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Expert consensus recommendations for the diagnosis and treatment of chronic non-bacterial osteitis (CNO) in adults

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Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/ard-2024-226446).

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Received 19 July 2024
Accepted 1 November 2024

To cite: Winter EM, Dekkers OM, Andreasen CM, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/ard-2024-226446

ABSTRACT

Background There is considerable practice variation in labelling, diagnosis and treatment of adults with sterile bone inflammation. We developed a expert consensus recommendations on the disease definition, diagnosis and treatment of this rare condition.

Methods Systematic literature review and Grading of Recommendations, Assessment, Development and Evaluations-based appraisal of evidence, two Delphi surveys and three digital and in-person consensus meetings with a multidisciplinary expert panel and patient representatives.

Results A consensus disease definition was developed and the term 'chronic non-bacterial osteitis' (CNO) is proposed to describe adults with sterile bone inflammation. For initial imaging evaluation of adults with suspected CNO, the panel recommends MRI or otherwise CT combined with nuclear imaging. Whole-body imaging at initial evaluation can be considered for diagnostic and prognostic purposes. Suggested first-line treatment in adults with active CNO includes non-steroidal anti-inflammatory drugs/cyclooxygenase 2-inhibitors. Second-line treatment preferably consists of intravenous bisphosphonates, and otherwise tumour necrosis factor-α inhibitors. Choice between them should be individualised, considering the presence of additional inflammatory features. The panel further discusses outcome measures, follow-up and management of adverse events and complications.

Conclusions and future perspectives These expert consensus recommendations are intended to support healthcare professionals worldwide in their care for adults with CNO. They also lay the groundwork for establishing international patient registries, translational research lines and multicentre trials, all of which are urgently required.

INTRODUCTION

Sterile bone inflammation (SBI) represents a rare and heterogeneous disease spectrum that affects children and adults.[1] Various terms are currently in use to describe patients with SBI, including chronic non-bacterial osteomyelitis, chronic recurrent multifocal osteomyelitis (CRMO), synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome, diffuse sclerosing osteomyelitis (DSO), pustulotic arthro-osteitis (PAO), sternocostoclavicular hyperostosis (SCCH) and more.[2] The disease definition of SBI is complex, owing to its broad clinical presentation and overlap with other autoinflammatory musculoskeletal and non-musculoskeletal disorders.[3–5] In adults, SBI mostly manifests as osteitis of the anterior chest wall, but the vertebrae, mandible and pelvis may also be involved.[6] Initial radiological signs comprise bone marrow oedema and osteolysis, while progressive structural alterations secondary to inflammation include sclerosis, hyperostosis, erosion, soft tissue ossification and joint ankylosis.[7] Apart from bone inflammation, patients may present with a range of other autoinflammatory features, including musculoskeletal features (inflammatory arthritis, sacroiliitis, dactylitis, enthesitis), dermatological features (palmoplantar pustulosis (PPP), psoriasis, hidradenitis suppurativa, severe acne), uveitis and inflammatory bowel disease.[2 8] The clinical management of SBI presents major challenges. Unifying diagnostic criteria are lacking, pathophysiology is largely unknown and there are no standard outcome measures or evidence-based treatment modalities.[9 10] Individuals with SBI endure high disease burden due to bone pain impacting daily functioning, and, especially without timely treatment, are at risk for complications such as skeletal deformities, compromised joint functionality, neurovascular entrapment or vertebral fractures.[7 11–15] The provision of care for patients with SBI is fragmented, spread across

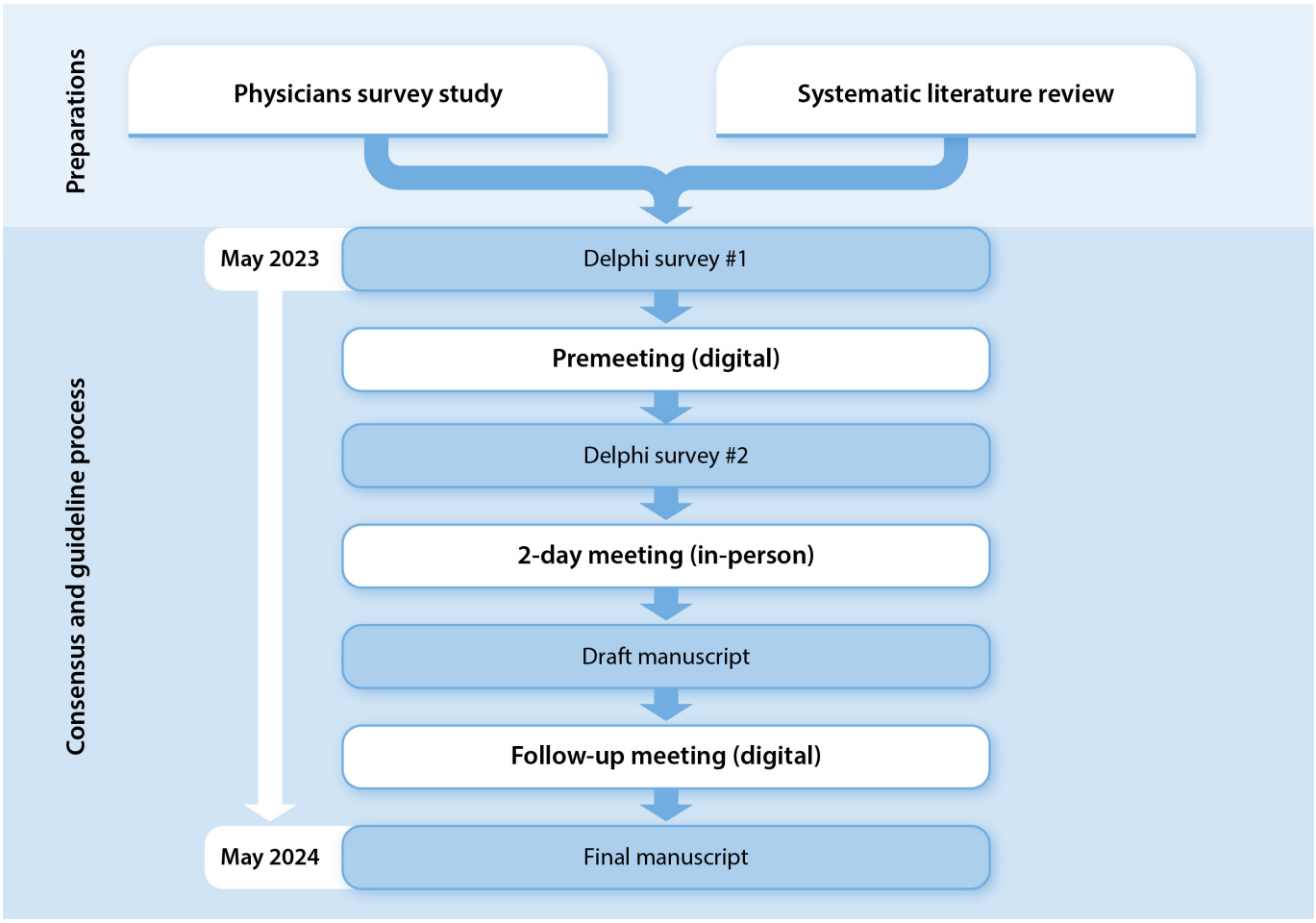

Figure 1 Schematic overview of consensus process.

diverse medical disciplines such as rheumatology, orthopaedic surgery and endocrinology, with wide variety in (off-label) treatment strategies.[2] Clearly, consensus recommendations and a research agenda are necessary steps towards clinical advancement for SBI. Recognising this imperative, we convened a consensus group to formulate a disease definition, to choose an overarching name for the SBI spectrum, systematically develop recommendations for the diagnosis and treatment and develop a research agenda.

We concentrate on chronic non-bacterial osteitis (CNO) that occurs in adulthood, acknowledging the distinct clinical differences between adult-onset and paediatric-onset forms of the disease. Patients with adult-onset CNO typically present with lesions confined to one or two areas in the axial skeleton. In contrast, childhood-onset CNO often follows a recurrent multifocal pattern, also involving appendicular bones, and is more clearly associated with systemic inflammation.[1 16] While the recommendations focus on adult (-onset) CNO, we recognise that paediatric patients wth CNO may transition into adulthood with ongoing disease activity. The applicability of these recommendations to such individuals will depend on the extent to which their disease resembles the adult phenotype, thereby ensuring that management strategies are appropriately tailored to their specific clinical characteristics. The consensus recommendations are intended to support healthcare professionals worldwide, especially those who are not situated at expert centres and encounter very limited numbers of adults with SBI. These generally include secondary care specialists working in rheumatology, endocrinology, clinical osteology, orthopaedics, radiology and nuclear medicine. Although we recognise the limited evidence supporting diagnostic and therapeutic recommendations for adults with SBI, we are confident that they represent a valuable synthesis of the best-available literature and clinical expertise. As such, it has the potential to enhance care for adults with SBI while future studies are awaited. The initial stage in developing recommendations for diagnosis and treatment involved choosing a unified name for the spectrum of SBI. After thoughtful discussion, the expert panel and patient representatives chose the term 'CNO' for this spectrum, with distinctions made based on age—adult CNO or paediatric CNO. The reasoning behind this is detailed later in this document, but from this point, for clarity, we will refer to the patient population of interest as '*adult CNO*'.

METHODS

This consensus project was initiated by ATL and EMW from the Center for Bone Quality of the Leiden University Medical Center. The project's scope was adults with SBI (previously labelled as chronic non-bacterial osteomyelitis, CRMO, SAPHO, PAO, SCCH, DSO and henceforth designated as adult CNO). The bone marrow oedema syndrome, traumatic causes of bone marrow oedema, spontaneous osteonecrosis and genetic syndromes like Majeed or deficiency of the interleukin (IL)-1 receptor antagonist were considered beyond the scope. The expert consensus recommendations were developed and

