

Title: The Incidence of Venous Thromboembolism in Children Following Colorectal Resection for Inflammatory Bowel Disease: A Multi-Center Study

Authors: Christina M. Bence ^a, Michael D. Traynor, Jr. ^b, Stephanie F. Polites ^b, Derrick Ha ^c, Pete Muenks ^d, Shawn D. St. Peter ^d, Matthew P. Landman ^e, John C. Densmore ^a, D. Dean Potter, Jr. ^{b,*}

Affiliations

^a Division of Pediatric Surgery, Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, USA

^b Division of Pediatric Surgery, Department of Surgery, Mayo Clinic, Rochester, MN, USA

^c Kansas City University of Medicine and Biosciences, Kansas City, MO, USA

^d Division of Pediatric Surgery, Department of Surgery, Children's Mercy Hospital, Kansas City, MO, USA

^e Division of Pediatric Surgery, Department of Surgery, Indiana University School of Medicine, Indianapolis, IN, USA

*Corresponding Author

D. Dean Potter, Jr., MD

Mayo Clinic

200 First Street SW

Rochester, MN 55905

Phone: (507) 284-8391

Fax: (507) 284-0058

Potter.d@mayo.edu

This is the author's manuscript of the article published in final edited form as:

Bence, C. M., Traynor Jr, M. D., Polites, S. F., Ha, D., Muenks, P., Peter, S. D. S., ... & Potter Jr, D. D. (2020). The Incidence of Venous Thromboembolism in Children Following Colorectal Resection for Inflammatory Bowel Disease: A Multi-Center Study. *Journal of Pediatric Surgery*. <https://doi.org/10.1016/j.jpedsurg.2020.02.020>

Abstract

Background/Purpose

Children with inflammatory bowel disease (IBD) have increased risk for venous thromboembolism (VTE). We sought to determine incidence and risk factors for postoperative VTE in a multicenter cohort of pediatric patients undergoing colorectal resection for IBD.

Methods

Retrospective review of children ≤ 18 yrs who underwent colorectal resection for IBD from 2010-2016 was performed at four children's hospitals. Primary outcome was VTE that occurred between surgery and last follow-up. Factors associated with VTE were determined using univariable and multivariable analyses.

Results

Two-hundred-and-seventy-six patients were included with median age 15 yrs [13,17]. Forty-two children (15%) received perioperative VTE chemoprophylaxis, and 88 (32%) received mechanical prophylaxis. DVT occurred in 12 patients (4.3%) at a median of 14 days postoperatively [8,147]. Most were portomesenteric (n=9, 75%) with the remaining catheter-associated DVTs in extremities (n=3, 25%). There was no association with chemoprophylaxis ($p>0.99$). On Cox regression, emergent procedure [HR 18.8, 95%CI: 3.18-111], perioperative plasma transfusion [HR 25.1, 95%CI: 2.4-259], and postoperative infectious complication [HR 10.5, 95%CI: 2.63-41.8] remained predictive of DVT.

Conclusion

Less than 5% of pediatric IBD patients developed postoperative VTE. Chemoprophylaxis was not protective but rarely used. Patients with risk factors identified in this study should be monitored or given prophylaxis for VTE.

Key Words: Inflammatory bowel disease; deep venous thrombosis; pediatric surgery; colectomy

Level of Evidence: Treatment Study, Level III

1. Introduction

Inflammatory bowel disease (IBD) is a known risk factor for venous thromboembolism (VTE) in adults, and national guidelines exist that direct chemoprophylaxis in this population [1,2]. Pediatric patients with IBD have also been shown to have increased incidence of VTE (deep venous thrombosis, DVT or pulmonary embolism, PE), though the data is less robust [3,4]. A recent review of the Kids' Inpatient Database demonstrated a 1% incidence of DVT in pediatric patients hospitalized with IBD, and the odds were twice as high for patients undergoing a major surgical procedure [4]. Similarly, in adult patients with IBD the risk of developing a VTE is as high as 2-3% following abdominal surgery.

The American College of Gastroenterology recommends chemical VTE prophylaxis in adults admitted with acute severe ulcerative colitis (UC) or during disease flares [1]. Currently there are no consensus guidelines for VTE prophylaxis in the pediatric population, and practice varies. VTE prophylaxis recommendations have been published for pediatric trauma patients, which generally support chemical prophylaxis in patients deemed to be high risk due to factors such as central line placement, prolonged immobilization, traumatic brain injury, and high injury severity score [5-7]. Similarly, the Association of Paediatric Anaesthetists of Great Britain and Ireland recently published practice guidelines for perioperative VTE prevention in pediatric surgical patients [8]. Their risk score includes a number of patient- and admission-related factors associated with VTE, and recommends considering perioperative chemoprophylaxis if >2 factors are present and bleeding risk is low. While one risk factor listed is an underlying inflammatory condition, it does not specifically account for acute IBD flare occurring in the setting of intra-abdominal operation.

