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Review

# Autoinflammatory bone diseases: Genetic mutations, clinical manifestations, and modern therapeutic approaches

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## ABSTRACT

Autoinflammatory bone diseases result from dysregulation of innate immune responses, leading to systemic inflammation and sterile inflammatory bone lesions. These disorders primarily affect children and adolescents but can persist into adulthood or present later. Chronic nonbacterial osteomyelitis (CNO) and its severe form, chronic recurrent multifocal osteomyelitis (CRMO), are the main phenotypes associated with these conditions. CNO serves as an umbrella term encompassing various presentations characterized by the insidious onset of local bone pain, typically exacerbated at night, with or without fever. Affected lesions commonly involve the metaphyseal regions of long bones, clavicle, spine, and pelvis, although any bone segment can be implicated. The etiology of CNO remains unclear, although familial predisposition exists, and a notable association with other inflammatory conditions, such as psoriasis, inflammatory bowel disease, and spondyloarthropathies, has been observed among sporadic CNO patients and their first-degree relatives, suggesting a genetic basis. Monogenic disorders, including deficiency of interleukin-1 receptor antagonist (DIRA) and PAPA syndrome (Pyogenic Arthritis, Pyoderma gangrenosum, and Acne), manifest prominent CNO symptoms. Syndromic forms, such as Majeed syndrome and Cherubism, also exemplify this association. CNO is diagnosed through exclusion, with whole-body magnetic resonance imaging (WB-MRI) regarded as the gold standard. MRI findings typically reveal bone cortical thickening, lytic lesions with sclerosis, and bone edema, while differential diagnoses must consider infections and malignancies. First-line treatment typically consists of nonsteroidal anti-inflammatory drugs (NSAIDs), while bisphosphonates and tumor necrosis factor-alpha (TNF-α) inhibitors may serve as effective second-line options. Although CNO is often benign, inadequate or delayed treatment can lead to severe complications, including valgus deformity, vertebral collapse, and limb length asymmetry.

**Keywords:** autoinflammatory diseases, bone diseases, osteomyelitis, chronic disease

## INTRODUCTION

The term “autoinflammatory disease” refers to a group of disorders characterized by recurrent inflammatory episodes that occur without elevated levels of autoantibodies or autoreactive lymphocytes.[1] Autoinflammatory bone diseases primarily affect children and include a subgroup with sterile bone inflammation as the main phenotypic feature.[2] It was first described in 1972 by Giedion et al. in four pediatric patients with subacute and chronic symmetric bone lesions.[3] However, it has been noted that the disease does not consistently manifest symmetrically and may display a recurrent nature over time. In 1980, Probst, Bjorksten, and Gustavson proposed the definition of *CRMO*.[4,5]

CNO/CRMO can be associated with other inflammatory conditions such as palmoplantar pustulosis (PPP), psoriasis vulgaris, severe acne, and Sweet syndrome.[6-9] It has also been reported that CNO/CRMO is linked to inflammatory

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bowel disease (IBD) and spondyloarthropathies.[10-13] CNO/CRMO is considered part of the spondyloarthropathy disorder family.[11]

The most common form of autoinflammatory bone disease is sporadic CNO, while bone involvement in many monogenic diseases can appear as sterile osteomyelitis. Three genetic diseases are prominently linked to CNO: DIRA, PAPA, and Majeed syndrome (LPIN2 mutations).[14-16] Several genes that can cause sterile osteomyelitis in human and animal models have been identified, including LPIN2, IL1RN, Pstpip2 (in mice), and FBLIM1.[17-20] Additionally, Cherubism is considered a syndromic form of CNO.[21,22]

The exact cause of sporadic CNO is not yet known, but the activation of NLRP3 inflammasome and increased proinflammatory cytokines in genetic forms of the disease classify it as an autoinflammatory syndrome.[23] The frequent occurrence of inflammatory diseases among first-degree relatives, as well as the occurrence of inflammatory diseases like IBD in accompanying first-degree relatives, suggests that sporadic CNO/CRMO may have a genetic component.[24,25]

## Nomenclature and classification of the disease

Autoinflammatory bone diseases have historically been referred to by various names. However, the term CNO has become the preferred, more inclusive designation, reflecting the disease's variable presentation, which is not always symmetric or multifocal. CRMO is considered a more severe and recurring form of CNO, characterized by multifocal and serious lesions.

The classification of autoinflammatory bone diseases also includes specific conditions with known genetic mutations, such as Majeed syndrome, DIRA, and PAPA syndrome. These genetically linked conditions help further elucidate the disease mechanisms in CNO/CRMO and provide insights into its pathophysiology (Table 1).[26-40]

## Epidemiology

CNO/CRMO are rare diseases. The exact frequency of the disease is not known, but in Germany, it affects 2 to 80 out of 100,000 people.[24,41] It has been reported to be more common in Europe and Scandinavian countries.[41] CNO/CRMO is an autoinflammatory disease, primarily in childhood. It is most commonly seen between the ages of 7 and 12.[41,42] Girls are affected 2 to 4 times more than boys.[41-43] While it is mainly observed during childhood, the condition can manifest as SAPHO syndrome in adulthood, especially when skin involvement is present.[40] It is rare to see it in children under 2 years old. In such cases, the condition may have a genetic cause, including DIRA, PAPA, Majeed syndrome, or part of a syndromic CNO, and should be investigated from this perspective.

