THERAPY IN PRACTICE

# An Update on the Pathogenesis and Treatment of Chronic Recurrent Multifocal Osteomyelitis in Children

Andrea Taddio[1,2] · Floriana Zennaro[1] · Serena Pastore[1] · Rolando Cimaz[3]

**Abstract** Chronic recurrent multifocal osteomyelitis (CRMO), also known as chronic non-bacterial osteomyelitis (CNO), is a rare inflammatory disorder that primarily affects children. It is characterized by pain, local bone expansion, and radiological findings suggestive of osteomyelitis, usually at multiple sites. CRMO predominantly affects the metaphyses of long bones, but involvement of the clavicle or mandible are suggestive of the diagnosis. CRMO is a diagnosis of exclusion, and its pathogenesis remains unknown. Differential diagnosis includes infection, malignancies, benign bone tumors, metabolic disorders, and other autoinflammatory disorders. Biopsy of the bone lesion is not often required but could be necessary in unclear cases, especially for differentiation from bone neoplasia. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment. Alternative therapies have been used, including corticosteroids, methotrexate, bisphosphonates, and tumor necrosis factor (TNF)-α inhibitors. No guidelines have been established regarding diagnosis and treatment options. This manuscript gives an overview of the most recent findings on the pathogenesis of CRMO and clinical approaches for patients with the condition.

✉ Andrea Taddio
   andrea.taddio@burlo.trieste.it

1   Institute for Maternal and Child Health, IRCCS "Burlo Garofolo", via dell'Istria 65/1, 34100 Trieste, Italy

2   University of Trieste, Piazzale Europa, 1, 34100 Trieste, Italy

3   Rheumatology Unit, Anna Meyer Children's Hospital, University of Florence, Viale Pieraccini 24, 50139 Florence, Italy

---

**Key Points**

• Chronic recurrent multifocal osteomyelitis is a chronic autoinflammatory bone disease that is usually benign except for when the spine is involved.

• Therapy needs to be better defined, but non-steroidal anti-inflammatory drugs are the current first-line treatment. Bisphosphonates are a good option for patients with spine involvement, and tumor necrosis factor-α inhibitors may be useful in patients with systemic features.

---

## 1 Introduction

Autoinflammatory bone diseases include a spectrum of disorders characterized by spontaneous activation of the innate immune system that leads to bone inflammation. These diseases have attracted medical attention in recent years and have been found to be associated with other clinical features and/or with autoinflammatory syndromes [1]. The most well understood autoinflammatory bone disorder is chronic non-bacterial osteomyelitis (CNO), which is characterized by the presence of one or more aseptic osteomyelitis lesions. Some authors prefer the term chronic recurrent multifocal osteomyelitis (CRMO) [2–4] because of the presence of multiple bone lesions and the recurrent nature of the disease. The two terms may be used interchangeably.

   CRMO is a rare non-infectious inflammatory bone disease characterized by recurrent bone pain. It affects mostly

children and adolescents, with a male: female ratio of 1:4 and an average age at time of diagnosis of 10 years. This clinical entity was described for the first time in 1972 by Giedion et al. [2] as an unusual form of symmetrical, chronic multifocal osteomyelitis with bone lesions. Many clinical series have been published since then, but the disease is still considered rare, with a prevalence ranging from 1:160,000 to 1:2,000,000 and an annual incidence of 1:250,000 to 1:1,000,000. However, the prevalence of CRMO is probably underestimated; a single-center retrospective study recently suggested its incidence may be comparable with that of infectious bone osteomyelitis [5].

The main aim of this review was to provide an update on the pathogenesis of and treatment options in CRMO for pediatricians dealing with inflammatory bone disorders.

## 2 Pathogenesis and Genetics

The etiology of CRMO is still debated. It has been demonstrated that infections are not involved in disease etiology: wide microbiological analysis results were consistently negative, and the ineffectiveness of antibiotics in treating CRMO supports this hypothesis [6].

It has been suggested that imbalance between pro-inflammatory cytokines (e.g., interleukin [IL]-6, IL-1β, tumor necrosis factor [TNF]-α) and anti-inflammatory cytokines (e.g., IL-10) may be centrally involved in CRMO pathogenesis [6] because these molecules play a role in bone resorption and remodeling through the activation of osteoblast and osteoclasts. Moreover, peripheral blood mononuclear cells from patients with CRMO in active disease stimulated in vitro with lipopolysaccharide (LPS) showed a significant increase in IL-1β release compared with healthy control cells, and immunohistochemistry staining of bone tissue revealed the expression of inflammasome components in CRMO osteoclasts [7]. Similar results suggesting reduced IL-10 and IL-19 expression and enhanced IL-20 expression in CRMO monocytes have been reported [8].

