4

Chronic Non-Bacterial Osteitis/Chronic Recurrent Multifocal Osteomyelitis

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1. Introduction

Chronic non-bacterial osteitis (CNO) is a rare disease, which is a great mimic of infectious osteomyelitis (*Table 1*). It is currently classified as an autoinflammatory osteopathy. Autoinflammatory diseases are a group of disorders characterized by seemingly unprovoked inflammation in the absence of high-titer antibodies or antigen-specific T-cells. CNO primarily affects children, although it can be seen in any age group (Girschick, Raab et al. 2005). It is a disease of unknown etiology that was first recognized 4 decades ago as a disorder of non-infectious bone inflammation. It was initially described as "subacute and chronic symmetrical osteomyelitis," which affected multiple bones either simultaneously or sequentially with a recurrent pattern (Giedion, Holthusen et al. 1972). Later, similar non-infectious osteitis has been described as both multifocal and unifocal disorder, with recurrent or monophasic course, and in association with other inflammatory conditions such as ankylosing spodylitis, psoriasis, and inflammatory bowel disease. Recurrent episodes of painful swollen lesions of the bone are noted, elevated ESR can occur, and radiographic changes can be confused with bacterial osteomyelitis. Negative findings on culture are the rule, and no improvement is noted with antimicrobial therapy.

Chronic Non-Bacterial Osteitis (CNO) /
Chronic Recurrent Multifocal Osteomyelitis
CNO is a non-infectious auto-inflammatory osteitis
It is more common in children than in adults
It can mimic bacterial osteomyelitis
It can affect any bone
This chapter will cover
Epidemiology and etiology
Clinical manifestations
Laboratory, histopathological and radiological assessment
Proposed role of osteoclasts in CNO disorders
How to differentiate CNO from other "mimicking" bone disorders
Treatment modalities (including biologics and bisphosphonates)
Natural history and expected long-term outcome

Table 1. Synopsis of chronic non-bacterial osteitis and outline of the chapter

Historically, CNO disorders have been described by many names, such as chronic recurrent multifocal osteomyelitis (CRMO), SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) syndrome, and diffuse sclerosing osteomyelitis affecting the mandible (DSO) (Soubrier, Dubost et al. 2001). In 2005, the term CNO was coined to describe all of these disorders, and the current understanding is that non-infectious inflammatory bone disorders present a clinical spectrum within which CRMO is the most severe form (Girschick, Raab et al. 2005). There have been further attempts to classify patients into defined groups (unifocal nonrecurrent, unifocal recurrent, multifocal nonrecurrent, multifocal recurrent) to establish diagnostic criteria and to find prognostic indicators, although such classification criteria have not been uniformly adapted (Beck, Morbach et al. 2010).

Because the clinical course of the patients may vary according to clinical subtype, in this chapter the term CNO will be used as an umbrella term to describe all of these inflammatory bone disorders, and the sub-categories of CRMO, SAPHO syndrome, DSO, etc. will be retained for subgroups of relevant CNO patients.

2. Epidemiology

Because CNO is a relatively new term, epidemiologic data is primarily available for the subcategory CRMO only. CRMO is recognized worldwide accounting for 2% to 5% of all osteomyelitis cases (Chun 2004). CRMO is primarily a disease of childhood, with the mean age at presentation around 10 years. The youngest age at CRMO presentation has been reported to be 6 months, and the oldest 55 years (Khanna, Sato et al. 2009). The true incidence and prevalence of CRMO remain unknown with more than 300 cases of classic CRMO reported in the literature. Several studies have demonstrated that the disorder is more common in girls than boys, with approximately 2:1 ratio. Although most of the initial reports of CRMO were from Scandinavian countries, later it has been recognized worldwide with no specific racial predilection (El-Shanti and Ferguson 2007).

There is only one existing study on the epidemiology of the general category of combined non-bacterial osteitis disorders. A recent German study reported an annual incidence of 0.4 per 100,000 children, with approximately 60 new patients diagnosed annually suggesting that this disorder is much more common than previously suspected (Jansson and Grote 2011).

3. Etiology and pathogenesis

Pathogenesis of CRMO/CNO continues to be poorly understood. It is not known what triggers the initial episode or why some patients have more persistent disease than others. Environmental, immunological, and genetic factors have been postulated as causative factors with varying evidence.

3.1 Environmental factors

Because of the intermittent nature of clinical symptoms, and clinical similarity to bacterial osteomyelitis, the search for infectious etiologies has been vigorous. Despite initial case reports suggesting that *Staphylococcus aureus, mycoplasma hominis, propionibacterium acnes, bartonella henselea* etc. could have been present in putative CRMO lesions, larger studies

have not confirmed a common infectious agent using standard bacterial cultures. More elaborate techniques, such as polymerase chain reaction (PCR) technique for microbial testing, including examination for mycobacteria, have also failed to disclose a causative infectious agent in patients with CRMO (Girschick, Raab et al. 2005). The presence of negative cultures and failure of CRMO symptoms to improve with antibiotic therapy make an infectious etiology very unlikely.

3.2 Possible immune mediated etiology

A possible immune-mediated etiology has been speculated, but immunologic evaluations of cases have not revealed abnormalities in T-cell subsets, oxidative burst of phagocytic cells, mononuclear cell response to mitogens, neutrophil chemotaxis, or phagocytosis. Antinuclear antibody (ANA) and rheumatoid factor have rarely been reported in association with classic CRMO (Chun 2004). A recent pediatric series with 37 CNO patients reported that 51.3% of patients had a low titer ANA level (1:80), and 8.1% of patients had titres ≥ 1:160 (Beck, Morbach et al. 2010). However, these levels of ANA were not different when compared with a healthy control group of age-matched children. Both local and systemic increase of tumor necrosis factor alpha (TNF-α) has been documented in active CRMO (Jansson, Renner et al. 2007). Because of the clinical similarity of CNO to a syndrome presenting with neonatal onset of sterile multifocal bone inflammation with periostitis and skin pustulosis associated with a deficiency of IL-1 receptor antagonist (DIRA) (Aksentijevich, Masters et al. 2009), the role of interleukin-1 in CNO has also been speculated but not confirmed (Eleftheriou, Gerschman et al. 2010).

3.3 Genetic factors

More recently, genetic origin for at least the CRMO subtype has been suggested secondary to observation of disease in siblings and monozygotic twins. The susceptibility focus has been indentified at 18q21.3-22 (Khanna, Sato et al. 2009) . The genetic origin of CRMO is further supported by identification of the *LPIN2* gene in Majeed syndrome (Khanna, Sato et al. 2009). This is an autosomal-recessive syndrome characterized by bone lesions identical to CRMO, congenital dyserythropoietic anemia, and inflammatory dermatosis. The exact function of *LPIN2* is unknown, but it has been postulated that if *LPIN2* plays a role in the regulation of the innate immune system, a defect in the protein would lead to increased production of inflammatory signals (El-Shanti and Ferguson 2007). Spontaneously occurring mouse models of CRMO have been identified that show an autosomal-recessive gene defect localized to the murine *pstpip2* gene (Khanna, Sato et al. 2009). The mice develop destruction of caudal and spinal vertebrae by 3 to 4 weeks of age, tail kinks by 6 to 8 weeks of age and additional hindfoot deformities by 3 months of age (Ferguson, Bing et al. 2006). *PSTPIP2* is highly expressed in macrophages, but it is not known how it contributes to inflammatory bone changes. The human *PSTPIP2* is located on chromosome 18q21.1, but its role in human CNO disorders has not been confirmed so far. However, although these findings suggest a possible genetic predisposition in selected inflammatory bone disorders, it is not known how genes play a role in the etiology of the various CNO disorders, which appear to have heterogeneous clinical presentation. Despite some CNO patients progressing to a spondyloarthropathy, HLA-B27 is not more common in CNO patients than in the general population (Beck, Morbach et al. 2010).

4. Diagnosing CNO

CNO remains a syndromic disorder, defined and diagnosed by a unique pattern of clinical, radiological, and histopathological findings. For the diagnosis of classic CRMO, all of the following criteria should be met: (a) the presence of one or more clinically or radiographically diagnosed bone lesions; (b) a prolonged course of at least 6 months with characteristic exacerbations and remissions; (c) typical radiographic lytic lesions surrounded by sclerosis with increased uptake on bone scan; (d) a lack of response to parenteral antibiotic therapy of at least 1 month's duration to cover clinically suspected organisms; and (e) a lack of an identifiable etiology (King, Laxer et al. 1987).

The suggested diagnostic guidelines for the non-bacterial osteitis disorders in general are presented in *Table 2* (Jansson, Renner et al. 2007). According to these criteria, the general diagnosis of nonbacterial osteitis is reached if two major criteria or one major criterion plus three minor criteria are found (Jansson, Renner et al. 2007). Accordingly to the authors, the more criteria that are met the more likely the diagnosis is CRMO. Although this scheme of diagnosis is not yet universally adopted, no other standardized diagnostic criteria exist for the CNO disorders.

Major Diagnostic Criteria	Minor Diagnostic Criteria
Radiologically proven osteolytic/sclerotic bone lesion	Normal blood cell count and good general state of health
Multifocal bone lesions	CRP and ESR mildly to moderately elevated
PPP[α] or psoriasis	Course is longer than 6 months
Sterile bone biopsy with signs of inflammation and sclerosis	Hyperostosis
	Association with other autoimmune diseases other than PPP or psoriasis
	Grade I or II relatives with autoimmune or autoinflammatory disorders or with NBO[β]

[α]PPP = palmoplantar pustulosis, NBO[β] = non-bacterial osteitis
Two major criteria or one major criterion plus three minor criteria are required for the diagnosis of non-bacterial osteitis (Reproduced with permission from Jansson, Renner et al. Classification of Non-Bacterial Osteitis, Rheumatology 2007;46:154-160)(Jansson, Renner et al. 2007)

Table 2. Proposed major and minor diagnostic criteria for nonbacterial osteitis

4.1 Clinical features

4.1.1 Musculoskeletal manifestations

Patients typically present with insidious onset of localized bone pain, associated with soft tissue and bone swelling. Although most patients present with a single symptomatic site, other sites of disease become apparent at imaging or during follow-up. The average number of sites per patient at CNO diagnosis has been reported to be 5.0 by using whole body (WB) magnetic resonance imaging (MRI) (Beck, Morbach et al. 2010) but during disease course the number per patient can range from 1 to 18 (Khanna, Sato et al. 2009). The common sites of skeletal involvement include the long tubular bones and clavicle, but lesions have been described

throughout the skeleton. Involvement of the lower extremity has been reported to be three times more common than disease in the upper extremity (Khanna, Sato et al. 2009).