**Table 1.** Genetic and Clinical Spectrum of Autoinflammatory Bone Diseases

| Disease/Disorder | Genetic Cause | Clinical Features |
|---|---|---|
| Chronic Nonbacterial Osteomyelitis (CNO) | Unknown genetic etiology in sporadic cases, potential genetic predisposition in some | Sterile bone inflammation and chronic bone pain can be associated with skin conditions and IBD |
| Chronic Recurrent Multifocal Osteomyelitis (CRMO) | Similar to CNO, may be more severe and recurrent | Multifocal, recurring sterile bone lesions, systemic inflammation |
| Majeed Syndrome | LPIN2 mutation | CRMO, congenital dyserythropoietic anemia, neutrophilic dermatosis |
| Deficiency of Interleukin-1 Receptor Antagonist (DIRA) | IL1RN mutation | Pustulosis, osteitis, periostitis, systemic inflammation, potentially life-threatening |
| Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) | PSTPIP1 mutation | Sterile arthritis, cystic acne, pyoderma gangrenosum |
| Cherubism | SH3BP2 mutation | Mandibular and maxillary bone lesions, jaw enlargement, tooth misalignment |
| SAPHO Syndrome | Unknown | Synovitis, acne, pustulosis, hyperostosis, osteitis, more common in adults |

CNO: chronic nonbacterial osteomyelitis; CRMO: chronic recurrent multifocal osteomyelitis; IBD: inflammatory bowel disease; IL1RN: gene encoding interleukin-1 receptor antagonist, related to DIRA; LPIN2: gene associated with Majeed syndrome; PSTPIP1: gene encoding proline-serine-threonine phosphatase interacting protein 1, related to PAPA syndrome; SAPHO: synovitis, acne, pustulosis, hyperostosis, osteitis; SH3BP2: gene encoding SH3-domain binding protein 2, related to cherubism

**Etiology and Pathogenesis**

The irregular expression of pro and anti-inflammatory cytokines plays a central role in the pathophysiology of CNO/CRMO. There is evidence linking the development of the Interleukin-10 (IL-10) pathway with CNO. Hofmann et al. have reported that peripheral blood monocytes stimulated with the Toll-like receptor 4 (TLR-4) agonist lipopolysaccharides (LPS) secrete significantly less in IL-10 than healthy control monocytes.[44,45] In patients with CNO/CRMO, levels of regulatory IL-10 and interleukin 19 (IL-19) are decreased in peripheral blood monocytes, while levels of proinflammatory cytokines interleukin 1 beta (IL-1B), interleukin 6 (IL-6), TNF-α , interleukin 8 (IL-8), and macrophage inflammatory protein (MIP) have been found to increase.[44,45] Therefore, one scenario in the pathogenesis of the disease involves increased NOD-like receptor protein 3 (NLRP3) activation due to decreased regulatory cytokines, with their mRNA products initiating the inflammatory process.[46] This cytokine dysregulation leads to an imbalanced resorption environment in the bone through the receptor activator of nuclear factor-kappa B (NF-kB) (RANKL) and soluble RANKL receptors responsible for osteoclast activation and differentiation.[47]

The triggering factors for this condition can be an infection or trauma in genetically predisposed individuals. In a study conducted by Bjorksten et al., 25% of patients with CNO/CRMO experienced trauma before the onset of the disease.[5]

CNO/CRMO is characterized as an autoinflammatory bone disease. Patients' bone cultures show no growth, indicating sterility in the affected areas. Antibiotics are ineffective during disease activation, but anti-inflammatory treatments have shown benefits.[48] In a small group of cases, it was demonstrated that azithromycin improved the radiological and clinical signs and symptoms of CNO.[49] This improvement may be due to the anti-inflammatory properties of azithromycin rather than to antimicrobial properties. Adults with SAPHO syndrome and children with CNO/CRMO often have lesions in their skin and bones that test negative on polymerase chain reaction (PCR) and culture tests.[43,49] In one series of adult patients with SAPHO, *Propionibacterium acnes* were cultured from the bone of 7 out of 15 patients tested.[50] In addition, some studies have isolated *Propionibacterium acnes*, *Mycoplasma*, and *Staphylococcus* in bone lesions, but a clear distinction between contamination and true infection could not be made.[51-53]

In recent years, there has been increasing support for the idea that CNO might be a genetic disease within the range of autoinflammatory disorders. Furthermore, in the largest groups of CNO patients, the prevalence of the disease among patients' relatives was higher. Some reports have also described families with multiple affected members or have reported a high incidence of psoriasis, IBD, and other chronic inflammatory conditions in first-degree family members of individuals with CNO, suggesting that there is a significant genetic component to disease susceptibility.[54]