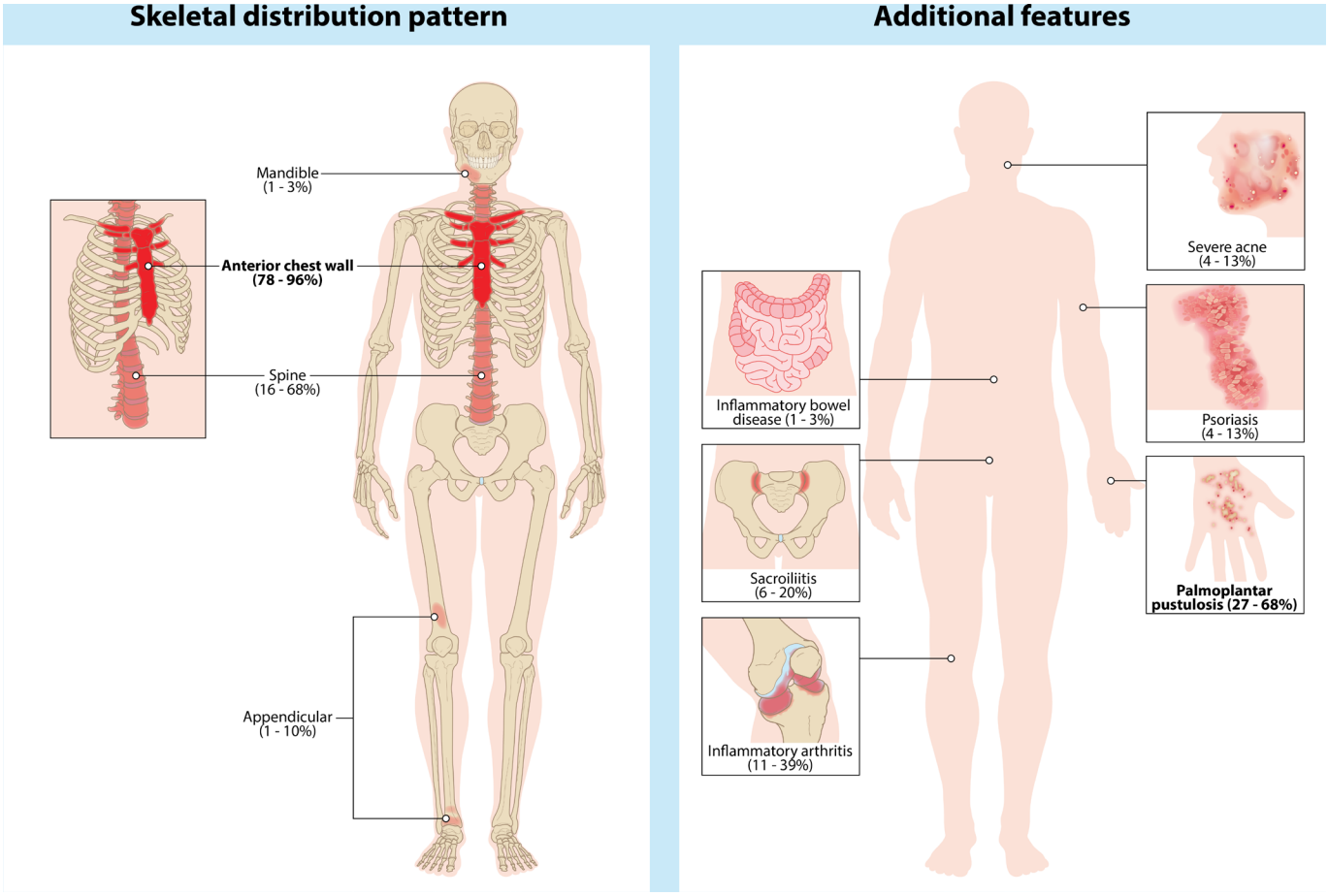

Figure 2 Visual representation of disease definition of adult CNO; skeletal distribution pattern of osteitis (left) and additional (extra)-skeletal features (right). Reported as 95% CI.

reported according to the Appraisal of Guidelines Research and Evaluation-Recommendations Excellence (see online supplemental file S1 for reporting checklist)[17] and endorsed by The European Calcified Tissue Society, The European Reference Network of Rare Bone Diseases (formally) and European Society of Endocrinology (pending final publication). An overview of the project's steps is outlined in figure 1. As a first step, we conducted a physician survey study mapping current clinical practices for adults with CNO, which is published elsewhere.[18] Based on this, the domains of interest for the consensus recommendations were chosen (see online supplemental file S2 for complete list). For all domains, a systematic literature review was performed and results were synthesised into summary of evidence tables, also including the survey study results (online supplemental file S3). Methods used for the systematic literature review with appraisal of evidence, including the Grading of Recommendations, Assessment, Development and Evaluations approach as outlined in the Cochrane Handbook for Systematic Reviews of Interventions[19] are detailed in online supplemental file S4. In-detail descriptions of the expert panel constitution and the decision-making process are presented in online supplemental file S4 as well. Briefly, we assembled a diverse and inclusive expert panel via inviting (a) all participants of the aforementioned physician survey study, (b) experts via relevant international networks and societies and (c) authors of scientific studies on CNO. Input from patient representatives was arranged with the Dutch CNO patient association. With the summary of evidence as resource for expert panel members, the consensus recommendations were subsequently developed over the course of two Delphi survey rounds (results outlined in online supplemental files S5 and S6) and three meetings (two digital and a 2-day in-person). All domains of interest were reviewed in the in-person meeting, as well as a research agenda. Ultimately, the complete panel assessed the final recommendations using a 0–10 Likert scale, where 0 represented no agreement and 10 signified full agreement. The metrics of agreement are presented in the recommendation tables, which include the mean score, SD and the percentage of panel members who rated the recommendation 8/10 or higher.

CONSENSUS STATEMENT: DISEASE DEFINITION

Based on the systematic literature review, Delphi results and panel discussions, it became evident that CNO represents a rare and clinically heterogeneous disease spectrum (see also online supplemental file S3, Q1A and Q1B for supportive evidence). It is not known whether the full spectrum shares the same autoinflammatory mechanisms, or whether it entails multiple (partially) distinct conditions. The connection between adult CNO and musculoskeletal rheumatic diseases such as axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA), which share similar features, remains similarly ambiguous, as does the link between adult and paediatric disease. Despite these uncertainties, the panel proposes the following disease definition to capture the concept of adult CNO (figure 2).

CNO in adults is a condition characterised by SBI, which affects one or multiple bones, and primarily manifests in the anterior chest wall. Adult CNO may exhibit different temporal patterns, including monophasic, chronic or relapsing-remitting.

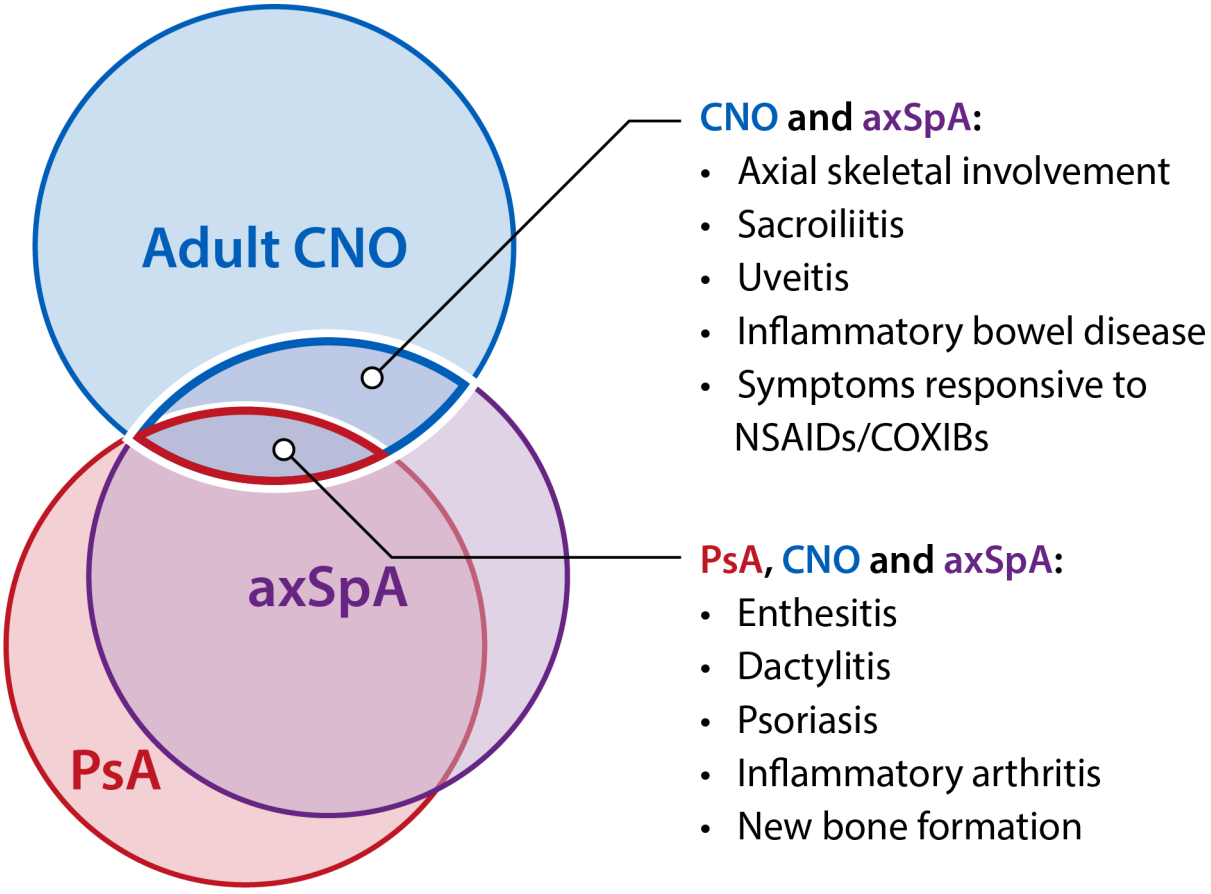

Figure 3 Venn diagram displaying conceptual overlap between adult chronic non-bacterial osteitis (CNO) and axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) based on features seen in the multiple conditions. COXIB, cyclooxygenase-2 inhibitor; NSAID, non-steroidal anti-inflammatory drug.

Typical imaging characteristics of bone inflammation include bone marrow oedema, osteolysis, increased tracer uptake on nuclear imaging and in later stages, sclerosis, erosions, hyperostosis (seen as endosteal and periosteal thickening), soft tissue ossification and ankylosis[7 11 20–26] (see online supplemental file S2, Q2A and Q2B for supportive evidence). While isolated bone inflammation is the most common presentation, additional features that may be seen are:

- Musculoskeletal: inflammatory arthritis, sacroiliitis and possibly enthesitis and dactylitis.
- Non-musculoskeletal: PPP, psoriasis, hidradenitis suppurativa, severe acne and rarely uveitis and inflammatory bowel disease.

Regarding the skeletal distribution, the panel recognises that the frequency of involvement sites is difficult to accurately estimate, due to three factors. First, estimates from published cohorts may be subject to referral bias, as certain distribution patterns prompt referral to specific specialists (eg, rheumatologists for multifocal appendicular involvement, orthopaedic evaluation for a unifocal lesion, anterior chest wall involvement and associated shoulder dysfunction). Second, the involvement of certain sites may be easier and faster to diagnose over others, which may distort estimates. Third, the presence of silent lesions in up to 67% of patients and the lack of routine whole-body imaging contribute to the potential underestimation of specific skeletal involvement sites.[20 23 27] Notwithstanding, the panel identifies the anterior chest wall, including the clavicles, upper ribs and sternum, as the most frequently involved sites, which is supported by recent meta-analyses reporting involvement rates between 78% and 96%.[2] Following this, the spine, appendicular skeleton, jaw and pelvis may be involved.[2 6 24 28] Based on clinical experience (without available supporting literature), the panel reports that most patients exhibit multifocal involvement, although cases affecting a single bone are also recognised.

Adult CNO may exhibit various additional features, some of which lead a clinical overlap with axSpA and PsA (figure 3). Although all features are susceptible to potential over-reporting or under-reporting, the most prominent among these is the presence, or history of PPP, reported in 37%–68% of patients. Additionally, non-erosive peripheral arthritis is observed in 11%–39% of cases, followed by psoriasis (4%–14%) and severe acne (4%–13%).[2 29–32] Uveitis, dactylitis, enthesitis, erosive arthritis, hidradenitis suppurativa, tonsillitis, periodontitis and inflammatory bowel disease have been documented in a few CNO cases, although prevalence estimates are highly uncertain.[33–35] Despite this variety of features, the panel's experience is that the vast majority of adult patients with CNO present with isolated osseous disease.

