

# Current Understanding of the Pathogenesis and Management of Chronic Recurrent Multifocal Osteomyelitis

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**Abstract** Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory disorder that primarily affects children. Its hallmark is recurring episodes of sterile osteomyelitis. The clinical presentation is insidious onset of bone pain with or without fever. Laboratory studies typically reveal nonspecific evidence of inflammation. Radiologic imaging and histologic appearance resemble those of infectious osteomyelitis. There is a strong association with inflammatory disorders of the skin and intestinal tract in affected individuals and their close relatives, suggesting a shared pathophysiology and supporting a genetic component to disease susceptibility. Two genetic syndromes have CRMO as a prominent phenotype—Majeed syndrome and deficiency of the interleukin-1 receptor antagonist—and suggest that interleukin-1 may be a key cytokine in disease pathogenesis. This review briefly summarizes the main clinical and radiologic aspects of the disease and then focuses on genetics and pathophysiology and provides an update on treatment.

**Keywords** Chronic recurrent multifocal osteomyelitis · CRMO · DIRA · Osteomyelitis · Pathogenesis · Management · Bone pain · Bone disease · Children · Chronic nonbacterial osteomyelitis · CNO · SAPHO syndrome · Vertebrae · Sweet's syndrome · Majeed syndrome · NSAIDs · Biphosphonates · Biologic agents

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## Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory bone disease that primarily affects children. Sterile bone inflammation presents with bone pain that is often worse at night. Laboratory studies may be normal or reveal only minor alterations in sedimentation rate, C-reactive protein, or complete blood count. Plain radiographs often reveal osteolytic lesions surrounded by sclerosis but may be normal early in the disease course. MRI is the most sensitive imaging modality, and whole body short tau inversion recovery (STIR) images are increasingly being utilized instead of bone scan to identify the extent of disease. Clinicians must be aware of CRMO as a diagnostic entity when evaluating a child who presents with clinical and histologic evidence of osteomyelitis, as there is often a diagnostic delay and unnecessarily prolonged treatment with antibiotics. A family or personal history of psoriasis or inflammatory bowel disease is supportive evidence that CRMO may be the underlying etiology in a child with culture-negative osteomyelitis.

## Common Clinical and Radiologic Features and Associated Disorders

Multiple names are used in the literature to describe disorders in which sterile osteomyelitis/osteitis is the primary clinical feature; these include chronic nonbacterial osteomyelitis (CNO); nonbacterial osteitis; and synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome, among others [1–3]. In the pediatric literature, the terms *CRMO* and *CNO* are often used interchangeably. In the adult literature, the term *SAPHO syndrome* is more frequently utilized. It is unclear at this time if SAPHO and CRMO/CNO are the

same disease presenting in different age groups, or if they represent different ends of a disease spectrum. For this review, the term CRMO is utilized for historical reasons.

CRMO typically presents with bone pain that is worse at night and occurs in the presence or absence of fever [1, 3–5]. The onset is typically insidious, and most children appear well. Swelling and warmth can occur overlying the affected areas, but there may be no objective findings on physical examination. One to nearly 20 sites can be involved at one time, most often the metaphyseal regions of the long bones, the clavicles, and the vertebral bodies [3, 4, 6•]. However, other sites, including the mandible, pelvis, and small bones of the hands and feet, also can be involved [3, 4, 6•]. Laboratory investigations often reveal mild elevations in white blood cell count and erythrocyte sedimentation rate (ESR), but both of these may be normal [1, 3, 4]. Tumor necrosis factor (TNF)- $\alpha$  levels may also be elevated [1, 7••]. Cultures of blood and bone are almost always negative, and sophisticated assays to identify evidence of a microbial etiology have been negative [8]. Conventional radiographs often reveal osteolytic lesions with surrounding sclerosis abutting the growth plate in the metaphyseal regions of the long bones [6•]. Clavicular lesions and mandibular lesions often have a more sclerotic appearance [6•]. Vertebral involvement can lead to collapse with subsequent vertebra plana or other deformity [4, 5, 6•]. Not all individuals have classic lesions, and the radiologic manifestations can be quite varied [6•]. The traditional approach to radiologic work-up of a child with suspected CRMO has been plain films of symptomatic areas followed by bone scan to determine the extent of disease (as lesions can be asymptomatic). However, bone scan also has limitations, as active lesions, particularly active metaphyseal lesions in the long bones, can be interpreted as normal growth plate uptake when symmetric disease is present. MRI is a more sensitive modality, avoids exposure to radiation, and allows determination of the extent of soft tissue involvement in addition to determining the degree of bone involvement [6•, 9].

