UNIVERSITA' DI PADOVA

Dipartimento di Medicina (DIMED)

UOSD – Malattie Trombotiche ed Emorragiche

INFLAMMATORY BOWEL DISEASE E DISTURBI DELLA COAGULAZIONE

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EXTENSIVE ARTERIAL AND VENOUS THROMBOSIS COMPLICATING CHRONIC ULCERATIVE COLITIS

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It is generally agreed that chronic ulcerative colitis is one of the most serious of the diseases that afflict the digestive tract of man. Its complications may be equally serious. Fortunately, they are rare, but, unfortunately, when they do occur in a given case they are likely to be multiple.[1]

One of the very serious complications of chronic ulcerative colitis is extensive thrombosis of the blood vessels. Among fifteen hundred cases of chronic ulcerative colitis which we have observed thrombophlebitis or arterial thrombosis which was extensive enough to become a grave clinical problem occurred in eighteen. Less serious subclinical thrombosis of small vessels, chiefly the veins, has occurred more frequently than extensive thrombosis. In patients who come to necropsy, emboli and thrombi have been found in various places, such as the pelvic plexuses, lungs, spleen and kidneys. Among the last forty-three of our patients who died of chronic ulcerative colitis, emboli and thrombi were found in fourteen.

The six cases reported here have been under our observation in the last two years, whereas nine other cases have been observed in the eight prior years. This suggests an increased incidence of this complication and made this report seem timely. Because some of these patients received the anticolitis serum, some observers might suggest that the thrombosis occurred as a result of its administration; however, in one case, in which the thrombosis was severe, the patient did not receive any serum, and this phenomenon has occurred in many other cases in which serum was not employed.

REPORT OF CASES

CASE 1.—A man, aged 26 years, came to the Mayo Clinic on Dec. 2, 1933, because of severe chronic ulcerative colitis, which had been present for a year. The condition had been progressive. His normal weight was 135 pounds (61.2 Kg.). He was a husky, athletic person, a university graduate and a teacher. Since his

From the Division of Medicine, the Mayo Clinic.

1. Bargen, J. A.: The Management of Colitis, edited by Morris Fishbein, Garden City, N. Y., Doubleday, Doran & Company, Inc., 1935.

Bargen J and Barker NW, Arch Inter Med, 1936

ECCO Statement 9A

The risks of ischaemic heart disease, cerebrovascular accident, and mesenteric ischaemia are modestly increased in IBD [EL 2], particularly in women [EL 3]. Systemic inflammation predisposes to premature atherosclerosis [EL 3]. Cardiovascular mortality has not been shown to be increased in IBD [EL 2]

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Incidenza

- The overall incidence rate of VTE in IBD patients has been estimated to be 1%-8%, although necropsy studies report an incidence of 40%.
- Two- to fourfold increased risk of VTE compared with healthy controls.
- The majority of studies did not show significant differences in the risk of VTE between Crohn's disease and ulcerative colitis.

UC (RR 2.57, 95%CI: 2.02-3.28; n 6 studies)

vs

CD (RR 2.12, 95%CI: 1.40-3.20; n 5 studies)

Murthy SK, Nguyen GC. Am J Gastroenterol 2011; Yuhara H *et al*. Aliment Pharmacol Ther 2013; Tan VP *et al*. J Gastroenterol Hepatol 2013; Tichelaar YI et al. Thromb Haemost 2012.

Manifestazioni cliniche

- Deep venous thrombosis
- Pulmonary embolism
- Portal vein thrombosis, Budd Chiari syndrome
- Cerebral venous sinus thrombosis
- Retinal vein thrombosis

Fattori di rischio per VTE nei pzt con IBD

IBD activity

Several studies reported IBD activity in 45% to 90% of patients at the time of VTE diagnosis.

According to the data from a large primary care database from United Kingdom, the risk of VTE was increased most prominently during[1]:

- a flare of IBD (HR 8.4, 95%CI: 5.5-12.8)
- chronic activity (HR 6.5, 95%CI: 4.6-9.2)
- clinical remission (HR 2.1, 95%CI:1.6-2.9)

[1]Grainge MJ *et al*. Lancet 2010

Fattori di rischio per VTE nei pzt con IBD

Hospitalization

A higher VTE rates in hospitalized IBD patients than in non-IBD hospitalized patients was observed.

