Open repair of abdominal aortic aneurysms in patients with vascular Ehlers-Danlos syndrome

James M. Dittman, MD,[a] Nallely Saldana-Ruiz, MD, MPH,[a] Karina Newhall, MD,[b] Peter H. Byers, MD,[c] Benjamin W. Starnes, MD, FACS,[a] *and* Sherene Shalhub, MD, MPH, FACS DFSVS,[a,d] *Seattle, WA; Rochester, NY; and Portland, OR*

ABSTRACT

Vascular Ehlers-Danlos syndrome (VEDS) is rare, affecting an estimated 1 per 50,000 individuals, and is associated with abdominal aortic aneurysms (AAAs), among other arteriopathies. We present three patients with genetically confirmed VEDS who underwent successful open AAA surgical repair and demonstrate that elective open AAA repair with careful tissue manipulation is safe and feasible for patients with VEDS. These cases also demonstrate that the VEDS genotype is associated with the aortic tissue quality (genotype—surgical phenotype correlation), with the most friable tissue encountered in the patient with a large amino acid substitution and the least friable tissue in the patient with a null (haploinsufficiency) variant. (J Vasc Surg Cases Innov Tech 2023;9:1-6.)

Keywords: Abdominal aortic aneurysm; COL3A1; Connective tissue disorder; Genetic aortopathy; Vascular Ehlers-Danlos syndrome

Vascular Ehlers-Danlos syndrome (VEDS) is a rare connective tissue disorder due to pathogenic variants in *COL3A1*, leading to defective or reduced type III collagen production.[1-6] Abdominal aortic aneurysms (AAAs) occur in 12% to 29% of patients with VEDS.[7-9] Surgical repair is associated with a high degree of morbidity and mortality in this population due to the decreased arterial wall tensile strength and inability to control hemorrhage.[2,7,10] Some have advocated avoiding elective repairs and operating only in the setting of life-threatening hemorrhage.[2,7,11] Contemporary data have demonstrated AAA repair can be performed safely.[8,9,12] We present elective open surgical repair for infrarenal AAA of three patients with genetically confirmed VEDS between 2020 and 2022 and describe our surgical technique and outcomes (Figs 1-3). The case series is approved by the University of Washington institutional review board and as part of the VEDS collaborative research study.[13]

OPERATIVE TECHNIQUE AND OUTCOMES

Preoperative medical optimization included 1 to 2 g of vitamin C daily and a beta-blocker and/or losartan.[14] We routinely instruct our patients with VEDS to take vitamin C because of anecdotal evidence of reduced bruising when vitamin C is taken. All three patients underwent general anesthesia, invasive blood pressure monitoring via a radial arterial line, and placement of a Foley catheter and received prophylactic antibiotics. The most experienced anesthesiologist available was engaged to obtain arterial and venous access during these cases. The operative blood pressure goals were to maintain a systolic blood pressure between 90 and 120 mm Hg and to avoid hypertension during aortic clamping. Cell saver and blood products were available. Admission to the intensive care unit (ICU) postoperatively was planned.

The abdominal aorta was exposed via a midline laparotomy from the xiphoid to the pubis. An Omni retractor was used to provide exposure, with deliberate and careful application of gentle pressure and padding of the retraction blades with laparotomy pads used as a cushion between each blade and the tissues. The transverse colon and small bowel were carefully mobilized (given anecdotal reports of iatrogenic finger perforation of the intestines with mobilization). The subcutaneous

From the Division of Vascular Surgery, Department of Surgery, University of Washington, Seattle[a]; the Division of Vascular Surgery, Department of Surgery, University of Rochester, Rochester[b]; the Department of Laboratory Medicine and Pathology, University of Washington, Seattle[c]; and the Division of Vascular and Endovascular Surgery, Department of Surgery, Oregon Health & Science University, Portland.[d]

This work was partially funded by gifts to the VEDS Collaborative Research Study by the Adventuresinlove4Andie Memorial Fund, Bella's Fight for Cure, the DEFY Foundation, the Lauren Tenney Memorial Fund, funds in memory of John DeMasi, the Semanoff family, the VEDS Warriors Unite, and the Women & Infants Hospital of Rhode Island neonatal intensive care unit registered nurses, among many others who generously gifted funds to support VEDS research.