Shortly after the initial description of CRMO, a strong association with other inflammatory diseases becomes apparent. Current estimates suggest that about 25% of individuals with CRMO have an associated inflammatory disorder—most often palmar plantar pustulosis [10–14], psoriasis vulgaris [14, 15], or inflammatory bowel disease (Crohn disease more so than ulcerative colitis, but also celiac disease) [1, 5, 16–22]. Other less-frequent associations include acne [1, 4], generalized pustulosis [23, 24••, 25••], Sweet syndrome [26–30], dyserythropoietic anemia [27, 31], pyoderma gangrenosum [5, 32, 33], sclerosing cholangitis [5, 20], inflammatory arthritis [1, 2, 5, 34], sacroiliac joint involvement [35], Still disease [36], Takayasu arteritis [37–39], antineutrophil cytoplasmic antibody-positive vasculitis [5, 40], Ollier disease (multiple enchondromatosis) [5], parenchymal lung disease

[41, 42], dermatomyositis (Ferguson, unpublished data), and tumoral calcinosis [43–45]. These associated inflammatory conditions are also enriched in the family members. Nearly 50% of first-degree or second-degree relatives of individuals with CRMO also have one of these associated conditions, most often some form of psoriasis or inflammatory bowel disease [1, 46], which suggests that there is a significant genetic component to disease susceptibility.

### Genetics of Chronic Recurrent Multifocal Osteomyelitis

There is a significant genetic contribution to CRMO disease susceptibility. The strongest evidence comes from the identification of two monogenic syndromic forms of CRMO (see Majeed syndrome and deficiency of the interleukin-1 receptor antagonist [DIRA] below), as well as reports of CRMO in three non-human animal models. The monogenic human forms of the disease include Majeed syndrome due to mutations in *LPIN2* and DIRA due to mutations in *IL1RN*. There are reports of CRMO in lemurs, mice, and dogs [47–51]. A gene defect causing CRMO in mice has been identified in two murine models of the disease as being due to defects in *pstpip2* [48, 49]. Canine hypertrophic osteodystrophy is a disorder with features similar to human CRMO that occurs primarily in large breed dogs, with the Weimaraner breed being particularly susceptible. Hypertrophic osteodystrophy is often triggered by vaccination and clusters in litters, suggesting a single gene defect [50–53].

There is also evidence that nonsyndromic or sporadic CRMO in humans has a genetic basis. Golla et al. [54] reported a susceptibility locus on human chromosome 18q21.3-18q22 in a small German CRMO cohort. Several reports have described families with multiple affected members or have reported a high incidence of psoriasis, inflammatory bowel disease, and other chronic inflammatory conditions in first-degree family members of individuals with CRMO [1, 46, 54–56]. Additional evidence of a possible genetic contribution to disease comes from studying the role of interleukin (IL)-10 in disease pathogenesis. In one small cohort, there was a purported association of CRMO with polymorphisms of the IL-10 promoter [7••, 57]. Another group of investigators found reduced IL-10 expression from lipopolysaccharide-stimulated CNO monocytes, impaired Sp1 recruitment, and reduced IL-10 promoter phosphorylation that occurred independent of IL-10 promoter polymorphisms [7••]. These are intriguing data that suggest that IL-10 may play a role in disease and need to be replicated. Other candidate genes, including *PSTPIP1*, *PSTPIP2*, *CARD15/NOD2*, and *IL1RN*, have been analyzed in small CRMO/CNO cohorts, and no definitive disease-causing mutations have been identified [1, 58, 59].

## Syndromic Forms of Chronic Recurrent Multifocal Osteomyelitis

### Majeed Syndrome

Majeed syndrome is an autosomal recessive disorder that presents with early-onset CRMO, dyserythropoietic anemia that often is accompanied by recurrent fever, and may be accompanied by a neutrophilic dermatosis (Sweet syndrome) [27, 31, 60, 61]. Majeed syndrome was first recognized as a clinical entity by Majeed in 1989. Since that time, there have been seven affected individuals described from three unrelated kindreds, with each family harboring a unique mutation in *LPIN2* [27, 31, 60–62]. The CRMO in Majeed syndrome tends to begin earlier (range, 3 weeks–19 months) and to be much more severe than the bone inflammation seen in non-syndromic CRMO. However, the distribution of bone lesions is similar, with the metaphyses of the long bones most commonly affected. Radiographic changes are also similar, although it is noteworthy that early on in the disease, conventional radiographs may be normal [31, 61]. Fever frequently accompanied the recurrent episodes of extremity pain and swelling, occurring in all seven children at some point in their disease course [27, 31, 60]. Several children had a periodicity to their symptoms, having episodes of fever and bone inflammation that lasted 2–4 days and recurred every 2–4 weeks [31].