The presence of chronic aseptic osteomyelitis in some syndromes characterized by inflammasome alterations, such as Majeed syndrome [1], cherubism [9], hypophosphatasia [10], and primary hypertrophic osteoarthropathy [11], have also led to suggestions that CRMO may itself be considered an autoinflammatory disease. In addition, chronic osteomyelitis is a feature of PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome, an autosomal-dominant genetic disease caused by mutations of the cluster of differentiation (CD)-2 binding protein 1 (*CD2BP1*) gene, which is involved in bone inflammatory pathways [12].

Similarly, sterile multifocal osteomyelitis, periostitis, and pustulosis are present from birth in DIRA (deficiency

of the IL-1–receptor antagonist), a rare autosomal-recessive disease resulting from mutations in the *IL1RN* gene encoding the IL-1 receptor antagonist [13].

Evidence for a genetic basis is also present in non-syndromic or sporadic CRMO [14]. In fact, the prevalence of inflammatory bone disease among patients' relatives varied between 12 and 32% in large cohorts of patients with CRMO [15], and several reports described families with multiple affected members [16] or a high incidence of psoriasis, inflammatory bowel disease, and other chronic inflammatory conditions in first-degree relatives [17]. This suggests a continuum between autoinflammation and autoimmunity. Additional evidence of a possible genetic contribution to the disease comes from studying the role of IL-10 in disease pathogenesis. One small study reported an association between CRMO and polymorphisms of the IL-10 promoter, and functional data suggest that IL-10 deregulation may play a role in disease pathogenesis [18, 19]. It was recently demonstrated that impaired mitogen-activated protein kinase (MAPK) signaling, reducing H3S10 phosphorylation and Sp1 recruitment to the IL-10 promoter, may lead to impaired gene expression, confirming a role for IL-10 [19].

Finally, homozygous mutation of the *pstpip2* gene in mice results in an autoinflammatory disease very similar to human CRMO [20, 21]. However, candidate genes, including *PSTPIP1, CARD15/NOD2*, and *IL1RN*, were not associated with CRMO in humans when analyzed in small cohorts [22, 23].

## 3 Clinical Presentation

CRMO is characterized by bone pain with insidious onset. Soft tissue swelling may accompany pain but is not necessarily always present. In about 30% of patients, adjacent joints are involved with articular effusions, synovial hypertrophy, and cartilage damage [5]. The lesions can affect any bone segment, but the more frequently reported locations include metaphyses of long bones (especially distal femur, proximal and distal tibia, and fibula), followed by pelvis, clavicle, and spine [15]. Involvement of the sternum, clavicle, or jaw is very suggestive of CRMO, whereas the skull is very rarely involved. Systemic symptoms are subtle and may include low-grade fever, malaise, or poor growth. Extra-articular manifestations include the skin (especially psoriasis, pustulosis of palms and soles, and acne) and intestines, most often Crohn's disease and less frequently ulcerative colitis [24]. In particular, 20% of patients with CRMO present with an inflammatory disease of the skin or intestines [5].

In adults, SAPHO syndrome is the combination of synovitis, acne, pustulosis of palms and soles, hyperostosis,

and osteitis and appears to be a more severe clinical picture of CRMO that occurs later in life [25].

Laboratory tests can show leukocytosis and raised inflammatory markers, but these findings are also frequently absent.

The clinical course is chronic with periods of relapse and even long periods of clinical remission. Prognosis depends on the severity of inflammation and the site of bone involvement. It has been reported that the disease can resolve completely in a median time of 7–20 years [26–29]. However, sequelae, from mild to debilitating, have been described in a considerable percentage of cases (up to 50% in some series), with the most common complications described being leg–leg discrepancy, kyphosis, vertebral collapse, growth arrest, and early closing of growth plates [5, 30].

As mentioned, CRMO may be a clinical feature of genetic autoinflammatory diseases. For instance, CRMO may be a distinctive feature of Majeed syndrome, an autosomal recessively inherited disease characterized by a more severe phenotype than CRMO. The onset of symptoms is usually in infancy or within the first 2 years of life, while chronic inflammatory osteomyelitis typically involves the small bones of the hands and feet and the metaphyses of long bones. The distinctive clinical course includes flares of bone pain and fever >38.5 °C for 3–4 days, recurring every 2–4 weeks and is associated with dyserythropoietic anemia [1].