Based on the paucity of relevant, patient-level data available to guide decision-making regarding VTE prophylaxis in pediatric patients undergoing surgery for IBD, we sought to determine the incidence of and risk factors for postoperative VTE in a multi-center cohort of pediatric patients. Further, we

wanted to evaluate current perioperative VTE prophylaxis practices and their impact on postoperative VTE rate.

2. Methods

2.1 *Study design*

A retrospective review of patients who underwent major colorectal surgery for IBD at four tertiary care children's hospitals was performed following IRB approval. All patients ≤ 18 years of age who underwent colon or rectal resection (procedure name including colectomy, proctectomy, ileocecectomy, or ileal pouch-anal anastomosis) for a diagnosis of Crohn disease (CD), ulcerative colitis (UC), or indeterminate colitis (IC) between January 2010 and June 2016 were included in the study. Exclusion criteria were procedures limited to the small bowel and perianal procedures. Patients were identified using diagnostic and procedure codes at each institution and eligibility was confirmed via review of the medical record.

2.2 *Data collection*

Demographic data were collected that included patient age, sex, IBD diagnosis, and any history of hypercoagulable state such as smoking, current oral contraceptive (OCP) use, sickle cell disease, personal cancer history, personal history of VTE, and known thrombophilia. Preoperative characteristics included duration of IBD symptoms, days in the hospital prior to the procedure, presence of a central venous catheter (CVC), parenteral nutrition (PN) administration, laboratory values within 30 days of the operation (hemoglobin, albumin, c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), red blood cell (RBC) transfusion within 14 days prior to the operation, and current medical therapy for IBD (corticosteroids, biologic therapy, and/or immunologic therapy).

Procedure type, acuity, operative time, perioperative blood product administration, and perioperative use of mechanical and/or chemical VTE prophylaxis were collected. Procedures were documented as laparoscopic (meaning all or a major portion of the operation was completed laparoscopically) or open (started as or immediately converted to a laparotomy). Postoperative variables

of interest included complications, hospital length of stay (LOS), intensive care unit (ICU) admission, and date of last known follow-up. The primary outcome was diagnosis of VTE (DVT or PE) at any point between surgery and last known follow-up. For those patients diagnosed with a postoperative VTE, pertinent details related to the diagnosis were also recorded including location of the thrombus, perioperative timing, whether the thrombus was symptomatic or diagnosed incidentally, association with a catheter or line, treatment, and time to resolution.

2.3. Statistical Analysis

Patient characteristics and outcomes were described through summary statistics, using median with interquartile range for continuous variables and frequency (%) for categorical variables. To analyze comparative data, Fisher's exact test was used for categorical variables and Wilcoxon rank-sum for continuous variables. We used a priori knowledge regarding risk factors for VTE to create a model using multivariable time-dependent analysis (Cox regression). Variables with p-value <0.2 on univariable analysis were included in a Cox regression model to calculate the adjusted hazard ratio and 95% confidence interval for VTE diagnosis after colorectal surgery in IBD. As one institution was missing data for a number of significant variables, these patients were excluded from the regression analysis. Further, variables with missing data that significantly affected the number of VTEs included in the model or that demonstrated collinearity with other included variables were excluded from the regression analysis. The excluded factors were preoperative laboratory values (albumin, CRP, ESR, and hemoglobin) and perioperative transfusion of RBCs or platelets. A p-value of < 0.05 was considered significant.

3. Results

3.1. Demographics and preoperative characteristics

A total of 276 patients were included in this study over a five-year period, with an overall 4.3% incidence of DVT diagnosed between the operation and date of last follow-up. There were no PEs diagnosed during the study period. On univariable analysis there were no significant differences in patient

age (median age 15 years, $p = 0.23$) or gender (54% female, $p = 0.24$) between those patients diagnosed with a DVT and those that were not (**Table 1**). Overall 134 patients (48.5%) had a diagnosis of UC, 125 (45.3%) a diagnosis of CD, and 17 (6.2%) a diagnosis of indeterminate colitis (IC), and though there was a trend toward UC being associated with a higher risk of DVT it was not statistically significant (58.3% vs 48.1%, $p = 0.12$). There were no differences in history of hypercoagulable state including smoking status, oral contraceptive use, known thrombophilia, or prior VTE, however the frequency of all of these factors combined was low (12%). Further, only one patient had a history of sickle cell disease and no patients had a personal history of cancer. Duration of disease was also not associated with the development of DVT (median duration 19.5 months, $p = 0.28$). Patients who received a preoperative RBC transfusion within 14 days of their operation did have a significantly higher incidence of postoperative DVT (50% vs 19.1%, $p = 0.019$). Preoperative length of stay (median 0 days, $p > 0.99$), presence of a CVC (28.2%, $p = 0.75$), and PN administration (26.8%, $p = 0.74$) were not associated with a higher incidence of DVT. A number of preoperative laboratory tests were included in the univariable analysis, though a large proportion of patients were missing some or all of these data. A lower preoperative albumin level (2.9 g/dL vs 3.6 g/dL, $p = 0.049$) along with higher CRP (54 mg/dL vs 5.6 mg/dL, $p = 0.003$) and ESR (50 mm/hr vs 26 mm/hr, $p = 0.005$) were all associated with higher incidence of DVT. Preoperative hemoglobin level was not significantly associated with DVT risk (median 10.7 g/dL, $p = 0.1$), nor was the use of any specific IBD medical therapy (55.8% on corticosteroids, 58.7% on biologic therapy, and 32.6% on immunologic therapy).

