**Scottish Paediatric & Adolescent Rheumatology Network**

**Chronic Non-Infective Osteitis (CNO): Diagnosis & Management**

Scottish Paediatric & Adolescent Rheumatology Network Chronic non- infective Osteitis - Guideline for diagnosis and management

**Objectives**

To provide guidance on the assessment, diagnosis and management of children with suspected or confirmed Chronic Non-Infective Osteitis (CNO), previously Chronic Recurrent Multifocal Osteomyelitis (CRMO). This autoinflammatory condition of the bony skeleton can cause significant morbidity. It is treatable and referral to Paediatric Rheumatology is recommended in all cases. This guideline aims to facilitate earlier diagnosis and treatment to promote improved outcomes for patients.

**Scope**

Children presenting with suspected or confirmed CNO.

**Audience**

All clinicians who encounter children and young people.

**Introduction**

Chronic Non-Infective Osteitis (CNO) is a rare autoinflammatory condition which results in sterile inflammatory lesions of the bony skeleton. The most common presenting complaints are bony pain and swelling. Clinical course varies and diagnostic delay is common, often resulting in significant pain for those affected. The differential diagnosis is wide, including infective and neoplastic lesions. Therefore it is a diagnosis of exclusion. Detailed history and examination will facilitate preliminary diagnosis and guide further investigation, management and referral.

**Clinical Features**

• Bony pain

Most common presenting complaint

Can be single site or multifocal

Can occur anywhere

Back, lower limbs, pelvis and clavicle often affected

Night pain common – need to exclude malignancy

• Bony swelling

Tends to be single site

Can occur anywhere

Clavicle, tibia and mandible often affected

• Associated Features

Fever - can be present, but not often – If present consider infection

Arthritis - may be present

Rash/Psoriasis – Look for/ask about family history (SAPHO syndrome – Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis)

**Diagnosis**

CNO is a diagnosis of exclusion. Important exclusions include infection, malignancy and Langerhans Cell Histiocytosis (LCH). Diagnosis is based on a combination of clinical and radiological features; namely sterile bony inflammatory lesions affecting one or more site, where other pathologies have been excluded. Diagnostic criteria have been proposed but not yet validated. Validation of such criteria could help achieve an earlier diagnosis and avoid unnecessary investigation.

**Investigations**

Imaging

• Plain X-ray of affected site – can be normal

• Localised MRI of affected site • Baseline whole body MRI at diagnosis to look for asymptomatic lesions/determine extent of disease/type of lesions (hyperostotic/osteitic)

• No place for nuclear medicine bone scans

Bloods (not diagnostic)

• FBC & film – To look for infection/malignancy.

• ESR & CRP – To look for inflammation/infection. Beware - both may be normal or elevated. Most common finding is moderately raised ESR (10-50) with normal CRP.

• Bone profile (Ca, PO4 , alk phos, PTH) – Often normal. Beware - A low ALP can sometimes indicate hypophosphatasia, a rare genetic condition of bones and teeth which can be misdiagnosed as CNO

• Vitamin D – Deficiency may contribute to bony pain.

• HLA B27 – Associated with SAPHO syndrome.

• Bone Biopsy & Culture - Should be done if felt necessary to exclude malignancy or infection e.g. atypical features, very high inflammatory markers. The most common histopathological finding in CNO is that of chronic inflammation/osteomyelitis. Culture will be sterile in CNO. Note – clavicular biopsies frequently result in keloid scars