4.1.2 Extra-bone and non-specific systemic manifestations

Arthritis is the most common extra bone manifestation, reported to occur in up to 80% of the patients over time in some large studies (Girschick, Raab et al. 2005). In a recent prospective German study of 37 pediatric CNO patients, arthritis was present in 38% initially (Beck, Morbach et al. 2010). Typically patients are systemically well with no additional features. However, 33% of children can have associated low grade fever and non-specific malaise (Schultz, Holterhus et al. 1999). Skin lesions are present in up to 30% of pediatric and adolescent patients with CNO and include pustulosis of the hands and feet, psoriatic skin lesions, severe pustular acne, Sweet syndrome, and pyoderma gangrenosum (Beretta-Piccoli, Sauvain et al. 2000). All the above-mentioned skin conditions share the common denominator of being aseptic lesions filled with neutrophils at some stage during the course of their development. The skin disease may precede or occur after the bone lesions, and the interval may be as long as 20 years (Azouz, Jurik et al. 1998). Inflammatory bowel disease is seen in association with CRMO in adult and pediatric patients in approximately 10% of cases and in the majority of cases, CRMO preceded the onset of inflammatory bowel disease by months to up to 5 years (Bousvaros, Marcon et al. 1999). Rarely, CRMO is seen in association with asymptomatic infiltration of the lung with pyogenic abscesses of the skin, cranial nerve lesions, Wegener's granulomatosis, and following leukemia diagnosis (Schultz, Holterhus et al. 1999).

4.2 Laboratory findings

4.2.1 Traditional laboratory tests

Unfortunately, traditional laboratory tests have been disappointing in CNO with no uniform criteria to detect active or remitted disease. For example, one can have clinically and radiologically active CNO with normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), so unfortunately "normal" values cannot be used to indicate "inactive disease"(Miettunen, Wei et al. 2009). However, because CNO is a diagnosis of exclusion, laboratory investigations can be used as supportive features for CNO diagnosis, and to help differentiate it from infectious or other etiologies. We recommend standard testing including blood count, ESR, CRP, serum ferritin, HLA-B27 and blood cultures. White blood cells may be minimally elevated. Very elevated ESR and CRP should prompt for a search for infectious osteomyelitis or a malignant process.

4.2.2 Novel laboratory tests

Based on the presence of osteolytic bone lesions on radiographs, increased osteoclasts in early CRMO lesions (Solau-Gervais, Soubrier et al. 2006), and beneficial effects of bisphosphonates, the role of osteoclasts seems intriguing in CNO disorders. In adult onset SAPHO syndrome, increased levels of serum osteocalcin have been observed in some patients, suggesting greater importance of bone resorption compared with bone formation in this disorder (Bjorksten and Boquist 1980; Mortensson, Edeburn et al. 1988; Rosenberg, Shankman et al. 1988; Yu, Kasser et al. 1989). At our center, we also utilize urinary N-telopeptide/urine creatinine ratio (uNTX/uCr) in selected cases. Urinary N-telopeptide is a

marker of collagen-1 breakdown that is traditionally used to monitor treatment response to bisphosphonates in adult patients with bone diseases characterized by accelerated bone turnover, such as Paget's disease of bone (Solau-Gervais, Soubrier et al. 2006; Ralston, Langston et al. 2008). UNTX/uCr is measured from the "spot urine" (2nd void in the morning) (Miettunen, Wei et al. 2009). We have found it to be particularly helpful following bisphosphonate therapy to identify patients whose osteoclast function has returned to normal. At our center, no patients have relapsed while their uNTX/uCr level remained suppressed below age-and sex determined levels, but approximately 50% of those patients whose uNTX/uCr level had returned to normal range relapsed. However, interpretation of uNTX/uCr can be challenging. Unlike adult patients, who have a clearly defined upper level of normal for uNTX/uCr at 65 nmol/mmol creatinine, pediatric patients require plotting of the uNTX/uCr values on age and sex specific graphs (Fig. 1.)

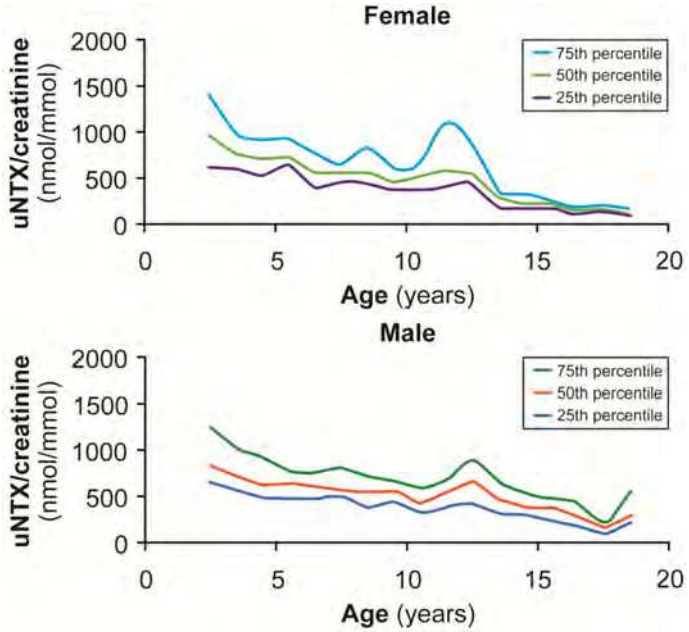


Fig. 1. Age and sex specific graphs for urinary N-telopeptide/urinary creatinine ratios (This figure and figures 10-13 are reproduced with permission from Miettunen, Wei, et al. "Dramatic pain relief and resolution of bone inflammation following pamidronate in 9 pediatric patients with persistent chronic recurrent multifocal osteomyelitisi (CRMO). Pediatr Rheumatol Online J 7:2)(Miettunen, Wei et al. 2009).

4.3 Histopathology

Because of similarity of radiographic appearance of CNO with bone infection or malignancy, we recommend a routine bone biopsy on all suspected cases. Histologically, bone lesions in all CNO categories (unifocal and multifocal, monophasic and recurrent) have similar acute and chronic features. Most commonly, an admixture of inflammatory cells, dominated by plasma cells and lymphocytes, with varying numbers of neutrophils and histiocytes, is present.

Increased osteoclasts and bone resorption can characterize early lesions (Chow, Griffith et al. 1999) (Giedion, Holthusen et al. 1972; King, Laxer et al. 1987; Rosenberg, Shankman et al. 1988). In chronic lesions, reparative changes of the osseous tissue (marrow fibrosis, trabecular osteoid apposition, periosteal hyperostosis) are present. Predominance of CD3 (+), CD45RO(+) T-cells which are mainly CD4 negative and CD8 positive has been reported (Girschick, Huppertz et al. 1999). CD68(+) macrophages or monocytes are common, while CD20(+) B cell infiltrates are uncommon (Girschick, Huppertz et al. 1999).

All these pathological changes, namely inflammatory infiltration of the marrow, active resorption of cortical lamellar bone and reactive woven bony deposition, are responsible for the radiographic picture of expansile and lytic areas occurring in conjunction with separate areas of sclerosis. Importantly, although bone biopsy can differentiate between a malignancy and CNO, histological examination alone cannot distinguish CNO from bacterial osteomyelitis (Girschick, Raab et al. 2005). Therefore extensive microbial investigation of the biopsy specimen with standard culture techniques to detect aerobic and anaerobic bacteria, mycobacteria, and fungi is mandatory. Additional studies using PCR to detect bacterial ribosomal DNA may be utilized.

4.4 Imaging

Radiological investigations have an important role in assessing the likelihood and confirming the extent of the disease and often include a combination of radiographs, isotope bone scans, computerized tomograms, and magnetic resonance imaging. Because the clinical presentation and radiological findings vary depending on the type of bone involved, this review first describes the general radiologic techniques and generalized findings, followed by a focused review of specific clinical and radiologic findings based on the type of bone involved.

4.4.1 Radiographs

The most common sites of disease are the metaphyses or metaphyseal equivalents, accounting for approximately 75% of all lesions in the series of Mandell et al (Mandell, Contreras et al. 1998). The sites of predilection are similar to those of acute hematogenous osteomyelitis in infants and children. The lesions are often but not always symmetric, round in appearance, are surrounded by thin sclerotic borders, and may be associated with periosteal new bone formation. Multifocal destructive bony changes in different stages of development and healing may be present, including lesions that are purely osteolytic, osteolytic and sclerotic, and purely sclerotic with or without periosteal elevation (Fig. 2.) (Khanna, Sato et al. 2009).

4.4.2 ^{99m}Technetium-phosphate bone scan

The findings on bone scan include mild to moderate increase in the uptake of the radionuclide in the lesion. The main contributions of a ^{99m}Technetium-phosphate bone scan are the ability to demonstrate activity at unsuspected sites, which are clinically silent at the time of scintigraphy, and the ability to detect lesions at sites which may be difficult to examine radiographically, e.g. in the spine or in the pelvic bones (Fig.3.) (Mortensson, Edeburn et al. 1988). Similar to all other imaging modalities, bone scan does not separate inflammatory from an infectious or malignant process. It is not a sensitive tool for assessing treatment response, as the bone scan can remain abnormal for months to years following an active CNO event.