In patients with DIRA, bone involvement includes multifocal osteolytic lesions and periosteal elevation along the metaphysis of multiple long bones. Involvement of the spine and skull has also been reported. Heterotopic ossification may occur around the hip and proximal femur. Epiphyseal ballooning of anterior ribs occurs in nearly 100% of affected infants. In these cases, the age of onset is very early, usually in the first weeks of life; disease onset is very severe, with joint swelling, a pustular rash, and pain on palpation of long bones [13].

Almost all patients with genetic forms of CRMO present with elevated inflammatory markers.

## 4 Diagnosis

No consensus exists on CRMO diagnosis, which is based on clinical, laboratory, and radiologic findings. Laboratory tests are fairly non-specific: blood count is usually normal, whereas inflammatory markers are generally only moderately increased, except for patients with associated systemic features such as fever [5].

### 4.1 Imaging Assessment

Plain X-rays are the first-line diagnostic investigation in a child with bone pain, albeit results can be normal in the early stages of disease. The first radiological findings are typically modifications in bone metaphyses, especially in close proximity to growth plates. Osteolytic and sclerotic lesions may be discovered, generally in the absence of periosteal reaction, in late stages of disease [31]. However, these findings are not mandatory, and other reports have shown radiological discontinuation of cortical bone.

Computer tomography (CT) scans usually provide better radiologic definition of bone structures. However, to limit radiation exposure, it is used only in cases where the diagnostic doubt remains very high. CT scans can also highlight the thickening of cortical bones, the areas of lysis mixed with sclerosis, and soft tissue edema (Fig. 1). All these radiological findings are very suggestive of CRMO.

The involvement of metaphyses and of multiple localizations are suggestive of CRMO. Thus, whole-body magnetic resonance imaging (MRI) is becoming increasingly important as it enables the easy identification of multiple bone lesions and inflammatory features such as soft tissue edema. It is probably more sensitive than bone scintigraphy [32]. CRMO inflammatory lesions produce an image with T1-weighted hypointensity, whereas a high signal appears in T2-weighted images [31] (Fig. 2). The lack of radiation is a further advantage of MRI over CT. MRI is also considered the best radiologic option, especially in the beginning of the disease compared with CT.

### 4.2 The Role of Biopsy

The role of bone biopsy is still debated as histologic features are non-specific; however, it plays an important role in ruling out malignancies, especially in cases with single bone lesions [31]. Histologic findings include inflammatory infiltrates comprising lymphocytes, plasma cells, histiocytes, and neutrophils. Immunohistochemistry demonstrates the predominance of CD8+ T cells (TCD8+): CD3+ , CD45RO+ , CD20+ , and CD68+ macrophages [3]. In the early phases of the disease, innate immune activation, with the presence of neutrophils, is predominant, whereas, in the later stages of the disease, monocytes, macrophages, lymphocytes, and plasma cells (as expression of adaptive immunity involvement), as well as osteolysis, sclerosis, and/or fibrosis, can be detected [33].

Given the complexity of the clinical picture, CRMO clinical diagnostic criteria have been proposed.

Jansson et al. [24] conducted a retrospective study to assess data on patients from a pediatric clinic and an orthopedic tertiary care clinic. Patients aged >3 years (n = 224) with either CRMO, proven bacterial osteomyelitis, malignant bone tumors, or benign bone tumors were identified. Univariate logistic regression was used to determine associations between single risk factors and a diagnosis of CNO, and multivariable logistic

Fig. 1 a Computed tomography of the spine. Coronal plane reconstruction. Well-defined lytic lesion of left inferior articular facet of T10 without clear signs of reactive sclerosis. The inferior articular facet of T9 appears normal. b Spine magnetic resonance imaging. Short time inversion recovery (STIR) sequence in the coronal plane. Focal area of hyperintensity of the left T9–T10 facet joint, for bone marrow edema, without thecal sac compression signs
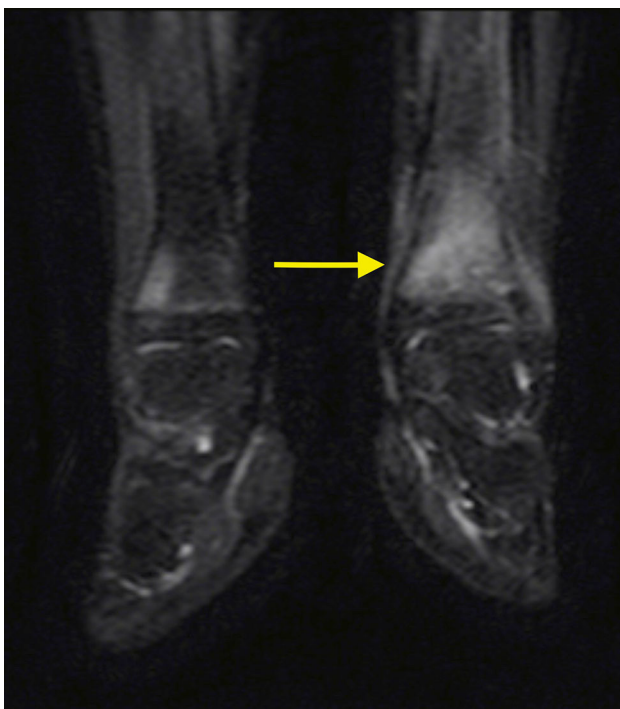