3.2. Perioperative characteristics

The most common surgical procedure was subtotal or total colectomy (43.5%), followed by ileocecectomy (35.1%), proctocolectomy or completion proctectomy with ileal pouch-anal anastomosis (IPAA; 14.2%), and partial colectomy with or without primary anastomosis (7.2%) (**Table 2**). Colectomy (subtotal or total) was associated with a significantly higher incidence of DVT compared to any of the other procedure types (75% vs 42.4%, $p = 0.035$). Further, operative acuity showed an association with development of DVT, with emergent procedures representing 33.3% of cases that ultimately developed a

DVT versus 4.2% of cases that did not ($p = 0.002$). Longer operative time showed a trend toward increased incidence of DVT, though it was not significant (431 min vs 278 min, $p = 0.06$). Operative technique (laparoscopic versus open) was not associated with a difference in DVT rates (83.7% of cases that did not develop DVT were performed laparoscopically vs 75% that did develop DVT; $p = 0.43$), though overall only 16.7% of cases were performed open.

Only 88 patients (32.1%) had sequential compression devices (SCDs) placed perioperatively for mechanical VTE prophylaxis, and even fewer (42, 15.3%) received perioperative chemoprophylaxis. Prophylactic practices varied significantly between institutions, with rates of mechanical prophylaxis ranging from 0-76% and chemoprophylaxis ranging from 0-34% depending on institution. Neither mechanical nor chemical VTE prophylaxis were associated with development of DVT ($p = 0.21$ and >0.99 , respectively), and due to the low frequencies and poor documentation we were unable to perform analyses based on timing of prophylaxis. There was no significant difference in postoperative bleeding complications in patients who received perioperative chemoprophylaxis versus those who did not (7.1% vs 2.6%, $p = 0.15$). Perioperative (intra- and post-operative) transfusion of RBCs was not associated with a higher incidence of DVT (14.5%, $p = 0.39$), though perioperative transfusions of plasma (16.7% vs 2%, $p = 0.038$) and platelets (16.7% vs 1%, $p = 0.016$) did show an association. Postoperatively, admission to the intensive care unit (4.2%, $p = 0.08$) and hospital length of stay (median 5 days, $p = 0.74$) were not significantly associated with development of DVT. The occurrence of any postoperative complication showed a strong association with increased incidence of DVT (75% vs 23.5%, $p < 0.001$). This was mostly due to the higher incidence of combined infectious complications including wound infection, intra-abdominal abscess, anastomotic leak, pneumonia, urinary tract infection, and sepsis in the DVT cohort (41.7% vs 9.8%, $p = 0.001$). The most common complication listed as “other” was postoperative ileus.

3.3. Follow-up

Median length of postoperative follow-up was 186 weeks, with a minimum of 11 days and maximum of 455 weeks. One patient died on postoperative day 7 prior to discharge due to sepsis and

multi-system organ failure. All other patients had at least one postoperative follow-up visit documented. Ninety-seven percent of patients had documented follow-up >60 days postoperatively.

3.4. Multivariable time-dependent analysis

Cox regression was performed to further evaluate the factors associated with postoperative DVT. Following exclusion of one institution's data as discussed in section 2.3, there were a total of 212 patients included in the regression analysis with 12 DVTs (5.7%). The variables selected for the regression were IBD diagnosis (UC, CD, or IC), OCP use, preoperative length of stay >1 day, preoperative RBC transfusion, colectomy (subtotal or total), emergent procedure, operative time >300 minutes, perioperative plasma transfusion, postoperative ICU admission, and occurrence of a postoperative infectious complication (**Table 3**). The factors that were found to significantly increase the risk of DVT on multivariable analysis were emergent procedure (HR 18.8, 95%CI: 3.18-111), perioperative plasma transfusion (HR 25.1, 95%CI: 2.4-259), and postoperative infectious complication (HR 10.5, 95%CI: 2.63-41.8).

3.5. DVT characteristics

A total of 12 DVTs were diagnosed during the study period, and no PEs were identified (**Table 4**). The most common DVT location was intra-abdominal (portomesenteric; 75%), followed by upper extremity (16.7%) and lower extremity (8.3%). All extremity DVTs were catheter-associated and symptomatic at diagnosis (3/3), while two-thirds of intra-abdominal DVTs were diagnosed incidentally (6/9). Median time from operation to diagnosis of a DVT was 14 days, with a range from four to 451 days. Of the four DVTs diagnosed >60 days following their initial colectomy, the first was a portal vein thrombus that presented symptomatically one-week after staged IPAA, the second was a catheter-associated basilic vein thrombus, and the remaining two were intra-abdominal DVTs that were diagnosed incidentally on imaging. Eleven of the 12 DVTs were treated with therapeutic anticoagulation, and median time to resolution was 5 weeks. One patient died while being treated for an intra-abdominal DVT on postoperative day 7 due to sepsis and multi-system organ failure.