The panel recognises that adult patients with CNO present mainly with bone pain, but symptomatology may vary significantly depending on the sites and the presence of additional features. According to recent literature, the typical age of presentation falls within the range of 29–46 years, and 60%–73% of the patients are female[2] (see online supplemental file S3, Q1C for supportive evidence). In early CNO, physical examination findings may reveal local soft-tissue swelling, erythema, tenderness and impairment of function. CNO may progress over time to the point where bony swelling becomes apparent, but due

Table 1 General recommendations

General recommendations	Level of evidence for clinical utility (see online supplemental file S3)	LoA, mean±SD	LoA, % ≥8
R1: consider referral to an expert centre for all adult patients with CNO, and refer difficult-to-treat patients if not done initially.	► ○○○	9.51±0.77	97.30%
R2: adults with CNO should be diagnosed and treated by a multidisciplinary team, led by an expert in this disease, preferably a rheumatologist. In the absence of a rheumatologist, a specialist with expertise in autoinflammatory and bone-related disorders should assume this role. The team should involve musculoskeletal imaging experts and other medical specialists according to the presence of additional features.	► ○○○	9.51±0.80	97.30%
R3: aim for long-term follow-up in all patients. When follow-up is discontinued, inform patients that their condition may return with similar but different features and involvement sites in the future.	► ○○○	9.54±0.73	97.30%

○ indicates 4-point scale ranging from very low to low to moderate to high according to the Grading of Recommendations, Assessment, Development and Evaluations approach.
CNO, chronic non-bacterial osteitis; LoA, level of agreement.

to the frequent diagnostic delay, patients often present with a bony swelling already at first consultation. According to the panel's clinical experience, systemic symptoms such as fever or unexplained weight loss are rare (fever noted in up to 14%, as reported in literature) and warrant further investigation to exclude other causes than CNO.[2]

CONSENSUS STATEMENT: NOMENCLATURE

The panel unanimously recognises that the multitude of names for 'adults with SBI' is confusing, inconvenient and burdensome for patients (see online supplemental file S3, Q3 for overview). From various names currently in use, several are deemed unsuitable by the panel, such as SCCH (too descriptive and narrow), PAO (excluding patients without PPP) and CRMO (a recurrent multifocal pattern is rare in adults). Although SAPHO is a widely recognised term, its broad scope makes it poorly applicable to the majority of patients who never develop additional features, leaving the S, A and P of the acronym largely unfulfilled. This idea is echoed by patient representatives, who prefer a concise name, not laden with features that often do not occur. Alternatively, 'chronic non-bacterial osteomyelitis' effectively captures the core disease feature, is short and inclusive and has recently been adopted in the paediatric community. However, the panel perceives that the term 'osteitis' better suits the pathology than 'osteomyelitis'. Therefore, CNO has been proposed to represent 'adults with SBI' in clinical and research practice. For paediatric CNO, a transition from 'osteomyelitis' to 'osteitis' is also anticipated. The panel recommends discontinuing the use of other historical names, both in adults and children.

GENERAL RECOMMENDATIONS

R1: Consider referral to an expert centre for all adult patients with CNO, and refer difficult-to-treat patients if not done initially.

Rationale

Due to the rarity of the condition and the limited evidence on diagnostics and treatment, the panel suggests considering referral to an expert centre for all patients, and specifically recommends referral of all difficult-to-treat patients if not done already (see 'Treatment recommendations' section). Depending on healthcare system, expert centres may include tertiary referral centres, specific government-appointed facilities and centres that are part of reference networks for rare diseases (table 1). The panel and patient representatives further recognise that a hub-and-spoke care model, involving periodic assessments at an expert centre with follow-up and treatment administered at nearby clinics, would be a patient-friendly approach, minimising travel while ensuring expertise with larger patient numbers.

R2: Adults with CNO should be diagnosed and treated by a multidisciplinary team, led by an expert in this disease, preferably a rheumatologist. In the absence of a rheumatologist, a specialist with expertise in autoinflammatory and bone-related disorders should assume this role. The team should involve musculoskeletal imaging experts and other medical specialists according to the presence of additional features.

Rationale

Adults with CNO should ideally be diagnosed and managed by a multidisciplinary team, preferably led by a rheumatologist. In the absence of a rheumatologist, another specialist with expertise in autoinflammatory and bone-related disorders, such as an endocrinologist or a clinician-osteologist, may take on this role, depending on the healthcare system (see online supplemental file S3, Q4 for current overview and quality appraisal). Close collaboration with musculoskeletal imaging experts is necessary in all patients, and other disciplines should be involved as necessary if additional features are present.

R3: Aim for long-term follow-up in all patients. When follow-up is discontinued, inform patients that their condition may return with similar but different features and involvement sites in the future.

Rationale

The panel agreed that development of new (rather than evolving existing) bone lesions is very rare in adults. Only in the anterior chest wall it is observed that more bones become involved in the inflammatory process, for example, progressing from one clavicle into rib and manubrial lesions. In other body parts, like the spine, the involvement of bones is usually already 'complete' at presentation. However, there are no known predictors to identify patients at risk for new lesions,[36–38] the disease may follow a relapsing-remitting course, and additional features like skin manifestations may occur long before or after the presentation of osteitis. Therefore, long-term follow-up in all patients is recommended. The frequency of follow-up visits varies according to local protocols, healthcare organisation policies, patient-specific factors and importantly, treatment type. Generally, the panel considers it advisable to schedule follow-up visits 3–6 months after the initial diagnosis, and with larger intervals (eg, every 12–24 months) after clinical stabilisation.

DIAGNOSTIC RECOMMENDATIONS

Across the different stages of diagnostic evaluation, differential diagnoses to consider in adults with suspected CNO include infectious osteomyelitis, malignant bone tumours, other rheumatic musculoskeletal diseases, Tietze's syndrome, metabolic bone diseases and sternoclavicular subluxation (table 2, figure 4). Clinical findings suggestive of these diagnoses are listed in table 3.

R4: Perform clinical evaluation with specific attention for additional features and fulfilment of axSpA and PsA classification criteria. Consider diagnostic involvement of relevant medical disciplines.

Rationale

In adults with suspected CNO, the panel recommends performing a thorough clinical evaluation including history of initial and presenting complaints, full medical history and family history of autoinflammatory or autoimmune diseases in first-degree relatives.[39] Atraumatic bone pain persisting for over 6 weeks, with inflammatory properties such as pain irrespective of motion, or during the night, is suggestive of CNO.[1 8 40–42] The patient should be assessed for other inflammatory features (figure 2). Involvement from a dermatologist, ophthalmologist and gastroenterologist can be considered depending on suspected features. It also is recommended to review whether there is fulfilment of classification criteria for axSpA or PsA, as this may have implications for clinical management.

R5: Conduct routine laboratory investigation with full blood and differential count, inflammatory markers, renal function, alkaline phosphatase, calcium, 25-hydroxy-vitamin D, parathyroid hormone levels and phosphate. Consider on case-by-case basis (eg, for differential diagnosis or pretreatment evaluation): bone turnover makers, anti-CCP, RF, HLA-B27.

Rationale

The panel acknowledges that most laboratory markers of inflammation lack specificity for adult CNO, but may be used to investigate differential diagnoses[2] (see online supplemental file S3, Q5 for supportive evidence). As part of the initial evaluation, the panel recommends routinely measuring complete blood count with white blood cell differential, and inflammation markers to assess the degree of systemic inflammation. Renal function should be included to assess the safety of medications. Alkaline phosphatase, calcium, 25-hydroxy-vitamin D, phosphate and parathyroid hormone levels should routinely be measured to exclude other metabolic bone diseases, such as osteomalacia, Paget's disease or hypophosphatasia. The following tests can be considered on a case-by-case basis:

- Bone turnover markers such as serum procollagen type I N propeptide (P1NP) and C-terminal telopeptide (CTx); these can be determined, preferably in fasting blood samples, to aid the evaluation of other metabolic bone diseases.[43–45]
- Anticitrullinated protein antibodies (anti-CCP) and rheumatoid factor (RF); in patients presenting with inflammatory (erosive) polyarthritis, elevated levels may support a diagnosis of rheumatoid arthritis.
- Human leucocyte antigen B27 (HLA-B27) typing; in cases with axial involvement or inflammatory back pain, these may support the diagnosis of axSpA. HLA-B27 positivity has so far not been shown to be associated with adult CNO.

R6: Perform imaging of the suspected region, giving priority to a modality suitable for assessing both activity and structural changes. MRI should be preferred but combined [^{99}mTc]Tc-HDP SPECT/CT or PET/CT with a bone-seeking radiotracer are reasonable alternatives.

Rationale

Imaging of the clinically suspected region plays a pivotal role in the diagnosis of adult CNO. The panel agrees that the goals of imaging at initial evaluation are to (1) visualise characteristic features associated with the condition, thereby aiding the diagnostic process and informing on prognosis and (2) assess inflammatory disease activity, should a diagnosis of CNO be confirmed. Achieving both goals using

Table 2 Diagnostic recommendations

Diagnostic recommendations	Level of evidence for clinical utility (see online supplemental file S3)	LoA, mean±SD	LoA, % ≥8
R4: perform clinical evaluation with specific attention for additional features (figure 2) and fulfilment of axSpA and PsA classification criteria. Consider diagnostic involvement of relevant medical disciplines.	► ○○○	9.51±0.65	100.00%
R5: conduct routine laboratory investigation with full blood and differential count, inflammatory markers, renal function, alkaline phosphatase, calcium, 25-hydroxy-vitamin D, parathyroid hormone levels and phosphate. Consider on case-by-case basis (eg, for differential diagnosis or pretreatment evaluation): bone turnover makers, anti-CCP, RF, HLA-B27.	► ○○○	9.27±0.87	97.30%
R6: perform imaging of the suspected region, giving priority to a modality suitable for assessing both activity and structural changes. MRI should be preferred but combined [^{99}mTc]Tc-HDP SPECT/CT or PET/CT with a bone-seeking radiotracer are reasonable alternatives.	► ○○○	9.32±1.53	94.59%
R7: consider performing whole-body imaging in all patients at initial evaluation to map clinically silent, but radiologically active lesions. Whole-body MRI (with sagittal spinal images) should be preferred, but [^{99}mTc]Tc-HDP SPECT/CT, PET/CT with a bone-seeking radiotracer or bone scintigraphy alone are reasonable alternatives.	► ○○○	8.92±1.79	86.49%
R8: do not perform routine bone biopsies. Reserve bone biopsies for cases with inconclusive imaging and/or suspicion of malignancy or infectious osteomyelitis.	► ○○○	9.51±0.73	100.00%

○ indicates 4-point scale ranging from very low to low to moderate to high according to the Grading of Recommendations, Assessment, Development and Evaluations approach. See table 3 for differential diagnoses. See table 4 for advantages and disadvantages of MRI versus CT+nuclear imaging.
Anti-CCP, anticitrullinated protein antibodies; axSpA, axial spondyloarthritis; CNO, chronic non-bacterial osteitis; HLA-B27, human leucocyte antigen B27 typing; LoA, level of agreement; [^{99}mTc]Tc-HDP SPECT/CT, technetium-labelled hydroxymethylene diphosphonate single positron emission CT; PET, positron emission tomography; PsA, psoriatic arthritis; RF, rheumatoid factor.