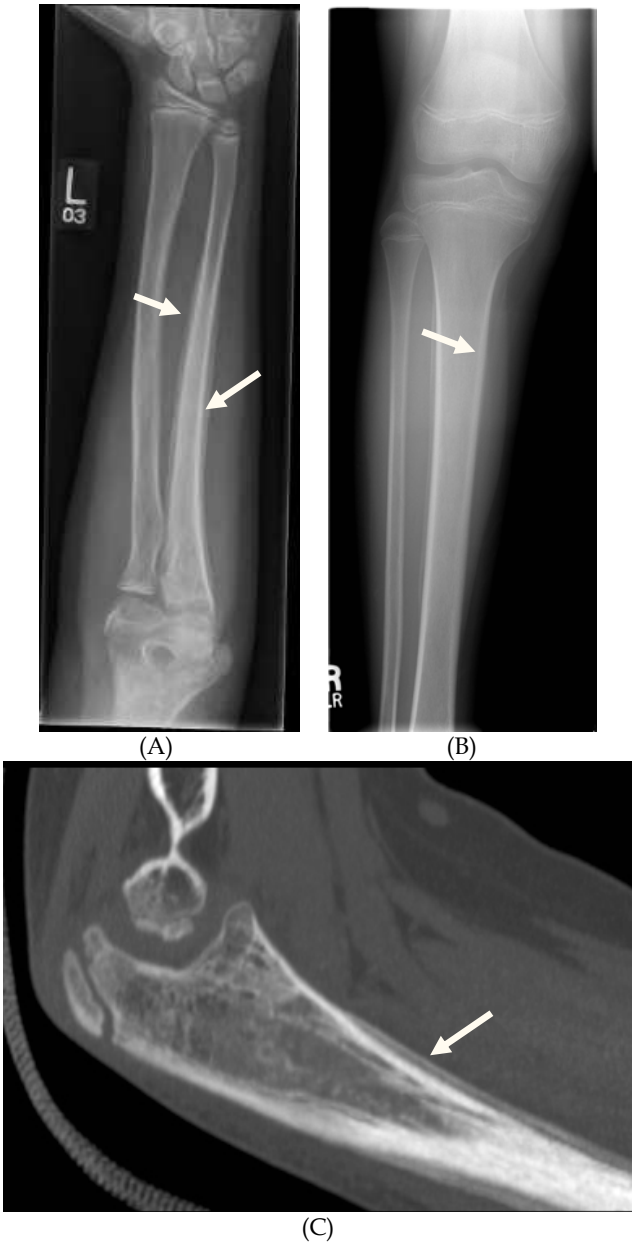
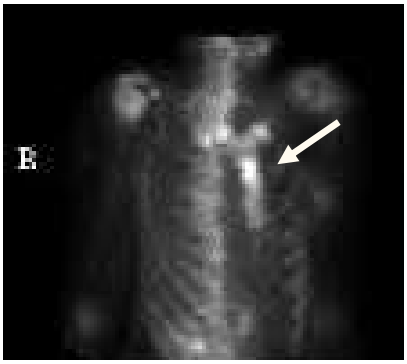


Fig. 2. **Anteriorposterior radiographs (A-B) and CT-scan (C)of a 12-year old boy with CRMO affecting the left ulna and right tibia**. Extensive single-layer subperiosteal reaction extends along the ulnar shaft (A) and tibial shaft (B) (arrows). The periosteal reaction affecting the left ulna is also nicely seen on CT (arrow). (This image and all subsequent images are reproduced with the written permission of the child/parents).



(A)

(B)

Fig. 3. **^{99m}Technetium-phosphate bonescan of a 19-year old female with multi-site CRMO.** (A). On delayed imaging, focused view of the chest wall reveals intense intake in the mid-sternal area (arrow). (B). Focused view of the knee area reveals additional intake in the right lateral femoral condyle, right patella and left tibial tubercle (arrows).

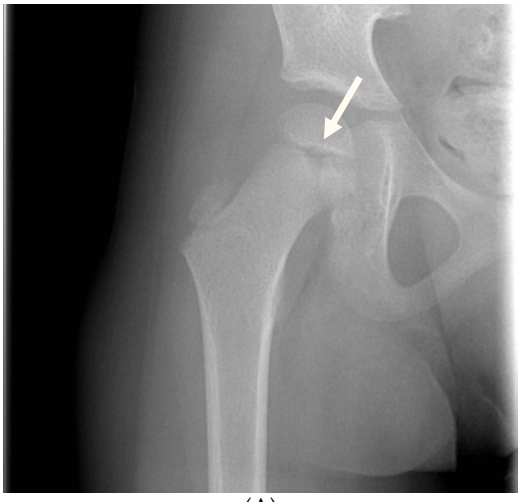
4.4.3 Computed tomography (CT)

CT-scan can be helpful as an initial step in differentiating an inflammatory process from a malignant one by showing a lack of soft-tissue mass and bone destruction in CNO. Because of radiation associated with CT, it is now used less often.

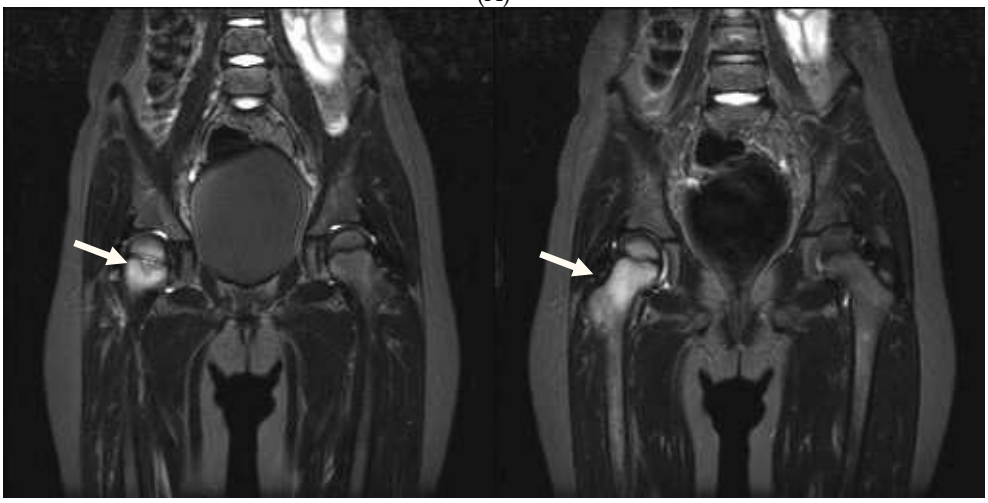
4.4.4 Magnetic resonance imaging (MRI)

MRI is emerging as the imaging modality of choice for initial diagnosis of CNO, and for monitoring its progress. It is a non-invasive imaging modality that is highly sensitive to active and remitted inflammatory lesions in bone and soft tissues in CRMO (Jurik and Egund 1997; Jurik 2004). In acute bone inflammation, an increased water content results in longer T1 and T2 relaxation times, and active CRMO lesions occur with increased signal intensity on short tau inversion recovery (STIR) or fat-saturated T2-weighted images and decreased signal intensity on T1-weighted images (Jurik 2004). Adjacent soft tissue edema can be present. MRI can detect abnormal bone marrow edema before changes are noted in x-ray of even bone scintigraphy (Fig.4.) (Girschick, Krauspe et al. 1998). Conversely, resolved CRMO is reflected by no signs of inflammation by MRI (Girschick, Raab et al. 2005).

While the classic MRI features of CNO/CRMO are indistinguishable from septic osteomyelitis, MRI can exclude abscess formation, sequestration, marrow infiltration, or



(A)



(B) (C)

Fig. 4. **Images of a 4.5-year old girl at CRMO diagnosis. (A).** Pre treatment right femoral radiograph: only subtle radiolucency is seen at the femoral metaphysis (arrow) despite severe hip pain. (B). Short-tau inversion-recovery (STIR) images of MRI performed at the same day confirms the focal lesion adjacent to the growth plate (B), but also shows extensive bone marrow edema in the proximal femur (C) (arrows).

sinus tracts, features commonly seen in chronic infective osteomyelitis (Robertson and Hickling 2001). MRI has been reported to be more specific and sensitive than plain radiography or isotope bone scan also in defining the extent of spinal lesions (Martin, Desoysa et al. 1996). Recently, whole body evaluation by MRI has been used to characterize all active CNO lesions at disease onset, and to systematically evaluate radiological treatment response (Beck, Morbach et al. 2010).

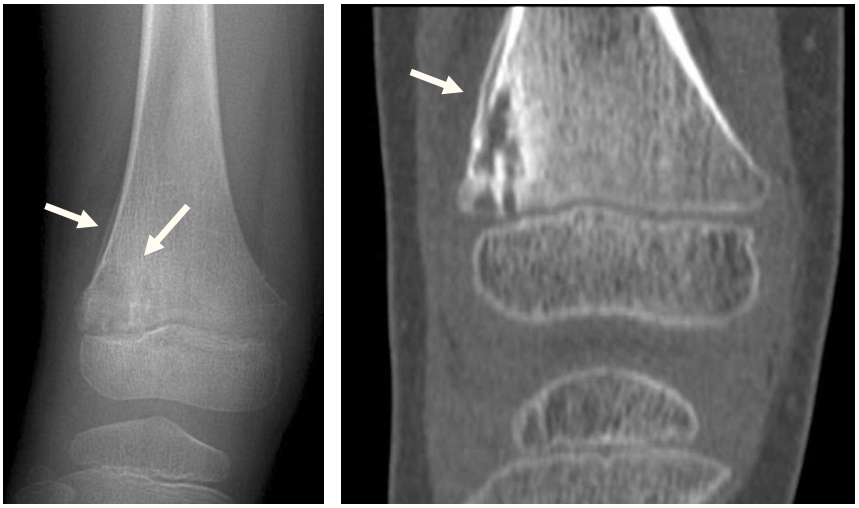
MRI can normalize relatively rapidly in inactive CRMO. From experience at this center, following initiation of bisphosphonate therapy, pelvic lesions can resolve within weeks, while vertebral and long bone lesions can persist longer and complete resolution may take 5-9 months after initiation of bisphosphonate therapy. At our center, whole-body MRI is restricted to patients with recalcitrant disease when bisphosphonates or biologic medications are contemplated, to better delineate the extent of bone involvement and to aid in deciding when to stop therapy.

