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REVIEW

Update on the diagnosis and treatment of CNO in children: a clinician's perspective

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Abstract

Chronic non-bacterial osteomyelitis (CNO) is caused by aseptic inflammation of bones, primarily driven by the innate immune system. CNO may display different clinical presentations (acute *vs* chronic, uni- *vs* multifocal) and is accompanied by other inflammatory disorders in up to a third of patients. Once considered a rare disorder, it has become clear that many patients were underdiagnosed. With increasing awareness and the development of total-body MRI protocols, CNO recognition and diagnosis have greatly improved. Our knowledge of the clinical manifestations and outcomes of CNO has been refined in recent years, especially thanks to the recruitment of large international series. Similarly, new insights into the pathogenesis have been gained by the development of mice models and identification of rare monogenic diseases that resemble CNO. Unfortunately, these advances have not been paralleled in the therapeutic management. In the absence of prospective controlled trials, therapeutic strategies still rely on low-level evidence studies. About half of the patients respond to first-line therapies, but a more refractory and/or chronic disease course requires additional treatments. This narrative review aims to provide the practicing physician with an update on CNO pathogenesis, clinical presentation, associated inflammatory conditions, and diagnostic investigations, and includes a concise summary of current therapeutic recommendations.
Conclusion: While major progresses have been made in the recognition and management of CNO, significant challenges remain, in particular regarding the treatment of refractory patients, and those with associated inflammatory disorders.

What is Known:

- *Many physicians caring for children will encounter patients suffering of (suspected) CNO. CNO diagnosis requires exclusion of numerous conditions included in the differential diagnosis, which may be challenging.*

What is New:

- *We provide an updated review of recent findings in the field CNO, including imaging and diagnostic strategies, associated inflammatory diseases and long-term outcomes data.*
- *We focus particularly on the challenges encountered by clinicians in the diagnosis and treatment of these patients.*
- *We highlight knowledge gaps in the understanding and treatment of CNO, that should stimulate future research.*

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Keyword Chronic non-bacterial osteomyelitis; Chronic recurrent multifocal osteomyelitis

Abbreviations

BRAF	V-raf murine sarcoma viral oncogene homolog B1
CNO	Chronic non-bacterial osteomyelitis
CRMO	Chronic recurrent multifocal osteomyelitis
IL (-1β, 1RN-6, -10, -19)	Interleukin (-1β, 1RN-6, -10, -19)
LPIN2	Lipin 2
MAP2K1	Mitogen-activated protein kinase kinase 1
MIBG	Metaiodobenzylguanidine
NSAIDs	Non-steroidal anti-inflammatory drugs
PSTPIP1	Proline-serine-threonine phosphatase interacting protein 1
RANK	Receptor activator of NF-κB
RANKL	Receptor activator of NF-κB ligand
SAPHO	Synovitis, acnea, pustulosis, hyperostosis, osteitis syndrome
TNFα	Tumor necrosis factor alpha
WB-MRI	Whole-body magnetic resonance imaging

Introduction

Chronic non-bacterial osteomyelitis (CNO) is considered a rare idiopathic inflammatory disorder, yet it represents one of the most common pathologies encountered by pediatric rheumatologists. The highest prevalence is found amongst children aged 7–12 years, but adult onset is observed. As for most immune-mediated diseases, females are more likely to be diagnosed with CNO than males (estimated male/female ratio ~ 1/2). Its actual incidence is higher than previously reported (estimated annual incidence of 0.4 and 1/100,000 children in Germany and Australia, respectively [1, 2]), and may be close to that of infectious osteitis in Western countries [3, 4]. Although CNO has been reported in most ethnicities, its frequency in other parts of the world is poorly known. Despite its prevalence and recognizable features, this condition remains frequently misdiagnosed, exposing some patients to unnecessary investigations and drugs, and delaying appropriate therapy. Most patients will encounter several different physicians (pediatrician, infectious disease specialist, orthopedist, oncologist) before being referred to a pediatric rheumatologist. Notably, many other names have been used to describe CNO: chronic sclerosing osteitis, chronic recurrent multifocal osteomyelitis (CRMO), etc. Some authors have suggested that CRMO refers to the more multifocal forms of CNO [5]. In the following, we will use the abbreviation CNO/CRMO to be consistent with the most recent literature.

In this review, we will first summarize the current understanding of CNO/CRMO pathophysiology. Next, we adopt a clinically oriented step-by-step approach and discuss its clinical presentation and useful investigations in the diagnosis. Finally, we will concisely address prognosis and therapy (Table 1).

Pathophysiology in a nutshell

Despite its frequency amongst rheumatological inflammatory disorders, the pathophysiology underlying CNO/CRMO has been relatively little studied. Detailed review of pathogenic mechanisms is outside the scope of this work [6]. Our current understanding relies on a variety of data, including clinical, radiological and histo-pathological observations, discovery of monogenic disorders resembling CNO/CRMO, and murine models.

