Der Balgrist

CRMO

Rheumaworkshop USZ 31. März 2022

Universitäre Klinik für Rheumatologie

Christoph Gorbach

Universitätsklinik Balgrist | Universität Zürich[UZH] | swiss olympic MEDICAL CENTER

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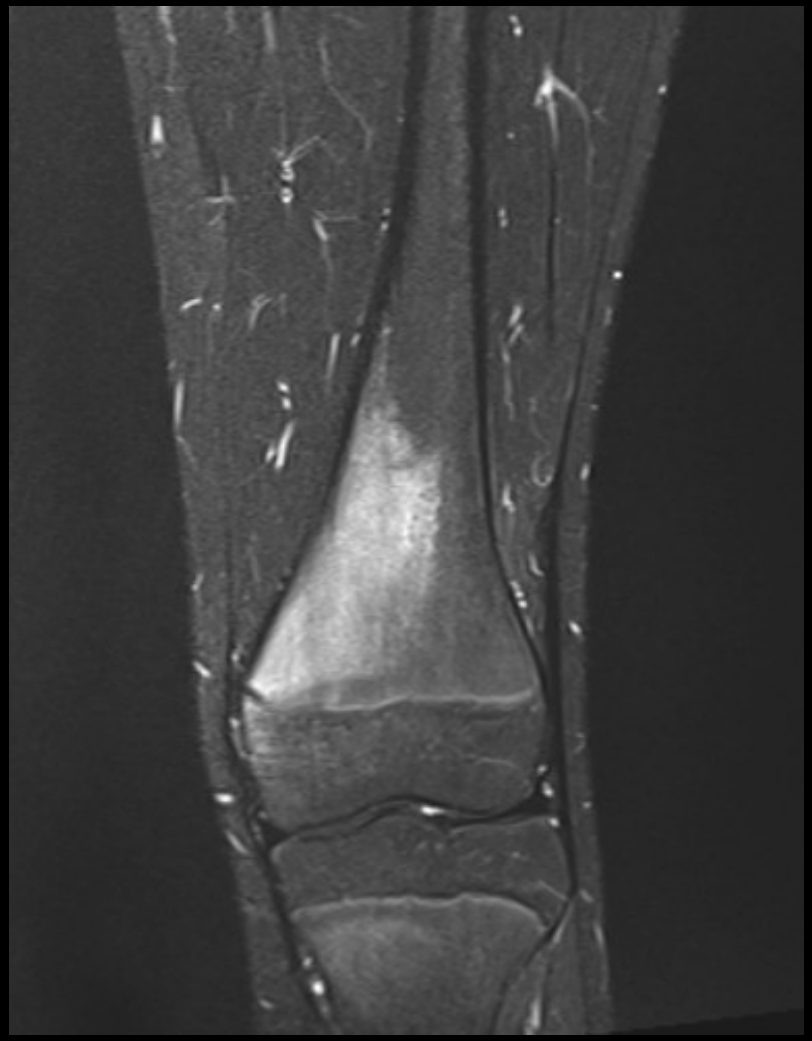

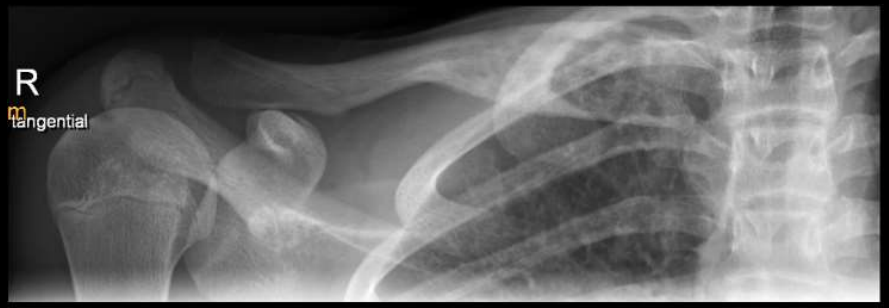

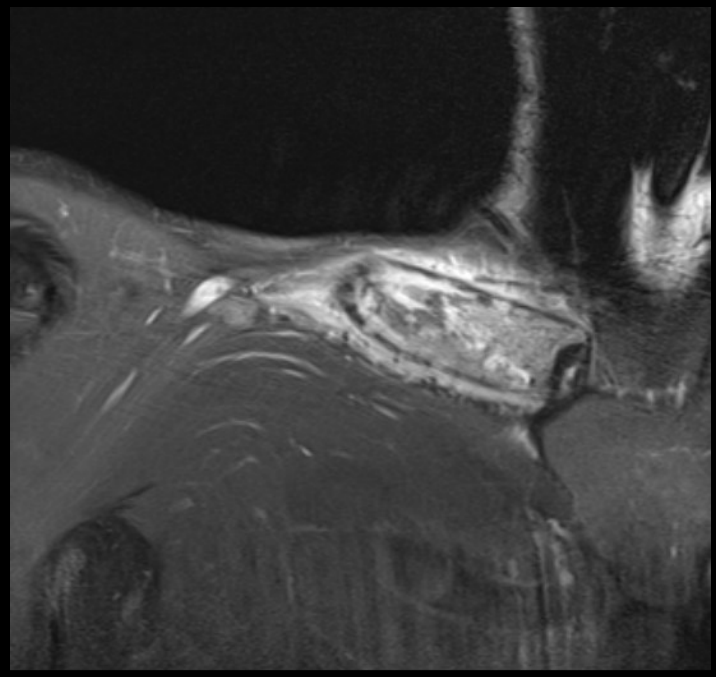

Universitätsklinik
Balgrist

(Chronic) non-bacterial Osteomyelitis (CNO)

