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Thromboembolic Disease in Inflammatory Bowel Disease

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A possible association between inflammatory bowel disease and thromboembolism was first noted shortly after IBD was first recognized. We now know that patients with IBD are about three times more likely than the general population to have a thromboembolic event. Although active disease is a risk factor, even patients with quiescent disease have an increased risk of deep vein thrombosis or pulmonary embolism. An awareness of this risk is important amongst physicians who manage patients with IBD as thromboembolic events have a high associated mortality and may be preventable by use of antithrombotic measures including low-molecular weight heparin in immobile sick inpatients.

INTRODUCTION

Whilst thrombosis and inflammation were originally thought of as unrelated and independent processes, it has become increasingly clear that they are intrinsically linked (1). An association between thromboembolism and inflammatory bowel disease (IBD), first proposed some 70 years ago, is now well recognized. But how much of an increase in risk of thromboembolism do patients with IBD incur and what are the reasons for it? In this article we shall address these issues and discuss what can be done to minimize this risk.

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HOW MUCH DOES IBD INCREASE THE RISK OF THROMBOEMBOLIC EVENTS?

Early attempts to quantify the relative increase in risk of developing thromboembolic complications in IBD were hampered by the lack of adequate control groups. Thus, in clinical studies spanning 60 years, the frequency of thromboembolic events in patients with IBD varied between 1% and 8%. Post-mortem data were also produced in an attempt to include patients who

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had suffered only subclinical events. Unfortunately, if anything these studies muddied the water further, finding evidence of thromboembolic disease in 7% to 41% of subjects (1). Although post-mortem studies reduce the chances of subclinical thromboembolism being overlooked, it is possible that perimortem changes result in an overestimate of its prevalence in IBD: again, without appropriate control groups, these data must be interpreted with caution.

Table 1
Frequency of thromboembolic events in patients with inflammatory bowel disease, rheumatoid arthritis and celiac disease. Each patient was matched with a healthy control. [Summarised from Miehsler, et al (2)]

IBD (n = 618)	*Rheumatoid arthritis (n = 243)*	*Coeliac disease (n = 207)*	*Matched healthy controls (1:1)*	P *Or (95% CI)*
6.2%	—	—	1.6%	P < 0.001 3.6 (1.7–7.8)
—	2.1%	—	2.5%	NS 0.7 (0.2–2.9)
—	—	1%	1.9%	NS 0.4 (0.1–2.5)

IBD: inflammatory bowel disease. OR: odds ratio 95%CI – 95% confidence intervals

Fortunately, two recent high quality studies have helped to define more clearly the increase in risk associated with IBD. Miehsler and colleagues (2) used a questionnaire to identify a history of thromboembolic disorders among 618 patients with IBD and subsequently confirmed the diagnosis by including only events that had been confirmed radiologically. A history of thromboembolism was also gathered for patients with rheumatoid arthritis (an inflammatory control group) and patients with celiac disease (a chronic gastroenterological disease control group). Each patient was matched with a healthy control, patients attending for preventive medical checks. The results (summarized in Table 1) showed that 6% of patients with IBD had a history of thromboembolism, about three times the rate in the matched healthy control group after adjustment for risk factors. Furthermore, an increase in thromboembolic events was not seen in the patients with rheumatoid arthritis or celiac disease compared with their control groups, suggesting that the risk of thromboembolism in IBD is specific to the disease and not just related to inflammation and/or gastrointestinal pathology.

The findings of this study supported a population-based cohort study published three years earlier (3). In this study, Bernstein and colleagues reported on the rate of hospitalization for either pulmonary embolism (PE) or deep vein thrombosis (DVT) among their IBD database cohort, numbering over 6,000. Each patient with IBD was matched for age, gender and postal address with 10 healthy controls. Incidence rates were calculated per 10,000 person years of follow-up and showed that the risk of having either a DVT or PE in association with IBD was 45.6 per 10,000 patient years of follow-up. By comparing the frequency of events between patients with IBD and controls, incidence rate ratios (IRR) were produced. These showed that patients with IBD were 3.5 (95% confidence interval (CI) 2.9–4.3) times more likely to have DVTs and 3.3 (95% CI 2.5–4.3) times more likely to have PEs than the healthy controls.

