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Review

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Review

Current and future advances in practice: SAPHO syndrome and chronic non-bacterial osteitis (CNO)

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Abstract

Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome is a rare, underdiagnosed disease with a wide clinical spectrum. Sterile bone inflammation, predominantly of the anterior chest, and skin manifestations (palmoplantar pustulosis, psoriasis vulgaris and acne) are the key features of SAPHO, which shares certain similarities with SpA. SAPHO is closely related to paediatric chronic non-bacterial osteitis (CNO), a spectrum of autoinflammatory bone diseases. The aetiology of SAPHO is considered multifactorial based on a complex interplay of genetic, immune and infectious factors. Despite the increasing awareness of SAPHO/CNO, diagnostic delay is common, as validated classification and diagnostic criteria are lacking. Treatment of SAPHO represents a challenge and includes anti-inflammatory drugs, antibiotics, bisphosphonates, synthetic conventional DMARDs and off-label use of anti-cytokine biologics and Janus kinase inhibitors. This review summarizes the current diagnostic and practical treatment approach to SAPHO/CNO and highlights the ongoing research endeavours concerning the definition and validation of diagnostic criteria, core domains and treatment.

Lay Summary

What does this mean for patients?

SAPHO/CNO are rare conditions affecting the bone in both children and adults and can result in severe pain and disability. There are several collaborative international efforts to improve our understanding of these conditions in how they impact individuals and their families and new attempts to improve diagnosis and treatment. It is clear that both diagnosis and treatment may require collaboration between paediatricians, dermatologists, rheumatologists, endocrinologists and radiologists in order to obtain the best outcomes for patients with these disorders.

Keywords: SAPHO, CNO, psoriatic arthritis, spondyloarthritis, pathogenesis, outcome measures, treatment, diagnostic criteria, classification criteria

Rheumatology key messages

- There is growing awareness of diagnosing and treating SAPHO/CNO among the global medical community.
- Ongoing research endeavours concerning the definition and validation of diagnostic criteria, core domains and treatment strategies are under way.
- The current treatment of SAPHO/CNO is based on clinical experience and expert opinion.
- The choice of treatment is guided by clinical phenotype (prominent musculoskeletal *vs* skin involvement), severity of the disease and geographic region.
- Joint rheumatology–dermatology collaboration may enhance favourable treatment outcomes.

Introduction

The acronym SAPHO (ORPHA: 793), which stands for synovitis, acne, pustulosis, hyperostosis and osteitis, was introduced into the medical literature in 1987 by the French Society of Rheumatology based on a national survey of 85 cases characterized by anterior thoracic and peripheral hyperostosis associated with palmoplantar pustulosis (PPP) and severe acne [1, 2]. Since the recognition of the clinical association between the occurrence of inflammatory sterile osteitis with bone hyperostosis and a variety of skin

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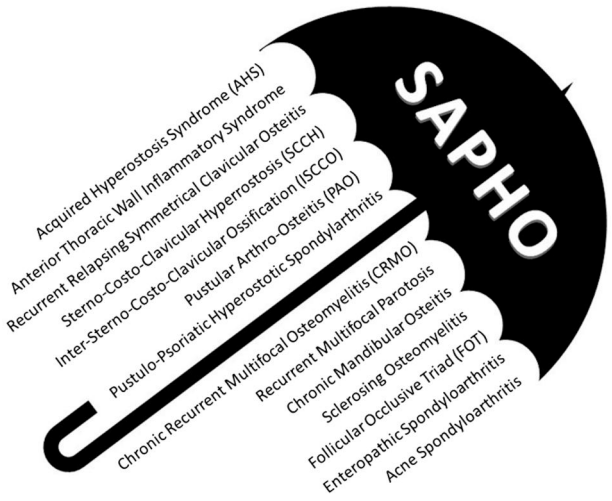

Figure 1. SAPHO umbrella. Reproduced from Depasquale *et al.* [11] with permission

manifestations in 1961 [3], various clinical phenotypes have been reported using multiple descriptive terms [4] (Fig. 1). The more commonly used nomenclature included pustulotic arthro-osteitis (PAO) syndrome, defined by Sonozaki in 1981 based on 53 Japanese cases of costoclavicular or manubriosternal region lesions associated with PPP [5, 6], sternocostoclavicular hyperostosis (SCCH, ORPHA: 178311) [7], pustulo-psoriatic hyperostotic SpA, acquired hyperostosis syndrome, acne-associated SpA and chronic recurrent multifocal osteomyelitis (CRMO, ORPHA: 324964) [8]. SAPHO syndrome denotes a clinical entity, applied mainly to adult patients, that encompasses various clinical manifestations with a key feature of focal or multifocal sterile osteitis, with predominant involvement of the anterior chest wall, commonly but not necessarily associated with skin manifestations, such as PPP, pustular psoriasis, severe acne or hidradenitis suppurativa (HS). In children and adolescents, autoinflammatory sterile bone disease, known as chronic non-bacterial osteitis (CNO), might represent the same entity as SAPHO syndrome with juvenile onset [9, 10]. CNO encompasses a wide clinical spectrum from mild and self-limited to severe chronic multifocal bone disease. The absence of a clear definition of the syndromes, agreed diagnostic and classification criteria and validated outcome measures precludes clinical trials to establish the treatment paradigm in SAPHO/CNO. At present, both diagnostic and treatment approaches to SAPHO/CNO are based on case series and expert opinion.

