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chronic recurrent multifocal osteomyelitis (CRMO)

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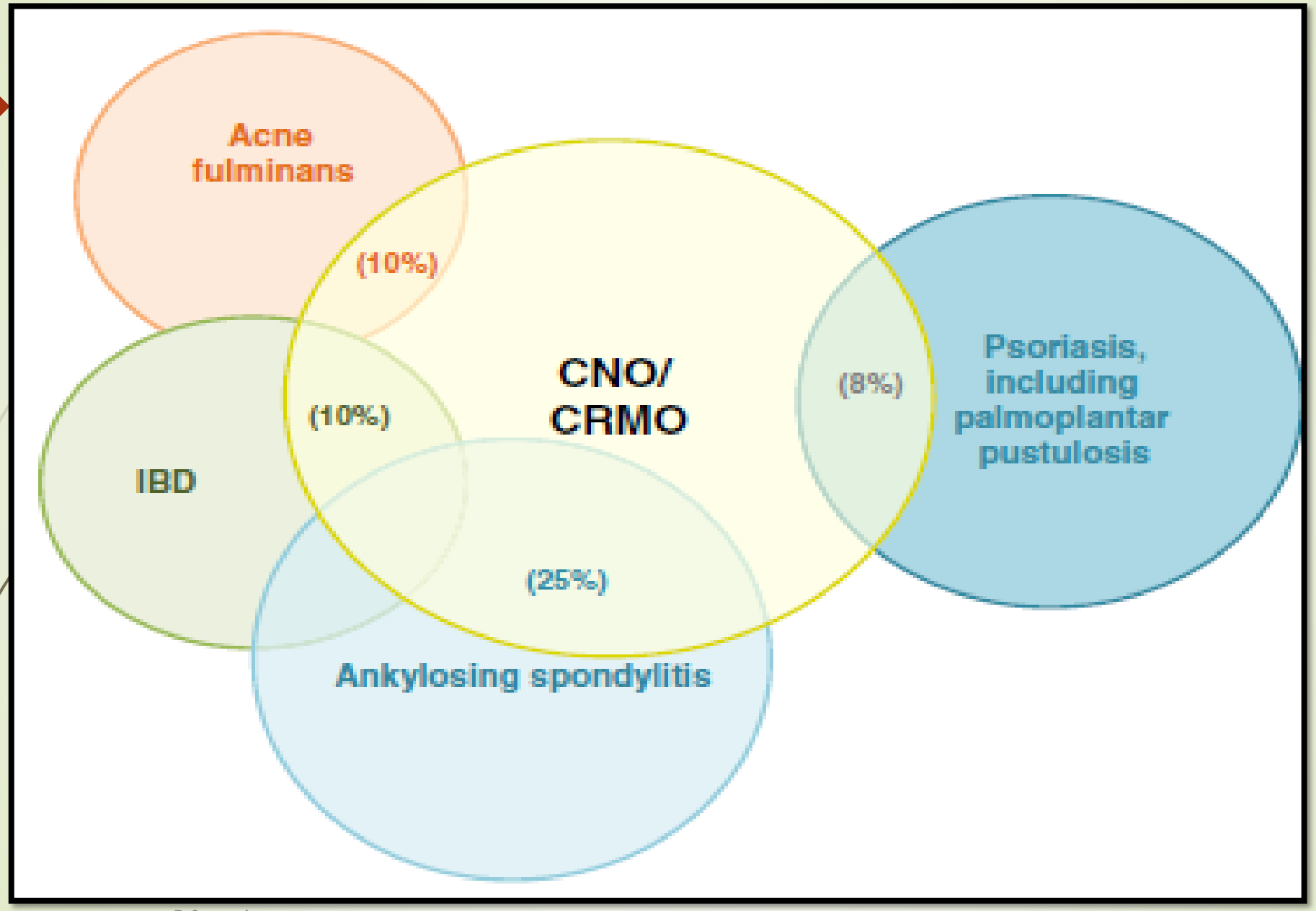
- CRMO is an **autoinflammatory** bone disorder.
- the exact molecular pathophysiology of CNO/CRMO remains vague
- variable defects in the TLR4/MAPK/inflammasome signaling cascade
- an imbalance between pro- and anti-inflammatory cytokines
- an activation of the innate immune system
- absence of high-titer autoantibodies and (at least initially)
- no involvement of autoreactive lymphocytes.

CNO: chronic noninfectious arthritis

Genetic Predisposition

- familial clusters of CNO patients
- associations with other inflammatory conditions, including inflammatory bowel disease, acne, ankylosing spondylitis, and psoriasis
- There are at least three human diseases involving chronic multifocal sterile osteomyelitis that are caused by single gene mutations:
- (i) Majeed syndrome (LPIN2 mutations),
- (ii) deficiency of interleukin-1 receptor antagonist (DIRA, mutations in IL1RN) and
- (iii) pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA, mutations in PSTPIP1).

