CASO CLÍNICO:
TROMBOSE E DOENÇA INFLAMATÓRIA

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Objetivos

- Apresentação caso clínico
- Interface doença inflamatória intestinal e trombose
- Anticoagulação

Caso clínico

- Menino, branco, natural e procedente de São José, Grande Florianópolis, Santa Catarina, no sul do Brasil.
- Aos 13 anos iniciou com crises de diarreia, 2 a 3 episódios ao dia, Bristol 5-7, 2 episódios de sangramento (em papel higiênico) dor perianal (fissura?). Dor abdominal média 3 X ao mês. Emagrecimento 10kg /6 meses.
- Após 6 meses, aparecimento lesões progressiva em região perianal. Negava lesões aftosas.
- História de bronquite (asma) na infância.
- 2 tios paternos IAM, óbito com 28 e 32 anos.

Exame físico

- palidez cutâneo mucosa +++/4+, sinais de desnutrição.
- abdome sem alterações
- importante edema, eritema e aspecto inflamatório perianal com presença de plicoma e fístula às 9 h.

Exames de imagem iniciais

- EDA/colonoscopia: úlcera duodenal e úlceras em íleo terminal.
- Eco doppler abdominal: espessamento do íleo terminal, hiperecogenicidade da gordura adjacente e linfonodomegalias mesentéricas ->compatíveis com doença de Crohn.
- Entero RM: espessamento íleo terminal, ectasia de vasos retos. Compatível com doença inflamatória intestinal em atividade, acometendo o íleo terminal.
- TC: arterite da aorta descendente na transição tóraco-abdominal. Espessamento da artéria mesentérica superior com afilamento importante, estenose por alteração circunferencial da parede com a luz com calibre de 1mm, com diâmetro longitudinal de 6 cm.

Diagnóstico

- Doença de Crohn Grave = A1 L1+L4 (úlcera duodenal + úlceras em íleo) B1p

Classificação Montreal modificada:

- Idade ao diagnóstico A1 ≤ 16 anos
  A2 17-40 anos
  A3 > 40 anos

- Distribuição/ localização: L1 – Ileal
  L2 – Colônica
  L3 – Ileocolonica
  L4 – Isolada TGI superior. Modificador se associado com TGI inferior, adicionar a L1-L3

- Comportamento: (doença perianal) B1 – Não estenosante / não penetrante
  B1p- Não estenosante / não penetrante com envolvimento perianal
  B2 – estenosante; B2p: estenosante com involvimento perianal
  B3 – Penetrante; B3p: penetrante com envolviomento perianal

Tratamento

- Iniciado tratamento com prednisona, azatioprina, substituído por metrotexate devido elevação de gama GT.
- Infliximabe

Evolução:

2 meses após inicio do tratamento apresentou nódulo em coxa esquerda seguido de edema e hiperemia trajeto vascular.

- **Tromboflebite safena magna direita**

48 h após quadro de dor tóraco lombar, ventilatório dependente seguido de dor em MIE

- **TEP** (cintilo**:** etapa perfusional - déficits perfusionais porção lingular do lobo superior pulmão E e porção basal do lobo inferior D. Na etapa inalatória irregularidades periféricas)

- **Tromboflebite safena magna esquerda**

- angioTC= Vasculite aorta torácica descendente e abdominal, mesentérica superior (80% obstrução), tronco celíaco, renal esquerda e carótida comum esquerda (40% obstrução).

TV superficial com evolução TVP

- 60-80% das tromboses superficiais ocorrem na safena magna
- Risco de TVP é negligenciado em pacientes com trombose superficial
- Meta-análise, 22 estudos > 4300 pacientes de TVS

  evoluíram para **TVP 18,1% e EP 7%**

Di Minno MND et al J Thromb Haemost 2016; 14: 964–72

Avaliação laboratorial

- Hemograma he 4,02 hb 10,1 ht 30,9 VCM 76,9 RDW 18,5 leuc 9050 S71/B9/L7,7M11,3/E0,10/Meta1
- Plaquetas 324 mil VPM 9.8 com macroplaquetas
- Ferritina 160,10 Pnta C reativa 334,9
- D'dímero 1594 a 1898 ng/mL fibrinogênio 724 mg/dL
- Antitrombina III 99,7% Anticardiolipina IgG 20 (positivo baixo) IgM 5 (negativo); FAN negativo
- Anticoagulante lúpico =1,35
- Anti-beta2 glicoproteína IgG e IgM negativos
- Homocisteína 6,49
- Troponina I <0,2 BPN normal
- CMV e EBV IgG reagentes, IgM não reagente. HIV, Hepatite B, C negativos, PPD não reator
- Gama GT 267 AST 27 ALT 31
- Calprotectina fecal = alta concentração (>200 µg/g)
- ANCA não reagente

Tratamento:

- HBPM e pulso metilprednisolona, seguido de AVK (RNI 2-3) e esquema anterior imunossupressão.

Controle ressonância

- 6 meses após novo quadro de Tromboflebite em coxa E =>

  pulso de metilprednisona 1 g/ 3 dias, rápida resolução

- AngioRM = Sinais de arterite, espessamento parietal aorta torácica descendente,

  aorta abdominal, artéria renal esquerda e artéria mesentérica superior.

OBS: Redução dos achados inflamatórios em comparação ao exame anterior. Não observado mais redução do calibre da carótida esquerda. Houve redução do estreitamento da a. mesentérica superior e da a. renal esquerda.

Evolução 2021

- Hb 14 Ht 43,9 leucócitos 9870 plaquetas 243.000
- VHS 3 - 6
- HbA1c 5,5%
- Creatinina 0,98
- PCR 6,5 – 48,9
- Vit B12 299 - 412
- Vit D-25 34,4
- CT 183 LDL 94,4; HDL 68
- Gama GT 111 TGP 16 TGO 11
- HLA B51 negativo
- Avaliação oftalmológica normal – sem uveíte

Tratamento atual

- Infliximabe= 400 mg IV/ 2 h (5 mg/kg) a cada 8 semanas
- MTX 1 ml SC 1 vez por semana => VO 25 mg 1 vez/semana (5cp de 2,5 mg 12/12h)
- Prednisona em desmame 50mg/dia => 20 mg/dia => 15 mg/dia
- Anticoagulação oral anti vit K (varfarina) 2,5 mg/ dia

Table 2. Prednisone or prednisolone tapering scheme [once-daily administration].

	Body weight		
Week	10–20 kg	20–30 kg	> 30 kg
1–3	20 mg	30 mg	40 mg
4	15 mg	25 mg	35 mg
5	15 mg	20 mg	30 mg
6	12.5 mg	15 mg	25 mg
7	10 mg	15 mg	20 mg
8	7.5 mg	10 mg	15 mg
9	5 mg	10 mg	10 mg
10	2.5 mg	5 mg	5 mg

As tapering schemes are largely based on empirical recommendations rather than on clinical trials, large variability exists among physicians. Shortening each stage from 7 to 5 days or any other tapering modification may be considered individually.

van Rheenen PF J Crohns Colitis.2020 Oct 7;jjaa161. doi: 10.1093/ecco-jcc/jjaa161

E agora, o que pensar?

- D. inflamatória intestinal - D. Crohn?
- D Behçet
- Vasculite - Takayasu?
- Behçet ou Takayasu mimetizando Crohn ou comorbidades?
- SAF relacionada à DII ou SAF soronegativa (seronegative APS)?
- Trombose associada ao tratamento?

Trombose venosa em doenças inflamatórias

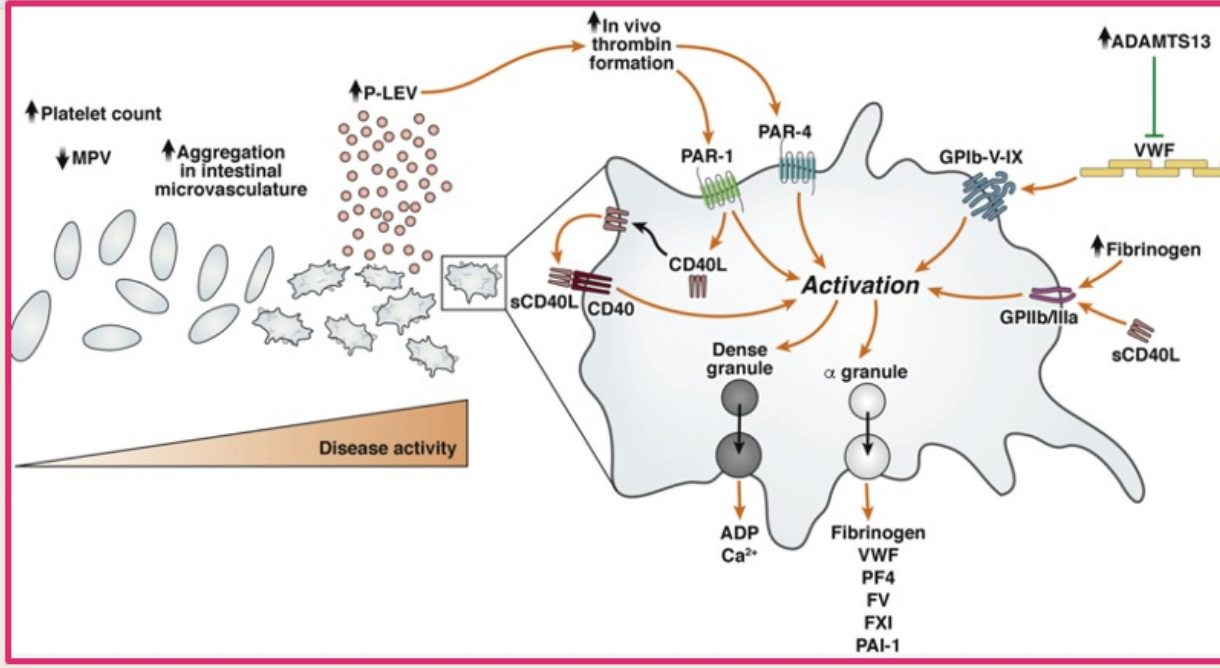
- Doenças inflamatórias sistêmicas com risco TEV:
  - D. de Behçet
  - D. inflamatória intestinal(DII)
  - Vasculites, espondilite anquilosante

Seyahi E et al Curr Opin Rheumatol 2020;32(1), 29–34
doi:10.1097/bor.0000000000000670
Lentz SR Hematol Am Soc Hematol Educ Program. 2016; 2016(1):180–187
doi: 10.1182/asheducation-2016.1.180.

Alguns comentários...

- VPM e doença inflamatória
- D Dímero
- Imunossupressão e risco trombótico

VPM



- Marcador atividade inflamatória e trombótica?

- **VPM ↓ em DII:**
  aumento megacariopoise -> plaquetose-> diminuição meia-vida
  plaquetas maiores são direcionadas para local de inflamação -> plaquetas circulantes VPM↓

- **VPM ↑** plaquetas jovens e reativas:

- Citocinas inflamatórias -> ploidia de megacariócitos, plaquetas maiores, > conteúdo de grânulos (aumento da agregação plaquetária, síntese e liberação de TXA2 e β-tromboglobulina), e expressão de moléculas de adesão.

Korniluk A at al Mediators Infamm 2019; 2019: 9213074
doi: 10.1155/2019/9213074
Lagrange J Clin Gastroenterol Hepatol 2021; 19(6):1088-97
doi.org/10.1016/j.cgh.2019.12.43

D Dímero em crianças

- Biomarcador para TEV limitado devido à alta sensibilidade e baixa especificidade.
- Baixo valor preditivo de TVP em crianças, principalmente se condições subjacentes (d cardíaca, trauma, neoplasia, d. inflamatória) = falso positivo.
- Adolescentes com baixa probabilidade clínica, D dímero normal pode excluir EP
- Valor de corte mais alto poderia ser mais específico para diagnóstico TVP e TEP

Avila L et al Am J Hematol. 2021;96(8):954-60.
doi: 10.1002/ajh.26212. Epub 202
Kanis J *Arch Dis Child* . 2018 ; 103 (9): 832 - 34
doi: 10.1136 / archdischild-2017-313315
Sharaf N et al Acad Emerg Med. 2018 Nov;25(11):1235-41.
doi: 10.1111/acem.13517

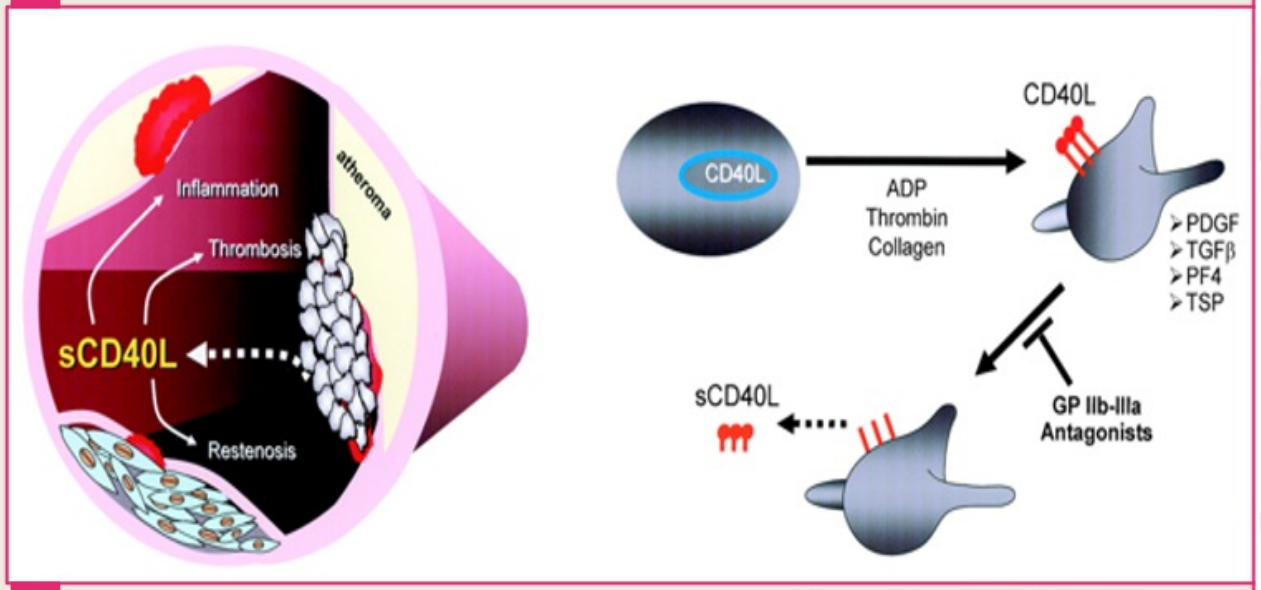
Terapias DII e Risco Trombose

Drug	Route of Administration	Therapeutic Indication	Risk of VTE	Comments
Mesalazine	Oral and topical	Mild-to moderate UC Prevention of postoperative recurrence of CD	Reduced	Specially designed studies are not available
Azathioprine/ 6-mercaptopurine	Oral	UC and CD maintenance of remission	Reduced	Specially designed studies are not available
CSs	Oral, intramuscular, intravenous, topical	Moderately to severely active UC or CD	Increased	Increased VTE risk also for intestinal acting steroids
MTX	Subcutaneous or intramuscular	CD maintenance of remission	Unclear	MTX needs folate supplementation to reduce hyperhomocysteinemia
Thalidomide	Oral	Steroid-resistant or steroid-dependent CD	Increased	VTE risk significantly increased when associated with CSs; VTE prophylaxis should be considered
Infliximab (and other anti-TNF-α)	Intravenous (IFX)Subcutaneous (ADA and GOL)	Steroid-resistant or steroid-dependent UC and CD	Reduced	Increased when IFX is associated with CS
Vedolizumab	Intravenous	Steroid-resistant or steroid-dependent UC and CD	Reduced	Paucity of data. Association with CS does not increase the risk
Ustekinumab	Intravenous (induction) followed by subcutaneous (maintenance)	Steroid-resistant or steroid-dependent CD	Reduced	Paucity of data
Tofacitinib	Oral	Moderately to severely active UC refractory to standard treatments	Unclear	Data from RCTs and observational studies are not sufficient to provide conclusive advice