- Hospitalized IBD patients vs randomly selected hospitalized non-IBD patients 1.7-fold increased rate of VTE compared with non-IBD patients.[1]

- In 2011, three studies were published showing a 1.1- to 3.1-fold higher risk of VTE in hospitalized IBD patients.[2-4]

[1]Nguyen GC and Sam J. Am J Gastroenterol 2008; [2]Saleh T *et al*. Clin Appl Thromb Hemost 2011; [3]Sridhar AR *et al*. J Crohns Colitis 2011; [4]Rothberg MB et al. J Hosp Med 2011

Fattori di rischio per VTE nei pzt con IBD

Surgery

The incidence of VTE between ptz with *vs* without IBD who underwent surgery in 211 hospitals participating in the American College of Surgeons National Surgical Quality Improvement Program was 2.5% vs 1.0% (aOR 2.03, 95%CI:1.52-2.70).[1]

The risk persisted even when procedures on small and large bowels were excluded (4.45-fold increased risk of VTE in IBD *vs* non-IBD ptz undergoing non-intestinal procedures).

Pregnancy

The aOR of VTE was substantially higher in women with CD (aOR 6.12, 95%CI:2.91-12.9) and UC (aOR 8.44, 95%CI: 3.71-19.2) compared with the non-IBD obstetric population.[2]

A similar study conducted in Sweden also showed an increased risk of VTE in pregnant IBD vs non-IBD pregnant ptz (aOR 2.65, 95%CI: 0.65-10.1 for CD; aOR 3.78, 95%CI: 1.52-9.38 for UC).[3]

[1]Merrill A and Millham F. Arch Surg 2012;[2]Nguyen GC *et al*. Clin Gastroenterol Hepatol 2009;
[3]Bröms G *et al*. Clin Gastroenterol Hepatol 2012.

Fattori di rischio per VTE nei pzt con IBD

IBD-phenotype risk factors

Fistulising disease was independently associated with a greater VTE risk (OR 1.39, 95%CI: 1.13-1.70).[1]

Colonic involvement in CD patients or extensive disease in UC patients was also associated with an increased VTE risk.[2]

CD patients with VTE typically had colonic disease involvement (ileocolonic in 56% and colonic in 23%), and most UC patients with VTE (76%) had pancolonic disease.

[1]Nguyen GC and Sam J. Am J Gastroenterol 2008; [2]Solem CA et al. Am J Gastroenterol 2004.

Fattori di rischio per VTE nei pzt con IBD

IBD-nonspecific acquired risk factors

Infection or inflammation, previous thromboembolism, age, smoking, malignancy, central venous catheter, immobilization, drugs (oral contraceptives, steroids), malnutrition.

Thrombophilic conditions*:

- FV Leiden; prothrombin mutation
- Deficiency of protein C, protein S, antithrombin
- Antiphospholipid antibody syndrome, hyperhomocysteinemia

*The rate of inherited thrombophilias in patients with IBD and VTE is estimated to be 15%-30%, which is similar to the rate in non-IBD patients and VTE in most studies.

Pharmacological effect on risk factors

Corticosteroids

Several mechanisms

5-aminosalicylic acid (5-ASA)

Conflicting results

Sulfasalazine and Methotrexate

Inhibit dihydrofolate reductase leading to folate deficiency ➔ hyperhomocysteinaemia