Author conflict of interest: none.

Presented in part (patient 3) at the Pacific Northwest Endovascular Conference Simulation Summit, May 26-27, 2022, Seattle, WA, and the Marfan Foundation E3 Conference, July 7-10, 2022, Newport Beach, CA.

Correspondence: Sherene Shalhub, MD, MPH, FACS, Division of Vascular and Endovascular Surgery, Oregon Health & Science University Heart and Vascular Service Line, Departments of Surgery and Molecular and Medical Genetics, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Mail Code OP11, Portland, OR 97239 (e-mail: Shalhub@ohsu.edu).

The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2468-4287

https://doi.org/10.1016/j.jvscit.2023.101194

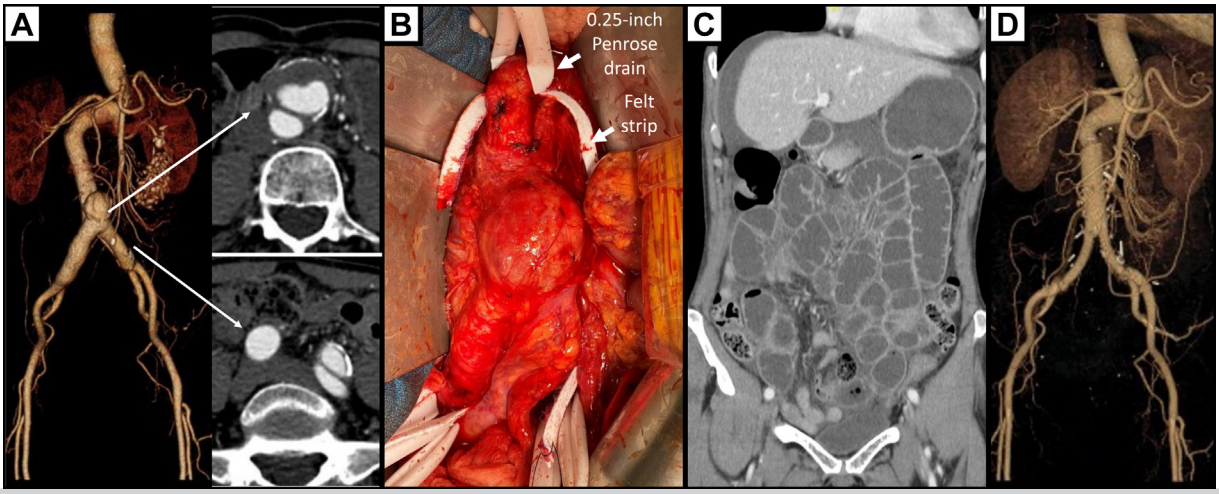

Fig 1. A 64-year-old woman with vascular Ehlers-Danlos syndrome (VEDS; *COL3A1* **C**.2200 C>A, p.Leu734Ile, functionally null variant). **A,** Three-dimensional postprocessing images of a computed tomography angiography examination demonstrating the infrarenal abdominal aortic aneurysm (AAA) and bilateral common iliac artery aneurysms with corresponding axial imaging sections. **B,** Intraoperative photograph demonstrating exposure of the AAA and right common iliac artery aneurysms. **C,** Coronal computed tomography image demonstrating dilated loops of small intestine. **D,** Three-dimensional postprocessing image of a computed tomography angiography examination demonstrating the aorto-bi-iliac bifurcated Dacron graft repair.