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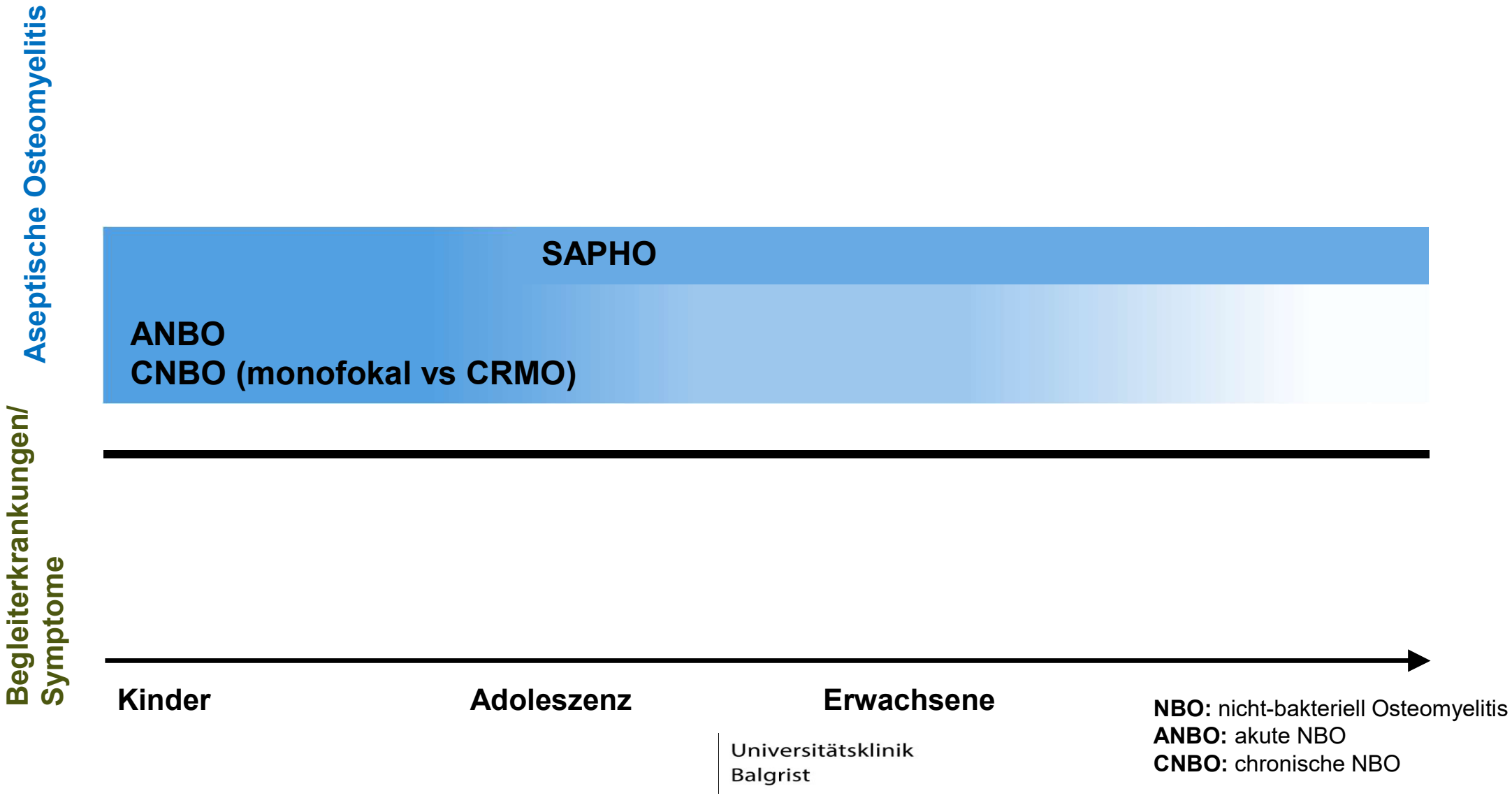
- Subacute and chronic „symmetrical“ Osteomyelitis, Giedion et al 1972
- Chronic recurrent multifocal Osteomyelitis (**CRMO**), Björkstén et al. 1978
- Synonyme: chronic multifocal symmetrical osteomyelitis, *pustulotic arthro-osteitis*, sclerosing osteitis
- SAPHO (Synovitis, Akne, Pustulose, Hyperostose, Osteitis), Chamot et al 1987

Spektrum der aseptischen/nicht-bakteriellen Osteomyelitis (NBO)