Azathioprine and 6-mercaptopurine

Inhibits platelet aggregation in vitro

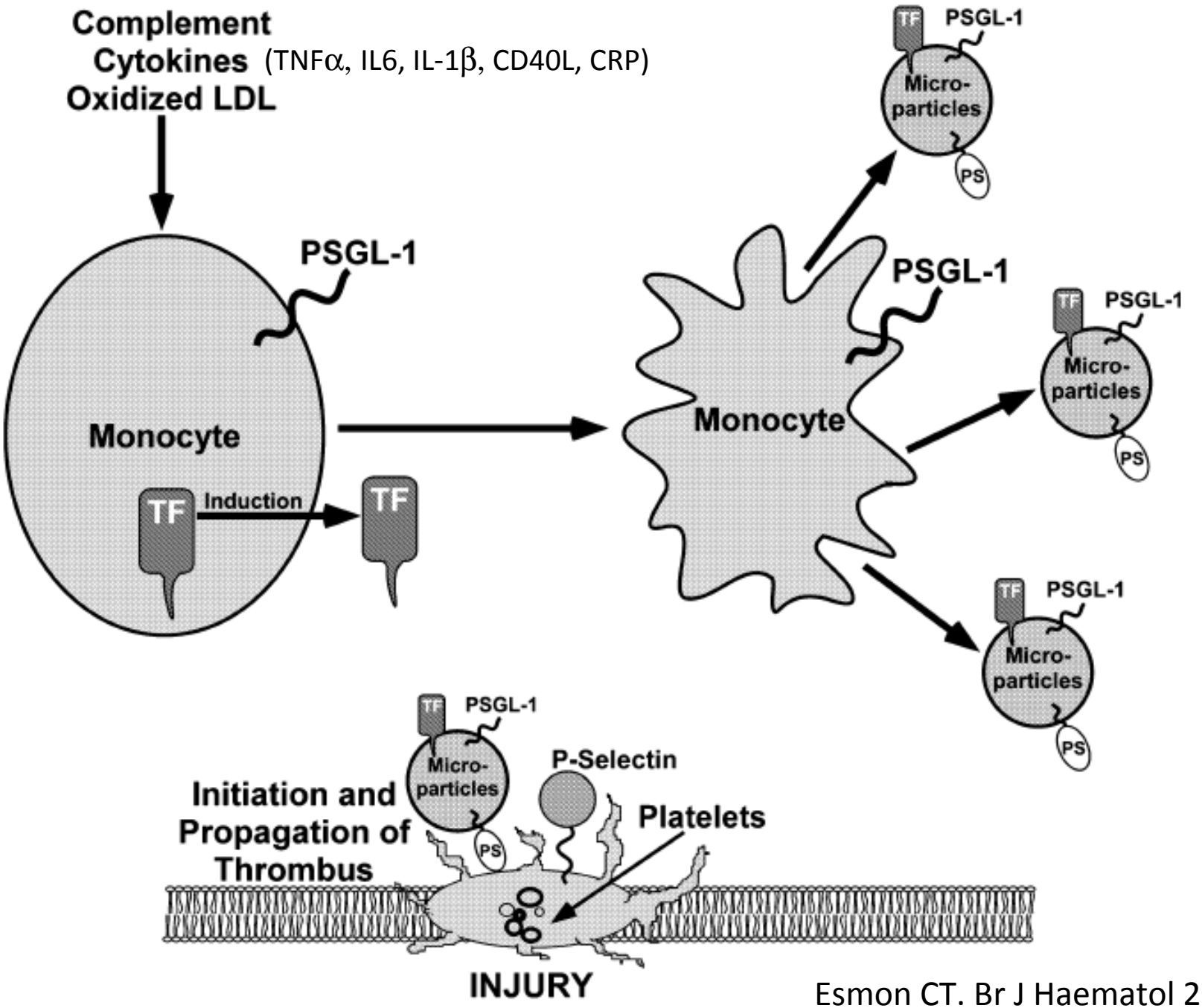
Cyclosporine

Associated with thrombogenicity in vitro and in vivo (i.e. increased platelet aggregation, activation of endothelial cells, impaired fibrinolysis through PAI-1 reduction).