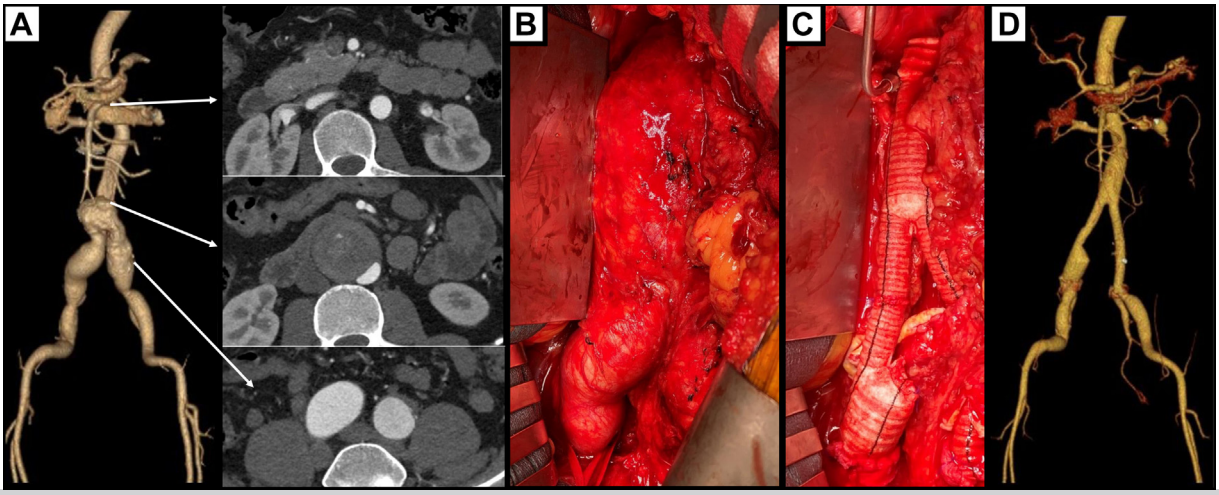

Fig 2. A 45-year-old man with vascular Ehlers-Danlos syndrome (VEDS; *COL3A1* **C**.1347+1delG, exon skip). **A,** Three-dimensional postprocessing images of a computed tomography angiography examination demonstrating the infrarenal abdominal aortic aneurysm (AAA) and bilateral common iliac artery aneurysms with corresponding axial imaging sections. **B,** Intraoperative photograph demonstrating exposure of the AAA and right common iliac artery aneurysms. **C,** Intraoperative photograph demonstrating interposition bifurcated aorto-bi-iliac 16 × 8-mm Dacron graft with a felt-reinforced anastomosis to the right common iliac artery using a flipped 16-mm limb from a second 16 × 8-mm Dacron graft to accommodate the right common iliac artery bifurcation. **D,** Three-dimensional postprocessing image of a computed tomography angiography examination demonstrating the aorto-bi-iliac bifurcated Dacron graft repair with the flared limb to the right common iliac artery.

adipose tissue and retroperitoneal fat and lymphatics were excessively fragile and bled easily. These tissues were dissected carefully and gently ligated as needed. The proximal neck of the infrarenal aorta was circumferentially dissected so that it could be wrapped circumferentially with a felt wrap when performing the proximal anastomosis. After the dissection, the proximal neck was circumferentially encircled with 0.25-in. Penrose drain (Fig 4) rather than umbilical tape or a vessel loop. A Penrose drain was chosen for two reasons: (1) to