Pivotal in the understanding of SAPHO/CNO are recent advances in the pathogenesis of CNO, pointing to dysregulation of pro- and anti-inflammatory cytokine expression and activation of a cytoplasmic multiprotein complex, the nucleotide-binding oligomerization domain (NOD-), leucine-rich repeat (LRR)- and pyrin domain-containing protein 3 (NLRP3) inflammasome [12, 13]. In addition, SAPHO/CNO poses a clinical challenge for different medical subspecialties, including rheumatologists, paediatricians, orthopaedics, radiologists and dermatologists. An ongoing international initiative aiming to improve disease definition and terminology, diagnostics and imaging, treatment and monitoring is under way (https://www.ese-hormones.org/media/tk2de0cz/preliminary-programme-consensus-initiative-adult-cno-sapho-meeting-october-2023.pdf).

The aim of this review is to shine a spotlight on SAPHO syndrome in the context of autoinflammatory bone disease and review the current diagnostic and practical treatment approach based on a literature review and expert opinion in the absence of informed evidence.

Epidemiology

SAPHO

SAPHO is considered a rare syndrome with a worldwide distribution. Cohorts of SAPHO patients have been reported in Europe [14–18], China [19–21], Japan [22, 23], North America [24] and Australia [25]. An estimated prevalence of SAPHO is <1:10 000 [26] and female predisposition was consistently observed in different geographic areas [14, 19, 20, 22, 27]. The disease is more prevalent in females <30 years of age [14, 16, 18–20, 22, 28]. In view of multiple overlapping terminology defining distinct subsets of the syndrome, atypical presentation in some cases and insufficient awareness of the disease, the true prevalence is underestimated. Thus a diagnostic delay of up to 9 years has been reported in different cohorts [16, 17, 19, 27], leading to irreversible structural changes and debilitating chronic symptoms, translating into high disease burden and disability.

CNO

CNO is a rare syndrome most commonly reported in White Caucasians, although all ethnicities can be affected [29, 30]. Disease onset typically occurs at 7–12 years of age and there is a female predominance (≈2:1) [31]. The prevalence of CNO has increased in recent years. In a survey of 148 children with newly diagnosed non-bacterial osteitis (age range 18 months–18 years) conducted in Germany, the incidence of the disease was estimated at 4/million in 2006–2008 [32]. In a tertiary paediatric centre in the northwest USA, the annual rate of CNO cases increased from 8 to 23/million children between 2005 and 2019 [33]. This observation may be explained by increasing awareness of CNO by different medical disciplines, along with a greater availability of imaging modalities, such as whole-body MRI and PET-CT. Yet the delay in diagnosis of CNO remains common [34, 35].

Clinical presentation

Osteoarticular manifestations

SAPHO (adults)

Osteoarticular manifestations encompass a wide spectrum of clinical patterns, including prevalent multifocal *vs* a rare form of localized bone lesions, and a varying clinical course ranging from self-limited, relapsing–remitting or chronic clinical disease. Osteoarticular manifestations can stand alone or in conjunction with skin disease. Inflammatory bone pain of the affected area is the most common presenting symptom and can be accompanied by tenderness, bone swelling and limited range of motion of the involved site. The clinical hallmark of SAPHO and PAO is involvement of the anterior chest wall, including the sternoclavicular, manubriosternal and costosternal joints, present in most patients [14, 22, 36] (Fig. 2). SCCH is an example of the SAPHO/CNO clinical subset affecting the sternum, medial ends of the clavicles and upper ribs. SCCH can appear as an isolated clinical entity or in conjunction with bone lesions of the spine, pelvis or mandible [27, 37].

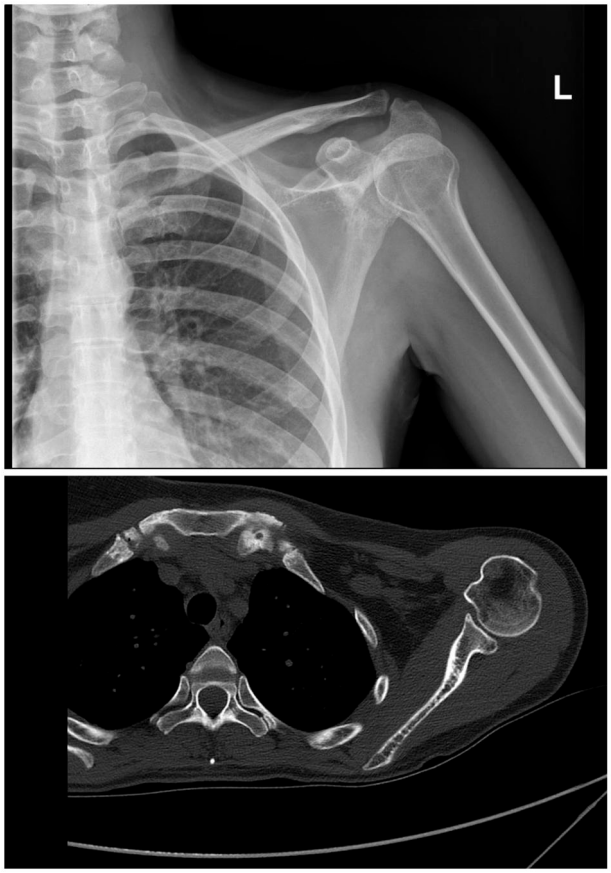

Figure 2. A 35-year-old female with SAPHO syndrome. X-ray and chest CT show left sternoclavicular arthritis with sclerotic changes in the proximal part of the clavicle, erosions and joint space narrowing