Previous discoveries have identified several single gene defects (LPIN2, Pstpip2, and IL1RN) that cause interleukin 1 (IL-1) mediated sterile multifocal osteomyelitis.[55-57] Lorden et al. demonstrated that LIPIN2 deficiency activates the NLRP3 inflammasome through altered P2X7 receptor function, supporting the classification of Majeed syndrome as an NLRP3 inflammasomopathy.[58] Recent gene discoveries have identified FBLIM1 as a susceptibility gene for CRMO, with mutations detected in a consanguineous family exhibiting the condition.[59] FBLIM1 is one of the most significantly differentially expressed genes in the bones of CRMO mice, playing a crucial role in IL-10-mediated anti-inflammatory responses and bone remodeling physiology.[45] Moreover, chronic osteomyelitis is a common characteristic of two monogenic diseases caused by mutations in genes related to the activation of the NLRP3 inflammasome or in the homeostasis of IL-1.[54] These diseases are known as PAPA and DIRA, respectively.[14,15] There may be a genetic association locus at chromosome 18q21.3–18q22 and CRMO.[60] This genetic association has not yet been linked to the pathophysiological development of CNO. Beginning in 2010, several case reports suggested a connection between CNO and familial Mediterranean fever (FMF)/MEFV gene mutations and the potential use of colchicine as a treatment option for CNO.[61]

Many animal models with autoinflammatory bone lesions result in genetic defects. Two mouse models have been developed: *CRMO mice* and *Lupo mice*. Both of these mouse models have mutations in pstpip2 and exhibit similar clinical features seen in humans. CRMO mice typically develop a severe clinical presentation.[62,63] Mouse pstpip2 shares similarities with human PSTPIP1 and PSTPIP2. PSTPIP1 modulates the NLRP3 inflammasome through its interaction with pyrin and is associated with genetic defects in the autosomal dominant autoinflammatory syndrome known as PAPA.[64,65]

**Clinical manifestations of CNO/CRMO**

The disease typically begins insidiously, with the main clinical symptom being localized bone pain.[41] This pain

can be sporadic or constant, often worsening at night and causing the person to wake up. Bone lesions typically cluster around the metaphysis, may present in atypical sites for bacterial osteomyelitis, such as the clavicle, and often show a symmetrical distribution when multiple.[11] Seventy-five percent of bone lesions occur in the perimetaphyseal region. All bones can be affected, but the metaphyseal regions of long bones are the most commonly affected. The long bones of the lower extremity are affected three times more frequently than the long bones of the upper extremity. The most frequent sites for CNO lesions include the femur, tibia, pelvis, calcaneus, ankle, vertebrae, and clavicle.[66-68] CNO is the most common cause of disease that affects the middle third of the clavicle in people of all ages.[69] Although vertebral involvement is less common, it is still important because it can lead to complications such as fractures, spinal cord compression, kyphosis, and scoliosis.[24,35] It typically affects the thoracic vertebrae most often. It may also present as unilateral sacroiliitis in the pelvis bones. Involvement of the small bones in the hands and feet is less common.[66-68]

Symmetric bone involvement is observed in 25-40% of patients.[41,42] Involvement is multifocal in up to 85% of all cases.[24] The number of osteomyelitis lesions can vary from one to at least 18 at any given time.[42] In a German study, the authors reported that patients with multifocal bone inflammation only experienced clinical symptoms at a median of one lesion.[24] In the study conducted by Girschick et al. 30 patients with CNO were followed for 5.6 years.[25] It was stated that the patients were divided into four groups: unifocal non-recurrent (30%), unifocal recurrent (10%), multifocal non-recurrent (30%), and multifocal recurrent (30%).

Additionally, a study reported that arthritis occurs in 40% of cases of chronic nonbacterial osteomyelitis.[41,68] In these cases, arthritis was found in 60% of adjacent joint lesions and 40% of distant joint lesions.[41,68] Clavicular lesions typically present with noticeable swelling, tenderness, and pain, while vertebral lesions may have a more gradual and subtle onset. Vertebral fractures and neurological deficits may arise. Pelvic involvement usually presents with unilateral sacroiliitis. Pain is a common symptom in all cases; fever may accompany pain in 17% to 33% of cases.[68] Constitutional symptoms such as weakness, fatigue, and weight loss may be present in approximately 15-20% of patients, but most patients with CNO appear clinically well except for pain.[70,71]

CNO is a systemic disease that affects the skin, joints, gastrointestinal tract, and lungs, and patients often show coexisting chronic inflammatory conditions.[41,68] In one study, 20–50% of patients were found to have or develop another autoimmune or inflammatory disease.[68,72] The most prevalent associated autoimmune and inflammatory diseases include arthritis, psoriasis, inflammatory bowel disease, vasculitis, myositis, fasciitis, and parotitis. Patients with these conditions generally present a higher number of bone lesions compared to those without concurrent inflammatory diseases.[68] These diseases may occur simultaneously or subsequently before the diagnosis of CNO. Studies have detected psoriasis in 2-17% of patients, palmoplantar pustulosis in 3-20%, and inflammatory bowel diseases in 3-7%.[73,74] Another disease commonly seen with CNO is FMF. Recently, cases demonstrating the link between FMF and CNO have been reported.[61]