It is now widely accepted that CNO/CRMO is primarily mediated by inappropriate activation of innate immune system components. This classification of CNO/CRMO in the family of "auto-inflammatory disorders" is backed up by several lines of evidence. First, an aberrant cytokine profile in the blood monocytes of CNO/CRMO patient has been described, including low expression of IL-10 and IL-19, and increased levels of IL-1β, TNFα, and IL6 [7]. How this imbalanced cytokine expression results in (or is triggered by) bone inflammation remains to be determined. It seems likely that bone resident cells are also involved: increased osteoclast differentiation and activation (through the RANK/RANKL pathway) has been described. Ultimately, the bone tissue will be the site of immune cell infiltration and hyperostosis (Fig. 1A–B). Radiographically, this is translated into the typical osteolytic lesions surrounded by a hyper-sclerotic rim.

The role of a genetic background in CNO/CRMO is highlighted by the existence of very rare monogenic disorders associated with chronic osteitis (e.g., mutations in *IL1RN*, *PSTPIP1*, or *LPIN2* [8, 9]). These genes encode proteins that are mainly involved in the regulation of the innate immune response. In mice models of chronic aseptic osteitis, the predominant role of the innate immune system has also been confirmed [10]. In these models, a contribution of the microbiome to the development of osteitis has also been suggested [11], which seems relevant in view of other inflammatory manifestations associated with CNO/CRMO (discussed later).

Table 1 Differential diagnosis of CNO/CRMO

Conditions	Suggestive context/features
Infectious	
Septic acute osteomyelitis	Fever, inflammatory syndrome, severe pain, usually unifocal
Subacute / chronic infectious osteomyelitis (*K Kingae*, mycobacterial or, fungal infections, Brodie abscess, etc.)	Systemic symptoms, immunocompromised (i.e. genetic defects in IL-12 and Interferon gamma pathways)
Tumoral	
Leukemia, lymphoma	Severe pain, general malaise, cytopenia, elevated LDH, lysis without sclerosis, radiolucent metaphyseal bands
Malignant bone tumors (osteosarcoma, Ewing sarcoma, metastatic neuroblastoma, other rare tumors)	Depending on the tumor type: ill-defined lytic lesion, aggressive periosteal reaction
Benign bone tumors (osteoid osteoma, bone cyst, hemangioma, enchondroma, other rare tumors)	Depending on the tumor type: lytic nidus in cortical bone or diaphysis, radiolucent or expansile lesion, etc
Langerhans histiocytosis, eosinophilic granuloma, other non-Langerhans histiocytosis	Skull lesions, punched out lesions without sclerosis, giant cells and granulomas on biopsy
Metabolic	
Hypophosphatasia (mild childhood form)	Premature decidual teeth loss (with intact root) or teeth abnormalities, short stature, low impact fractures with delayed consolidation Radiolucent area in metaphysis
Vitamin C deficiency (bone scurvy)	Severe food restriction pattern, autistic spectrum disorder
Primary hypertrophic osteoarthropathy	Digital clubbing, pachydermia, acral osteolysis
Genetic	
Majeed syndrome, DIRA syndrome (Deficiency of IL1R antagonist), PAPA syndrome (Pyogenic Arthritis, Pyoderma gangrenosum, and Acne), cherubism	Neonatal / infantile onset, diffuse pustular rash, sustained inflammatory syndrome, aplastic anemia, severe mandibular overgrowth
Miscellaneous	
Microgeodic phalangeal syndrome	Unifocal, painless phalangeal lesion
Osteonecrosis	High dose steroids, sickle cell anemia, metabolic diseases
Fibrous dysplasia	Intramedullary, expansile lesion with well-defined borders
Fractures, stress factures	Trauma history, osteoporosis, radiological features
Spondyloarthropathy	Associated arthritis, enthesitis. Bone marrow edema, sacroiliitis
Caffey disease (infantile cortical hyperostosis)	Very young age, periosteal new bone formation *i.e.* of long bone diaphysis, ribs, mandible
Gorham-Stout disease	Evolution towards bone vanishment
Tendinitis, osteochondritis, periarticular pathologies	Depending on context
Benign musculoskeletal pains (hyperlaxity, benign nocturnal limb pains, physical deconditioning, etc.),	Normal imaging and clinical examination (besides moderate joint hypermobility), long pain-free intervals, normal first-line investigations

Although high-titer autoantibodies cannot be detected in CNO/CRMO patients, a potential implication of adaptive immune system components in CNO/CRMO pathogenesis remains possible and requires further investigation. The lymphocytic and plasma cell infiltration on bone biopsy in a subgroup of patients might be an indirect clue in favor of this possibility.