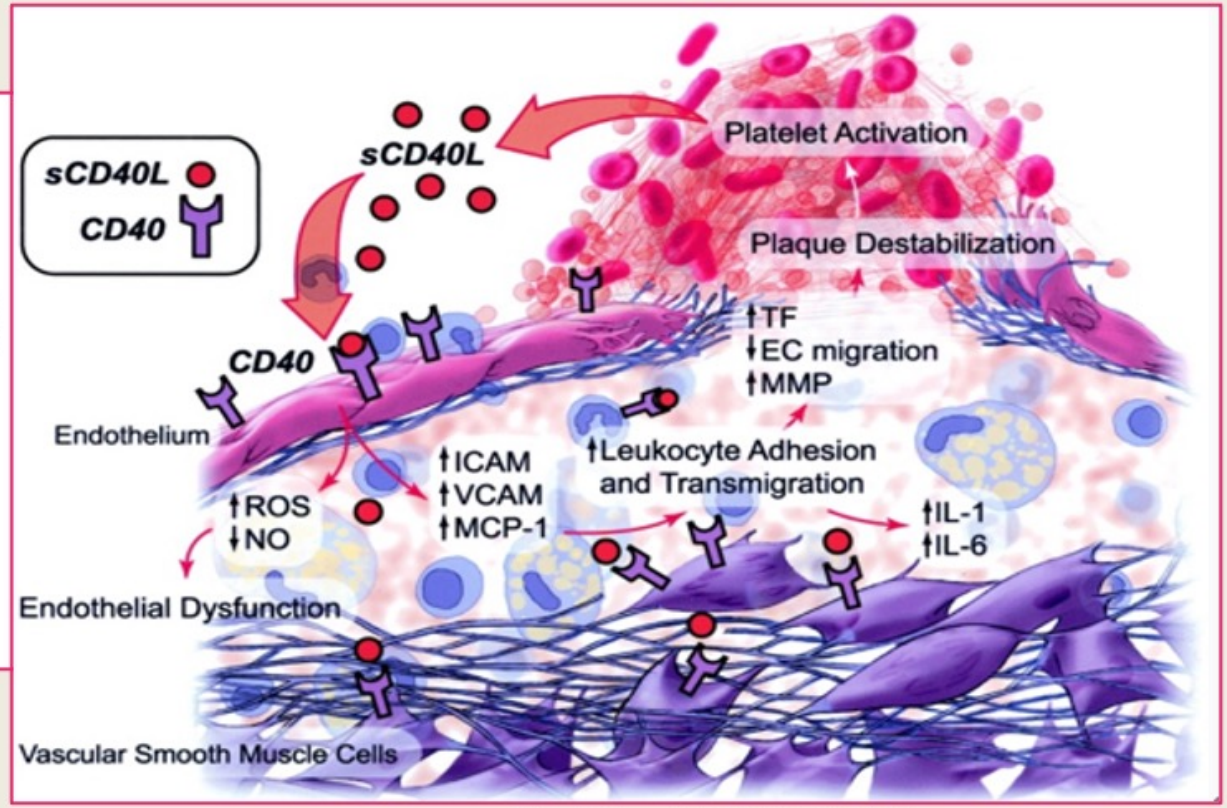
Abbreviations: corticosteroids, CS; Crohn's disease, CD; ulcerative colitis, UC; infliximab, IFX; adalimumab, ADA; golimumab, GOL; methotrexate, MTX; venous thrombo-embolism, VTE; tumor necrosis factor, TNF; randomized controlled trial, RCT.

Papa A J. Clin. Med. 2020; 9: 2115
https://doi.org/10.3390/jcm9072115

Infliximabe e trombose



Circulation 106(8), 896-9

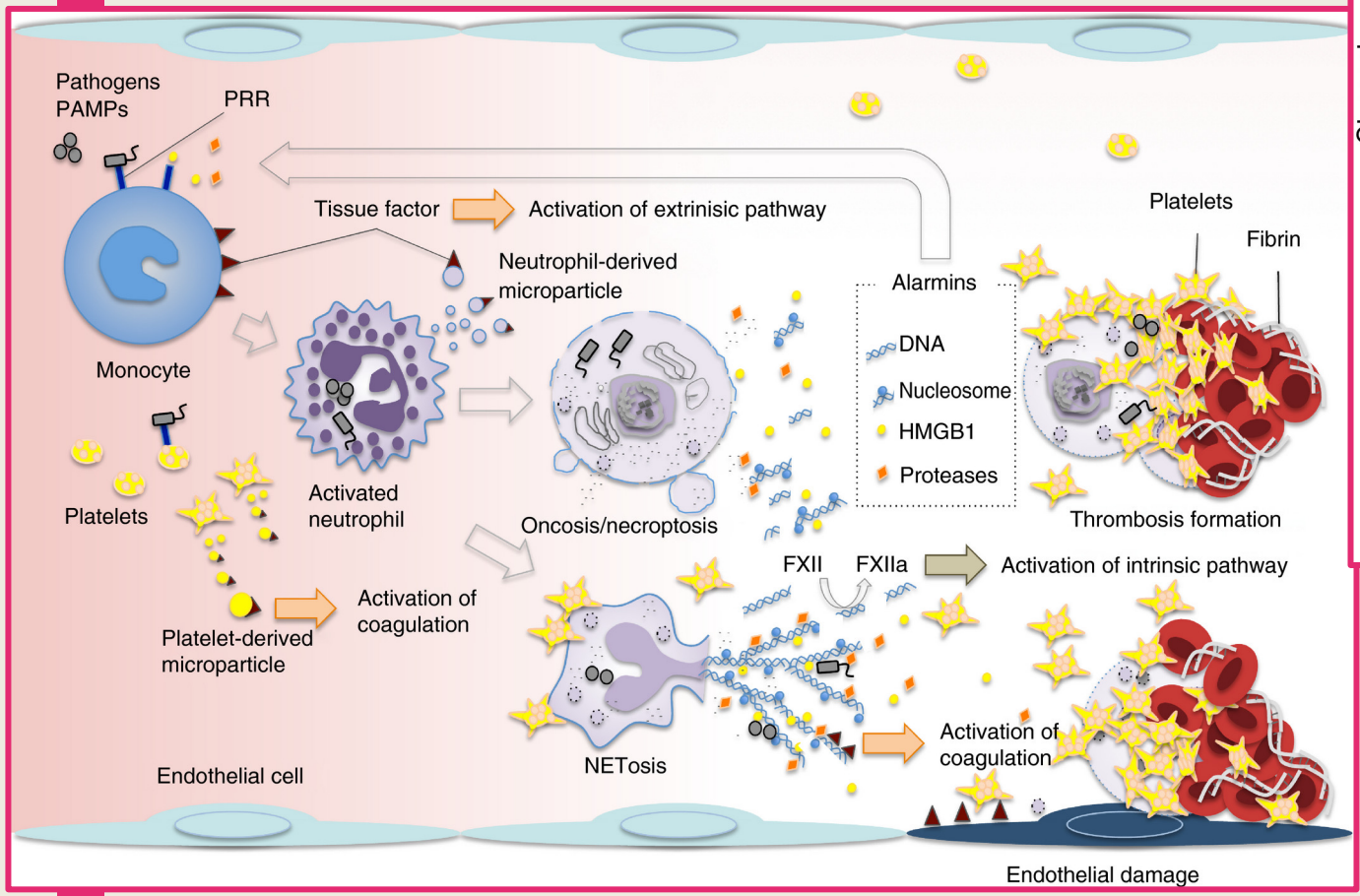


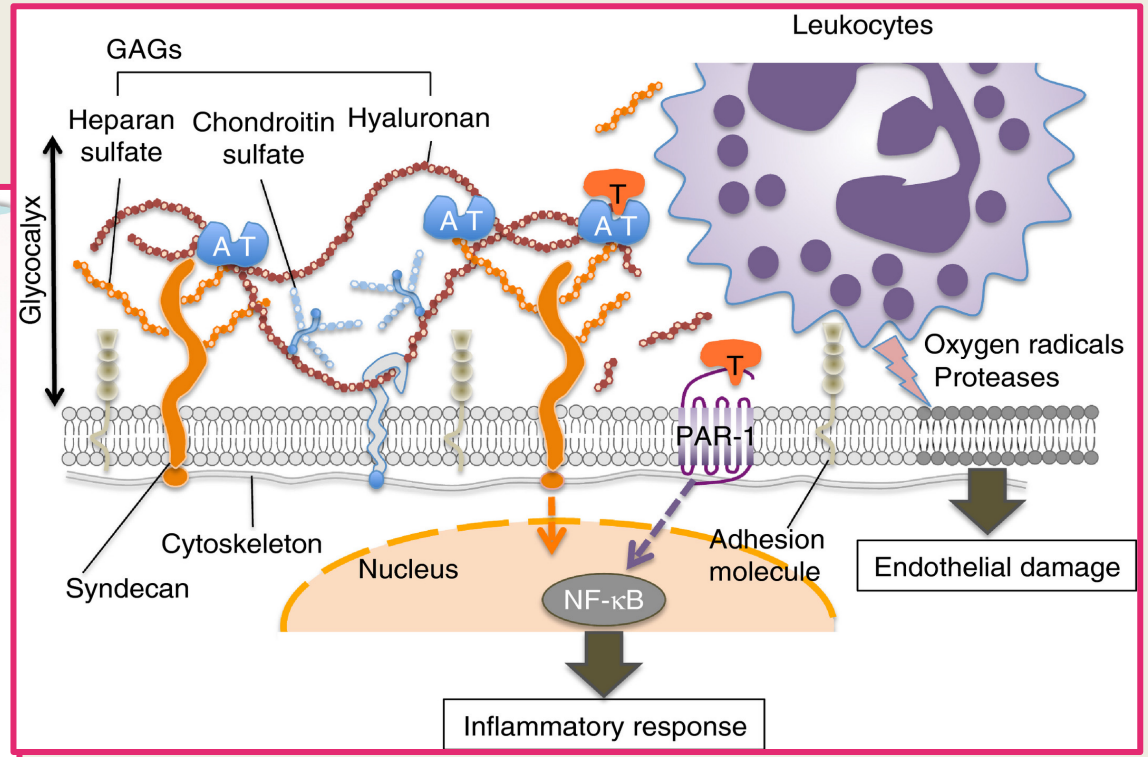
Circulation 108(16), 1917-23

- Infliximabe < risco de trombose
  ↓ reduz micropartículas circulantes e bloqueia a via sinalização CD40 / sCD40L => inibe expressão de VCAM1, da adesão leucócitos e do Fator tecidual

1. Sarlos P et al J Crohn's Colitis 2018;12: 489–98 doi: 10.1093/ecco-jcc/jjx162.
2. Higgins P et al Clin Gastroenterol Hepatol 2015; 13: 316–21
3. Danese S et al J. Immunol. 2006,176, 2617–24.