4.5 Imaging appearances of specific bones affected by CNO/CRMO

4.5.1 Long bones

The most commonly affected sites in all CNO disorders involve the long bones, and the most frequent anatomic sites (two-thirds of patients) with bilateral bony changes include the distal femora or proximal tibiae (Mandell, Contreras et al. 1998). Patients present with "deep bone pain" that can be associated with palpable tenderness, bone enlargement, soft tissue erythema and swelling, and increased heat.

Radiographs reveal typically circular radiolucent lesions, periosteal elevation, and/or bone remodeling. With the older lesions abutting the joint space, localized growth abnormalities with premature epiphyseal fusion or overgrowth can be present. A peculiar finding can be a well-demarcated osteolytic lesion with a pyramidal shape, located in the metaphysis of the tubular bones adjacent to the physis (Fig. 5.) (Mortensson, Edeburn et al. 1988) . Over time, remodeling occurs and osteolytic lesions may heal completely (Giedion, Holthusen et al. 1972).



(A) (B)

Fig. 5. **Images of a 4.5-year old girl at CRMO diagnosis.** (A). Anteroposteorior radiograph of the right distal femur reveals an ill-demarcated focal pyramidal lesion in the lateral aspect of the distal right femur associated with single-layered periosteal reaction and soft-tissue edema. (B).A coronal reformat from CT images of the distal femur better delineates the bony changes.

4.5.2 Clavicle

Up to 30% of all CRMO lesions are located in the clavicle (Khanna, Sato et al. 2009). Clinically, the patients present with local swelling and pain, and may have associated restriction in the shoulder movement and thoracic outlet syndrome from nerve compression (Azouz, Jurik et al. 1998). Isolated clavicular area involvement is a well-described entity and is known as "sternocostoclavicular hyperostosis" (Azouz, Jurik et al. 1998). Clavicular hyperostosis is more common in adults, with the usual age at presentation being 30-50 years. In SAPHO syndrome, clavicular area involvement is characterized by osseous hypertrophy and soft-tissue ossification at the sternum, clavicle, and upper ribs. There seems to be a higher prevalence of clavicular disease in CRMO patients with palmoplantar pustulosis or acne fulminans (Khanna, Sato et al. 2009).

Radiographs initially reveal mixed lytic and sclerotic lesions, often with clavicular expansion that is located in the mid-portion. Periosteal reaction can be robust. Over time, the clavicle may remain sclerotic and thickened even in the absence of clinical symptoms (Giedion, Holthusen et al. 1972). In adults the disease course can be complicated by ligamentous ossification and bony bridging across the sternoclavicular joint and between the clavicle and the anterior part of the upper ribs (Azouz, Jurik et al. 1998). These changes are not seen in children. Bone scintigraphy can reveal a characteristic "bullhorn" pattern of increased uptake in the sternoclavicular region, with the sternoclavicular joints as the "horns" and the manubrium as the "head" (Sidhu, Andrews et al. 2003). MRI may not differentiate early clavicular CNO from Ewing's sarcoma, and can demonstrate robust soft tissue edema (Fig.6.).

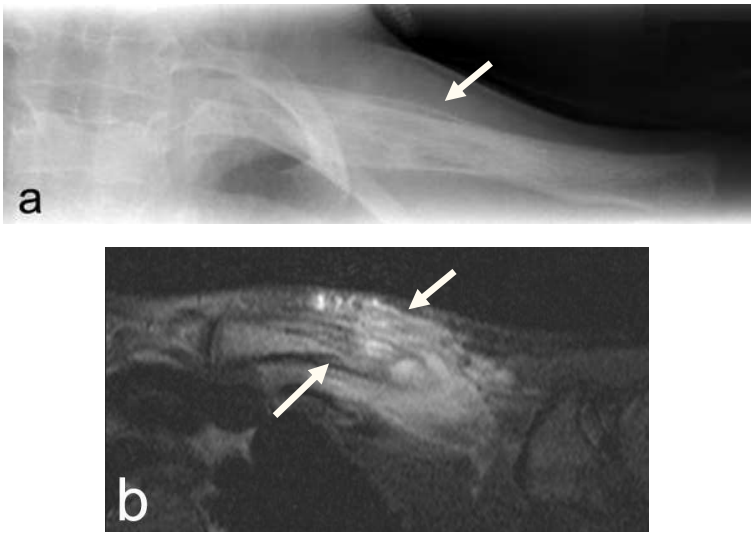
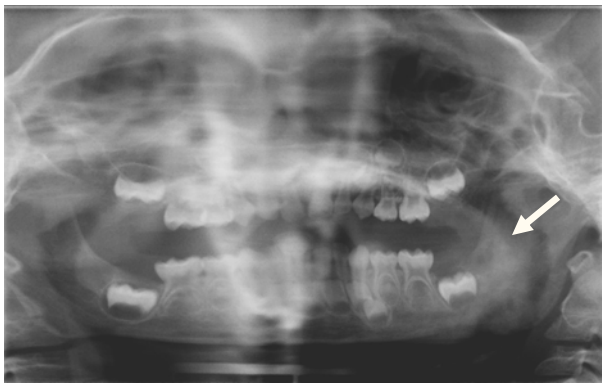


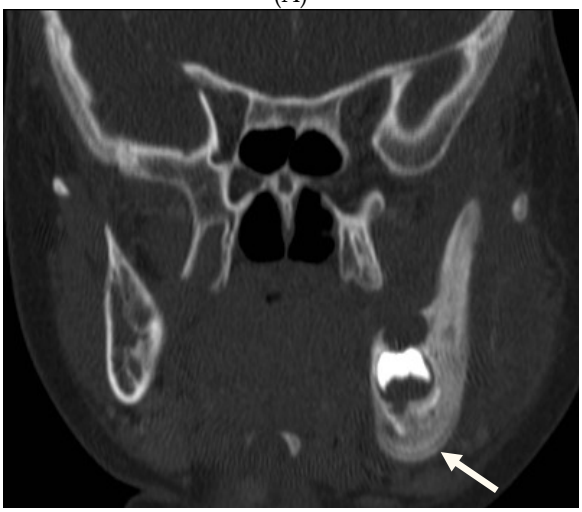
Fig. 6. **Images of CRMO lesion involving the left clavicle in a 7-year old girl.** (A). Plain radiograph of the left clavicle demonstrates periosteal new bone formation (arrow). (B). Axial (fat-saturated, T2-weighted MRI performed at the same time demonstrates hyper-intense T2 signal within the clavicle with marked soft tissue inflammation (arrows) (Miettunen, Wei et al. 2009).

4.5.3 Mandible

CRMO can involve the mandible in about 5% of cases (Khanna, Sato et al. 2009). Mandibular lesions are most often seen by dentists or oral and maxillofacial surgeons and in dental literature mandibular involvement is known by the name mandibular osteitis or diffuse sclerosing osteomyelitis (Suei, Tanimoto et al. 1995). Patients experience recurrent pain and swelling typically in one half of the mandible. Trismus and paresthesia can develop. Occasionally progression of the disease leads to involvement of the temporomandibular joint or temporal bone. Mandibular CNO can be difficult to treat, and the cosmetic deformity can be distressing to the patient (Fig. 7).



(A)



(B)

Fig. 7. **Imaging data of CNO lesion involving the left mandible in a 4-year old girl.** (A). Panorex of the mandible shows sclerosis and enlargement of the left mandibular angle and ramus (arrows). A few small focal lucencies are seen with the lesion. (B). A coronal reformat image of non-contrast CT scan confirm the findings on plain X-ray with additional finding of periosteal reaction (arrows).

Radiographs are commonly normal at disease onset. Early findings are discrete, thin zones of increased density parallel to the lower border of the mandible. Later, the radiographic appearance is characterized by mixed sclerotic and lytic lesions or by diffuse sclerosis (Soubrier, Dubost et al. 2001). At times local cortical bone deficit at the mandibular angle and/or shortening of roots are present. Radionucleide imaging can be helpful in early lesions, as the uptake of ^{99m}Tc is extremely intense, even if the radiographs are still normal. CT scan shows unilateral enlargement of the mandible, with thickening of cortical and trabecular bone. Subperiosteal bone formation and endosteal sclerosis are typically present (Van Merkesteyn, Groot et al. 1988).

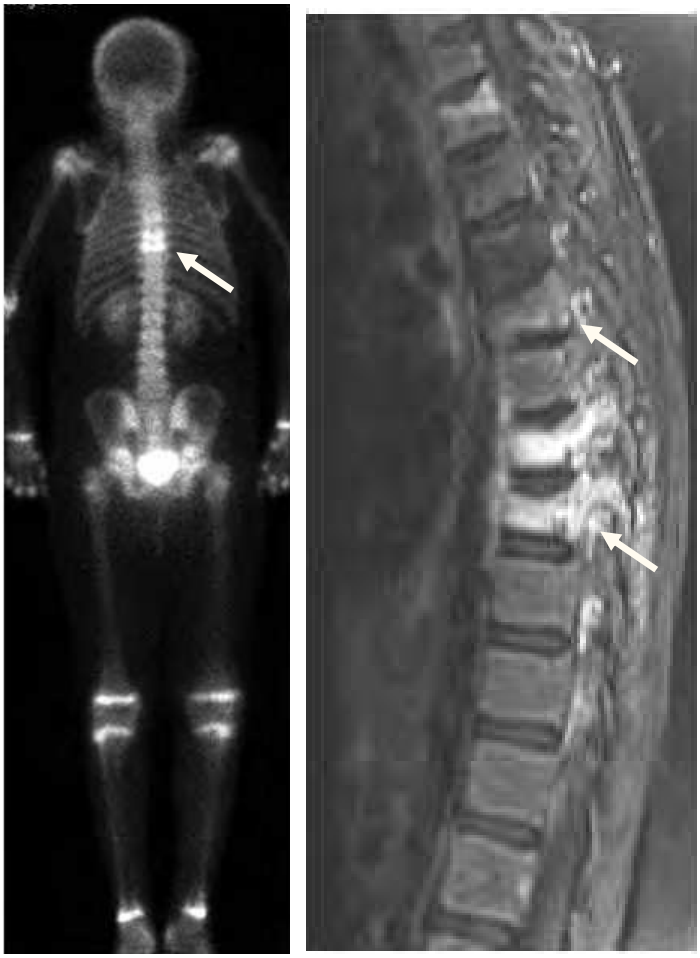
4.5.4 Spine

Initial presentation with primary spinal involvement has been reported to occur in only about 3% of patients with classic CRMO (Anderson, Heini et al. 2003), but vertebral lesions accompany other bone lesions in up to 24% of CNO patients at initial presentation (Jansson and Grote 2011). Typically patients complain of localized back pain, but can also present with anterior chest pain from referred pain. Up to 40% may develop vertebral crush fractures (Jansson and Grote 2011).