Der Balgrist



NBO: nicht-bakteriell Osteomyelitis
ANBO: akute NBO
CNBO: chronische NBO

Epidemiologie

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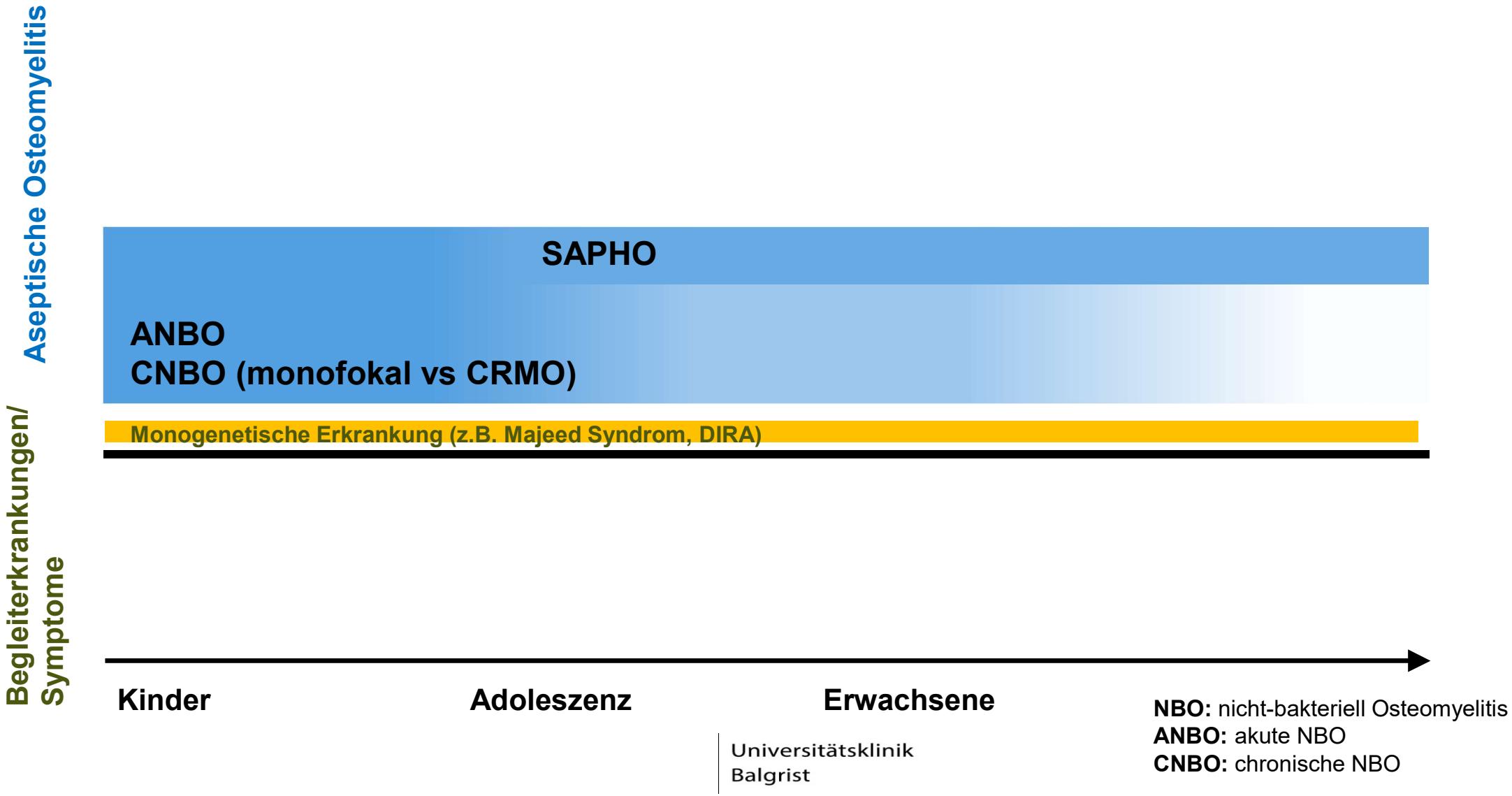
- Inzidenz von 1:1‘000‘000
- 2-5% aller Osteomyelitiden
- ♀:♂ (2:1)
- Durchschnittsalter beim Auftreten 10. LJ, bei ca. 10% nach 18. LJ
- Mögliche genetische Prädisposition

Buch K et al. Calcified Tissue International.2019;104:544–553.
Wipff J et al. Arthritis & Rheumatology.2015;67(4):1128–1137.
Zha D.Y. Journal of Translational Autoimmunity.2021;4.

Spektrum der aseptische Osteomyelitis (NBO)

Der Balgrist



NBO: nicht-bakteriell Osteomyelitis
ANBO: akute NBO
CNBO: chronische NBO

Pathophysiologie

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- Dysregulation/Dysbalance von pro- und anti-inflammatorischen Zytokinen
  - ↑ Expression von IL-1, IL-6, IL-20 und TNFα
  - ↓ Expression von IL-10 und IL-19

Hofmann S.R. et al. Clinical Immunology.2011;141:317–327.
Hofmann S.R. et al. Rheumatol Int.2016;36:769–779.
Buch K et al. Calcified Tissue International.2019;104:544–553.