These studies show clearly that there is an increased risk of thromboembolism in patients with IBD and give some indications of its magnitude. To put this risk into context, for every 10 years of disease, a patient with IBD has about a one in 25 chance of having a DVT or PE.

CHARACTERISTICS OF PATIENTS WHO HAVE THROMBOEMBOLISM EVENTS

Can we identify which patients with IBD whose risk of thromboembolism is greatest?

Age

Age is a well defined risk factor for thromboembolism and applies as much to patients with IBD as it does to the general population. However, the overall increase in risk of having a thromboembolic event in patients with

IBD is greatest in the younger age groups (3). For example, in Bernstein's study, the IRR for DVT or PE was six for IBD patients aged under 40, but only 2.8 for those aged over 60. In addition, a Swedish study showed that thromboembolic events occur, on average, at a younger age in patients with IBD (53 years) than in healthy controls (64 years)(4). Nevertheless, the absolute risk remains highest in older patients with IBD: going back to Bernstein's study, the risk in the over 60's was 10 times greater than in the under 40's (3).

Disease Location

A review of patients from the Mayo clinic, Rochester, MN, with ulcerative colitis (UC) who had suffered a thromboembolic event identified that three quarters had pancolonic disease but only 2% proctitis (5), an observation replicated in two other reports. Similarly, in patients with Crohn's disease nearly 80% had colonic involvement. These findings suggest that the extent of colonic involvement may be a risk factor for thromboembolic events.

Disease Activity

Of course, a risk related to disease extent has some overlap with disease activity. It is, therefore, not surprising that active disease has been shown to be a risk factor for thromboembolism. For example, 80% of patients in the series from the Mayo had active disease at the time of their thromboembolic event (5). However, patients with inactive IBD are also at increased risk of developing DVT or PE; in an earlier series from the Mayo clinic, one third of events were seen in patients with quiescent disease (6).

Combining the data about disease activity and extent, it might be predicted that colectomy would decrease the prothrombotic tendency, at least in UC. Indeed, thromboembolism has even been suggested as an indication for surgery (6). However, in the later series from the Mayo clinic (5), among the patients with UC who had had a thromboembolic event, 25% had undergone previous proctocolectomy. More importantly, in patients whose thromboembolic event predated their surgery, recurrence rates were identical to those in patients whose colons remained intact. As with some other extraintestinal manifestations of UC, "curative" surgery does not remove the increased risk of thromboembolism.

WHAT THROMBOEMBOLIC EVENTS OCCUR?

Although DVT and PE are the commonest and best described thromboembolic events in patients with IBD, the literature abounds with reports of thromboses of almost all arteries and veins in the body. Hence, mesenteric ischemia can be an important, if unusual cause of abdominal pain in patients with IBD (7), and cerebral venous sinus thrombosis must be considered in patients presenting with a headache (8). Considering this, it is perhaps surprising that there has been little data to suggest that patients with IBD have a higher incidence of either ischemic heart disease or cerebrovascular disease: undoubtedly the disproportionate representation of smokers in Crohn's disease and nonsmokers in UC confounds the issue. However, an abstract presented at this year's Digestive Diseases Week describes an increase in risk in patients with IBD aged 60 years or more of having a cerebrovascular or cardiovascular event. (Bernstein et al, DDW 2007).

WHY IS THERE AN INCREASED RISK OF THROMBOEMBOLISM?

Several factors contribute to the increased risk of thromboembolic disease in IBD. First, there are factors related to the disease itself. For example, thrombocytosis is a well known manifestation of active IBD. Indeed, not only are platelets increased in number in IBD but they also behave abnormally, displaying an increase in their activation, and aggregation with each other and with leucocytes (9,10). Some of these abnormalities relate to disease activity whilst others do not. The same applies to a host of disturbances in coagulation and hemostasis that have been described in patients with IBD. It is clear from these studies that IBD is a prothrombotic condition, that there is evidence of ongoing coagulation and that inflammation plays an important role in the predisposition to thrombosis (1,11) (Table 2).