Infliximab

Decrease platelet activity (i.e. the down regulation of the CD40/CD40L pathway)
Significant decrease in the amounts of circulating microparticles
Has been associated with the development of antiphospholipid antibodies

Horbor M et al. Journal of Cronhn and Colitis, 2016



Esmon CT. Br J Haematol 2005

Coagulative cascade

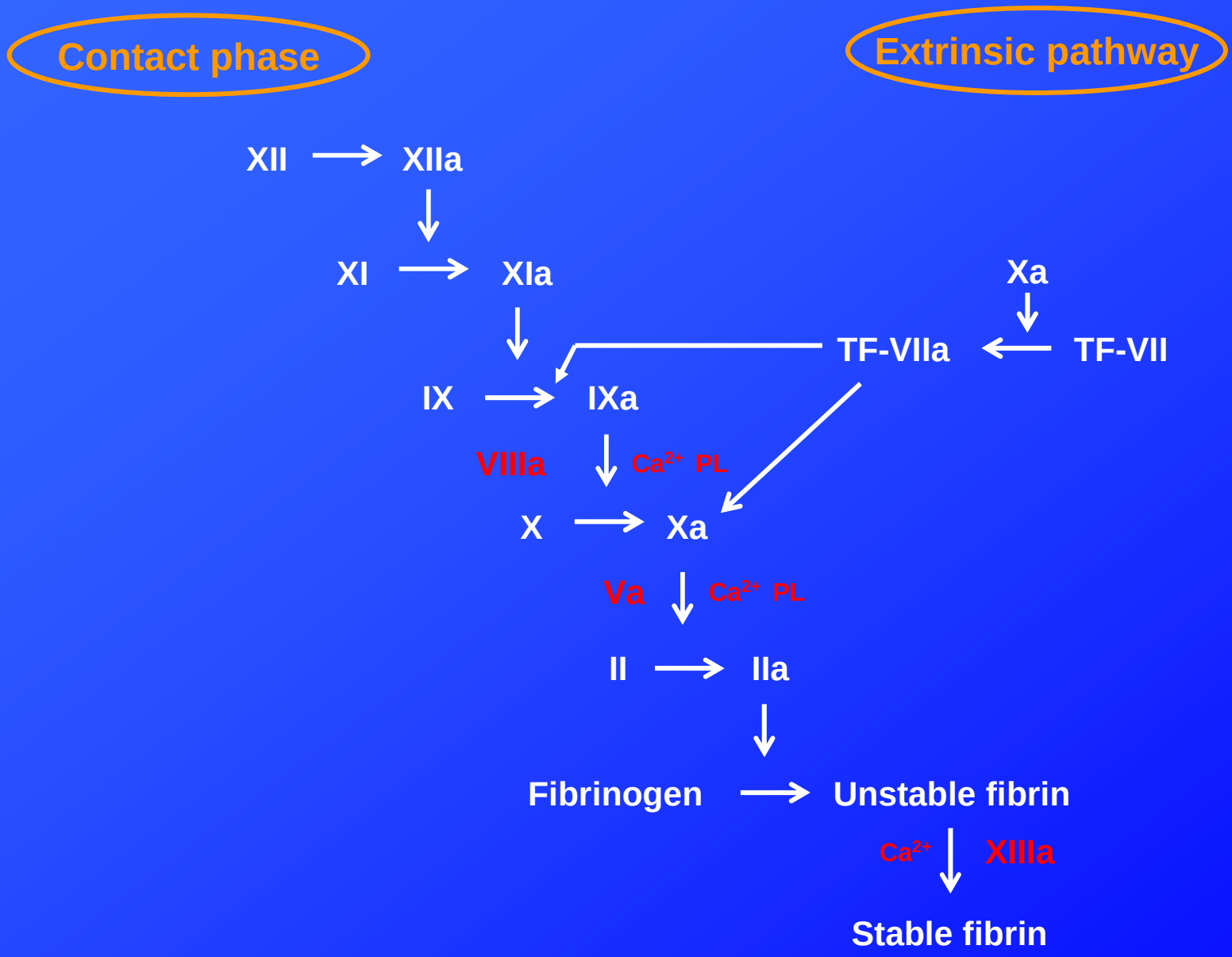


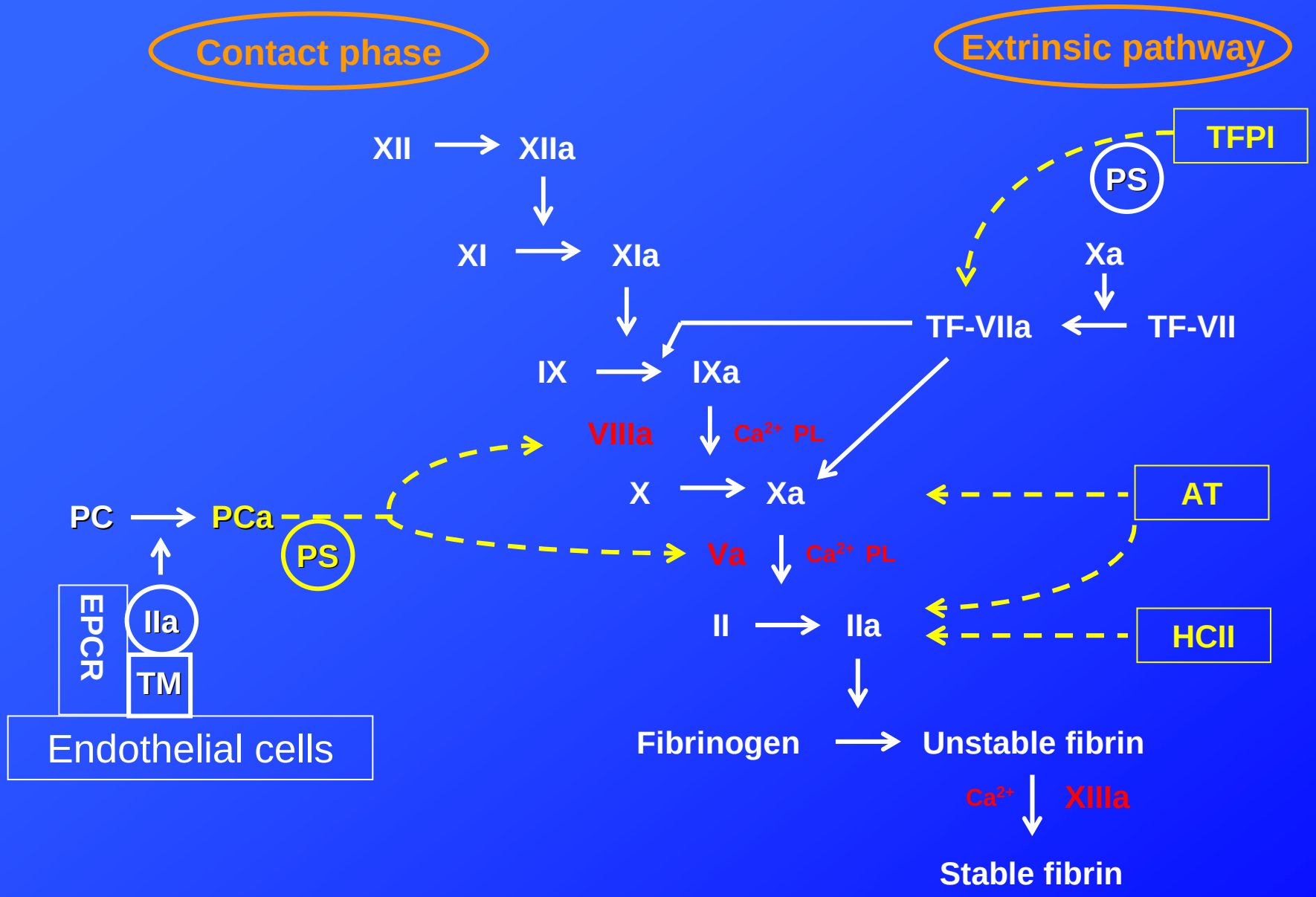
Table 2 Prothrombotic risk factors and abnormalities associated with inflammatory bowel disease