Spinal and sacroiliac involvement is the second common osteoarticular manifestation in SAPHO and PAO, affecting up to 50% of patients [19, 20, 38–40], with the thoracolumbar spine reported as the most frequent site of involvement [41, 42]. The axial skeleton manifestations may present as vertebral corner lesions, spondylodiscitis, osteolytic lesions, osteitis, osteosclerosis with the development of hyperostosis, paravertebral ossifications and asymmetric sacroiliitis [41, 43]. The ilium bone may be involved in association with adjacent sacroiliitis [41]. A large Chinese study ($n = 354$) that compared the characteristics of patients with SAPHO with and without spinal and sacroiliac lesions reported that the former were older at disease onset and had higher disease activity despite more aggressive treatment [20]. Consistently, another study reported that SAPHO patients with spinal involvement had longer disease duration and higher inflammatory markers compared with patients without spinal disease [40]. As axial manifestations of SAPHO share clinical and radiological features of axial SpA, it is considered by some as a variant of SpA [44, 45]. Yet, several distinct radiological features pertinent to SAPHO compared with axial SpA should be noted, including a predilection to the thoracic spine, consecutive vertebral involvement in a particular 'kissing' appearance with preserved intervening disc spaces, a different form of syndesmophytes (non-marginal *vs* marginal) and paravertebral ligamentous ossifications (anterior and segmental *vs* diffuse and posterior), respectively [42]. Spinal MRI features differentiating between SAPHO syndrome and SpA include bone marrow oedema of the spinal anterior corner and swelling of the intervertebral disc, endplate, anterior thoracic wall and paraspinal soft tissue [46]. In addition, the prevalence of sacroiliitis is significantly lower in SAPHO compared with SpA [46]. Peripheral synovitis, commonly oligoarticular and asymmetric, is reported in up to one-third of SAPHO patients [4, 21]. In one study, peripheral arthritis was more common in patients who were <25 years old at onset than in older patients [16]. Mandibular involvement, a form of diffuse sclerosing sterile osteitis, usually sparing the temporomandibular joint, can be present as a distinct localized subset of SAPHO, mainly in young women [47, 48]. Notably, involvement of the long bones is infrequent in adult patients with SAPHO.

CNO (children and young adolescents)

CNO is an autoinflammatory bone disease with a wide clinical phenotype. The clinical presentation of CNO includes focal bone pain and swelling of the affected site as reported by Björkstén *et al.* in 1978 [49]. Notably, asymptomatic bone lesions are common in patients with CNO [29, 50, 51], justifying early recognition of bone lesions at disease onset using whole-body imaging (such as whole-body MRI or PET-CT). If left untreated, persistent inflammation can result in bone destruction, growth disturbances, pathological fractures, leg-length discrepancy and consequent functional limitations (such as limping). In general, all sites of the skeleton may be affected, except for the neurocranium [52]. Different from SAPHO, bone lesions in paediatric CNO patients primarily affect the epiphyses and metaphyses of the long bones of the lower extremities, with the femur, tibia and pelvis reported as the most commonly involved sites [13, 51, 53]. Up to 25% of patients develop peripheral arthritis [51, 54]. Spinal involvement is not uncommon and mostly affects the thoracic spine at multiple levels [55]. In a US cohort of 42 patients with CNO/CRMO, 33% had spinal disease, with kyphosis and scoliosis present in one-quarter and vertebral height loss in one-third of children at spinal disease recognition [56]. A subset of patients with CNO develop unilateral sacroiliitis that may progress to SpA in a later stage [57]. Sternum involvement is not typical for CNO, in contrast to SAPHO. Constitutional symptoms such as fever, fatigue, night sweats and weight loss may present in a minority of patients [10]. While overall most patients have favourable outcomes [58], varying recurrence rates of disease are reported [10, 13].

Based on a large French cohort of paediatric patients with CRMO, three distinct subgroups were distinguished based on the disease phenotype and prognosis [59]. Female patients with a unifocal form of CRMO and infrequent clavicle involvement and inflammatory syndrome had a mild phenotype and favourable prognosis. Male patients with the multifocal form of CRMO and inflammatory syndrome had the most severe phenotype and poor outcomes [59]. Real-world data based on the German National Pediatric Rheumatologic Database (NPRD), which collects long-term data on children and adolescents with CNO, found the predictors associated with a severe disease course: the site of inflammation (pelvis, lower extremity, clavicle), increased ESR and multifocal disease at first documentation [58].

Clinicians should be aware of a clinical overlap between CNO and juvenile SpA (SpA), including enthesis-related arthritis (ERA) [60], viewed by some as the same disease spectrum [61]. While there are common clinical features of axial

disease, sacroiliitis and peripheral involvement, CNO has a distinct disease phenotype. Different from juvenile SpA, patients with CNO have no male predominance. The key diagnostic clues of CNO include inflammatory bone lesions affecting the metaphysis of the long bones and commonly asymptomatic spinal involvement, in contrast to the dominant axial involvement in juvenile SpA. Peripheral inflammatory arthritis associated with enthesitis is more common in ERA compared with CNO [61]. In a long-term follow-up, CNO may evolve into SpA, in particular presenting with unilateral sacroiliitis [57], supporting the hypothesis of the continuum of the disease spectrum. Furthermore, both conditions share common comorbidities, including psoriasis, inflammatory bowel disease and skin manifestations, as discussed below.

Skin manifestations

Different forms of skin manifestations are present in most patients with SAPHO, as globally reported [4, 14, 16, 19, 20, 23, 27, 28, 62]. PPP is the most prevalent skin manifestation across the globe [44], with severe acne, psoriasis vulgaris, HS [24, 63] and pyoderma gangrenosum [64, 65] reported in the decreasing order of frequency. PPP and psoriasis vulgaris are recognized as a common denominator between SAPHO and psoriatic SpA, while other pustular dermatoses, such as acne vulgaris and HS, not typical for the latter, represent the difference between the two entities. Skin lesions mainly precede osteoarticular manifestations by several years [4, 5, 16, 19, 20, 38] but can appear simultaneously or after the onset of osteoarticular manifestations in some cases. Skin manifestations tend to run an independent clinical course from osteoarticular manifestations [16]. Remarkably, in a long-term follow-up study of 120 cases, skin manifestations (PPP and psoriasis vulgaris) were associated with axial osteitis [14]. Skin manifestations, especially the severe forms, are commonly associated with a protracted course and resistance to treatment [4, 24].