Dyserythropoietic anemia was present in all affected individuals, with hemoglobins ranging from 4.0 to 10.5 g/L and mean corpuscular volume ranging from 59 to 68 fl [27, 31, 60, 61]. However, the microcytic anemia may not be present at birth [61] but was detected in all by 9 months of age [27, 31, 60]. Repeated transfusions were needed in six of seven patients [27, 31, 60]. Failure to thrive was reported in six of seven cases, and hepatomegaly was noted in all but one [27, 43, 60, 61]. Sweet syndrome ( $n=2$ ) was a presenting feature in two brothers in the original Majeed syndrome kindred but has not been described in subsequent cases [27]. Less common features included neonatal cholestatic jaundice ( $n=1$ ) and mild neutropenia ( $n=1$ ) [61]. All had marked elevations of ESR (68–127 mm/h), and one had marked elevations of serum alkaline phosphatase (three to seven times normal). One boy was observed to 21 years and ultimately developed joint flexion contractures and had marked failure to thrive (<5th% in height and weight), delayed sexual maturation, and unusual facial features with maxillary hyperplasia and frontal bossing [31].

Three unique *LPIN2* mutations have been identified in patients with Majeed syndrome: a missense mutation (S734L), a frame shift mutation (T180fs), and a splice site mutation (R776Sfs). *LPIN2* encodes LIPIN2, a member of the three-member LIPIN family. All three of the mammalian lipins act as phosphatidate phosphatase (PAP) enzymes,

which play important roles in glycerolipid biosynthesis [63, 64]. Mutations in *Lpin1* in mice cause lipodystrophy, fatty liver, hypertriglyceridemia, glucose intolerance, peripheral neuropathy, and atherosclerosis [65–68]. However, *LPIN* mutations in humans do not result in a phenotype that has a clear connection to fat metabolism. For instance, mutations in *LPIN1* in humans cause recurrent myoglobiuria, but not lipodystrophy or other lipid abnormalities [69•, 70]. Likewise, there is no clear link to fat metabolism based on the phenotype seen in Majeed syndrome. However, Donkor et al. [71••] demonstrated that the conserved serine at amino acid 734 that is mutated to a leucine in Majeed syndrome is critical for PAP activity in an in vitro murine system. Mutating that serine abolished PAP activity without altering the other functions of lipin2, including its ability to associate with microsomal membranes or its transcriptional coactivator activity for peroxisome proliferator-activated receptor-response elements [71••]. This suggests that the Majeed phenotype results from loss of PAP activity in LIPIN2 [71••]. However, how this results in sterile osteomyelitis, dyserythropoietic anemia, neutrophilic dermatosis, recurrent fever, and the other phenotypic features of Majeed syndrome remains unclear.

NSAIDs and oral corticosteroids have been used to treat Majeed syndrome, with variable success. The long-term outcome with these treatment strategies has been poor, with marked failure to thrive and permanent joint deformities [27, 31, 60, 61]. A recently published abstract reported clinical, laboratory, and radiologic improvement with IL-1 blockade in two affected brothers, further supporting the notion that Majeed syndrome is an autoinflammatory disorder [72].

### Deficiency of the Interleukin-1 Receptor Antagonist

DIRA is an autosomal recessive, potentially life-threatening disorder that presents in the neonatal period with generalized pustulosis, osteitis, periostitis, and systemic inflammation due to mutations in *IL1RN* [24••, 25••]. It is a newly recognized autoinflammatory disorder that can mimic neonatal sepsis. In 1994, Prose et al. [73] described a female with neonatal-onset pustular psoriasis with CRMO and spontaneous fractures, but it was not until 2009 that it was recognized as a distinct syndrome, when two groups simultaneously reported the clinical syndrome and the gene defect [24••, 25••]. To date, 13 mutation-proven cases have been described [24••, 25••, 74•, 75•].

The most common presentation is development of a mild to severe pustular skin rash at birth or in the first several weeks of life accompanied by elevations in white blood cell count, platelets, ESR, and C-reactive protein [24••, 25••, 74•, 75•]. Respiratory distress and hepatomegaly may also be presenting features [24••, 25••, 75•]. Fever is typically absent at presentation but may develop later in some patients

[24••, 25••], [74•, 75•]. Osteitis often presents several weeks after the skin manifestations, typically manifesting as pain with movement [24••, 74•, 75•]. Only 30% (4 of 13) had objective swelling involving the site of bone inflammation at the time of diagnosis of the osteitis [24••, 74•]. Bone, skin, and blood cultures are negative for pathogens, and antibiotic therapy does not result in clinical improvement [24••, 25••, 74•, 75•].