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Table 2. Baseline characteristics of the patients in the French national CRMO cohort (n =178)*

Age, mean ± SD years	16.4 ± 4.7
No. female/male	123/55
Age at onset of symptoms, mean ± SD years	9.8 ± 3
Age at diagnosis, mean ± SD years	10.9 ± 2.9
Time from symptom onset to diagnosis, mean ± SD months	17.3 ± 24.8
No. of clinical localizations per patient, mean ± SD	2.7 ± 1.8
Clinical unifocal form of CRMO	54 (30)
Local inflammatory aspect†	77 (43)
Arthritis	20 (11)
Fever	36 (20)
Extraosseous involvement	21 (12)
Family history	51 (32)‡
Inflammatory syndrome	119 (67)
HLA–B27 positive	6 (7)§
ANA positive	9 (12)¶
No. of radiologic lesions per patient, mean ± SD	3.5 ± 2.9
On radiography	1 ± 0.9
On isotopic bone scanning	2.5 ± 1.7
On MRI	3.1 ± 3.3

Wipff J et al. Arthritis & Rheumatology.2015;67(4):1128–1137.

RHEUMATOLOGY

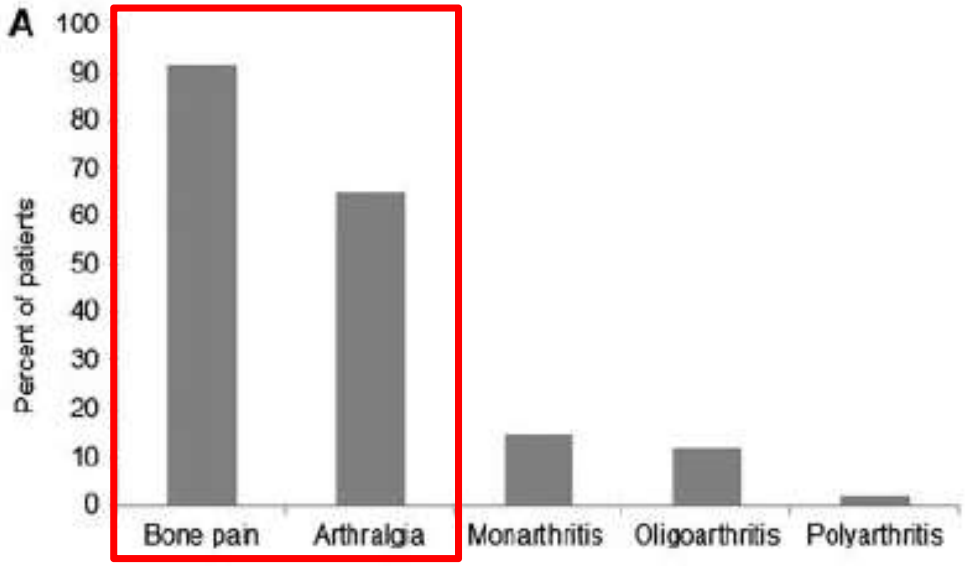
Rheumatology 2018;57:1203–1211
doi:10.1093/rheumatology/key058
Advance Access publication 27 March 2018

Der Balgrist

Original article

The multifaceted presentation of chronic recurrent multifocal osteomyelitis: a series of 486 cases from the Eurofever international registry

FIG. 2 Inflammatory musculoskeletal manifestations associated with chronic non-bacterial osteomyelitis



Girschick H. et al. Rheumatology.2018;57:1203-1211.