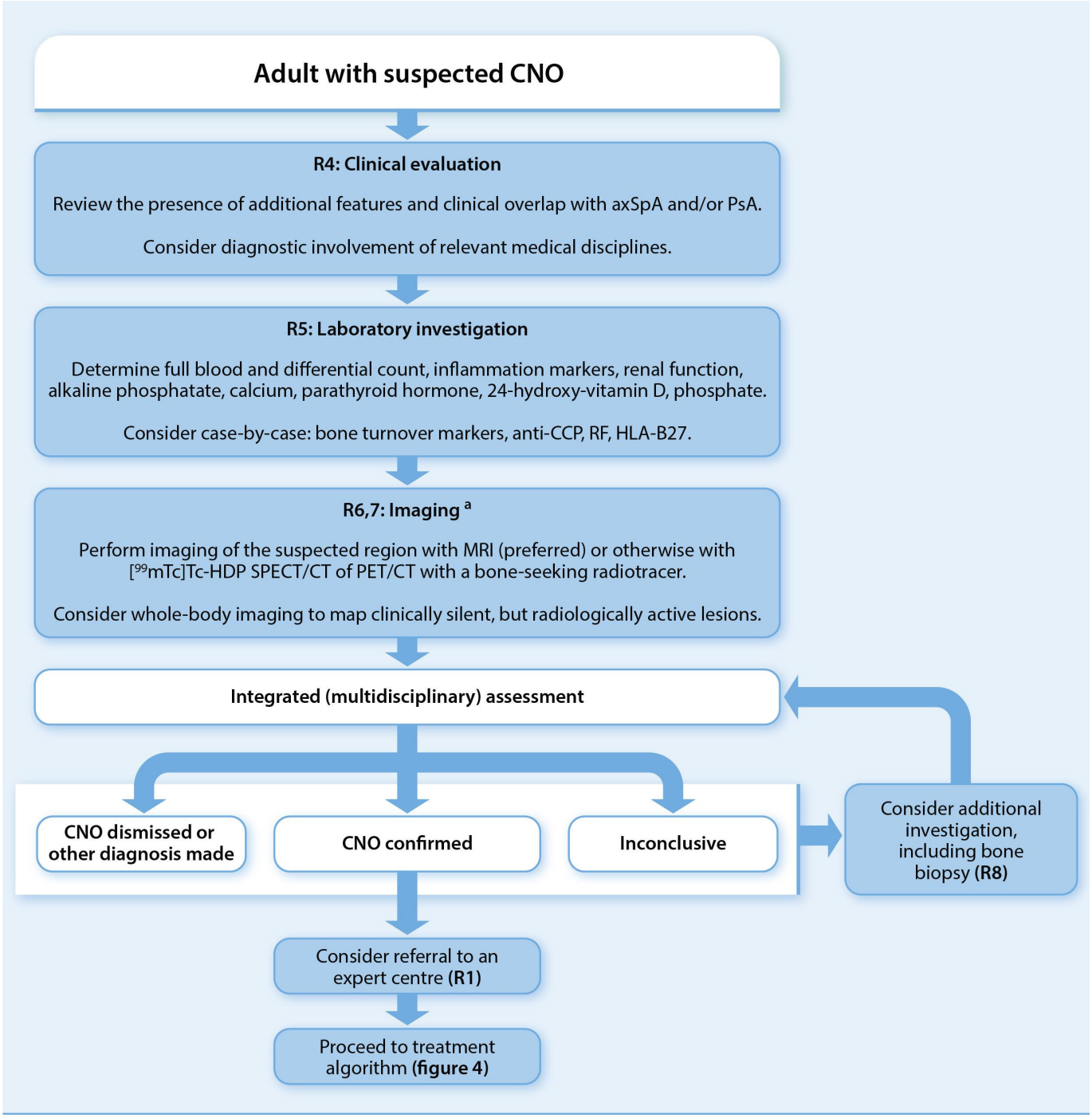

Figure 4 Diagnostic algorithm for adult CNO. ANA, antinuclear antibody and immunofluorescence pattern; anti-CCP, anticitrullinated protein antibodies; CNO, chronic non-bacterial osteitis; HLA-B27, human leucocyte antigen B27 typing; PET, positron emission tomography; RF, rheumatoid factor; [99mTc]Tc-HDP SPECT/CT, technetium-labelled hydroxymethylene diphosphonate single positron emission CT. [a]See table 4 for advantages and disadvantages of MRI and CT+nuclear imaging.

a single scan is feasible with either MRI or CT combined with a bone scintigraphy technique. Examples of the latter are technetium-labelled hydroxymethylene diphosphonate single positron emission CT ([99mTc]Tc-HDP SPECT/CT) and positron emission tomography (PET)/CT with a bone-seeking radiotracer such as sodium fluoride[7 23 46–48] (see online supplemental file S3, Q6A and Q6B for supportive evidence). The specific scan properties of MRI and [99mTc]Tc-HDP SPECT/CT or PET/CT are listed in table 4. The panel recommends MRI for the initial evaluation of adult CNO, but considers [99mTc]Tc-HDP SPECT/CT or PET/CT a reasonable alternative, for the following reasons.

CT provides excellent visualisation of structural changes secondary to inflammation, which are often already seen at initial evaluation owing to diagnostic delays.[7] These include sclerosis, erosions, hyperostosis (seen as endosteal and periosteal thickening), soft tissue ossification and ankylosis[7 20–25] (see online supplemental file S3, Q2A and Q2B for supportive evidence). Structural changes are useful for the diagnosis of CNO due to their specificity, and are valuable

Table 3 Differential diagnostic considerations in suspected adult CNO

Differential diagnosis	Specifically consider when presentation includes:
Infectious osteomyelitis	Systemic symptoms such as fever and chills, presumable port of entry, solitary bone lesion, significantly elevated CRP or ESR, bactaeremia
Malignant bone tumour	Unexplained weight loss, solitary bone lesion with quick growth, cortical destruction or perpendicular periosteal new bone formation on imaging
Psoriatic arthritis	Psoriasis (current, history or family history in first-degree relatives), inflammatory articular disease (joint, spine, entheseal), nail dystrophy, dactylitis, juxta-articular new bone formation on hand or foot radiography
Axial spondyloarthritis	Inflammatory back pain, sacroiliitis, asymmetrical inflammatory arthritis, enthesitis, dactylitis, uveitis, psoriasis, inflammatory bowel disease, pain responsive to NSAIDs, family history, HLA-B27 positivity, elevated CRP
Rheumatoid arthritis	Symmetrical polyarthritis, specifically of small joints, characteristic erosions, anti-CCP or RF positivity, elevated CRP or ESR
Osteoarthritis	Older age at onset, history of strain or occurrence at dominant side, osteoarthritis in other locations, bony swelling (depending on site; may be seen with sternoclavicular involvement), subchondral sclerosis or cysts, characteristic osteophytes and joint space narrowing on imaging
Tietze's syndrome	Pain in costosternal transitions, unilateral, self-limiting symptoms after weeks-months and not due to intercostal enthesitis in psoriatic arthritis
Paget's disease	Family history, pelvic or skull localisation, raised alkaline phosphatase, deformities, characteristically mixed osteolytic and osteosclerotic aspect on imaging, age of onset usually >50 years
Osteomalacia	Generalised bone pain and muscle weakness, low serum phosphate, elevated alkaline phosphatase, low 25-hydroxy-vitamin D, increased parathyroid hormone, bone demineralisation on imaging
Hypophosphatasia	Generalised bone pain and muscle weakness, dental abnormalities, low alkaline phosphatase levels, bone demineralisation on imaging, mixed lytic and sclerotic lesions
Fibrous dysplasia	Bone deformities, neurological symptoms in case of skull involvement, other endocrinopathies in case of McCune-Albright syndrome, expansive, lytic, ground-glass lesions on imaging
Anterior sternoclavicular subluxation	Recent trauma, unilateral swelling of sternoclavicular joint, history of connective tissue disorder like Ehlers-Danlos syndrome
Bone bruise	Recent trauma, adjacent trauma-related lesions, self-limiting symptoms after 1–2 months
Other rare differential diagnoses for CNO in adults: (osseous manifestations of) sarcoidosis, gout, Langerhans cell histiocytosis, osteonecrosis with certain involvement sites (eg, avascular osteonecrosis), ascorbic acid deficiency, Erdheim-Chester disease	
Anti-CCP, anticitrullinated protein antibodies; CNO, chronic non-bacterial osteitis; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; NSAIDs, non-steroidal anti-inflammatory drugs ; RF, rheumatoid factor.	

for prognosis since they reflect the degree of accumulated skeletal damage. Structural changes are well visualised with CT, which can conveniently be combined with bone scintigraphy techniques ([^{99}mTc]Tc-HDP SPECT/CT or PET/CT) to evaluate disease activity, with increased radiotracer uptake representing heightened osteoblastic activity. Of note, bone scintigraphy *without* CT is inadequate for diagnosis of CNO, as radiotracer uptake is highly non-specific and correlation with structural features is thus crucial. A disadvantages of [^{99}mTc]Tc-HDP SPECT/CT and PET/CT is that it only detects patients with CNO with structural changes that have accumulated over time. As awareness for CNO is rising, the panel anticipates physicians encountering patients earlier in their disease course, in which other features like bone marrow oedema and osteolysis are more prominent (see online supplemental file S3, Q2A and Q2B for supportive evidence). Although bone marrow oedema lacks specificity due to its occurrence in other conditions and also healthy individuals,[21 25 46 49 50] the panel concurs that this feature is generally helpful in the diagnostic process, particularly if it is seen in typical skeletal sites for CNO (eg, anterior chest wall, spine and mandible). The key relevance of bone marrow oedema as an early and activity-related disease feature requires a preference for the use of MRI. Other advantages of MRI include the detection of soft tissue involvement and neurovascular structures, and the lack of ionising radiation. Although somewhat less optimal than CT, MRI also provides fair visualisation of structural changes (see online supplemental file S3, Q2C for supportive evidence). Based on their properties, the panel recommends MRI for the initial evaluation of adult CNO, but agrees that CT with nuclear imaging ([^{99}mTc]Tc-HDP SPECT/CT or PET/CT with bone-seeking radiotracer) are other reasonable options. A combination of MRI and CT may be used in certain circumstances. The panel also acknowledges that CT provides better visualisation of the anterior chest wall, as CT can detect subtle structural changes and is less affected by breathing artefacts.[7 51] The panel agrees that plain radiographs are of limited use for adult CNO, as they have low sensitivity, do not provide information about disease activity and are less suitable to assess the anterior chest wall, spine and mandible.[7 52] Furthermore, the progression of these lesions over time can provide critical information, aiding in the exclusion of differential diagnoses. Hence, previous imaging should be given considerable attention in the diagnostic process. This approach may render repeated examinations unnecessary

Table 4 Relevant scan properties of [^{99}mTc]Tc-HDP SPECT/CT or PET/CT versus MRI for initial evaluation of adult CNO

Feature	[^{99}mTc]Tc-HDP SPECT/CT or PET/CT	MRI
Detection of new bone formation	Very good	Fair
Detection of bone inflammation	Fair (visualised through bone turnover)	Good
Detection of soft tissue inflammation	Poor	Good
Ease of performance	Good	Fair
Ease of interpretation	Fair	Poor
Ionising radiation	Considerable	None
Contraindications	Few	Metal, claustrophobia
CNO, chronic non-bacterial osteitis; [^{99}mTc]Tc-HDP SPECT/CT, technetium-labelled hydroxymethylene diphosphonate single positron emission CT; PET, positron emission tomography.		

or assist in selecting a complementary imaging technique in complex cases.