Clinical presentation

The typical clinical presentation of CNO/CRMO is chronic localized pain in any bone. Reportedly, up to 30% of patients may have unifocal involvement [12]. Figure 1C shows the distribution pattern of osteitis in pediatric CNO/CRMO. Distal metaphyses of the lower limb long bones are the most frequently affected sites (Fig. 2A–F). Vertebrae, pelvic bones, and clavicle (in particular the medial part) are also frequently involved (Fig. 2A, E–F). The latter is considered to be a typical location, very suggestive of CNO/CRMO diagnosis [13]. Notably, discovery of clinically asymptomatic lesions during the workup is frequent, especially when using whole-body magnetic resonance imaging (WB-MRI) (see the next section).

The pain is typically moderate, worsens at night, and responds to NSAIDs. Most children and adolescents can follow their normal daily life activities, leading to a delay in seeking medical advice or perform investigations [12]. In the absence of associated extra-osseous manifestations, the physical examination is frequently unremarkable besides

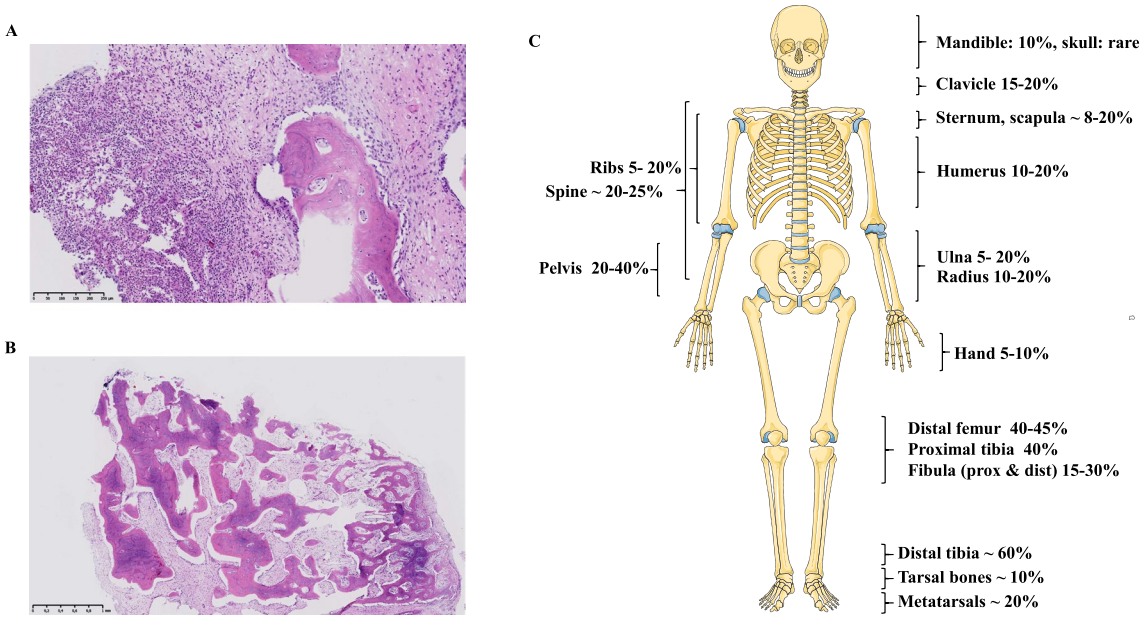

Fig. 1 Histological features and spatial distribution of osteitis in CNO/CRMO. **A-B**. Bone tissue displays mixed inflammatory infiltration **A**, hyperostosis and sclerosis **B** in CNO/CRMO (courtesy of Prof. Christine Galant). **C.** Distribution of bone lesions in CNO/CRMO. Adapted from [48] and [18], two studies of 37 and 75 paediatric CNO/CRMO patients with systematic total body MRI. Figure prepared with the help of https://smart.servier.com/

moderate pain elicited by pressure on bone structures. Bone or soft tissue swelling are frequently noted when the clavicula or the distal tibia/fibula are involved (Fig. 2G), or in the case of associated arthritis. Skin redness or warmth are rather suggestive of septic osteomyelitis. Systemic symptoms (i.e., weight loss, general malaise), severe pain, and/or limitation are not typical and should also alert the physician. Box 1 shows the red flags in CNO/CRMO diagnosis that should raise the suspicion for an alternative diagnosis or an associated condition (see next sections). Of note, fever at CNO/CRMO onset is not uncommon (reported in ~ 15–20% of patients) but should lead to definitive exclusion of infectious osteitis and malignancy [12, 13]. Finally, clinicians will also be on the lookout for extra-osseous manifestations involving skin and/or its appendages, or gastro-intestinal system.

