

Update in Pediatric Rheumatology

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Disclosures

- Shareholder in Inonis Pharmaceuticals and Compass Pathways

6 year old girl with 1 month of right knee pain

Osgood Schlatter
CNO
infection
Malignancy
Psoriatic arthritis
fracture
Muscle strain
Fat pad impingement
Osteoid osteoma
SLE
JIA
Depression
Viral arthritis
"growing pains"
Serum sickness
IBD arthritis
Reactive arthritis
Complex Regional Pain Syn.
Amplified MSK pain / fibromyalgia
Anxiety
tendonitis
scurvy
plica
Pat. Fem. Syn.
Phantom limb

6 year old girl with 1 month of right knee pain

If you could ask only one question to simplify the differential, what would it be?

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Osteoid osteoma

A general approach to MSK pain

FOUR CATEGORIES OF PAIN (PLUS OTHER)

Mechanical

Worse with use:
(afternoon evening)
Moderate - severe
Localized
minimal "itis":
(not warm or swollen)

Pat. Fem. Syn.
Plica
Fracture
Tendonitis
"growing pains"
Osgood Schlatter
Fat pad impingement
Muscle strain
...

Inflammatory

Worse with rest:
(morning)
Mild "stiffness"
Arthritis:
(warm, swollen, LROM)

Psoriatic arthritis
Viral arthritis
Reactive arthritis
Serum sickness
IBD arthritis
JIA
SLE
...

Psychogenic

Anytime
Fluctuates with mood
(Note: mood affects all
types of pain)

Depression
Anxiety
...

Nociplastic

All the time
Severe "burning,
stinging, electric"
Worse to touch
Allodynia

Complex regional
pain syndrome
Amplified MSK pain /
Fibromyalgia
Phantom limb
...

Other

Severe Pain
Doesn't fit schema

Malignancy
Osteoid osteoma
Infection
CNO/CRMO
scurvy
...

The category determines treatment

Mechanical

Rest
Ice
NSAID
Immobilization
Physical Therapy
Orthopedics

Inflammatory

NSAID
Immunosuppression

Psychogenic

Psychiatry

Nociplastic

Physical Therapy
CBT
Neuromodulator
Multidisciplinary pain clinic

Other

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Back to the history

- 6 yo girl with right knee pain for 1 month. The pain occurs daily in the anterior right knee fluctuating during the day from mild to severe **worse with walking** causing a limp. At times the pain can be severe enough to limit walking. **No preceding injury, new activities**, or infection. She has no fevers, weight loss, rash, diarrhea, or abdominal pain. The pain partially responds to ibuprofen. She does not wake at night from pain.
- Social History: Has a new kitten. Normal diet including fruits.
- Family history: **Father with psoriasis**.
- Physical exam is normal including **no obvious swelling**, and no pain on palpation or range of motion.

Narrowing the differential

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What evaluations do you want?

Useful tests for evaluation of MSK pain?

- CBC
 - Cytopenias suggest malignant dz.
 - High WBC raises concern for infection or autoimmune dz.
- ESR and/or CRP
 - Inflammation can be seen with infection, autoimmune or malignant dz.
 - Caution: normal inflammatory markers do not exclude rheumatologic dz.
- Xray
 - Assess for bone lesions from infection, autoimmune, or malignant dz.

The obligatory ANA slide from rheumatology

- ANA is not helpful as part of the diagnostic work up for this patient
- For example:
 - ANA 1:2560 – Even high ANA can be seen in the absence of rheumatologic disease and does not increase the likelihood of autoimmune disease in this patient
 - ANA 1:160 – Very common
 - ANA neg. – Still could be rheumatologic (**> half of JIA pts have neg ANA**)

Results

- CBC:
 - WBC 15K with high neutrophils
 - HCT 35%
 - PLT 550K
- ESR 30
- CRP 20 mg/L
- Right knee Xray – sclerosis of the right distal femur abutting the pysis



Iyer, RS, et. al. Amer J.
Roentgenology.
doi.org/10.2214/AJR.09.7212

When things do not fit think “other”