R7: Consider performing whole-body imaging in all patients at initial evaluation to map clinically silent, but radiologically active lesions. Whole-body MRI (with sagittal spinal images) should be preferred, but [^{99}mTc]Tc-HDP SPECT/CT, PET/CT with a bone-seeking radiotracer or bone scintigraphy alone are reasonable alternatives.

Rationale

The panel extensively deliberated whether routine whole-body imaging is advisable for the diagnosis and initial evaluation of adult CNO. It is known that up to 67% of patients may have clinically silent, but radiologically active lesions, which remain undetected if imaging is only conducted in clinically suspect areas[11 20 23 27] (see online supplemental file S3, Q6C for supportive evidence). According to the panel, performing routine whole-body imaging at initial evaluation offers two key advantages. First, it allows for accurate mapping of the disease, potentially supporting the CNO diagnosis when lesions follow a specific distribution. Second, whole-body imaging may affect clinical management when numerous silent lesions may be interpreted as more severe or aggressive disease, or when silent lesions carry a complication risk (eg, vertebral collapse with highly active spinal lesion). However, it should be stressed that it is unclear whether identifying these silent lesions will lead to better patient outcomes (see online supplemental file S3, Q6C for appraisal of evidence). The panel, therefore, *suggests* considering routine whole-body imaging at the initial evaluation of adult CNO. The panel emphasises that whole-body imaging is not a strict prerequisite for diagnosis, and should not come at the expense of good-quality regional imaging. Techniques to be considered include whole-body MRI (with sagittal images of the spine), [^{99}mTc]Tc-HDP SPECT/CT, PET/CT or plain bone scintigraphy.

R8: Do not perform routine bone biopsies. Reserve bone biopsies for cases with inconclusive imaging and/or suspicion of malignancy or infectious osteomyelitis.

Rationale

The panel recommends against routinely perform bone biopsies in adults with suspected CNO and considering these only in cases where the recommended imaging is inconclusive, and/or suspicion of malignancy or infectious osteitis is high. Suspicion of malignancy is raised in scenarios characterised by involvement of a single bone, atypical locations for CNO, rapid lesion growth, evidence of cortical destruction on imaging, the presence of overt and/or severe systemic symptoms such as unexplained weight loss. Infection may be more likely in patients with fever, significantly raised inflammation parameters, a suspected infection source or confirmed bacteraemia.

TREATMENT RECOMMENDATIONS

The diverse clinical presentation of adult CNO renders formulating uniform treatment recommendations challenging. These recommendations thus centre on *osteitis* and its associated morbidity, the core feature of the disease. In patients with additional features and/or fulfilment of criteria for axSpA and PsA, established treatment protocols should be followed, with treatment preferably targeting both osteitis and the additional feature(s). Furthermore, it should be stressed that the treatment recommendations for adult CNO are largely based on low-level evidence and expert opinion. Currently, all drugs listed are used off-label based mainly on evidence from observational studies and case reports (table 5, figure 5).

R9: Use the following treatment goals and outcome measures in CNO management.

- **Relieving symptoms, as evaluated by bone pain likely caused by osteitis.**
- **Maintaining/Regaining functional capacity, as evaluated by range of motion, fatigue, patient-reported functional capacity and quality of life.**
- **Reducing inflammation, as evaluated by focal inflammatory signs on physical examination (if present), inflammation markers (if previously raised) and radiological signs of inflammation such as bone marrow oedema or increased tracer uptake in the clinically and/or radiologically suspect lesions.**
- **Preventing (the progression of) structural musculoskeletal damage.**

Rationale

Clinicians and patient representatives identified four treatment goals and associated outcome measures in adult CNO. Recognising that validated sets of outcome measures are yet to be developed, the following is meant as a practical tool to support clinical management. The panel unanimously agrees that the patient's well-being should be the primary consideration across all goals. However, laboratory test results and imaging findings may help to assess if symptoms can be attributed to active disease, since pain may also derive from neuropathic or nociplastic mechanisms and structural changes in the skeleton.[53]

1. *Relieve symptoms*: the panel recommends pain as the main outcome measure, preferably measuring its severity on a visual analogue scale or numerical rating scale. While acknowledging the relevance of other types of pain to the patient, the focus should be on pain that can reasonably be attributed to osteitis.
2. *Regain and maintain functional capacity*: the panel recommends that this goal is evaluated by assessing the active and passive range of motion in the affected part of the skeleton and patient-reported outcomes such as fatigue and quality-of-life, which can be measured with standardised questionnaires such as Brief Pain Inventory and Health Assessment Questionnaire Disability Index.[54 55]
3. *Reduce inflammation*: the panel emphasises that this is an important treatment goal, as inflammation contributes to symptoms in the acute phase, and likely to risk of skeletal damage over time. Outcome measures include bone pain that is likely caused by osteitis (just as in goal 1), focal inflammatory signs on physical examination (if present at initial evaluation), inflammation markers (if elevated at initial evaluation) and radiological signs of inflammation such as bone marrow oedema and increased tracer uptake in the clinically and/or radiologically suspect lesions. For the latter, the panel emphasises that longitudinal studies are needed to elucidate the validity, utility and clinical relevance of bone marrow oedema or tracer uptake as an outcome measure, as it is known that both may persist despite resolution of symptoms (see online supplemental file S3, Q2C for summary of evidence).[56 57] The relevance of asymptomatic bone marrow oedema or tracer uptake may depend on the location(s) and extent of disease, and may influence treatment decisions in some cases to protect the structural integrity of functionally

Table 5 Treatment recommendations

Treatment recommendations	Level of evidence (see online supplemental file S3)	LoA, mean±SD	LoA, % ≥8
R9: use the following treatment goals and outcome measures in CNO management: ► Relieving symptoms, as evaluated by bone pain likely caused by osteitis. ► Maintaining/Regaining functional capacity, as evaluated by range of motion, fatigue, patient-reported functional capacity and quality of life. ► Reducing inflammation, as evaluated by focal inflammatory signs on physical examination (if present), inflammation markers (if previously raised) and radiological signs of inflammation such as bone marrow oedema or increased tracer uptake in the clinically and/or radiologically suspect lesions. ► Preventing (the progression of) structural musculoskeletal damage.	► ○○○	9.24±1.01	97.30%
R10: disease activity assessment at initial evaluation (see text for further details) ► Assess disease activity based on clinical symptoms (bone pain likely caused by osteitis) and radiological measures (bone marrow oedema or increased tracer uptake in the clinically and/or radiologically suspect lesions). Include the presence of focal inflammatory signs and elevation of inflammation markers if applicable. The following categories can be used as guidance: 1. Corresponding clinical symptoms and radiological disease activity: consider these patients as *active CNO* and initiate treatment. 2. Neither clinical symptoms nor radiological disease activity: consider these patients as *inactive CNO* and do not start treatment. 3. Clinical symptoms without radiological disease activity: consider these patients as *probably inactive CNO*, and first investigate other causes of pain. 4. Radiological disease activity without clinical symptoms: consider these patients as *likely not having clinically relevant CNO activity*, and decide on treatment in shared decision.	► ○○○	9.16±0.76	100.00%
R11: treatment response evaluation during follow-up (see text for further details) ► Conduct a treatment response evaluation between treatment steps, primarily based on clinical measures, but integrate radiological and biochemical measures as appropriate. ► Declare sufficient/insufficient response based on improvement, no change or worsening on relevant measures, with the individual patient context and predetermined treatment goals as reference.	► ○○○	9.27±0.69	100.00%
R12: general treatment recommendations ► Provide patient education and lifestyle recommendations. ► Consider physiotherapy and dental examination. ► Short courses of oral prednisolone or intra-articular glucocorticoid injections may be considered as bridging options, awaiting the effect of other agents, throughout the treatment steps. Avoid the long-term use of glucocorticoids.	► ○○○	9.05±1.37	91.89%
R13: first-line treatment ► Start NSAIDs/COXIBs in maximum tolerated and approved dosage in adults with active CNO. – Consider directly adding/advancing to second-line treatment in patients with spinal bone lesions with risk of vertebral collapse and in patients presenting with significant accumulated skeletal damage. ► Evaluate treatment response at 2–4 weeks: – In case of sufficient response, continue and re-evaluate response at 12 weeks. Consider tapering or on-demand treatment in case of sustained sufficient response. – In case of insufficient response at 2–4 weeks or later, consider an NSAID/COXIB rotation or add/advance to second-line treatment.	► ○○○	9.30±0.81	100.00%
R14: second-line treatment ► Start IVBP (generally preferred) or TNFi, depending on patient characteristics. ► csDMARDs can be considered, especially in patients with inflammatory polyarthritis, but it is not necessary to trial these before considering TNFi. ► Evaluate treatment response at 3–6 months: – In case of sufficient response, continue and re-evaluate response at 6–12 months. Consider tapering in case of sustained sufficient response. – In case of insufficient response, exchange for TNFi or IVBP or consider combination therapy. Similarly, re-evaluate response at 6–12 months. Consider tapering (one-by-one) in case of sustained sufficient response.	► ○○○	9.05±0.81	97.30%
R15: third-line treatment ► Refer patients with insufficient response to IVBP and TNFi (or combined) to an expert centre, where a range of other third-line treatment options may be considered (see text for details).		9.54±0.65	100.00%
R16: complications and adverse effects of treatment ► Be aware of the neurovascular complications in patients with anterior chest wall involvement and of the risk of vertebral fractures in patients with spinal involvement. ► Monitor adverse treatment effects according to established guidelines.		9.46±0.77	100.00%

○ indicates 4-point scale ranging from very low to low to moderate to high according to the Grading of Recommendations, Assessment, Development and Evaluations approach.
See table 6 for agents and dosages to consider.
axSpA, axial spondyloarthritis; CNO, chronic non-bacterial osteitis; COXIB, cyclooxygenase-2 inhibitor; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IVBP, intravenous bisphosphonates; LoA, level of agreement; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; TNFi, tumour necrosis factor-α inhibitors.

important joints and bones and reduce the risk of complications.

4. *Prevent (the progression of) structural musculoskeletal damage*: this is monitored by imaging studies that depict secondary structural changes, as well as indirectly by the clinical assessment.

The panel recommends that the caring team should discuss and agree on treatment goals with patients before the start of treatment, as goals may vary among individuals and across different stages of the disease and influence treatment response evaluation (see R11).