Differential diagnosis and investigations

There are no validated and widely approved diagnostic criteria and/or tests for CNO/CRMO, requiring the physician to carefully exclude any other bone disorder that may mimic the condition. Table 1 summarizes main conditions to consider in the differential diagnosis, and their evocative context. In particular, infectious osteomyelitis, benign or malignant bone tumor, and hemopathies should be ruled out in the first place. As a consequence, multidisciplinary concertation is essential (pediatrician, infectious disease specialist, radiologist, oncologist, orthopedist, rheumatologist). CNO/CRMO is universally regarded as a "diagnosis of exclusion," yet there is no consensus on how each patient should be investigated. Patients with typical presentation can often be diagnosed after clinical evaluation by an experienced physician and a reasonably targeted set of investigations [13]. Scores have been proposed to help the diagnosis but lack external validation [14]. The most challenging cases remain those with an acute, febrile, and inflammatory presentation, mimicking (uni or multifocal) infectious osteomyelitis or malignancies (~ 15–20% of CNO/CRMO cases [12, 13]). In these cases, it is often necessary to start empiric antibiotic treatment (preferably after biopsy) and evaluate response to therapy. Importantly, multifocal involvement does not exclude septic osteomyelitis (i.e., caused by *Streptococcus pyogenes*, *Staphylococcus aureus*, or *Streptococcus pneumoniae*).

Box 2 summarizes most useful investigations. We discuss some of these in more detail in the following paragraph.

Standard blood tests are unspecific but necessary in the differential diagnosis. Complete blood cell count is mostly normal. White cell count may be mildly elevated, with frequently mild monocytosis or neutrophilia. Cytopenia is uncommon and should alert for hematologic malignancies. Inflammatory markers are typically normal or moderately elevated.

Imaging studies are key to the diagnosis: input from an experienced pediatric and/or musculo-skeletal radiologist