**Clinical Pathway**

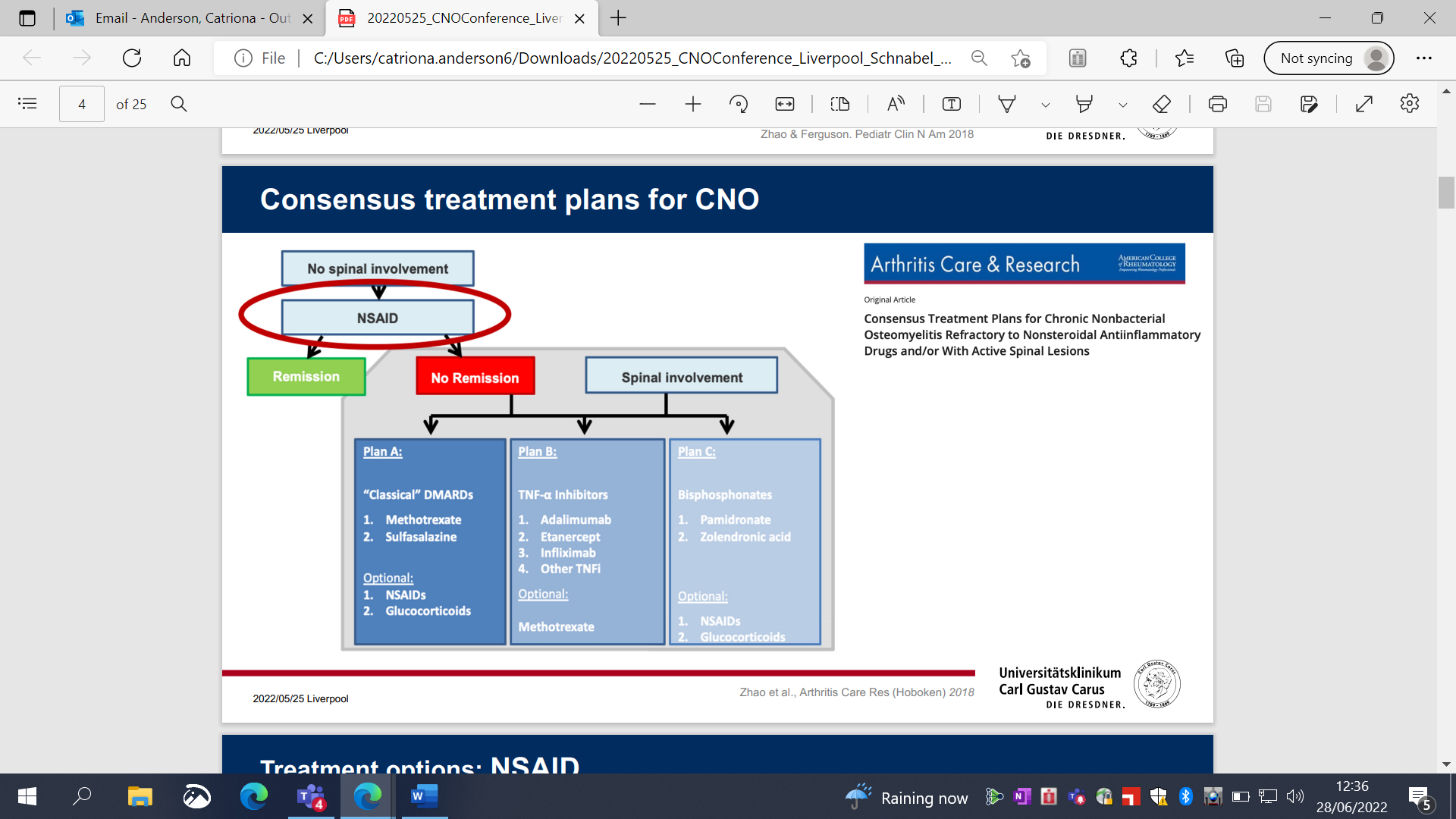
All children with suspected or confirmed CNO should be referred to a Paediatric Rheumatologist for assessment, management and monitoring. Children with CNO may develop significant chronic pain and early, appropriate management may reduce this.

**Management**

There is no clear evidence base regarding management of CNO and there is an absence of high quality randomised controlled trials due to its rarity. In the absence of this, treatment recommendations are often empiric and in the main based on consensus opinion or small retrospective case series. Treatment practice varies worldwide. Treatment is given for those who are symptomatic or have spinal lesions (due to risk of fracture). Patients may have a relapsing and remitting course and should have regular clinical review 3-4 monthly to assess progress (interval can be extended in periods of quiescence).