Fig. 2 Ankle section of T2-short time inversion recovery (STIR) whole-body magnetic resonance image of a patient with chronic recurrent multifocal osteomyelitis. The *arrow* shows hyperintensity of bone with edema of soft tissues. The patient presented with clinical involvement of both mandible and ankle

regression was used to assess simultaneous risk factor associations with CRMO. Based on these criteria, the diagnosis may be fulfilled if at least two major criteria, or one major plus two minor criteria, are present [24]. The major criteria are the presence of at least two bone lesions, psoriasis or palmoplantar pustulosis, radiological presence of osteolytic or sclerotic bone lesions, and sterile bone biopsy with signs of inflammation, fibrosis, and/or sclerosis. Minor criteria are normal blood count and good general state of health, only mild-to-moderate elevation of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), observation time of >6 months, hyperostosis, association with other autoimmune diseases apart from palmoplantar pustulosis or psoriasis, and the presence of grade I or II relatives with autoimmune or autoinflammatory disease or with CRMO.

Moreover, some authors have proposed a clinical score to facilitate clinical diagnosis and reduce the number of invasive procedures or unnecessary bone biopsies [34]. According to the diagnostic criteria, a score <28 indicates a CRMO diagnosis is unlikely (nominal predictive negative value of 97%), a score >29 and <38 indicates a possible diagnosis of CRMO (possibility of CRMO about 80%), and a score of >39 indicates a very likely diagnosis of CRMO (nominal predictive positive value of 97%). It is important to highlight that this score is neither validated nor commonly used in clinical practice; however, the score suggests that a positive clinical diagnosis of CMRO may be made in the absence of biopsy.

Biomarkers for CRMO diagnosis and its follow-up have been recently proposed; IL-12, monocyte chemoattractant protein (MCP)-1, and soluble IL (sIL)-2R seem to act as markers for treatment response. However, these results need to be confirmed in larger cohorts of patients [35].

## 5 Treatment

No consensus or guidelines exist on the treatment of CRMO, and most evidence comes from small case series or retrospective cohorts. To our knowledge, no randomized controlled trials relating to CRMO treatments have been published or are currently enrolling. Table 1 summarizes the most common treatment options. In the following, we provide more detail on the drugs used most often in CRMO treatment.

## 5.1 Non-Steroidal Anti-Inflammatory Drugs

NSAIDs are considered the first-line treatment, with good responses reported in small case series [36], albeit clinical remission is not always achieved. The main role of this treatment is pain control, but NSAIDs may also prevent bone damage as they are involved in prostaglandin control [33]. Studies have demonstrated that the rate of clinical remission with NSAIDs is very wide ranging, from 27 [37] to 80% [15, 30]. Their mechanism of action mostly relates to an anti-inflammatory effect on bone; however, which NSAIDs should be considered the best treatment option is unclear, and most NSAIDs are used interchangeably.

The NSAIDs most commonly used in CRMO are ibuprofen, diclofenac [38], indomethacin [39], and naproxen; however, naproxen is the only NSAID to have been evaluated prospectively. A study in 37 patients with CRMO found that 43% of patients experienced a good response at 1 year of follow-up; improvement was demonstrated clinically as well as radiologically, and quality of life also improved [40].

As the action of NSAIDs starts after at least 4 weeks of therapy, it is important to maintain the treatment for at least 1 month before declaring a failure [38].

## 5.2 Corticosteroids

Corticosteroids are the most effective anti-inflammatory drugs; their effects are mediated either by direct binding of the glucocorticoid/glucocorticoid receptor complex to glucocorticoid-responsive elements in the promoter region of genes or by an interaction between this complex and other transcription factors, particularly activating protein-1 or nuclear factor (NF)-κB. These drugs inhibit many inflammation-associated molecules such as cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules [41].

Oral corticosteroids have been proposed for patients with CRMO who do not respond to NSAIDs and as a first-line treatment choice with a very good response rate [42]. The most commonly used corticosteroid preparation is prednisolone.

## 5.3 Sulfasalazine and Methotrexate

Sulfasalazine is usually used in patients with associated inflammatory bowel disease; however, no reports indicate it works better than do NSAIDs.

