEM M, EDIRNE Y: Polyarteritis nodosa with perforation of the cecum. *Turk J Gastroenterol* 2012; 23: 188-9.
20. IKOMA N, FISCHER UM, COVINSKY M *et al*.: Ileal perforation in a young female with Churg-Strauss syndrome. *Am Surg* 2014; 80: 94-6.
21. BULUS H, KOCAK E, YAVUZ A, AKKOCA M, COSKUN A, KOKLU S: Intestinal perforation as the initial presentation of Wegener's granulomatosis. *Rheumatol Int* 2013; 33: 2957-8.
22. SKAIFE P, LEE S, RAMADWAR M, MAITRA D, EDWARDSON KF: Intestinal perforation as a presentation of Wegener's granulomatosis. *Hosp Med* 2000; 61: 286-7.
23. GUILLEVIN L: Maintenance treatment of ANCA-associated vasculitides. *Clin Exp Rheumatol* 2017; 35 (Suppl. 103): S199-201.
24. ELEFANTE E, MONTI S, BOND M *et al*.: One year in review 2017: systemic vasculitis. *Clin Exp Rheumatol* 2017; 35 (Suppl. 103): S5-26.
25. YILDIRIM AC, KOCAK E, YILDIZ P *et al*.: Multiple intestinal perforation in a patient with Wegener's granulomatosis: a case report and review of the literature. *Gastroenterol Clin Biol* 2010; 34: 712-5.
26. YOSHIYA K, IMAMURA Y, NAKAJI Y *et al*.: Successful surgical intervention for rectal perforation due to polyarteritis nodosa: report of a case. *Surg Case Rep* 2017; 3: 43.