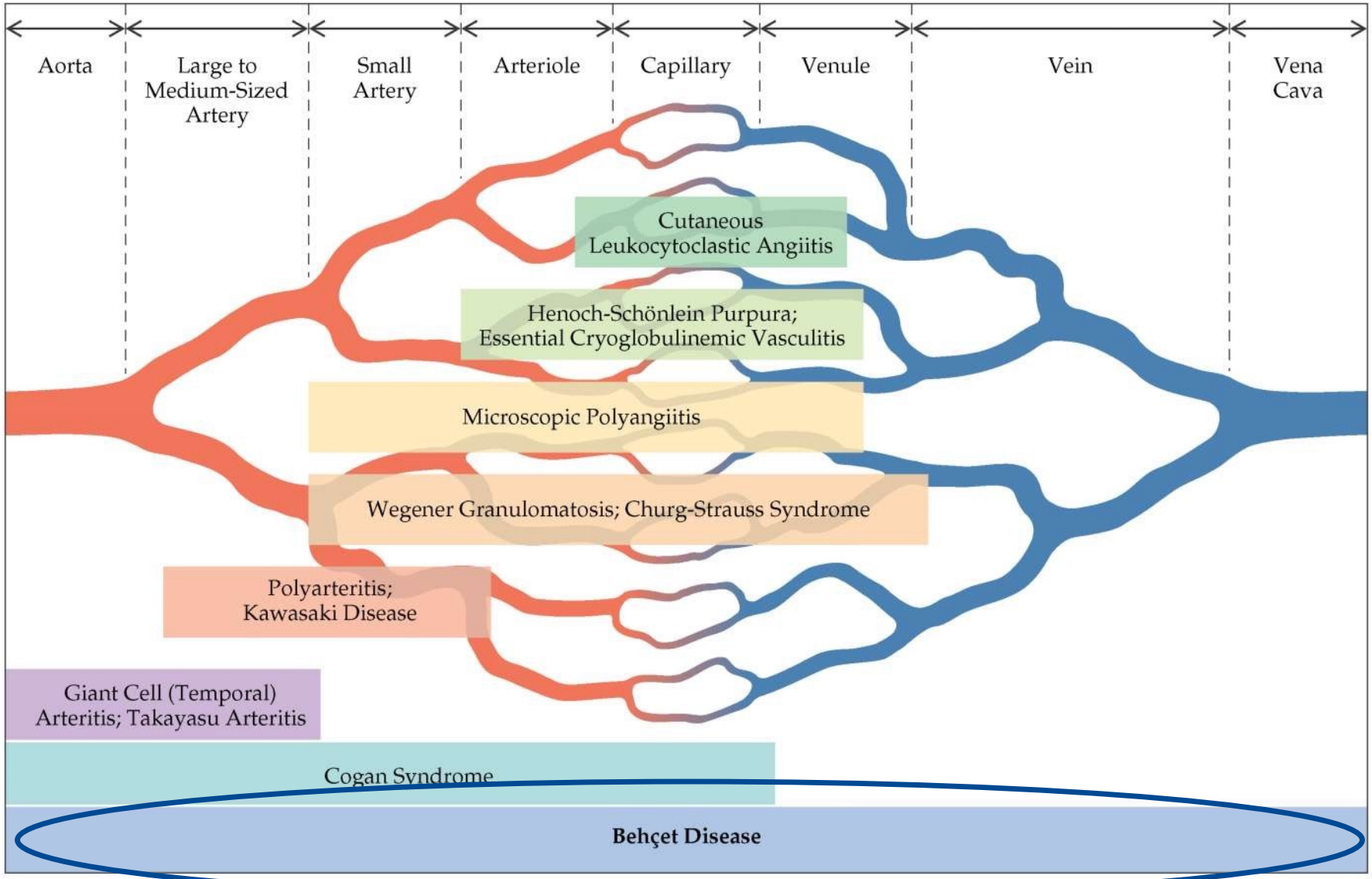
Sektion für Rheumatologie und entzündliche Systemerkrankungen
III. Medizinische Abteilung

Was ist Neu- Behcet Syndrom 2024

Das Behcet-Syndrom

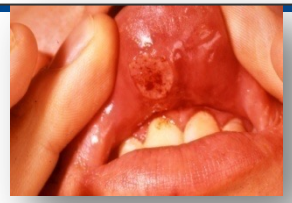
Prof. Dr. med. Ina Kötter

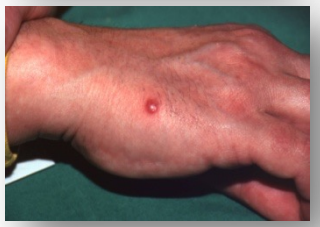
BEHCET-SYNDROM

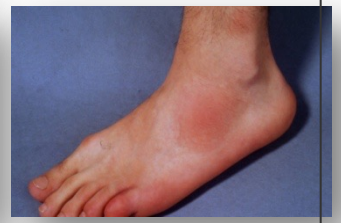


Jennette et al., Arthr. Rheum 2012; 65:1-11

SYMPTOMATIK BS

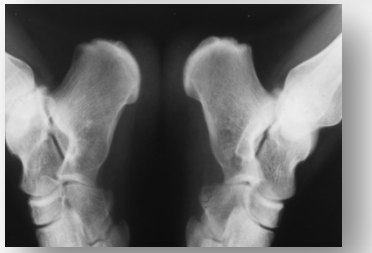


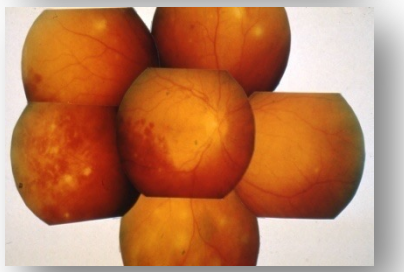


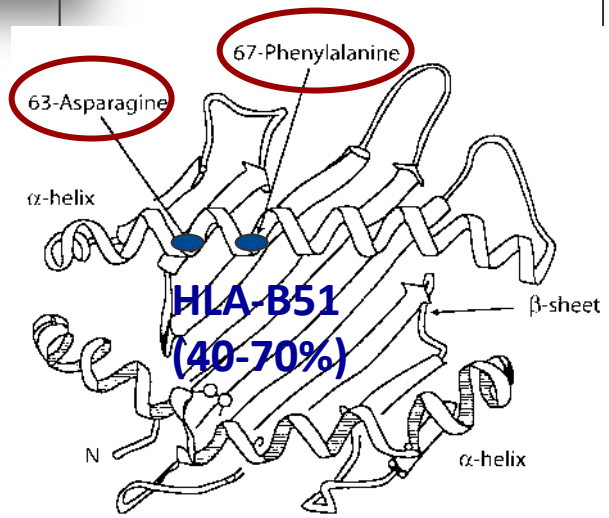


90 bis 100%
(genitale Ulzera
60 – 80%)

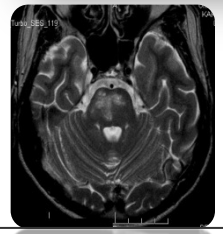
41 bis 94%





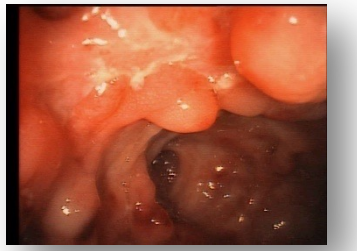


HLA-B51
(40-70%)