**Table 1** Most common treatment options for chronic recurrent multifocal osteomyelitis

| Treatment options | Dosage | Length of treatment[a] |
|---|---|---|
| First-line treatments | | |
| NSAIDs | | |
|   Ibuprofen | 30–40 mg/kg/day in 3–4 divided doses | 1–3 months |
|   Indometacin | 1–2 mg/kg twice daily | 1–3 months |
|   Naproxen | 5–7.5 mg/kg twice daily | 1–3 months |
|   Diclofenac | 2–3 mg/kg in 3 divided doses | 1–3 months |
| Corticosteroids | | |
|   Prednisolone | 1–2 mg/kg once daily | 15–30 days then tapering |
| Second-line treatment | | |
|  Sulfasalazine | 10–15 mg/kg 4 times daily | 1–3 months |
|  Methotrexate | 15–20 mg/m$^2$ once weekly sc | 6 months |
| Bisphosphonates | | |
|   Pamidronate | 1–3 mg/kg/day for 3 consecutive days every 3 months[b] | 9 months |
| | or | |
| | 1 mg/kg/day for 1 day every month | 6 months |
| Anti-TNFα | | |
|   Infliximab | 5 mg/kg/dose. Infusions at time 0, 2, and 6 weeks then every 8 weeks | 12 months |
|   Etanercept | 0.8 mg/kg/dose/week | 6 months |
|   Adalimumab | 24 mg/m$^2$ every 2 weeks | 6 months |

*NSAIDs* non-steroidal anti-inflammatory drugs, *sc* subcutaneous, *TNF* tumour necrosis factor

[a] Length of treatment is intended as the minimum time to treat patients, but therapy can be prolonged according to clinical status

[b] First infusion 0.5 mg/kg

Methotrexate is a well-known treatment in rheumatologic conditions, especially in juvenile idiopathic arthritis. It inhibits purine and pyrimidine synthesis, accounting for its efficacy in cancer therapy, but many studies have also focused on the adenosine-mediated anti-inflammatory effects of methotrexate.

Methotrexate has been used in CRMO but does not seem to be very effective in this clinical setting [43]. In a cohort of 70 children with CRMO [44], only 20% of patients treated with methotrexate experienced clinical remission.

Bisphosphonates and/or TNF-α inhibitors have been used with variable effects in patients who did not respond to first-line treatment.

### 5.4 Bisphosphonates

Although how bisphosphonates exert their anti-inflammatory effect is unclear, it has been suggested that they may modify the release of proinflammatory cytokines acting on local effector cells, such as resident macrophages, osteoclasts, and fibroblasts [45].

Bisphosphonates have been used in CRMO since 2001 with good clinical effects and durable responses [46]. Simm et al. [47] and Miettunen et al. [48] treated five and nine patients with CRMO, respectively, with bisphosphonate infusions and reported a decrease in pain, symptomatic improvements, and radiologic improvement in bone lesions. Although which subsets of patients could benefit more from treatment with bisphosphonates remains unclear, studies suggest they are more effective in patients with multifocal lesions [15], spinal involvement [49], and—interestingly—mandible involvement [50].

Pamidronate is the most used bisphosphonate, but neridronate has also been demonstrated to be effective [51]. A randomized trial on the use of pamidronate in patients with CRMO is ongoing (ClinicalTrials.gov identifier: NCT02594878), but results are not yet available.

We share the opinions of Stern and Ferguson [4], De Cunto et al. [51], and Hedrich et al. [33] that bisphosphonates should be used in patients when NSAIDs and corticosteroids have failed and no systemic feature is present and possibly as first-line treatment in patients with spinal involvement [52].

### 5.5 Tumor Necrosis Factor Inhibition

TNF-α is considered a key protein in inflammation, and many treatments for autoinflammatory and autoimmune disorders use TNF-α inhibition. Moreover, TNF has been implicated in pathological bone resorption, activating osteoblasts and tissue stromal cells to express the receptor activator of NF-kB (RANK) ligand (RANKL). In addition, TNF can act directly on osteoclast precursors, often in synergy with RANKL, to promote osteoclastogenesis [53].

TNF-α inhibitors have been used in patients with CRMO. Infliximab was the first biologic used [54], but etanercept and adalimumab have also been demonstrated to be effective [55, 56]. They have primarily been used in and benefitted [15] the roughly <10% of patients who did not achieve clinical remission with previous treatment. In our opinion, TNF-α inhibitors should be considered when bisphosphonates fail or as an alternative when systemic features (e.g., fever) are present.