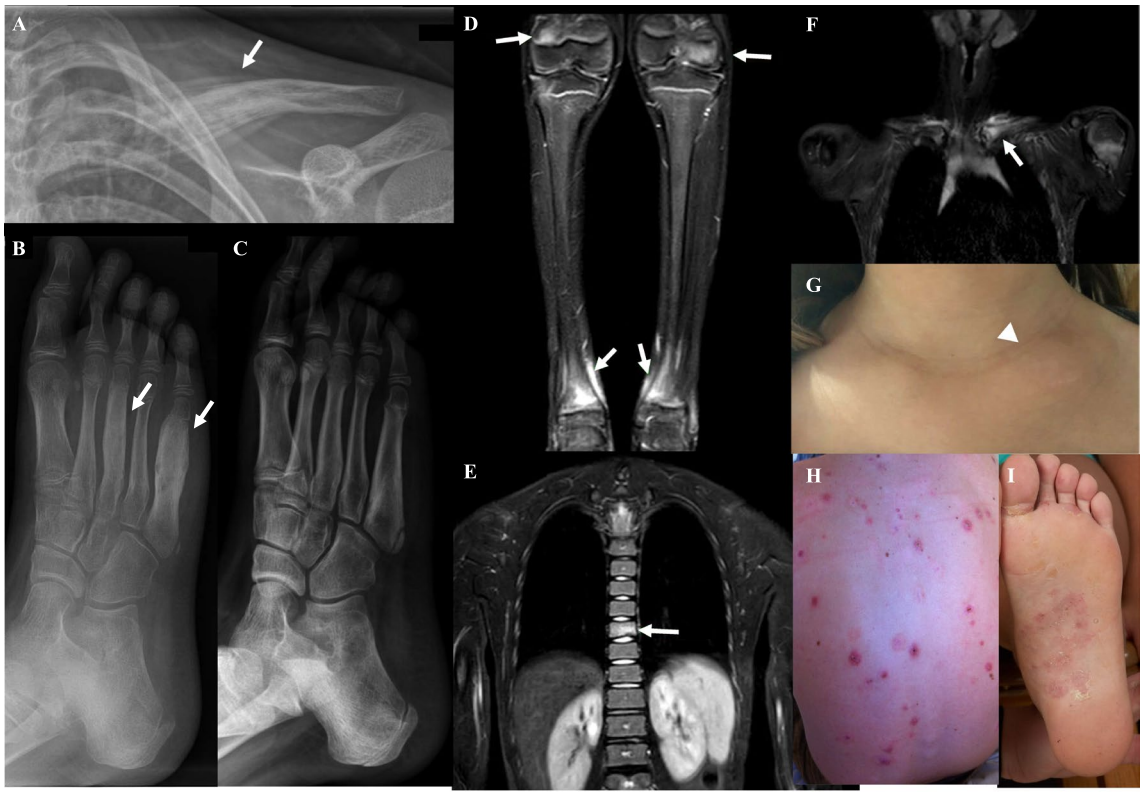

Fig. 2 Typical aspect of CNO/CRMO Radiographs findings in CNO/CRMO (**A-C**). Typical CNO/CRMO lesion on the medial clavicle portion, with osteolysis and periosteal reaction (**A**, arrow). CNO/CRMO lesions of the 3rd and 5th metatarsal bones showing osteolysis and hyperostosis (**B**, arrows). Favorable evolution of the lesions after 1.5 years of treatment (**C**). MRI findings in CNO/CRMO (**D-F**): hyper intense signal (STIR-TSE sequence) in lower limbs epiphysis/metaphysis (**D**), thoracic spine (**E**), and clavicle (**F**). White arrows show osteitis. Panel **D** also demonstrates perilesional soft-tissue edema, and **E** spontaneous compression fracture of T9. **G**. Typical clinical aspect of clavicle CNO/CRMO involvement: sensitive (spontaneous or on palpation) or painless tumefaction of medial clavicle (arrowhead). **H.** Aseptic pustulosis on the back of a patient with clavicle CNO/CRMO. **I:** palmoplantar rash associated with CNO/CRMO

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 periostal reaction) or localization (e.g. diaphysis, skull, etc.)
Unifocal lesion
Immunocompromised patient
Onset < 2 years, familial history
Absence of response to NSAIDs or bisphosphonate

is often strongly contributive. Many infectious, tumoral (benign or malignant), or metabolic disorders can present radiological similarities with CNO/CRMO. Figure 3 presents illustrative examples of such conditions. Details on the specific radiological features are outside the scope of this paper; interesting reviews can be found in references [15–18]. Here we will mainly discuss the advantages and limitations of each imaging modality.

Radiographs are often used as the first line of investigation and are useful for identifying bone lesions and assessing the extent of bone involvement. They typically show mixed osteolytic and sclerotic lesions and periosteal reaction is possible (Fig. 2A–C). However, they have limited sensitivity, particularly in the early stages of the disease when lesions may remain occult. Therefore, while radiographs are often used for initial assessment, they are often complemented by sensitive "next generation" imaging modalities.

Whole-body magnetic resonance imaging (WB-MRI) is the method of choice for diagnosing and monitoring CNO/CRMO [19, 20]. WB-MRI often leads to the diagnosis of CNO/CRMO by ruling out other conditions, particularly infectious, benign tumors or malignant disease [15, 21]. MRI provides images of bone and soft tissue and detects early inflammatory changes that are not visible on radiographs. Fluid-sensitive T2 and short tau inversion recovery

Box 2 Non-exhaustive list of useful investigations to consider in the work up of suspected CNO/CRMO

Systematic

- CRP, ESR
- Haemogram
- LDH, uric acid
- Blood culture
- Radiographs (on symptomatic localizations)
- MRI: centered on symptomatic lesions or (preferentially) whole-body
- Spine radiographs or MRI (if WB-MRI is not performed)

Based on patient's presentation

- Blood smear, buffy coat
- Bone biopsy with histology and microbial investigations (culture, PCR, etc.)
- Bone marrow biopsy
- PET-CT
- Bone CT-scan
- Search for somatic mutations in bone biopsy specimen (BRAF, MAP2K1, …)
- Vitamin C level, Ca, Ph, Vitamin D, Alkaline phosphatase
- Quantiferon or intradermal tuberculin test
- SPECT—CT or high-resolution CT scan
- MIBG scintigraphy, urinary catecholamines
- Genetic testing to exclude inborn error of immunity or inborn bone metabolic disorder (*ALPL*, *HPGD,* …)
- Fecal calprotectin, (preferentially before starting NSAIDs), gastrointestinal evaluation

(STIR)–weighted sequences allow the detection of signal changes, i.e., bone marrow edema, which is the hallmark of active inflammation (Fig. 2D–F). WB-MRI allows the identification of multiple bone lesions, a key feature of CNO/CRMO, and a confident differential diagnosis with infectious osteomyelitis and skeletal malignancies by demonstrating the absence of "marrow replacement" by tumor tissue or abscesses and the absence of soft tissue mass (soft tissue edema can be observed in active forms). WB-MRI is particularly useful in children and adolescents to avoid repeated radiation exposure. WB-MRI has been shown able to detect subclinical skeletal sites of disease and to allow non-invasive follow-up and assessment of lesion response to treatment. CNO/CRMO-specific standardization in reading and reporting of WB-MRI has been proposed to harmonize lesion description, quantification, and response assessment [22, 23].

Computed tomography (CT) is not the first choice for CNO/CRMO because of its relatively high radiation dose and limited anatomical coverage. It has also inferior soft tissue contrast and, most importantly, bone marrow contrast compared to MRI.

Whole skeleton screening using technetium-99 m bone scintigraphy has been replaced by WB-MRI and should only be considered in countries with limited access to MRI [24].