CNO (children and young adolescents)

Skin manifestations are present in up to 20% of patients with CNO and include PPP, psoriasis, acne and undifferentiated pustules [29, 51]. An Italian study of 14 patients with paediatric SAPHO syndrome reported two different patterns of skin involvement: PPP and acne–HS [66]. In the PPP group, all patients were female, characterized by a prepubertal disease onset with osteoarticular manifestations, followed by the appearance of PPP in the following 6 months and good response to treatment. In the acne–HS group, most patients were males with skin disease onset in puberty, followed by osteoarticular manifestations in the following year. This group had a severe refractory skin disease that required in most cases the addition of biologic therapies [66]. Acne fulminans was rarely reported, predominantly in male adolescents with involvement of the axial skeleton and arthritis [67].

Pathogenesis

The precise pathogenesis of SAPHO remains unknown. Genetic, immunological and infectious factors have been investigated, but a definitive causative link has yet to be established. CNO is considered an autoinflammatory bone disease characterized by systemic inflammation in the absence of autoantibodies or antigen-specific T cells. Recent advances in understanding the molecular pathophysiology of CNO/CRMO pointing to cytokine imbalance and innate immune system dysregulation leading to increased osteoclastic activation and bone remodelling through the aberrant activation of the NLRP3 inflammasome [13, 68] may shed light on the mechanisms responsible for the development of SAPHO.

Genetic factors

CNO

The genetic basis of CNO relates to familial clusters of CNO/CRMO, animal models of CNO/CRMO [e.g. proline–serine–threonine phosphatase-interacting protein 2 (PSTPIP2)-deficient mice [69] and Ali18 mice [70, 71] and monogenic forms of CNO: Majeed syndrome (OMIM 609628) and deficiency of the IL-1 receptor antagonist (DIRA) (OMIM 612852) [10, 68]. Majeed syndrome represents a severe familial form of early-onset CNO/CRMO associated with dyserythropoietic anaemia and neutrophilic dermatoses [72]. Majeed syndrome is caused by a recessive loss-of-function mutation in the *LPIN2* gene leading to activation of the NLRP3 inflammasome and high expression of IL-1β [73]. DIRA is another early-onset inflammatory disease associated with multifocal osteitis, periostitis and pustulosis, caused by loss-of-function mutations in *IL1RN* encoding the IL-1 receptor (IL-1R) antagonist [74, 75]. The absence of IL-1Ra function results in unopposed signalling through the IL-1R, which leads to overproduction of pro-inflammatory cytokines and chemokines. Rapid response of the inflammatory disease manifestations with IL-1 inhibitors suggests a prominent role of IL-1 in disease pathogenesis [74, 76]. To date, no direct genetic cause has been identified in the sporadic form of CNO. Yet, a genetic predisposition seems to contribute to disease development in concordance with other factors. For example, mutations in PSTPIP2 may be the genetic candidates for the autoinflammatory phenotype seen in the chronic multifocal osteomyelitis (cmo) mouse [69, 77] and genetic variants in the *FBLIM1* gene, which codes for a filamin-binding protein involved in the regulation of bone remodelling [78], increase the susceptibility to CNO in some [79, 80] but not other [81] studies. Yet, mutations in the human equivalent of PSTPIP2 have not been found in CNO/CRMO patients [10].

In SAPHO, no genetic associations have been established, such as class II HLA antigens [15], LPIN2, PSTPIP2, NOD2 [82] and FBLIM1 [18].

Immune dysregulation

CNO

While the precise immunopathology of CNO remains elusive, cytokine dysregulation in innate immune cells and NLRP3 inflammasome activation are now recognized as important factors in disease development and persistence [10, 13, 68, 83]. The imbalanced expression of downregulated anti-inflammatory cytokines (IL-10 and IL-19) and upregulated pro-inflammatory cytokines (IL-1, IL-6, TNF-α, IL-20) leads to increased osteoclast differentiation and activation through enhanced interaction between receptor activator of nuclear factor κB (RANK) and its soluble ligand RANKL on osteoclast precursor cells [83]. Concurrently, activation of the NLRP3 inflammasome leads to the activation of pro-inflammatory caspase-1, which eventually leads to an increase in pro-inflammatory IL-1b, triggering TNF-α and IL-6 expression [84]. A pathophysiological inflammasome-

independent role of pro-inflammatory IL-1β is confirmed by the cmo mouse model, as IL-1RI- or IL-1β-deficient mice do not develop aseptic osteomyelitis, in contrast to NLRP3- or caspase-1-deficient mice that develop disease [85, 86]. Consistently, increased pro-inflammatory cytokine IL-1β and reduced IL-10 expression in *ex vivo* isolated monocytes were demonstrated in bone tissue biopsies from CRMO patients compared with Langerhans cell histiocytosis or healthy controls [83]. These data provide a rationale for targeting of IL-1R or IL-1β as a therapeutic strategy in CNO. Notably, the cmo mouse model shows that, in addition to neutrophils and macrophages, mast cells may be adjunctive cellular contributors to bone inflammation in CMO/CRMO [87].