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), markers of inflammation, are typically within normal limits or only slightly elevated. In patients with chronic nonbacterial osteomyelitis, higher levels of CRP and ESR indicate a greater likelihood of involvement in multiple sites.[68]

Chronic anemia caused by the disease can be identified during a blood test. The white blood cell count is typically within the normal range or slightly elevated, with a slight increase in either monocytes or neutrophils.[41,42] Autoantibodies usually test negative, and the condition is not linked to HLA B27.[25,42] High levels of TNF-α and IL-6 in the blood indicate dysregulation of cytokines in the development of the disease.[42,75] Additionally, to make a clear diagnosis, it is important to ensure that serum lactate dehydrogenase, uric acid, calcium, phosphorus, and alkaline phosphatase levels in patients are all within normal limits.

**Diagnostic imaging studies**

The diagnosis of chronic nonbacterial osteomyelitis largely depends on radiological findings. The most commonly used initial imaging study is conventional radiography, followed by MRI if the radiographic findings are inconclusive. MRI is considered the standard technique due to its high specificity in characterizing CNO lesions, non-invasive nature, and lack of exposure to ionizing radiation.[76]

In a child suspected of having CNO/CRMO, the first step should be to take a plain radiograph of the area of pain, as it is low-cost and non-invasive. In the early stages of

the disease, findings may not be visible on radiography. In a longitudinal case series involving 31 children diagnosed with CRMO, as confirmed by Falip et al. it was found that 40% of long bone lesions, 55% of vertebral lesions, and 75% of pelvic lesions appeared normal on plain radiographs.[77] In some patients, a radiolucent appearance may be present due to bone lesions. In the chronic stages, the lesions become sclerotic as new bone forms, resulting in a dense radiopaque appearance on X-rays. Mixed osteolytic and sclerotic lesions at the metaphysis of the long bones are one of the most common radiological findings.[78] Epiphyseal and diaphyseal involvement is unusual but may occur. The radiographic presentation of CNO typically includes focal mixed, lytic, or sclerotic lesions, as well as hyperostosis and periosteal reactions.[77,78] Involvement of the clavicle and vertebrae typically starts as a destructive lesion in the bone, with progressive sclerosis and hyperostosis noted during periods of healing and recurrence of attacks.[35,71] Involvement in the pelvic bones is often characterized by a sclerotic appearance and may manifest as sacroiliitis.[78]

Exposure to ionizing radiation, along with difficulty distinguishing between active CNO lesions and inactive disease, limits the usefulness of Computed Tomography (CT) imaging as a diagnostic method, particularly in the pediatric population.[76]

MRI is considered the best imaging technique for CNO and the most appropriate method for both diagnosing and monitoring the condition over time. It has a high sensitivity, with the ability to detect lesions in the lower limbs up to 100% of the time.[79,80] WB-MRI has been recognized as the preferred imaging method for monitoring disease. If the WB-MRI is not available, regional MRIs can be used. It is recommended to scan sequences of the entire body using fat-suppressed short tau inversion recovery (STIR) or T2-weighted sequences turbo inversion recovery measurement (TIRM) with the coronal window and also to scan the vertebrae using the sagittal window. Active CNO lesions may display signs of bone marrow edema, which can appear as hypointense (dark) on T1-weighted MRI but hyperintense (bright) on STIR and T2-weighted sequences. The importance of a WB-MRI scan lies in its ability to detect lesions that may be asymptomatic in many patients. In the context of disease monitoring, hyperostosis and osteitis may signify the progression of CNO and frequently manifest as hypointense areas on both T1- and T2-weighted MRI scans.[76] Additionally, at the time of diagnosis, WB-MRI (TRIM/STIR) is usually used to identify inflammatory bone lesions and periosteal and soft tissue involvement and to exclude diseases in the differential diagnosis.

Technetium-99m bone scintigraphy has traditionally been utilized to detect asymptomatic lesions initially. However, it should not be used if WB-MRI is accessible because MRI is significantly more effective at identifying clinically silent chronic nonbacterial osteomyelitis lesions. Moreover, in the pre-pubertal period, the metaphyseal and epiphyseal regions are already highly vascularized in bone scintigraphy, which could result in misinterpretation of a lesion in a non-lesioned area or physiological involvement in a patient with bilateral metaphyseal involvement.[81] Additionally, scintigraphy is not recommended for pediatric patients due to the risk of radiation exposure.