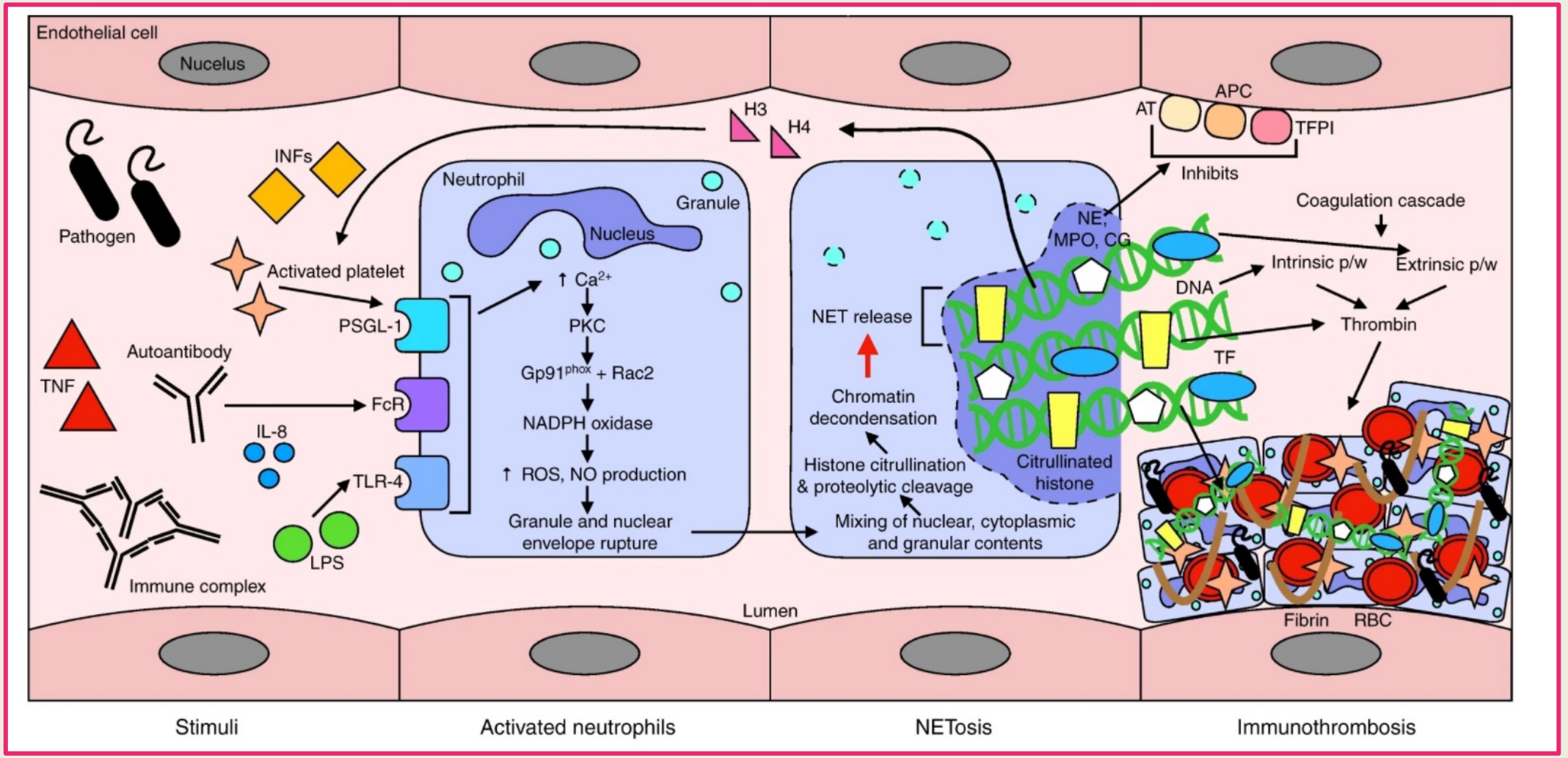
Imunotrombose





Iba T et al J Thromb Haemost 2018; 16: 231–41
doi.org/10.1111/jth.13911

Imunotrombose



evidências limitadas em crianças.
sepse e doenças autoimunes => vias fisiopatológicas semelhantes

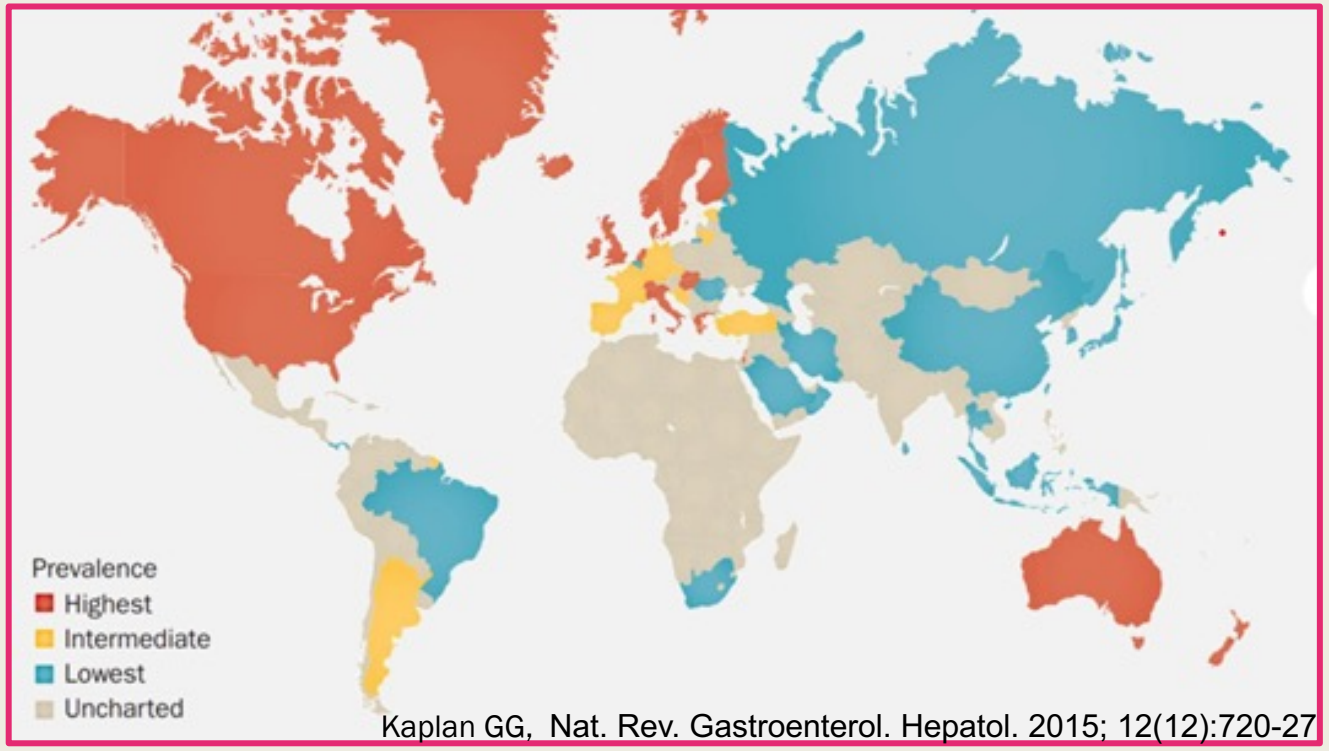
T Franchi et al Pediatr Res 2019; 86:19 – 27
doi.org/10.1038/s41390-019-0343-6

Doença Inflamatória Intestinal - DII

- > 5 milhões de pessoas mundo, aumento incidência anual
- Prevalência: EUA, Canadá e alguns países europeus 120-130 /100 mil hab.
- Brasil 13,25 (12 a 55) /100 mil hab

  53,83% D. Crohn
- Incidência 7 /100 mil habitantes
- 15 a 40 anos
- 25% diagnóstico <18 anos,

  25% < 10 anos 4% <5 anos



Kaplan GG, Nat. Rev. Gastroenterol. Hepatol. 2015; 12(12):720-27

Rosen JM JAMA Pediatr. 2015; 169(11): 1053–1060.
doi: 10.1001/jamapediatrics.2015.1982

DII e trombose

- Os pacientes com DII alto risco TEV - 3 a 15 X mais do que os pacientes sem DII.

  Risco aumentado de trombose arterial (IAM, isquemia esplâncnica , AVE)

- **Crianças:**

  Crianças hospitalizadas (exacerbação doença) com DII versus sem DII risco 6 X mais TEP e TVP

  RR de TEV crianças hospitalizadas com DII=

  DC 2,37 (IC 95% 2,16-2,61) Colite ulcerativa 1,99 (95% CI 1,51-2,64)

  DII com TEV aumenta: dias internação hospitalar (5 vs. 11), necessidade UTI (4,8% vs. 30,2%) ;

  custo total (32.800 vs. 123.000); mortalidade intra-hospitalar (0,2% vs. 1,5%) todos com P <0,001.

Kappelman MD et al .Gut. 2011;60(7):937-93

Nguyen GC et al. Gastroenterology 2014; 146: 835-48.e836

Chien K et al JPGN 2021;72(5): 748–51

Journal of Crohn's and Colitis, 2021, 1–10
https://doi.org/10.1093/ecco-jcc/jjab113
Advance Access publication June 27, 2021
Original Article

Original Article

Inflammatory Bowel Disease Increases the Risk of Venous Thromboembolism in Children: A Population-Based Matched Cohort Study

- Estudo com 3593 crianças com DII X 16.289 sem DII:
- incidência em 5 anos de TEV 10.000 pessoas/ano =

  DII **31,2** (IC95% 23,7-41,0) X sem DII **0,8** (95% CI 0,4-1,7)
- TEV (TVP E TEP) menos episódios em doença de Crohn do que a colite ulcerativa

Kuenzig ME.J Crohn's Colitis 2021, 1–10
https://doi.org/10.1093/ecco-jcc/jjab113

ORIGINAL ARTICLE: GASTROENTEROLOGY: INFLAMMATORY BOWEL DISEASE INFOGRAPHIC

Venous Thromboembolism in Pediatric Inflammatory Bowel Disease: A Case-Control Study

*Elana B. Mitchel, *Sara Rosenbaum, *Christopher Gaeta, †Jing Huang, ‡Leslie J. Raffini, *Robert N. Baldassano, §Michelle R. Denburg, and *Lindsey Albenberg

Estudo 2008 a 2018, crianças internadas

DII e TEV (n 23) X DII sem TEV (n = 111)

Characteristics, N = 23	N (%) or median (IQR)
Age at clot in years	17 (13.5–18.2)
Time from IBD to clot diagnosis in months	2.3 (0.8–41.8)
VTE was indication for admission	11 (48)
Admitted in previous 2 months	6 (26)
Admitted to the ICU	8 (35)
Started on anticoagulation	21 (91)
Duration of anticoagulation in months	3.8 (2.3–7.6)*
Occurrence of clot resolution	20 (87)
Time to resolution of clot in months	2.3 (1.4–3.1)
Required additional intervention (ie, thrombolysis)	5 (22)
Bleeding complication on anticoagulation	0 (0)
Recurrence of clot in subsequent encounter	1 (5)

ICU = intensive care unit.
*Does not include 2 patients who were still on anticoagulation at the end of the study period.

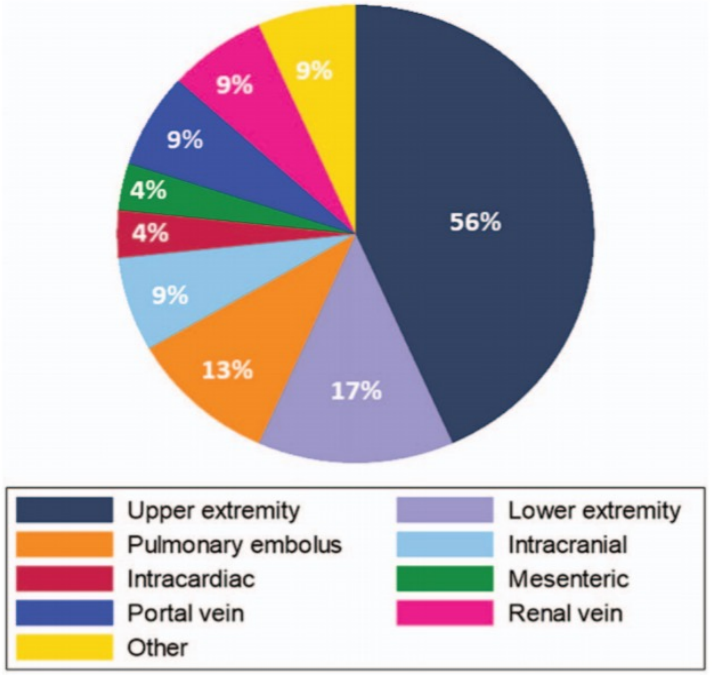


FIGURE 1. Location of venous thromboembolism in the 23 cases. *Single patient could have more than 1 clot location.

Mitchel E B et al J Pediatr Gastr Nutr 2021; 72 (5), 742-47.
doi: 10.1097/MPG.0000000000003078.

DII e TEV

Resulta de:

- Estado hipercoagulabilidade com doença em atividade
- Fatores de risco associados: CVC, imobilidade, cirurgia grande porte, corticoterapia tabagismo, SAF, hiperhomocisteinemia, obesidade, neoplasias, terapia hormonal, predisposição genética.

Fatores de risco para TEV = CVC e corticóide fatores de risco independentes para TEV em crianças.

TABLE 3. Univariate and multivariable model to assess risk factors for venous thromboembolism

Factor	Case, N = 23	Control, N = 111	Univariate OR	(95% CI)	*P* value*	Multivariable OR	(95% CI)	*P* value*
Age at hospitalization, years	16.88 (13.51–18.17)	16.87 (14.85–18.11)	–	–	–	–	–	–
Sex								
Male	12 (52)	55 (49)	–	–	–	–	–	–
Race								
White	20 (87)	97 (87)	–	–	–	–	–	–
Age at IBD diagnosis (years)	13.42 (10.03–17.10)	12.89 (9.12–15.52)	1.08	(0.93–1.24)	0.31	–	–	–
BMI *z* score	−0.47 (−1.55 to 0.80)	−0.24 (−1.08–0.59)	0.92	(0.66–1.30)	0.65	–	–	–
IBD type								
Crohn disease	14 (60.9)	80 (72.1)	–	–	–	–	–	–
Ulcerative colitis	7 (30.4)	24 (21.6)	1.88	(0.63–5.58)	0.26	2.65	(0.35–20.36)	0.35
Indeterminate colitis	2 (9)	7 (6.3)	2.25	(0.33–15.10)	0.41	0.45	(0.00–1517.13)	0.85
Disease activity score								
Remission/mild	9 (40.9)	33 (33.7)	–	–	–	–	–	–
Moderate	6 (27.3)	45 (45.9)	0.49	(0.16–1.52)	0.22	0.57	(0.11–2.90)	0.50
Severe	7 (31.8)	20 (20.4)	1.02	(0.27–3.84)	0.98	0.34	(0.46–2.50)	0.30
CVC present	15 (65.2)	10 (9.0)	25.3	(5.68–112.80)	<0.001	77.68	(6.86–880.6)	<0.001
Steroid exposure	17 (74)	51 (46.0)	4.5	(1.50–13.72)	0.01	12.7	(1.28–126.4)	0.03
Infliximab exposure	6 (26.1)	38 (34.2)	0.66	(0.24–1.83)	0.42	0.55	(0.12–2.64)	0.46
Admission duration, days	10 (7, 24)	5 (3, 7)	1.18	(1.07–1.29)	0.001	–	–	–
ICU admission	8 (34.78)	2 (1.80)	18.90	(4.0–89.32)	<0.001	–	–	–
Admission in the preceding 2 months	6 (26.10)	16 (14.7)	2.10	(0.73–6.05)	0.17	–	–	–
Platelet count at admission	335.0 (249.0–445.0)	376.5 (273.5–459.5)	1.00	(0.99–1.00)	0.23	–	–	–
Birth control use	2 (22.22)	15 (29.41)	0.56	(0.10–3.09)	0.51	–	–	–

BMI = body mass index; CI = confidence interval; CVC = central venous catheter; ICU = intensive care unit; OR = odds ratio.
**P* value significance defined as <0.05.