Abnormalities of coagulation
↑ TF, factors VII, FXII, FXI, FX and FV, prothrombin and fibrinogen
↓ AT, protein C, protein S, EPCR, TM and TFPI
↑ Prothrombin fragment 1+2, TAT complexes, fibrinopeptide A and fibrinopeptide B
↓ Factor XIII
Abnormalities of fibrinolysis
↓ t-PA
↑ PAI-1 and TAFI
↑ D-dimer
Abnormalities of platelets
↑ Number, activation (CD40L and P-selectin) and aggregation
Abnormalities of endothelium
↓ NO
↑ vWF

PAI-1: Plasminogen activator inhibitor 1; MTHFR: Methylenetetrahydrofolate reductase; TF: Tissue factor; AT: Antithrombin; EPCR: Endothelial cell protein C receptor; TM: Thrombomodulin; TFPI: Tissue factor-pathway inhibitor; TAT: Thrombin-antithrombin; t-PA: Tissue plasminogen activator; TAFI: Thrombin-activatable fibrinolysis inhibitor; CD40L: CD40 ligand; vWF: von Willebrand factor.

Magro F et al. World J Gastroenterol 2014

Coagulative cascade



La bilancia coagulativa

Sdr. trombofilica → stato ipercoagulabile → ↑ rischio trombotico

Deficit di fattori → stato ipocoagulabile → ↑ rischio emorragico

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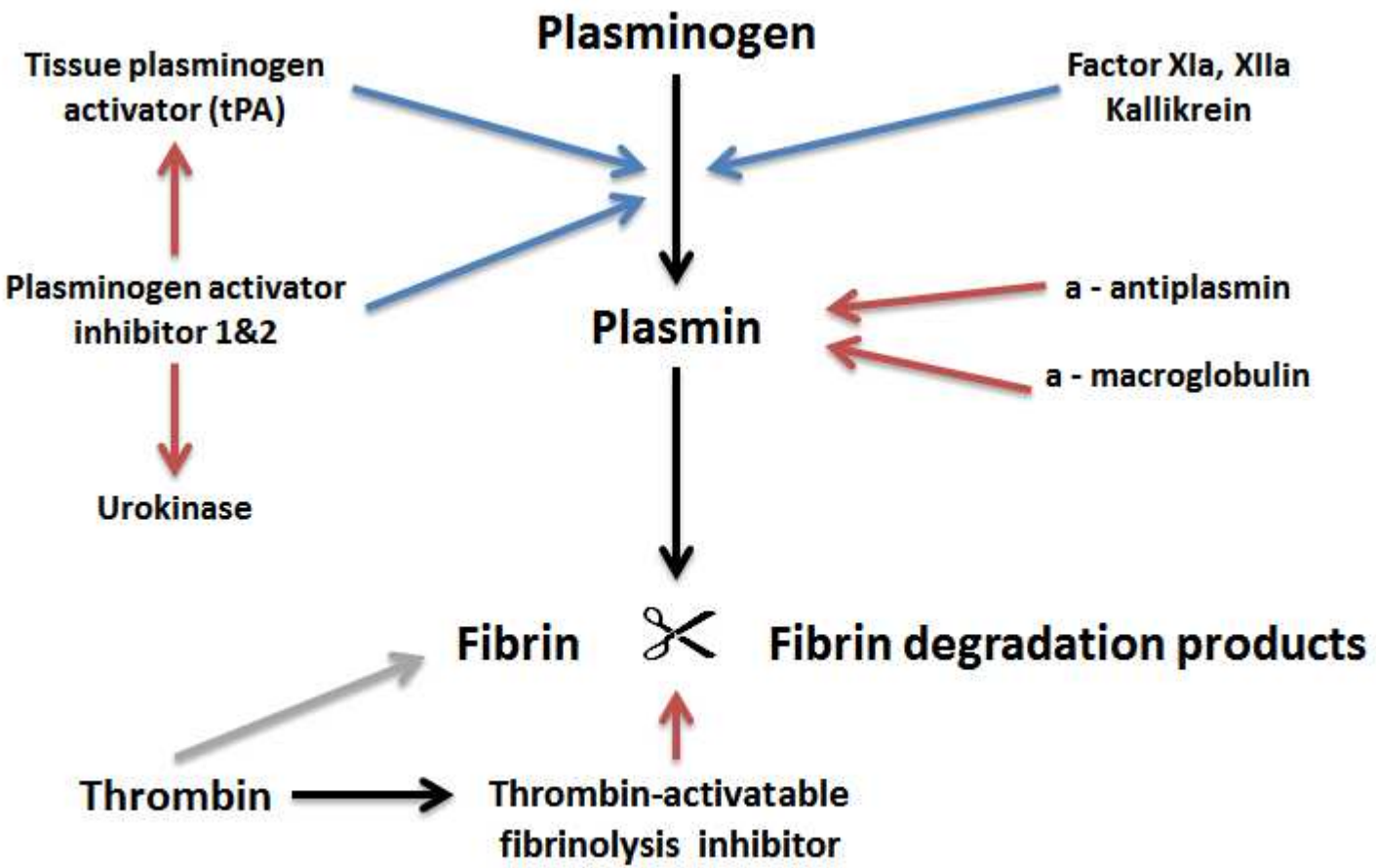