Proline-Serine-Threonine Phosphatase Interacting Protein 1


Acne fulminans
(10%)
IBD
(10%)
CNO/ CRMO
(8%)
Psoriasis, including palmoplantar pustulosis
(25%)
Ankylosing spondylitis

SAPHO

- **In adults , patients with CNO are usually diagnosed with SAPHO :** synovitis, acne, pustulosis, hyperostosis, and osteitis
- symptoms may be caused by paraosseous inflammation, involving peripheral nerves and/or vessels, skin or bowel inflammation, and synovitis.
- Some CNO patients develop sacroiliitis, and some patients may progress from childhood CNO to spondylarthropathies in later life stages

Majeed syndrome

- early-onset multifocal osteomyelitis, dyserythropoietic anemia, and joint contractures.
- loss of function mutations in the LPIN2 gene, encoding for the lipin 2 protein, a phosphatidate phosphatase (PAP) that plays a role in lipid metabolism.
- Lipin2- deficient monocytes produce high amounts of proinflammatory cytokines IL-6 and TNFa when stimulated by saturated fatty acids.
- Overexpression of LPIN2 on the other hand reduces inflammatory cytokine levels
- it is an IL-1β-mediated disease
- markers improve in response to IL-1β blockade, while TNFa blockers have almost no effect

DIRA Deficiency of IL-1 receptor antagonist

- early-onset destructive sterile bone lesions (osteitis and periostitis) and sterile pustulosis of the skin.
- If left untreated, DIRA leads to a severe systemic inflammatory response syndrome and respiratory
- uncontrolled IL-1β signaling.
- Treatment with recombinant IL-1 receptor antagonist results in prompt disease control

PAPA

- Pyogenic arthritis, pyoderma gangrenosum, and acne
- caused by mutation in the PSTPIP1 gene, involved in regulation of the actin cytoskeleton.
- PSTPIP1 binds to pyrin, a central negative regulator of the NLRP3 inflammasome.
- Therapeutic options for PAPA are local and/or systemic steroids,TNFa blockers, and IL-1 blocking agents .

Clinical signs

- **include bone pain, local swelling, rarely skin redness and heat, associated skin manifestations (including palmoplantar pustulosis, psoriasis, and acne), sometimes mildly elevated temperatures, and pathological fractures (usually of affected vertebral bodies).**
- **Non-infectious arthritis can be present in up to 30% of patients** Clinically and also radiologically, arthritis of adjacent or remote joints may be present
- **inflammatory parameters (WBC, white blood cell count; CRP, ,ESR, erythrocyte sedimentation rate) are usually normal or mildly elevated.**

Table 1. Baseline characteristics of children with CNO (n = 56).

Variable	Value
Demographic characteristics	
Female/male, n	33/23
Age at symptom onset, yrs, median (range)	10.8 (3–17.2)
Age at diagnosis, yrs, median (range)	11.1 (3–17.9)
Delay in diagnosis, mos, median (range)	3.0 (0.02–60)
Clinical characteristics	
No. painful localizations per patient, median (range)	1 (1–7)
Local inflammatory signs, n (%)§	27 (48)
Loss of function, n (%)*	27 (48)
Fever, n (%)†	6 (11)
Arthritis, n (%)	20 (36)
Arthritis distant to CNO lesions, n (%)	7 (13)
Inflammatory bowel disease, n (%)‡	6 (11)
Palmoplantar pustulosis, n (%)	5 (9)
Sequelae, n (%)**	19 (34)

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Original article

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

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TABLE 1 Patients original home country

Country	Patients (*N* = 486)
Germany	190
Italy	144
Denmark	66
France	31
Spain	17
Saudi Arabia	8
Switzerland	8
Australia	5
Romania	4
Russia	3
Argentina	2
India	2
Hungary	2
Croatia	1
Lithuania	1
Netherlands	1
Japan	1
Chile	1
Greece	1

clinical , imaging signs

Hermann 486 cases

- bone pain 92%,
- joint pain/ arthralgia 65%,
- bone deformity 15%

Imaging

- osteitis in 327 patients (70%),
- osteoporosis in 14 (3%),
- osteolytic lesions in 105 (22%)
- hyperostosis in 68 (15%)
- Thus CRMO (more than one lesion) could be noted in 71, 77 and 69% of patients, respectively.

- mostly affecting children and adolescents
- Disease onset before 2 years of age is extremely uncommon and should prompt considering differential diagnoses.
- CNO/CRMO most frequently involves metaphyses of long bones, the pelvic bones, the vertebral column, or the shoulder girdle/clavicle

- 25% pelvic
- 23% vertebral,
- 19% clavicle
- 15% tarsal,
- 10% chest,
- 3% carpal,
- 3% cranial

Table 1 Distribution of different lesions by imaging

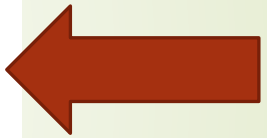
Site affected	Number of detected lesion	% of total lesions $n = 162$
Pelvis	14	9
Femur	16	10
Tibia	40	25
Fibula	8	5
Small bone in foot	16	10
Humerus	7	4
Radius	5	3
Ulna	4	2
Mandible	1	1
Clavicle	12	7
Ribs	6	3
Sternum	1	1
Vertebra	32	20
- Cervical	*(2)*	*(1)*
- Thoracic	*(18)*	*(11)*
- Lumbar	*(3)*	*(2)*
- Sacral	*(8)*	*(5)*
- Coccyx	*(1)*	*(1)*
Total	162	100