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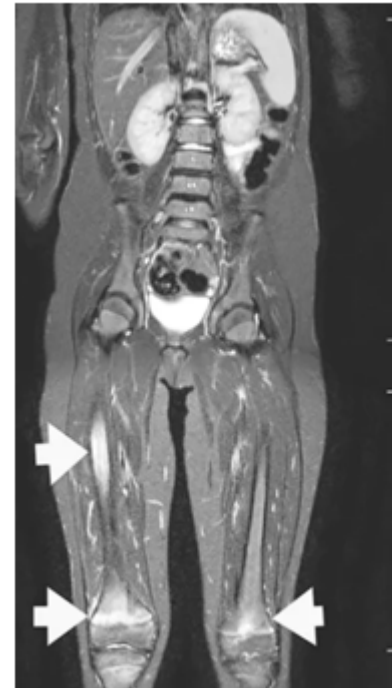
Differential of the “other” category

- Malignancy
 - Leukemia, Ewing's, Neuroblastoma, Langerhans Cell Histiocytosis (LCH), etc.
 - Look for destructive lesions, periosteal reaction, skull lesions, soft tissue mass.
- Infection
 - Pyogenic infections cause acute severe pain and are very inflamed
 - Consider slow growing or zoonotic organisms: mycobacteria, endemic fungi, Bartonella.
- Scurvy – Uncommon but it happens
- Chronic Non-bacterial Osteomyelitis / Chronic Recurrent Multifocal Osteomyelitis fits subacute course with mild inflammation – look for additional lesions

****Recommend whole body MRI**

Additional work up

- Infectious disease evaluation including Tb Bartonella and endemic fungi was negative
- Vitamin C level was normal
- Whole body MRI shows multifocal lesions in metaphyseal bone without vertebral lesions.



Kraus, MS, et al. Ped. Radiol.
doi.org/10.1007/s00247-022-05478-5

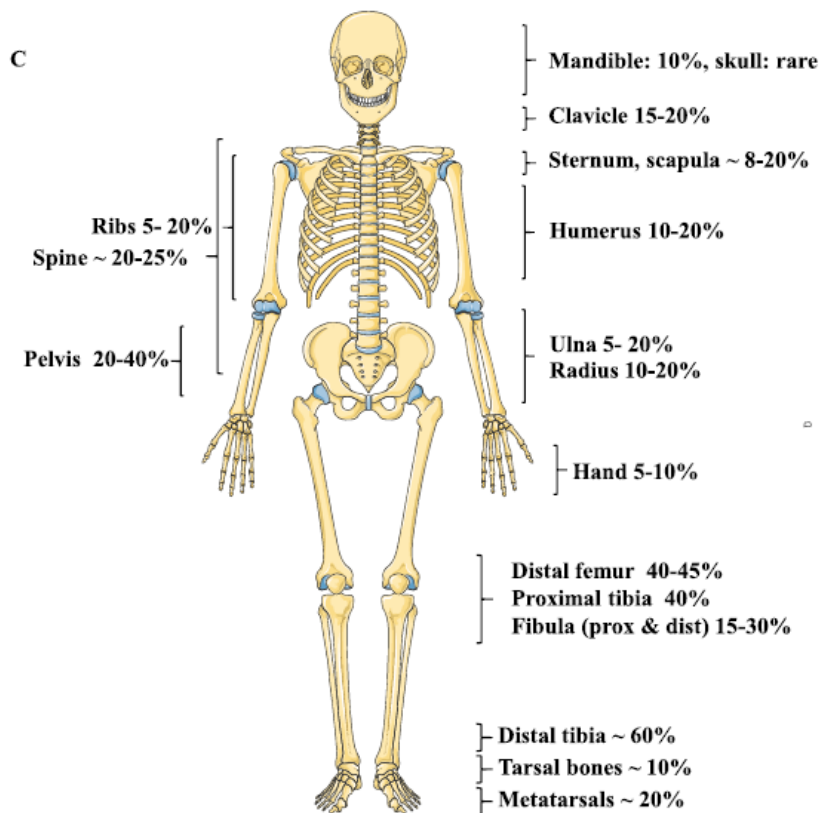
Diagnosis

**Chronic Non-bacterial Osteomyelitis - CNO
(aka Chronic Recurrent Multifocal Osteomyelitis – CRMO)**

Historical perspective

- Initial case report by Keipert and Campbell (1970)
 - Recurrent episodes over 7 years of pain and swelling affecting clavicles and tibia
 - Labs with elevated inflammatory markers
 - Initially diagnosed as atypical Juvenile Rheumatoid Arthritis
 - Treated with NSAIDs
- Girschick et al. described spectrum of disease in a German cohort (2005)
 - May be monophasic or recurrent
 - May be single lesion or multiple
 - Most severe variant is Chronic Recurrent Multifocal Osteomyelitis (CRMO)
- There are no specific diagnostic findings - diagnosis of exclusion ruling out infectious and malignant disease