**Treatment Options**

In 2018, CARRA published Consensus Treatment Plans for children with CNO who were refractory to NSAIDs or had active spinal lesions1 (below).  These were based on a survey sent to members of CARRA, 95% of treating physicians who responded (41% response rate) use NSAIDs as first-line treatment in children with a new diagnosis of CNO ([24](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R24)). For patients who failed NSAID treatment, the most commonly used treatments were reported as methotrexate (67%), TNFi (65%), and bisphosphonates (46%) ([24](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R24)). These results guided the development of consensus treatment plans (CTPs).



Each of these treatment options will be discussed in turn with evidence base.

**NSAIDS**

Available Evidence:

A prospective study of 37 children with CNO on naproxen found 43% of them to be symptom free at 6-months2. Mean disease activity estimated by the patient/physician and the physical aspect of health-related quality of life including functional ability (global assessment/childhood health assessment questionnaire and childhood health assessment questionnaire) and pain improved significantly. Forty-one percent of our patients showed radiological relapses, but 67% of them were clinically silent.

A retrospective case series including 56 patients suggested NSAIDs work in the majority of patients (2/3), but there was > 50% failure after 2-3 years7.

Recommendation:

Non-steroidal anti-inflammatory drugs (NSAIDS) should be the first step in patients **without spinal involvement.**

High-dose Ibuprofen or Naproxen as per Children’s BNF can be given with gastroprotection.

Suggest give 3 months of treatment and assess response (clinically +- radiologically at clinician’s discretion)

Good response to NSAIDS – observe and review.

Poor response to NSAIDs or spinal involvement – consider change of treatment.

**DMARDS**

**Methotrexate and Sulfasalazine**

Evidence:

There are a few small studies that mention Methotrexate use in CNO, with remission rates varying from 20-24% 3-6. In a study where patients on methotrexate had a 44% remission rate, 67% of patients had a concomitant rheumatological condition rather than CNO alone.

A couple of studies mention sulfasalazine use in CNO. One showed involving 22 patients showed an 18% complete remission rate, similar to that seen with Methotrexate6. Another larger study with 47 patients, showed 38% complete remission rate5.

Most literature reported variable success of methotrexate (MTX) and sulfasalazine (SSZ) in patients with poor responses to NSAIDs or frequent relapses. Other DMARDs were rarely used. Five articles have reported treatment of DMARDs in CNO with level IV evidence. Jansson et al. ([19](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R19)), Catalano et al. ([23](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R23)), and Kaiser et al. ([20](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R20)) documented poor responses to SSZ, MTX, and azathioprine in children with CNO. Borzutzky et al. ([17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R17)) and Wipff et al. ([18](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R18)) showed relatively lower remission rates (18–20%) and efficacy (38–41%) in children treated with MTX or SSZ. There was poor tolerance of MTX and dosing was not reported in most studies.

Recommendation:

Methotrexate is a treatment option for CNO, but may be especially useful for those with associated arthritis or other rheumatological conditions (suggested dosing as per children’s BNF JIA dose).

Both will require regular blood monitoring as per local protocols.

Sulfasalazine is a treatment option for CNO (suggested dosing as per children’s BNF JIA dose).

Both will require regular blood monitoring as per local protocols.

SPARN Treatment Flowchart

Diagnosis of CNO – (if patient has spinal lesions – go to step 2).