In addition to being related to coagulatory abnormalities, disease activity increases the risk of throm-

Table 2
Possible factors contributing to an increased risk of thromboembolism in IBD with some examples [Irving, et al (1) for review]

Disease Related	*General*
Platelet	**Related to active disease**
• ↑ Platelet activation	• Fluid depletion
• ↑ Platelet-leucocyte aggregation	• Immobility
• Thrombocytosis	• Central venous cannulation
	• Hospitalization
Hypercoagulation	
• ↓ Proteins C+S	**Disease associations**
• ↑ Clotting factors	• Smoking
• ↑ Fibrinogen	• Oral contraceptive pill (?)
• ↑ Tissue factor activity	
	Medication
Decreased fibrinolysis	• Corticosteroids
• ↑ Plasminogen activator inhibitor	• Methotrexate*
• ↓ Tissue-type plasminogen activator	• Sulfasalazine*
Endothelial abnormalities	**Nutrition**
• ↑ Circulating von Willebrand's factor	• B_6 deficiency*
• ↑ Anti-endothelial cell antibodies	• B_{12} deficiency*
	• Folate deficiency*
	• ↑ Lipoprotein A
	Increased need for surgery

*By causing hyperhomocysteinaemia

boembolism in other ways. Active IBD is often characterized by diarrhea which may result in fluid depletion. This can be further exacerbated by decreased oral intake associated for example with obstructive symptoms and abdominal pain. Patients with severely active disease require admission to the hospital; this results in decreased mobility and, in extremely sick patients, the placement of central venous catheters. Drug therapy can also predispose to thromboembolism: steroids can increase the prothrombotic tendency and both sulfasalazine and methotrexate contribute to folate deficiency which in turn can cause hyperhomocysteinaemia, a prothrombotic state. This latter phenomenon is also exacerbated by deficiency of vitamins B_{12} and B_6 both of can occur in IBD. Finally, many patients with IBD end up requiring surgery and are at risk of developing perioperative DVTs or PEs.

The genetic basis to IBD is being slowly unraveled. However, whether there is an association between IBD and inherited thrombotic disorders, either as a co-inherited trait or even as a pathogenetic factor, has been much debated recently. A recent meta-analysis examined the frequency of the three most commonly inherited risk factors for thromboembolism, factor V Leiden mutation, G20210A mutation in the prothrombin gene and homozygous C677T mutation in the menthylenetetrahydrofolate reductase gene. This study found that the frequency of these mutations was not increased in patients with IBD. However, given that some series have shown that up to one third of patients with IBD who have had a thromboembolic event have an inherited coagulopathic tendency, it would seem reasonable to screen for them in

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such patients (5). Certainly a positive result would be a powerful argument for consideration of lifelong anticoagulation.

WHAT CAN BE DONE TO REDUCE THE RISK OF THROMBOEMBOLISM?

Thromboembolic events in patients with IBD have been associated with a mortality rate of up to 36% at one year (6). Even when more recent data are examined, a mortality of 22% at 1.8 years is still striking (5). Given that it is likely that some thromboembolic events are preventable, what can be done to decrease their frequency? First and foremost, an awareness of the risk is most important. The majority of thromboembolic events occur in patients with another risk factor for thromboembolism in addition to IBD (2,5). Awareness of this risk in IBD not only allows preventive measures to be instituted, but also expedites diagnosis and treatment of events should they occur. Amongst patients in hospital, correcting fluid depletion and nutritional deficiencies, encouraging mobility and avoiding inessential central venous cannulation may all decrease the risk of thromboembolism. Because they would need to be enormous, and would carry difficult ethical implications, clinical trials are unlikely to be performed comparing differing regimens of preventive antithrombotic therapy in IBD. Nevertheless, low molecular weight heparin should be considered for all patients admitted to hospital with active IBD, particularly if they are likely to be largely in bed while in the hospital; these interventions are cheap and safe (12,13). The only exceptions to this rule are the very rare patients presenting primarily with major lower GI bleeding in whom antithromboembolism stockings should be used.

When should long-term formal anticoagulation be considered? Patients with recurrent thromboembolic events should be considered for lifelong anticoagulation as should those with an inherited procoagulant disorder who have had one such episode. However, as long-term anticoagulation is not without risk, it is important to consider each case on its merits and to discuss the pros and cons with the patient.

In summary, patients with IBD, particularly those with active extensive disease, are at increased risk of thromboembolic disease. The increase in relative risk is greatest in young people, but the absolute risk highest in the elderly. Thromboprophylactic therapy should be considered for all hospitalized patients with IBD and concurrent risk factors should be minimized. It is important to remember that thromboembolism can kill and is, at least some of the time, preventable. ■

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