Fibrinolysis (simplified) - Blue arrows denote simulation, red arrows inhibition

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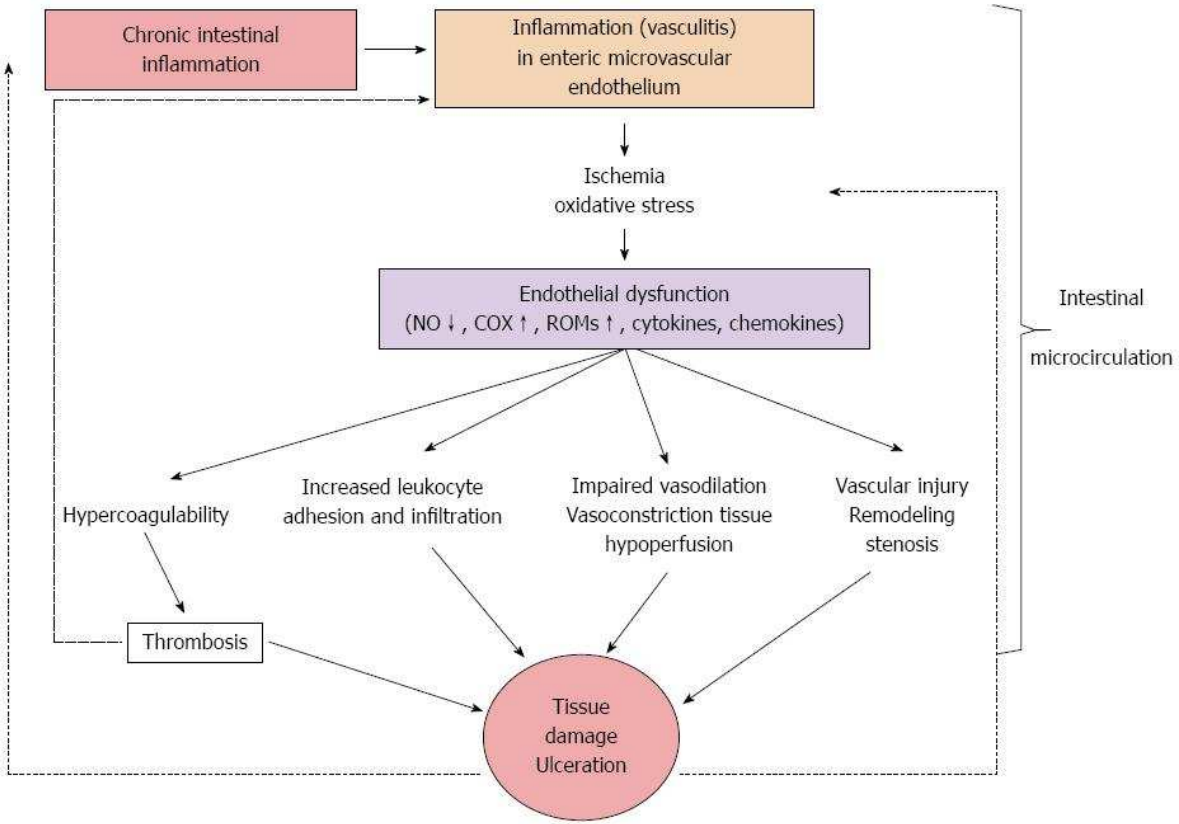

Zezos P et al. World J Gastroenterol 2014

Treatment (I)

Treatment of VTE in IBD patients follows the same protocols as for non-IBD patients.