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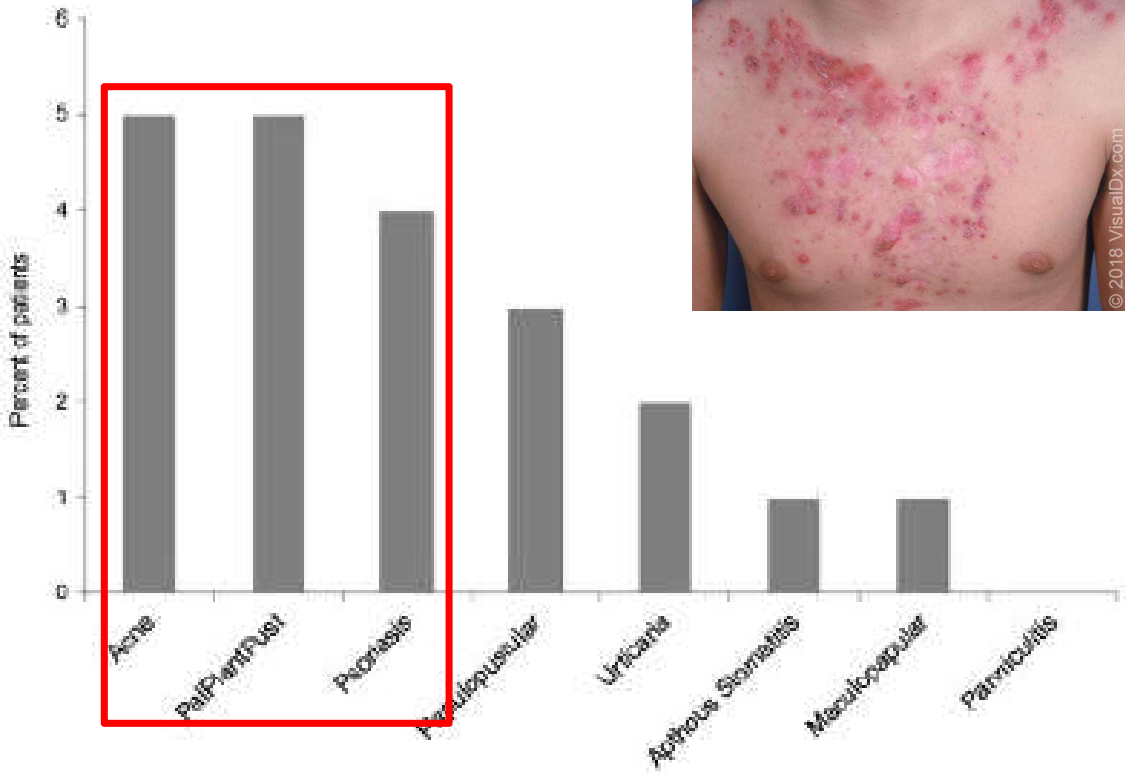
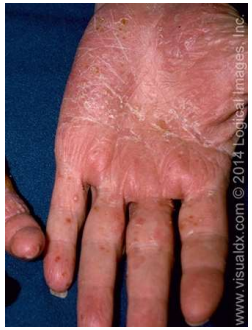
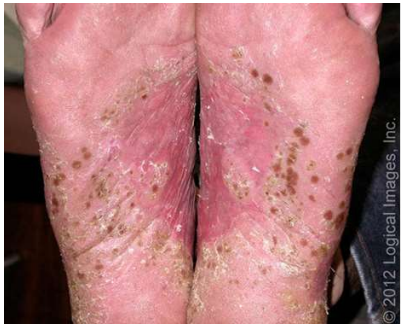
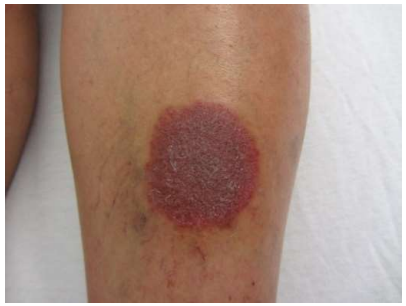
FIG. 1 Inflammatory mucocutaneous manifestations associated with chronic non-bacterial osteomyelitis









Girschick H. et al. Rheumatology.2018;57:1203-1211.

https://www.uptodate.com/contents/sapho-synovitis-acne-pustulosis-hyperostosis-osteitis syndrome?search=sapho&source=search_result&selectedTitle=1~20&usage_type=default&display_rank=1#H1668977891

Klinik

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- Schmerzen während der Nacht wie auch unter tags
- Lokale Druckempfindlichkeit, Schwellung und Überwärmung möglich
- Schmerzhafte Bewegungseinschränkung der Gelenke
- Systemische Manifestationen in ca. 17%
- Humorale Entzündungsreaktion in 10-90% der Fälle
- 1/3 der Patienten mit zusätzlichen entzündlichen Erkrankungen (z.B. dermatologische Manifestationen, CED, Arthritis)

Koryllou et al. Children.2021;8:551.
Girschick H. et al. Rheumatology.2018;57:1203-1211.

Spektrum der aseptische Osteomyelitis/Knochenödems

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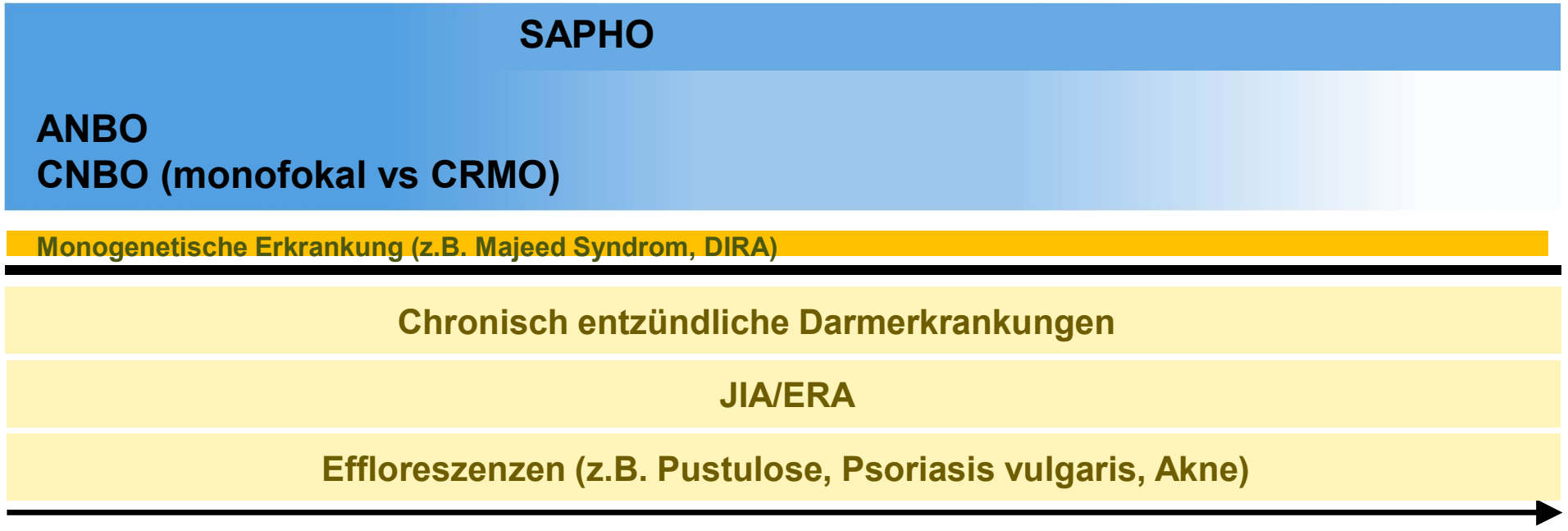
Aseptische Osteomyelitis