Radiographs may demonstrate vertebral erosion, osteolytic lesions with "square outline" within the vertebral bodies, sclerosis and mild collapse with reduction of disc space (Mortensson, Edeburn et al. 1988; Kayani, Syed et al. 2004). Complete vertebral collapse (vertebra plana) is more rare (Schilling 2002). All vertebrae from the mid-cervical spine to the sacrum can be potentially affected. A characteristic MRI finding is a subchondral endplate fracture-like line associated with increase in signal in the vertebral marrow (Anderson, Heini et al. 2003). Multifocal disease is common, with spontaneous healing and new lesions presenting over a period of years. MRI is particularly useful in determining the activity of lesions, as healed lesions have abnormal contour but normal marrow, or show fatty replacement of normal red marrow (Fig. 8.). Spinal CNO can initially be confused with pyogenic vertebral osteomyelitis. However, unlike pyogenic vertebral osteomyelitis, CNO involving the vertebrae is not associated with involvement of the intervertebral disc, and typically several vertebral bodies are involved at different levels with one or several normal intervening vertebrae.

4.5.5 Pelvis

CNO of the pelvic bones can be difficult to diagnose, and its incidence is not known. It typically presents as insidious onset of deep pain localized to sacroiliac or other pelvic bone areas. The preferred sites in the pelvis include the metaphyseal equivalents—such as the ischiopubic synchondrosis and the sacroiliac joints. Initial radiographs may be normal. MR imaging shows edema in active lesions and occasionally demonstrates associated soft-tissue inflammation. Additionally, lytic lesions or sclerosis of the iliac wings can be present (Fig.9.). CRMO of the pelvic synchondrosis tends to heal without sequalae (Khanna, Sato et al. 2009). Sacroiliac joints should be assessed carefully for asymmetry, as patients with CRMO may evolve into a spondyloarthropathy with unilateral or less commonly, bilateral sacroiliitis.



(A) (B)

Fig. 8. **Imaging data of a 13-year old boy with CRMO involving multiple vertebrae.** (A). ^{99m} Tc Bone Scan demonstrates increased uptake in several thoracic vertebrae (arrow). (B). MRI with gadolinium demonstrates abnormal enhancement in several vertebrae consistent with inflammation along with vertebral collapse (arrows).

4.5.6 Hands and feet

CRMO is more common in the small bones of the feet than those in the hands. Typical sites of involvement in the feet include tarsal bones such as the calcaneous and talus, which are metaphyseal equivalents, or the metatarsals and phalanges which are short tubular bones. The radiographic findings are similar to those in other sites of the disease with lytic lesions with surrounding sclerosis, periosteal reaction and soft tissue swelling. Patients may develop localized growth abnormalities as a result of premature physeal closure with metatarsal and phalangeal involvement (Khanna, Sato et al. 2009).

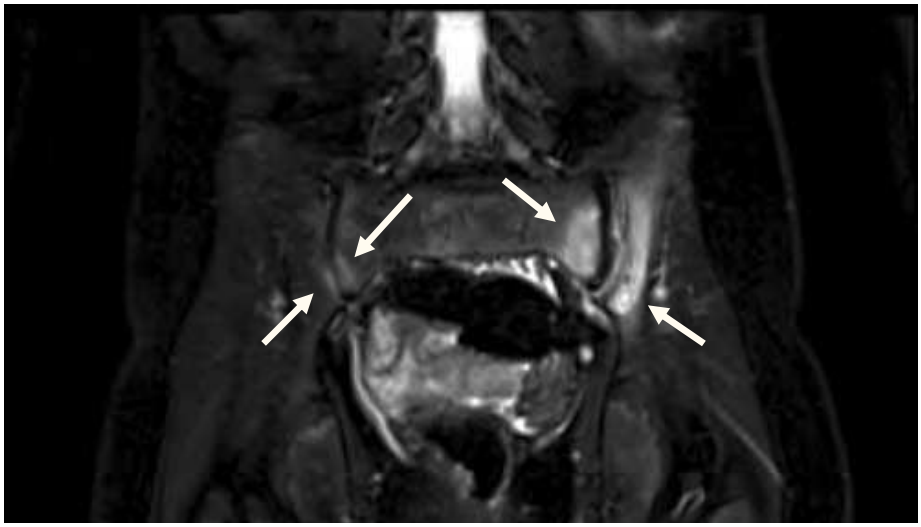


Fig. 9. **Pelvic MRI of a 6-year old girl with multisite CRMO.** On T2-weighed images with fat saturation, there are bilateral increased T2 signal intensities involving the periarticular region of the sacroiliac joints as well as the iliac bones mainly noted on the left side (arrows).

5. Differential diagnosis and related disorders

The differential diagnosis of CNO disorders includes other diseases that produce either bone swelling or osteolysis. Bone swelling is produced by Caffey's disease (infantile cortical hyperostosis), Camurati-Engelmann disease (progressive diaphyseal dysplasia), mono-ostotic Paget's disease, and fibrous dysplasia (Kaftori, Kleinhaus et al. 1987). By virtue of the combination of expansile, destructive, or regenerative bony changes, CNO can produce radiologic changes simulating neoplasia, such as osteoid osteoma, Ewing's sarcoma, osteosarcoma, osteoblastoma, leukemia, non-Hodgins lymphoma, Langerhans histiocytosis, and metastasis. Their diagnosis requires bone biopsy. Finally, it should be emphasized that even though chronic inflammation constitutes the common histopathologic change in both CNO and infectious osteomyelitis, CNO is not associated with abscess formation, fistula, or sequestra (*Table 3*).

6. Treatment

The treatment of CNO remains empiric due to the lack of controlled studies. Because there are no generally accepted treatment protocols available, the treatment approach depends on the severity of pain, location of bone lesions, and the perceived risk for long term complications if the inflammation is not controlled.

While in the past, treatment used to focus on symptom control, the availability of MR imaging to detect active and remitted lesions has made it clear that some CNO lesions truly remit while others remain persistently active. Thus the treatment focus is shifting to achieving clinical and radiologic remission (Beck, Morbach et al. 2010). These new goals have generated an interest in the development of outcome measures tools for CNO

Variable	Chronic non-bacterial osteitis	Bacterial Osteomyelitis
Clinical features		
Bone pain +/- localized soft tissue swelling	+++	+++
Unifocal bone involvement	+	+++
Multifocal bone involvement	+++	<4%
Recurrent symptoms	+++	-
Systemic features		
Fever	+	+++
Arthritis adjacent to affected bone	+	+
Skin disease (psoriasis, etc)	≤10%	-
Inflammatory bowel disease	≤10%	-
Laboratory investigations		
Elevated ESR and CRP	+	+++
Elevated white blood cells	+	+++
Blood culture reveals organism	-	+++
Culture of bone biopsy reveals organism	-	+++
Imaging		
Radiographs Periosteal elevation, osteolysis, sclerosis	+++	+++
^{99m}Technetium-phosphate bone scan Increased uptake at affected areas	+++	+++
Magnetic Resonance Imaging (MRI)		
Abscess, fistula or sequestra	-	+
Contiguous vertebral body involvement with intervening disc involvement	-	+
Treatment response		
Nonsteroidal anti-inflammatory agents	50-70% response	-
Antibiotics	-	+++ (Practical pearl: CRP is expected to decrease by approximately one half each day following successful antibiotic therapy)

- = Typically not present
+ = low-grade to moderate, but exact incidence is not known
+++ = high grade, present in > 50% of cases
ESR = erythrocyte sedimentation rate, CRP = C-reactive protein

Table 3. Description of similarities and differences between chronic non-bacterial osteitis and bacterial osteomyelitis.

disorders. One ongoing prospective study, which follows newly diagnosed patients with CNO with serial MRIs at predetermined points over 5 years (Beck, Morbach et al. 2010), has utilized a novel scoring system for assessing CNO activity and severity. It comprises of newly defined pediatric CNO core set (PedCNO), laboratory analysis, and sequential whole-body MRI. This study aims to capture the clinical and radiological treatment response over time in patients who are treated with the currently acceptable sequence of medications, namely initially with naproxen, and in recalcitrant cases with a short course of oral steroids and addition of sulfasalazine as a disease modifying anti-rheumatic drug. The preliminary results of the study after 1 year are presented below in the section on non-steroidal anti-inflammatory agents. The ultimate results of this study will be important in helping identify poor prognostic indicators at disease presentation for more persistent disease.