Bone biopsy is performed less frequently than in the past: in patients with typical clinical and radiological presentation, without significant biological inflammation, experienced clinicians may reasonably avoid this procedure. A score has been proposed to help the decision-making to proceed or not with bone biopsy, but this has not been externally validated and their sensitivity is unclear [13]. In other cases, bone biopsy remains necessary to exclude infectious osteomyelitis or malignancy. Histology may demonstrate multiple patterns of inflammatory infiltrate (lymphocytic, granulocytic, mixed), sclerosis, and/or non-specific findings (Fig. 1A–B) [4]. Of note, bone culture is usually negative, but in some cases it may be positive for *Cutibacterium acnes* or *Staphylococcus species*, possibly as a result of skin contamination [25, 26]. Altogether, encouraging advances in the diagnostic potential of imaging techniques have indeed reduced the rate of bone biopsies, yet CNO/CRMO remains a diagnosis of exclusion; and bone biopsy is the key investigation to perform when there is any doubt or suspicion of alternative diagnosis.

Depending on the context, other targeted investigations may be useful (Table 1 and Box 3). For example, additional radiological studies may be required (i.e., bone CT scan for specific benign or malignant tumors, MIBG scintigraphy for neuroblastoma, etc.). Exclusion of acquired (vitamin C deficiency, phosphocalcic disorder) or inborn (hypophosphatasia, primary hypertrophic osteoarthropathy) metabolic bone disorders may also be required. Additional analyses on bone biopsies may be useful if atypical infections or histiocytic disorders are suspected (mycobacterial or fungal stains and cultures, search for somatic *BRAF* or *MA2K1* mutations, etc.).

Associated inflammatory conditions

Depending on series, up to a third of patients will have an associated inflammatory condition that may be present at diagnosis or appear later in the disease course [4, 12, 27, 28]. Thus, CNO/CRMO has a clear association with other inflammatory disorders of the skin such as psoriasis and the gastrointestinal tract such as Crohn's disease, as shown in Table 2. Peripheral arthritis is also reported in CNO/CRMO. Finally, CNO/CRMO patients may manifest sacroiliac joint disease and enthesitis [29]. SAPHO (synovitis, acnea, pustulosis, hyperostosis, osteitis) syndrome refers to a clinical entity characterized by inflammation of bone, joint, and skin (Fig. 2H–I). SAPHO has been mainly used in the adult literature but a unifying terminology "CNO" (with or without extra-osseous