Mitchel E B et al J Pediatr Gastr Nutr 2021; 72 (5), 742-47.
: 10.1097/MPG.0000000000003078

Alterações na DII que contribuem para trombose

↑citocinas inflamatórias, ↑aumento da regulação do fator tecidual e ↓fibrinólise

Lentz SR. *Hematol Am Soc Hematol Educ Program*. 2016;**2016**(1):180–87

Abnormalities of Coagulation
↑ Fibrinogen
↑ Factors V, VIII, IX
↑ Prothrombin fragment 1 + 2, fibrinopeptide A and B, TAT complex
↓ Factor XIII/subunit A factor XIII
↓ Protein C, protein S, antithrombin
↓ TFPI

Abnormalities of Platelets
↑ Number, activation, aggregation

Abnormalities of Fibrinolysis
↓ tPA
↑ PAI, TAFI
↑ D-dimer, FDP, FgDP

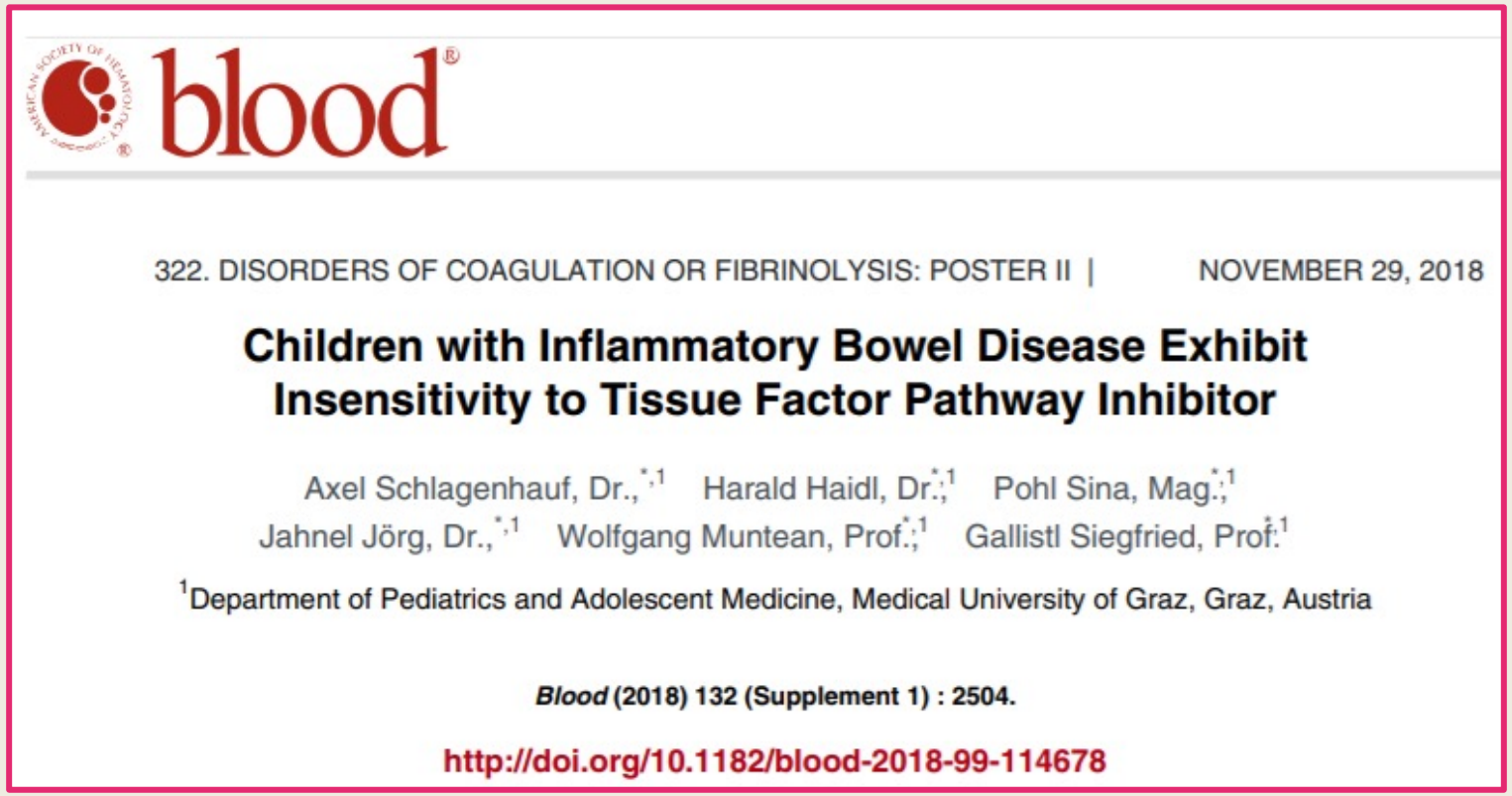
Endothelial Abnormalities
↑ Circulating thrombomodulin, ECPR, and von Willebrand factor
↓ Tissue thrombomodulin and EPCR

Nutritional Abnormalities
↑ Homocysteinemia, lipoprotein A
↓ Vitamin B6, Vitamin B12, folates

Immunological Abnormalities
Antibodies: antiphospholipid, antiprotein S, antiendothelial cells, anti-tPA

Abbreviations: inflammatory bowel disease, IBD; thrombin anti-thrombin, TAT; tissue factor pathway inhibitor, TFPI; tissue-type plasminogen activator, tPA; plasminogen activator inhibitor PAI; thrombin-activatable fibrinolyis inhibitor, TAFI; fibrin degradation products, FDP; fibrinogen degradation products, FgDP; endothelial protein C receptor, EPCR.

Alteração inibição TFPI em DII



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Children with Inflammatory Bowel Disease Exhibit Insensitivity to Tissue Factor Pathway Inhibitor

Axel Schlagenhauf, Dr.,[*,1] Harald Haidl, Dr.,[*,1] Pohl Sina, Mag.,[*,1]
Jahnel Jörg, Dr.,[*,1] Wolfgang Muntean, Prof.,[*,1] Gallistl Siegfried, Prof.[*,1]

[1]Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

Blood (2018) 132 (Supplement 1) : 2504.

http://doi.org/10.1182/blood-2018-99-114678

Alteração microvascular em DII

ORIGINAL ARTICLE: GASTROENTEROLOGY: INFLAMMATORY BOWEL DISEASE CME

Measurement of Microvascular Function in Pediatric Inflammatory Bowel Disease

Rebecca Winderman, Simon S. Rabinowitz, Katherine Vaidy, and Steven M. Schwarz

See "Measurement of Microvascular Function in Pediatric Inflammatory Bowel Disease" by Morhardt and Winter on page 608.

ABSTRACT

Background and Aims: Altered vascular flow is known to both play a role in the pathogenesis and influence the severity of inflammatory bowel disease (IBD). This phenomenon has been described in other systemic conditions and contributes to disease progression by facilitating inflammation and thrombosis. Microvascular dysfunction may represent an early sign of generalized vascular disease (VD). It manifests by failure to achieve a normal response of vasodilation and increased blood flow following a period of vaso-occlusion. Although thromboembolic complications are well described in IBD, their pathogenesis is not fully understood. This study sought to assess microvascular responsiveness in pediatric subjects with IBD, by recording postocclusion peripheral arterial pulsatile volume changes.

Patients and Methods: A total of 32 pediatric subjects were studied, including 16 with IBD and 16 age-matched controls. All patients with IBD were in clinical remission, and none had known VD. Vascular reactivity was evaluated using the Itamar Medical EndoPAT2000, a noninvasive device utilizing plethysmography to measure microvascular flow. Results were reported as the reactive hyperemia index (RHI), indicating post- to preocclusion pulsatile volume changes.

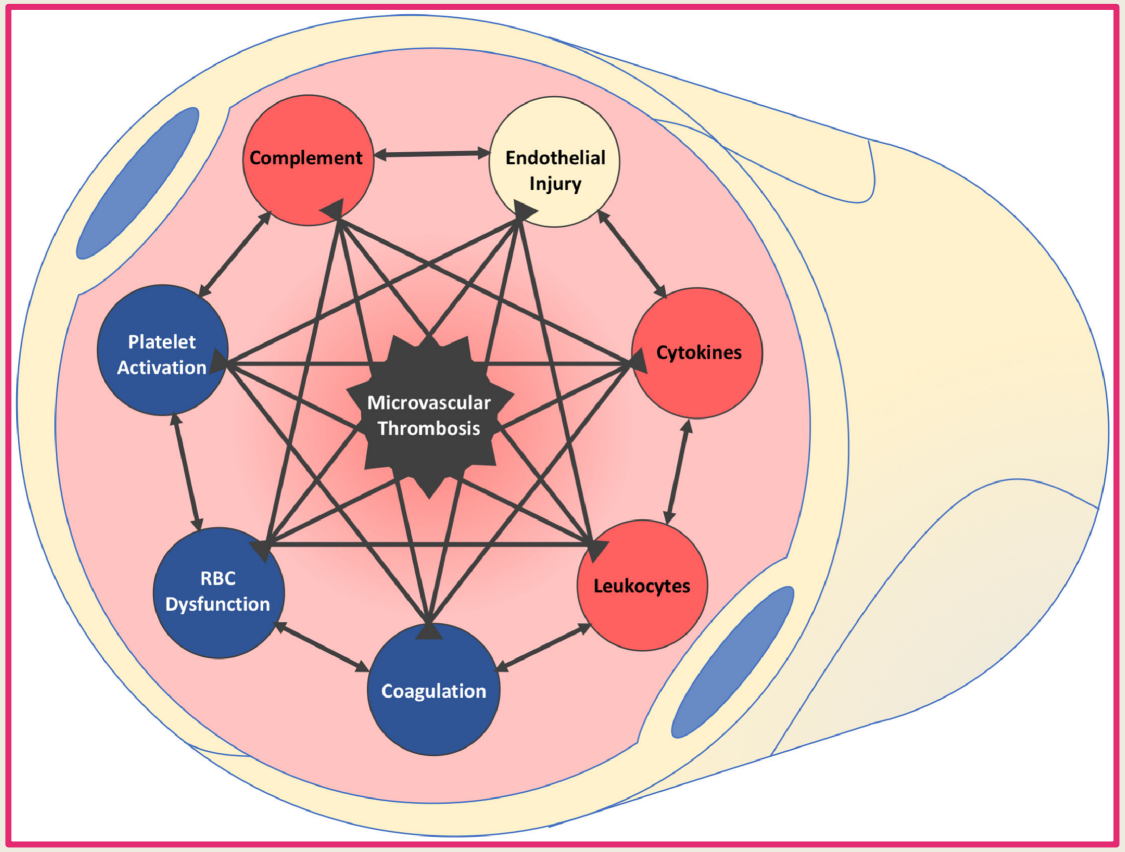
Results: Baseline characteristics, including body mass index, plasma lipid levels, hemoglobin, and serum albumin, were similar in both study groups. All patients with IBD were in clinical remission, assessed by standard disease activity scoring methods. Measurements of microvascular function indicated patients with IBD exhibited a mean RHI both within the range

What Is Known

- Children with inflammatory bowel disease are at increased risk for vascular disease and thromboembolic complications.
- A noninvasive method to measure microvascular hyperemic responsiveness has been validated for determining vascular disease risk in adults and in a small number of children with inflammatory bowel disease.

What Is New

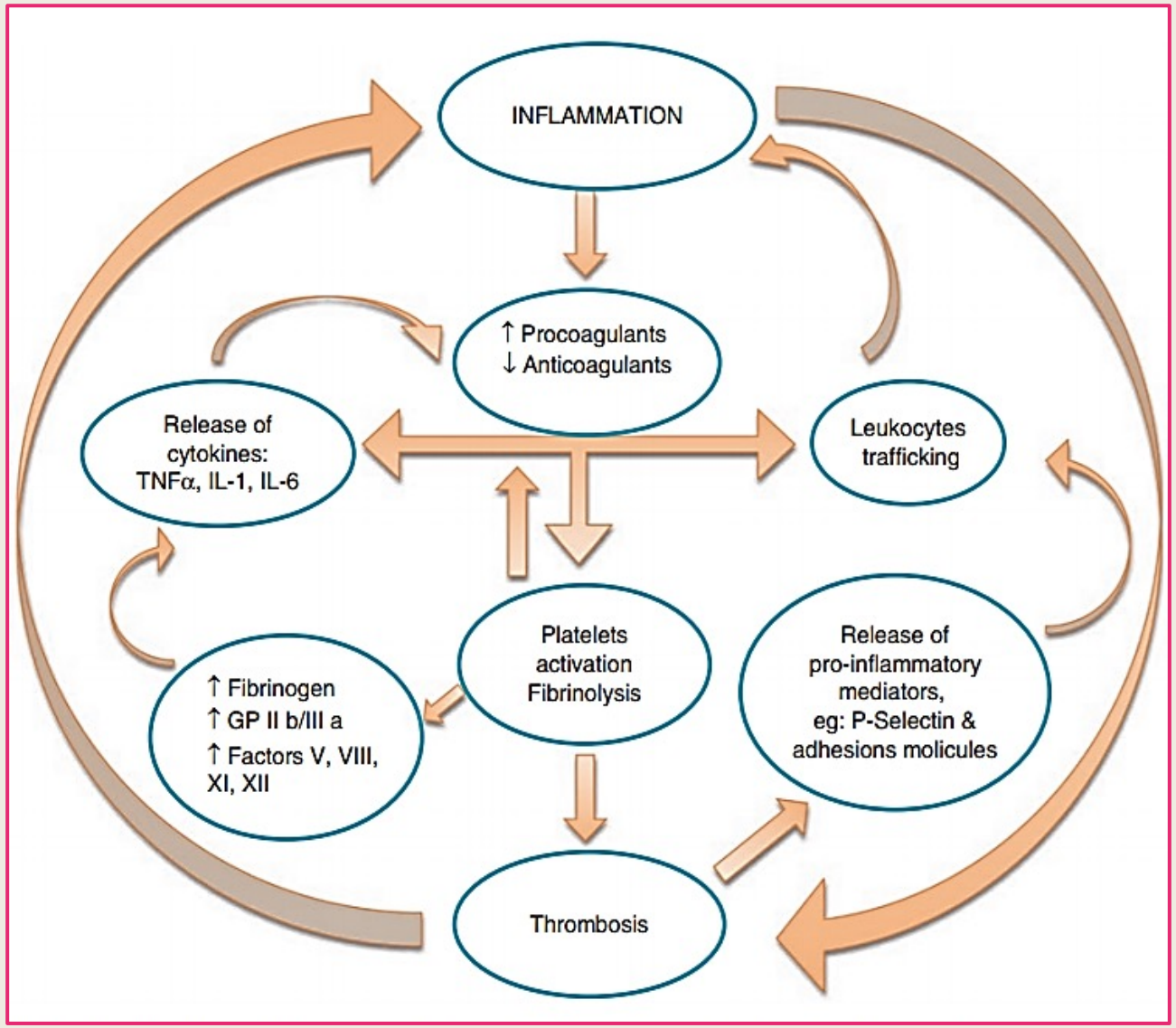
- In comparison with age-matched controls, pediatric inflammatory bowel disease patients in clinical remission demonstrate an attenuated reactive hyperemic response associated with increased vascular disease risk.
- Standard measures of inflammatory bowel disease activity appear insufficient for evaluating vascular disease risk.
- Noninvasive measurement of microvascular function represents an important screening tool to determine vascular disease risk in pediatric inflammatory bowel disease.