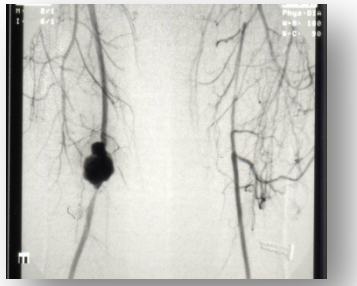


8 bis 31%

Beginn 2-4 Jahre
nach EM



3 bis 30%



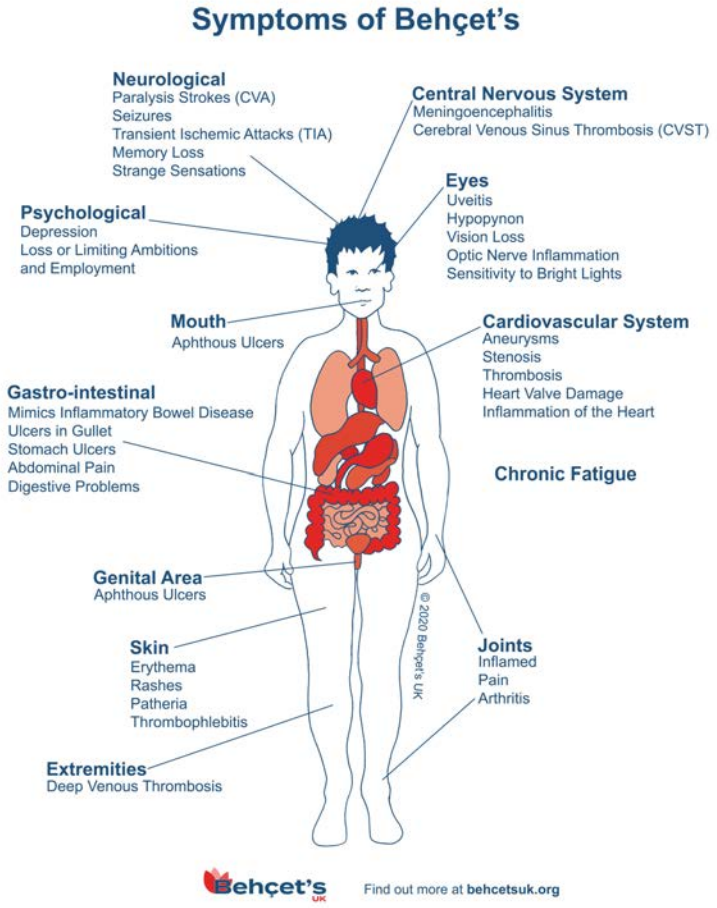
27% (88% venös)

Epididymitis
(4-31%)

Urogenital
(< 1%)

Myositis

Pathergie
15-30%



CLUSTER BS

Phänotyp I
Isoliert mucocutan

Phänotyp II
Arthritis-
ass. mit mucocutan,
Papulopusteln
Enthesitis, Akne, Arthritis

Phänotyp III
Vaskulär
Arteriell und venös oft assoziiert
In 20% ohne weitere BS
Stigmata zu Beginn
Männliches Geschlecht

Phänotyp IV
Okulär
In 20% ohne weitere BS
Stigmata zu Beginn
Fraglich mit ZNS Bet. Ass.

Phänotyp V
Parenchymatös neurologisch
In 6% anfangs ISG Kriterien nicht erfüllt
Ass. Uveitis, männl. Geschlecht, HLA B51

Phänotyp VI
Gastrointestinal

Seyahi E., Phenotypes in BS, Internal and Emergency Medicine 2019;14:677-689

SONDERFORM BS

Zeitschrift für Rheumatologie

Übersichten

Z Rheumatol
https://doi.org/10.1007/s00393-023-01371-0
Angenommen: 19. April 2023

Redaktion
Ulf Müller-Ladner, Bad Nauheim
Uwe Lange, Bad Nauheim

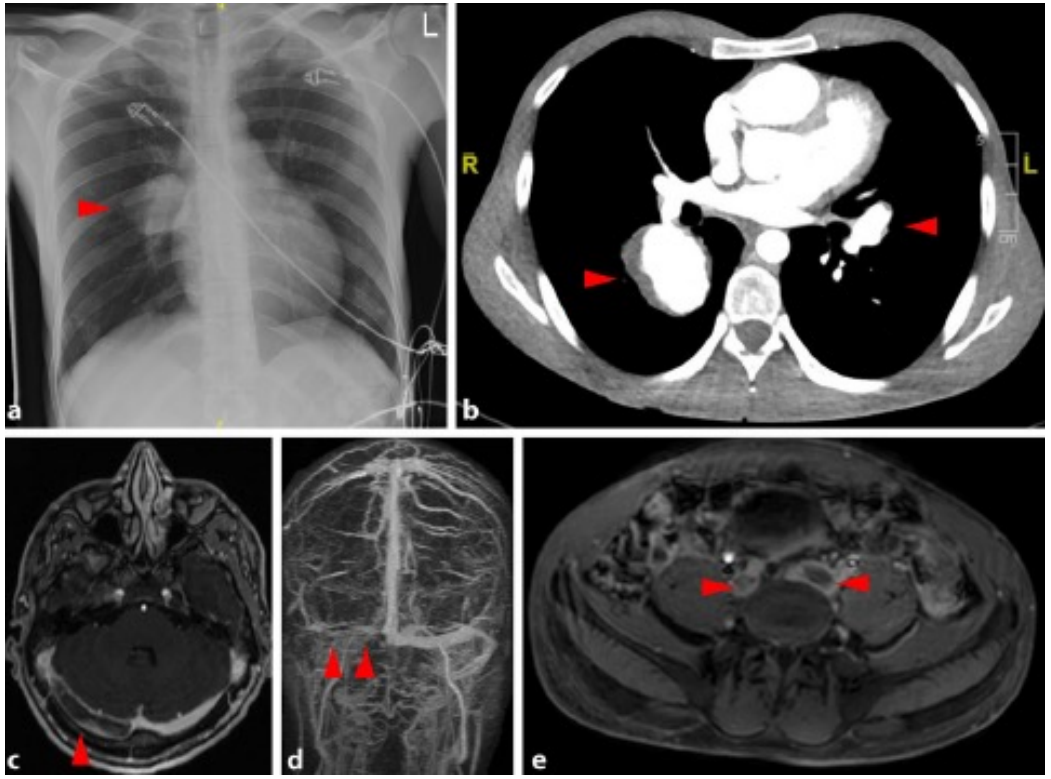
Hughes-Stovin-Syndrom: eine lebensbedrohliche Manifestation des Behçet-Syndroms

Nikolas Ruffer[1] · Martin Krusche[1] · Konstanze Holl-Ulrich[2] · Fabian Lötscher[3] · Ina Kötter[1,4]

[1] III. Medizinische Klinik und Poliklinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Deutschland
[2] Konsultations- und Referenzzentrum für Vaskulitis-Diagnostik, Labor Lademannbogen MVZ GmbH, Hamburg, Deutschland
[3] Universitätsklinik für Rheumatologie und Immunologie, Inselspital, Universitätsspital Bern, Bern, Schweiz
[4] Klinik für Rheumatologie und Immunologie, Klinikum Bad Bramstedt, Bad Bramstedt, Deutschland

Tab. 1 Klassifikationskriterien für das Hughes-Stovin-Syndrom (HSS) gemäß HSS International Study Group [8]

(a)	Thrombotische Manifestationen des venösen oder arteriellen Systems: rezidivierende Thrombophlebitiden, tiefe Venenthrombosen, Sinusvenenthrombosen, intrakardiale Thromben, arterielle Thrombosen
(b)	Normales Gerinnungsprofil: Anti-Cardiolipin-Antikörper, β2-Glykoprotein, Faktor-V-Leiden, Prothrombin, Protein C und S
(c)	Computertomographie der Pulmonalarterien/Pulmonalisangiographie (CTPA): Zeichen pulmonalarterieller Aneurysmen (mit oder ohne intraaneurysmaler in-situ-Thrombose), Kontrastmittelanreicherung im Bereich der pulmonalarteriellen Gefäßwand