Laboratory analysis

Hermann 486 cases

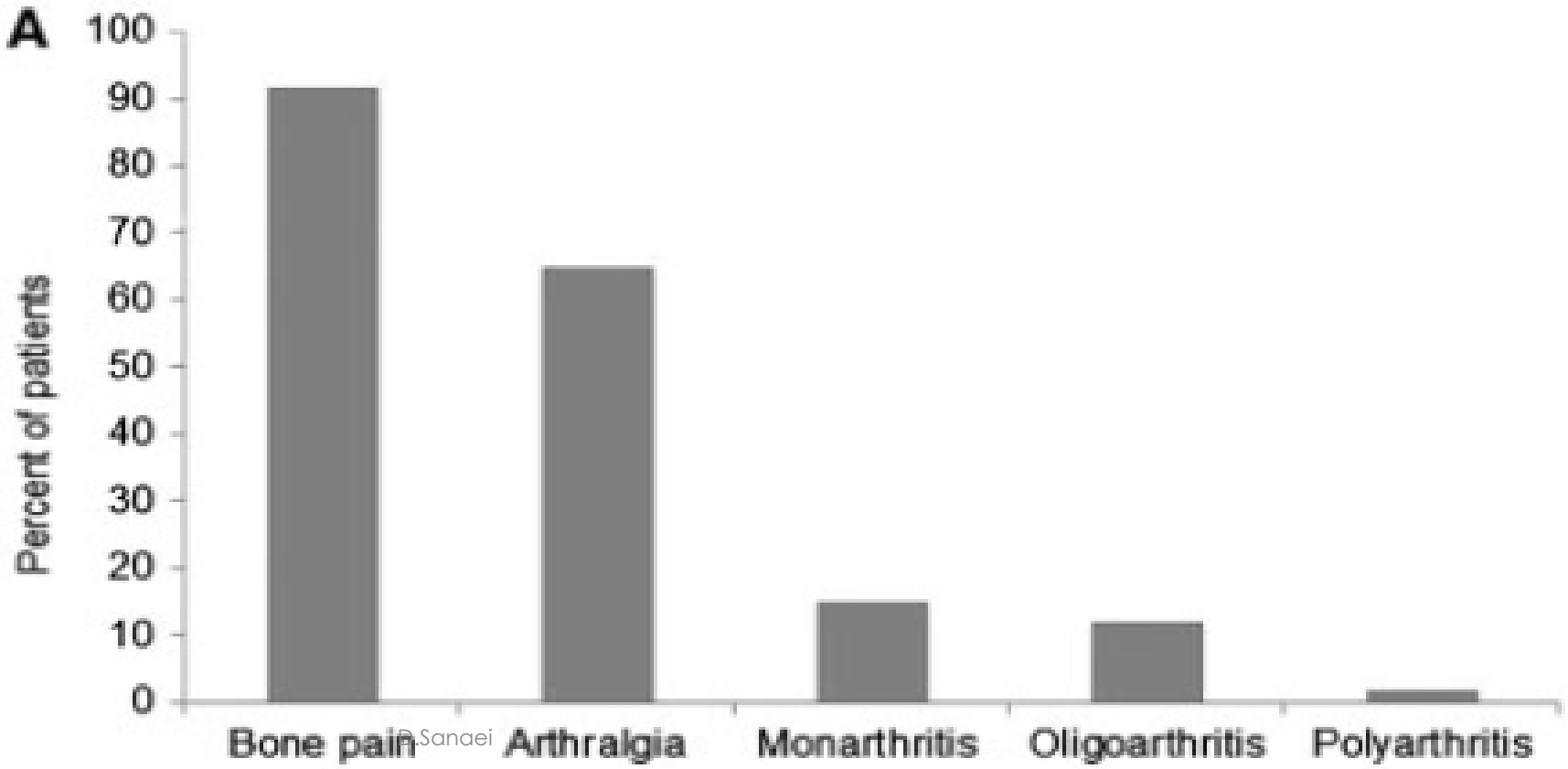
- elevated ESR : 59%
- elevated CRP : 49%,
- elevated white blood cell count : 14%
- elevated serum amyloid A : 12%.
- No relevant elevation was noted for IgD, IgG, IgA or IgM.
- HLA-B27 was present : 7.9%
- elevated ANA titers: 38%

Inflammation markers, mean ± SD	
Leukocytes, 4.5–12.5 GPt/l	8.2 ± 2.4
Thrombocytes, 150–400 GPt/l	366 ± 99
Neutrophils, 43%–57%	52.4 ± 13.1
Lymphocytes, 30%–45%	33.0 ± 11.1
Monocytes, 0%–6%	8.1 ± 2.1
CRP, > 5 mg/l	16.9 ± 43
ESR, > 15 mm/h	31.7 ± 24.4
Autoantibodies	
HLA-B27–positive, n = 43, n (%)	9 (21)
ANA-positive, n = 34, n (%)***	5 (15)