Distribution of typical CNO lesions



Two main phenotypic patterns:

- Multifocal with tibial involvement
- Pauci focal with clavicular spinal disease
- Common: Clavicle, vertebrae, tibia
- Uncommon: **Skull, hands, diaphyses**

Triaille, C, et al. E. J. Peds.
doi.org/10.1007/s00431-024-05823-w

Adronikou, et al. Clin. Radiol. DOI:
[10.1016/j.crad.2019.02.021](https://doi.org/10.1016/j.crad.2019.02.021)

2025 the first validated classification criteria

Step 1, Verify entry criteria (ALL should be present):

1. Bone pain and/or musculoskeletal functional limitation ≥ 6 wk
2. Age of onset < 18 y
3. Abnormal findings from radiograph and/or advanced imaging including MRI, CT, bone scintigraphy at nonarthritic bone sites^a

Step 2, Verify exclusion criteria (NONE should be present):

1. Confirmatory evidence of mutually exclusive mimicker diseases^b
2. Platelet $< 100,000/\text{mm}^3$
3. Pathological LDH concerning for malignancy^c
4. Complete and sustained clinical and laboratory response to antimicrobial treatment alone

Step 3, Add the scores: Add the highest value from each of the 9 domains below. A score of ≥ 55 is required to classify a patient as having CNO.

Bone biopsy ^d	Score	Hemoglobin (normal range varies by age)	
• Signs of inflammation ^e AND fibrosis	17	• ≥ 10 g/dL	8
• Signs of fibrosis only	11	• < 10 g/dL	0
• Signs of inflammation only	9	Fever (oral/temporal temperature above 38°C and not related to common infections)	
• No signs of inflammation or fibrosis	0	• Absence of fever	8
Age at the onset of symptoms		• Presence of fever	0
• ≥ 3 y	17	Erythrocyte sedimentation rate (normal range: 0-20 mm/h)	
• < 3 y	0	• < 60 mm/h	8
Sites of bone lesions based on imaging		• ≥ 60 mm/h	0
• Clavicle and/or mandible	16	C-reactive protein (normal range: 0-10 mg/L)	
• Sites other than clavicle, mandible, skull, or hand	9	• < 30 mg/L	8
• Skull or hand without clavicle or mandible	0	• ≥ 30 mg/L	0
Distribution pattern of bone lesions based on imaging			
• Multifocal lesions (in ≥ 2 bones) with symmetrical pattern (bilateral involvement of at least one bone)	9		
• Multifocal without any symmetrical pattern of bone involvement	7		
• Unifocal without whole-body imaging such as WBMRI, PET/CT performed	3		
• Unifocal with whole-body imaging performed	0		
Coexisting conditions prior to the diagnosis of CNO			
• Inflammatory bowel disease (IBD)	9		
• Cutaneous condition ^f without IBD	8		
• Axial arthritis ^g without cutaneous condition or IBD	5		
• None	0		

Zhao, Y, et al. Arthritis and Rheum. DOI 10.1002/art.43137

When should we biopsy?

Box 1 Red flags that should raise the suspicion for an alternative diagnosis or an associated condition

Red flags in CNO/CRMO diagnosis

Severe pain (e.g. can't bear weight, unable to walk)

High fever, general malaise, weight loss

Acute, rapidly progressive symptoms onset

Additional clinical findings (abdominal mass, lymphadenopathies, etc.)

Highly elevated CRP, increased LDH, cytopenia

Atypical radiological feature (lysis without sclerosis, aggressive periosteal reaction) or localization (e.g. diaphysis, skull, etc.)