R10: Assess disease activity based on clinical symptoms (bone pain likely caused by osteitis) and radiological measures (bone marrow oedema or increased tracer uptake in the clinically and/or radiologically suspect lesions). Include the presence of focal inflammatory signs and elevation of inflammation markers if applicable.

The following categories can be used as guidance:

1. Corresponding clinical symptoms and radiological disease activity: consider these patients as active CNO and initiate treatment.

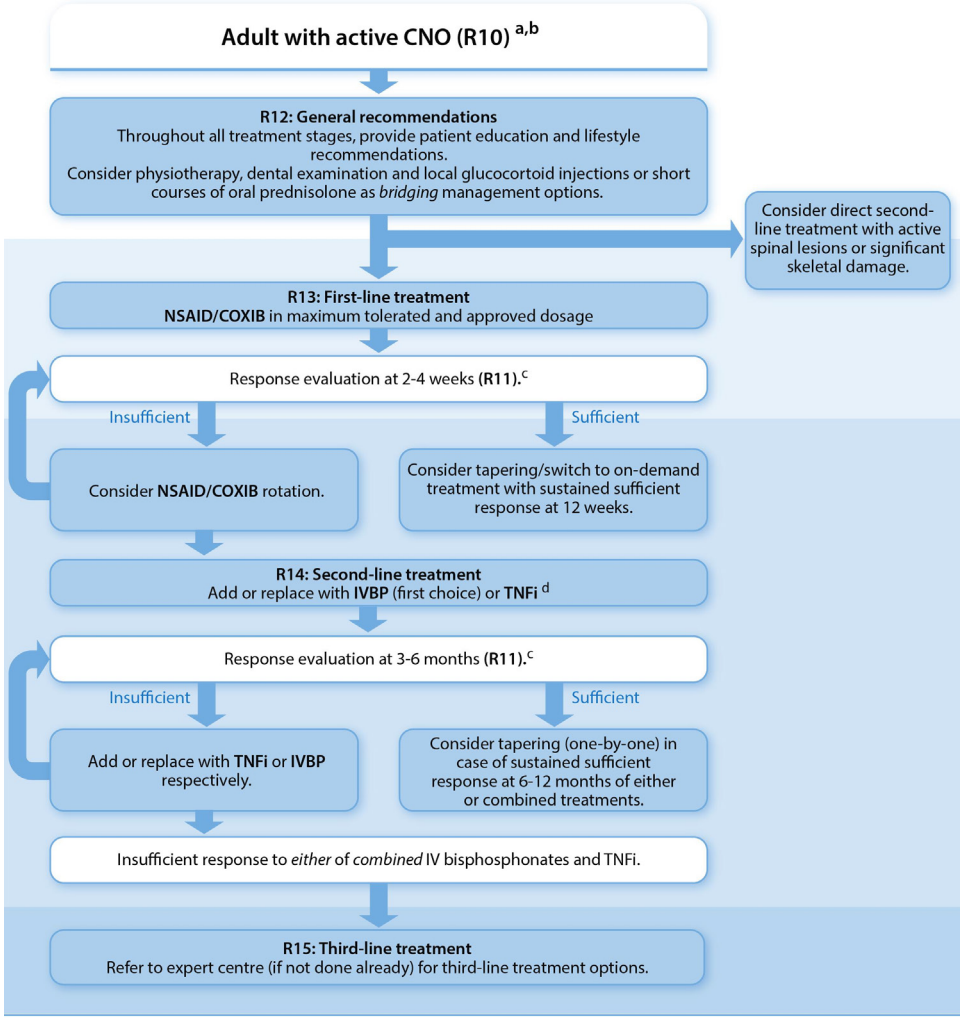

Figure 5 Treatment algorithm for adult CNO. axSpA, axial spondyloarthritis; CNO, chronic non-bacterial osteitis; COXIB, cyclooxygenase-2 inhibitor; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IVBP, intravenous bisphosphonates; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; TNFi, tumour necrosis factor-α inhibitors. [a]Active CNO defined as corresponding clincal and radiological disease activity, optionally with focal inflammatory signs and/or elevated inflammation parameters. See **R10** for details. [b]In case of additional features or clinical overlap with axSpA and/or PsA, follow established treatment protocols and align with treatment for osteitis where possible. [c]Declare sufficient/insufficient response based on clinical measures mainly, but integrate radiologic and biochemical measures as appropriate, with the individual patient context and predetermined treatment goals as reference. See **R11** for details. [d]csDMARDs may be consided as step 2 treatments too, especially in cases with concomitant polyarthritis.

2. Neither clinical symptoms nor radiological disease activity: consider these patients as inactive CNO and do not start treatment.

3. Clinical symptoms without radiological disease activity: consider these patients as probably inactive CNO, and first investigate other causes of pain.

4. Radiological disease activity without clinical symptoms: consider these patients as having no clinically relevant CNO activity, and decide on treatment in shared decision.

Rationale

Defining disease activity in adult CNO is challenging due to the lack of evidence supporting existing definitions and measures. According to the panel, disease activity assessment should primarily be based on clinical symptoms of bone pain likely caused by osteitis, and radiological measures of bone marrow oedema/increased tracer uptake in the clinically and/or radiologically suspect lesions. Clinical signs of focal inflammation and elevated inflammatory markers may contribute to the overall assessment, but they are observed in only a small number of patients, making them limitedly informative for the majority. Using clinical symptoms and radiological parameters as leading reflectors of disease activity, the panel identified four main categories of patients as guidance.

1. *Corresponding clinical symptomsand radiological disease activity*: this category of patients should be regarded as having *active CNO*. These patients may exhibit focal inflammatory signs and elevated inflammation markers as well, but these are not required to speak of active CNO. The panel recommends that treatment is initiated in patients with active CNO.
2. *Neither clinical symptoms nor radiological disease activity*: this category of patients should be regarded as *inactive CNO*. Should elevated inflammation markers be seen, alternative causes should be investigated as the relation to CNO is less likely. The panel recommends that these patients do not require treatment.

3. *Clinical symptoms without radiological disease activity*: the panel would consider these patients as probably *inactive CNO*, and recommends evaluating other causes of pain before treating osteitis. Myalgia, central sensitisation, neuropathic pain and pain originating from structural changes, such as mechanical issues related to ankylosis, are potential alternative causes.[53]
4. *Radiological disease activity without clinical symptoms*: the panel leans towards classifying this group as having no clinically relevant CNO activity, particularly if there are no focal inflammatory signs or elevated inflammation markers. This classification is based on the lack of evidence that treating patients with asymptomatic radiological activity improves outcomes. Similarly, there is no evidence that withholding treatment in such cases results in worse outcomes. In addition, common imaging methods, such as [^{99}mTc]Tc-HDP SPECT/CT, can reveal imprinted tracer uptake patterns regardless of symptoms.[58] Since the panel recommends prioritising patient symptoms in clinical management, this typically means refraining from treatment in cases of asymptomatic radiological activity. It is important to recognise that, although this is a patient-centred approach, it disregards subclinical osteitis, which could, in theory, cause long-term skeletal damage. Therefore, the decision to start treatment should be made through careful shared decision-making. Particular cases in which treatment may be justified despite the absence of pain are those in which radiological activity poses a direct risk of complications, such as highly active spinal lesions or imminent vertebral collapse. In such cases, patients should be counselled on the potential burdens and benefits of treatment as part of the shared decision-making process (see also R14).

R11: Conduct a treatment response evaluation between treatment steps, primarily based on clinical measures, but integrate radiological and biochemical measures as appropriate. Declare sufficient/insufficient response based on improvement, no change or worsening on relevant measures, with the individual patient context and predetermined treatment goals as reference.

Rationale

Defining treatment response criteria for adult CNO presents several challenges. First, the prognostic value of various outcome measures is unknown. Additionally, response may manifest in one domain (eg, reduced bone pain caused by osteitis) but not in others (eg, persistent bone marrow oedema or increased tracer uptake in the clinically and/or radiologically suspect region). Lastly, determining response adequacy is always partly subjective, contingent on baseline conditions and individual patient context. Hence, the assessment of treatment response should be made by the treating physician, integrating clinical, biochemical (if applicable) and radiological measures within the patient's context and predetermined treatment goals. As guidance, the panel outlines three common scenarios:

1. *Improvement in all disease activity domains*: an improvement in clinical and radiological activity, along with biochemical measures (if applicable) is an all-round effect and thus can be considered as *sufficient response*.
2. *No change or worsening in all disease activity domains*: unchanged or worsened clinical and radiological activity along with biochemical measures (if applicable) can be considered as *insufficient response*.
3. *Improvement in some, but not all disease activity domains*: inconsistent effect on clinical and radiological measures, along with biochemical measures (if applicable) may be considered as *sufficient or insufficient*, depending on patient context and treatment goals.

The panel wishes to stress that, despite the importance of radiological measures in declaring treatment response, routine follow-up imaging is not required in all patients. In patients with evident clinical (and optionally biochemical) improvement, follow-up imaging is not essentially required to confirm sufficient response. Naturally, in patients with lack of or differential clinical or biochemical improvement, *local* follow-up imaging is helpful to incorporate radiological response in the final assessment and to facilitate shared decision-making. Apart from treatment response evaluations, local follow-up imaging may also be considered if the differential diagnosis needs to be explored further, or when new symptoms arise or complications such as vascular occlusion, nerve compression or fractures are suspected. Routine follow-up whole-body scans are not typically recommended after the initial evaluation but may be a valid option in specific cases, such as for patients with extensive disease which is difficult to assess with local imaging.

R12: Use the following as general treatment recommendations:

- **Providepatient education and lifestyle recommendations**
- **Consider physiotherapy and dental examination**
- **Consider short courses of oral prednisolone or intra-articular glucocorticoid injections as bridging options, awaiting the effect of other agents. Avoid the long-term use of glucocorticoids.**

R12: As general treatment recommendations: provide patient education and lifestyle recommendations, consider physiotherapy and dental examination, and consider short courses of oral prednisolone or intra-articular glucocorticoid injections as bridging options, awaiting the effect of other agents. Avoid the long-term use of glucocorticoids.

Rationale

The panel recommends that patient education should be given (specifically because CNO is a rare disorder and often diagnosed after significant delay). Lifestyle recommendations are to be given to all patients as well, including smoking cessation, weight control and regular physical activity, thereby contributing to general health. The panel recommends considering physiotherapy in adult patients with CNO to optimise physical functioning. Dental examination may further be considered, to evaluate the presence of concomitant infections which have been suggested to be associated with CNO,[35 59–64] as well as to ensure adequate dental hygiene before the start bisphosphonate therapy to mitigate the small risk of osteonecrosis of the jaw. Regarding the use of glucocorticoids, the panel agreed that intra-articular glucocorticoid injections may provide short-term relief in patients with joint involvement and can be considered when awaiting the effect of other treatments (see online supplemental file S3, Q13 for summary of evidence). The same also holds for oral glucocorticoids, which may be helpful as bridging option in short courses with fast tapering. As the evidence supporting glucocorticoids in CNO is scarce, management should in no way rely on these agents, also given their adverse effect profile.[37 65 66]

Glucocorticoids may even pose controversial effects, as they promote bone resorption, possibly worsening the accelerated bone turnover that is seen in CNO lesions. However, exact impact of glucocorticoids on CNO lesions, and its relevance in clinical practice, is unknown.