Hermann Girschick *et al.*

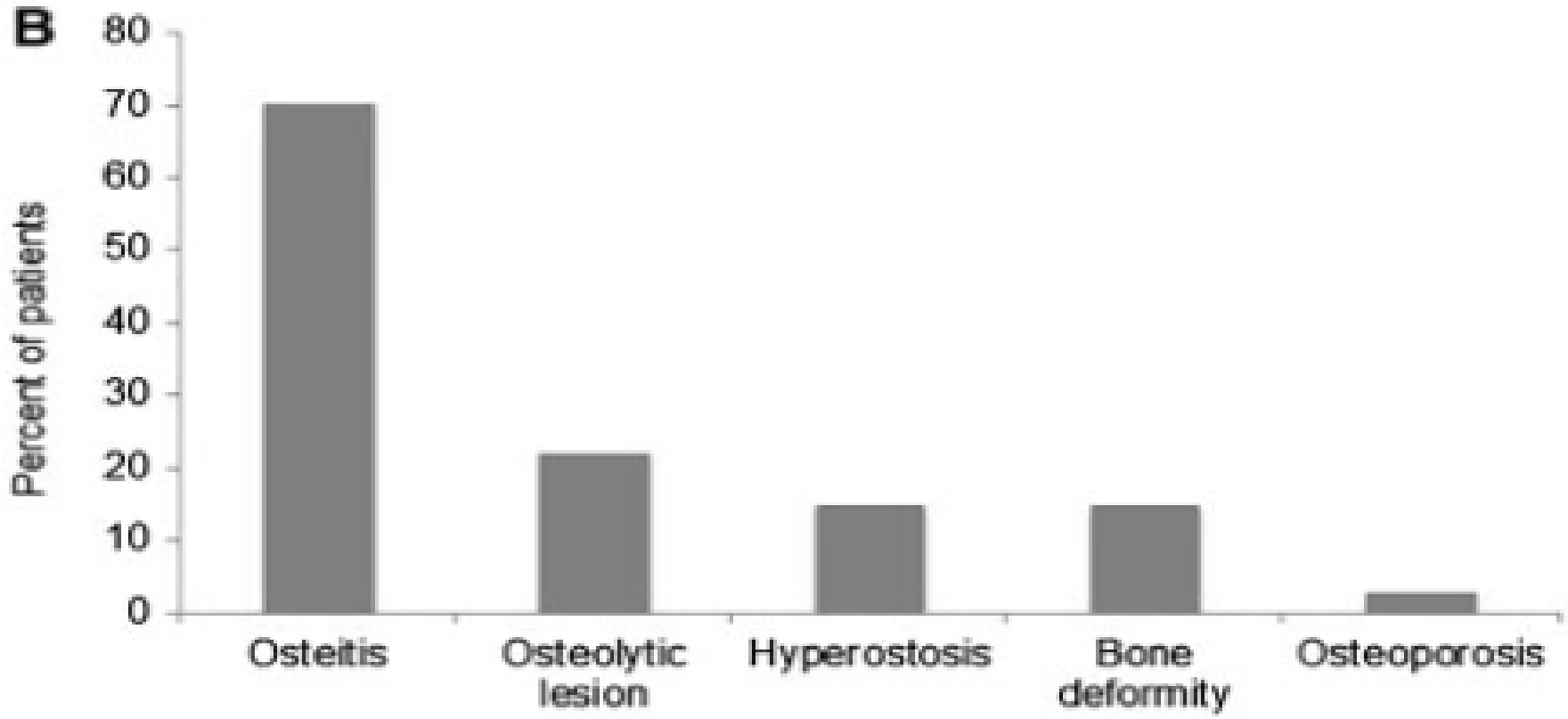
Fig. 2 Inflammatory musculoskeletal manifestations associated with chronic non-bacterial osteomyelitis



Hermann 486 cases

Imaging : To exclude other diseases

- plain radiographs: as radiolucent, osteolytic, or sclerotic lesions, but may remain normal in early stages.
- (MRI) are highly sensitive: bone edema even before bone erosions and sclerosis develop
- Strongly T2-weighted sequences (Turbo Inversion Recovery Measurement, TIRM) and/or gadolinium-enhanced T1 sequences with fat saturation enhanced T1 sequences with fat saturation: inflammatory bone lesions and/or periosseous affections



Musculoskeletal manifestations were reported in 486 patients. Relative frequencies of (**A**) clinical and (**B**) imaging features of patients are given.

Hermann 486 cases

- 37% metaphyseal,
- 23% epiphyseal,
- 15% diaphyseal,

- **Arthritis: Overall, 29% of patients were reported to be affected by arthritis**

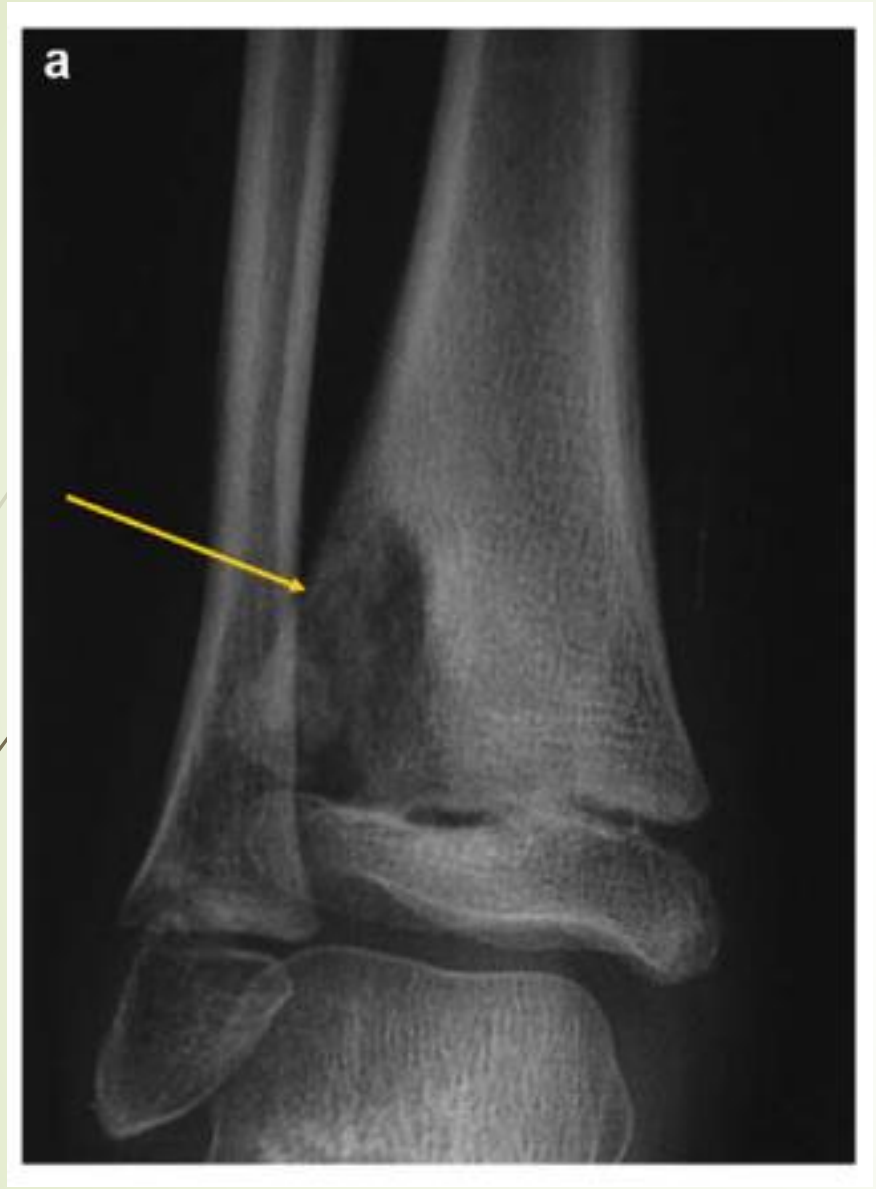
- monoarthritis in (15%),
- oligoarthritis (two to four joints affected) in (12%)
- polyarthritis (five or more joints affected) in (2%).