Begleiterkrankungen/ Symptome



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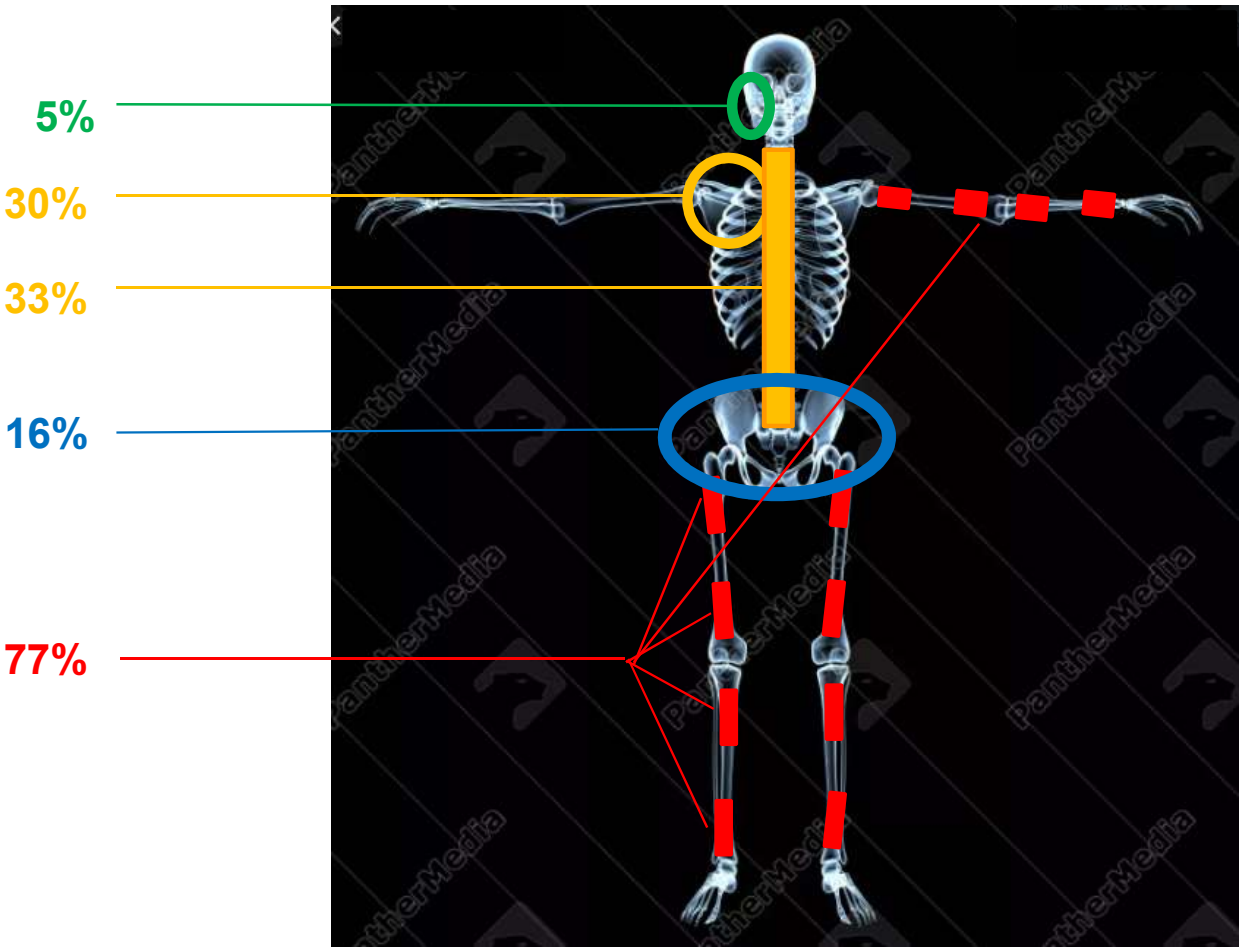
Lokalisation



Khanna G et al. RadioGraphics.2009;29:1159–1177.
Buch K et al. Calcified Tissue International.2019;104:544–553.
https://bildagentur.panthermedia.net/m/lizenzfreie-bilder/4480347/menschliches-skelett-roentgenbild