The bone disease in DIRA can be quite severe if not diagnosed and treated early. Nearly all the infants had extensive bone involvement with multifocal osteolytic lesions involving the long bones and vertebral bodies, marked periostitis (particularly evident in the proximal femurs), and widening of the medial clavicle and anterior rib ends [24••, 25••, 74•, 75•]. Involvement of the vertebral bodies can be quite extensive and destructive. Five of 13 reported patients have had vertebral involvement, and of those, 60% have had permanent deformity of the spine, including vertebral fusion, nonunion of the odontoid with C1, C2 subluxation, and vertebral collapse leading to gibbus deformity [24••, 75•]. The histologic features resemble those seen in CRMO. The skin involvement may be very mild or extensive, with pustulosis seen in all but one. Other reported cutaneous manifestations include pathergy in three cases (23%) [24••, 75•], psoriatic-like nail changes in four cases (31%) [24••], oral ulcers in three cases (23%) [24••], abscess formation in one case (8%) [75•], and pyoderma gangrenosum in one case (8%) [24••]. The histologic features of the pustular rash resemble those of pustular psoriasis [24••, 25••, 74•, 75•].

Other manifestations have included the development of interstitial lung disease in two of the seven infants who had pulmonary symptoms [24••, 25••], deep vein thrombosis associated with indwelling venous catheters in three cases (23%) [25••, 74•, 75•], vasculitis (8%) [24••], perivertebral soft tissue fibrosis (8%) [75•], and central nervous system inflammation with encephalomalacia (8%) [24••]. Several children had failure to thrive, but how much of this was due to chronic steroids versus chronic inflammation is unclear.

Empiric treatment with anakinra in two affected infants resulting in rapid and sustained improvement in all aspects of the disease pointed to IL-1 pathway dysregulation and was the key observation that led to the identification of the gene defect [24••, 25••]. To date, 6 different deleterious mutations in *IL1RN* have been identified in 13 affected children from 10 unrelated kindreds. Twelve of 13 affected children have homozygous mutations in the gene [24••, 25••, 75•], while the other child is a compound heterozygote (E77X and T47TfsX4) [74•]. The most common mutation is E77X, which was present in six affected children from four kindreds (including one allele in the compound heterozygote) [24••, 74•, 75•]. Other mutations include N52KfsX25, Q54X, D72\_I76del, T47Tfs, and two patients had a 175-kb deletion on chromosome 2q13. The chromosome 2q13

deletion encompasses *IL1RN* in addition to five additional IL1 family members, including *IL36RN* (also known as *IL1F5*), and the two patients homozygous for this deletion seemed to have more severe disease than those without the deletion [24••, 25••]. Interestingly, mutations in *IL36RN* (*IL1F5*), the gene that encodes IL-36 receptor antagonist, have been reported to cause generalized pustulosis without bone inflammation [76••].

Prior to the identification of the gene defect in DIRA, outcomes were poor, with a 33% mortality rate in one case series ( $n=9$ ) with death from systemic inflammatory response syndrome (SIRS) at 2 months, 21 months in two patients, and death from complications of interstitial lung disease at 9.5 years of age [24••]. However, the patient reported by Prose et al. [23] in 1994 with generalized pustulosis and CRMO lived at least into her late-teens. She was resistant to treatment with prednisone, methotrexate, dapsone, and PUVA (psoralen+UVA) therapy but improved on etretinate, 1–1.5 mg/kg per day, with flare when the dose was reduced [23]. Since the identification of the gene defect, all affected children have been treated with anakinra, which uniformly produced marked improvement. Skin manifestations resolved within days of initiation of anakinra, and the osteitis resolved radiographically over the subsequent 3–4 months, except in one patient with marked abnormal epiphyseal involvement that is more typical of skeletal changes seen in neonatal-onset multisystem inflammatory disorder [77]. The amount of anakinra (administered by subcutaneous injection) required to result in resolution of clinical evidence of inflammation and to normalize the C-reactive protein ranged from 1 to 5 mg/kg per day. All but one child was able to completely wean off corticosteroids after the initiation of anakinra [24••]. Given that DIRA is a potentially fatal disorder, prompt recognition and institution of anakinra therapy is essential and results in a good short-term outcome. The long-term outcome of anakinra-treated DIRA has yet to be established.