### 5.6 Anti-Interleukin-1 Beta

Given that CRMO is considered an autoinflammatory disease, some authors suggest that IL-1 inhibition could be a useful therapeutic approach [57]; however, no evidence of their efficacy in CRMO has yet been found, except in patients with inflammatory osteitis secondary to autoinflammatory syndromes.

## 6 Conclusion

CRMO is not completely understood but probably belongs to the family of autoinflammatory diseases. No diagnostic criteria have been defined, and diagnosis remains one of exclusion, sometimes requiring a biopsy. The prognosis is usually benign, although spine involvement can cause kyphosis or scoliosis, leading to chronic deformities. Studies are needed to improve understanding of the role of possible biomarkers in disease prognosis and to assist clinicians in choosing the best treatment options. NSAIDs remain the first-line treatment option for most patients, followed most frequently by TNF-α inhibitors and bisphosphonates as second-line treatments. Given CRMO is thought to be an autoinflammatory disease, IL-1 inhibition can also be considered a valid treatment option.

## References

1. Majeed HA, Kalaawi M, Mohanty D, Teebi AS, Tunjekar MF, Al-Gharbawy F, et al. Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet syndrome in two siblings. J Pediatr. 1989;115:730–4.

2. Giedion A, Holthusen W, Masel LF, Vischer D. Subacute and chronic "symmetrical" osteomyelitis. Ann Radiol (Paris). 1972;15:329–42.

3. Bjorksten B, Boquist L. Histopathological aspects of chronic recurrent multifocal osteomyelitis. J Bone Jt Surg Br. 1980;62:376–80.

4. Stern SM, Ferguson PJ. Autoinflammatory bone diseases. Rheum Dis Clin North Am. 2013;39:735–49.

5. Schnabel A, Range U, Hahn G, Siepmann T, Berner R, Hedrich CM. Unexpectedly high incidences of chronic non-bacterial as compared to bacterial osteomyelitis in children. Rheumatol Int. 2016;36:1737–45.

6. Gamble JG, Rinsky LA. Chronic recurrent multifocal osteomyelitis: a distinct clinical entity. J Pediatr Orthop. 1986;6:579–84.

7. Scianaro R, Insalaco A, Bracci Laudiero L, De Vito R, Pezzullo M, Teti A, et al. Deregulation of the IL-1β axis in chronic recurrent multifocal osteomyelitis. Pediatr Rheumatol Online J. 2014;17(12):30.

8. Hofmann SR, Kubasch AS, Ioannidis C, Rosen-Wolff A, Girschick HJ, Morbach H, et al. Altered expression of IL-10 family cytokines in monocytes from CRMO patients result in enhanced IL-1β expression and release. Clin Immunol. 2015;161:300–7.

9. Papadaki ME, Lietman SA, Levine MA, Olsen BR, Kaban LB, Reichenberge EJ. Cherubism: best clinical practice. Orphanet J Rare Dis. 2012;7(suppl 1):S6.

10. Whyte MP. Physiological role of alkaline phosphatase explored in hypophosphatasia. Ann NY Acad Sci. 2010;1192:190–200.

11. Castori M, Sinibaldi L, Mingarelli R, Lachman RS, Rimoin DL, Dallapiccola B. Pachydermoperiostosis: an update. Clin Genet. 2005;68:6477–86.

12. Smith EJ, Allantaz F, Bennett L, Zhang D, Gao X, Wood G, et al. Clinical, molecular, and genetic characteristics of PAPA syndrome: a review. Curr Genomics. 2010;11:519–27.

13. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, van Royen-Kerkhoff A, et al. N Engl J Med. 2009;360:2426–37.

14. Golla A, Jansson A, Ramser J, Hellebrand H, Zahn R, Meitinger T, et al. Chronic recurrent multifocal osteomyelitis (CRMO): evidence for a susceptibility gene located on chromosome 18q21.3-18q22. Eur J Hum Genet. 2002;10:217–21.

15. Wipff J, Costantino F, Lemelle I, Pajot C, Duquesne A, Lorrot M, et al. A large national cohort of French patients with chronic recurrent multifocal osteitis. Arthritis Rheumatol. 2015;67:1128–37.

16. Ben Becher S, Essaddam H, Nahali N, Ben Hamadi F, Mouelhi MH, Hammou A, et al. Recurrent multifocal periostosis in children. Report of a familial form. Ann Pediatr (Paris). 1991;38:345–9.

17. Bousvaros A, Marcon M, Treem W, Waters P, Issenman R, Couper R, et al. Chronic recurrent multifocal osteomyelitis associated with chronic inflammatory bowel disease in children. Dig Dis Sci. 1999;44:2500–7.