SAPHO

As only limited data related to immune regulation in SAPHO syndrome have been available, most information is currently derived from studies conducted in paediatric patients with CNO/CRMO. SAPHO is considered by some as an adult variant of CNO/CRMO, based initially on innate immune dysregulation, which is followed by the activation of adaptive immune mechanisms and effector T cells.

The inflammatory response in SAPHO is supported by an increased serum level of pro-inflammatory cytokines: TNF-α, IL-6, IL-8, IL-18 and IL-23. Activation of the Th17 axis was also observed in patients with SAPHO [88], as well as a depletion of peripheral natural killer cells and an imbalance of Th17 and regulatory T cells [89].

As neutrophil dysfunction plays an important role in inflammatory disorders, the function of neutrophils was investigated in a mother and daughter affected by a SAPHO syndrome–like disease. The major finding showed that the patients' cells displayed aberrant production of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-derived reactive oxygen species (ROS) [90]. However, a follow-up study in a small cohort of patients with SAPHO did not find any aberrant generation of intracellular ROS in neutrophils in patients with SAPHO compared with controls [91]. Recently, transcriptome analysis of the differentially expressed genes in peripheral neutrophils from patients with SAPHO revealed an overactive neutrophil recruitment profile [92], indicating the complexity of neutrophil activation in SAPHO.

In view of prominent osteoarticular manifestations, the osteoclast differentiation pathway is considered significantly impaired in patients with SAPHO. A distinct expression of cytokines was shown in patients with active *vs* inactive disease, with increased IL-6, RANKL and RANKL:osteoprotegerin ratio and decreased TGF-β1 level, respectively [93–95], supporting the aberrant osteoclast differentiation pathway in SAPHO. A genome-wide association study, further validated by whole-exome sequencing, also identified aberrant osteoclast differentiation pathways involved in SAPHO syndrome [96].

Importantly, SAPHO is viewed by some experts as a subset of SpA [44], in view of the clinical overlap with SpA-related diseases, such as a close association with skin manifestations in the spectrum of psoriasis, spinal manifestations closely related to SpA and common patho-immunological profile (dysregulation of the Th17 axis) [45]. The arguments against this concept are based on the lack of genetic association with HLA-B27, the presence of osteitis not typical for SpA and the clinical response to biologics not used in patients with SpA, such as anti-IL-1 [97] or anti-IL-6 [98].

Infectious factors

Infectious factors warrant special attention, as a microbial aetiology was postulated for SAPHO in the 1980s, suggesting that bone lesions may be caused by a low-virulence pathogen or an autoimmune response triggered by a viral or bacterial pathogen [99, 100]. A recent multicentre retrospective epidemiologic survey of 165 PAO patients showed focal infection was detected in 74 (45%) patients: tonsillar infection in 41 (25%), sinusitis in 8 (5%), odontogenic infection in 40 (24%) and others [22]. Several studies reported the isolation of *Cutibacterium acnes*, formerly *Propionibacterium acnes*, from bone specimens from some patients with SAPHO [99–104], while other studies found no evidence of infection in bone biopsies of paediatric patients with CNO [105] and adult patients with SAPHO [38]. *C. acnes* is an ordinary skin, low-virulent saprophyte involved in the pathogenesis of acne that can trigger NLRP3 inflammasome activation and IL-1β, IL-8 and TNF-α processing and secretion in monocytes/macrophages [106]. A relative deficiency of the metabolic transcription factor forkhead box 01 in the nucleus of sebaceous cells in acne and psoriatic lesions may facilitate *C. acnes* escape from innate immunity to persist in a latent state in bone cells [107], supporting the hypothesis that SAPHO may be triggered by persistence of *C. acnes* in genetically predisposed individuals. In support of the infectious aetiology, clinical response to treatment with doxycycline [108] and azithromycin [109] was reported in several cases of SAPHO and CNO [29]. In contrast, the loss of efficacy of antibiotic treatment after its discontinuation [101] stands against this hypothesis. It is important to mention that dental infection, sinusitis, nasopharyngitis and oral dysbiosis are considered important contributors to the pathogenesis of PAO in Japan [4, 5, 22, 38]. The role of microbial exposure as a trigger of immune dysregulation in SAPHO/CNO requires further research.

Diagnostic approach

In the absence of established validated classification and diagnostic criteria, the diagnosis of SAPHO and CNO/CRMO requires a high index of suspicion and is based on typical clinical features and imaging. Differential diagnosis includes infectious, neoplastic, metabolic, granulomatous diseases and monogenic autoinflammatory bone disorders in children [13]. As clinical presentation and disease course can be insidious, intermittent and variable, misdiagnosis is common. To illustrate the clinical challenge of the diagnosis, a study of 64 patients with SAPHO in Germany revealed that after the onset of the first combination of musculoskeletal and dermatologic symptoms, a mean time to diagnosis was 3.8 ± 5.3 years and involved a mean number of 5.7 ± 3.4 physicians per patient [17]. The SAPHO-diagnosing medical specialties were rheumatologists in 70%, radiologists in 14%, general practitioners in 9%, dermatologists in 6%, orthopaedists in 5% and others in 8%. Before the final diagnosis of SAPHO, 72% of patients were diagnosed with at least one other diagnosis, including degenerative disorders, psychosomatic disorders, neoplastic disorders, Tietze's syndrome, neurodermitis and Lyme disease [17]. Therefore, a multidisciplinary approach is warranted for a prompt diagnosis and further joint decisions on optimal disease management.