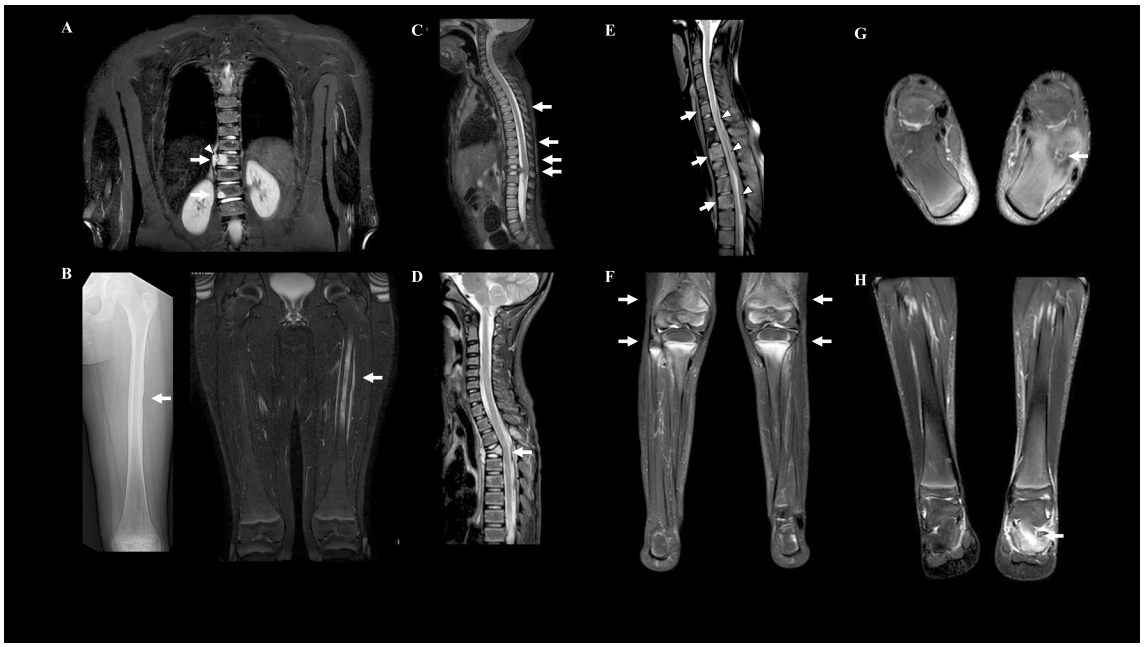

Fig. 3 Iconographic illustration of the imaging appearance of several conditions included in the differential diagnosis of CNO/CRMO **A.** Vertebral metastasis of neuroblastoma in a 10 years old boy. MRI (coronal 2D STIR), shows abnormal signal in vertebral bodies (arrow), vertebral collapse and peri-vertebral soft tissue mass (arrowhead). **B.** Femoral metastasis of neuroblastoma. Radiograph (left panel) shows irregular cortical thickening and heterogenous bone density (arrow). MRI (right panel,coronal T2 sequence) shows abnormal hyper-intense signal in the diaphysis with soft tissue extension (arrow). **C.** Spontaneous vertebral compression fractures in a toddler with leukemia. MRI (sagittal view T2) shows collapse of multiple vertebral bodies and discrete heterogeneity of the bone marrow signal (arrows). **D.** Langerhans cell histiocytosis in a 10 years old girl. MRI (STIR sequence) shows vertebra plana, bone marrow edema of posterior vertebral arch and extension to prevertebral soft tissues (arrow). **E.** Lymphoma in a 16-year-old female patient. MRI (sagittal STIR) of the cervicothoracic spine shows multiple foci of bone marrow replacement (arrows); extraosseous spread to epidural spaces (arrowheads) is not seen in benign inflammatory disease, but suggests multifocal tumor involvement of the skeleton. A targeted bone biopsy of a bone lesion confirmed the diagnosis of lymphoma. **F.** Vitamin C deficiency in a six years old boy. MRI image (coronal 2D STIR) shows homogenous, symmetrical high signal intensity of the bone marrow in distal femur and proximal tibia metaphyses (arrows). **G-H.** Osteoid osteoma in an adolescent. Coronal (G, STIR sequence) and axial (H, T2 SPAIR sequence) MRI views show extensive left calcaneum edema, associated with presence of a typical "nidus" (arrows)

manifestations) probably best reflects the spectrum of the diseases spanning from pediatric to adulthood.

The association of CNO/CRMO with skin, intestinal, and axial joints inflammatory disorders points toward a link with the family of spondyloarthropathies. As a matter of fact, CNO/CRMO may evolve into typical spondyloarthritis on the long term [30]. These inflammatory disorders also share some physio-pathological aspects, such as predominant involvement of the innate immune system, dysregulation of several cytokine pathways (i.e., TNFα, IL17, IL12/IL23 axis), and recognized role of the interaction with the microbiome [31–33]. Interestingly, some monogenic conditions causing osteitis also present with skin or joint inflammation (e.g., deficiency of IL1R antagonist (DIRA) syndrome and pyogenic arthritis, *Pyoderma gangrenosum*, and acne (PAPA) syndrome). These observations led several authors to classify CNO/CRMO within the spectrum of spondyloarthropathies and psoriatic arthritis [34–36].

In conclusion, recognizing and tracking these associated disorders is paramount both for diagnosis and for appropriate management.

Management

A detailed review of the management of CNO/CRMO is beyond the scope of this review (see international consensus plans reviewed in [37]). We will outline in the following paragraphs the main strategies used. Notably, therapy is mostly based on individual experience, case reports, and case series. Consequently, treatment of CRMO/CNO remains little codified, and variable across centers. Unfortunately, no randomized control trial has been conducted in this pathology, and all drugs are currently used off label. The recent development of consensus treatment plans is expected to harmonize clinical practice across centers [37]. We will outline this approach in the following paragraphs.

Table 2 Inflammatory disorders associated with CNO/CRMO

Associated disorder	Estimated rate in CNO/CRMO patients (4)
Skin	10–30%
Psoriasis (pustular or vulgaris)	
Severe acnea, acnea conglobata	
Hidradenitis suppurativa	
Neutrophilic dermatosis (Sweet syndrome)	
Pyogenic granuloma	
Dissecting cellulitis of the scalp	
Gastro-intestinal	10%
Crohn	
Rectocolitis ulcerosa	
Joints and entheses	20–30%
Arthritis	
Spondyloarthropathy	
Other conditions	Sporadic reports
Takayasu, ANCA-associated vasculitis, myositis, etc	

Therapy in CNO/CRMO should aim to (i) control pain and inflammation, (ii) avoid complications of prolonged bone inflammation (bone fractures, deformation, and growth disturbance), (iii) maintain a favorable toxicity risk/benefit balance of the treatment, and (iv) take into account-associated inflammatory diseases. Usually, the first therapeutic agents are non-steroidal anti-inflammatory drugs (NSAIDs), in association with gastric protection. Naproxen is often used at 10 mg/kg daily (in two doses), and can be increased to maximum 15 mg/kg daily. In published series, first-line NSAIDs (as monotherapy or associated with short term steroids) are effective to control clinical manifestations in about half of patients after 3 to 6 months [28, 38].