R13: As first-line treatment, start non-steroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors in maximum tolerated and approved dosage in adults with active CNO. Consider directly adding/advancing to second-line treatment in patients with spinal bone lesions with risk of vertebral collapse and in patients presenting with significant accumulated skeletal damage.

- **Evaluate treatment response at 2–4 weeks after initiation**
- **In case of sufficient response, continue and re-evaluate response at 12 weeks. Consider tapering or on-demand treatment in case of sustained sufficient response.**
- **In case of insufficient response at 2–4 weeks or later, consider a non-steroidal anti-inflammatory drug (NSAID)/cyclooxygenase-2 inhibitor (COXIB) rotation or add/advance to second-line treatment.**

Rationale

It should be emphasised that no randomised controlled trials (RCTs) exist to inform the optimal treatment choice and duration in adult CNO. As first-line treatment in adults with active CNO, panel recommends starting NSAIDs/COXIBs in maximum tolerated and approved dosage for 2–4 weeks. This may be followed by a trial of another NSAID/COXIB if the first did not provide benefit or was not tolerated[67 68] (see online supplemental file S3, Q10 for summary of evidence). For patients with prior NSAIDs/COXIBs usage, it is advisable to confirm adherence to the most optimal regimens. The panel recommends treatment response evaluation at 2–4 weeks after initiation. In patients with sufficient response, treatment can be continued; switching to on-demand treatment or dose tapering can be considered with sustained sufficient response at 12 weeks. For patients with insufficient response at 2–4 weeks (or later if response was initially sufficient), the panel suggests adding/advancing to second-line treatments. Direct progression, without NSAID/COXIB trial, to second-line treatments is suggested for:

- Patients with spinal bone lesions with risk of vertebral collapse, for example, due to extensive bone marrow oedema in a full vertebral body.[69 70] The panel specifically suggests starting intravenous bisphosphonates (IVBP) in these patients directly (with the addition of tumour necrosis factor-α inhibitors (TNFi) if indicated based on additional features).
- Patients with significant accumulated skeletal damage, for example, existing vertebral collapse or severe joint or vertebral ankylosis and erosions.

For both groups, it should be noted that evidence on better clinical outcomes with earlier and more aggressive treatment is lacking, making this a fully eminence-based suggestion.

R14: As second-line treatment, start IVBP (generally preferred) or TNFi, depending on patient characteristics. Conventional synthetic disease-modifying antirheumatic drugs can be considered, especially in patients with inflammatory polyarthritis, but it is not necessary to trial these before considering TNFi.

- **Evaluate treatment response at 3–6 months**
- **In case of sufficient response, continue and re-evaluate response at 6–12 months. Consider tapering in case of sustained sufficient response.**
- **In case of insufficient response, exchange for TNFi or IVBP or consider combination therapy. Similarly, re-evaluate response at 6–12 months. Consider tapering (one-by-one) in case of sustained sufficient response.**

Rationale

As second-line treatment, the panel recommends IVBP and TNFi as reasonable treatment options (see table 6 for specific agents and dosages to consider, see online supplemental file S3, Q11 for summary of evidence).[2 32 38 43 44 71–103] Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) may be considered in this treatment line as well, especially in cases with inflammatory polyarthritis, but the majority of the panel recognises that there is more supportive observational evidence for IVBP and TNFi in the treatment of osteitis.[2 32 37 71 89 91 104–107] In any case, the panel considers it unnecessary to trial csDMARDs before considering TNFi, like it is required in, for example, rheumatoid arthritis. Regarding IVBP and TNFi, the panel

Table 6 Agents and dosages to consider for main treatment classes

Class	Agents and dosages to consider in active treatment phase (non-tapering dosages) ***Of note: these depend on local regulations and guidelines***
NSAIDs/COXIBs	Naproxen 375–1100 mg/day in two doses Diclofenac starting at 150 mg/day in divided doses, maintenance 75–100 mg/day in divided doses Indomethacin 150 mg/day in divided doses Ibuprofen 1800 mg/day in divided doses Celecoxib 200–400 mg/day in divided doses Etoricoxib 90 mg/day (or temporarily 120 mg/day) Piroxicam 20 mg/day in one dose Meloxicam 15 mg/day in one dose
IVBP	Pamidronate intravenously 3×30 mg on 3 consecutive days, every 3 months* Pamidronate intravenously 45–90 mg (or 1 mg/ kg), every month or every 3 months* Zoledronate intravenously 5 mg, according to symptoms†
TNFi	Infliximab 3–5 mg/kg intravenously at 0, 2 and 6 weeks, and henceforth 3–5 mg/kg every 6–8 weeks or subcutaneously 120 mg/2 weeks Etanercept 50 mg/week, subcutaneously Adalimumab 40 mg/2 weeks, subcutaneously Golimumab 50 mg/4 weeks, subcutaneously (may be increased to 100 mg depending on weight) Certolizumab 400 mg/4 weeks or 200 mg/2 weeks, subcutaneously (compatible with all trimesters of pregnancy[118])

*According to clinical experience of the panel, pamidronate seems to be more effective for pain reduction than zoledronate.
†Zoledronate carries logistical advantages, with—generally—fewer infusions and associated admissions, thereby decreasing treatment burden and costs.
CNO, chronic nonbacterial osteitis; COXIB, cyclooxygenase-2 inhibitor; IVBP, intravenous bisphosphonates; NSAID, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor-α inhibitors.

recommends IVBP as the first preferred option, due to the more favourable adverse effects profile (see also R16), lower costs, the fact that IVBP allow for on-demand treatment courses and the relative ease of discontinuing treatment. IVBP are specifically recommended in patients with active spinal lesions, although it should be noted there are no data on whether IVBP can prevent complications in these patients. TNFi may be preferred over IVBP in patients with primarily axial involvement, sacroiliitis or additional features like inflammatory arthritis uveitis or inflammatory bowel disease (resembling an axSpA phenotype). Ultimately, the choice should be based on patient profile, contraindications to particular treatments, cost considerations, logistics and patient factors and preferences, including pregnancy considerations in females. During second-line treatment, NSAIDs/COXIBs can be maintained when having been partially effective.

Response evaluation to IVBP and TNFi is recommended at 3–6 months after initiation. In patients with sufficient response, the panel suggests continuing treatment and re-evaluate at 6–12 months (from baseline). While there is no evidence on the preferred treatment duration in adult CNO, the panel majority suggests that after 6–12 months of sustained sufficient response, dose or interval tapering can be considered. In this decision, the risk of flare after treatment discontinuation should be weighed against the negative consequences of long-term treatment, including complications (see also *R16*) and patient burden. In patients with an insufficient response at 3–6 months, switching to TNFi or IVBP, or considering combination therapy, may be appropriate, with a similar re-evaluation at 6–12 months. In case of combination therapy and sustained sufficient response at 6–12 months, taper the first-started drug first, and consider tapering the second-started drug after another 6–12 months of sustained sufficient response.

If disease reactivation occurs during tapering, treatment may be resumed. However, if disease remains inactive during tapering, the panel suggests it may be appropriate to discontinue treatment at a certain point, depending on patient-specific factors and at the discretion of the physician. On disease reactivation after a drug-free period, previously effective treatment regimens may be restarted.

R15: Refer patients with insufficient response to IVBP and TNFi (or combined) to an expert centre, where a range of other third-line treatment options may be considered.

Rationale

Difficult-to-treat patients with insufficient response to first-line and second-line treatments need to be referred to an expert centre if not already done, to optimise management. Strategies may include the re-evaluation of diagnosis (possibly by bone biopsy, if not performed initially), re-evaluation of disease activity (addressing the question of whether persistent pain likely derives from ongoing inflammation, or may have alternative sources as outlined before), referral to a pain specialist in case of suspected neuropathic or nociplastic pain, optimisation of comorbidity management and psychosocial support. In cases of a confirmed active disease, IL-17 inhibitors (IL-17i), Janus kinase inhibitors (JAKi) or IL-12/23i, and IL-23i are third-line pharmacological treatment options, but it should be noted that evidence on these treatment options is even more limited (see online supplemental file S3, Q12 for summary of evidence). IL-17i may be specifically considered in patients with overlapping features of axSpA or PsA, such as sacroiliitis, dactylitis, enthesitis, psoriasis, although paradoxical psoriatic skin lesions have been reported in patients with CNO with PPP. JAKi has been reported to improve both osteitis and skin manifestations of the CNO spectrum, and may be administered if not contra-indicated based on cardiovascular risk profile and cancer risk. IL-23i has mostly been evaluated in CNO patients with PPP, with joined efficacy for skin and osteitis symptoms. For IL-12/23i, reported effects on osteitis are yet highly inconsistent. Concerning surgical intervention, the panel underscores the scarcity and variability of data in adult CNO (see online supplemental file S3, Q12 for summary of evidence). Due to the invasive nature of surgical procedures, and challenging anatomical regions such as the anterior chest wall and spine, the panel suggests that consideration for surgery should be reserved for cases with evident hyperostotic complications and localised disease. Any decision for surgery should involve a multidisciplinary team comprising internal and surgical background physicians situated at an expert centre.

R16: Be aware of the neurovascular complications in patients with anterior chest wall involvement and of the risk of vertebral fractures in patients with spinal involvement. Monitor adverse treatment effects according to established guidelines.

Rationale

During follow-up, clinicians should be aware of the neurovascular complications in patients with anterior chest wall involvement, such as subclavian vein obstruction and thoracic outlet syndrome, and of the small risk of vertebral or clavicular fractures should these bones be involved[25 108–111] (see online supplemental file S3, Q15 for summary of evidence). Regarding adverse treatment effects, the panel recommends following established guidelines. Briefly, physicians should be aware of gastrointestinal and cardiovascular side effects of NSAIDs/COXIBs. For patients receiving IVBP, common side effects include acute phase reactions, which may be reduced with dose spread, longer infusion times or additional anti-inflammatory medication in severe cases (table 6).[112] Rare but serious complications include atypical femoral fractures and osteonecrosis of the jaw.[113] These complications have mainly been seen in oncological patients; the absolute risk for patients with CNO appears very low. This may be due to the relatively low cumulative dosage received as compared with those needed to treat tumour-induced hypercalcaemia. Risk may be further reduced by ensuring good dental hygiene before treatment and seeking surgical advice in case of dental procedures under bisphosphonate treatment. Patients receiving TNFi predominately face a higher infection risk and should be monitored accordingly. It is conventional practice that these patients are screened for latent infection and vaccinated for relevant pathogens before start of treatment.[114] Also, there is some evidence suggesting that anti-TNF-α can trigger psoriasis (‘paradoxical psoriasis’) and this has been reported in several CNO cases[80 82 115] (see online supplemental file S3, Q11 for summary of evidence). Since adult CNO has a clear female predisposition and frequently occurs at childbearing age, it is imperative to provide explicit guidance on the safety of various medications before, during and after pregnancy and nursing.[2]

CONCLUSIONS AND FUTURE PERSPECTIVES

This international initiative developed a first consensus statement regarding the disease definition of adults with SBI. It was agreed by the panel collectively to label this disease spectrum as CNO in adults (adult CNO), and no longer use terms like SAPHO syndrome, SCCH, PAO and CRMO. Building on this shared definition and name, the panel developed a first set of multidisciplinary consensus recommendations for diagnosis and

treatment of adult CNO. The main goal of this document is to assist clinicians in providing optimal care for their patients, as well as to limit practice variation and standardise care pathways over disciplines and countries.