Step 1

Regular NSAIDs - anti-inflammatory dose eg. Ibuprofen or Naproxen

Consider gastroprotection Assess response Good response to NSAIDS; observe and review

Review at 3 months: No/poor response to NSAIDs; Move to step 2

Step 2

Pamidronate infusion (bloods, Calcium supplements, dosing regimens as per SPARN protocol – Appendix 2) (Adalimumab can be used as an alternative if considered appropriate eg significant dental caries or foreseeable need for possible future orthopaedic/maxfax surgery) Appendix 3 for price comparison Assess response Good response to Pamidronate and asymptomatic; observe and review. Good response to Pamidronate but symptoms recur; Further Pamidronate (single monthly dose or 3 doses every 3 months) max total of 12 doses Poor response to Pamidronate; Move to Step 3 Step 3 Anti-TNF e.g. Adalimumab or Infliximab Ensure baseline bloods including TB screening (CXR and Quantiferon) prior to starting Assess response at 3 months Step 4: Consider change of Biologic

**TNF Inhibitors**

Evidence:

Recommendations:

CXR and Quantiferon before starting

Will require regular blood monitoring as per local protocols.

Consider monitoring adalimumab and infliximab levels/antibodies if available.

Consider addition of a co-medication (can be low dose) such as Methotrexate, sulfasalazine, MMF to reduce risk of antibody formation with Adalimumab and Infliximab.

**Bisphosphonates and TNF Inhibitors**

**Pamidronate and Zolendronic Acid**

**Bisphosphonates** inhibit osteoclast activity, thereby likely stopping inflammatory bone loss. Pamidronate furthermore has inhibitory effects on pro-inflammatory cytokine expression [[68](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8040271/#bib68)].

Different treatment regimens have been reported and are commonly used in clinical practice: 1 ​mg/kg/dose (max. 60 mg/dose) every month, or 1 ​mg/kg/dose (max. 60 mg/dose) on 3 consecutive days every 3 months for 9–12 months. Another approach is to implement these on an ad hoc/as required basis, rather than giving regularly. Treatment regimen is at the discretion of the responsible clinician.

Because of potential side-effects and the long biological half-life of bisphosphonates, they should only be considered in otherwise treatment refractory cases or in individuals with primary vertebral involvement and structural damage [[55](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8040271/#bib55),[68](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8040271/#bib68)].

Evidence:

A small number of articles have reported treatment of CNO with Pamidronate.

Kerrison and colleagues reported significant pain relief and improved activity and well-being with pamidronate use in seven children (three with spinal lesions) who failed NSAIDs10.

Simm et al.11and Miettunen et al12 demonstrated the effectiveness of Pamidronate in children with CNO refractory to NSAIDs. Over 80% of patients had pain relief and more than 90% of patients in Miettunen’s study showed resolution of bone lesions on MRI after six months of treatment. Gleeson and colleagues reported pain relief with pamidronate in six of seven children who failed NSAIDs13. Of five children with spinal fractures, three had follow-up x-rays showing regression of height loss in affected vertebrae in response to pamidronate therapy. Hospach et al.14 reported complete resolution of hyperintensity signal of active spinal lesions after three to six cycles of pamidronate and a median interval of 13 months follow-up with MRI in eight of nine children with CNO refractory to NSAIDs. Roderick et al. treated 11 children with CNO refractory to NSAIDs with four cycles of pamidronate at 1 mg/kg/day on three consecutive days every three months15. Two patients showed a good response, six a moderate response, one a mild response, while two failed to respond based on repeated whole body MRIs. Schnabel et al. described pamidronate to be highly effective in CNO patients refractory to standard treatment with NSAIDs and/or glucocorticoids16.

A small, randomized double-blinded, placebo-controlled pilot trial of 14 patients by Andreasen et al, investigated the efficacy of Pamidronate in reducing radiological and clinical disease activity in CNO. From baseline to week 36, the radiological disease activity score (using CT of anterior chest wall) decreased from 5 [4-7] to 2.5 [1-3] in the pamidronate group, but did not change in the placebo group (p = 0.04). From baseline to week 36, VAS pain and VAS global health tended to decrease more in the pamidronate than in the placebo group (p = 0.11, p = 0.08). Physical functioning (HAQ) and health-related quality of life (EQ-5D, SF-36) did not change. Biomarkers of bone turnover decreased only in the pamidronate group (p ≤ 0.02). The authors concluded that Pamidronate may improve radiological and clinical disease activity in CNO8.