Histologic and microbial analysis of bone biopsies

Hermann 486 cases

A total of 281 single bone biopsies were reported (60% of 467 patients).

- **predominantly lymphocytic 31%**
- **granulocytic 40 %**
- **a mixture of both 32%**
- **sclerotic 23%**
- **inconclusive results 21%**
- edema, hyperemia,
- marrow fibrosis
- and osteonecrosis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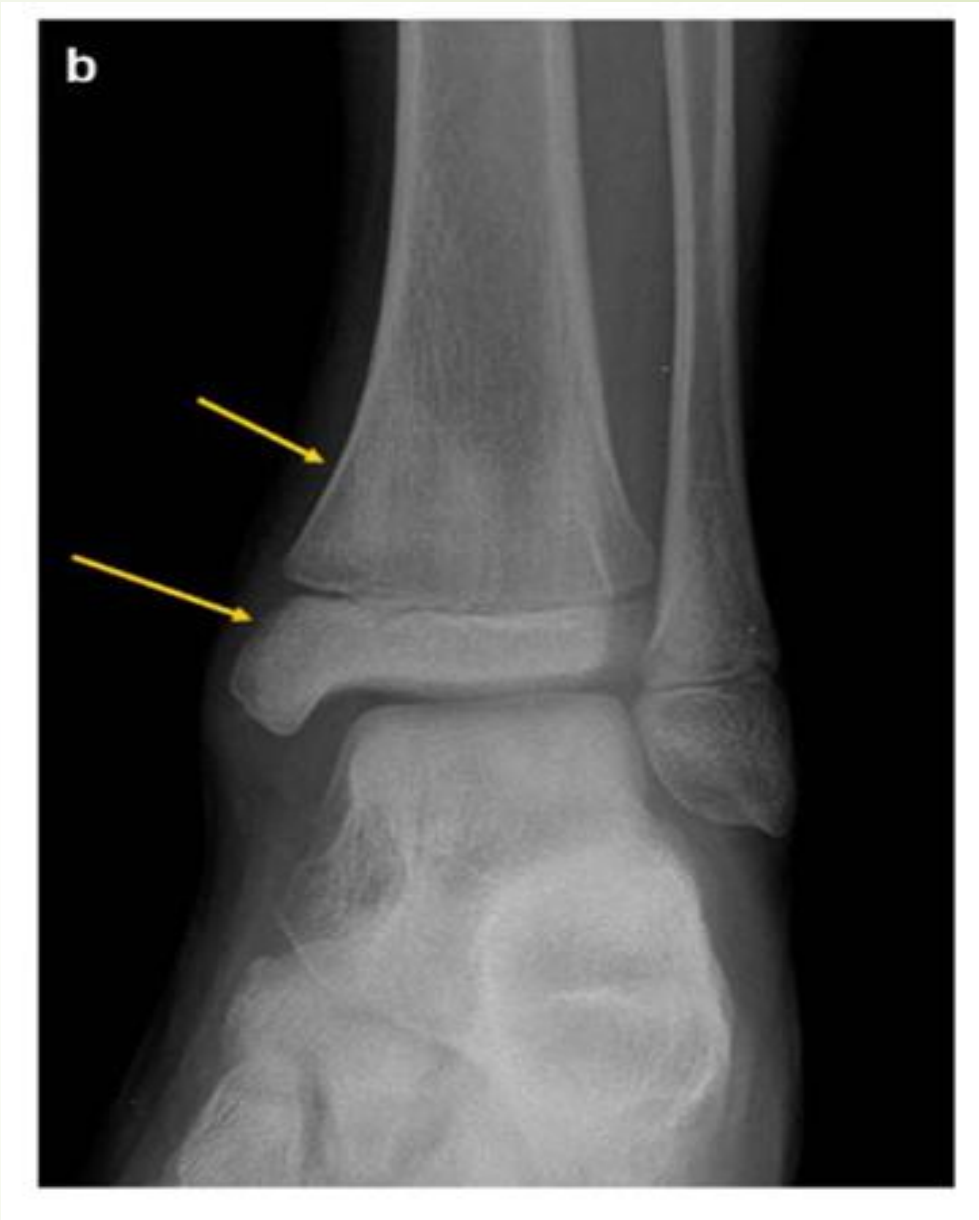
b

Imaging: Keep in mind/key point

- *MRI is an integral part in therapy monitoring*
- *bone marrow changes might persist even in complete clinical remission*

bone biopsies

usually performed to exclude

- chronic infection: bacterial osteomyelitis, tuberculosis, etc
- Malignancies: leukemia, lymphoma, primary and secondary bone tumors
- immunodeficiency (e.g., defects in the IL-12: interferon axis that may be accompanied by mycobacterial infections),
- Langerhans cell histiocytosis (LCH)
- other autoinflammatory disorders (e.g. Majeed syndrome DIRA ,or PAPA)
- other systemic disease.