18. Hamel J, Paul D, Gahr M, Hedrich CM. Pilot study: possible association of IL10 promoter polymorphisms with CRMO. Rheumatol Int. 2012;32:555–6.

19. Hofmann SR, Morbach H, Schwarz T, Rösen-Wolff A, Girschick HJ, Hedrich CM. Attenuated TLR4/MAPK signaling in monocytes from patients with CRMO results in impaired IL-10 expression. Clin Immunol. 2012;145:69–76.

20. Ferguson PJ, Bing X, Vasef MA, Ochoa LA, Mahgoub A, Waldschmidt TJ, et al. A missense mutation in pstpip2 is associated with the murine autoinflammatory disorder chronic multifocal osteomyelitis. Bone. 2006;38:41–7.

21. Grosse J, Chitu V, Marquardt A, Hanke P, Schmittwolf C, Zeitlmann L, et al. Mutation of mouse Mayp/Pstpip2 causes a macrophage autoinflammatory disease. Blood. 2006;107:3350–8.

22. Beck C, Girschick HJ, Morbach H, Schwarz T, Yimam T, Frenkel J, et al. Mutation screening of the IL-1 receptor antagonist gene in chronic non-bacterial osteomyelitis of childhood and adolescence. Clin Exp Rheumatol. 2011;29:1040–3.

23. Huber AM, Lam PY, Duffy CM, Yeung RS, Ditchfield M, Laxer D, et al. Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up. J Pediatr. 2002;141:198–203.

24. Jansson A, Renner ED, Ramser J, Mayer A, Habad M, Meindl A, et al. Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. Rheumatology (Oxford). 2007;46:154–60.

25. Beretta-Piccoli BC, Sauvain MJ, Gal I, Schibler A, Saurenmann T, Kressebuch H, et al. Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome in childhood: a report of ten cases and review of the literature. Eur J Pediatr. 2000;159:594–601.

26. Prose NS, Fahrner LJ, Miller CR, Lay-field L. Pustulas psoriasis with chronic recurrent multifocal osteomyelitis and spontaneous fractures. J Am Acad Dermatol. 1994;31:376–9.

27. Bjorksten B, Gustavson KH, Ericksson B, Lindholm A, Nordstrom S. Chronic recurrent multifocal osteomyelitis and pustulosis palmoplantaris. J Pediatr. 1978;93:227–31.

28. Jurik AG, Helmig O, Ternowitz T, Moller BN. Chronic recurrent multifocal osteomyelitis: a follow-up study. J Pediatr Orthop. 1988;8:49–58.

29. Andersson R. Effective treatment with interferon-α in chronic recurrent multi-focal osteomyelitis. J Interferon Cytokine Res. 1995;15:837–8.

30. Catalano-Pons C. Clinical outcome in children with chronic recurrent multifocal osteomyelitis. Rheumatology (Oxford). 2008;47:1397–9.

31. Wipff J, Adamsbaum C, Kahan A, Job-Deslandre C. Chronic recurrent multifocal osteomyelitis. Jt Bone Spine. 2011;78:555–60.

32. Guérin-Pfyffer S, Guillaume-Czitrom S, Tammam S, Koné-Paut I. Evaluation of chronic recurrent multifocal osteitis in children by whole-body magnetic resonance imaging. Jt Bone Spine. 2012;79:616–20.

33. Hedrich CM, Hofmann SR, Pablik J, Morbach H, Girschick HJ. Autoinflammatory bone disorders with special focus on chronic recurrent multifocal osteomyelitis (CRMO). Pediatr Rheumatol Online J. 2013;11:47.

34. Jansson AF, Müller TH, Gliera L, Ankerst DP, Wintergest U, Belohradsky BH, et al. Clinical score for nonbacterial osteitis in children and adults. Arthritis Rheum. 2009;60:1152–9.

35. Hofmann SR, Kubasch AS, Range U, Laass MW, Morbach H, Girschick HJ, et al. Serum biomarkers for the diagnosis and monitoring of chronic recurrent multifocal osteomyelitis (CRMO). Rheumatol Int. 2016;36:769–79.

36. Handrick W, Hörmann D, Voppmann A, Schille R, Reichardt P, Tröbs RB, et al. Chronic recurrent multifocal osteomyelitis–report of eight patients. Pediatr Surg Int. 1998;14:195–8.

37. Pastore S, Ferrara G, Monasta L, Meini A, Cattalini M, Martino S, et al. Chronic nonbacterial osteomyelitis may be associated with renal disease and bisphosphonates are a good option for the majority of patients. Acta Paediatr. 2016;105:e328–33.