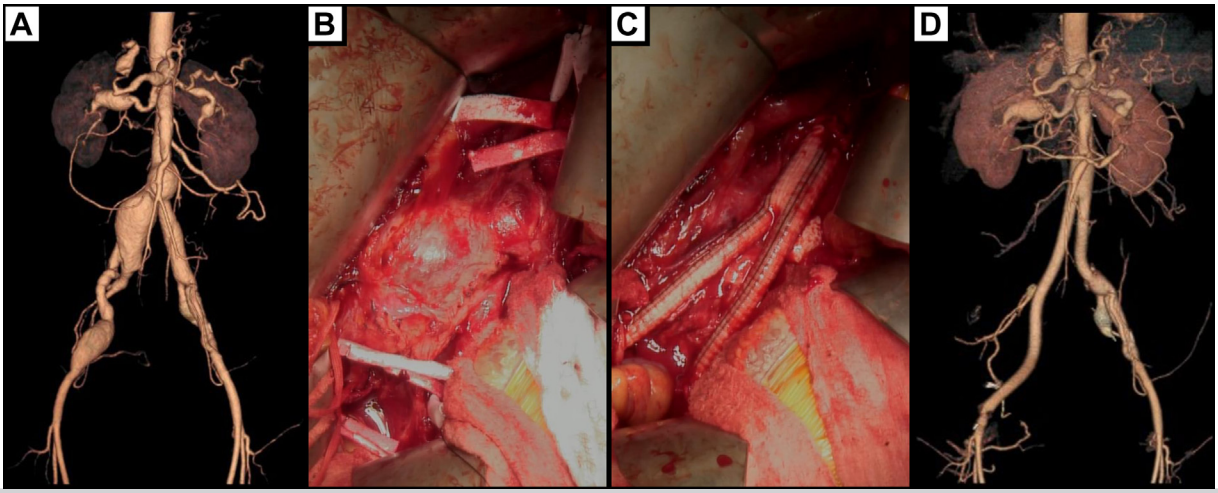

Fig 3. A 38-year-old woman with vascular Ehlers-Danlos syndrome (VEDS: *COL3A1* c.718 G>C, p.Gly240Arg, missense variant). **A,** Three-dimensional postprocessing image of a computed tomography angiography examination demonstrating the abdominal aorta with an infrarenal abdominal aortic aneurysm (AAA), 3.7-cm right common iliac and external iliac artery aneurysms, and celiac, hepatic, superior mesenteric, and bilateral renal artery aneurysms. **B,** Intraoperative photograph demonstrating exposure of the AAA and right common iliac artery aneurysm. **C,** Dacron graft after repair. **D,** Three-dimensional postprocessing image of a computed tomography angiography examination demonstrating the aortic—right common femoral artery and left common iliac artery bifurcated Dacron graft and ligation of the right internal iliac artery origin.