### Treatment of Chronic Recurrent Multifocal Osteomyelitis

The treatment of CRMO has been largely empiric. NSAIDs are often the first line of treatment, with reported response rates of up to 80%. Several agents have been utilized for those who fail or only have a partial response to NSAIDs, including short courses of oral corticosteroids, chronic oral corticosteroids, methotrexate, sulfasalazine, colchicine, and azithromycin [78•]. More recently, TNF-blocking agents and bisphosphonates have been increasingly utilized. The literature on treatment is primarily made up of retrospective assessment of response to treatment in case reports or small series. There are a few prospective studies of response to

treatment in CRMO/CNO, but no randomized trials have been performed, primarily because of the rare nature of the disease.

#### Prospective Assessment of NSAIDs

Beck et al. [79••] recently performed a prospective analysis of a German cohort of children with CRMO, assessing their response to NSAIDs during the 1 year of treatment as measured at 0, 3, 6, and 12 months. They studied 37 children (65% female; age range, 2–16 years) with newly diagnosed with CRMO (including 1 with Crohn disease and 2 with hypophosphatasia) who had not been treated with antibiotics or anti-inflammatory medications. Six (17%) had associated cutaneous disease, including three with palmo-plantar pustulosis, two with acne conglobata, and one with psoriatic nail changes. The children were treated with 14 days of prednisone (2 mg/kg per day for 7 days, with a subsequent taper) and with naproxen (15 mg/kg per day divided twice daily) continuously for 12 months. At 6 months, sulfasalazine (20 mg/kg per day) was added only for study participants with no or insufficient response to naproxen. The patient with Crohn disease was treated with naproxen, sulfasalazine, corticosteroids, and azathioprine at study initiation [79••].

Radiographic lesions were determined by a variety of modalities, including utilizing plain radiographs and bone scan, followed by MRI of the region of affected lesions or whole body MRI. Twenty-one of the 37 patients had whole body MRI performed at all 4 visits (0, 3, 6, and 12 months). Overall, the mean time to diagnosis was 5 months after symptom onset. Nearly 80% of children had multifocal disease at some point during their 12 months of follow-up. Forty-three percent of patients were asymptomatic on naproxen at 6 months. There was a statistically significant progressive improvement of the number of clinical foci (pain, functional impairment, or swelling) over the course of the study in this cohort—from a total of 79 at onset of the study to 19 foci by 12 months ( $P<0.05$ ). The number of radiologically apparent lesions began at 184 for the cohort and progressively fell to 81 by 12 months. Sulfasalazine was used in five patients (four started at 6 months due to insufficient response to naproxen and the one patient with Crohn disease). After initiation of sulfasalazine, the CRMO overall disease activity estimates by patients, physicians, and Childhood Health Assessment Questionnaire improved. The radiologic outcome revealed that two became lesion free, one had a decrease in lesions, and two patients had no improvement in number of lesions [79••].

Overall, the patient outcome was good in this homogeneous cohort of German children. However, there were some subgroups of patients for whom this approach may not be optimal, including those with arthritis and those with

vertebral involvement. In this cohort, arthritis was diagnosed in nearly 40% (14 of 37) of patients at presentation [79••]. Of those patients, 100% continued to have arthritis at 3 months, 50% at 6 months, and 21% at 12 months [79••]. Vertebral involvement was present in nearly 20% (7 of 37) [79••]. Three of 37 patients developed pathologic fractures during the course of the study, including 2 of 7 patients with spine involvement [79••]. This approach may not be optimal for those with spine involvement or peripheral arthritis, but further studies are needed.

#### Bisphosphonates and Biologic Agents

A biologic agent (most often a TNF inhibitor) or bisphosphonates are increasingly being used in children with CRMO who have failed standard therapy. There are nearly 50 case reports or case series documenting response of pediatric-onset CRMO to bisphosphonates, including 1 prospective study of the response to pamidronate in 9 children with CRMO [30, 78•, 80•, 81•, 82–90]. The participants in the prospective study by Miettunen et al. [80•] had CRMO for an average of 18 months at the time of first treatment. Pamidronate was administered monthly or every 3 months and was continued until there was radiologic resolution of bone inflammation as assessed by MRI. There was prompt resolution of pain within days of treatment. The mean time to complete MRI resolution of bone inflammation was 6 months (range, 2–12 months). The mean time of follow-up was 31 months, during which time four patients developed MRI-confirmed disease flares. All four responded to retreatment with pamidronate [80•]. The reported cases of childhood CRMO/CNO/SAPHO treated with bisphosphonates, for which details are available for each individual treated, are summarized in Table 1. Overall, the response to bisphosphonates (predominately pamidronate) appears very favorable, with approximately 80% experiencing improvement. Some experienced complete remission following treatment with a single course of pamidronate, but most needed repeated dosing to maintain disease control.