Laboratory tests

CNO

Consistent with SAPHO, no pathognomonic laboratory findings were identified in CNO/CRMO [13, 31]. Inflammation markers such as ESR and CRP are mostly within the normal range [51] but can be mildly elevated [29, 50] without correlation with clinical manifestations or response to treatment [30]. Notably, high ESR in patients with multifocal disease at presentation predicted a severe disease course in one study [58]. In fact, significantly elevated inflammation markers should prompt the exclusion of underlying infection [110]. A varying frequency of positive ANA (up to 39%) was reported in different CNO cohorts [59, 111], without correlation to disease severity [29]. The prevalence of HLA-B27 ranges from ≈7% [29, 59, 111] to 15–16% [51, 54]. Remarkably, there was no evidence for a difference in the presence of arthritis or number of bone lesions in HLA-B27-negative or -positive patients [51]. HLA-B27 genotype frequency was higher in three European CNO populations ($n = 572$) compared with local controls ($n = 33\,256$) [112]. This association was much stronger in male compared with female patients (odds ratio 1.99, corrected P-value = .015), suggesting that carriage of HLA-B27 may be associated with a greater risk of developing CNO, particularly in males [112]. Preliminary reports indicate a potential set of serum inflammatory parameters, including IL-6, CCL-11/eotaxin and others, to act as a biomarker of CNO [113] for future use following validation of the proposed test.

SAPHO

Currently there are no pathognomonic laboratory findings of SAPHO syndrome. Variable rates of elevated inflammatory markers (ESR and CRP) were observed in different cohorts of SAPHO [16, 19, 20, 23, 38, 62] and adult CNO [27]. Markers of bone metabolism were mainly unreported, except for alkaline phosphatase, which was increased in up to 17% of patients [27], and matrix metalloproteinase-3, which was increased in 26% of patients in one study [38]. Importantly, no clinical correlation between the value of inflammatory markers and disease activity or progression was confirmed [19]. A low prevalence of positive autoantibodies, including RF and ANA, without any specific profile or clinical correlation, was reported in some studies [16, 19, 20, 27, 114]. Notably, elevated serum IgG4 levels (>1400 mg/dl) were detected in 23% (12/52) of a Chinese cohort of SAPHO patients [115]. Patients with elevated serum IgG4 levels had significantly higher pain scores, higher inflammatory markers and higher axial disease activity scores (BASMI and ASDAS) compared with patients with normal serum IgG4 levels [115]. The clinical implication of this finding needs to be explored further. Indeed, a global physician survey indicated that inflammation and bone markers were regarded as unhelpful for diagnostic and monitoring purposes of SAPHO/adult CNO [116]. HLA-B27 carriage was reported in 4–30% of SAPHO/adult CNO patients by some [14, 16, 27, 62, 117, 118] but not by other studies [28]. In a long-term follow-up study of 120 patients with SAPHO, positive HLA-B27 antigen was not associated with a particular pattern of distribution of arthritis or osteitis [14]. Notably, Japanese patients with axial disease were HLA-B27 negative [5].

Imaging

Imaging plays a key role in the diagnosis of SAPHO and CNO. As subclinical lesions are common, early detection of the disease burden is especially important at the initial evaluation. Radiographic features differ based on the location of osteoarticular disease and disease stage [43]. Early lesions are typically osteodestructive as opposed to later osteoproliferative lesions [43]. Radiographically, hyperostosis appears as osteosclerosis with thickening of the trabeculae and cortex and narrowing of the medullary canal. Coexisting osteosclerotic and osteolytic lesions can often be seen in the metaphyses of the long bones of the lower extremities and around the sternoclavicular joint [119]. In practice, conventional plain radiography is the first step in the evaluation of SAPHO/CNO syndrome, whereas MRI is considered the preferred imaging modality for diagnosis [44, 116].

SAPHO

Bone scintigraphy. Radionuclide bone scan is useful for surveying the entire skeleton for multiple bone lesions, including subclinical ones [43, 62]. The typical bull's head sign indicating increased uptake *in* the sternoclavicular region is characteristic of SAPHO/PAO with sternoclavicular involvement [120]. Based on whole-body scintigraphy, SAPHO syndrome can be classified into different clinical patterns, as suggested by a study of 157 Chinese patients with SAPHO [39]. Yet the use of this modality is limited given the risk of ionizing radiation exposure but may be the only method of whole-body imaging in some places.

CT. CT scan outlines the location and extent of bone lesions with high spatial resolution. This imaging modality is useful in delineating the anterior chest involvement. Furthermore, although at the risk of high radiation dose, a whole-spine CT has unique advantages over radiographs in demonstrating spinal lesions and their extent with high resolution [42].

MRI. MRI has several advantages over other imaging modalities, such as high sensitivity for depicting early lesions, distinguishing active from chronic lesions and the lack of radiation. Therefore, MRI has evolved in recent years as a leading modality for diagnosis and monitoring SAPHO/CNO. MRI can detect active inflammatory lesions and osteitis indicated by bone marrow oedema as well as image soft tissue. Structural lesions, such as erosions, hyperostosis and ankylosis, can also be seen on MRI (T1 sequence). The characteristic MRI findings of the anterior chest wall lesions in SAPHO patients include a triad of enthesitis, synovitis and osteitis, with prominent lesions in the first rib area [36]. Spinal MRI can detect the characteristic lesions seen in patients with SAPHO: vertebral corner lesions, non-specific spondylodiscitis, osteolytic lesions with variable degrees of vertebral body collapse, osteosclerosis, hyperostosis, paravertebral ossification and sacroiliitis [121]. Whole-body MRI should be performed in CNO for the detection and distribution of symptomatic and clinically silent multifocal bone and soft tissue lesions [13]. Two radiological scores developed for the assessment of the severity and disease activity of CNO lesions are the Radiologic Index for Non-bacterial Osteomyelitis [57] and ChRonic non-bacterial Osteomyelitis MRI scoring [122]. Application of a machine learning algorithm shows the potential in differentiating CNO lesions from growth-related

bone marrow changes on whole-body MRI, further improving the precision of this modality [123]. The importance of early recognition of spinal involvement in CNO/CRMO by whole-body MRI has been recently emphasized, as kyphosis and scoliosis occur in one-quarter and vertebral height loss in one-third of children at spinal disease recognition [56]. The overall number of bone lesions identified on MRI correlates with clinical severity scores at initial imaging [124]. Moreover, quantitative imaging features, such as volume and T2 signal intensity of bone lesions, can be useful for the prediction of clinical response [125]. Whole-body MRI is further valuable for identifying complications and monitoring the response to treatment [126–128].