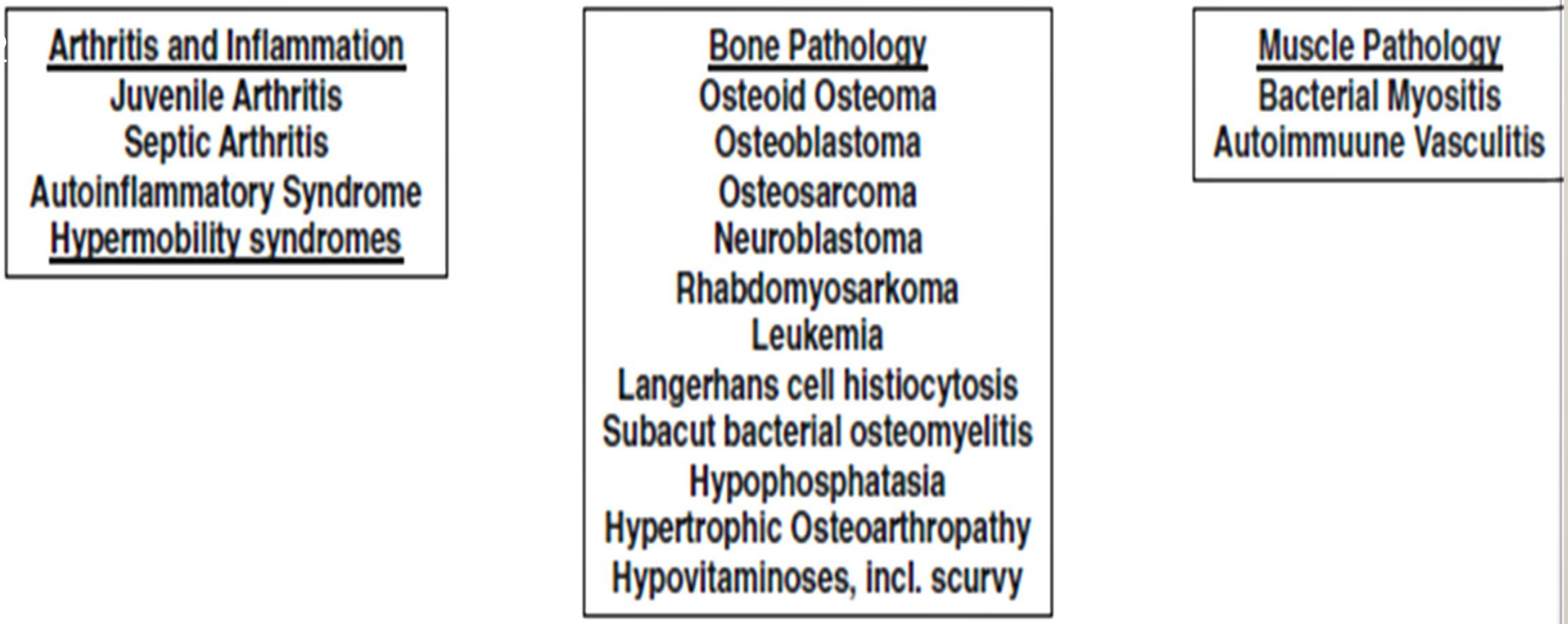

Fig. 1 Differential diagnosis of chronic non-bacterial osteomyelitis in childhood

Table 1
Differential diagnoses to CNO (may be incomplete).

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

Table 1. Differential diagnosis of CNO/CRMO. CNO—Chronic non-bacterial osteomyelitis, CRMO—Chronic recurrent multifocal osteomyelitis.

Common Differential Diagnosis of CNO/CRMO:
Primary malignant bone diseases:
• Ewing sarcoma
• Osteosarcoma
• Bone metastases
• Primary non-Hodgkin lymphoma of bone
Benign bone diseases:
• Osteoid osteoma
• Osteoblastoma
• Chondroblastoma
• Cystic bone tumor
Hematological diseases:
• Leukemia
• Lymphoma
• Langerhans cell histiocytosis of bone
• Non Langerhans cell histiocytosis
Metabolic diseases:
• Hypophosphatasia
• Vitamin C deficiency
Auto-inflammatory diseases:
• Chronic arthritis
• PSTPIP1-associated auto-inflammatory diseases
Others:
• Infectious osteomyelitis
• Avascular necrosis (osteonecrosis)
• Amplified musculoskeletal pain syndrome/complex regional pain syndrome
• Growing pain
• Cherubism
• Fibrous dysplasia

- **CNO/CRMO remains a diagnosis of exclusion.**

CRMO

Roderick et al. Pediatric Rheumatology (2016) 14:47
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- The presence of typical clinical findings (bone pain +/- localized swelling without significant local or systemic features of inflammation or infection)
- AND
- The presence of typical radiological findings (plain x-ray: *showing combination of lytic areas, sclerosis and new bone formation* or preferably STIR MRI: *showing bone marrow edema +/- bone expansion, lytic areas and periosteal reaction)*
- *AND EITHER*
- *Criterion 1:* more than one bone (or clavicle alone) without significantly raised CRP (CRP < 30 g/L).
- OR
- Criterion 2: if 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.