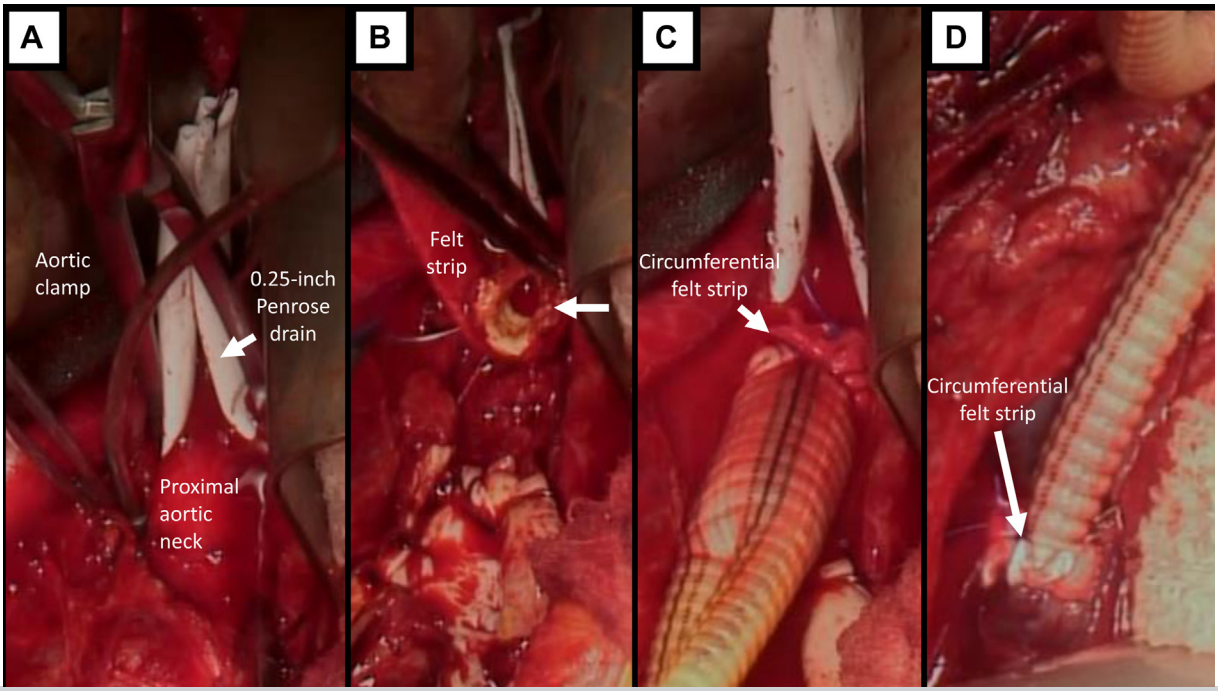

Fig 4. Intraoperative images demonstrating technical considerations during open abdominal aortic aneurysm (AAA) repair in patients with vascular Ehlers-Danlos syndrome (VEDS). **A,** Placement of a 0.25-in. Penrose drain around the proximal neck of the aorta to serve as a broad-based handle and padding for aortic clamp placement. **B,** Transected aortic neck (*arrow*) and felt strip. **C,** Completed proximal anastomosis with a circumferential felt strip. **D,** Completed distal left common iliac artery anastomosis with a circumferential felt strip.

distribute the force over a broader surface area, given reports of iatrogenic arterial transection with vessel loops; and (2) to provide padding at the site of aortic clamp placement. The common iliac arteries were also exposed, dissected circumferentially, and encircled with 0.25-in. Penrose drains.

Before clamping, systemic heparin was administered for a goal activated clotting time of >200 IU/kg (typically, 50-70 IU/kg). After aortic cross-clamping, the aneurysm sac was opened, and back bleeding lumbar arteries were ligated with 2-0 silk sutures, with gentle landing of the knots to avoid tearing the back wall. The proximal anastomosis was performed end to end, with felt wrapping of the transected aneurysm neck using 3-0 Prolene suture.[12] The circumferential felt wrap was used to reinforce against the arterial fragility. The iliac anastomosis was also performed end to end with circumferential felt reinforcement using 4-0 Prolene suture. The rest of the operation was conducted in the typical fashion. The abdomen was then closed with running 0-looped polyglyconate (Maxon; Medtronic) sutures and the skin with staples.

For patient 3, three variations during the repair were encountered and/or performed. First, this patient's *COL3A1* variant was a large amino acid substitution, and we predicted that we would encounter excessive tissue fragility based on her personal history and known literature suggestive of a more severe phenotype of VEDS with large amino acid substitutions.[15] Thus, the operation was started with exposure of the right common femoral artery (CFA) to evaluate the tissue integrity, and once deemed satisfactory, the procedure ensued. CFA exposure was needed for the repair because she had a 3.7-cm right external iliac artery requiring repair. If the CFA tissue had appeared too fragile for repair, the plan was to cancel the operation. This was based on historical fears that the tissue could not "hold" suture.[7] Second, the right internal iliac artery origin was transected and ligated with interrupted 5-0 Prolene sutures over pledgets after being clamped using a Wylie hypogastric clamp over a 0.25-in. Penrose drain. Also, the iliac limb on that side was tunneled anatomically deep to the right inguinal ligament overlaying the distal external iliac artery to perform an end-to-end anastomosis to the CFA with circumferential felt reinforcement using 5-0 Prolene suture. The ureter was identified, mobilized, and protected to prevent injury. Third, adhesions were present between the left common iliac artery and vein, leading to an ~2-cm longitudinal tear in the vein requiring initial control with digital pressure, proximal and distal pressure with cherry sponge sticks, and primary repair with interrupted pledgeted 4-0 Prolene sutures. This contributed to a significant portion of the 6000-mL estimated blood loss. Although our approach to avoid injury to the iliac veins involves careful dissection of the iliac artery off the vein, these dense distal adhesions did not become apparent until the iliac artery had been further mobilized during clamping.

The patients were admitted to the ICU. Patients 1 and 2 were extubated in the operating room, and patient 3 was extubated after transfer to the ICU on the evening of the operation. Intravenous fluid resuscitation was tailored to 0.5 mL/kg/h to avoid over-resuscitation. Systolic blood pressure was maintained between 90 and 120 mm Hg. Intravenous vitamin C was administered (1 g twice daily).

Postoperative follow-up ranged from 7 to 26 months (Table). Patient 1 returned at 1 month after discharge with a small bowel obstruction. This was resolved with nonoperative management of bowel rest and nasogastric tube decompression. None of the patients developed incisional hernias, anastomotic pseudoaneurysms, or new arterial aneurysms or dissections for the duration of follow-up.