**Histology**

A bone biopsy should be considered as it can be very helpful in making a differential diagnosis but not necessarily for confirming a diagnosis. Confirming the diagnosis of CNO is often necessary. This is especially important because bone malignancies sometimes resemble CNO in isolated bone lesions. Clavicular and multifocal involvement or accompanying conditions such as palmoplantar pustulosis or psoriasis vulgaris can strongly indicate CNO. Some experts argue that a biopsy may not be necessary in these cases of CNO. However, if there is insufficient evidence for a diagnosis of CNO, caution should be exercised as serious conditions like intraosseous lymphoma and other neoplasms can sometimes mimic CNO. A biopsy is recommended in cases with a significant and persistent increase in acute phase responses, alongside hematological abnormalities such as anemia, leukopenia, or thrombocytopenia, especially in patients with atypical localization and poor overall health. This is particularly important to rule out malignancy.

In a typical CNO biopsy, the early stages may show an abundance of neutrophils, while the later stages may reveal an increase in lymphocytes and plasma cells, indicating chronic inflammation.[82]

**Diagnostic challenges in CNO/CRMO**

CNO is diagnosed by exclusion, relying on clinical symptoms, imaging investigations, and a bone biopsy that yields negative cultures. Currently, there are no validated or widely accepted clinical criteria for the disease. The diagnosis is confirmed by ruling out other bone-related diseases. Jansson et al. introduced a clinical scoring system to assist in diagnosis and treatment.[41] Roderick et al. suggested using the Bristol criteria to reduce the need for biopsy in certain patients.[83] The validity of these diagnostic criteria for pediatric patients is crucial, particularly since

the Bristol stool form scale is used exclusively to assess children and adolescents. 3% of the patients involved in Jansson's study were over 18 years old. For both criteria, radiological imaging is the essential method for diagnosis. The typical appearance on a radiological image (such as multifocal or clavicular) accompanying localized bone pain is usually enough to make a diagnosis.

In the differential diagnosis of the disease, malignancy and infections should be ruled out first. Malignant bone tumors such as leukemia, lymphoma, primary bone lymphomas, osteosarcoma, and Ewing sarcoma, as well as bone metastases of tumors (especially neuroblastoma), are some of the malignant causes. The main infectious causes include acute/subacute/chronic infectious osteomyelitis, septic arthritis, and bone involvement of mycobacterial diseases. Other conditions: Langerhans cell histiocytosis, avascular necrosis, scurvy, hypophosphatasia, cherubism, skeletal dysplasia, benign bone tumors (osteoid osteoma, enchondroma, osteoblastoma), fibrous dysplasia, and growing pains listed in the causes (Table 2).

**Treatment**

In practice, NSAIDs are commonly the first-line treatment for patients without vertebral involvement. They provide quick symptom relief and control bone inflammation in some CNO/CRMO patients. However, over 50% of patients experience flare-ups within two years of treatment.[84] Beck et al. conducted a prospective study involving a cohort of German children with CRMO and assessed their response to NSAIDs over a one-year treatment period.[85] In this group, arthritis was initially diagnosed in almost 40% (14 out of 37) of patients. All of these patients had arthritis at 3 months, 50% at 6 months, and 21% at 12 months. Vertebral involvement was found in nearly 20% (7 out of 37) of patients. Three out of 37 patients experienced pathological fractures during the study, including 2 out of 7 patients with spine involvement.[85] NSAIDs inhibit cyclooxygenase (COX) enzymes and reduce inflammasome assembly.[86] Commonly used NSAIDs include naproxen, indomethacin, and sulfasalazine, especially in patients with concurrent inflammatory bowel disease.

**Table 2.** Comprehensive Differential Diagnosis Framework for CNO/CRMO: A Systematic Approach to Exclude Infections, Malignancies, and Genetic Disorders

| Disease Groups | Conditions |
|---|---|
| Infections | • Osteomyelitis<br>• Bacterial<br>• Mycobacterial<br>• Fungal |
| Malignant Bone Tumors | • Osteosarcoma<br>• Ewing sarcoma<br>• Bony Metastases (Neuroblastoma) |
| Benign Bone Tumors | • Osteoid osteoma<br>• Osteoblastoma<br>• Fibrous dysplasia<br>• Enchondromatosis<br>• Hemangiomatosis<br>• Bone Cysts |
| Hematological Malignancies | • Leukemia<br>• Lymphoma<br>• Langerhans cell histiocytosis |
| Metabolic Bone Disorders | • Hypophosphatasia |
| Genetic Disorders | • DIRA<br>• PAPA<br>• Majeed syndrome<br>• Cherubism |
| Primary Immune Deficiency | • Defects of IFN-gamma/IL-12 axis (favoring mycobacterial infections) |
| Miscellaneous | • Hypovitaminosis C (Scurvy) |

DIRA: Deficiency of Interleukin-1 Receptor Antagonist, PAPA: Pyogenic Arthritis, Pyoderma gangrenosum, Acne syndrome, IFN: Interferon, IL-12: Interleukin-12

Corticosteroids, like NSAIDs, reduce prostaglandin production by inhibiting phospholipase A2.[87] Corticosteroids also suppress proinflammatory cytokines (IL-1, IL-6, TNF-α), regulated by NFκB[87]. Corticosteroids rapidly control inflammation in 79% of cases but often fail to achieve long-term remission. Low-dose prednisone (0.1-0.2 mg/kg/day) can be used as a 'bridging therapy' until disease-modifying antirheumatic drugs (DMARD) take effect. While corticosteroids are effective in controlling inflammation, the majority of cases do not achieve long-term remission.[84,87] Traditional non-biologic DMARDs like methotrexate (MTX) and sulfasalazine can be effective, though data remains conflicting.[88] In patients who do not respond to NSAIDs treatment, non-biological DMARDs such as methotrexate and sulfasalazine can be used.