Ruffer et al., Z Rheumatol 2023

BS- PATHOGENESE

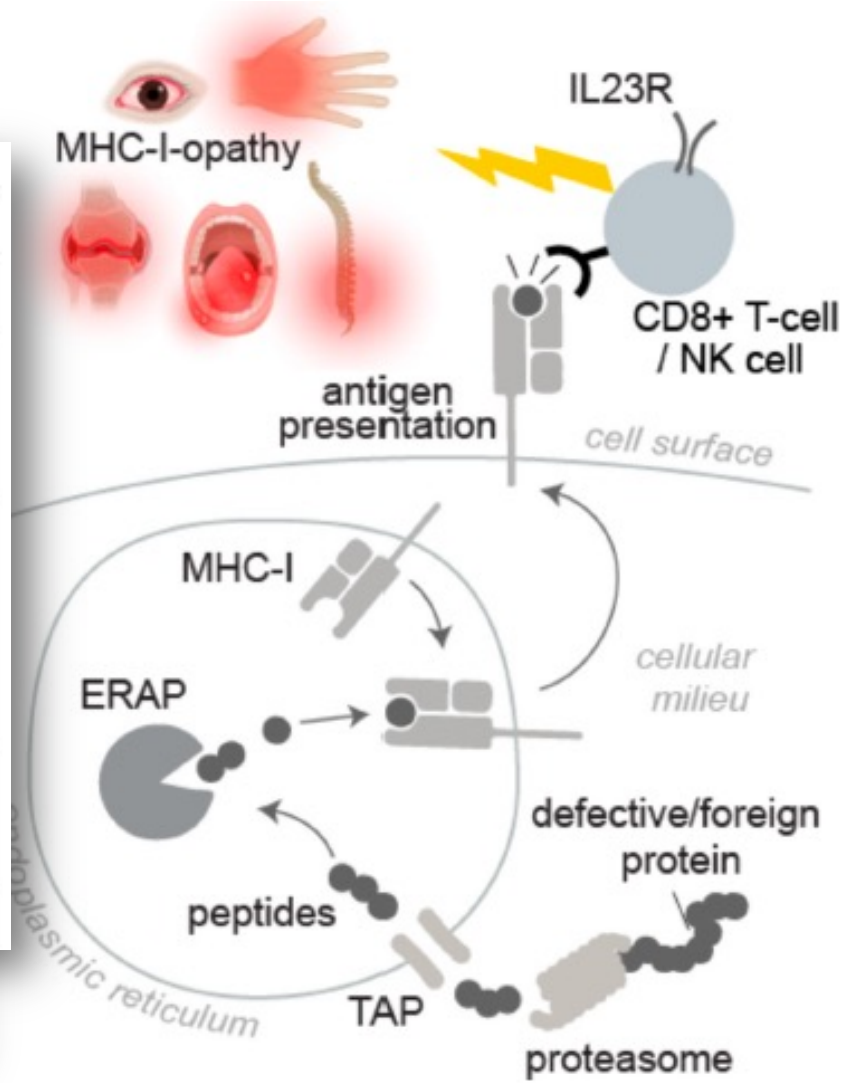
OPEN ACCESS

EULAR study group on 'MHC-I-opathy': identifying disease-overarching mechanisms across disciplines and borders

Table 2 Reported HLA class I associations in four MHC-I-opathies

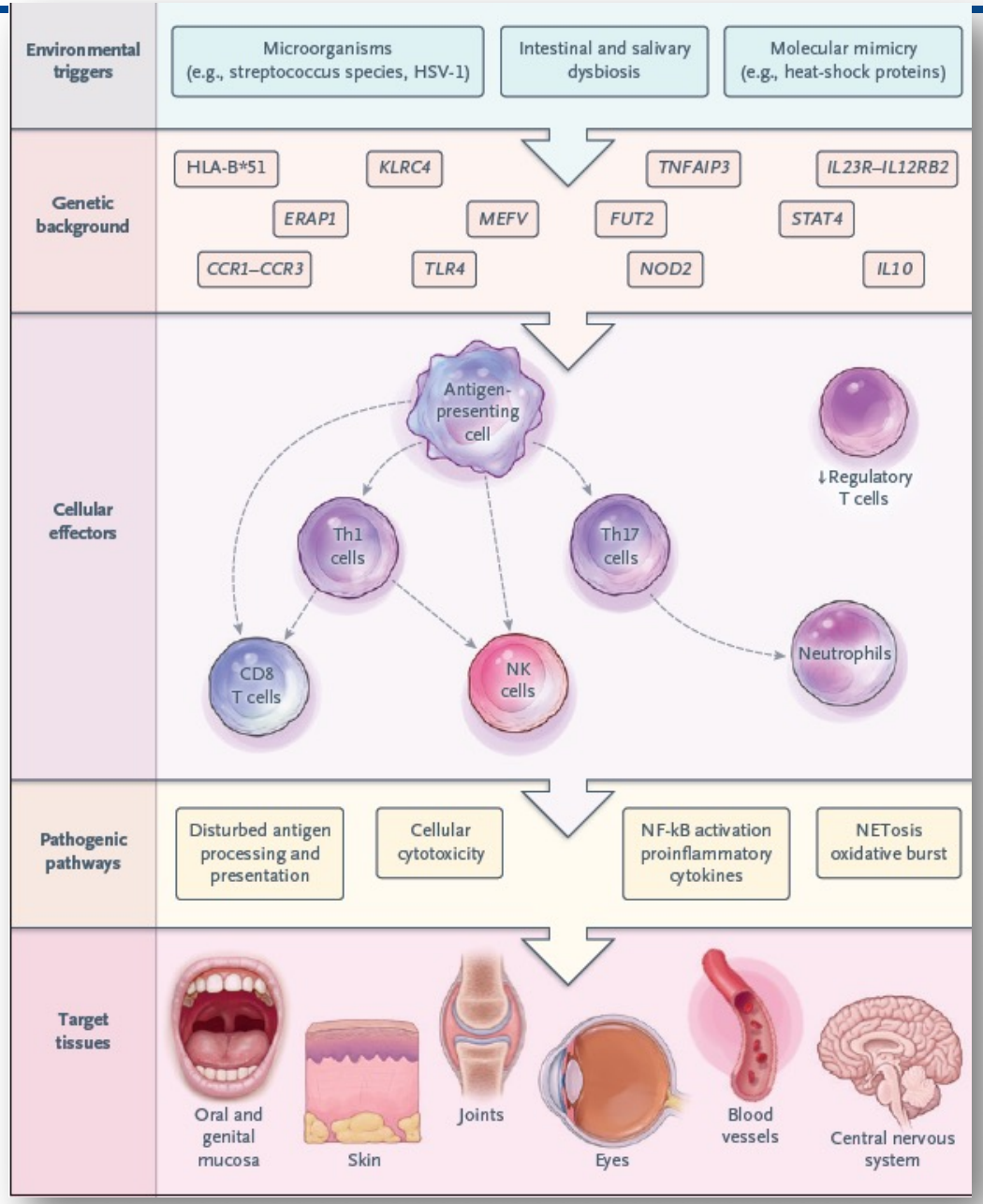
MHC-I-opathy	Prevalence	Primary HLA class I association	% cases negative for primary HLA class I allele	Independent* HLA class I associations
Birdshot uveitis	1-5/500 000	HLA-A*29:02	0	HLA-A*30[13 14] HLA-A*33[14]
Spondyloarthritis†	0.5%	HLA-B*27	– <30	HLA-B*40[85 86] HLA-A*02[85] HLA-B*07[85] HLA-B*57[85] HLA-C*15[86]
Behçet's Disease	0.19-120/100 000[9]	HLA-B*51	~30–70	HLA-A*02[87] HLA-B*27[87] HLA-B*57[87] HLA-A*03[87] HLA-B*15[87] HLA-B*49[87] HLA-A*26[87 89] HLA-C*07[89]
Psoriasis	2–4%	HLA-C*06:02	~30–70	HLA-A*02[122] HLA-B*27[122] HLA-B*07[122] HLA-C*07[176]