On subgroup analysis of the patients found to have portomesenteric DVTs, 78% (7/9) underwent subtotal or total colectomy, 78% were performed laparoscopically, and the median operative time was 455 minutes (IQR = 385-471 mins). In comparison to the patients that were diagnosed with extremity DVTs, there were no significant differences in procedure type (2/3; 67% subtotal or total colectomy), laparoscopic technique (67% laparoscopic), or operative time (median OR time = 359 mins; IQR = 140-655 mins) compared to patients with portomesenteric DVTs (all $p > 0.05$).

4. Discussion

This study sought to identify risk factors associated with VTE specifically in pediatric patients who undergo colorectal resection for IBD. We found a 4.3% incidence of DVT in this multi-institutional cohort, the majority being incidentally found intra-abdominal thromboses. No PEs occurred during the study period. Multivariable regression analysis identified emergent procedure, perioperative plasma transfusion, and postoperative infectious complications as independent predictors of DVT.

Inflammatory bowel disease is a known risk factor for VTE, with prior literature identifying a prevalence ratio of 1.8 in pediatric patients with IBD compared to other hospitalized children [9]. Further, children with IBD who undergo intra-abdominal operations are at even greater risk of thrombotic events [3,4]. Studies in adult patients have found that active disease flares increase the risk of VTE in IBD patients as well [1,2]. While we did not specifically assess for active disease in this study, it can be inferred by other variables such as preoperative LOS, preoperative RBC transfusion, inflammatory markers (CRP, ESR), and acuity of the procedure. A number of these variables were associated with postoperative DVT on univariable analysis, and emergent procedure was identified as an independent predictor on multivariable regression.

There is a growing body of evidence noting the interaction between coagulation and inflammation, which is attributed to enhancement of the hypercoagulable state and increased endothelial damage due to inflammatory mediators [10]. A number of pro-inflammatory molecules have been

associated with the development of VTE including CRP, IL-6, IL-8, and TNF-alpha. We found similar results in this study, as CRP and ESR levels were significantly higher in patients diagnosed with DVT. These laboratory tests are not routinely checked in all patients prior to surgery, however, so we were unable to include these markers in our regression analysis. Lending further weight to the association between active inflammation and VTE is the finding that postoperative infectious complications were predictive of DVT in our data. This association has been described previously in other patient populations including those with hematologic malignancies and osteomyelitis [11-13]. It is important to consider the level of active inflammation present when determining whether to prescribe mechanical or chemical VTE prophylaxis to IBD patients undergoing colorectal surgery. Further, the duration of the postoperative pro-inflammatory, hypercoagulable state is not well-defined in children but has been shown to extend for up to two to six weeks in adults [14,15]. Our data found a median postoperative time of two weeks prior to DVT diagnosis, however there were a number of events that occurred much further out than that. Some adult literature discusses the potential benefits of extending postoperative chemoprophylaxis during this time, similarly to standard practice following colorectal surgery for cancer [15]. It is also important that gastroenterologists be aware of the increased risks that recent surgery and active inflammation have on the development of VTE in IBD patients as they will ultimately be responsible for following these patients long-term.

Another interesting finding in this study was the association between perioperative plasma transfusion and DVT. It is pertinent to note that the number of patients who received a plasma transfusion was low (4 patients without DVT vs 2 patients with DVT), however it remained an independent predictor of DVT after regression analysis. There is prior data to suggest that blood transfusions are associated with increased risk of VTE in both adults and children [16,17]. Further, a study out of the adult trauma literature identified a 25% increase in VTE risk for each unit of fresh frozen plasma (FFP) transfused in patients who required less than four units of RBCs [18]. It is not uncommon for patients with active IBD to undergo colectomy for intractable bleeding, or to manifest an inflammatory coagulopathy

intraoperatively necessitating transfusion of blood or coagulation factors. Yet these data would encourage physicians to be prudent in administering perioperative blood products to patients undergoing surgery for IBD, and to consider postoperative VTE prophylaxis in these patients as soon as is medically safe. Further, the American College of Gastroenterology recommends chemical prophylaxis with low-molecular-weight heparin for adult patients in an acute flare even with active bleeding from their UC, as it has not been shown to worsen hemorrhage [1,19].