For patients refractory to NSAIDs, and patients with spinal lesions or with elevated fracture risk, additional treatments are required. Consensus treatment plans have been proposed to limit treatment practice variation and allow comparative effectiveness studies; these suggest three second-line options, ie …. [37], i.e. (i) methorexate or sulfasalazine, (ii) TNFα inhibitors ± methotrexate, and (iii) bisphosphonates. IV bisphosphonates are efficient (most experience exist for pamidronate 1 mg/kg during 1–3 days every 3 months) [39]. Bisphosphonates are also chosen as first-line therapy by some physicians (i.e., for therapeutic adherence reasons or out of fear for exceptional side effects associated with long-term NSAIDs [40]). A short course of corticosteroids is sometimes used for their rapid efficacy on the inflammatory component. Disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, sulfasalazine, and TNF-blockade (or combination of these agents), are also used after NSAID failure, although their efficacy has been less well documented. In the (relatively rare) patients refractory to these therapies, other biological DMARDs are used [4].

As stated above, co-existence of other inflammatory diseases (up to a third of patients) will also guide the therapeutic choice. Patients with multiple organ inflammation are frequently challenging to treat. Intuitively, one could think that therapy will act similarly on these conditions. Yet, clinical experience has taught us that multiple manifestations can behave differently in the same patients in terms of response to therapy. The management of these patients is even more complex as some of these manifestations can possibly be triggered by a drug given for a first disease (e.g., the development of paradoxical psoriasis in a patient treated by TNFα blockade for a spondyloarthropathy) [41]. In general, TNFα blockade is a good choice for most extra-osseous manifestations associated with CNO/CRMO [27]. Add-on methotrexate can also be efficient in some cases.

Monitoring of response to therapy is mainly clinical, with use of control MRI if refractory bone inflammation or complications are suspected. The management of radiologically active disease in asymptomatic patients (without spinal involvement) is a matter of debate [42, 43]. An important point to bear in mind is the overall good long-term prognosis of pediatric CNO/CRMO: in most patients, the disease follows a relapsing/remitting course but will eventually resolve, mostly without sequelae [43]. Consequently, most physicians treat CNO/CRMO for 1–2 years before attempting to stop therapy in case of persistent remission [28, 38]. Yet, it must be stressed that no clinical trial has investigated the best treatment tapering strategy.

So far, reported long-term outcomes have been based on cohort studies and are rather variable [27, 43]. Recent studies have highlighted that the proportion of patients reaching long-term remission may be lower than originally anticipated [42, 43]. This is especially true when disease activity is defined by MRI lesions, rather than physician global assessment [43]. Patients with associated inflammatory diseases may be more likely to follow a prolonged chronic course [27, 44]. The most frequent complication encountered on the long run is persistent pain (in patients with refractory osteitis but also in absence of active inflammatory lesions), while vertebral fractures (the most common structural damage) are reported in 5–25% of patients [14, 43, 45].

Physiotherapy is needed in case of amyotrophy, functional limitations, or physical deconditioning. Sporting activities should be encouraged, except for patients with elevated fracture risk. In this case, it is usually advised to wait for the effect of bisphosphonates before engaging in potentially traumatic activities. Chronic amplification pain syndrome occasionally develops in some patients and can be challenging to distinguish clinically from persistently active disease. In these cases, control regional MRI will aid the physician. The differentiation is crucial to avoid overtreatment, and

plan psychological support and follow-up in algology [46, 47]. In some patients, pain amplification syndrome and persistent active inflammation can also coexist.

Conclusion

CNO/CRMO is a chronic inflammatory bone disease that can be challenging to recognize for the primary care physician. Although progress has been made, there is still need to increase awareness for this condition, to allow prompt referral and patient management in rheumatology. The underlying pathophysiology remains poorly understood: although some very rare monogenic disorders associated with noninfectious osteitis have been identified, most patients have "idiopathic" CNO/CRMO. Clinical research on CNO/CRMO has long been limited to small descriptive cohorts, but recent international efforts have demonstrated that its frequency is higher than previously estimated. With the development of consensus therapeutic recommendations, the definition of a standardized disease activity scoring system and the establishment of large prospective registries, knowledge of response to therapy, and long-term outcomes will improve in the coming years [4, 22, 39]. Disappointingly, there are no randomized controlled trials available for this disease. For instance, data comparing efficacy and tolerability of first-line NSAIDs *vs* bisphosphonates would be highly relevant for physicians. Other outcomes (e.g., treatment duration and withdrawal strategies, third-line therapies) could also be investigated. Currently, the main daily challenges for the clinician managing these patients are as follows: (i) early recognition of the condition to avoid invasive procedures and unnecessary medications in patients with typical presentation; (ii) therapeutic choices in refractory cases or in those with associated inflammatory conditions. Ultimately, it is hoped that clinical/radiological/biological prognostic markers will be discovered to optimize the monitoring of disease activity and define the most effective therapeutic strategies.

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Declarations

Competing interests The authors declare no competing interests.

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