Differentialdiagnose

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Disease (group)	Examples
Bone tumors	Malignancies, including: - Ewing sarcoma - Osteosarcoma - Bone metastases (e.g. neuroblastoma, Fig. 3A) Benign tumors, including: - Osteoid osteoma, osteoblastoma
Hematological malignancies	Leukemia, lymphoma (Fig. 3C)
Metabolic disease	Hypophosphatasia
Bone infection	Bacterial osteomyelitis
Primary immune deficiency	Defects of IFN-gamma/IL-12 axis (favoring mycobacterial infections) (Fig. 3B)
Vitamin deficiency	Scurvy/vitamin C deficiency (box 1)
Other autoinflammatory diseases with bone involvement	- Deficiency of IL-1 receptor antagonis (DIRA) - Pyogenic Arthritis, Pyoderma gangrenosum and Acne (PAPA) - Majeed syndrome - Cherubism
Others	- Langerhans cell histiocytosis (Fig. 3D) - Fibrous dysplasia (Fig. 3E) - Bone cysts

Zha D.Y. Journal of Translational Autoimmunity.2021;4.

Diagnose

Der Balgrist

- Ausschluss anderer Erkrankungen
  - Anamnese, Klinik, Bildgebung, Labor, Histologie
- Bildgebung:
  - **Ganzkörper-MRI: Für qualitative und quantitative Beurteilung/Standortbestimmung**
  - 3-Phasenskelettszintigraphie
  - Konventionelles Röntgen
  - CT: ev. zur genaueren Beurteilung osteolytischer und osteosklerotischer Läsionen
  - **Initial:** Knochenödem, osteolytische u./o. sklerotische Veränderung
  - **Später:** Hyperostose, Periost- und Weichteilreaktionen
- Labor:
  - BB Diff, CRP, BSR, LDH, Harnsäure, ALP, Vitamin D
  - ev. BK, HLA-B27
- Biopsie zur Differenzierung einer bakteriellen Osteomyelitis oder Tumor
  - unspezifische entzündliche Knochenveränderungen

Diagnostische Kriterien

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Jansson criteria[1]	Bristol criteria[2]
Major criteria	**Required**
1. Radiologically proven osteolytic/sclerotic bone lesion 2. Multifocal bone lesions 3. PPP or psoriasis 4. Sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis	1. The presence of typical clinical findings (bone pain +/– localized swelling without significant local or systemic features of inflammation or infection) 2. The presence of typical radiologic findings (preferably STIR MRI showing bone marrow edema +/– bone expansion, lytic areas and periosteal reaction or plain radiograph showing combination of lytic areas, sclerosis, and new bone formation)
Minor criteria	**Plus one of the following**
A. Normal blood count and good general state of health B. CRP and ESR mildly to moderately elevated* C. Observation time longer than 6 months D. Hyperostosis E. Associated with other autoimmune diseases apart from PPP or psoriasis F. Grade I or II relatives with autoimmune or autoinflammatory disease or with nonbacterial osteomyelitis	A. More than 1 bone (or clavicle alone) involved without significantly raised CRP (CRP <30 g/L) B. Unifocal disease other than clavicle, or CRP >30 g/L, with bone biopsy showing inflammatory changes (plasma cells, osteoclasts, fibrosis, or sclerosis) with no bacterial growth whilst **not** on antibiotic therapy
Threshold of diagnosis: ≥2 major criteria or 1 major plus 3 minor criteria	**Threshold of diagnosis:** Both 1 **AND** 2, plus A **OR** B

Roderick M.R. et al. Pediatric Rheumatology.2016;14:47.
Jansson A et al. Rheumatology. 2007;46(1):154-160.
uptodate.com

Behandlung

https://de.dreamstime.com/nsar-drogenakronym-der-nichtsteroidalen-antirheumatika-konzept-auf-tafel-drogen-akronymkonzept-image197910335

Behandlung - NSAR

Der Balgrist

- NSAR: Besserung in 52%, Remission in 39%[1,2]

1. Girschick H. et al. Rheumatology.2018;57:1203-1211.
2. Kostik M.M. et al. Rheumatology International.2020;40:97–105.

Behandlung

Der Balgrist

Published in final edited form as:
Arthritis Care Res (Hoboken). 2018 August ; 70(8): 1228–1237. doi:10.1002/acr.23462.

Consensus Treatment Plans for Chronic Nonbacterial Osteomyelitis Refractory to Nonsteroidal Anti-Inflammatory Drugs and/or with Active Spinal Lesions

1. Methotrexat oder Sulfasalazin (plus NSAR u./o. GC)
2. TNF-Hemmer (plus NSAR u./o. GC, oder MTX)
3. Bisphosphonat (plus NSAR u./o. GC)

Zao Y et al. Arthritis Care Res.2018;70(8):1228–1237.

Behandlung

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- Methotrexat: Remission in 38%[1]
- Glucocorticoide: Remission in 37%[2]

1. Wipff J et al. Arthritis & Rheumatology.2015;67(4):1128–1137.
2. Girschick H. et al. Rheumatology.2018;57:1203-1211.

Behandlung

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- Bisphosphonate (42%, 82%)[1]
  - bei WS- und Mandibula-Befall ev. Erstlinientherapie[1,2]
  - Pamidronat mit gutem klinischen und radiologischem Ansprechen[3]
- Biologika
  - TNF (46 – 89%)[4]
  - IL-1-Inhibitoren mit variablem Ansprechen

1. Bhat et al. Pediatric Rheumatology.2019;17:35.
2. Kostik M.M. et al. Rheumatology International.2020;40:97–105.
3. Andreasen CM et al. Scand J Rheumatol.2020;49:312–322.
4. Koryllou et al. Children. 2021;8:551.