Though there are strong recommendations for chemical VTE prophylaxis in adult patients with IBD, this data is lacking in children. Our study found very low rates of both mechanical and chemical prophylaxis, and practice varied considerably by institution. For mechanical prophylaxis, a total of 32.1% of patients had SCDs placed in the operating room, and this percentage ranged from 0-76% depending on institution. Chemical prophylaxis was even less common, with overall 15.3% of patients receiving perioperative dosing which again ranged from 0-34% depending on institution. We found no significant differences in DVT rates or postoperative bleeding complications based on prophylaxis, however with such low utilization it is difficult to make any conclusions. Interestingly, a recent study utilizing the National Surgical Quality Improvement Program-Pediatric (NSQIP-P) database did not find IBD to be an independent risk factor for VTE in general surgery patients undergoing abdominopelvic operations [20]. This is in contrast to a number of other large database studies in both the adult and pediatric literature that have demonstrated IBD to be independently predictive of VTE in both hospitalized patients and those undergoing colorectal resections [9,21,22]. While there were a number of limitations with the NSQIP-P study, including small sample size of IBD patients and no limitations on the type of abdominopelvic procedures included, another plausible reason for the lack of significance could be that overall VTE prophylaxis has become more commonplace in the surgical management of IBD and may be reflected in patient outcomes.

A final note-worthy finding in our study was the high incidence of intra-abdominal DVTs. Seventy-five percent of the identified DVTs were portomesenteric, with two-thirds of these being

asymptomatic and found incidentally on imaging. Prior data has found that portomesenteric venous thrombosis (PMVT) is not uncommon following colorectal surgery for IBD, and that it is likely an under-recognized complication [23]. Postoperative time to presentation is often weeks after discharge, and PMVT has been found to be associated with emergent operations and elevated CRP similar to our findings. Symptoms, when present, include abdominal pain, fever, and nausea/vomiting [24]. Our data found no correlation between PMVT and laparoscopic technique, which is similar to other findings in the literature [25,26]. There is conflicting data as to the morbidity associated with PMVT following colorectal surgery, though some small series have identified associated hepatic abscesses or at the extreme end of the spectrum septic thrombophlebitis of the portal vein [24,27]. Most studies recommend a course of therapeutic anticoagulation when PMVT is recognized so as to prevent further progression and poor outcomes.

This retrospective multi-institutional study has several limitations. The impact of laparoscopic pneumoperitoneum duration and pressure measurements is not collected in this dataset. While four institutions contributed data, one institution had incomplete variables collected and so these patients could not be included in the multivariable regression model. This significantly affects the power of our statistical analyses. Further, we were unable to evaluate the effect of timing of VTE prophylaxis on postoperative DVT rate due to the low frequencies of both mechanical and chemical prophylaxis in our cohort. Sub-analysis of patients diagnosed with DVTs was also limited due to low sample sizes. Future prospective study with greater sample sizes is needed to further validate our results.

Based on the findings of this study in addition to documented rates of VTE in other cohorts evaluating pediatric IBD patients, we would recommend perioperative mechanical VTE prophylaxis in all patients undergoing abdominal surgery for IBD, and to consider chemical prophylaxis in this high-risk population on an individualized basis. Other risk factors for DVT identified here include emergent procedure, perioperative plasma transfusion, and postoperative infectious complications. We are unable to determine efficacy of prophylactic VTE chemoprophylaxis in our cohort as utilization of prophylaxis was

so low. As our study is limited by its retrospective nature, further prospectively collected data is needed to develop practice guidelines regarding VTE risk in pediatric patients undergoing colorectal resection for IBD.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Journal Pre-proof

References

- [1] Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroent.* 2019; 114(3):384-413.
- [2] Nguyen GC, Bernstein CN, Bitton A, Chan AK, Griffiths AM, Leontiadis GI, Geerts W, Bressler B, Butzner JD, Carrier M, Chande N, Marshall JK, Williams C, Kearon C. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. *Gastroenterology.* 2014; 146(3):835-848.
- [3] Antiel RM, Hashim Y, Moir CR, Rodriguez V, Elraiyah T, Zarroug AE. Intra-abdominal venous thrombosis after colectomy in pediatric patients with chronic ulcerative colitis: incidence, treatment, and outcomes. *J Pediatr Surg.* 2014; 49(4):614-617.
- [4] McKie K, McLoughlin RJ, Hirsh MP, Cleary MA, Aidlen JT. Risk factors for venous thromboembolism in children and young adults with inflammatory bowel disease. *J Surg Res.* 2019; 243:173-179.
- [5] Carillo LA, Kumar A, Harting MT, Pedroza C, Cox CS Jr. Venous thromboembolism risk factors in a pediatric trauma population. *Pediatr Surg Int.* 2019; 35(4):487-493.
- [6] Landisch RM, Hanson SJ, Cassidy LD, Braun K, Punzalan RC, Gourlay DM. Evaluation of guidelines for injured children at high risk for venous thromboembolism: A prospective observational study. *J Trauma Acute Care Surg.* 2017; 82(5):836-844.
- [7] Leeper CM, Vissa M, Cooper JD, Malec LM, Gaines BA. Venous thromboembolism in pediatric trauma patients: Ten-year experience and long-term follow-up in a tertiary care center. *Pediatr Blood Cancer.* 2017; 64(8): doi: 10.1002/pbc.26415.
- [8] Morgan J, Checketts M, Arana A, Chalmers E, Maclean J, Powis M, Morton N; Association of Paediatric Anaesthetists of Great Britain and Ireland Guidelines Working Group on Thromboprophylaxis in Children. Prevention of perioperative venous thromboembolism in pediatric patients: Guidelines from the Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI). *Paediatr Anaesth.* 2018; 28(5):382-391.