Fluorodeoxyglucose (FDG) PET/CT. FDG PET/CT is useful in differentiating active lesions from inactive bone lesions and excluding metastatic disease in challenging cases [129]. This modality showed a moderate to substantial agreement in revealing anterior chest wall and axial skeletal lesions compared with CT and bone scan [130]. The use of FDG PET/CT is restricted to tertiary centres.

Ultrasound (US). US is a diagnostic tool for evaluation of synovitis, enthesitis and early anterior chest wall inflammation [131]. Synovitis with a power Doppler signal has been detected in sternoclavicular joints and peripheral joints of patients with SAPHO syndrome compared with controls [132].

Bone biopsy

SAPHO

In the absence of a pathognomonic histopathological pattern, the main indication for the performance of bone biopsy in a workup of SAPHO syndrome is the exclusion of alternative diagnoses, especially malignancy and infection. Histopathological findings can range from acute to chronic inflammatory features, with early bone lesions demonstrating polymorphonuclear infiltrates resembling infectious osteomyelitis [117]. Later disease stages are characterized by mononuclear cell infiltration and enlarged sclerotic tubercula with increased marrow fibrosis [117]. An immunohistology analysis of a bone sample from a Japanese patient with SAPHO showed excessive production of osteoblasts, but not osteoclasts, contributing to increased bone formation, including abundant osteoid and woven bone pain [133]. This type of bone formation indicates fragile and mechanically weak bone, resulting in bone pain [133]. However, recent international surveys reflecting global clinical practice indicate that bone biopsy is not needed in most cases of SAPHO diagnosis [44, 116].

CNO

Bone biopsy is reserved for cases where the clinical or radiological findings are inconclusive for CNO or in case of a focal lesion to exclude alternative diagnoses [10, 31]. As in the case of SAPHO, there is no pathognomonic histopathological pattern for CNO. The histological findings within early CNO lesions include cellular infiltrate of monocytes and neutrophils, whereas infiltrates of monocytes, lymphocytes and plasma cells with varying degrees of sclerosis and fibrosis are present in the late lesions [134, 135].

Diagnostic criteria and outcome measures

SAPHO

In Japan, Sonozaki *et al.* [136] were pioneers in setting the first diagnostic criteria for PAO in 1981 based on a combination of PPP and costoclavicular or manubriosternal involvement. These criteria have been recently updated and modified, including the anatomic location of anterior chest wall involvement, incorporation of lesions other than the anterior chest wall into the diagnostic criteria and incorporation of MRI in addition to simple radiographs for early diagnosis, specifying detailed imaging findings [6] (Table 1). In Europe, Chamot *et al.* [2] proposed in 1987 the first set of diagnostic criteria for SAPHO based on clinical grounds. These criteria have undergone several revisions. The criteria proposed by Kahn *et al.* [117] in 1994 included pathologically confirmed osteitis with or without characteristic skin manifestations. The 2003 diagnostic criteria, based on a cohort of 120 patients with SAPHO, included the combination of characteristic osteoarticular and skin manifestations, requiring an exclusion of concurrent inflammatory bowel disease, bone infection and tumours (Table 1) [137]. These diagnostic criteria

Table 1. Diagnostic criteria for SAPHO syndrome and PAO

Benhamou *et al.* (1988) [2]	Kahn and Khan (1994) [117]	Kahn (2003) [137]	Modified Sonozaki criteria (2022) [6]
At least one of the following four conditions: osteoarticular manifestations of acne conglobate, acne fulminans or hidradenitis suppurativa; osteoarticular manifestation of PPP; hyperostosis (of the anterior chest wall, limbs or spine) with or without dermatosis; CRMO involving the axial or peripheral skeleton with or without dermatosis	At least one of the following three conditions: chronic recurrent multifocal sterile and axial osteomyelitis, with or without dermatosis; acute, subacute or chronic arthritis associated with PPP, pustular psoriasis or sarcoid arthritis; any sterile osteitis associated with PPP, pustular psoriasis or sarcoid arthritis	At least one of the following five conditions: bone–joint involvement associated with PPP and psoriasis vulgaris; bone–joint involvement associated with SA; isolated sterile hyperostosis/osteitis; CRMO (children); bone–joint involvement associated with chronic bowel diseases Exclusions: infectious osteitis, tumoral conditions of bone and non-inflammatory condensing lesions of the bone	The first obligatory criterion with either a second or third criterion: history and/or current diagnosis of PPP by a dermatologist; anterior chest wall lesions fulfilling both (a) tenderness or swelling and (b) imaging abnormality (X-ray or MRI) X-ray: bone sclerosis, hyperostosis, bone production, erosion, syndesmophyte, ankylosis MRI: Bone marrow oedema (BME)/osteitis, chronic changes non-bacterial musculoskeletal (MS) lesions (bone, joint, spine, SI joints) other than anterior chest wall area fulfilling the below criteria: lesion with tenderness/pain plus imaging abnormality (X-ray or MRI) X-ray: spine (endplate lesions) and same as above. MRI same as above

frame a broad and heterogeneous entity of SAPHO and lack clinical validation.