TNF-α plays a key role in CNO by activating osteoclasts.[41,75] In the last years, successful use of biological agents like TNF-α inhibitors has been reported. In a study by Borzutzky et al., 10 out of 11 patients using TNF-α antagonists responded positively, with a 46% remission rate.[68] Eleftheriou et al. assessed three pediatric patients receiving TNFα-blocking agents for CRMO or SAPHO.[89] All three patients showed clinical improvement. However, one patient had to stop the therapy early due to an invasive fungal infection. Catalano-Pons et al. reported findings from a cohort of 40 pediatric cases in a French dataset, in which two patients had been treated with TNFα antagonists.[72] However, the specifics of the treatment response were not thoroughly outlined. Similarly, a case report of five children with refractory CNO/CRMO showed radiological improvement during ongoing treatment, and another recent report found similar effects in four children who were treated with etanercept.[90,91] In the large French cohort, which included 178 patients with CRMO, 8 out of 9 patients who received anti-TNF therapy achieved remission.[92]

Induction of clinical and radiological remissions in response to cytokine blockade has been reported, especially in patients with extraosseous manifestations who may benefit from cytokine blockade therapy. The blockade of IL-1 using anakinra has shown positive outcomes in managing osteitis and arthritis; however, its effects on mucocutaneous manifestations remain inconsistent.[93,94] Given the clinical parallels between SAPHO syndrome and psoriasis, the interleukin 17A (IL-17A) neutralizing antibody secukinumab has been effectively used in treating patients with SAPHO.[95] IL-6 inhibitors are another promising therapy, but there is currently inadequate research on the drug's effectiveness and reliability. Other biologic medications have been used in case reports that include interferon alpha (INF-α) and gamma (INF-γ).[96,97]

Bisphosphonates inhibit osteoclast activity. Intravenous pamidronate has shown positive outcomes[97-100]. This therapy likely treats CNO by inactivating osteoclasts, reducing pain, and possibly through anti-inflammatory effects.[87] Pamidronate can be administered in two protocols: 0.5 mg/kg/day initially, followed by 1 mg/kg/day (maximum 60 mg) on days 2 and 3 every 3 months for 3-4 courses, or 1 mg/kg monthly for 1-6 months. Symptom improvement is often observed after the first infusion.[100] Bisphosphonates show effects within a few weeks, and the duration of intravenous treatment in case reports varies from 1 to 4 years, averaging 1.5 years.[101,102] Recent studies involving pediatric patients with osteogenesis imperfecta have demonstrated that oral alendronate and intravenous pamidronate exhibit equivalent efficacy.[44,90] In studies by Miettunen et al. and Hospach et al., clinical and radiological improvement was seen in 100% of patients (9/9 and 7/7, respectively) after pamidronate treatment.[98,100]

Roderick et al., Gleeson et al., and Simm et al. reported over 80% clinical improvement with pamidronate.[101-103] The most frequently observed adverse events are mild flu-like symptoms lasting one day post-infusion. Osteonecrosis of the jaw is a potential but currently unreported side effect of pamidronate in children with CNO. To mitigate this risk, pediatric patients should undergo dental screening and have wisdom teeth extracted before initiating pamidronate treatment. Furthermore, elective dental procedures should be deferred for at least six months following therapy.[100]

Compared to adult CNO/CRMO treatment, a higher percentage of children with CNO were treated with anti-TNFs and bisphosphonates, while more adults received traditional DMARDs. Recent reports show promise in using non-TNF biologic DMARDs (bDMARDs) for treating CNO, more commonly in adults than children. In adults with CNO, the primary non-TNF agents utilized are anakinra, ustekinumab, secukinumab, and tocilizumab.[104,105]

Promising studies on protein kinases and the microbiome are emerging. Changes in the gut microbiome affect disease outcomes in CMO mice. Acne and IBD are also linked to imbalanced microbiomes in humans with CNO/CRMO. Therefore, modifications made to the microbiome could potentially manage CNO/CRMO in genetically susceptible individuals or even prevent the development of the disease. Differences in microbiomes may explain

why antibiotics have been effective in certain CNO/CRMO patients, as reported in early studies.[106,107]

In conclusion, NSAIDs are the first-line treatment for CNO but are insufficient for remission. If unresponsive to treatment, non-biological DMARDs (methotrexate, sulfasalazine) can be used. Temporary use of low-dose steroids is an option. For spine or growth plate involvement, bisphosphonates (pamidronate, zoledronic acid) or biologics (etanercept, adalimumab, infliximab) should be initiated early due to the risk of long-term effects.