A single-centre retrospective study including 51 patients, treated children with multifocal or spinal bone inflammation and clinical disease activity not responding to NSAIDs with an early onset 2-year Pamidronate regimen9. Whole body MRI was performed at time of diagnosis, and at years 1 and 2 in 88%, 84%, and 91% of cases, respectively. During the first year, the total number of radiologically active lesions and number of spinal lesions per patient declined (p = 0.01). Clinically inactive disease was recorded in 12/32 children (38%). However, 8/12 children (67%) experienced clinical relapse. The authors concluded that Pamidronate might contribute to improvement in clinical and radiological disease activity in such patients, especially after 1 year of treatment. However, children with continuously active disease after 2 years of pamidronate treatment were seen.

Zhao et al. reported rapid response to treatment with zoledronic acid in combination with the TNF inhibitor infliximab. While very promising and effective in a small cohort, the combination of zoledronic acid and infliximab does not allow an assessment of the exact contribution of each therapeutic [[39](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8040271/#bib39)].

Some paediatric centres use Zolendronic acid for their CNO patients with reported good effect, though no formal evidence as yet.

Recommendations:

Bisphosphonates are an appropriate treatment choice for patients with CNO refractory to NSAIDs or those with spinal involvement.

There is more evidence in the literature relating to Pamidronate, however Zolendronic acid is used in some paediatric centres and may be particularly advantageous in those patients in whom cannulation is difficult as it can be given less often.

Ensure patients have up to date dental review prior to starting

See separate SPARN Protocols for further details – patients will need calcium supplementation/bloods pre treatment.

**TNF Inhibitors**

Published data on the use of tumor necrosis factor (TNF)-alpha inhibitors (TNFi) in CNO are more limited. Eight articles have reported treatment of TNFi in CNO with level IV evidence. A small cohort study (n=4) reported by Eleftheriou et al. showed decreased pain in children with CNO after infliximab treatment (n=3) and anakinra (n=1, later switched to adalimumab) ([16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R16)). Borzutzky et al. ([17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R17)) and Wipff et al. ([18](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R18)) observed the highest rates of clinical remission (46%) or efficacy (89%) from TNFi compared to glucocorticoids, methotrexate, sulfasalazine, and NSAIDs. Jansson et al. ([19](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R19)), reported disease remission induced by infliximab in two patients who failed NSAIDs, glucocorticoids, DMARDs, and pamidronate. Recently, a combination of infliximab and methotrexate with or without zolendronic acid significantly improved clinical, laboratory, and imaging results in 9 children with CNO ([8](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R8)). However, Kaiser et al. showed poor response to TNFi in children with CNO in that only two of seven patients achieved remission (not defined) ([20](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R20)). On the other hand, etanercept was effective in all five patients in a small childhood series ([21](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R21)). Anti-interleukin (IL)-1 has been reported in fewer pediatric cases ([20](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R20)). In an adult cohort (n=6), anakinra improved the patient global assessment of disease activity within one month in five patients ([22](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938153/#R22)).

**Pamidronate Vs TNF Inhibitors**

An international multi-centre retrospective study by Schnabel et al, looked at 91 patients who received Pamidronate alone, TNF inhibitors alone, or a combination of both sequentially9. Both therapies were associated with clinical [remission](https://www.sciencedirect.com/topics/medicine-and-dentistry/spontaneous-remission) at 6 months, and reduction of [bone lesions](https://www.sciencedirect.com/topics/medicine-and-dentistry/bone-lesion) on MRI at 12 months. While not reaching statistical significance, pamidronate resulted in faster resolution of MRI lesions. Fewer flares were observed with TNFi. Failure to respond to pamidronate was associated with female sex [p = 0.027], more lesions on MRI [p = 0.01] and higher [CRP](https://www.sciencedirect.com/topics/medicine-and-dentistry/c-reactive-protein) levels [p = 0.03].

**Other**

Evidence base is limited but other treatments such as anakinra or secukinumab may be considered at the clinician’s discretion.