CNO

Several groups have proposed diagnostic or classification criteria, none of which have been prospectively validated at this stage [110, 111, 138]. The common denominator of these criteria includes disease duration of ≥6 months, stable clinical appearance and the presence of multifocal bone lesions with a typical appearance on imaging or a unifocal lesion with no evidence of infection or malignancy [10]. The use of the suggested criteria may obviate the need for biopsy in some patients.

As there is an obvious need for validated classification criteria for both SAPHO and CNO, new developments in this field include an initiative to develop validated outcomes in collaboration with OMERACT, a program of work designed to achieve consensus on diagnosis and treatment of SAPHO/CNO, and new ACR/EULAR classification criteria for CNO. Because of the close overlap between SAPHO and CNO, international research groups currently collaborate on developing a core domain set for both entities to be used in observational studies and clinical trials [139].

The OMERACT group is led by Melissa Oliver from Indiana University (Indianapolis, IN, USA). A number of stages of the OMERACT process have been completed, the aim being to develop a core set of outcomes for clinical trials involving people with SAPHO/CNO. At the moment, the group has completed a scoping review, focus groups of patients, online discussion boards and a Delphi exercise, the results of which are a shorter list of candidate core domains. Further work is now needed to reduce the number of these domains and to provide definitions and instruments accordingly.

The work designed to achieve consensus on diagnosis and treatment of SAPHO/CNO is led by a group from Leiden, The Netherlands, specifically Anne Leerling and Liesbeth Winter. Several Delphi rounds and meetings have been conducted. The group has already published a literature review to provide background for the current initiative [27]. In addition, work done by the ACR and EULAR has resulted in the development of new classification criteria for childhood CNO, although these have only been published in abstract form at the moment (Proposed classification criteria for pediatric CNO and CRMO explained; https://www.acrconvergencetoday.org/proposed-classification-criteria-for-pediatric-cno-and-crmo-explained/).

In parallel, based on the Chronic Nonbacterial Osteomyelitis International Registry (CHOIR), a clinical disease activity score has been developed and validated for CNO monitoring and assessment of treatment effectiveness [140].

Treatment of SAPHO

The evidence-based treatment algorithm in SAPHO is lacking in clinical randomized trials [4, 141–143] in this rare disease. Treatment choice is based on case reports, case series, retrospective reports and several open-label trials. In fact, a wide spectrum of therapeutic agents are in off-label use to treat SAPHO, extrapolated from treatment approaches in psoriasis, severe acne, PPP, PsA and SpA [4, 141, 144]. To date, there are no data on long-term efficacy, adverse events and outcomes of different treatments in SAPHO. The treatment of SAPHO has been extensively reviewed in recently published articles [4, 141–143]. The treatment options range from antibiotic regimens and tonsillectomy used in Japan, NSAIDs (generally considered as the first-line treatment), corticosteroids, bisphosphonates, DMARDs, anti-cytokine biologics and Janus kinase inhibitors (used as advanced lines of treatment). There are no treatment protocols outlining the treatment choice and sequence. Currently a multicentre randomized double-blind clinical trial for evaluation of the efficacy and safety of etanercept in patients with SAPHO is ongoing (NCT06011889; https://clinicaltrials.gov/study/NCT06011889?cond=SAPHO%20Syndrome&rank=3).

CNO

Currently there are no approved pharmacological treatments for CNO/CRMO. The development of consensus treatment plans (CTPs) by members of the Childhood Arthritis and Rheumatology Research Alliance for the first 12 months of therapy for CNO patients refractory to NSAID monotherapy and/or with active spinal lesions was the first step in reaching an international consensus on the approach to treatment [145]. The three CTPs include methotrexate or sulfasalazine, TNF inhibitors with optional use of methotrexate and bisphosphonates. Short courses of glucocorticoids and continuation of NSAIDs are permitted for all regimens [145]. Recently, an international group of 14 CNO experts and 2 patient/parent representatives was assembled to generate consensus to inform and conduct future randomized controlled trials in CNO [146].

Conclusion

SAPHO and CNO are rare conditions of bone with both autoinflammatory and autoimmune features. Both diseases can range from a monophasic low-grade condition to a polyphasic, multisite condition with severe impact. The rarity of SAPHO/CNO has precluded research efforts in the past, but new collaborations and consensus initiatives should lead to an agreed definition and validated outcome measures. The main topics for the upcoming research agenda are presented

Table 2. Research agenda

1. Development of classification and diagnostic criteria (Leiden) of SAPHO/CNO. International collaboration to provide cases and controls are required for the development and validation of classification criteria.
2. Data collection on phenotypes and the relation to imaging and genetics in well-defined patients.
3. Development of a core outcome set (OMERACT) and subsequent development of composite measures of disease activity in both SAPHO and CNO.
4. Determination of the significance of asymptomatic lesions in CNO.
5. Head-to-head randomized placebo controlled clinical trials to compare the efficacy of bisphosphonates/TNF inhibitors/IL-17 inhibitors. This requires clear inclusion/diagnostic criteria and standardized outcome measures.
6. Evaluation of the natural history of both diseases, prognosis and optimal treatment duration.

in Table 2. Once these are in place, the research community will be in a better place to examine pathophysiology and natural history and to carry out appropriate randomized controlled trials of treatments, including strategy trials and head-to-head studies.

Data availability

No new data were generated in support of this research.

Authors' contributions

V.F. performed the literature review and wrote the first draft of the article. Other authors reviewed and edited this draft. All authors approved the final draft of the article.

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