Childhood Arthritis and Rheumatology Research Alliance (CARRA) treatment plan, along with our clinical experience and literature data, forms the basis for our clinical practice treatment scheme, as presented in Table 3.

### Treatment duration, monitoring, and long-term outcomes

There is a lack of large prospective cohort studies on CNO patients from childhood to adulthood. Retrospective studies show that early, adequate treatment and follow-up lead to positive outcomes in CNO. Although there is no consensus on when to stop treatment, a long-term plan is essential due to the disease's fluctuating course.[98,100]

Studies show CNO may resolve within 12-18 months, but 50% of patients experience flare-ups around 29 months on average. These findings emphasize the necessity of long-term monitoring of CNO patients.[84,108] Remission rates are favorable (50-80%), but more than half of CNO children experience a flare-up within the first year.[109,110]

Current literature suggests that symptoms typically improve slowly over time, with the majority of children making a full recovery. However, some children may experience persistent disease activity despite intensive treatment.[72] Delayed, inadequate, and prematurely terminated treatment can lead to complications related to the disease. Complications in CNO may already be present at the time of diagnosis or accumulate over time. Wipff et al. found that of the 178 pediatric patients studied, 25% experienced lasting effects after an average follow-up duration of three years.[92] The most common complication is vertebral compression fractures, seen in about 10% of patients at diagnosis.[111] Jansson et al. reported that 50% of vertebrae showed pathological fractures.[41]

European cohorts generally show better outcomes, but functional and cosmetic issues from hyperostosis are common. Scoliosis, kyphosis, leg length discrepancy, and growth problems are common long-term issues in CNO.[41,112] Complications related to the disease in the musculoskeletal system include malocclusion, valgus deformity, muscle atrophy, thoracic outlet syndrome, chronic arthritis, and spondyloarthropathies.[111]

CNO patients had significant limitations in their quality of life; a study using Pediatric Quality of Life Inventory Generic Core Scales 4.0 (PedsQL4.0) found that physical and school functions deteriorate as CNO progresses.[113]

A Turkish study reported that, despite treatment, CNO negatively affected patients' quality of life. These effects impacted patients' physical, social, emotional, and academic lives.[114]

**Table 3.** Comprehensive treatment approaches for CNO/CRMO: From first-line therapies to advanced biologic interventions

| Treatment Stage | Options |
|---|---|
| First-Line Treatment (NSAIDs) | • Naproxen<br>• Indomethacin |
| Non-Responsive Cases<br>(Spinal involvement or Resistant Cases) | • DMARDs (Methotrexate, Sulfasalazine (especially in the presence of IBD))<br>• Corticosteroids (Low-dose bridging therapy) |
| Biologic Agents | • TNF-α inhibitors (Etanercept, Adalimumab)<br>• IL-1 blockade (Anakinra)<br>• IL-17A (Secukinumab)<br>• IL-6 inhibitors |
| Bisphosphonates | • Pamidronate<br>• Zoledronic acid |

DMARDs: disease-modifying antirheumatic drugs; IBD: inflammatory bowel disease; IL-1: interleukin-1; IL-17A: interleukin-17A; IL-6: interleukin-6; NSAIDs: nonsteroidal anti-inflammatory drugs; TNF-α: tumor necrosis factor-alpha

## Genetic autoinflammatory syndromes with bone inflammation

### Majeed syndrome

Majeed Syndrome is an uncommon autosomal recessive condition first identified by Majeed in 1989. The classic triad in Majeed Syndrome includes early onset CRMO, congenital dyserythropoietic anemia, and neutrophilic dermatosis. The mutation responsible for Majeed syndrome is in LPIN2, which encodes LIPIN2.[16,17] LIPIN2 is a member of the LIPIN family, which is involved in glycerolipid biosynthesis as a phosphatidate phosphatase (PAP). Homozygous mutations in LPIN2 have been identified in seven unrelated families featuring five distinct mutations.[115] The LPIN2 mutation in humans does not appear to produce lipid abnormalities.[17] The phenotypic characteristics of Majeed syndrome are proposed to arise from the loss of PAP activity in LIPIN2.[116] This mutation appears to impact the PAP activity without affecting other lipid and metabolic functions of lipin2. Lorden et al. defined Majeed syndrome as an inflammasomopathy by demonstrating that LIPIN2 is a negative regulator of the NLRP3 inflammasome.[58]

CRMO typically begins in infancy but can present as late as 6 years old. Severe bone pain, soft tissue swelling, and fever are typical features of exacerbation. Flares occur every 3 or 4 months. There is a significant increase in acute phase response during attacks. Its histology and radiology are identical to CRMO. Similar to CRMO, it does not respond to antibiotics. Neutrophilic dermatosis, a phenotypic feature of the disease, is reported in only 14% of patients.[117,118] Psoriasis has also been reported in carrier patients.[2]

Children with Majeed syndrome experience varying degrees of anemia, from mild to severe, sometimes requiring transfusions. The anemia is typically microcytic. A bone marrow biopsy shows dyserythropoiesis with abnormal normoblasts.[117,118] Corticosteroids partially improve bone and skin inflammation, but anemia is less responsive. NSAIDs help with pain relief, while colchicine is ineffective.[117] Two brothers did not respond to TNF inhibitors but showed improvement with IL-1 beta-blockade in clinical, laboratory, and radiologic outcomes.[118] This supports the idea that Majeed syndrome is an autoinflammatory condition.