- [9] Vu LT, Nobuhara KK, Lee H, Farmer DL. Determination of risk factors for deep venous thrombosis in hospitalized children. *J Pediatr Surg*. 2008; 43(6):1095-1099.
- [10] Branchford BR, Carpenter SL. The role of inflammation in venous thromboembolism. *Front Pediatr*. 2018; 23(6):142.
- [11] Bakalov V, Tang A, Yellala A, Kaplan R, Lister J, Sadashiv S. Risk factors for venous thromboembolism in hospitalized patients with hematological malignancy: An analysis of the National Inpatient Sample, 2011-2015. *Leuk Lymphoma*. 2019; doi: 10.1080/10428194.2019.1666380.
- [12] Bouchoucha S, Benghachame F, Trifa M, Saied W, Douira W, Nessib MN, Ghachem MB. Deep venous thrombosis associated with acute hematogenous osteomyelitis in children. *Orthop Traumatol Surg Res*. 2010; 96(8):890-893.
- [13] Cohoon KP, Ashrani AA, Crusan DJ, Petterson TM, Baiey KR, Heit JA. Is infection an independent risk factor for venous thromboembolism? A population-based, case-control study. *Am J Med*. 2018;131(3):307-316.
- [14] Faye AS, Wen T, Ananthakrishnan AN, Lichtiger S, Kaplan GG, Friedman AM, Lawlor G, Wright JD, Attenello FJ, Mack WJ, Lebwohl B. Acute venous thromboembolism risk highest within 60 days after discharge from the hospital in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2019; doi: 10.1016/j.cgh.2019.07.028.
- [15] McKechnie T, Wang J, Springer JE, Gross PL, Forbes S, Eskicioglu C. Extended thromboprophylaxis following colorectal surgery in patients with inflammatory bowel disease: A comprehensive systematic review. *Colorectal Dis*. 2019; doi: 10.1111/codi.14853.
- [16] Goel R, Patel EU, Cushing MM, Frank SM, Ness PM, Takemoto CM, Vasovic LV, Sheth S, Nellis ME, Shaz B, Tobian AAR. Association of perioperative red blood cell transfusions with venous thromboembolism in a North American registry. *JAMA Surg*. 2018; 153(9):826-833.

- [17] Rothstein DH, Cairo SB, Schaefer BA, Lautz TB. Association of perioperative red blood cell transfusion with postoperative venous thromboembolism in pediatric patients: A propensity score matched analysis. *Pediatr Blood Cancer*. 2019; 66(10):e27919.
- [18] Zander AL, Olson EJ, Van Gent JM, Bandle J, Calvo RY, Shackford SR, Peck KA, Sise CB, Sise MJ, King BS. Does resuscitation with plasma increase the risk of venous thromboembolism? *J Trauma Acute Care Surg*. 2015; 78(1):39-43.
- [19] Ra G, Thanabalan R, Ratneswaran S, Nguyen GC. Predictors and safety of venous thromboembolism prophylaxis among hospitalized inflammatory bowel disease patients. *J Crohns Colitis*. 2013; 7(10):e479-485.
- [20] Cairo SB, Lautz TB, Schaefer BA, Yu G, Naseem HU, Rothstein DH. Risk factors for venous thromboembolic events in pediatric surgical patients: Defining indications for prophylaxis. *J Pediatr Surg*. 2018; 53(10):1996-2002.
- [21] Alhassan N, Trepanier M, Sabapathy C, Chaudhury P, Liberman AS, Charlebois P, Stein BL, Lee L. Risk factors for post-discharge venous thromboembolism in patients undergoing colorectal resection: a NSQIP analysis. *Tech Coloproctol*. 2018; 22(12):955-964.
- [22] El-Dhuwaib Y, Selvasekar C, Corless DJ, Deakin M, Slavin JP. Venous thromboembolism following colorectal resection. *Colorectal Dis*. 2017; 19(4):385-394.
- [23] Kayal M, Radcliffe M, Plietz M, Rosman A, Greenstein A, Khaitov S, Sylla P, Dubinsky MC. Portomesenteric venous thrombosis in patients undergoing surgery for medically refractory ulcerative colitis. *Inflamm Bowel Dis*. 2019; doi: 10.1093/ibd/izz169.
- [24] Remzi FH, Fazio VW, Oncel M, Baker ME, Church JM, Ooi BS, Connor JT, Preen M, Einstein D. Portal vein thrombi after restorative proctocolectomy. *Surgery*. 2002; 132(4):655-661.