Este estudo comprovou que pctes com maior alteração da função microvascular deveriam ser monitorados para trombose com o índice médio de hiperemia reativa

Brayan M A Transl Res 2020; 225:105-30
doi.org/10.1016/j.trsl.2020.05.006

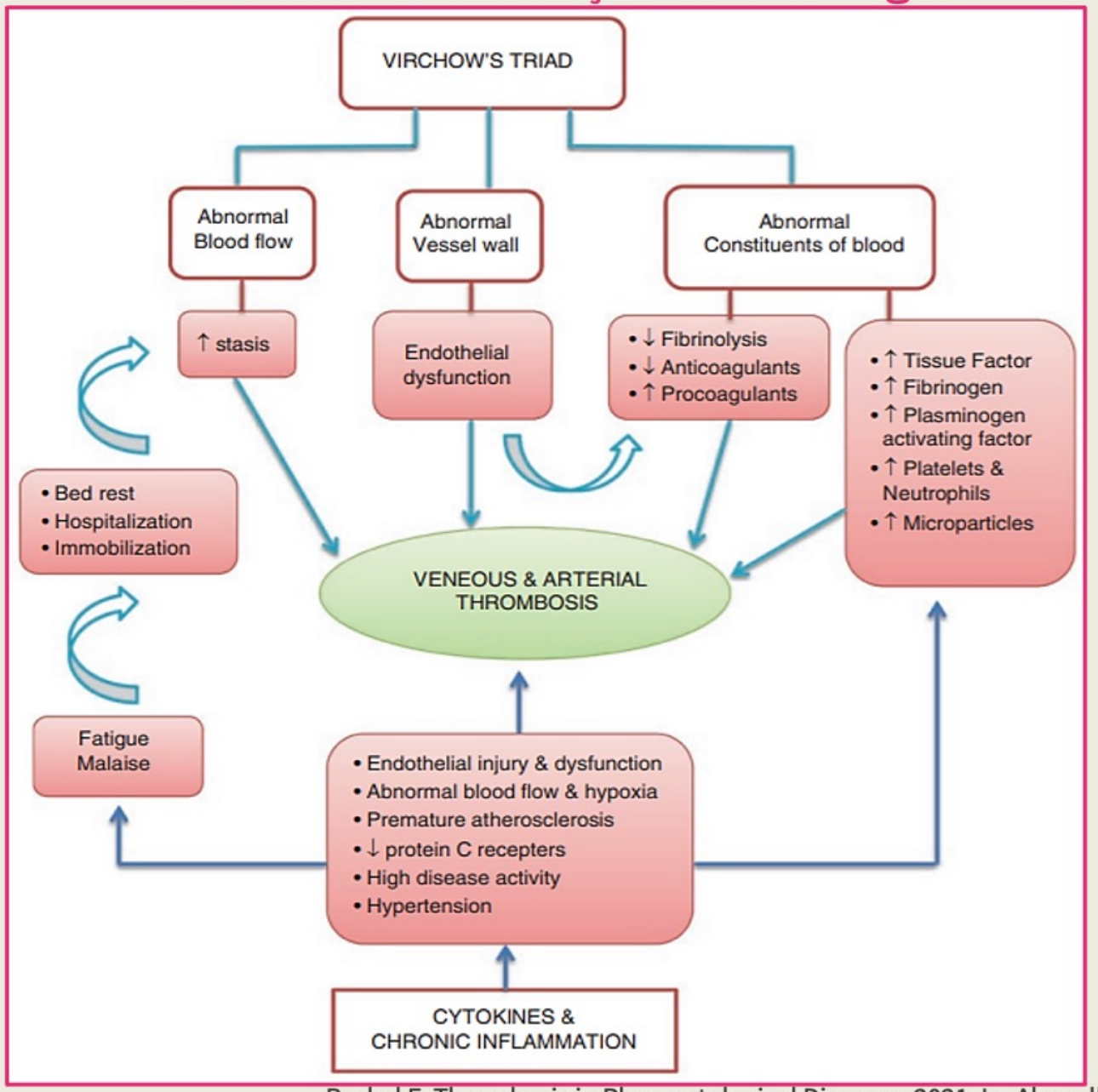
Tromboses em doenças reumatológicas



Papel multifatorial da inflamação na indução do estado de hipercoagulabilidade em doenças reumatológicas autoimunes

Bashal F. Thrombosis in Rheumatological Diseases, 2021. In: Almoallim H., Cheikh M. (eds) Skills in Rheumatology. https://doi.org/10.1007/978-981-15-8323-0_12

Tromboses em doenças reumatológicas



Bashal F. Thrombosis in Rheumatological Diseases, 2021. In: Almoallim H., Cheikh M. (eds) Skills in Rheumatology. https://doi.org/10.1007/978-981-15-8323-0_12

Valenti *et al. Pediatric Rheumatology* (2017) 15:33
DOI 10.1186/s12969-017-0162-4

Pediatric Rheumatology

REVIEW Open Access

Intestinal Behçet and Crohn's disease: two sides of the same coin

Simona Valenti, Romina Gallizzi, Dominique De Vivo and Claudio Romano*

Abstract

Behçet's disease (BD) and Crohn's disease (CD) are chronic immune-mediated, inflammatory disorders affecting many different systems (joints, skin, eyes, gastrointestinal and biliary tracts). Both disorders have fluctuating courses and when gastrointestinal symptoms are prevalent, differential diagnosis can be difficult. BD involves the gastrointestinal tract in 10–15% of cases with localized lesions in the ileocecal region. The clinical picture is heterogeneous with various clusters of disease expression. CD is a chronic inflammatory disorder, which can affect any part of the intestinal tract, as well as extra-intestinal tissue. Factors that contribute towards the pathogenesis of both disease include the host's genetic profile, and immune system, and environmental factors such as the gut microbiota. The aim of this manuscript is to provide a narrative review of clinical features of BD and CD, highlighting the importance of differential diagnosis and therapeutic approach, especially in the presence of gastrointestinal involvement. A comprehensive search of published literature using the Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/) database was carried out to identify all articles published in English from 1999 to October 2016, using 4 key terms: "Behçet Disease", "Intestinal Behçet's Disease", "Crohn's Disease" and" Inflammatory Bowel Disease".

Keywords: Behçet disease, Crohn's disease, Inflammatory bowel diseases, Intestinal Behçet disease

	Crohn's disease	Behcet's disease
Clinical manifestations	Abdominal pain, diarrhoea, rectal bleeding, nausea, vomiting, weight loss and fever	Oral and genital ulcers, joints and neurological involvement
Extra intestinal manifestations	Uveitis, arthritis, pyoderma gangrenosum, erythema nodosum, iron deficiency anaemia	Uveitis, arthritis, pyoderma gangrenosum, erythema nodosum, vaso-occlusive disease and thrombotic events
Histological features	Discontinuous distribution of longitudinal ulcers, aphthous and cobblestone appearance, focal cryptitis and epithelioid granulomas	Mucosal inflammation and ulceration; signs of vasculitis.
Most involved gender	Female	Male
Genetic predominant factor	NOD2/CARD15 (16p12-q13), CXCL16 (17p13), STAT6 (12q13), TLR4 (9q33), CARD9 (9q34.3)	HLA-B51
Therapy	Systemic corticosteroids 5-ASA/sulfasalazine Thiopurines or AZA/6-MP Anti TNF-α agents Nutritional therapy	Colchicine Systemic corticosteroids Mycophenolate mofetil Cyclophosphamide Thiopurines or AZA/6-MP Anti TNF-α agents
Surgery	Patients refractory to medical treatment or with complications	Refractory to medical treatment or with complications such as perforations, fistulae formation, and massive gastrointestinal bleeding

Valenti et al. Pediatric Rheumatology (2017) 15:33
DOI 10.1186/s12969-017-0162-4

Review Article
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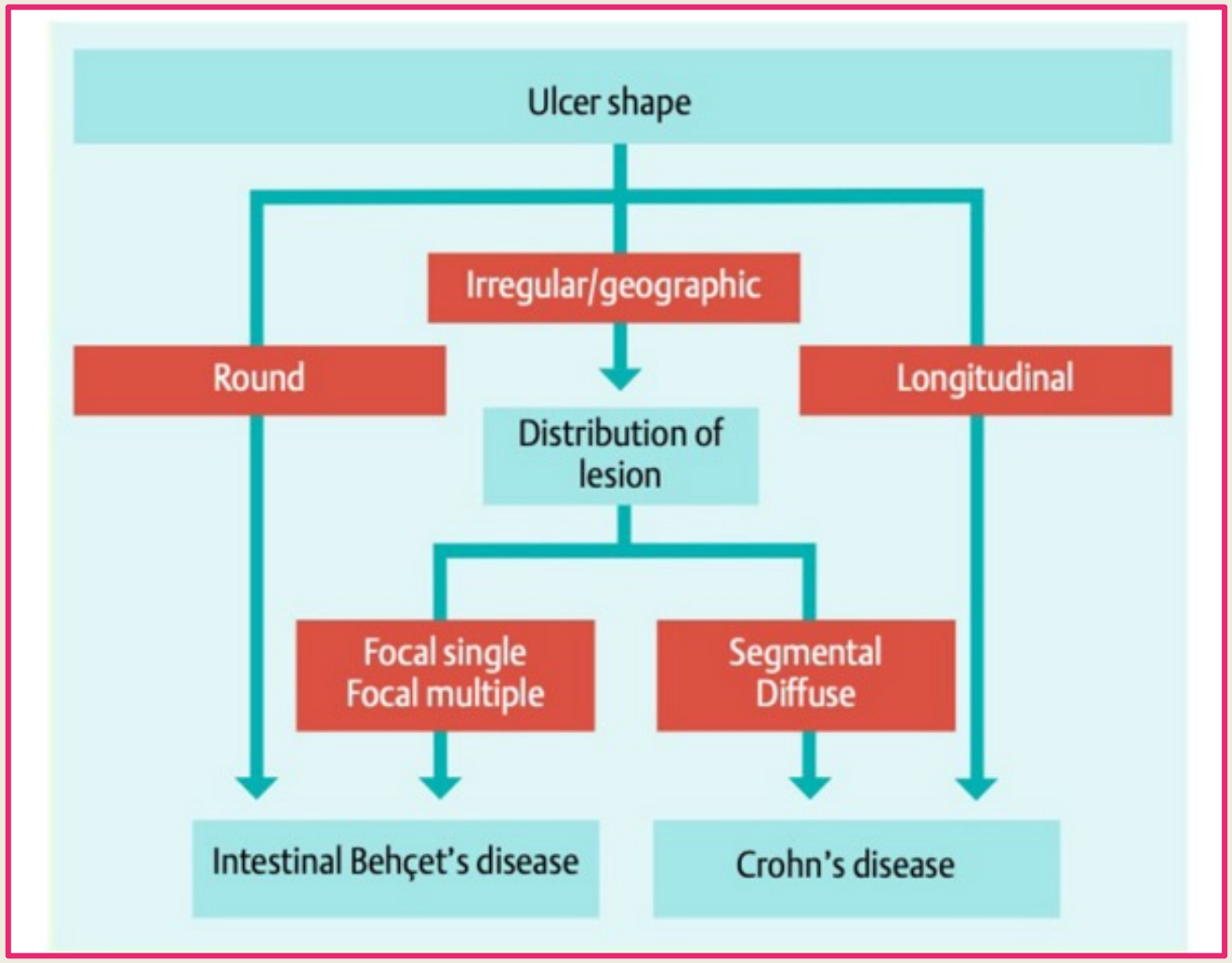
Intestinal Behçet's Disease: A True Inflammatory Bowel Disease or Merely an Intestinal Complication of Systemic Vasculitis?