Behandlung

Der Balgrist

Treatment options	Dosage	Length of treatment[a]
First-line treatments		
NSAIDs		
Ibuprofen	30–40 mg/kg/day in 3–4 divided doses	1–3 months
Indometacin	1–2 mg/kg twice daily	1–3 months
Naproxen	5–7.5 mg/kg twice daily	1–3 months
Diclofenac	2–3 mg/kg in 3 divided doses	1–3 months
Corticosteroids		
Prednisolone	1–2 mg/kg once daily	15–30 days then tapering
Second-line treatment		
Sulfasalazine	10–15 mg/kg 4 times daily	1–3 months
Methotrexate	15–20 mg/m^2 once weekly sc	6 months
Bisphosphonates		
Pamidronate	1–3 mg/kg/day for 3 consecutive days every 3 months[b]	9 months
	or	
	1 mg/kg/day for 1 day every month	6 months
Anti-TNFα		
Infliximab	5 mg/kg/dose. Infusions at time 0, 2, and 6 weeks then every 8 weeks	12 months
Etanercept	0.8 mg/kg/dose/week	6 months
Adalimumab	24 mg/m^2 every 2 weeks	6 months

NSAIDs non-steroidal anti-inflammatory drugs, *sc* subcutaneous, *TNF* tumour necrosis factor

[a] Length of treatment is intended as the minimum time to treat patients, but therapy can be prolonged according to clinical status

[b] First infusion 0.5 mg/kg

Taddio A et al. Pediatr Drugs.2017;19:165–172.

Physikalische Massnahmen

Der Balgrist

- Verbesserung der Lebensqualität
- Verhinderung Abnahme der Knochendichte

Koryllou et al. Children.2021;8:551.

Verlauf/Prognose

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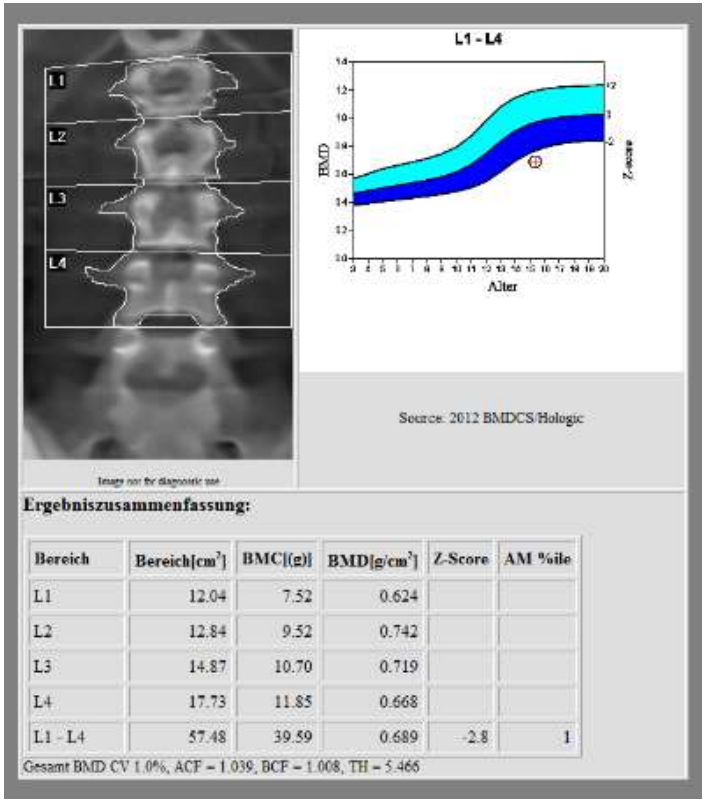
- 50% beschwerdefrei nach einem Jahr, 40% nach 5 Jahren
- Krankheitsaktivität in 52% (Beobachtung über 22 – 68 Monate)
- 50% mit Rezidiv nach durchschnittlich 29 Monaten
  - Rezidivrate von 16 – 83%
- Remission: kürzere Zeit zur Diagnose, ev. ♀

Zha D.Y. Journal of Translational Autoimmunity.2021;4.
Girschick H. et al. Rheumatology 2018;5712031211.
Schnabel A. et al. The Journal of Rheumatology.2017.
Wipff J et al. Arthritis & Rheumatology.2015;67(4):1128–1137.

Komplikationen

- Deformationen
- Wirbelkörperfrakturen (ca. 10-20%) - DEXA
- Neurale Kompression
- Chronische Schmerzen (ca. 8%)



Bereich	Bereich[cm²]	BMC[(g)]	BMD[g/cm²]	Z-Score	AM %ile
L1	12.04	7.52	0.624		
L2	12.84	9.52	0.742		
L3	14.87	10.70	0.719		
L4	17.73	11.85	0.668		
L1 - L4	57.48	39.59	0.689	-2.8	1

Lenert et al. Curr Opin Rheumatol.2020;32:421–426.

Vielen Dank für Ihre Aufmerksamkeit!