DISCUSSION

Open repair is the preferred approach for patients with connective tissues disorders, including VEDS. We have described specific operative technique modifications for open surgical repair of infrarenal AAAs in patients with VEDS. These cases highlight several points. First, AAA elective repair can be performed safely in patients with VEDS.[8,9] Elective surgery is anticipated to have superior outcomes than waiting for rupture to occur before offering repair. It is well established that elective AAA repair has superior outcomes to repair of ruptured AAAs for all patients, and those with VEDS should not be the exception.[16]

Second, the aortic tissue quality is dependent on the underlying *COL3A1* variant type, thus demonstrating a genotype–surgical phenotype correlation. The most friable aorta was encountered in the patient with the large amino acid substitution and the least friable aorta in the patient with the null (haploinsufficiency) variant. This finding is consistent with the natural history of VEDS in which clear variations exist in the phenotype and survival according to the underlying variant type, with null *COL3A1* variants associated with the mildest clinical phenotype.[4,8] On a practical level, understanding the type of *COL3A1* variant can help with preoperative surgical planning and anticipating the quality of the tissue to be encountered.

To address the lack of tissue tensile strength, we recommend circumferentially reinforcing the proximal and distal anastomoses with felt strips during the repair to support the integrity of the anastomoses or pledgeted repairs should single suture repairs be needed.[12] Additional repair techniques include gentle tissue retraction, avoiding excessive tissue manipulation, using atraumatic or padded clamps or, as we demonstrated, using Penrose drains as padding during clamping commitment with clamp placement and avoiding repeated clamp applications, avoiding the use of vessel loops and/or umbilical tape, and not using intraoperative hypertension.[12] The availability of cell saver and blood products with the anticipation of the possible need for a massive transfusion is imperative because transfusions are required in 38% of open AAA repair in the general population and patients with VEDS are at increased risk of bleeding.[17-19]

Table. Clinical patient characteristics and operative details

Pt. No.	Sex	Age at AAA repair; AAA diagnosis; and VEDS diagnosis, years	*COL3A1*	Family history	Other arteriopathy	Indication for repair	Repair configuration	EBL, mL	Length of stay, days	Follow-up, months
1	Female	64; 58; 58	c.2200 C>A; p.Leu734* (null variant)	Yes	Left common iliac artery dissection	Symptomatic infrarenal 40-mm saccular AAA with dissection (Fig 1, *A*)	Aorto-bi-iliac 16 × 8-mm bifurcated Dacron graft (Fig 1, *B* and *D*)	1800	7	26
2	Male	45; 38; 38	c.1347+1delG (exon skip)	No	Bilateral CIA aneurysms (25 mm); left renal artery aneurysm (12 mm)	Infrarenal 53 mm AAA with dissection (Fig 2, *A*)	Aorto-bi-iliac 16 × 8-mm bifurcated Dacron graft with 16-mm limb to right CIA (Fig 2, *B-D*)	1000	7	15
3	Female	38; 26; 15	c.718 G>C; p.Gly240Arg (missense, glycine substitution)	Yes	Carotid cavernous fistula, spontaneous hemoperitoneum with cardiac arrest, visceral aneurysms, right CIA aneurysm with dissection (37 mm), right external iliac artery aneurysm (37 mm)	37-mm External iliac artery aneurysm; AAA (35 mm; Fig 3, *A*)	Aortic–right CFA and left CIA 16 × 8-mm bifurcated Dacron graft; ligation of right internal iliac artery origin (Fig 3, *B-D*)	6000	15	7

AAA, Abdominal aortic aneurysm; *CFA*, common femoral artery; *CIA*, common iliac artery; *EBL*, estimated blood loss.

Finally, a multidisciplinary team approach to perioperative care is essential for successful repair. This includes perioperative education regarding VEDS presentations with the care teams, careful invasive catheter placement, judicious postoperative fluid resuscitation, avoidance of postoperative hypertension, and monitoring for VEDS-related complications, including postoperative bleeding, intestinal perforation, and pneumothorax.[6,17]

Knowledge of the VEDS diagnosis allows for the team approach in care and is thought to contribute to improved outcomes.[6,8] Although we focused on the technical aspects of AAA repair, data from the longitudinal VEDS natural history study (VEDS collaborative research study) on the outcomes of AAA repair in a larger cohort are forthcoming.[13]

CONCLUSIONS

Open AAA repair for patients with VEDS is feasible in the setting of a known diagnosis, knowledge of the *COL3A1* variant, modification of the surgical technique to support the lack of aortic and arterial tissue tensile strength, and use of multidisciplinary perioperative team approach. These cases demonstrate a genotype–surgical phenotype correlation in VEDS and add to our growing understanding of surgical repair options for this population.