References

1. Consensus Treatment Plans for Chronic Nonbacterial Osteomyelitis refractory to NSAIDS and/or with active spinal lesions. Zhao et al, Arhtritis Care Res, 2018.
2. Chronic nonbacterial osteomyelitis in childhood: prospective follow up during the first year of anti-inflammatory treatment. Beck et al, Arthritis Research and Therapy, 2010.
3. Variability in phenotype and response to treatment in chtonic nonbacterial osteomyelitis; the Irish experience of a national cohort OLeary et al, Ped Rheum 2021
4. Comparison of different treatment approaches of paediatric chronic non-bacterial osteomyelitis. Kostek et al. Rheum Intern 2019
5. The multifaceted presentation of chronic recurrent multifocal osteomyelitis: a series of 486 cases from the Eurofever international registry. Girschick et al, Rheumatology 2018
6. Pediatric chronic nonbacterial osteomyelitis Borzutzy et al, Rheum Intern 2012
7. Treatment Response and Longterm Outcomes in Children with Chronic Nonbacterial Osteomyelitis, Anja Schnabel, Ursula Range, Gabriele Hahn, Reinhard Berner and Christian M. Hedrich, The Journal of Rheumatology July 2017, 44 (7) 1058-1065; DOI: <https://doi.org/10.3899/jrheum.161255>
8. Pamidronate in chronic non-bacterial osteomyelitis: a randomized, double-blinded, placebo-controlled pilot trial, Andreasen et al, Scand J Rheumatol, 2020 Jul;49(4):312-322.
9. Response to Early-onset Pamidronate Treatment in Chronic Nonbacterial Osteomyelitis: A Retrospective Single-center Study, Andreasen et al, J Rheumatol, . 2019 Nov;46(11):1515-1523. doi: 10.3899/jrheum.181254. Epub 2019 Apr 15.
10. Kerrison C, Davidson JE, Cleary aG, Beresford MW. Pamidronate in the treatment of childhood SAPHO syndrome. *Rheumatology (Oxford)*2004;43:1246–51.
11. Simm P, Allen R, Zacharin M. Bisphosphonate Treatment in Chronic Recurrent Multifocal Osteomyelitis. *J Pediatr.*2008;152:571–575. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/18346517)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=J+Pediatr&title=Bisphosphonate+Treatment+in+Chronic+Recurrent+Multifocal+Osteomyelitis&author=P+Simm&author=R+Allen&author=M+Zacharin&volume=152&publication_year=2008&pages=571-575&pmid=18346517&)]
12. 11. Miettunen PM, Wei X, Kaura D, Reslan WA, Aguirre AN, Kellner JD. Dramatic pain relief and resolution of bone inflammation following pamidronate in 9 pediatric patients with persistent chronic recurrent multifocal osteomyelitis (CRMO) *Pediatr Rheumatol Online J.*2009;7:2.
13. Gleeson H, Wiltshire E, Briody J, Hall J, Chaitow J, Sillence D, et al. Childhood Chronic Recurrent Multifocal Osteomyelitis: Pamidronate Therapy Decreases Pain and Improves Vertebral Shape. *J Rheumatol.*2008;35:707–712.
14. Hospach T, Langendoerfer M, Kalle T von, Maier J, Dannecker GE. Spinal involvement in chronic recurrent multifocal osteomyelitis (CRMO) in childhood and effect of pamidronate. *Eur J Pediatr.*2010;169:1105–11.
15. Roderick M, Shah R, Finn A, Ramanan AV. Efficacy of pamidronate therapy in children with chronic non-bacterial osteitis: disease activity assessment by whole body magnetic resonance imaging. *Rheumatology (Oxford)*2014;53:1973–6.
16. Schnabel A, Range U, Hahn G, Berner R, Hedrich CM. Treatment Response and Longterm Outcomes in Children with Chronic Nonbacterial Osteomyelitis. *J Rheumatol.*2017 jrheum.161255.