Table 1. Similarities and Distinctions of Intestinal Behçet's Disease (BD) with Crohn's Disease

	Similarities	Distinctions
Genetics	*Interleukin (IL)-10* and the *IL-23R-IL-12RB2* loci	*Human leukocyte antigen-B51* allele *MHC class I related gene A*
Immunology	Activation of innate and adaptive immune system Increased Th1, Th17, CD4+ and CD8+ T cell, and γδ+ T cell activities Increased Th1-type cytokines The rate of anti-Saccharomyces cerevisiae antibodies detection is remarkably higher Bacterial contribution to the disease development	Serum anti-Herpes simplex virus-1 antibodies in the patients with BD were significantly higher than controls Heat shock protein (HSP) stimulate γδ+ T cells in BD patients because of homology between *Streptococcus sanguis* and human HSP Anti-endothelial cell antibody
Clinical findings	Wide variation of abdominal symptoms from mild discomfort to hematochezia Similar extra-intestinal manifestations	Rare anorectal involvement in intestinal BD Possible ischemic damage from vasculitis
Endoscopic findings	Segmental involvement Various type of ulcerations are able to seen Grossly normal looking intervening mucosa Mucosal healing is closely related with favorable clinical course	Fewer number of lesion Large size of ulceration Round or oval shaped ulceration Relatively more discrete and elevated border of ulceration
Histologic findings	Non-specific inflammation (lymphocytic or neutrophilic infiltrations)	Vasculitis can be seen Absence of non-caseating granuloma
Disease activity index	Concordance with clinical disease activity Discordance with endoscopic disease activity	Highly weighted general condition of patient and abdominal pain Less concern for laboratory test and diarrhea
Treatment	5-amino-salicylates/sulfasalazine, corticosteroids, thiopurines, thalidomide, and biologic agents are used for intestinal lesion	Concomitant use of medications for systemic BD is frequent
Prognosis	Similar admission, operation, and post-operative recurrence rate	Higher cumulative rate in use of corticosteroids and immunomodulators



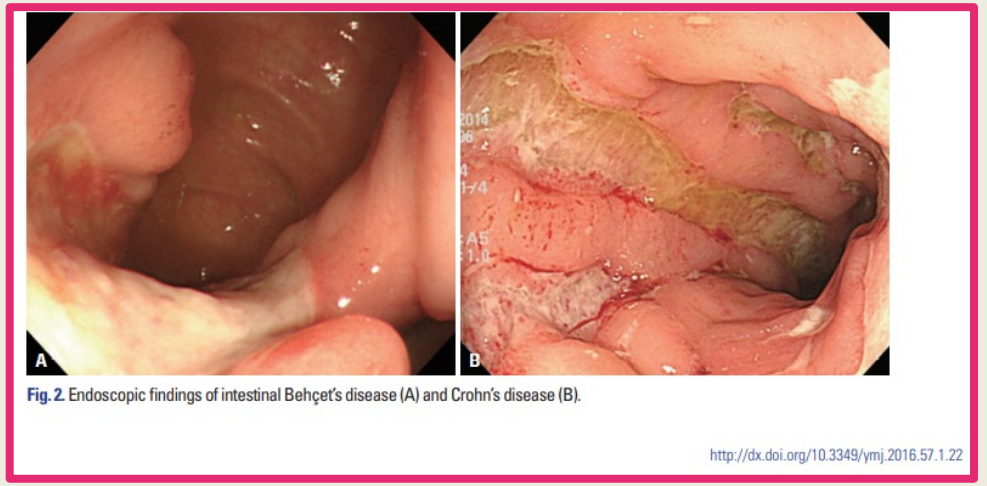


Fig. 2. Endoscopic findings of intestinal Behçet's disease (A) and Crohn's disease (B).

http://dx.doi.org/10.3349/ymj.2016.57.1.22

Lee SK, et al. Endoscopy 2009;41:9-16 https://doi.org/10.1055/s-0028-1103481

TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
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Differentiation between intestinal Behçet's disease and Crohn's disease based on endoscopy

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Background/aim: Differentiating intestinal Behçet's disease (BD) from Crohn's disease (CD) is highly challenging, as they often mimic each other in terms of clinical manifestations. Endoscopy is an important modality for distinguishing bowel lesions. The study was designed to identify clinical manifestations that are easily confused and to evaluate the efficacy of endoscopy for distinguishing intestinal BD from CD by several overlapping signs.

Materials and methods: The data from 111 patients with intestinal BD and 81 patients with CD were retrospectively analyzed. Logistic regression was applied to establish a prediction model based on endoscopic findings for the differential diagnosis. The diagnostic efficacy of endoscopy was verified using the area under the receiver operating characteristic (ROC) curve.

Results: Among intestinal BD patients mucocutaneous lesions were the leading clinical manifestations. Gastrointestinal symptoms were common in CD but were rare in intestinal BD ($P < 0.001$). CD patients with moderate-to-severe activity were more common than intestinal BD patients presenting with equivalent activity ($P < 0.05$). Independent factors that distinguished intestinal BD from CD were solitary ulcer in the ileocecal area ($P < 0.001$), perianal abscess ($P = 0.049$), single segment ($P < 0.001$), round intestinal ulcer ($P = 0.013$), intestinal obstruction ($P = 0.035$), and fistula ($P < 0.001$). The scores ranged from −2 to 3. The area under the ROC curve was 0.874 (95% CI: 0.823–0.926) ($P < 0.001$). With a score of 1.5 as the diagnostic cutoff value, the sensitivity and specificity were 76.3% and 80.6%, respectively.

Conclusion: Mucosal injuries were rarer in patients with intestinal BD than in those with CD. The differentiation model combining several endoscopy features appeared to be reliable for distinguishing between intestinal BD and CD.

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Volume 2017, Article ID 3918746, 7 pages
https://doi.org/10.1155/2017/3918746

Hindawi

Research Article

Comparison between Intestinal Behçet's Disease and Crohn's Disease in Characteristics of Symptom, Endoscopy, and Radiology

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Aim. To evaluate different parameters in differentiating intestinal BD from CD. *Methods.* The medical records of inpatients with intestinal BD and CD were retrospectively reviewed. The univariate value of different parameters was analyzed, respectively. A differentiation model was established by pooling all valuable parameters together. Diagnostic efficacy was evaluated, and a receiver operating curve (ROC) was plotted. *Results.* Forty-two BD patients and ninety-seven CD patients were reviewed. Demographic and clinical parameters that showed significant value included diarrhea, fever, perianal disease, oral ulcers, genital ulcers, skin lesions, and musculoskeletal lesions. Endoscopic parameters reaching clinical significance included multiple-site lesions, lesions confined to the ileocecal region, longitudinal ulcers, round or oval ulcers, punch-out ulcers, ulcers with discrete margin, ulcer size > 2 cm, stricture of bowel, and anorectal involvement. Radiologic parameters aiding the differentiation included involvement segments ≤ 3, asymmetrical pattern of involvement, intraluminal pseudopolyp formation, target sign, stricture with proximal dilation, comb sign, and fistula. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of the differentiation model were 90.5%, 93.8%, 92.8%, 86.4%, and 95.8%, respectively. The cutoff value was 0.5 while the area under the ROC curve was 0.981. *Conclusion.* The differentiation model that integrated the various parameters together may yield a high diagnostic efficacy in the differential diagnosis between intestinal BD and CD.

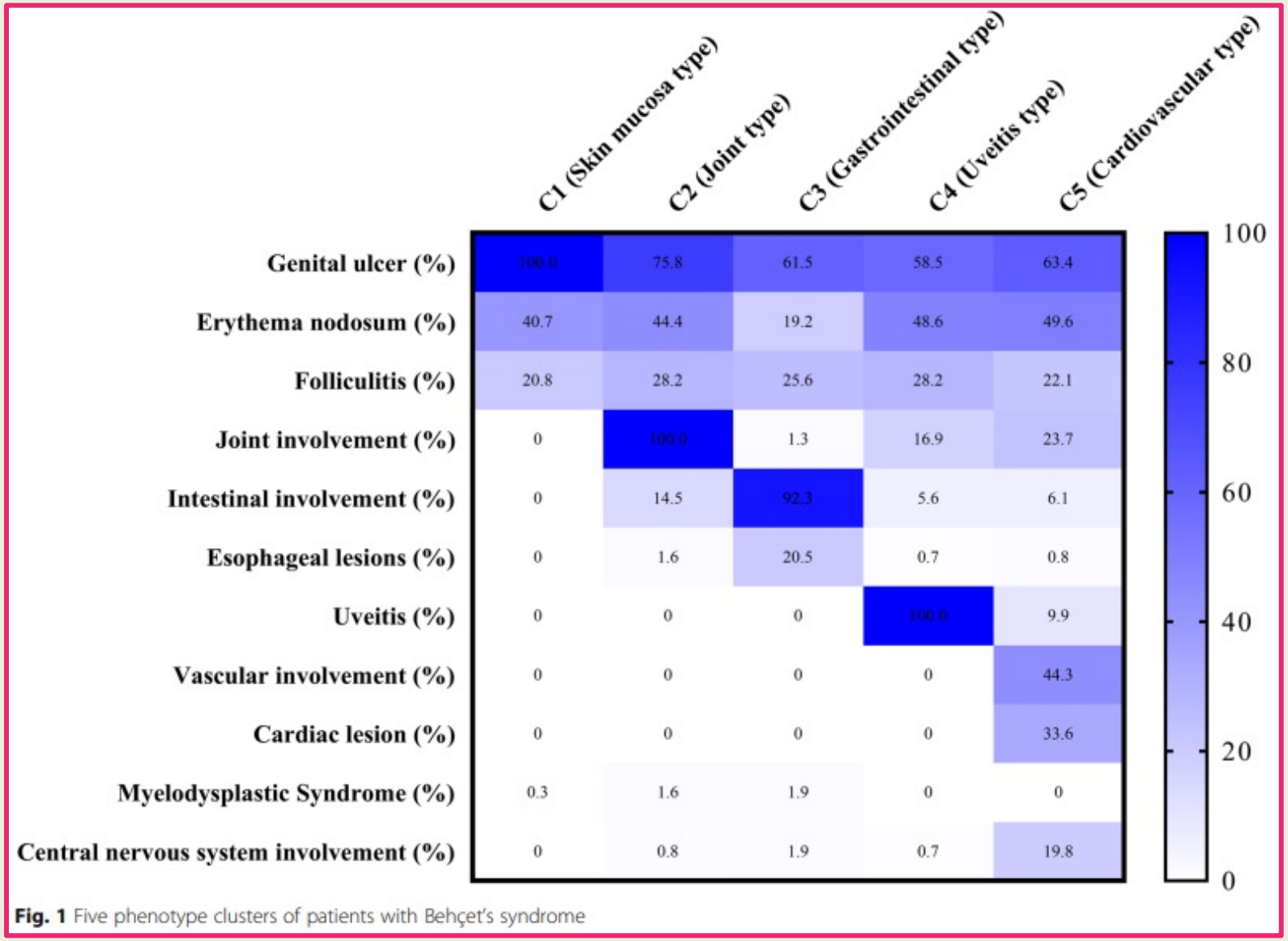
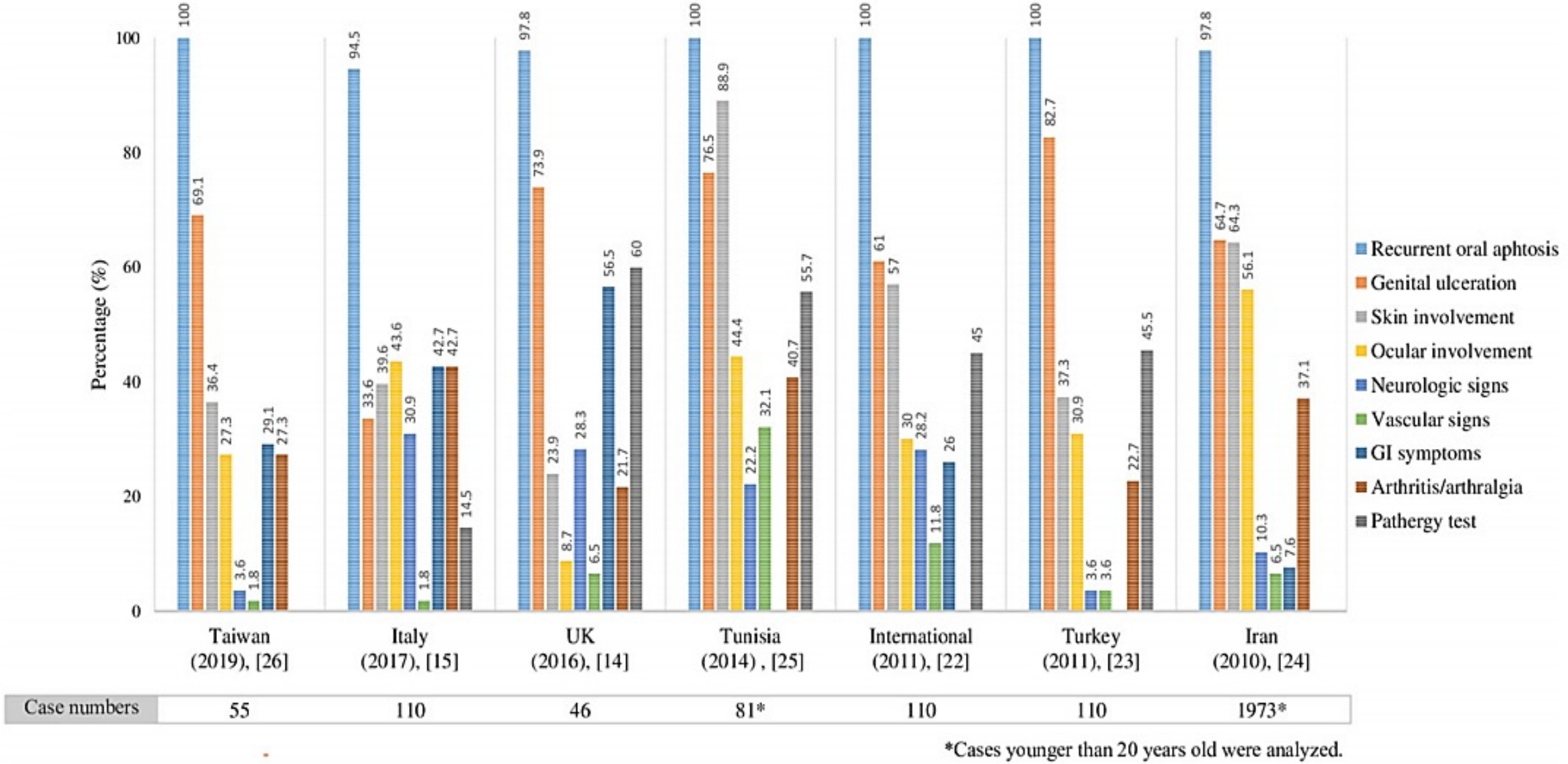


Fig. 1 Five phenotype clusters of patients with Behçet's syndrome

Zou et al. Arthritis Res Ther 2021; 23:45
doi.org/10.1186/s13075-021-02429-7



Percentage of the clinical features of pediatric Behçet's disease in different geographic regions

Hu YC, et al. Clinic Rev Allerg Immuno 2020 Aug.
doi: 10.1007/s12016-020-08809-2.

Vasculites em DII

- Vasculites associadas com DII:
- Takayasu
- Granulomatose com poliangiite (GPA), granulomatose de Wegener,
- Vasculite cutânea isolada
- Vasculite SNC

	% GI involvement	Preferred GI site	Possible GI complications	Remarks
IgAV	50%-75%	Small intestine	Intussusception, bowel wall ischaemic necrosis, perforation, haemorrhagic ascites, acalculous cholecystitis, pancreatitis, biliary cirrhosis	Faecal calprotectin: possible marker for GI involvement
KD	20%-35%	Small intestine hepatobiliary system	Paralytic ileus, duodenal perforations, obstruction or pseudo-obstruction, gallbladder hydrops, pancreatitis, cholangitis	GI involvement: possible marker for severity disease
PAN	24%-41%	Small and large intestine	Haemorrhage, infarction, perforation	DD with DADA2 in cases with early onset, severe organ involvement (ie stroke), especially with a positive parents' history or consanguinity/ endogamy
TA	10%-30%	Small and large intestine	Perforation	Possible association with inflammatory bowel disease
AAV	MPA: 58% GPA: 36% EGPA: 40%-46%	Small and large intestine	Haemorrhage	
BD	10%-40%	Ileum, caecum	Abscesses, fistulae, perforation, infarction, haemorrhage, thrombosis of hepatic veins, inferior vena cava, portal vein, Budd-Chiari syndrome	Faecal calprotectin, anti-α-enolase antibodies: possible markers for GI involvement DD with Crohn's disease Possible association with myelodysplastic syndromes with trisomy 8

Abbreviations: AAV, ANCA-associated vasculitis, BD, Behçet's disease, DADA2, deficiency of adenosine deaminase 2, EGPA, eosinophilic granulomatosis with polyangiitis, DD, differential diagnosis, GI, gastrointestinal, GPA, granulomatosis with polyangiitis, IgAV, IgA vasculitis, KD, Kawasaki disease, MPA, microscopic polyangiitis, PAN, polyarteritis nodosa, TA, Takayasu arteritis.