*Identified by statistical adjusting for primary associated HLA class I allele.
†Majority of data are from genetic studies in ankylosing spondylitis. Includes both risk and protective alleles.
‡Uveitis anterior is the main subtype reported in PsO, PsA, SpA, whereas in Behçet's multiple anatomical subtypes of uveitis are reported. BU manifests as posterior uveitis.
§Psoriasiform lesions: refers to the several types of psoriasis; classical plaque psoriasis, guttate, nail lesions and erythematous as well as pustular lesions.
¶Pustular lesions: covers acneiform, papulopustular and non-follicular pustules.
**Vasculitis in PsO as well as in PsA and SpA vasculitis is in the large vessels (aortitis); in B27-AU and BU not reported outside the eye; in Behçet's vasculitis is in all types of vessels, arteries and veins.
BU, birdshot uveitis; PsA, psoriatic arthritis; PsO, psoriasis; SpA, spondyloarthritis.



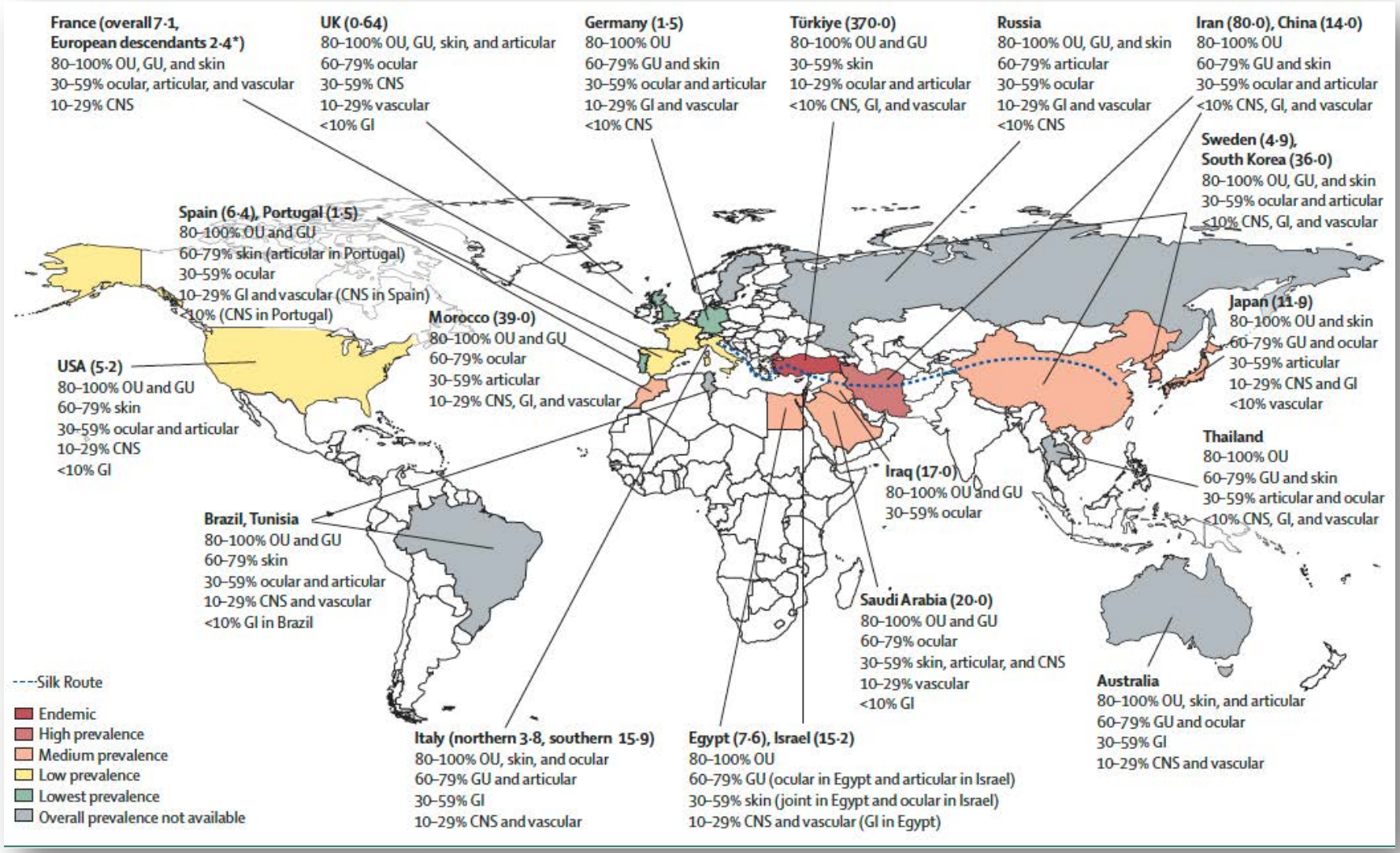
Kuiper et al., Ann Rheum Dis 2023

BS- PATHOGENESE



Saadoun et al., N Engl J Med 2024;390:640-51. DOI: 10.1056/NEJMra2305712

EPIDEMIOLOGIE BS



Häufigkeit in D: 0.6/100.000 (??)

Erstmanifestation zwischen dem 20. Und 40. LJ

Männer zu Frauen 3 : 1 (Deutsche: 1:1)

Schwerere Verläufe bei jungen Männern

Emmi et al., Lancet 2024, https://doi.org/10.1016/S0140-6736(23)02629-6

DIAGNOSEKRITERIEN ISG

Tab. 1 ISG(international study group)-Kriterien 1990 zur Klassifikation

Rekurrierende orale Aphthose	Kleine oder große aphthöse oder herpetiforme Ulzerationen, die mindestens 3-mal in einer 12-monatlichen Periode wiederkehren
Zusätzlich 2 der folgenden Manifestationen	
Rekurrierende genitale Läsionen	Aphthöse Ulzerationen oder Vernarbungen
Augen-läsionen	Uveitis anterior, Uveitis posterior oder Zellen im Glaskörper bei der Spaltlampenuntersuchung oder retinale Vaskulitis, beobachtet von einem Ophthalmologen
Hautläsionen	Erythema nodosum, Pseudofollikulitis, oder papulopustulöse Läsionen oder akneiforme Knötchen bei postadoleszenten Patienten ohne Steroidtherapie
Positiver Pathergietest	Intrakutaner Nadelstich mit einer 21-G-Kanüle am Unterarm (Innenseite), abgelesen durch einen Arzt nach 24–48 h

Criteria for diagnosis of Behçet's disease

INTERNATIONAL STUDY GROUP FOR BEHÇET'S DISEASE*

5 sets of criteria for diagnosis of Behçet's disease are in use—a problem which has hindered interpretation of different studies and collaborative research. An international study group, which included at least one proponent of 4 of the sets, was formed to derive new, internationally agreed diagnostic criteria for Behçet's disease. Data on 914 patients with Behçet's disease, from 12 centres in 7 countries, were compared with controls from the same centres. The new set of diagnostic criteria—which requires the presence of oral ulceration plus any two of genital ulceration, typical defined eye lesions, typical defined skin lesions, or a positive pathergy test—was simpler to use and had an improved discriminatory performance than its predecessors.