Treatment of CNO/CRMO

- **NSAIDs**
- **NSAIDs (e.g., naproxen) are usually applied as first-line therapy in CNO/CRMO patients.**
- **children, known to respond better than adults**
- **Naproxen is the most prescribed NSAID, usually at a dose of 10 mg/kg (maximum 500 mg) twice daily : usually well tolerated**
- **it should be maintained for at least one month before evaluating the response .**
- **NSAIDs clinical improvement : In more than 50% of all patients within the first 12 months and a decrease in the number of radiological bone lesions in the first three months**
- **less effective in cases with spinal involvement.**
- **NSAIDs mainly effective in CNO with peripheral involvement, particularly unifocal forms or clavicle involvement**

Glucocorticoids

- In cases of persistent bone pain or systemic inflammation despite 3 months of NSAID treatment, a second-line treatment should be considered
- can be used as a short-term treatment
- not recommended as a long-term treatment due to the well-known side effects.
- usually apply 2 mg/kg oral prednisone per day plus NSAIDs over 5 to 10 days.
- In cases who first respond to corticosteroid treatment but then flare, high-dose steroids (2 mg/kg/day) can be repeated and supplemented by low-dose corticosteroids (0.1– 0.2 mg/kg/day) over a longer period, e.g., to "bridge" until DMARDs are working.

- NSAIDS are effective in a large subset of patients within the first 1–2 years of treatment.
- more than 50%of patients flare after 2 years
- Corticosteroids : quickly and effectively control inflammatory activity, but rarely induce long term remission.

Second-line treatments

- In individuals who fail to reach clinical and (if vertebrae are involved) radiological remission or relapse again, bisphosphonates, TNFa inhibitors, sulfasalazine, or methotrexate (MTX) should be considered.
- DMARDs Disease-modifying antirheumatic agents, such as methotrexate, their success is extremely variable among the different studies: in 20% of patients , 38%; 15% , 22% of the patients ,66%, and 83% of patients achieving at least a partial disease remission
- In patients with vertebral body involvement and structural damage, aggressive treatment should be discussed initially, e.g., with bisphosphonates

Bisphosphonates (BPs)

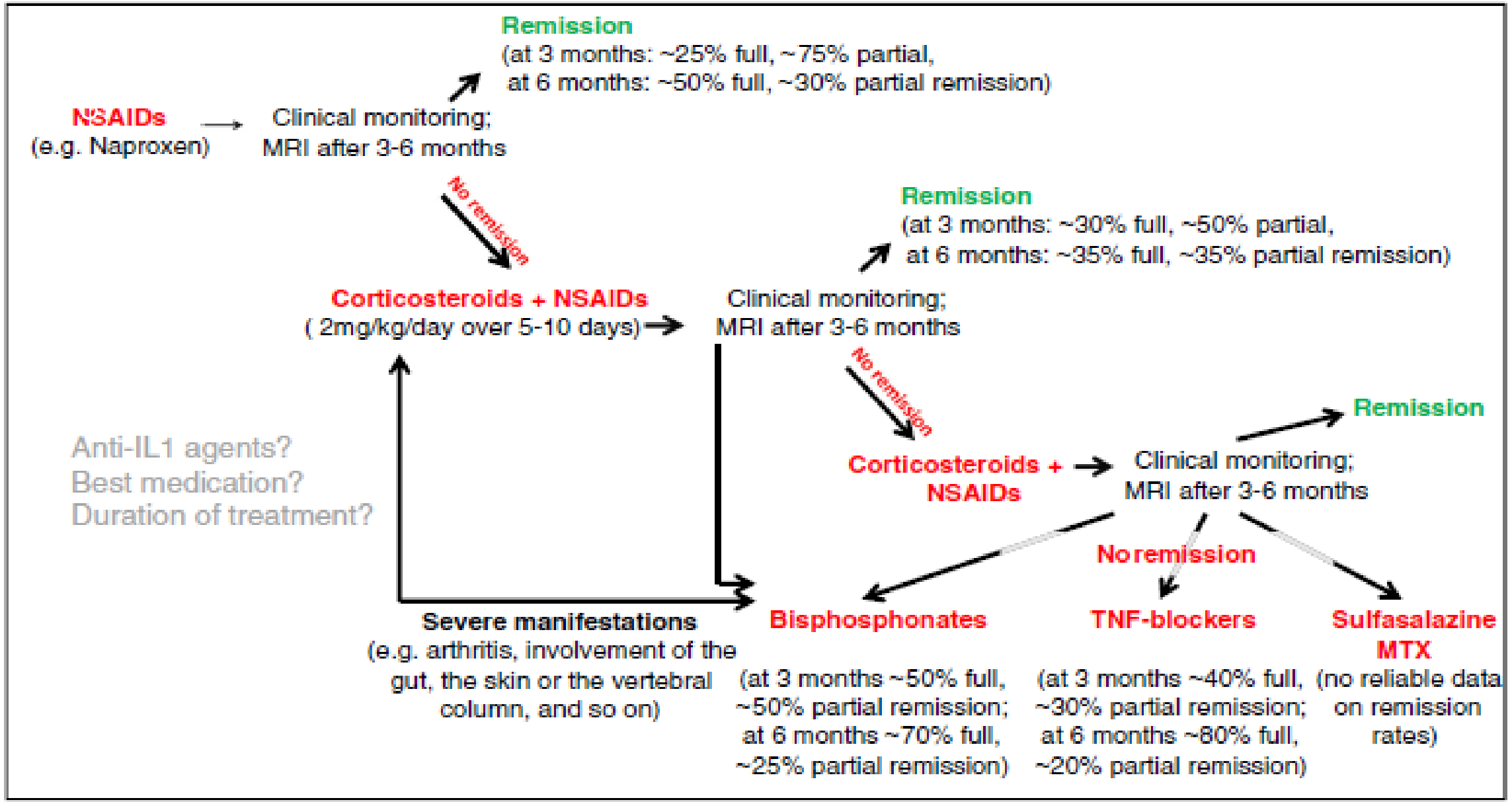
- proved an effective treatment for CNO lesions for almost 20 years.
- The most studied one is **pamidronate**, usually prescribed at a dose of 1 mg/kg/dose (maximum 60 mg/dose) every month, or 1 mg/kg/dose (maximum 60 mg/dose) for 3 consecutive days every 3 months
- The main benefits of treatment with BPs are related to their anti-inflammatory and pain-relief effects.
- A high efficacy in CNO patients with vertebral involvement