Trapani S et al Acta Paediatr. 2020;109:2226–2236. https://doi.org/10.1111/apa.1538

Vasculitis in patients with inflammatory bowel diseases: A study of 32 patients and systematic review of the literature

Main demographic data and clinical characteristics of 32 patients with both IBD and vasculitis enrolled in the Vasculitis Clinical Research Consortium (VCRC) longitudinal studies, followed in Canadian Vasculitis research network (CanVasc) centers and/or in the University of Toronto's IBD clinic

Patient ID	Sex	Inflammatory bowel disease			Vasculitis					
		Type	Age at dx (years)	Treatment	Type	Age at dx (years)	Clinical characteristics	Treatment	Length of follow-up (years)	Disease status and treatment at last follow-up
Large-vessel vasculitis										
1	F	CD	24	5-ASA	TAK	27	CONST, VASC, MSK, ART (+)	PDN, AZA	28	Recent flare; on PDN, MTX
2	F	CD	52	AZA, hemicolectomy	TAK	58	CONST, VASC, MSK, ART (+)	PDN, AZA	7.5	In remission; on AZA
3	F	CD	25	PDN, AZA, IFX, ADA	TAK	25	CONST, ARTH, ART (+)	PDN, AZA, IFX	5.5	In remission; on PDN, AZA, IFX
4	M	CD	13	IFX	TAK	17	CONST, HTN, VASC, MSK, ART (+)	PDN, MTX, IFX	1	In remission; on PDN
5	F	CD	15	5-ASA, PDN, IFX	TAK	17	CONST, VASC, ART (+)	MTX	NA	In remission; on PDN
6	F	CD	8	BUD, IFX, ileostomy, subtotal colectomy	TAK	17	CONST, HTN, VASC, PNS, SEM, CoA, ART (+)	PDN, AZA, MTX, RTX IFX, LEF, ADA, ABT, aortic stent	4.5	Recurrent flares; on PDN, MTX, IFX
7	F	CD	9	AZA, IFX, ADA subtotal colectomy	TAK	20	CONST, VASC, MSK, ART (+)	PDN, MTX	(new dx)	on PDN, MTX
8	F	CD	27	5-ASA, PDN, AZA, IFX	TAK	27	CONST, HTN, VASC, renal, ART (+)	PDN, AZA, MTX, IFX	8	NA
9	F	UC	16	5-ASA, PDN, 6-MP	TAK	29	CONST, VASC, ART (+)	PDN, ADA	1	Active disease; on PDN, ADA
10	F	UC	20	5-ASA	TAK	42	CONST, VASC, CNS, ART (+)	PDN, MTX	4	In remission; on PDN, MTX
11	F	UC	18	5-ASA, PDN, 6-MP	TAK	38	CONST, ART (+)	–	(new dx)	–
12	F	UC	34	PDN	TAK	49	CONST, VASC, PNS, ocular, ART (+)	PDN	(new dx)	on PDN
13	M	UC	30	PDN	GCA	57	CONST, PNS, PMR, ocular, ENT, biopsy (+)	PDN	1.5	In remission; on PDN
ANCA-associated vasculitis										
14	F	CD	8	5-ASA, 6-MP, MTX, IFX, ADA	GPA	20	CONST, MSK, CUT, ocular, ENT, PUL, atypical-ANCA (+), PR3 (+), biopsy (+)	PDN, MTX, Plasma exchange	(new dx)	PDN, MTX, Plasma exchange
15	F	UC	33	5-ASA	GPA	39	CONST, MSK, CUT, renal, ENT, c-ANCA (+), PR3 (+)	PDN, MTX, AZA, CYC	9	Low disease activity; on PDN
16	M	UC	58	5-ASA	GPA	71	CONST, CUT, PUL, c-ANCA (+), PR3 (+)	PDN, MTX	1	In remission; on PDN
17	F	UC	5	NA	GPA	55	CONST, MSK, ocular, ENT, c-ANCA (+), PR3 (+)	PDN, MTX	2	Recent flare; on PDN, RTX
18	F	UC	40	5-ASA, PDN, colectomy	GPA	50	CONST, ENT, PNS, PUL, C-ANCA (+), PR3 (+), biopsy (+)	PDN, CYC	14	In remission; on PDN
19	F	UC	52	5-ASA	GPA	54	CONST, MSK, renal, ocular, ENT, C-ANCA (+), PR3 (+), biopsy (+)	PDN, AZA, CYC	1	In remission; on PDN, AZA
20	F	CD	29	5-ASA	EGPA	65	CONST, MSK, CUT, PNS, asthma, PUL, c-ANCA (+)	PDN, AZA, CYC	6	In remission; on PDN, MMF
21	F	UC	14	5-ASA	EGPA	17	CONST, ocular, ENT, asthma, PUL, cardiac, p-ANCA (+)	PDN, AZA, MTX	10	In remission; off treatment
Cutaneous vasculitis										
22	M	CD	26	PDN, AZA, IFX	LCV	41	CUT, biopsy (+)	PDN, IFX	0.5	Active disease; on AZA, IFX, starting COL
23	F	CD	43	MTX	LCV	51	CONST, CUT, biopsy (+)	PDN, MTX	1	Active disease; on PDN, MTX, will begin IFX
24	M	CD	38	PDN, IFX	LCV	49	CONST, MSK, CUT, biopsy (+)	PDN	0.5	Active disease; on PDN, will begin IFX
25	M	CD	59	5-ASA	LCV	59	CONST, CUT, biopsy (+)	PDN, MTX	4	In remission; on MTX
26	F	UC	30	5-ASA	Cutaneous PAN	21	CUT	PDN, MTX, AZA, MMF	11	In remission; on MTX
Other vasculitis										
27	M	CD	13	5-ASA, PDN, MTX, IFX	Kawasaki	10	NA	NA	6	In remission; on IFX and MTX for CD
28	M	CD	13	PDN	IgA vasculitis	34	Renal, biopsy (+)	COL	6	Recurrent uveitis; considering MTX
29	M	CD	47	MTX, IFX	PAN	42	CONST, MSK, PNS	PDN, MTX	6	In remission; on MTX, IFX

Sy A, et al. Semin Arthritis Rheum.2016;45(4)475-482
Doi:10.1016/j.semarthrit.2015.07.2006

Rheumatology International
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Rheumatology
INTERNATIONAL

CASE BASED REVIEW

Takayasu arteritis in an adolescent with Crohn's disease

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Abstract

Crohn's disease (CD) and Takayasu arteritis (TA) are two distinct clinical entities. The likelihood of both diseases coexisting is low, and although CD co-occurs with all types of vasculitis, TA is the most common subtype. Herein, the case of a 15-year-old female, diagnosed with TA following an initial diagnosis of CD, is reported. A review of the literature, including a systemic review of the case reports and case series of children and adolescents up to the age of 21, with both CD and TA, follows the case description. In total, 28 cases of TA and CD were retrieved. The median age of patients was 14.8 years, they were mostly females (72%) and the median time between the two diagnoses was 3.7 years. In the majority of cases, CD was diagnosed first and TA followed. Computed tomography angiography and magnetic resonance angiography were the preferred imaging modalities to assist diagnosis.

- Coexistência de AT e DC em paciente, teoricamente 1 em cada 10 milhões de indivíduos

1	Yassinger 1976 [16]	15/F	CD	3 years	Hypertension, convulsions	CS, 5-ASA	Supportive
2	Owyang 1979 [17]	15/F	CD	2 years	Anterior chest pain	5-ASA	Aneurysmectomy
3	VanElburg 1992 [18]	14/F	TA	ND	Malaise, recurrent fever		CS
4	Hilario 1998 [19]	15/M	CD	4 years	ND	CS, 5-ASA, NSAIDs	CS, AZA
5	Levitsky 2002 [20]	12/F	CD	8 years	Substernal chest pain	CS, 5-ASA	Surgical treatment
6	Ohta 2003 [21]	16/F	TA	ND	Fever		CS
7	Baqir 2007 [22]	20/F	CD	1 year	Abdominal pain, weight loss	ND	ND
8	Dumarey 2007 [23]	18/F	ND	ND	ND	CS	CS
9	Kellermayer 2008 [24]	12/F	CD	5 years	Nausea, emesis	CS, 5-ASA, 6MP, infliximab	CS, 5-ASA, 6MP, infliximab
10	Liu 2009 [25]	17/M	TA	1 year	Fatigue, upper limp sourness	CS, 5-ASA	CS, axillary artery bypass
11	Katoh 2010 [26]	20/ F	CD	4 years	Anterior neck pain	Infliximab	CS
12	Ratuapli 2010 [27]	16/ M	CD+TA	ND	Hypertension, abdominal pain, nausea, vomiting, constipation, weight loss	CS, MTX, infliximab, AZA	CS, MTX, infliximab, AZA
13	Calderón 2010 [28]	20/F	CD	ND	Exacerbation of CD, abnormal blood pressure, systolic murmur	CS, 5-ASA, MTX	CS, AZA, infliximab
14	Kusunoki 2011[3]	15/F	CD	10 years	General fatigue, low-grade fever, painful sensations in left arm	5-ASA	CS, CY, valve replacement + coronary artery bypass
15	Taddio 2013 [29]	13/M	CD	1 year	Dyspnea at rest and at night, weakness	CS, AZA	CS, AZA, 5-ASA, CYC
16	Caruana Galizia 2015 [30]	17/F	CD	1 year	Anorexia, nausea, abdominal pain, low back pain	CS,5-ASA	ND
17	Sy 2016 [15]	13/M	CD	4 years	ND	Infliximab	Infliximab, CS, MTX
		15/F	CD	2 years	ND	CS, 5-ASA, infliximab	MTX
		8/F	CD	9 years	ND	Infliximab, CS, ileostomy, subtotal colectomy	Infliximab, CS, MTX, rituximab, adalimumab, aortic stent
		9/F	CD	11 years	ND	AZA, infliximab, adalimumab, subtotal colectomy	CS, MTX
18	Miyakawa 2016 [31]	19/M	CD	ND	Fever	CS, infliximab	ND
19	Talathi 2018 [32]	11/F	CD	At the same time	Abdominal and chest pain, fever, weight loss, diarrhea	Infliximab, MTX	Infliximab, MTX
20	Scheicht 2019 [33]	21/F	CD	ND	Left shoulder pain, malaise, mild abnormal pain	CS, 5-ASA (stopped because of remission)	CS, MTX, adalimumab
21	Takeuchi 2020 [34]	10/M	CD	7 years	Perianal abscess, fever, diarrhea Neck pain	CS, 5-ASA, AZA, infliximab, tacrolimus, adalimumab, ileocolectomy, allogeneic hemopoietic stem cell transplantation	CS, CYC, tocilizumab, AZA, allogeneic hemopoietic stem cell transplantation
22	Kollen 2020 [35]	6/M	CD	3 years	Back and chest pain, fever	Infliximab, AZA	CS, MTX
23	Evirgen Sahin 2020 [36]	15/F	CD	1 year	Unilateral neck pain	CS, AZA	ND

Síndrome antifosfolípide - Interface trombose e inflamação

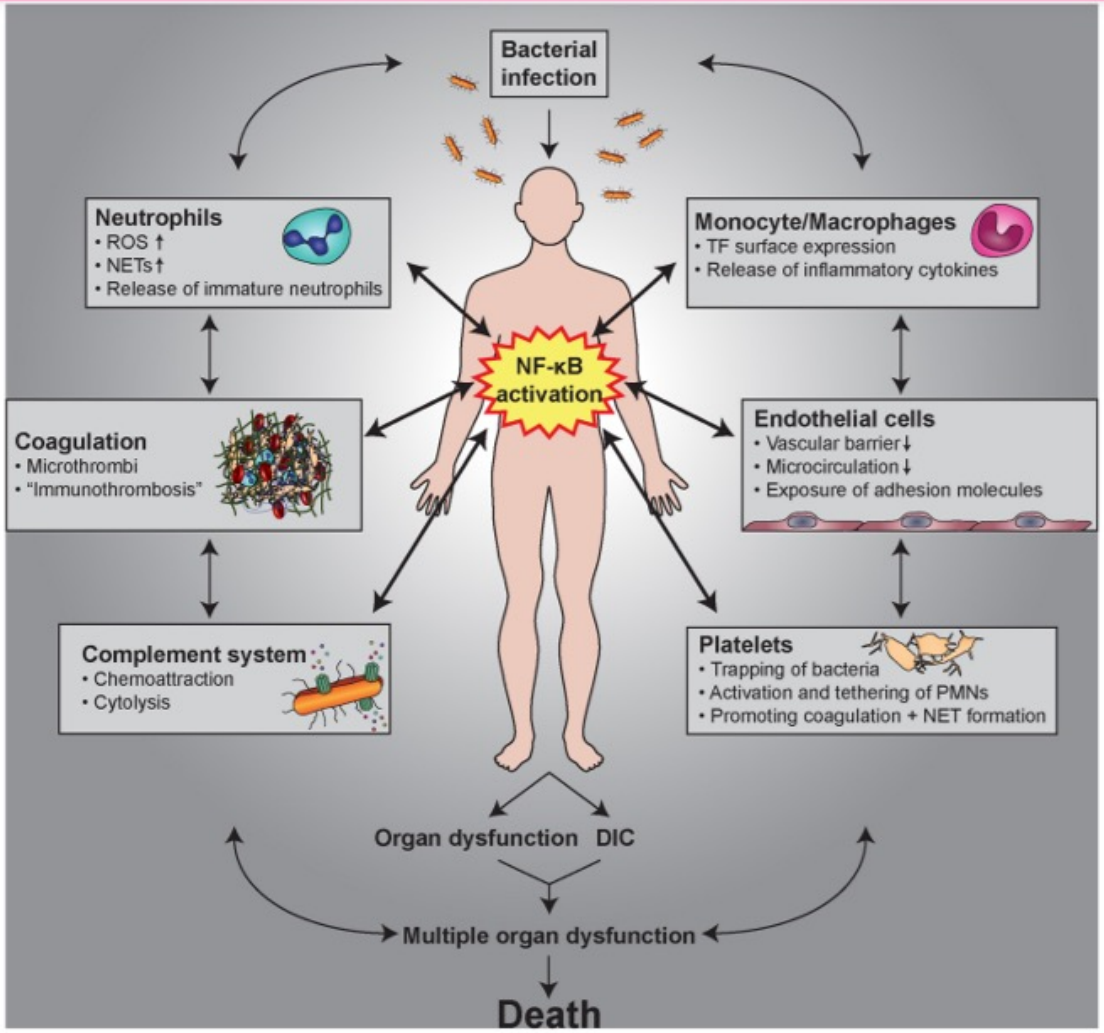


FIGURE 7 | Hallmarks of sepsis as a thrombo-inflammatory disease. Multiple, complex interactions between monocytes/macrophages, endothelial cells, platelets, the complement system, coagulation, and neutrophils are found under septic conditions. Activation of NF-κB causes not only the release and/or the generation of a multitude of pro-inflammatory mediators, but also the induction of pro-coagulatory mechanisms, which lead to the clinical signs and symptoms of sepsis.