The suggested scoring system by Beck *et al* is comprehensive, and we recommend its use in clinical practice, although it may need to be modified as new knowledge about pathogenesis of CNO becomes available. The five items that comprise the CNO core set are presented in *Table 4*. The definition of improvement is analyzed as follows: for the PedCNO30 (PedCNO50, PedCNO70) score, at least 30% (50%, 70%) improvement in at least three out of five core set variables, with no more than one of the remaining variables deteriorating by more than 30% is required. The current short-coming of the proposed core set reflects the lack of specific laboratory markers in CNO, and therefore the inclusion of ESR in the core-set may not reflect true disease activity in CNO. From this author's point of view, it is essential to include MRI evaluation at least in clinical trials, as it can be difficult or impossible to assess disease activity on radiographs or bone scintigraphy, which do not differentiate between an active inflammatory bone lesion and chronic damage from previously active lesions.

Item
Erythrocyte sedimentation rate (ESR)
Number of radiological lesions
Severity of disease estimated by the physician on 10-cm visual analogue scale (VAS), "0" = no disease activity, "10" = the most severe activity possible
Severity of disease estimated by the patient or parent on 10-cm VAS
Childhood health assessment questionnaire (CHAQ)[α]

[α]CHAQ is the most widely used functional status measure in pediatric rheumatology

Table 4. PedCNO (pediatric chronic non-bacterial osteomyelitis) core set (Beck, Morbach et al. 2010).

6.1 Traditional medications

6.1.1 Non-Steroidal Anti-Inflammatory Agents (NSAIDs)

NSAIDs currently are the first choice for the treatment of initial CNO episodes and relapses. The most common NSAID is naproxen (10-15 mg/kg/day in 2 divided doses), which has been reported to be effective in up to 70% of patients regarding symptom control (Schultz, Holterhus et al. 1999). However, there are new emerging data that suggest that NSAIDs rarely induce true remission in CNO. The data from a recent prospectively followed cohort of 37

children with CNO indicate that naproxen induces a clinically asymptomatic state in 43% of patients after 6 months, and in 51% at 12 months. However, the corresponding percentages for radiologic resolution using serial WB MRIs were much lower, at 14% at 6 months and 27% at 12 months (Beck, Morbach et al. 2010). New lesions occurred in 41% of patients during the first year despite anti-inflammatory treatment. The authors concluded that NSAIDs were not able to reach remission (radiologically defined) in the majority of patients during/after 1 year.

6.1.2 Corticosteroids

Corticosteroids have been used with variable success. Currently, corticosteroids are recommended as "bridging" therapy only when NSAIDs have failed, and use of disease modifying drugs is initiated. One recommended schedule consists of oral glucocorticoids for 1 week at 2 mg prednisone/kg/day, followed by discontinuation stepwise by 25% every 5 days (Girschick, Zimmer et al. 2007). Intravenous methylprednisolone pulses have been reported to be effective in selected refractory cases but no uniform treatment protocol exists (Holden and David 2005).

6.1.3 Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Methotrexate, sulfasalazine (20 mg/kg/day), colchicine, etc. have been tried with varying success in recalcitrant CNO. Traditionally DMARDs have been reserved for patients with frequent relapses or if NSAIDs must be discontinued because of ineffectiveness or side effects (Girschick, Zimmer et al. 2007). However, because of the recent evidence that NSAIDs fail to induce radiologic remission in the majority of the patients, use of DMARDs may increase as information becomes available regarding risk factors for non-response to NSAID therapy. The only currently known indicator for resistance to NSAID therapy includes multifocal lesions at presentation (Catalano-Pons, Comte et al. 2008). Beck *et al* have suggested that NSAIDs be augmented by DMARDs already at diagnosis for such patients (Beck, Morbach et al. 2010). However, no recommendations exist which DMARD would be the most beneficial.

6.2 Novel treatment modalities

6.2.1 Bisphosphonates

Bisphosphonates are anti-osteoclastic agents and their beneficial effect in CNO/CRMO is postulated to be secondary to their ability to inhibit bone resorption, to have pain modifying effect, and to suppress proinflammatory cytokines, such as TNF-α, interleukin (IL)-6, and IL-1(Miettunen, Wei et al. 2009). They are usually recommended if the above treatment approaches with NSAIDs, bridging treatment with oral corticosteroids, and addition of DMARD(s) are not successful. Pamidronate is the most commonly used bisphosphonate in pediatric CNO patients, although some patients have also received alendronate (Eleftheriou, Gerschman et al. 2010).

6.2.1.1 Bisphosphonate treatment protocol

The total number of patients treated with bisphosphonates remains small worldwide, and no generally accepted treatment protocols are available. At our center, we have treated 12 pediatric patients with pamidronate with excellent clinical and radiological response. Our pre-pamidronate work-up and suggested monitoring during treatment are presented in

Table 5. We do not use bisphosphonates if the spine z-score is above "0" because of the potential for making bones less flexible with risk for secondary fractures. Renal investigations are performed because of the potential nephrotoxicity of bisphosphonates.

Base line Investigation/monitoring	During follow-up
Radiological	
MRI[α] of the affected lesion	One month after pamidronate is completed, and then at time of suspected flare
DEXA[β] scan for bone density	Annually during pamidronate treatment, and before re-treatment is considered
Renal ultrasound	No, unless clinically indicated
Laboratory	
Bone specific markers	
uNTX/uCr[µ] ratio (spot urine, using the 2nd void sample of the morning), serum alkaline phosphatase	On day 3 of the 1st treatment, preceding each treatment, and at time of suspected flare
Other laboratory investigations	
ESR[¤], CRP[§], complete blood count	At monthly intervals during pamidronate treatment
Serum calcium	Preceding each treatment, and at time of completion of each infusion
Other suggested monitoring	
PedCNO[∞] core set	At monthly intervals during pamidronate treatment, and at time of suspected flare
Screening for extra-skeletal manifestations: *palmoplantar pustulosis, psoriasis, or inflammatory bowel disease*	At each follow-up visit
Dental examination	Yearly during pamidronate treatment

[α] MRI= magnetic resonance imaging; [β]DEXA = dual-energy X-ray absorptiometry; [µ]uNTX/uCr = urinary N-telopeptide/urinary creatinine; [¤]ESR = erythrocyte sedimentation rate; [§]CRP= C-reactive protein ; [∞] PedCNO core set = pediatric chronic non-bacterial osteomyelitis core set

Table 5. Pre-pamidronate workup, and investigations/monitoring during pamidronate treatment

A specific treatment protocol, presented in *Table 6*, is in use at our center, but it needs to be emphasized that these guidelines have not been validated in clinical trials. Because "the minimally effective dose" of pamidronate is not known, and because of potential associated side effects, our current treatment protocol is aimed to ameliorate pain, to improve radiologic lesions, and to have the ability to re-treat if the patient relapses. For the initial course of pamidronate, if there is complete pain resolution after 4 months of treatment, no

Medication	Subsequent doses	Suggested duration of treatment
Pamidronate		
Initial 3-day cycle: Day 1: 0.5mg/kg/day (up to 30mg/day) Days 2-3:1mg/kg/day (up to 60mg/day)	*1-day infusion monthly:* 1mg/kg/day (up to 60mg/day)	Initially 4 months, then re-assess
Calcium	500-1000 mg of elemental calcium/day	During pamidronate treatment
Vitamin D	400-800 international units/day	During pamidronate treatment

Table 6. Suggested pamidronate treatment protocol

further pamidronate is given. In case of whole-body MRI confirmed CNO flare, those patients with only single active lesion receive one day pamidronate treatment only, and patients with ≥ 2 lesions receive once monthly 1-day pamidronate. All patients are re-imaged with whole body MRI after 3 months to determine potential need for further treatment. The total yearly dose of pamidronate is limited to ≤ 9mg/kg/year. If the spine z-score improves to above "0" during follow-up, we do not give further pamidronate.

6.2.1.2 Side effects associated with bisphosphonates

Approximately 30-60% of patients may develop fever, myalgia, and bone pain, which occur with the first infusion only. These are felt to reflect the standard acute phase response with bisphosphonate therapy, and the symptoms respond to regular Tylenol and resolve within 12-48 hours (Miettunen, Wei et al. 2009). Some patients may develop acute phlebitis within 12-24 hours at the intravenous cannula site, and this can mimic acute infection. Serum calcium is measured just preceding each infusion, and one hour after completion of infusion to monitor for possible bisphosphonate induced hypocalcemia.

Patients are counseled regarding the potential long term side effects involved in the use of bisphosponates, including the theoretical risk for fetal bone formation in future pregnancies, and the potential for jaw necrosis. Although there have been no pediatric cases of jaw necrosis, we recommend no elective dental extractions or braces during pamidronate treatment, and preferably during 18-months following the final pamidronate treatment. All patients undergo a dental examination prior to starting bisphosphonates, and at 6-12-monthly intervals during treatment (Miettunen, Wei et al. 2009).

6.2.1.3 Expected clinical and MRI response

There are now reports in the literature confirming the efficacy of bisphosphonates in several adult patients with inflammatory osteitis (Kerrison, Davidson et al. 2004; Solau-Gervais, Soubrier et al. 2006), in pediatric and adult onset SAPHO syndrome (Compeyrot-Lacassagne, Rosenberg et al. 2007), in pediatric patients with chronic inflammatory lesions of the mandible (Gleeson, Wiltshire et al. 2008; Simm, Allen et al. 2008), and in several cases of CRMO (Bjorksten and Boquist 1980). Vertebral re-modeling has been reported in

3 pediatric CRMO patients including improvement of kyphosis in one patient who presented with vertebral fractures pre-pamidronate (Gleeson, Wiltshire et al. 2008). The improvement in pain and resolution/decrease in associated soft tissue swelling is expected to occur within the first week following the first 3-day pamidronate treatment. MRI documented improvement in CNO lesions lags behind the pain response, and occurs within weeks to months (Figs. 10., 11., and 12.) (Miettunen, Wei et al. 2009). By current reports, approximately 70% of CNO patients have long lasting symptom control following pamidronate. The exact rate of relapse is not known, but is reported between 30-100% (Kerrison, Davidson et al. 2004; Miettunen, Wei et al. 2009). The time to relapse has varied from 9 to 17 months following completion of the initial course of pamidronate, and most relapsed patients have responded equally well to re-treatment with pamidronate (Kerrison, Davidson et al. 2004; Compeyrot-Lacassagne, Rosenberg et al. 2007; Miettunen, Wei et al. 2009). However, pamidronate has not been uniformly effective in all patients, or in all CNO lesions in individual patients (Gleeson, Wiltshire et al. 2008; Eleftheriou, Gerschman et al. 2010).