- [25] Gorgun E, Sapci I, Onder A, Ozuner G, Liska D, Stocchi L, Delaney CP. Factors associated with portomesenteric venous thrombosis after total colectomy with ileorectal anastomosis or end ileostomy. *Am J Surg.* 2018; 215(1):62-65.
- [26] Han JW, Kong SH, Shin CI, Min SK, Min SI, Kim TH, Yang JY, Oh SY, Suh YS, Lee HJ, Yang HK. Portomesenteric vein thrombosis after gastric surgery. *Gastric Cancer.* 2016; 19(4):1135-1143.
- [27] Sinagra E, Aragona E, Romano C, Maisano S, Orlando A, Virdone R, Tese L, Modesto I, Criscuoli V, Cottone M. The role of portal vein thrombosis in the clinical course of inflammatory bowel diseases: report on three cases and review of the literature. *Gastroenterol Res Pract.* 2012; doi: 10.1155/2012/916428.

Table 1. Patient demographics and preoperative characteristics.

	Postoperative DVT			p-value
	All (N = 276)	No (N = 264)	Yes (N = 12)	
Age (years); median [IQR]	15 [13,17]	15 [13,17]	16 [15,17]	0.23 ^w
Sex (% female)	149 (54%)	145 (54.9%)	4 (33.3%)	0.24 ^e
IBD Diagnosis				0.12 ^e
UC	134 (48.5%)	127 (48.1%)	7 (58.3%)	
CD	125 (45.3%)	122 (46.2%)	3 (25%)	
IC	17 (6.2%)	15 (5.7%)	2 (16.7%)	
History of hypercoagulable state				
Current or former smoker (N = 266)	6 (2.3%)	6 (2.4%)	0	>0.99 ^e
Current OCP use	17 (6.2%)	15 (5.7%)	2 (16.7%)	0.16 ^e
Known thrombophilia	5 (1.8%)	5 (1.9%)	0	>0.99 ^e
Prior VTE (N = 214)	5 (2.3%)	4 (2%)	1 (8.3%)	0.25 ^e
Preoperative characteristics				
Duration of disease (mos); median [IQR]	19.5 [7,48]	20 [8,48]	9 [2.5,54]	0.28 ^w
Preop LOS (days); median [IQR]	0 [0,5]	0 [0,5]	2.5 [1,5.5]	0.1 ^w
RBC transfusion within 14 days (N = 274)	56 (20.4%)	50 (19.1%)	6 (50%)	0.019^e
Presence of CVC	78 (28.2%)	74 (28%)	4 (33.3%)	0.75 ^e
PN administration	74 (26.8%)	70 (26.5%)	4 (33.3%)	0.74 ^e
Lab tests within 30 days; median [IQR]				
Albumin (g/dL) (N = 161)	3.6 [2.9,4.1]	3.6 [2.9,4.1]	2.9 [2.8,3.2]	0.049^w
CRP (mg/dL) (N = 137)	5.8 [2.3,20.3]	5.6 [2.1,17.9]	54 [25,100]	0.003^w
ESR (mm/hr) (N = 129)	27 [15,50]	26 [14,49]	50 [45,78]	0.005^w
Hemoglobin (g/dL) (N = 204)	10.7 [9.5,12.3]	10.8 [9.5,12.3]	9.7 [8.7,11.1]	0.1 ^w
IBD medical therapy				
Corticosteroids	154 (55.8%)	146 (55.3%)	8 (66.7%)	0.56 ^e
Biologic therapy	162 (58.7%)	156 (59.1%)	6 (50%)	0.56 ^e
Immunologic therapy	90 (32.6%)	87 (33%)	3 (25%)	0.76 ^e

All numerical values documented in number (%) unless otherwise stated.

Statistical tests: ^w Wilcoxon rank-sum, ^e Fisher's exact

Abbreviations: DVT, deep venous thrombosis; IQR, interquartile range; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn disease; IC, indeterminate colitis; OCP, oral contraceptive; VTE, venous thromboembolism; LOS, length of stay; RBC, red blood cell; CVC, central venous catheter; PN, parenteral nutrition; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