Lancet 1990; **335**: 1078–80.

Introduction

The clinical triad of uveitis with oral and genital ulceration was probably first recognised by Hippocrates,[1] but bears Behçet's name after his descriptions of the illness some 50 years ago.[2–4] The disease is heterogeneous with variable involvement of many organ systems, the exact cause is unclear, and there is no universally accepted diagnostic test: thus diagnosis of Behçet's disease has relied on identification of several of its more typical clinical features. However,

*Participants.—France: B. WECHSLER; Iran: F DAVATCHI, Japan: Y. MIZUSHIMA; Tunisia: M. HAMZA, Turkey. N. DILSEN, E. KANSU, H. YAZICI; UK: C. G. BARNES, M. A. CHAMBERLAIN, D. G. JAMES, T. LEHNER; USA: J. D. O'DUFFY. Data processing centre.—A. S RIGBY, J. GREGORY, A. J. SILMAN Correspondence to Dr A. J. Silman, Arthritis and Rheumatism Council Epidemiology Research Unit, Manchester University Medical School, Manchester M13 9PT, UK.

DIAGNOSEKRITERIEN ICBD

Symptom	Punkte
Okuläre Veränderungen	2
Genitale Aphthen	2
Orale Aphthen	2
Hautläsionen	1
Neurologische Manifestationen	1
Vaskuläre Manifestationen	1
Positiver Pathergie-Test	1*

*der Pathergie Test ist optional, ein positives Ergebnis kann für den Score verwertet werden.

ICBD Kriterien
Sensitivität 95%,
Spezifität 90%

ISG Kriterien
Sensitivität 85%,
Spezifität 96%

Score	Fälle %	Kontrollen %	Plausibilität MB	Einfache Klassifikation
≤1	<1	11	Fast sicher kein BS	Kein BS
2	1	72	BS sehr unwahrscheinlich	
3	4	9	BS möglich, aber unwahrscheinlich	
4	14	5	BS wahrscheinlich	BS
5	32	3	BS hochwahrscheinlich	
6	48	<1	BS fast sicher	

International Team for the Revision of the International Criteria for Behcet's D. 2014.
The International Criteria for Behcet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 28:338-47

DIAGNOSE BEHCET SYNDROM

Rheumatology, 2023, **00**, 1–8
https://doi.org/10.1093/rheumatology/kead101
Advance access publication 2 March 2023
Original Article

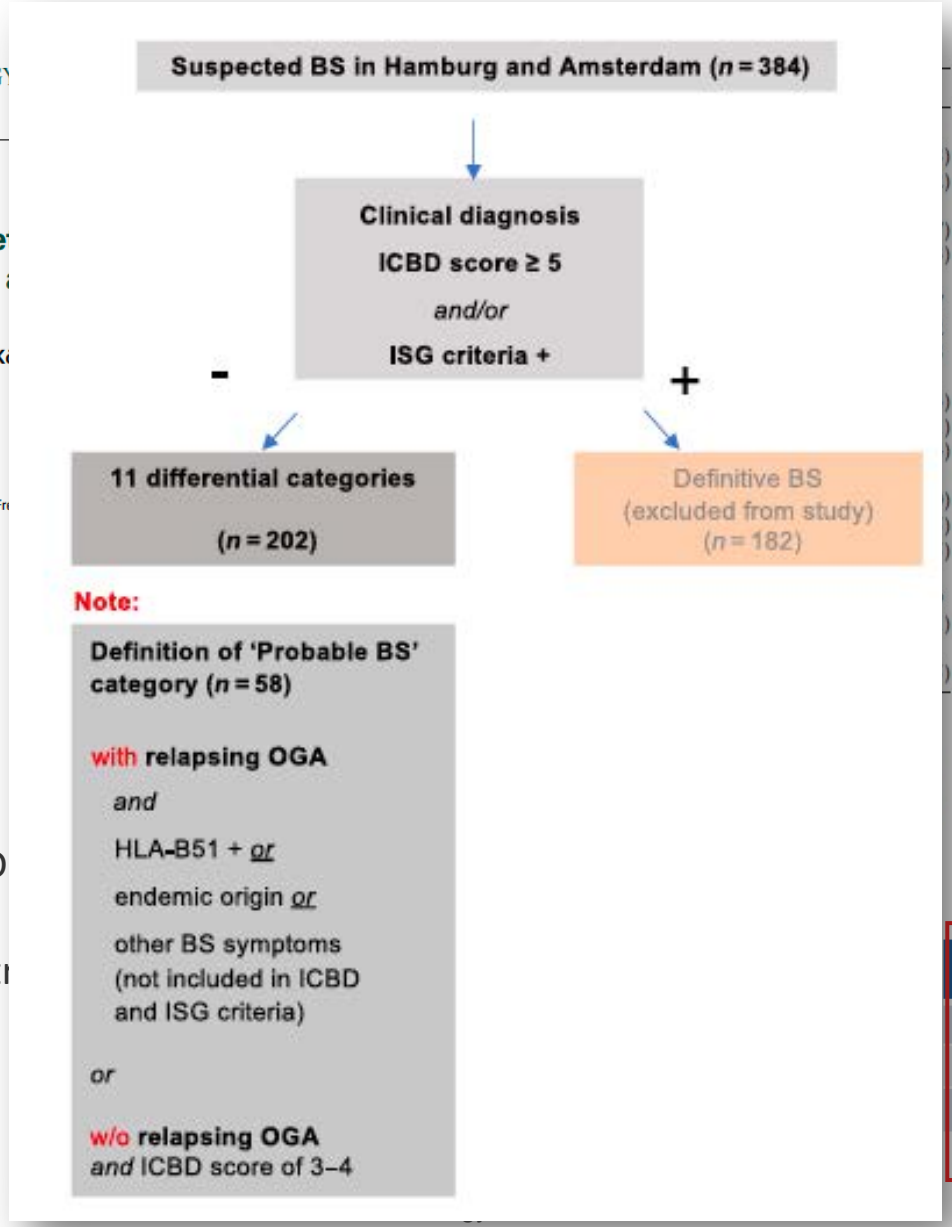
British Society for Rheumatology RHEUMATOLOGY

Clinical science

When it looks like Behçet's syndrome but is some… else: differential diagnosis of Behçet's syndrome: … two-centre retrospective analysis

Fabian Lötscher [1*,†], **Floor Kerstens**[2,3,†], **Martin Krusche**[4], **Nikolas Ruffer**[4], **Ina K… Franktien Turkstra**[2,3] ; **EULAR Study Group on MHC-I-opathy**

[1]Department of Rheumatology and Immunology, Bern University Hospital, University of Bern, Bern, Switzerland
[2]Amsterdam Rheumatology & Immunology Center, Reade, Amsterdam, The Netherlands
[3]Department of Rheumatology, Reade location Jan van Breemen, Amsterdam, The Netherlands
[4]III Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[5]Department of Rheumatology and Immunology, Klinikum Bad Bramstedt, Bad Bramstedt, Germany
*Correspondence to: Fabian Lötscher, Department of Rheumatology and Immunology, Bern University Hospital, University of Bern, Fr… Switzerland. E-mail: fabu99@gmx.ch
†F.L. and F.K. contributed equally to the manuscript and share first authorship.