Unifocal lesion

Immunocompromised patient

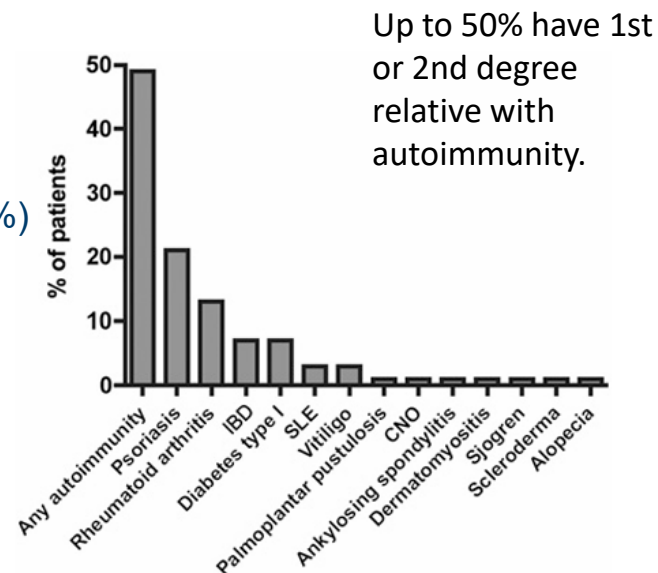
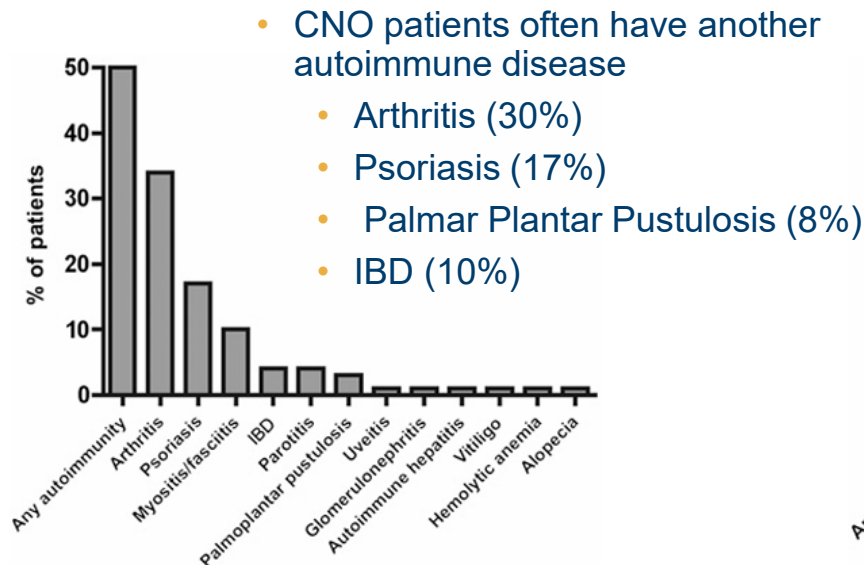
Onset < 2 years, familial history

Absence of response to NSAIDs or bisphosphonate

Triaille, C, et al. E. J. Peds.
doi.org/10.1007/s00431-024-05823-w

Pathogenesis of CNO

Evidence for immune dysregulation in CNO

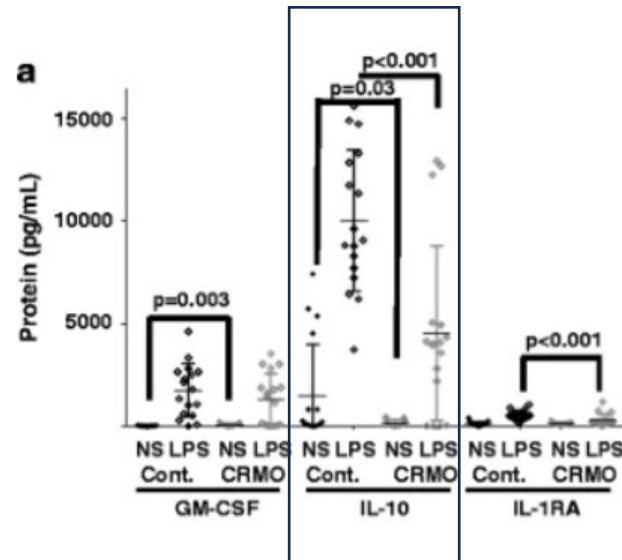


(Borzutzky A, et al. doi-org.ezp-prod1.hul.harvard.edu/10.1542/peds.2011-3788)