### Deficiency of the interleukin-1 receptor antagonist

DIRA is an autosomal recessive autoinflammatory disorder. Prose and colleagues first described DIRA in 1994, and it was recognized as a distinct syndrome in 2009.[14] DIRA is caused by a mutation in IL1RN, and symptoms typically present within the first week of life. DIRA can be life-threatening, mimicking neonatal sepsis. Early recognition is crucial to prevent organ damage and death.[119-121]

The typical clinical features consist of widespread pustulosis, osteitis, periostitis, and systemic inflammation.[119-121] Skin inflammation occurs in 95% of affected infants, and cultures of the lesions are negative.[119-121] Within the first few weeks after birth, a pustular rash and signs of inflammation throughout the body develop. Despite high systemic inflammation markers, fever is usually absent. Osteitis is then detected weeks after the rash appears.[119-121]

As the disease progresses, destructive multifocal bone involvement, widespread osteitis in long bones, rib epiphyseal enlargement, and significant bone deformities occur.[119-121] These bony lesions typically affect long bones and vertebral bodies, with a preference for the proximal femur. Vertebral collapse due to osteolytic lesions may occur, leading to cervical fusion. Pulmonary involvement occurs in approximately 50% of infants with DIRA. In two infants, interstitial lung disease has been reported, and another infant died of respiratory failure due to systemic inflammatory response syndrome (SIRS).[119-121] Another life-threatening complication is central nervous system vasculitis. The disease is potentially fatal, with a 30% mortality rate. Antibiotics are ineffective in DIRA.[122] Most patients improved with high doses of corticosteroids. Genetic understanding has improved outcomes with IL-1 blockers like anakinra. Anakinra treatment leads to rapid and dramatic improvement within days.[14]

### Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA)

PAPA is an autoinflammatory disease with autosomal dominant inheritance caused by mutations in PSTPIP1, which encodes the PSTPIP1 protein. Affected patients present with sterile erosive arthritis in childhood. Synovial fluid taken shows a significant increase in polymorphonuclear cells.[15] Cystic acne and pyoderma gangrenosum are the typical skin manifestations of the disease.[15] In the literature, a patient with PAPA disease was reported to have CNO/CRMO and clinical improvement in lesions was observed 6 months after starting treatment with the IL-1 receptor antagonist anakinra for bone lesions.[123]

### Cherubism

Cherubism is a genetic bone disorder that affects the mandible and maxilla.[21,22] It was first described by Jones in 1933. Most children with this disorder are aged 2 to 7.[21,22]

The condition is marked by symmetrical, progressive, and extensive multilocular cystic lesions primarily affecting the mandible, although the maxilla can also be involved, albeit less frequently. [21,22] Similar multilocular cysts are observed in Noonan syndrome and are regarded as part of the Noonan spectrum.[124] This enlargement can lead to misalignment of the teeth, tooth loss, and difficulties with chewing. Jaw enlargement typically regresses after puberty begins. In 2001, heterozygous mutations in the SH3BP2 gene were identified in 12 affected families.[124]

In numerous immune cells, particularly osteoclasts, SH3BP2 can induce phosphorylation, thereby influencing signaling pathways. Mutations in this regulatory protein lead to unregulated bone resorption in the jaw.[124] Cherubism remains challenging to manage. Recently, two patients underwent treatment with adalimumab, but it was ineffective.[125] Another recent case reported no improvement in a patient treated with adalimumab and oral bisphosphonates.[126]

## CONCLUSION

Sterile bone inflammation is a defining characteristic of autoinflammatory bone disorders such as CNO and CRMO. These conditions are frequently linked with skin and gastrointestinal tract inflammatory disorders, suggesting common immunological mechanisms. Familial cases of CNO/CRMO have shed light on the underlying pathophysiology. Clinically, the presentation of CNO/CRMO ranges from mild, self-limiting episodes to severe, recurrent manifestations. WB-MRI is a crucial diagnostic tool, enabling the identification of asymptomatic lesions without the risks associated with radiation exposure. Nevertheless, the optimal management strategies for CRMO remain unclear, underscoring the need for prospective studies to compare therapeutic interventions and assess the long-term safety and efficacy of biological treatments in pediatric populations.

## Author contribution

The authors declare contribution to the paper as follows: Review conception and design: KB; literature review: HMK; draft manuscript preparation: HMK. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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