- anticorpos anti-fosfolípides podem se ligar a TLR na superfície de macrófagos.
- ativação da coagulação e resposta inflamatória: FT, citocinas, NF-κB, TNF-α

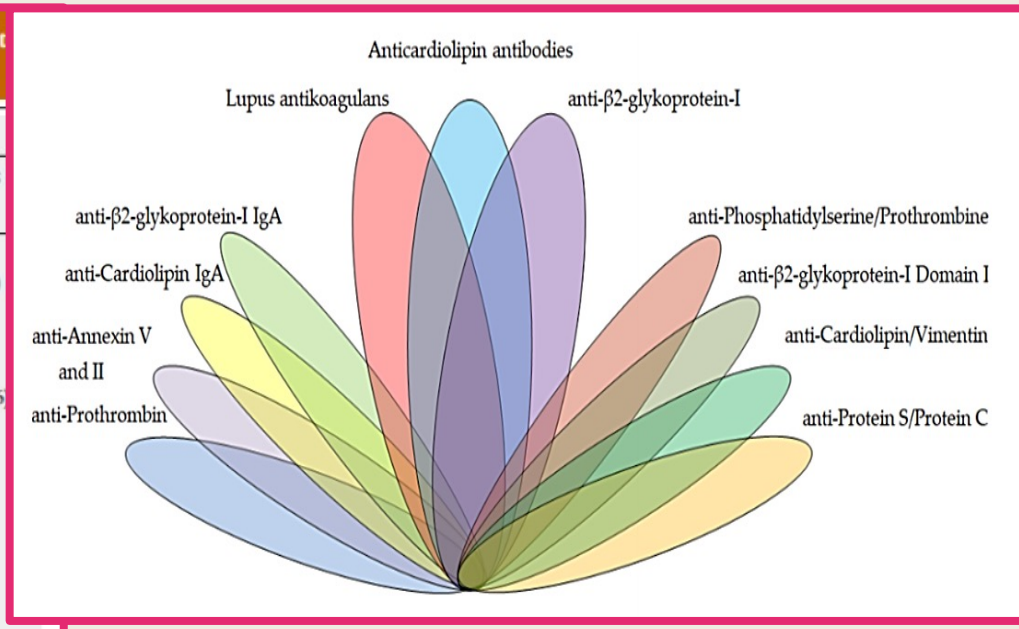
Mussbacher M Front Immuno 2019 4;10:85
doi: 10.3389/fimmu.2019.0008

Anticorpos Antifosfolípideos em DII

Table 6 Antiphospholipid antibodies, thrombophilia markers and clinical characteristics of total Crohn's disease according t presence and type of thrombosis *n* (%)

Factor	Follow-up of CD Total Cohort from diagnosis (*n* = 265)				
	No thrombosis (*n* = 251)	Arterial thrombosis (*n* = 3)	Venous thrombosis (*n* = 11)	No pregnancy loss (*n* = 146)	Pregnancy loss (*n* = 10)
Male/female	104/147	1/2	7/4	146/0	10/0
Age at presentation (yr)[1]	25.0 (19.0-33.0)	40.0 (28.0-42.0)	29.5 (23.3-39.3)	26.0 (20.0-35.0)	25.5 (21.0-35.0)
Frequent relapse	48 (20.2)	0 (0.0)	4 (36.4)	33 (24.1)	2 (20.0)
Previous thrombosis	1 (0.4)[3]	0 (0.0)	4 (36.4)[3]	2 (1.4)	0 (0.0)
Smoking habits yes	48 (19.1)	0 (0.0)	3 (27.3)	22 (15.1)	2 (20.0)
Follow up time from diagnosis, mo[1]	102.2 (63.3-172.8)[2]	149.9 (130.8-219.8)	186.3 (142.0-244.2)[2]	109.0 (61.8-184.6)	136.5 (95.4-180.6)
Positive markers (%)					
Anti-β2-GPI IgG and/or IgM	4.8	0	9.1	4.9	10
Anti-β2-GPI IgA	2.8	0	0	4.9	0
ACA IgG and/or IgM	12.1	0	27.3	13.9	10
ACA IgA	19.0	66.7	0	20.1	10
Anti-PS/PT IgG and/or IgM	14.6	50.0	36.4	18.3	40
Anti-PS/PT IgA	8.9	50.0	9.1	7.7	10
At least 1 APLA pos	48.0	66.7	54.5	52.8	60
At least 2 APLA pos	16.1	33.3	9.1	18.1	10
At least 3 APLA pos	3.2	0	9.1	4.9	0
Thrombophilia markers[3] (%)					
LA	7.5	0	0	5.1	0
PS deficiency (inherited and/or acquired)	8.1	0	25.0	12.7	0
ATIII deficiency (inherited and/or acquired)	0	0	0	0	0
PC deficiency (inherited and/or acquired)	3.0	0	0	4.8	0
FV Leiden	5.9[4]	0	42.9[4]	7.8	0
FII20210A	5.9	0	16.7	7.8	0

[1]Median (IQR); [2]Using Kruskal-Wallis test ($P \leq 0.01$); [3]Using χ^2-test with Yates correction ($P \leq 0.05$); [4]Serologic and genetic markers of thrombophilia were available in 105 patients. pts: Patients; APLA: Antiphospholipid antibodies; β2-GPI: Beta2-glycoprotein-I; ACA: Anti-cardiolipin antibody; PS/PT: Phosphatidylserine/prothrombin complex.



Biomedicines 2021, 9, 166

Formação de a. antifosfolipídeos em pcts com D Crohn sem necessariamente aumento risco trombose.

Sipeki N et al World J Gastroenterol 2015; 21(22): 6952–64.
doi:10.3748/wjg.v21i.22.6952

SAF soronegativa

- Pacientes com manifestações clínicas de SAF, repetidamente negativos para todos os critérios de um anticorpo antifosfolipídeo.
- SAF-SN podem apresentar positividade de outros anticorpos aCL / Vim, anti-PS / PT, anti-β2GPI IgA e aCL IgA.
- Pacientes com SAF-SN correm o risco de complicações trombóticas recorrentes e complicações da gravidez; tratamento profilático de longo prazo é, portanto, necessário Por este motivo, tem se mostrado cada vez mais benéfico revisar os critérios laboratoriais de SAF
- A introdução de anticorpos antifoslípideos adicionais na prática laboratorial de rotina certamente representará uma ferramenta útil para diagnósticos de SAF-SN mais precisos e rápidos

Trugliia et al.

Anticoagulação DII

- A DII leva a um risco aumentado de TEV recorrente comparado a pacientes sem DII.
- probabilidade de recorrência 5 anos após a descontinuação da terapia anticoagulante foi maior entre os pacientes com DII do que entre os pacientes sem DII.
- fatores de risco nos pacientes pediátricos com DII:
  - crianças mais idade,
  - cateter venoso central,
  - nutrição parenteral
  - doença em atividade
  - TEV prévio,
  - história familiar de TVE,
  - uso de corticosteróides,
  - mobilidade limitada
  - hipercoagulabilidade identificada.

Nylund NM, et al. J Pediatr Gastroenterol Nutr 56, 485–91
Chien, K.A., et al. J of Pediatric Gastroenterol Nutr, 2017; 66(2):1
doi:10.1097/MPG.0000000000001690

Anticoagular por quanto tempo?

TABLE 4. Length of treatment and reason for discontinuation of anticoagulation in incident cases of IBD and thrombosis

Subject no.	IBD subtype	VTE event(s)	Months treated	Reasons for discontinuation
1	UC	CSVT, PE, splenic, portal, hepatic veins*	12	Anti-cardiolipin antibodies negative, thrombus stable
2	UC	CSVT	3	Thrombus resolved
3	UC	CSVT	7	GI bleeding, thrombus resolved
4	UC	IVC, bilateral lower extremities	18	Splenic/portal colectomy, IVC filter in place, thrombus stable but not resolved
5	CD	Vertebral artery dissection and stroke (recurrent)	6, 8†	Thrombus resolved, vertebral artery embolization
6	CD	PE	3	Anti-cardiolipin antibodies negative, thrombus resolved
7	UC	CVL	3	Thrombus resolved
8	UC	CVL	1.5	Thrombus resolved
9	UC	CVL (recurrent)	28‡	Transferred to adult care on anticoagulants
10	UC	IMV	0	Partial resolution on prophylactic anticoagulation

CD = Crohn disease; CSVT = cerebral sinus venous thrombosis; CVL = central venous line–associated clot; GI = gastrointestinal; IBD = inflammatory bowel disease; IMV = inferior mesenteric vein; IVC = inferior vena cava; PE = pulmonary embolism; UC = ulcerative colitis; VTE = venous thromboembolism. * CSVT, PE, splenic, portal, and hepatic veins thromboses were concurrent. † Treated for 6 months with low-molecular-weight heparin, transitioned to aspirin, and then had recurrent thromboembolism and returned to low-molecular-weight heparin treatment for 8 months until a definitive vascular procedure was performed. The subject is being maintained on aspirin. (Aspirin is helpful in primary prophylaxis for arterial thromboembolism. It is not used for prophylaxis for venous thromboembolism.). ‡ On and off low-molecular-weight heparin for a total of 28 months because of compliance issues and multiple recurrent events.

Zitomersky NL, et al JPGN 2013;57: 343–47

Recorrência TEV em doenças imunes

Disease type	Study type	Proportion of patients with VTE recurrence	Cumulative incidence (5 y)	NOS score	Main limitation(s)
SLE, negative/unknown APS serology					
Gladman and Urowitz[29]	RC	23% (4/17)	N/A	2	Unclear definition for VTE in general/no follow-up times
Alarcón-Segovia et al[30]	RC				
Negative for ACl at 2 SD		5% (1/20)	N/A	3	1. Lacking classification of VTE (phlebitis/proximal VTE)
Negative for ACl at 5 SD		11% (3/28)	N/A		2. Lacking data on how VTE was treated
Ren et al[31]	RC	25% (51/201) (OR vs. non-SLE: 1.48)	N/A	4	Only DVT, unclear treatment/definition of recurrent VTE
Brouwer et al[32]	CS and RC[a]	Overall patients without APS: 2/9 (22%)	N/A	4	
		Patients with unprovoked index VTE: 0/4 (0%)			
Behcet's disease					
Ahn et al[33]	RC	Only AC: 75% (3/4) Pooled patients with immunosuppression: 9% (3/33)	N/A	4	1. No follow-up time 2. Small subgroups 3. Only DVT of the legs
Desbois et al[34]	RC	34% (100/296)	CR est.: 36.5%	5	
Tascilar et al[35]	RC	35% (312/882)	1-KM est.: 38.4%	4	~10% index and recurrent events not VTE
Yaşar et al[36]	RC	25% (24/96)	N/A	4	
Inflammatory bowel disease					
Solem et al[37]	RC	10.3% (10/98)		2	
Novacek et al[38]	RC (IDB) vs. PC (control)	Unprovoked index event: 26/86 Provoked index event: 8/30	1-KM: 33.4%	9	
Unselected patients with autoimmune disease					
Cosmi et al[39]	PC	10% (3/30)	N/A	6	Definition of autoimmune disease lacking

Abbreviations: AC, anticoagulation; ACl, anticardiolipin antibodies; APS, antiphospholipid antibodies; CR, competing risk; CS, cross-sectional; DVT, deep vein thrombosis; Est., estimate; IBD, inflammatory bowel disease (Crohn's and ulcerative colitis); KM, Kaplan–Meier; N/A, not available; NOS, Newcastle-Ottawa scale; OR, odds ratio; PC, prospective cohort; RC, retrospective cohort; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.

Borjas-Howard et al

Recomendações profilaxia trombose em crianças com DII

- Diagnóstico e tratamento precoce de trombose reduz significativamente o risco de morbimortalidade.
- Intervenções não farmacológicas: mobilização, hidratação e compressão ou dispositivos pneumáticos para todos os > 12 anos com DII hospitalizados
- Anticoagulação profilática dependerá dos fatores de risco do paciente e de uma abordagem de cuidado multidisciplinar, incluindo pediatria geral, hematologia e gastroenterologia.
- Não há nível de evidência elevado para prevenção de TEV nessa população, a profilaxia não é utilizada de forma padronizada.

Cheng K et al World J Gastroenterol 2020 Mar 28; 26(12): 1231–1241.
doi: 10.3748/wjg.v26.i12.1231

Nguyen GC et al *Gastroenterology* 2014; 146:835–848
oi: 10.1053/j.gastro.2014.01.042

Conclusões:

- ❑ Há risco elevado de trombose em pacientes com doenças inflamatórias intestinais, principalmente para doença em atividade;
- ❑ A profilaxia em crianças com doenças inflamatórias ainda necessita de estudos para avaliar os reais riscos e benefícios -> ensaios clínicos multicêntricos
- ❑ Indicação para pacientes adolescentes e que já apresentaram TEV
- ❑ Avaliar a presença de comorbidades ou multimorbidades associadas e biomarcadores para definição de novas diretrizes e tempo de tratamento.

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