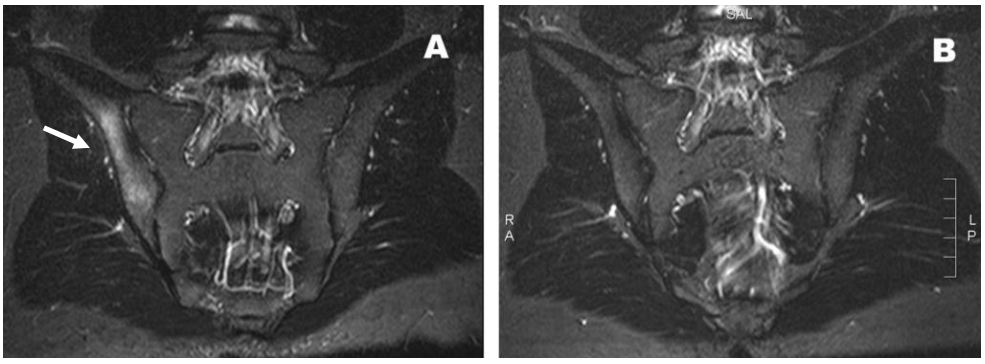


Fig. 10. (A). Pre-pamidronate treatment (MRI) with gadolinium demonstrates enhancement consistent with inflammation in the right sacroiliac area. (B). Post treatment MRI with Gadolinium 6 weeks after first treatment with pamidronate: No enhancement (Miettunen, Wei et al. 2009).

6.2.1.4 Expected response of bone remodeling markers following bisphosphonates

There is only one existing report regarding bone remodeling markers in pediatric CRMO patients (Miettunen, Wei et al. 2009). At our center, we did not show generalized increase in bone resorption markers or in markers of bone formation compared to age-specific norms. Although four out of nine patients in our series had baseline uNTX/uCr values above the 75th % percentile for age, we hypothesized that this increase most likely reflected the on-set of puberty, rather than increase from CRMO related osteolysis.

All patients had an expected decrease in uNTX/uCr following pamidronate, and interestingly no patient relapsed while his/her bone turnover remained suppressed below age and sex-specified norms (Miettunen, Wei et al. 2009) (Fig. 13). It is therefore tempting to speculate that bone and adjacent soft tissue inflammation may require functioning osteoclasts for clinical manifestations. However, further studies are required on the role of osteoclasts and on the potential use of uNTX/uCr in pediatric and adult CNO disorders.

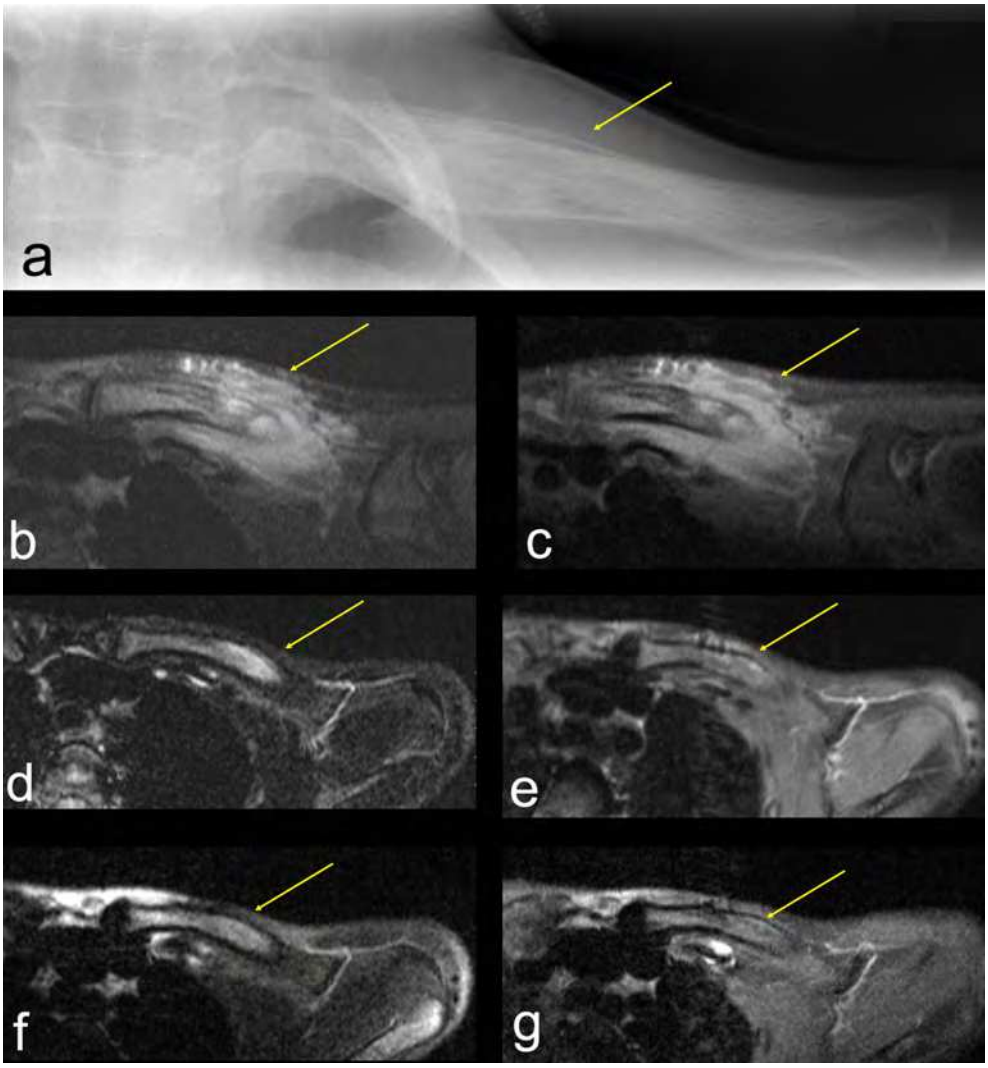


Fig. 11. **Imaging data of CRMO lesion involving left clavicle in a 7-year old girl pre- and post pamidronate treatment**. (A). Pre-treatment imaging. Radiograph of the left clavicle demonstrates periosteal new bone formation (arrow). (B –C). Pre-treatment MRI: (B) Axial (fat-saturated, T2-weighted) and (C) post gadolinium MRI: Hyper-intense T2 signal with post-contrast enhancement is seen within the clavicle (arrow) with marked soft tissue inflammation (arrow). (D-E). Post-treatment MRI (5 months after initiation of treatment with pamidronate) with the same technique as B and C, respectively. The intra-osseous abnormal signal has significantly improved, and marked soft tissue abnormality has almost completely resolved. (F-G). Post-treatment MRI (8 months after initiation of treatment with pamidronate) with the same technique as B and C, respectively, reveals complete resolution of the intra-osseous abnormal signal (Miettunen, Wei et al. 2009).

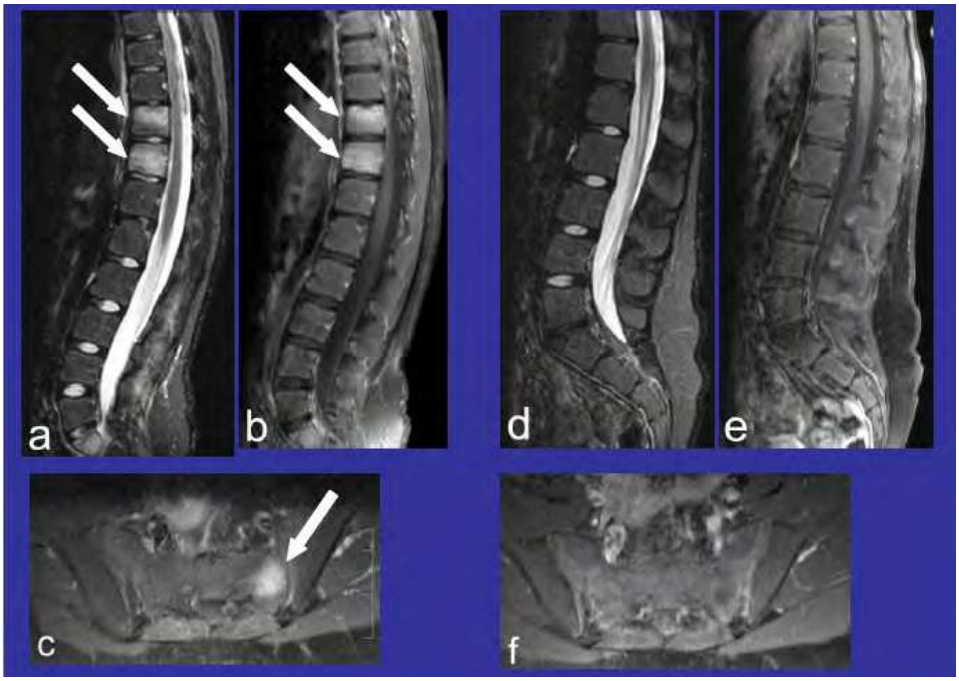


Fig. 12. **CRMO involving the spine in a 10-year old girl. (A-C)**. MR images at sagittal plane (A and B) and axial plane (C) using STIR (Short TI inversion recovery) sequence (A) and post-contrast spin-echo T1-weighted sequence (B and C) reveal abnormal signal in vertebral bodies of T10, T11, and S1 (arrows), as well as sacral ala (arrow). (**D-F)**. MR images using the same technique obtained 5-months later. Complete resolution of the previously seen abnormal signal (Miettunen, Wei et al. 2009).