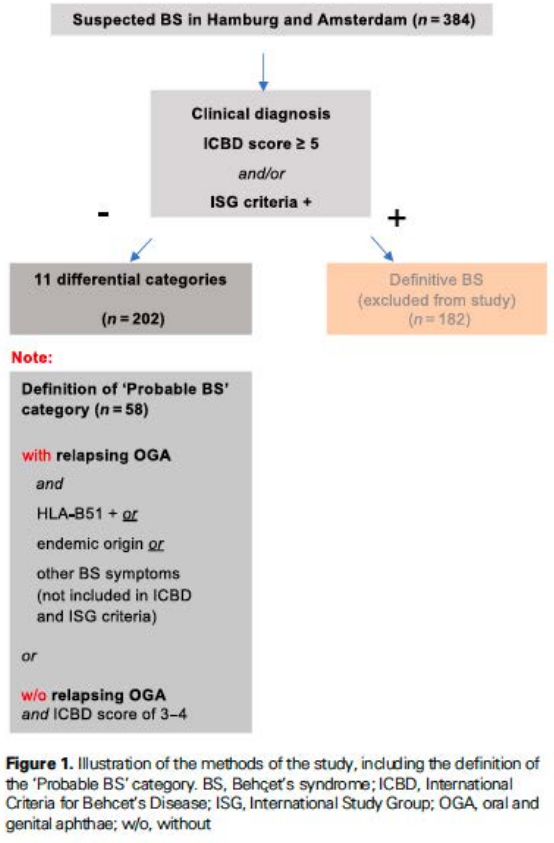


Figure 1. Illustration of the methods of the study, including the definition of the 'Probable BS' category. BS, Behçet's syndrome; ICBD, International Criteria for Behcet's Disease; ISG, International Study Group; OGA, oral and genital aphthae; w/o, without

CUT OFF ICBD 4:

Sensitivität 93,5%, Spezifität 75,5%

Cut Off ICBD 5:

Sensitivität 75,8%, Spezifität 97,2%

- 75 Patienten (37,1%) erfüllten die ICBD … mit einem Score >=4
- 3 Patienten erfüllten die ISG Kriterien t… anderer Diagnose als BS

4	5	6	7	8	9	10	All
0	78	48	40	13	3	0	182
40	0	0	0	0	0	0	58
31	3	0	1	0	0	0	144

DIAGNOSE BEHCET SYNDROM

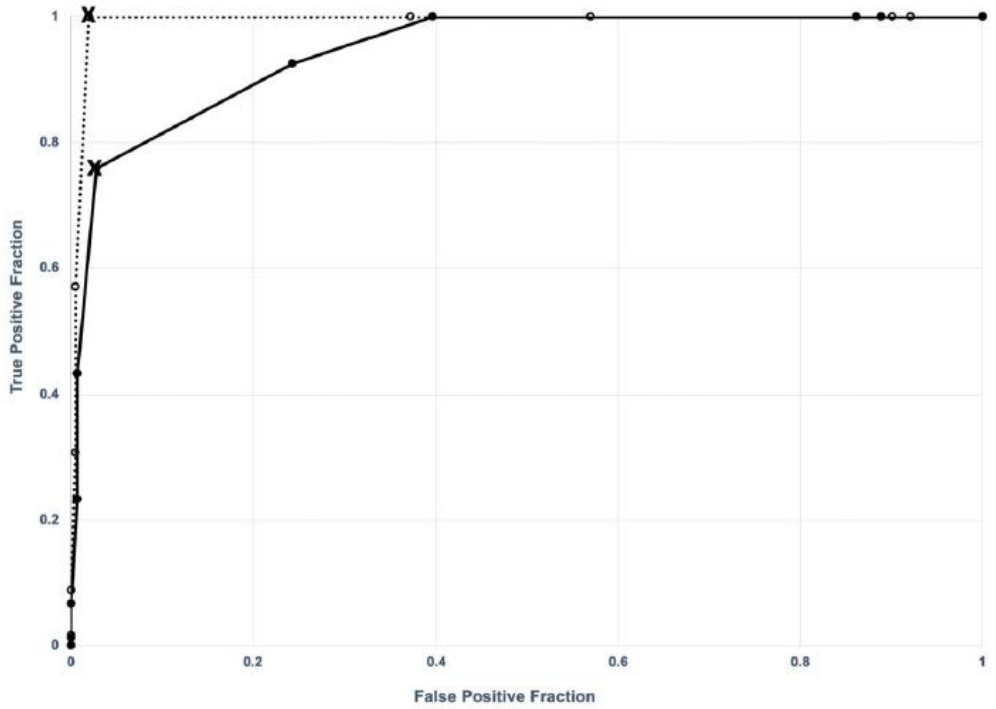
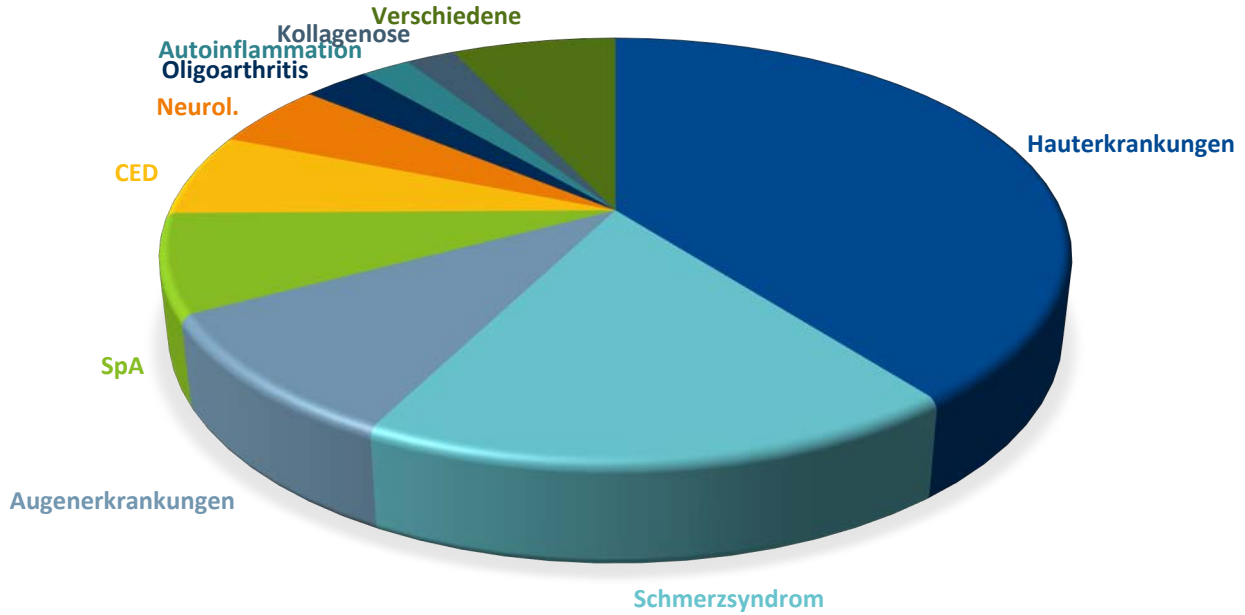


Figure 2. Receiver operating characteristic curve of the discrimination power of the ICBD criteria in this cohort. Solid line with filled-in dots: patients from the 'probable BS' category were counted as BS patients. Dotted line with circles: patients from the 'probable BS' category were counted as differential diagnoses without BS. X: ICBD score of 5 points (on both curves). The individual graphs and the corresponding ICBD figures can be viewed in the supplementary data (see Supplementary Data S1, available at *Rheumatology* online). BS, Behçet's syndrome; ICBD, International Criteria for Behcet's Disease