Low-molecular-weight heparin is most commonly used initially

Long-term treatment usually comprises vitamin K antagonists or the new, non-vitamin K antagonist oral anticoagulants (i.e. Dabigatran, Rivaroxaban, Apixaban, and Edoxaban).

Horbor M et al. Journal of Cronhn and Colitis, 2016

Treatment (II)

The duration of treatment depends on the balance between the risk of recurrence [previous history, risk factors] and the risk of treatment induced bleeding.

Indefinite anticoagulant therapy can be discussed with IBD patients who present with a VTE episode while in clinical remission without another provoking factor.

Thromboprophylaxis should be considered for all inpatients with IBD.

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Bleeding complications

Veroux M, Angriman I, Ruffolo C, Barollo M, Buffone A, Madia C, Caglià P, Fiamingo P, D'Amico D. **Severe gastrointestinal bleeding in Crohn's disease.** Ann Ital Chir. 2003 Mar-Apr;74(2):213-5.

Belaiche J, Louis E, D'Haens G, Cabooter M, Naegels S, De Vos M, Fontaine F, Schurmans P, Baert F, De Reuck M, Fiasse R, Holvoet J, Schmit A, Van Outryve M. **Acute lower gastrointestinal bleeding in Crohn's disease: characteristics of a unique series of 34 patients. Belgian IBD Research Group.** Am J Gastroenterol. 1999 Aug;94(8):2177-81.

Driver CP, Anderson DN, Keenan RA. **Massive intestinal bleeding in association with Crohn's disease.** J R Coll Surg Edinb 1996;41:152–4.

Pardi DS, Loftus EV Jr, Tremaine WJ, Sandborn WJ, Alexander GL, Balm RK, Gostout CJ. **Acute major gastrointestinal hemorrhage in inflammatory bowel disease**. Gastrointest Endosc. 1999 Feb;49(2):153-7.

Farmer RG. **Lower gastrointestinal bleeding in inflammatory bowel disease.** Gastroenterol Jpn. 1991 Jul;26 Suppl 3:93-100.

Robert JR, Sachar DB, Greenstein AJ. Severe gastrointestinal hemorrhage in Crohn's disease. Ann Surg. 1991 Mar;213(3):207-11.

Suggerimenti

Considerare sempre il rischio emorragico (es. storia clinica di sanguinamento, presenza di insufficienza renale, piastrinopenia, discoagulopatia).

Nel trattamento iniziale e a medio termine (primi 2-3 mesi) preferire eparina. Durante il primo mese a dosi terapeutiche poi continuare con i 2/3 della dose in monosomministrazione.

Se terapia con Coumadin mantenere INR target intorno a 2.

Eseguire Eco-Doppler seriati per monitorare l'andamento "strumentale" (oltre che clinico) della malattia.

In casi selezionati eseguire studio ipercoagulabile completo.

Nella profilassi considerare sempre che via sia almeno 1 fattore di rischio (oltre alla malattia in fase attiva).

Conclusions

In IBD, there is an increased risk of thromboembolic events due to inflammation, nutritional deficiencies, hospitalisations, drugs, surgery and inherited and/or acquired prothrombotic factors.

Clinicians should be aware of these risks so that adequate prophylactic actions can be taken in all IBD ptz with flares, particularly in ptz who are hospitalised, submitted to surgery or undergoing treatment.

In the presence of signs and symptoms suggestive of thrombotic disease it is necessary to carry out a diagnostic test.

Treatment of VTE in IBD ptz follows the same protocols as for non-IBD ptz.

SAFETY FIRST

MIND THE BLEEDING

Teatro anatomico

Grazie per l'attenzione!