TNF- blockers

- etanercept, adalimumab, infliximab
- mainly after failure of other treatments,
- an efficacy ranging between 46 and 89%, shown by clinical remission in 3 months
- More recent : an efficacy ranging between 50 and 90.9% of cases

anakinra, canakinumab, and rilonacept

- IL-1 blockers are considered as an effective treatment in monogenic forms of CNO.



Chronic Recurrent Multifocal Osteomyelitis (CRMO): Presentation, Pathogenesis, and Treatment

Sigrun R. Hofmann[1]

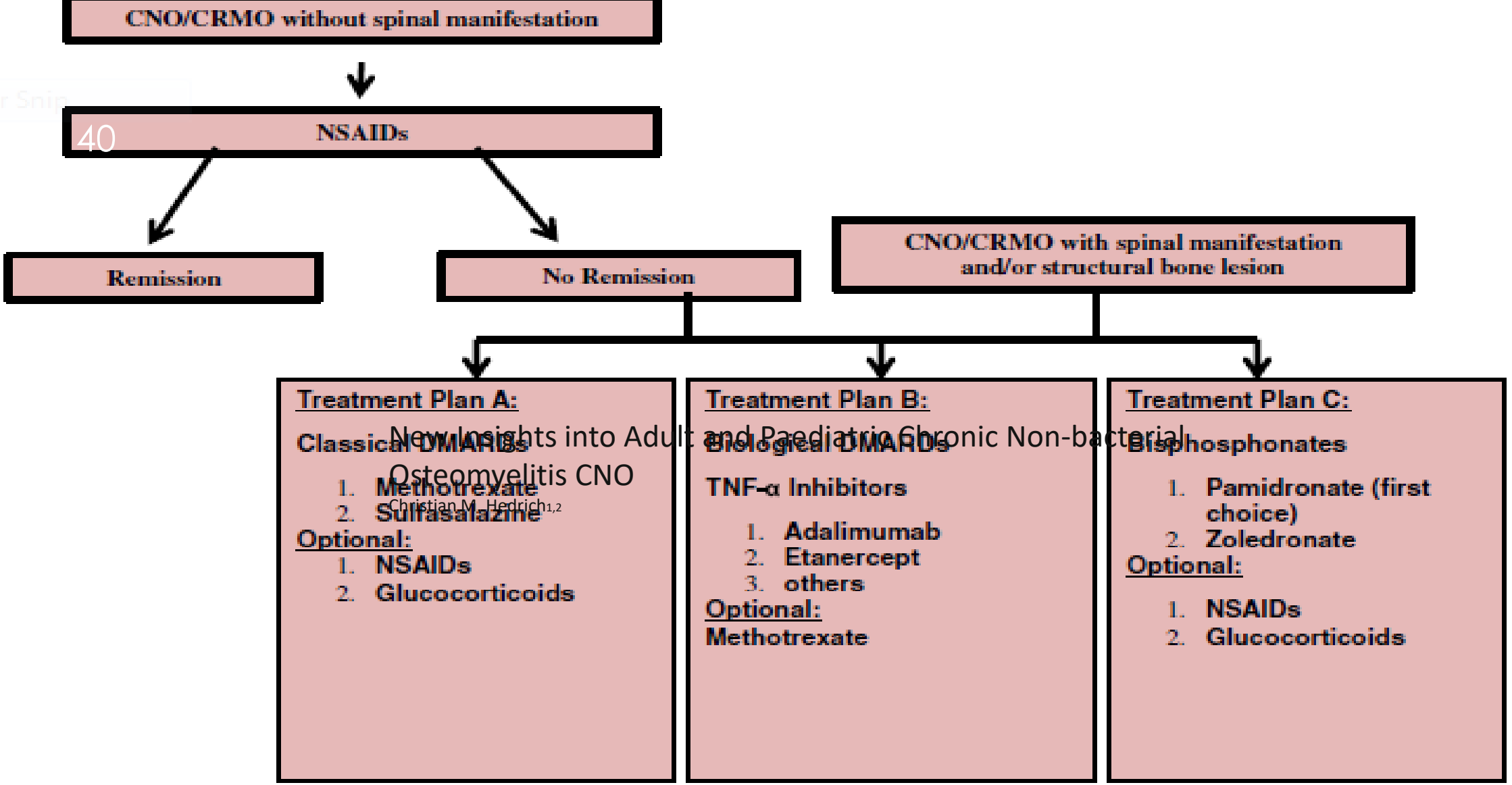


Fig. 3 Proposed treat-to-target protocol for childhood CNO

New Insights into Adult and Paediatric Chronic Non-bacterial Osteomyelitis CNO

Christian M. Hedrich[1,2]

- **Treatment goals are clinical and, in the case of vertebral involvement, radiological remission.**
- **Monitoring clinical and MRI scans after 3 to 6months.**
- **biomarkers (IL-12, MCP-1, sIL-2R) may act as markers for treatment response to NSAIDs**

Thanks for your attention