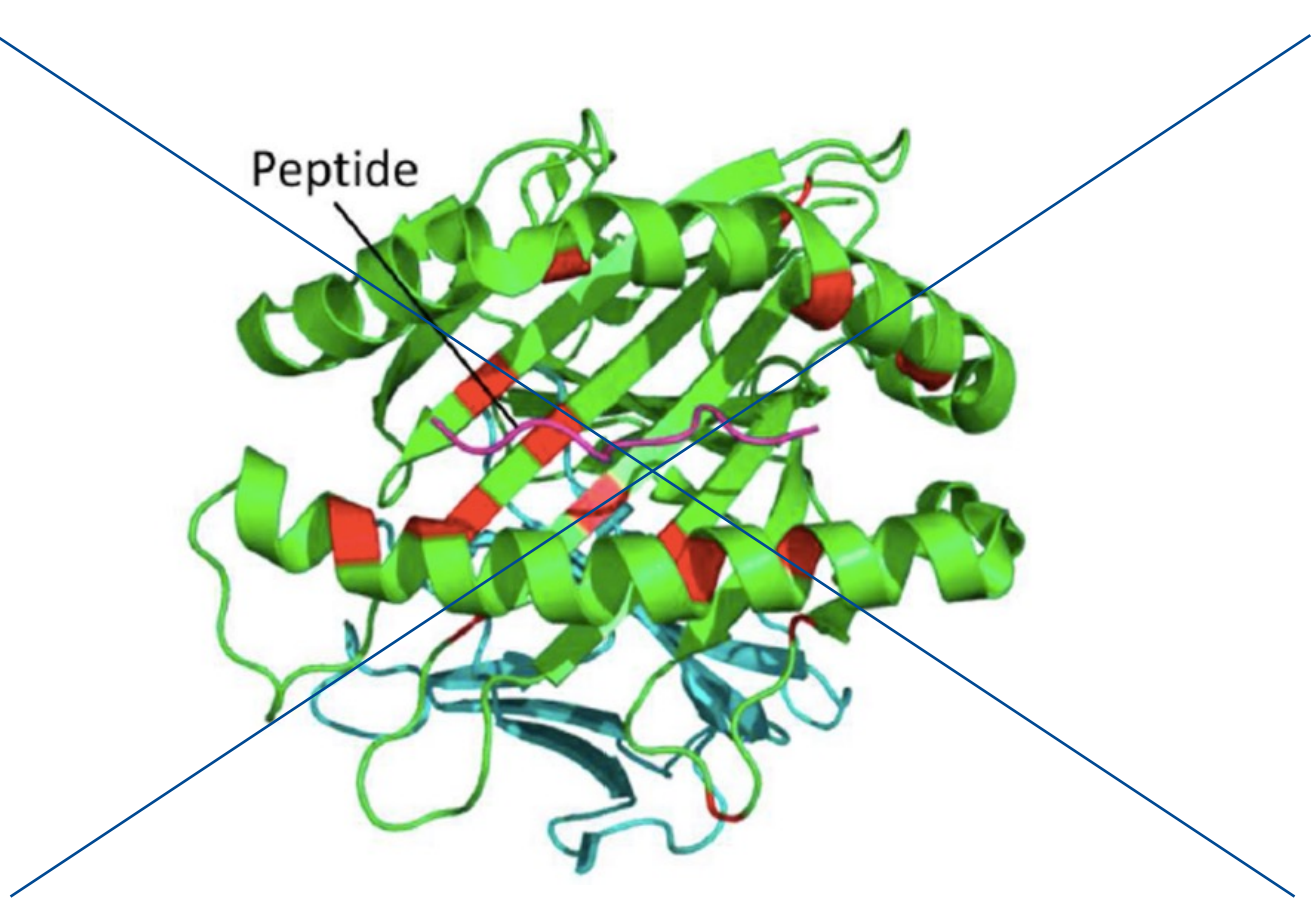
DIFFERENZIALDIAGNOSEN



Haut. 28,2%,
Schmerzsyndrom 12,9%,
Auge 6,9%,
SPA 5,4%, CED 4,5%, Neuro 3,5%, Arthritis 2%,
Autoinflammation 1,5%, Kollagenose 1,5%,
Verschiedene 5%

Lötscher et al., Rheumatology 2023

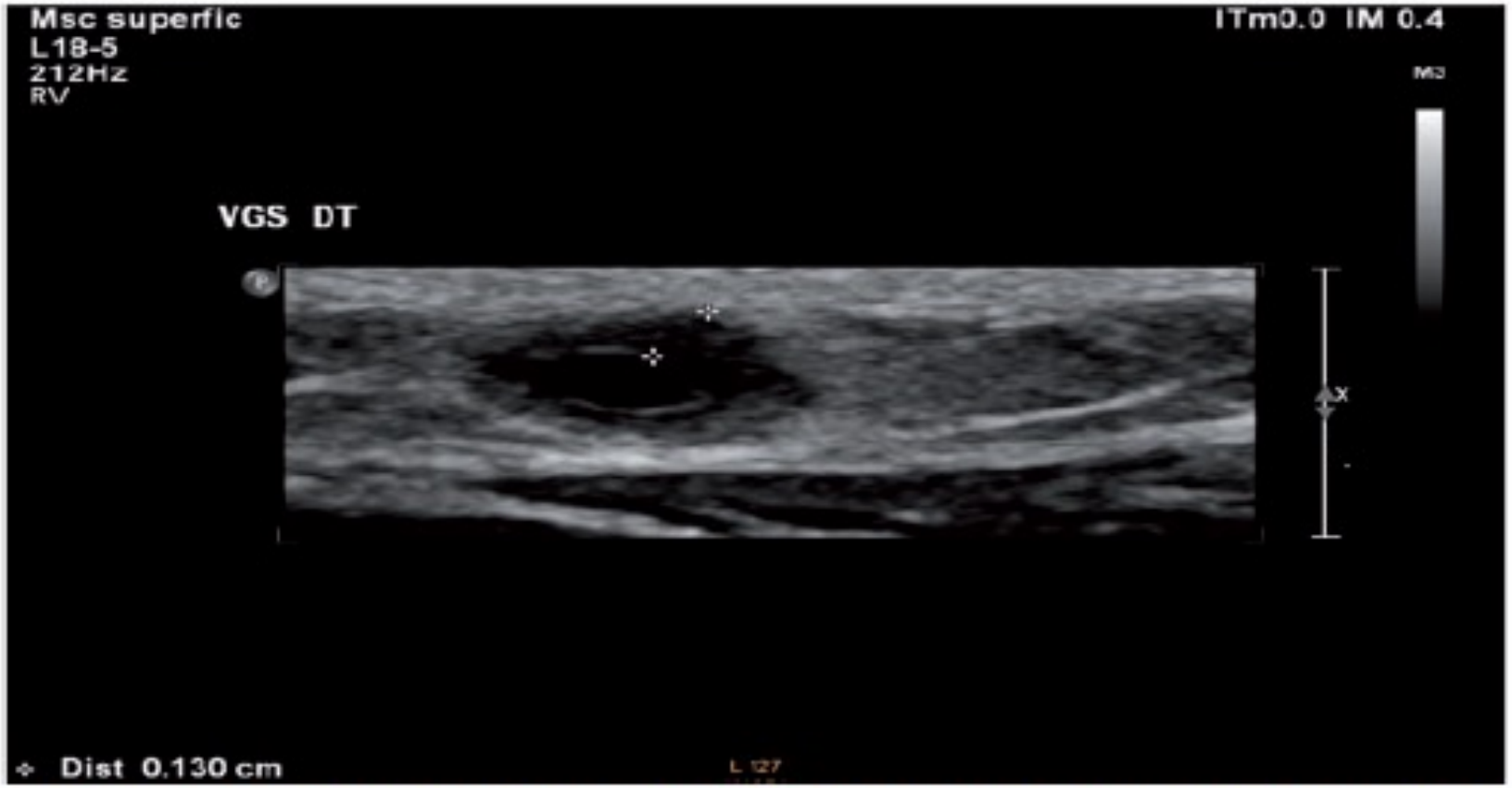
HLA-B51 gehört nicht zu den Dx Kriterien