There are more than 20 reports in the literature detailing the use of TNF inhibitors in CRMO [21, 30, 81•, 82, 84, 91–95]. The reported cases of childhood CRMO/CNO/SAPHO treated with TNF inhibitors are summarized in Table 2. An additional five patients were reported in an abstract by Stern et al. [96], who reported improvement in three of five patients treated with anti-TNF agents. Overall, the response to TNF inhibition is mixed, with 65% documenting clinical improvement and 35% reporting no improvement. Many who failed TNF inhibitors had a response to pamidronate, and vice versa. There is considerably less in the literature about the use of other biologics in CRMO. Recently, there have been a few reports on the use of IL-1 blockade in sporadic cases of pediatric and adult CRMO, with mixed

**Table 1** Bisphosphonate treatment in childhood-onset CRMO/SAPHO<sup>a</sup>

Patient	Age at treatment (sex)	Age at onset	Bones involved	Imaging utilized	Associated diagnosis	Prior Rx used	Treatment	Response to bisphosphonate treatment	Reference
1	18 y (female)	?	Mandible, spine, long bone	CT	Acne, PPP	CS, MTX, AZA, cyclosporine, MMF, colchicine, interferon- $\gamma$ , etanercept, infliximab	PAM	Transient response	[30]
2	10 y (male)	8 y	Clavicles, long bones, other <sup>b</sup>	X-ray	–	NSAID, MTX, AZA	PAM	Partial response	[81•]
3	7 y (female)	7 y	Long bones	X-ray, MRI, bone scan	–	CS, MTX, SSZ, AZA, colchicine, IA CS	PAM, risedronate	Failed PAM, improvement with risedronate and IA CS	[81•]
4	15 mo (male)	15 mo	Long bones, other <sup>b</sup>	X-ray	PPP	Interferon- $\gamma$ , NSAID, colchicine, IA CS, infliximab, adalimumab	PAM	Transient response	[81•]
5	6 y (female)	6 y	Ankles, anterior chest wall, clavicles	Bone scan	? Ps	CS, NSAID, SSZ, adalimumab	PAM	Minimal improvement	[81•]
6	17 y (male)	17 y	Spine	X-ray, MRI	–	NSAID, CS, SSZ, AZA, infliximab	Alendronate	Transient improvement	[82]
7	16 y (female)	6.5 y	Long bones	X-ray, bone scan, MRI	–	CS, MTX	PAM	Marked clinical improvement	[83]
8	11 y (female)	10 y	Clavicle, long bone	X-ray, bone scan	–	NSAID, CS	PAM	Marked clinical and radiological improvement	[83]
9	14 y (male)	9 y	Clavicle, long bone	X-ray, bone scan	–	NSAID, CS	PAM	Marked clinical improvement	[83]
10	7 y (female)	6.5 y	Long bones	X-ray, bone scan	–	NSAID	PAM	Clinical remission <sup>c</sup>	[83]
11	14 y (female)	11 y	Long bones	X-ray	–	NSAID	PAM	No response	[83]
12	14 y (male)	?	Spine	MRI	–	NSAID, CS, etanercept	PAM	Clinical remission <sup>c</sup> , MRI improvement	[84]
13	13 y (male)	?	Spine	MRI	–	NSAID, CS	PAM	Clinical remission <sup>c</sup> , MRI improvement	[84]
14	15 y (female)	?	Spine	MRI	–	NSAID, CS, SSZ, etanercept, adalimumab	PAM	Clinical remission <sup>c</sup> , MRI improvement	[84]
15	8 y (female)	?	Spine	MRI	–	NSAID, CS, infliximab, adalimumab	PAM	Clinical remission <sup>c</sup> , MRI improvement	[84]
16	11 y (female)	?	Spine	MRI	Arthritis	NSAID, CS, etanercept, infliximab	PAM	Clinical remission <sup>c</sup> , MRI improvement	[84]
17	13 y (female)	?	Spine	MRI	–	NSAID, CS, MTX, etanercept	PAM	Clinical remission <sup>c</sup> , MRI improvement	[84]
18	13 y (female)	?	Spine	MRI	–	NSAID, CS, etanercept	PAM	Clinical remission <sup>c</sup> , MRI improvement	[84]
19	5 y (female)	4.8 y	Long bones, mandible	X-ray, MRI, bone scan	–	NSAID, antibiotic	PAM	Clinical and CT improvement, but side effects	[85]