Table 2. Perioperative characteristics.				
	All (N = 276)	Postoperative DVT		p-value
		No (N = 264)	Yes (N = 12)	
Procedure type				
Colectomy (subtotal or total)	120 (43.5%)	111 (42.0%)	9 (75%)	0.035^e
Ileocectomy	97 (35.1%)	95 (36%)	2 (16.7%)	
Proctocolectomy with IPAA	19 (6.9%)	19 (7.2%)	0	
Completion proctectomy with IPAA	20 (7.3%)	20 (7.6%)	0	
Partial colectomy with anastomosis	14 (5.0%)	13 (4.9%)	1 (8.3%)	
Partial colectomy with ostomy	6 (2.2%)	6 (2.3%)	0	
Acuity				
Emergent	15 (5.4%)	11 (4.2%)	4 (33.3%)	0.002^e
Urgent	108 (39.1%)	103 (39%)	5 (41.7%)	
Elective	153 (55.5%)	150 (56.8%)	3 (25%)	
Operative characteristics				
OR time (mins); median [IQR] (N = 214)	287 [180,407]	278 [180,401]	431 [255,520]	0.06 ^w
Operative technique				
Open	46 (16.7%)	43 (16.3%)	3 (25%)	0.43 ^{e0.43e}
Laparoscopic	230 (83.3%)	221 (83.7%)	9 (75%)	
Periop SCDs placed (N = 274)	88 (32.1%)	82 (31.3%)	6 (50%)	0.21 ^{e0.21e}
Periop VTE chemoprophylaxis (N = 274)	42 (15.3%)	40 (15.3%)	2 (16.7%)	>0.99 ^{e>0.99e}
Periop RBC transfusion	40 (14.5%)	37 (14%)	3 (25%)	0.39 ^{e0.39e}
Periop plasma transfusion (N = 214)	6 (2.2%)	4 (2%)	2 (16.7%)	0.038^{e0.038e}
Periop platelet transfusion (N = 214)	4 (1.4%)	2 (1%)	2 (16.7%)	0.016^{e0.016e}
Postop ICU admission (N = 214)	9 (4.2%)	7 (3.5%)	2 (16.7%)	0.08 ^{e0.08e}
Postoperative complications				0.001^{e0.001e}
Wound infection/dehiscence	8 (11.4%)	8 (13.1%)	0	
Intra-abdominal abscess	6 (8.5%)	4 (6.6%)	2 (16.7%)	
Anastomotic leak	6 (8.6%)	6 (9.8%)	0	
Bowel obstruction requiring operation	7 (10%)	6 (9.9%)	1 (8.3%)	
Pneumonia	3 (4.3%)	2 (3.3%)	1 (8.3%)	
Sepsis	6 (8.5%)	5 (8.2%)	1 (8.3%)	
Bleeding complication	9 (12.9%)	8 (13.1%)	1 (8.3%)	
Urinary tract infection	2 (2.9%)	1 (1.6%)	1 (8.3%)	
Other	23 (32.9%)	21 (34.4%)	2 (16.8%)	
Postop LOS (days); median [IQR]	5 [4,7]	5 [4,7]	4.5 [3,9]	0.74 ^w

All numerical values documented in number (%) unless otherwise stated.

Statistical tests: ^w Wilcoxon rank-sum, ^e Fisher's exact

Abbreviations: DVT, deep venous thrombosis; IQR, interquartile range; IPAA, ileal pouch-anal anastomosis; OR, operating room; SCDs, sequential compression devices; VTE, venous thromboembolism; RBC, red blood cell; ICU, intensive care unit; LOS, length of stay

Table 3. Cox regression analysis of postoperative DVT.				
Independent variable	HR	St. Err.	95% CI	p-value
Diagnosis				
UC	Ref.			
CD	4.5	6.98	(0.22, 93.2)	0.33
IC	0.68	0.78	(0.07, 6.57)	0.74
OCP use	3.37	2.98	(0.59, 19.1)	0.17
Preoperative LOS >1 day	0.77	0.72	(0.12, 4.79)	0.78
Preoperative RBC transfusion	3.59	3.71	(0.47, 27.2)	0.22
Colectomy (subtotal or total)	8.21	12.9	(0.38, 178)	0.18
Emergent procedure	18.8	17.1	(3.18, 111)	0.001
OR time >300 mins	4.44	3.72	(0.86, 22.9)	0.08
Perioperative plasma transfusion	25.1	29.9	(2.4, 259)	0.007
Postoperative ICU admission	0.3	0.31	(0.04, 2.29)	0.24
Postoperative infectious complication	10.5	7.4	(2.63, 41.8)	0.001
Model $\chi^2 = 36.58$, $p = 0.0001$ N (subjects) = 212, n (DVT) = 12 Abbreviations: DVT, deep venous thrombosis; HR, hazard ratio; St. Err, standard error; CI, confidence interval; Ref., reference; UC, ulcerative colitis; CD, Crohn disease; IC, indeterminate colitis; OCP, oral contraceptives; LOS, length of stay; RBC, red blood cell; OR, operating room; ICU, intensive care unit				

Table 4. Postoperative DVT characteristics.	
Characteristic	All DVTs (N = 12)
Location	
Upper extremity	2 (16.7%)
Lower extremity	1 (8.3%)
Intra-abdominal (portomesenteric)	9 (75%)
Symptomatic	6 (50%)
Catheter-associated	3 (25%)
Time from operation to diagnosis (days); median [IQR]	14 [8,147]
Treated with therapeutic anticoagulation	11 (91.7%)
Time to resolution (weeks); median [IQR]	5 [4,12]
All numerical values documented in number (%) unless otherwise stated. Abbreviations: DVT, deep venous thrombosis; IQR, interquartile range	