International Team for the Revision of the International Criteria for Behcet's D. 2014.
The International Criteria for Behcet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 28:338-47

BS- DIAGNOSE: NEUE MÖGLICHKEITEN

FIG. 1 Hypoechogenic thickening of the wall of the great saphenous vein



Healthy Controls | Behçet Disease | Antiphospholipid Syndrome | Ankylosing Spondylitis | Non-Inflammatory DVT | Venous Insufficiency | Systemic Vasculitis

0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

● Right CFV Thickness ◇ Left CFV Thickness

Alibaz-Öner et al., Rheumatology 2021

BS-THERAPIE-STANDARD EULAR

Recommendation

2018 update of the EULAR recommendations for the management of Behçet's syndrome

Gulen Hatemi,[1] Robin Christensen,[2] Dongsik Bang,[3] Bahram Bodaghi,[4] Aykut Ferhat Celik,[5] Farida Fortune,[6] Julien Gaudric,[7] Ahmet Gul,[8] Ina Kötter,[9] Pietro Leccese,[10] Alfred Mahr,[11] Robert Moots,[12] Yesim Ozguler,[1] Jutta Richter,[13] David Saadoun,[14,15,16,17] Carlo Salvarani,[18] Francesco Scuderi,[19] Petros P Sfikakis,[20] Aksel Siva,[21] Miles Stanford,[22] Ilknur Tugal-Tutkun,[23] Richard West,[24] Sebahattin Yurdakul,[1] Ignazio Olivieri,[25] Hasan Yazici[1]

Milder Verlauf
mukokutan, Arthritis, keine Augenbeteiligung keine schwere Organmanifestation

Ineff. oder unverträglich

Colchicin

Azathioprin

Ineff. oder unverträglich

Bei im Vordergrund stehenden oralen Aphthen Apremilast

Ciclosporin A

Ineff. oder unverträglich

TNFi (IFX, ADA, auch ETA möglich) oder IFN alpha

Mittelschwerer Verlauf
Uveitis anterior, Thrombophlebitiden, periphere Thrombosen oder mild plus prognostisch ungünstige Faktoren

Azathioprin oder CSA

Ineff. oder unverträglich

TNFi oder IFN-alpha

Thrombosen:
Antikoagulation max. 3 Monate, wichtig ist die Immunsuppression

Schwerer Verlauf
Uveitis posterior, Colitis,ZNS Beteiligung, arterielle Aneurysmata, V.Cava Thrombose oder miitelschwer plus prognostisch ungünstige Faktoren

TNFi oder IFN alpha (TNF-ANTIKÖRPER, vorzugsweise IFX oder ADA)

Gastrointestinal:
Mesalazin und Budesonid, bei Ineffektivität AZA TNFi (Antikörper)

ZNS Beteiligung:
KEIN CSA, dieses kann ZNS Manifestationen begünstigen. TNFi /Antikörper) ist dem CYC zu bevorzugen

Arterielle Aneurysmata;
Primär Cyclophosphamid Chriurgie und Stenting möglichst erst nach effektiver Immunsuppression

Hatemi G, *et al. Ann Rheum Dis* 2018;**77**:808–818. doi:10.1136/annrheumdis-2018-213225 Kötter I. Z Rheumatol in press DOI: 10.1007/s00393-020-00899-9

Hatemi G, *et al. Ann Rheum Dis* 2018;**77**:808–818. doi:10.1136/annrheumdis-2018-213225

BS-THERAPIE- WIN, TCZ

The Journal of Rheumatology 2023;50:916–23
doi:10.3899/jrheum.221106
First Release April 1 2023

Tocilizumab in Behçet Disease: A Multicenter Stu
30 Patients

Mohamed-Yacine Khitri[1], Alessandra Bartoli[1], Georgina Maalouf[1], Alban Dero
Giacomo Emmi[4], Omer Karadag[5], Gerard Espinosa[6], Mathilde Leclercq[7], Ga
Mathieu Vautier[1], Patrice Cacoub[1], and David Saadoun[1]

Table 3. Case series of patients with BD treated with TCZ.

Reference	n	Clinical Manifestations	Previous Treatments	TCZ Indication	Route of TCZ Administration (IV or SC)	TCZ-Associated Treatments	Clinical Outcomes (%)	Prednisone Daily Dose, Baseline to M6, mg	SAEs	Median Follow-Up Under TCZ, mos, median (IQR)	Relapse, n (mos of TCZ therapy)
Zhong[35]	10	Vascular disease (10), arterial (10), venous (2), mucocutaneous (10), GI (1), uveitis (1), joints (2)	GCs (10), CYC (7), MMF (2), AZA (2), TAC (1)	Vascular disease (10)	IV (10)	GCs (9)	Vascular: CR (50), PR (40), NR (10) Cutaneous: CR (100)	55 to 8	None	27 (7-35)[a]	1 (7)
Ding[20]	7	Vascular disease (7), arterial (7), venous (2)	GCs (7), CYC (7), AZA (5), MTX (2), TAC (1), ETN (1), LEF (2)	Vascular disease (7)	IV (7)	GCs (7), AZA (5), CYC (4), LEF (1), MTX (1)	Vascular: CR (43), PR (43)[b]	27 ± 17 to 9 ± 3	None	19 (4-33)[a]	None
Atienza-Mateo[21]	16	Uveitis (16), mucocutaneous (10), neurological (5), joints (7), venous (1), and GI (1)	MTX (13), CsA (8), AZA (6), CYC (3), MMF (1), ADA (10), IFX (7), GOL (3), CNK (1), CZP (1), ETN (1), COL (3), THD (1)	Uveitis (14): CME (9), RV (5) and neurological BD (2)	IV (13), SC (3)	MTX (3), AZA (3), MMF (1), and CsA (1)	Ocular: CR (63), PR (19), NR (19) Neurological BD: CR (60), PR (20)[b] Joints: CR (29), PR (29), NR (43)	NA	Severe infusion reaction (1), cellulitis with sepsis (1)	20 (9-45)	None
Liu[31]	11	Neurological (11), mucocutaneous (11), uveitis (3), joints (2), vascular (2)	GCs (11), CYC (8), AZA (6), MTX (5), CsA (2), TAC (1), MMF (1), intrathecal injection of dexamethasone and MTX (5), IFX (5), IFN-α (3), daclizumab (1)	Neurological BD (11)	IV (11)	GCs (11), MTX (3), CYC (3), AZA (2)	Neurological: CR (18), PR (82)	69 ± 17 to 16 ± 16	None	13 (3-23)	2 (8; 18)
Eser Ozturk[27]	5	Uveitis (5) and vascular disease (1)	GCs (5), AZA (5), CsA (4), IFN-α (5), IFX (5), ADA (2), MMF (1), PSTA injections (2), IV dexamethasone injection (4), bevacizumab ocular injection (1)	Uveitis (5): CME (4), RV (3)	IV (5)	Oral GCs (3), AZA (2), CsA (1), IV dexamethasone injection (1)	Uveitis: CR (100); CME: CR (75), PR (25); RV: CR (100)	NA	None	11 (5-19)	None

Effektiv bei 25 (83%)
18 CR (60%), 7 PR (23%)

- Uveitis 18/30 -67% CR
- Neurologisch 5/30 - 60% CR
- Mucocutan/artikulär 7/30 – 42%

Signifikante PDN Reduktion n. 6 Monater

20% milde NW, 3 SAE (10%)- Pneumonie,

Khitri et al., J Rheumatol 2023

Diskussion/Fragen