- Adults with CNO typically have a syndrome of Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO)

Evidence for immune dysregulation in CNO (continued)

- Monocytes from CNO patients make less anti-inflammatory cytokines IL-10 and IL-19 after LPS stimulation

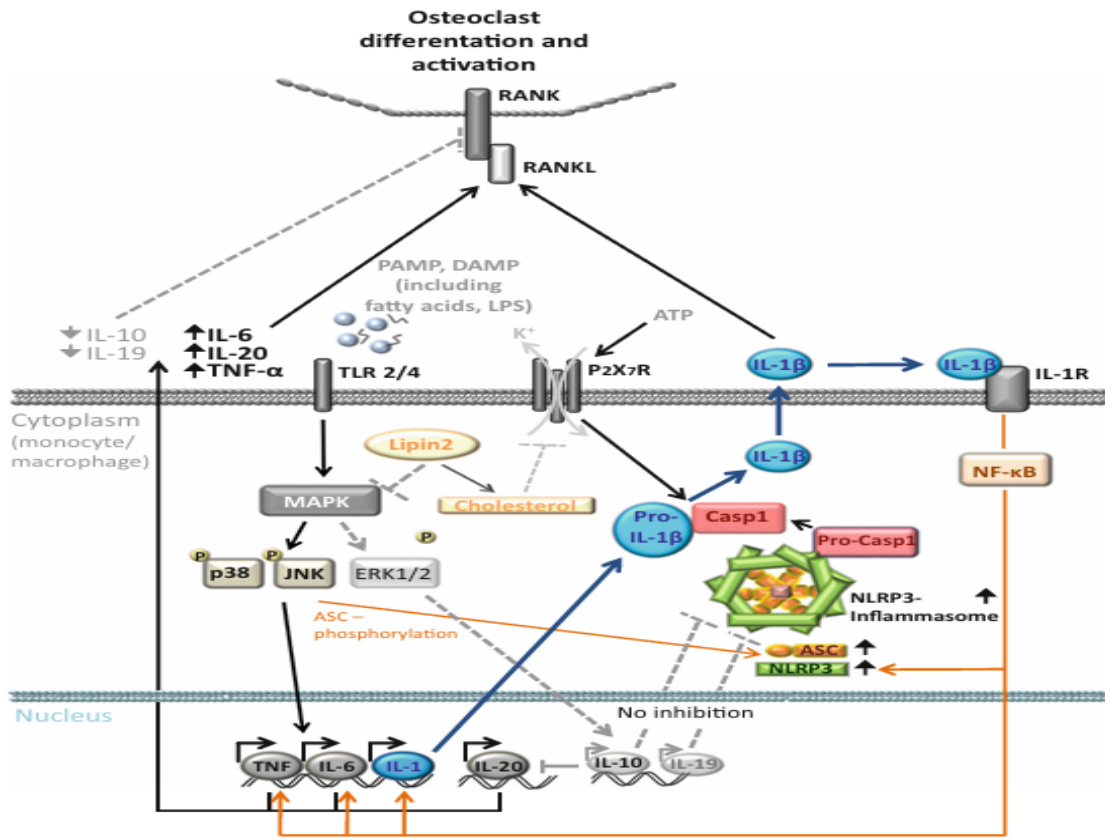


(Hofmann, SR, et al.
doi.org/10.1007/s11914-017-0405-9)

Evidence for immune dysregulation in CNO (continued)

- Monogenic diseases involving osteitis improve with immune blockade
 - Majeed Syndrome [LPIN2] – Responsive to IL-1 blockade
 - Deficiency of IL-1R antagonist (DIRA) [ILRN] -> Responsive to IL-1 blockade
 - Mouse model CNO [PSTPIP2] -> Responsive to IL-1 blockade

Proposed pathogenesis of CNO



CNO is proposed to be an autoinflammatory disease in which dysregulation of innate immunity results in sterile bone inflammation causes increased osteoclast differentiation and activation ultimately resulting in bone lesions

(Hofmann, SR, et al.
doi.org/10.1007/s11914-017-0405-9)