6.2.1.5 Current recommendations for bisphosphonates

At the present time, we reserve the use of bisphosphonates to patients who have severe pain or functional limitation which fails to respond to traditional medications. In addition, because up to 40% of patients with vertebral CNO have associated crush fracture(s), we recommend that such patients are considered for pamidronate therapy early after diagnosis, especially if severe pain and incipient fractures are present.

6.2.2 Biologic therapy

The principle behind the use of biologic therapy in CNO is based on the observation that there is increased TNF expressed locally and systemically in CNO disorders (Eleftheriou, Gerschman et al. 2010). There are no controlled trials so far, and the results have been more encouraging in adults. Overall, TNF-alpha (TNF-α) blocking agents seem to have the most beneficial effect. TNF is a proinflammatory cytokine that has a wide range of effects, including granulocyte recruitment and activation, induction of edema, activation of coagulation, induction of granuloma formation, and activation of T and B cells (Carpenter, Jackson et al. 2004).

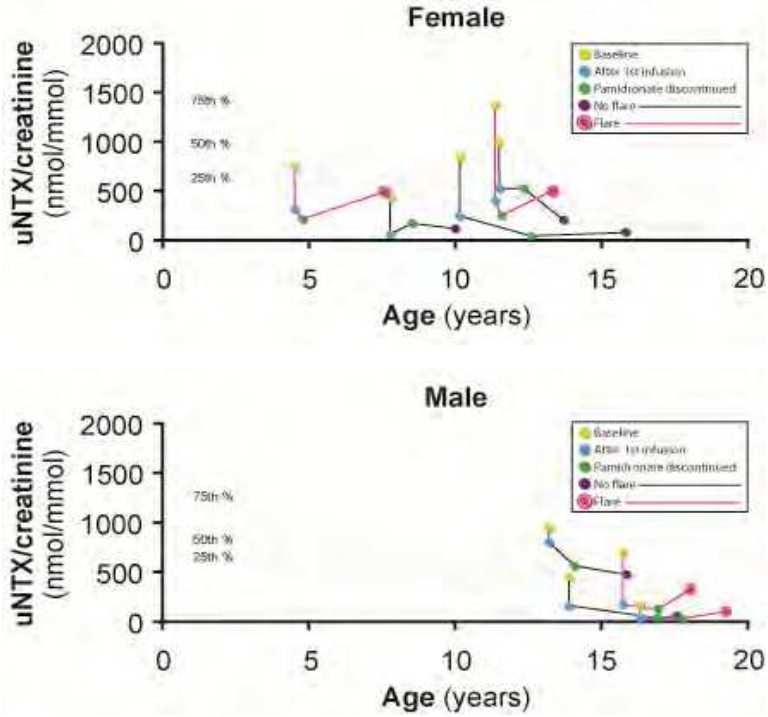


Fig. 13. **Urinary N-telopeptide/urinary creatinine ratio (uNTX/uCr) in girls (*upper panel*) and in boys (*lower panel*).** Data is shown for each individual patient prior to the first intravenous pamidronate treatment; just after the first treatment; at the time of pamidronate discontinuation; and either at the time of last follow-up for patients who did not flare or at the time of CRMO flare. Continuous lines represent the 75th (*top*), 50th (*middle*), and 25th (*bottom*) percentile, respectively, of the reference range for healthy subjects (Miettunen, Wei et al. 2009).

6.2.2.1 Biologic treatment protocol(s)

There are no specific CNO treatment protocols for biologic agents, and the dosing regimens and pre-treatment work-up have typically followed the existing ones for other inflammatory diseases, such as rheumatoid arthritis or inflammatory bowel disease. Because of the risk of re-activating tuberculosis while on biologic therapy, the minimum pre-biologic work-up includes Mantoux skin test and chest radiograph in selected cases. The reader is encouraged to follow the specific local guidelines for pre-biologic work-up, as geographic variations exist.

6.2.2.2 Side effects to biologic medications

Infections remain the most worrisome side effect from biologic therapy, and patients are encouraged to seek medical attention urgently if they developed fever, systemic symptoms, or are otherwise unwell. Autoimmune diseases, such as systemic lupus erythematosus, can rarely develop following biologic therapy. In recent years, a concern has been raised about

potential increased risk of malignancies but so far the data are inconclusive (Horneff, Foeldvari et al. 2010).

6.2.2.3 Expected clinical response

In adults, there are at least 20 patients with various CNO disorders who have experienced a beneficial effect from anti TNF-α blockers. Infliximab, a chimeric monoclonal IgG1k antibody directed against TNF-α, has resulted in clinical and at times radiologic improvement in sternal hyperostosis, clavicular osteitis, and SAPHO syndrome (Eleftheriou, Gerschman et al. 2010). Infliximab has also resulted in remission of Crohn's disease associated CRMO (Carpenter, Jackson et al. 2004). The improvement in symptoms occurred within 2 weeks in most patients, although some patients had loss of efficacy with ongoing treatment, and others experienced relapse of symptoms within 6 months after infliximab withdrawal. Only 4 pediatric patients have so far been reported in detail, and all of these patients had received adjunctive therapy that could have contributed to some of the reported efficacy. Infliximab (given at a dose of 6 mg/kg followed by infusions at weeks 2, 6 and then every 8 weeks) was partially helpful in 3 patients, although therapy was discontinued due to suspected fungal skin infection in one patient, and the remaining 2 patients required infliximab every 4 weeks because of symptom recurrence with every 8-weekly infusions (Eleftheriou, Gerschman et al. 2010). Adalimumab (a fully humanized IgG1 anti-TNF-α monoclonal antibody) was helpful in 1 pediatric SAPHO patient with sustained response to at least 15 months. Anakinra (a recombinant IL-1 receptor antagonist) resulted in good symptom control in one patient at 6 weeks, with gradual loss of treatment efficacy by 12 months with new bone lesions and psoriasis-like rash (Eleftheriou, Gerschman et al. 2010).

6.2.2.4 Current recommendations for biologic medications

The current recommendations for biologic therapy in pediatric CNO include consideration of anti-TNF therapy for recalcitrant CNO that is refractory to bisphosphonates (Eleftheriou, Gerschman et al. 2010). The role of anti-IL-1 therapy remains unclear.

6.3 Surgery

Surgical decortications of the affected bone can result in symptom relief (Carr, Cole et al. 1993). However, symptoms often recur, and repeated surgical procedures are required.

7. Course of the disease and prognosis

7.1 Natural history

CNO has a relapsing and remitting course with a variable prognosis. Although majority of patients with CNO have resolution of symptoms post-pubertally, the bone pain in active disease is severe. In addition, long-term studies reveal that up to a quarter of patients have persistent disease, with risk for poorer quality of life, and difficulty in achieving vocational goals (Huber, Lam et al. 2002). Some patients may have up to 25 years of ongoing pain, and without treatment, the episodes of pain vary between months to years. Currently, despite traditional treatment, about 7-25% of patients develop long term sequelae including growth retardation caused by premature closure of epiphyses, bone deformities, premature osteoarthritis, kyphosis, and thoracic outlet syndrome (Schultz, Holterhus et al. 1999). Up to

40% of pediatric patients with vertebral lesions develop vertebral crush fractures (Jansson and Grote 2011).

7.2 Risk factors for persisting disease

Very few studies have analyzed predictive factors for persistent evolution of CRMO. There is one existing study on long term outcome of 40 patients with childhood onset CRMO which suggests that young patients at the onset of the disease with a high number of bony sites seem to be at risk for persistent disease (Catalano-Pons, Comte et al. 2008).

7.3 Extra-bone manifestations

Between 30-80% of CNO patients develop arthritis, including seronegative spondyloarthropathy, over the years. Extra-skeletal inflammatory disorders may emerge, the most common manifestations being palmoplantar pustulosis and psoriasis (30-80% of patients), and inflammatory bowel disease (10% of patients).

8. Conclusions

Clinicians caring for children should be familiar with CNO because it typically occurs during childhood and is a diagnostic mimic of infectious osteomyelitis and malignancies. CNO should be included in the differential diagnosis of patients presenting with suspected unifocal osteomyelitis. Because other sites of bone involvement may be asymptomatic, a bone scan is recommended for patients with negative bacterial cultures of bone biopsy and poor response to antimicrobial agents. Prompt diagnosis of CNO will allow patients to avoid the risks associated with lengthy courses of antibiotic therapy and repeat bone biopsies. NSAIDs are recommended as the first-line agent; DMARDs and short courses of oral steroids are then tried; and bisphosphonates should be considered when vertebral or treatment-resistant CNO is present. Biologic treatment may be considered in selected cases. However, because of the recent discovery that persistent CNO may be more common than previously suspected (Beck, Morbach et al. 2010), the suggested treatment paradigms may well change. The focus of future research will be on the etiology of CNO, with the ultimate goal of developing therapies that can result in true remission. Validation of the proposed pediatric CNO disease activity core set is required, along with the development of tools to identify poor prognostic indicators for persistent disease.

Currently, there is no cure for CNO. Although the individual case series on effects of bisphosphonates and of biologic therapy suggest that clinical and radiologic remission is possible in selected patients with these medications, these results are uncontrolled and observational. There is now a great need for a randomized controlled trial, with participation of many centers, to help define the place of these newer treatment modalities in the management of pediatric CRMO and other CNO disorders.

9. Acknowledgment

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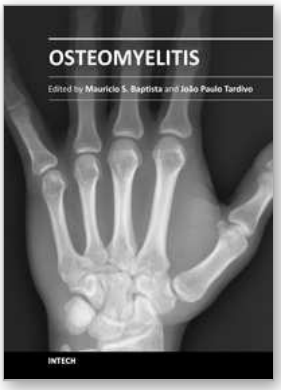

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If you want to learn more about osteomyelitis you should not miss this book. The editors are professionals and scientists working in health sciences and the chapters have been prepared by experts in the field, covering subjects related with the fundamentals of osteomyelitis and new diagnosis and treatment tools. You will have the opportunity to review concepts as well as to learn state-of-the-art alternatives for diagnosis and treatments.

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