38. Job-Deslandre C, Krebs S, Kahan A. Chronic recurrent multifocal osteomyelitis: five-year outcomes in 14 pediatric cases. Jt Bone Spine. 2001;68:245–51.

39. Abril JC, Ramirez A. Successful of treatment of Chronic Recurrent Multifocal Osteomyelitis with indomethacin. J Ped Orthop. 2007;27:587–91.

40. Beck C, Morbach H, Beer M, Stenzel M, Tappe D, Gattenlöhner S, et al. Chronic nonbacterial osteomyelitis in childhood: prospective follow-up during the first year of anti-inflammatory treatment. Arthritis Res Ther. 2010;12:R74.

41. Van der Velden VH. Glucocorticoids: mechanism of action and anti-inflammatory potential in asthma. Mediators Inflamm. 1998;7:229–37.

42. Ishikawa-Nakayama K, Sugiyama E, Sawazaki S, Taki H, Kobayashi M, Koizumi F, et al. Chronic recurrent multifocal osteomyelitis showing marked improvement with corticosteroid treatment. J Rheumatol. 2000;27:1318–9.

43. Kaiser D, Bolt I, Hofer M, Relly C, Berthet G, Bolz D, et al. Chronic nonbacterial osteomyelitis in children: a retrospective multicenter study. Pediatr Rheumatol Online J. 2015;13:25.

44. Borzutzky A, Stern S, Reiff A, Zurakowski D, Steinberg EA, Dedeoglu F, et al. Pediatric Chronic nonbacterial osteomyelitis. Pediatrics. 2012;130:e1190–7.

45. Iannitti T, Rosini S, Lodi D, Frediani B, Rottigni V, Palmieri B. Bisphosphonates: focus on Inflammation and Bone Loss. Am J Ther. 2012;19:228–46.

46. Coinde E, David L, Cottalorda J, Allard D, Bost M, Lucht F, et al. Chronic recurrent multifocal osteomyelitis in children: report of 17 cases. Arch Pediatr. 2001;8:577–83.

47. Simm PJ, Allen RC, Zacharin MR. Bisphosphonate treatment in chronic recurrent multifocal osteomyelitis. J Pediatr. 2008;152:571–5.

48. Miettunen PM, Wei X, Kaura D, Reslan WA, Aguirre AN, Kellner JD. Dramatic pain relief and resolution of bone inflammation following pamidronate in 9 pediatric patients with persistent chronic recurrent multifocal osteomyelitis (CRMO). Pediatr Rheumatol Online J. 2009;7:2.

49. Hospach T, Langendoerfer M, von Kalle T, Maier J, Dannecker GE. Spinal involvement in chronic recurrent multifocal osteomyelitis (CRMO) in childhood and effect of pamidronate. Eur J Pediatr. 2010;169:1105–11.

50. Compeyrot-Lacassagne S, Rosenberg AM, Babyn P, Laxer RM. Pamidronate treatment of chronic noninfectious inflammatory lesions of the mandible in children. J Rheumatol. 2007;34:1585–9.

51. De Cunto A, Maschio M, Lepore L, Zennaro F. A case of chronic recurrent multifocal osteomyelitis successfully treated with neridronate. J Pediatr. 2009;154:154–5.

52. Hofmann SR, Schnabel A, Rösen-Wolff A, Morbach H, Girschick HJ, Hedrich CM. Chronic nonbacterial osteomyelitis: pathophysiological concepts and current treatment strategies. J Rheumatol. 2016;43:1956–64.

53. Zhao B, Grimes SN, Li S, Hu X, Ivashkiv LB. TNF-induced osteoclastogenesis and inflammatory bone resorption are inhibited by transcription factor RBP-J. J Exp Med. 2012;209:319–34.

54. Deutschmann A, Mache CJ, Bodo K, Zebedin D, Ring E. Successful treatment of chronic recurrent multifocal osteomyelitis with tumor necrosis factor-alpha blockage. Pediatrics. 2005;116:1231–3.

55. Eisenstein EM, Syverson GD, Vora SS, Williams CB. Combination therapy with methotrexate and etanercept for refractory chronic recurrent multifocal osteomyelitis. J Rheumatol. 2011;38:782–3.

56. Barral Mena E, Freire Gómez X, Enríquez Merayo E, Casado Picón R, Bello Gutierrez P, de Inocencio Arocena J. Non-bacterial chronic osteomyelitis: experience in a tertiary hospital. An Pediatr (Barc). 2016;85:18–25.

57. Ferguson PJ, Laxer RM. New discoveries in CRMO: IL-1$\beta$, the neutrophil, and the microbiome implicated in disease pathogenesis in Pstpip2-deficient mice. Semin Immunopathol. 2015;37:407–12.