REFERENCES

1. Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet 2017;175:8-26.
2. Eagleton MJ. Arterial complications of vascular Ehlers-Danlos syndrome. J Vasc Surg 2016;64:1869-80.
3. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med 2000;342:673-80.
4. Schwarze U, Schievink WI, Petty E, Jaff MR, Babovic-Vuksanovic D, Cherry KJ, et al. Haploinsufficiency for one COL3A1 allele of type III procollagen results in a phenotype similar to the vascular form of Ehlers-Danlos syndrome, Ehlers-Danlos syndrome type IV. Am J Hum Genet 2001;69:989-1001.
5. Shalhub S, Byers PH, Hicks KL, Coleman DM, Davis FM, De Caridi G, et al. A multi-institutional experience in vascular Ehlers-Danlos syndrome diagnosis. J Vasc Surg 2020;71:149-57.
6. Oderich GS, Panneton JM, Bower TC, et al. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. J Vasc Surg 2005;42:98-106.
7. Shalhub S, Black JH 3rd, Cecchi AC, et al. Molecular diagnosis in vascular Ehlers-Danlos syndrome predicts pattern of arterial involvement and outcomes. J Vasc Surg 2014;60:160-9.
8. Shalhub S, Byers PH, Hicks KL, et al. A multi-institutional experience in the aortic and arterial pathology in individuals with genetically confirmed vascular Ehlers-Danlos syndrome. J Vasc Surg 2019;70:1543-54.
9. Freeman RK, Swegle J, Sise MJ. The surgical complications of Ehlers-Danlos syndrome. Am Surg 1996;62:869-73.

10. Benrashid E, Ohman JW. Current management of the vascular subtype of Ehlers-Danlos syndrome. Curr Opin Cardiol 2020;35:603-9.
11. Brooke BS, Arnaoutakis G, McDonnell NB, Black JH 3rd. Contemporary management of vascular complications associated with Ehlers-Danlos syndrome. J Vasc Surg 2010;51:131-8; discussion: 8-9.
12. Sage L, Russo ML, Byers PH, et al. Setting a research agenda for vascular Ehlers-Danlos syndrome using a patient and stakeholder engagement model. J Vasc Surg 2020;72:1436-44.e2.
13. Frank M, Adham S, Seigle S, et al. Vascular Ehlers-Danlos syndrome: long-term observational study. J Am Coll Cardiol 2019;73:1948-57.
14. Frank M, Albuisson J, Ranque B, et al. The type of variants at the COL3A1 gene associates with the phenotype and severity of vascular Ehlers-Danlos syndrome. Eur J Hum Genet 2015;23:1657-64.
15. Zettervall SL, Soden PA, Buck DB, et al. Significant regional variation exists in morbidity and mortality after repair of abdominal aortic aneurysm. J Vasc Surg 2017;65:1305-12.
16. Malfait F, De Paepe A. Bleeding in the heritable connective tissue disorders: mechanisms, diagnosis and treatment. Blood Rev 2009;23:191-7.
17. Osborne Z, Hanson K, Brooke BS, et al. Variation in transfusion practices and the association with perioperative adverse events in patients undergoing open abdominal aortic aneurysm repair and lower extremity arterial bypass in the vascular quality initiative. Ann Vasc Surg 2018;46:1-16.
18. Carless PA, Henry DA, Moxey AJ, O'Connell DL, Fergusson DA. Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2003;4:CD001888.
19. Byers PH, Belmont J, Black J, et al. Diagnosis, natural history, and management in vascular Ehlers-Danlos syndrome. Am J Med Genet C Semin Med Genet 2017;175:40-7.

Submitted Nov 28, 2022; accepted Apr 10, 2023.