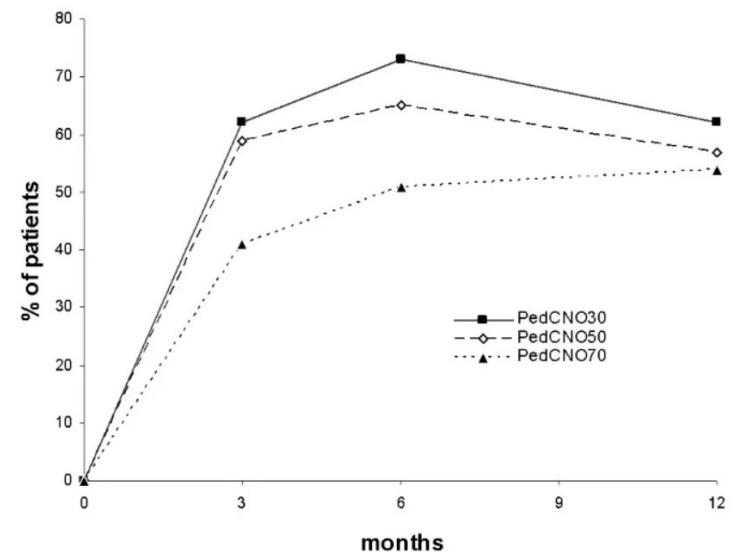
Treatment of CNO

Treatment paradigm

- Caveat: No RCTs - all medications used off-label
- Reason to treat:
 - Provide symptom relief
 - Prevent complications e.g vertebral compression
- Historically , the similarity to spondyloarthropathy resulted in the use of similar treatments as indicated in 2017 survey of Rheumatologists:
 - First line - NSAIDS (95%)
 - Second line – methotrexate (67%), anti-TNF agents (65%), bisphosphonate (46%)

Prospective evaluation of NSAID as initial therapy

- Beck followed a cohort of 37 German patients on naproxen as initial treatment for 6 months with MRI performed q3months.
 - 43% Symptom free @ 6 mo
 - 27 % had no lesions on MRI @12 mo
 - BUT 41% had new lesions on MRI @12 mo and 2/3 of those were asymptomatic



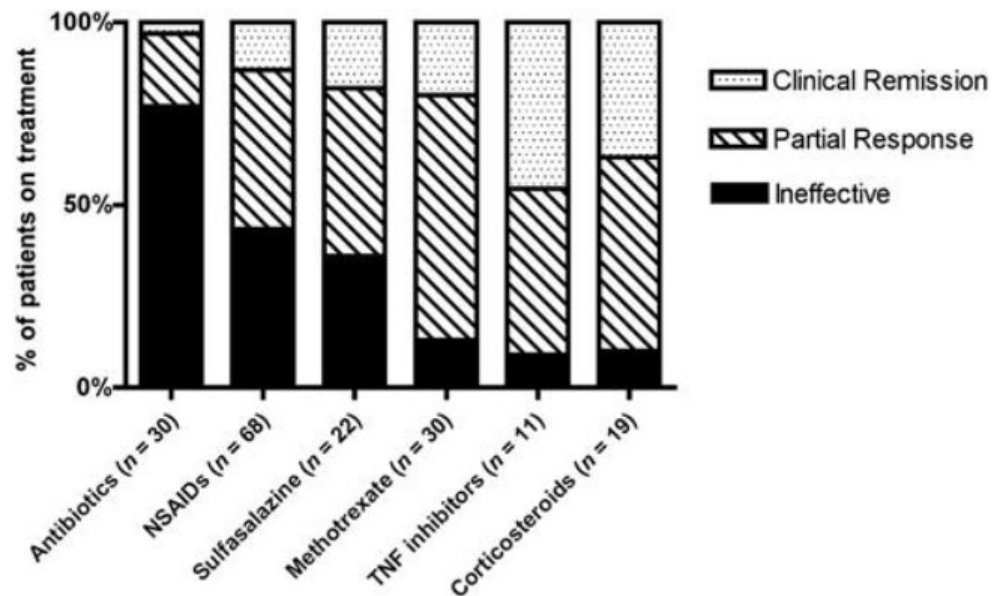
(Beck, C et al. 2010 doi.org/10.1186/ar2992)