**Table 1** (continued)

Patient	Age at treatment (sex)	Age at onset	Bones involved	Imaging utilized	Associated diagnosis	Prior Rx used	Treatment	Response to bisphosphonate treatment	Reference
20	9 y (female)	6.7 y	Mandible	X-ray, CT	–	NSAID, CS, antibiotic, debridement	PAM	Transient improvement; CT improvement, but side effects	[85]
21	16 y	10 y	Clavicle, long bones	X-ray	–	NSAID, CS	Neridronate	Clinical and MRI improvement	[86]
22	11 y (male)	9 y	Mandible, long bones	CT, bone scan	–	Antibiotic, debridement, NSAID	PAM	Marked clinical improvement	[87]
23	16 y (female)	10 y	Clavicle	X-ray, CT	Acne	NSAID	PAM	Partial clinical response	[88]
24	16 y (female)	11 y	Anterior chest wall, clavicle, spine, long bones	CT, MRI, bone scan	Pustular Ps	NSAID, CS, SSZ, MTX	PAM	Marked clinical improvement	[88]
25	14 y (female)	8 y	Clavicle, SI, long bones	Bone scan	–	NSAID, MTX	PAM	Partial clinical response	[88]
26	15 y (female)	8 y	Clavicle, long bones	CT, MRI, bone scan	–	NSAID, CS	PAM	Partial clinical response	[88]
27	16 y (female)	7 y	Spine, SI	X-ray, MRI, bone scan	Pustulosis	NSAID	PAM	Sustained remission	[88]
28	15 y (female)	15 y	Anterior chest wall, long bones	MRI, bone scan	–	NSAID	PAM	Transient improvement	[88]
29	9 y (female)	8 y	Spine, pelvis	X-ray, MRI, bone scan	–	NSAID	PAM	Clinical improvement	[88]

<sup>a</sup>The case series of Miettunen et al. [80•] ( $n=9$ ), Gleeson et al. [90] ( $n=7$ ), and Kuijpers et al. [89] ( $n=1$ ) do not provide detailed information on each patient and thus are not included in this table  
<sup>b</sup>Hand and foot

<sup>c</sup>Clinical remission indicates resolution of symptoms  
 AZA azathioprine; CRMO chronic recurrent multifocal osteomyelitis; CS corticosteroid; IA intra-articular; MMF mycophenolate mofetil; MTX methotrexate; PAM pamidronate; PPP palmoplantar pustulosis; Ps psoriasis; SI sacroiliac joint; SSZ sulfasalazine

**Table 2** TNF antagonist treatment in childhood CRMO/SAPHO

Patient	Age at diagnosis (sex)	Age at onset, y	Bones involved	Imaging	Associated diagnosis	Prior treatment used	TNF treatment	Response to TNF antagonist treatment	Reference
1	18 y (female)	?	Mandible, spine, long bones	CT	Acne, PPP	CS, MTX, azithromycin, CSA, MMF, colchicine, IFN- $\gamma$ , PAM	Etanercept, infliximab	Transient improvement	[30]
2	9 y (female)	7	Spine, chest wall	Bone scan, MRI	–	NSAID	Etanercept	Clinical and radiological improvement	[91]
3	4 y (male)	4	Foot, spine	Bone scan, MRI	–	NSAID, CS, MTX	Etanercept	Clinical remission <sup>a</sup> , radiological improvement	[92]
4	12 y (female)	12	Long bones	X-ray, MRI	–	NSAID, CS, MTX	Etanercept	Clinical improvement	[92]
5	9 y (female)	9	Right clavicle	X-ray	Crohn's disease	CS, 6-MP, AZA	Infliximab	Clinical and radiological improvement	[21]
6	10 y (male)	8	Clavicles, long bones <sup>b</sup>	X-ray	–	NSAID, MTX, PAM, AZA	Infliximab	Clinical improvement	[81•]
7	7 y (female)	7	Long bones	X-ray, MRI, bone scan	–	CS, PAM, MTX, SSZ, AZA, colchicine, IA CS, risedronate	Infliximab	Clinical improvement <sup>c</sup>	[81•]
8	15 mo (male)	?	Long bones <sup>b</sup>	X-ray	PPP	IFN- $\gamma$ , NSAID, IA CS, colchicine, PAM	Infliximab, adalimumab	Failed infliximab; clinical remission with adalimumab <sup>a</sup>	[81•]
9	17 y (male)	17	Spine	X-ray, MRI	–	NSAID, CS, SSZ, AZA, ALE	Infliximab	Clinical remission <sup>a</sup>	[82]
10	16 y (female)	8	Mandible, SI, long bones	MRI, CT, bone scan	–	NSAID, antibiotic, calcitonin, CS	Infliximab	Clinical remission <sup>a</sup> , radiological improvement	[93]
11	15 y (male)	?	SI	CT scan, MRI	Acne	Isotretinoin, NSAID, IA CS, SSZ	Etanercept	Clinical improvement	[94]
12	14 y (male)	?	Spine	MRI	–	NSAID, CS	Etanercept	No response	[84]
13	13 y (female)	?	Spine	MRI	–	NSAID, CS, SSZ	Etanercept, adalimumab	No response	[84]
14	5 y (female)	?	Spine	MRI	–	NSAID, CS	Infliximab, adalimumab	No response	[84]
15	6 y (female)	?	Spine	MRI	Arthritis	NSAID, CS	Etanercept, infliximab	No response	[84]
16	11 y (female)	?	Spine	MRI	–	NSAID, CS, MTX	Etanercept	No response	[84]
17	12 y (female)	?	Spine	MRI	–	NSAID, CS	Etanercept	No response	[84]
18	15 y (male)	15	Anterior chest wall, SI, long bones	X-ray, bone scan	Acne	Isotretinoin, NSAID, CS, MTX	Etanercept	Clinical improvement	[95]