Efficacy of second line agents

Retrospective review of 70 cases in Boston and Los Angeles between 1985 and 2009

- 57% had a response to NSAID
- 91% response to MTX
- 91% response to anti-TNF

NOTE: Because this is retrospective, therapies are not standardized. Also, potentially confounded by severity or associated diseases

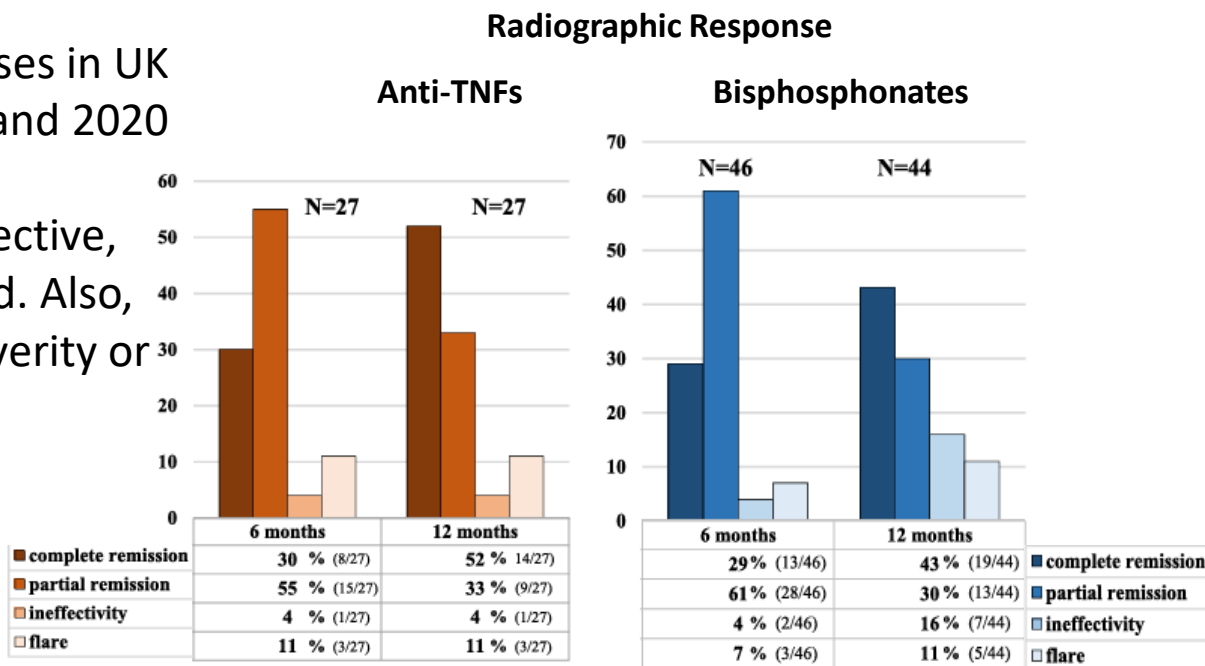


(Borzutzky A, et al. [doi-org.ezp-prod1.hul.harvard.edu/10.1542/peds.2011-3788](https://doi.org/10.1542/peds.2011-3788))

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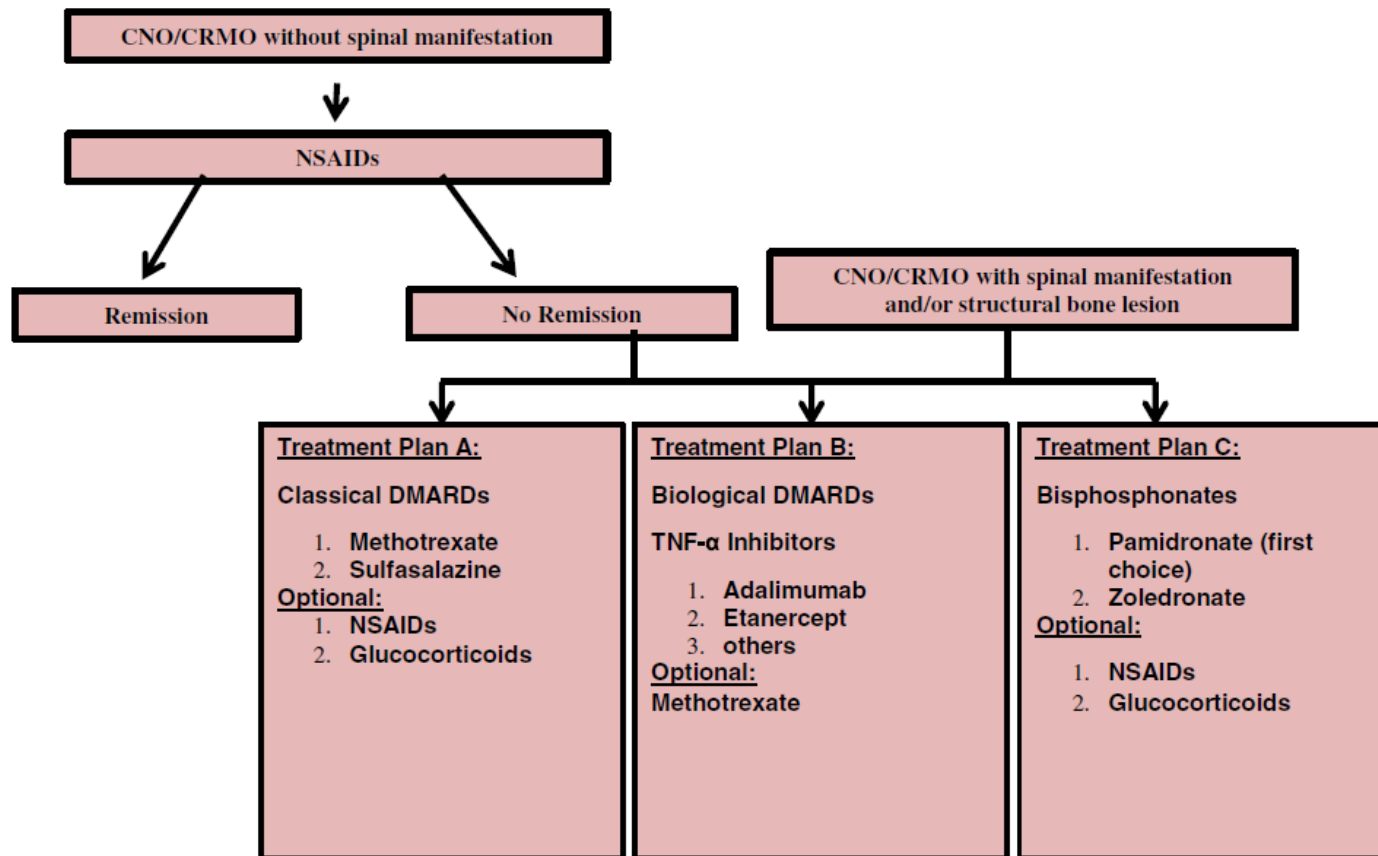
Retrospective review of 91 cases in UK and Germany between 2002 and 2020

NOTE: Because this is retrospective, therapies are not standardized. Also, potentially confounded by severity or associated diseases



(Scnabel A, et al. 2022 DOI: 10.1016/j.clim.2022.109018)

In 2019, consensus treatment algorithm developed to standardize care



Many favor pamidronate if vertebral involvement

Future directions for treatment

- Based on the proposed pathogenesis, additional medications are being tried for refractory CNO and SAPHO syndrome
 - IL-1 blockade
 - IL-17 blockade
 - JAK inhibitors

Follow up on our patient

- We started her on naproxen 10 mg/kg BID and she had improvement in her pain
- Regardless of symptoms, she will be monitored every 6-12 months by whole body MRI to assess for new structurally significant lesions especially vertebral lesions.

Thank You

- Take Home Points:
 - Lumping pain into 4 broad categories helps get patients to the right place.
 - The most important historical clue as to the cause of joint pain is when the joint pain occurs.
 - You have to have “-itis” to have arthritis. Exam shows warmth, swelling or limited motion. (Ultrasound can help identify effusion)
 - Labs are not helpful in diagnosing most JIA but are helpful in excluding other causes.
 - Criteria based diagnoses are useful for research, but gestalt is more important in clinical practice.