<sup>a</sup> Clinical remission indicates resolution of symptoms

<sup>b</sup> Hand and foot

<sup>c</sup> Infliximab was stopped because of suspected (unconfirmed) skin fungal infection

<sup>d</sup> Anterior uveitis, left exophthalmos

6-MP 6-mercaptopurine; ALE alendronate; AZA azathioprine; CRMO chronic recurrent multifocal osteomyelitis; CS corticosteroid; CSA cyclosporine; IA intra-articular; IFN interferon; MMF mycophenolate mofetil; MTX methotrexate; PAM pamidronate; PPP palmoplantar pustulosis; SI sacroiliac joint; SSZ sulfasalazine; TNF tumor necrosis factor



results. In one case, CRMO developed in a 41-year-old man who had failed pamidronate. Six years later, he developed classic Still disease. He was treated with anakinra and had sustained resolution of the bone lesions and systemic symptoms [36]. Another case involved a 47-year-old woman with SAPHO syndrome (acne conglobata, palmoplantar pustulosis, anterior chest wall osteitis, monoarticular peripheral arthritis) who failed to improve after 6 months of sulfasalazine treatment [97]. Because the patient's peripheral blood mononuclear cells secreted increased amounts of IL-1 $\beta$  when stimulated in vitro, the patient was given a trial of anakinra, 100 mg/d. After 3 months of anakinra, her bone pain, cutaneous lesions, and systemic symptoms disappeared, plus her clinical evidence of arthritis resolved and laboratory evidence of inflammation normalized. There was radiologic resolution of osteitis of the manubrium with improvement in uptake of the sternoclavicular joint [97]. A third case reported a 6-year-old with CRMO who had persistently active disease despite treatment with intravenous steroid pulses and pamidronate. Measurement of serum cytokines revealed elevations of IL-1 receptor antagonist, suggesting IL-1 pathway activation and prompting the clinicians to treat with anakinra, 2 mg/kg per day, which resulted in resolution of all her symptoms at 6 weeks, but a flare of her disease 12 months later despite continued anakinra therapy [81•].

The optimal use of bisphosphonates and biologics remains unclear. Safety concerns for malignancy and infection exist for the TNF-blocking agents, while osteonecrosis of the jaw, atypical femur fractures, and uncertain long-term side effects on a growing skeleton are concerns for bisphosphonates. The use of IL-1 inhibitors in CRMO is very limited, but data from both syndromic forms of the disease suggest that IL-1 may be an important cytokine in CRMO.

## Conclusions

CRMO can occur as an isolated entity or as part of a syndrome. Infantile-onset CRMO should trigger genetic testing for defects in LPIN2 or IL1RN. Majeed syndrome presents with CRMO and a congenital dyserythropoietic anemia with or without Sweet syndrome. DIRA presents with multifocal osteitis, marked periostitis, and generalized pustulosis. Treatment for DIRA is with IL-1 inhibition. The best treatment for Majeed syndrome remains to be defined. For most children, the onset of CRMO is at a later age and may occur with psoriasis or inflammatory bowel disease. Treatment for those children with bone and skin inflammation or with bone and intestinal inflammation should be geared toward treating both end organs (bone and skin or bone and gut); a TNF inhibitor may be needed in this group. Those with isolated CRMO are typically treated with

NSAIDs alone prior to escalation to disease-modifying antirheumatic drugs, TNF inhibitors, or bisphosphonates. Permanent bone deformity can occur, particularly when vertebral bodies are involved, often warranting more aggressive treatment. For most, CRMO is a disorder that resolves after many years, most often without permanent sequelae.

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- Of importance
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