A major challenge encountered during the development of recommendations was the scarcity of high-quality evidence, as large-scale epidemiological studies and RCTs specific to CNO are lacking. Consequently, the recommendations largely rely on expert opinion, small cohort studies and case reports. Recognising the importance of ongoing research into CNO, the consensus recommendations serve as a foundation for future collaborative studies. As part of the in-person meeting of this initiative, future research priorities were defined by the panel and patients representatives (box 1).

Of priority, the establishment of an international registry for adult patients with CNO is necessary to close the gaps in current knowledge on the clinical, laboratory and radiological course of the disease. A minimal dataset for a CNO registry as proposed by the panel is provided in online supplemental file S7. As direct spin-off of this initiative, possibilities are explored to build an international registry. Requirements for such a registry include formal governance structures that safeguard data access and management, as well as the infrastructure for patients to enter patient-reported outcome measures through digital questionnaires.[116] Candidate research questions to be addressed by the registry include regional comparison of clinical phenotype, incidence of new bone lesions and structural skeletal damage during follow-up and the prognostic relevance of asymptomatic radiological inflammation.

As for pathophysiology, an understanding of CNO's underlying mechanisms is currently limited. It is crucial to obtain both systemic and local signatures of inflammatory activity in CNO, as identification of these drivers is crucial to guide the development or repurposing of treatments. To achieve this, the establishment of an international biobank with systemic (peripheral blood) and local (bone or joint specimens) biomaterials is needed. Subsequently, collaboration between centres to exchange biomaterials and relevant techniques is needed (eg, immunophenotyping, gene expression profiling, spatial transcriptomics). A direct next step involves crafting a grant proposal with collaborators experienced in translational research, with the aim of launching such a project in the near future.

In the domain of treatment, there is clear need to conduct RCTs to validly assess efficacy of different treatments. An RCT comparing intravenous pamidronate against placebo is currently running, and subsequent trials should preferably compare efficacy between IVBP agents (eg, pamidronate against zoledronate), TNFi against placebo, TNFi against IVBP or other biologics based on immunological signatures as discovered in translational studies.[10] The panel deliberated that randomising patients with CNO to a placebo group is ethically acceptable, provided they have the option to receive NSAIDs/COXIBs and the placebo phase is short and succeeded by an open-label intervention phase. To conduct these trials, there is need for a set of validated classification criteria and outcome measures for adult CNO, the latter being currently underway.[117]

This consensus initiative has strengths and limitations. Regarding strengths, this is the first attempt to develop recommendations for the management of adults with CNO, based on the best available evidence, international expertise and in collaboration with patient representatives. The initiative was inclusive by involving numerous disciplines from a wider range of countries, recognising the widespread experience with CNO. The involvement of the Dutch CNO patient association ensured patient representation in identifying treatment goals, outcome measures and research priorities. In addition, the inclusion of different syndromes causing SBI under a single entity, named CNO, will facilitate

Box 1 Future research priorities as identified by consensus panel and patient representatives

Future research priorities as identified by consensus panel

Fundamentals

⇒ Development and validation of classification criteria for adult CNO.

⇒ International registry and biobank for adult patients with CNO including clinical, laboratory, radiological, treatment data, patient-reported outcomes and storage of specimens.

Pathophysiology and biomarkers

⇒ Environmental and/or genetic risk factors that trigger CNO (*specifically emphasised by patient representatives*).

⇒ Underlying mechanisms for and characteristics of pathophysiological cascade, including systemic and local inflammation, increased bone turnover and structural tissue changes; identification of therapeutic targets.

⇒ Primary drivers of site-specific nature of the disease.

⇒ Predictors/Biomarkers of disease progression or the development of new involvement sites.

⇒ Predictors/Biomarkers of response to specific treatments.

Clinical trials and drug approval

⇒ Development and validation of a (stratified) CNO disease activity score in adults to use as study end point in clinical trials, including patient-reported measures, imaging and relevant biomarkers.

⇒ Randomised clinical trials, specifically those comparing IVBP against placebo (running; EUDRACT 2020-001068-27), TNFi against placebo, IVBP against TNFi, pamidronate against zoledronate and other biologics as relevant based on translational study results. Double-blind, placebo-controlled design (allowing NSAIDs/COXIBs in both groups), followed by open-label extension.

Imaging

⇒ Prognostic relevance of radiological inflammation in patients with clinical remission, and utility of follow-up imaging in patients with clinical remission.

⇒ Diagnostic accuracy of CT (+nuclear imaging) and MRI (±nuclear imaging) in diagnosis of adult CNO, including comparative analysis.

⇒ Radiological evolution of adult CNO in larger patient numbers: frequency of progressive structural change, frequency of new lesion sites and utility of whole-body imaging at diagnosis and during follow-up.

Specifically emphasised by patient representatives

Research priorities additionally identified by patient representatives:

⇒ Strategies to reduce diagnostic delay.

⇒ Factors associated with relapse and remission.

⇒ Role of physical therapy, diet and other lifestyle factors on disease outcomes.

CNO: chronic non-bacterial osteitis, COXIB: cyclooxygenase-2 inhibitor, IVBP: intravenous bisphosphonates, NSAID: non-steroidal anti-inflammatory drugs, TNFi: tumour necrosis factor-α inhibitors

the conduction of larger research studies to address the unmet needs in the care of patients with CNO. Limitations of this initiative mainly pertain to the limited evidence supporting the recommendations, potentially compromising the validity of the recommendations. Nevertheless, the text consistently highlights the absence of evidence, and significant emphasis is placed on weighing the risks and benefits of specific clinical approaches. As such, the panel believes the recommendations are of value, especially given the lack of alternative resources. A second limitation is the comparatively low representation of American and Asian experts relative to those from Europe, despite considerable efforts made to include voices from all continents in the process. Recognising this gap, we designed the recommendations to be flexible, allowing it to be adapted to various healthcare systems in different countries, and aim at addressing this issue by further actively enhancing geographical diversity in future updates.

Moving forward, the next steps for this project involve the dissemination and implementation of the consensus recommendations, which requires extensive communication through relevant networks in rheumatology, endocrinology, orthopaedics, radiology and paediatric rheumatology. The panel perceives they are relatively easy to implement, as the recommendations pertain to relatively low patient numbers and were developed considering differences in the availability of diagnostic tests and treatment between healthcare systems. Despite being flexible, the recommendations offer a structured overview of diagnostic and management considerations for clinicians and helps patients understand what to expect. A potential challenge may arise from the limited reimbursement and accessibility of TNFi in certain regions. However, alternatives to TNFi are proposed. Anticipating future revisions of the recommendations, the panel hopes for further advancements in research to provide a more robust scientific foundation for updates.

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Acknowledgements The authors would like to thank Anda Kars and Evianne Smit, board members of the Dutch CNO patient association and patient representatives, for their contribution to the consensus recommendations. The authors would like to thank Timothy Bray, Martine Cohen-Solal, Matteo Colina, Davide Firinu, Victoria Furer, Nuria Guañabens, Gilles Hayem, Kassim Javaid, Aurni Jayatilleke, Karen Lindsay, Aleksander Lenert, Ron Laxer, Yasmine Makhlouf, Karen Partington, Marion Roderick, Athimalaipet Ramanan, Bing Thio, Alexander van Tongel, Marleen van de Sande, Yongdong Zhao, Marco Matucci-Cerinic and Mikhail Kostik for their contributions to the initiative, including completion of the Delphi surveys. The authors further thank Annelies Smit for supporting the round-table session during the in-person meeting, and Zoe Konsta for her contribution to the systematic literature review. Credits for the figure graphics are extended to Manon Zuurmond, medial illustrator. The authors thank the European Calcified Tissue Society, European Reference Network of Rare Bone Diseases and European Society of Endocrinology for endorsing this initiative. During the preparation of this work, the authors used ChatGPT, solely to improve language and readability. The authors reviewed all suggested improvements and take full responsibility for the content of the publication.

Contributors Conceptualisation: ATL and EMW. Data curation: ATL. Formal analysis: ATL. Funding acquisition: EMW. Investigation: ATL. Methodology: ATL, EMW, OMD. Supervision: ATL, EMW, OMD. Visualisation: ATL. Validation: ATL. Writing—original draft: ATL, EMW, OMD. Writing—review and editing: all authors.

Funding This consensus initiative received financial support from Leiden University Fund (LUF) and the Dutch Research Council (NWO).

Competing interests SD'A: consulting and speaking fees from AbbVie, Amgen, Bristol-Myers Squibb, Janssen, Lilly, MSD Italy, Novartis, Pfizer and UCB. GA: speaking fees and advisory boards of UCB, Novartis, AbbVie. DD: speaking fees and honoraria for participation in advisory boards from UCB, Pfizer, Novartis, BMS, MSD, Janssen, AbbVie, Lilly and Aenorasis. TD: speaker for Canon MS, Novartis, MSD, UCB and Roche. Advisory board: Lilly; Grant/Support: Canon MS, ASASDW: speaking fees and member of advisory board of AbbVie, BMS, MSD, Pfizer, Nordic Pharma, UCB, Novartis, Lilly, Janssen, Galapagos, Celltrion. BH: grants, personal fees and other from UCB, Kyowa Kirin, Eli Lilly, Amgen, Thornton & Ross and Gedeon-Richter and Fresenius Kabi outside the submitted work. KGH: consulting fees from AbbVie, lecture fees from MSD, Novartis, Pfizer. Co-founder of BerlinFlame. MK: received consulting fees and/or honoraria from AbbVie, Amgen, Asahi-Kasei Pharma, Ayumi Pharma, BMS, Chugai, Daiichi Sankyo, Eisai, Gilead, Janssen, Lilly, Novartis, Pfizer, Tanabe-Mitsubishi and UCB. WL: speaking fees and member of advisory boards of Amgen, UCB, Pfizer, Galapagos. EMW: speaking fees and member of advisory boards of Amgen and UCB.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Buch K, Thuesen ACB, Brøns C, *et al*. Chronic Non-bacterial Osteomyelitis: A Review. *Calcif Tissue Int* 2019;104:544–53.
2 Leerling AT, Dekkers OM, Appelman-Dijkstra NM, *et al*. Clinical and therapeutic diversity in adult chronic nonbacterial osteomyelitis (CNO) of the sternocostoclavicular region: a meta-analysis. *Rheumatol (Oxford)* 2023;62:512–22.
3 Koné-Paut I, Mannes I, Dusser P. Chronic Recurrent Multifocal Osteomyelitis (CRMO) and Juvenile Spondyloarthritis (JSpA): To What Extent Are They Related? *J Clin Med* 2023;12:453.
4 Singhal S, Landes C, Shukla R, *et al*. Classification and management strategies for paediatric chronic nonbacterial osteomyelitis and chronic recurrent multifocal osteomyelitis. *Expert Rev Clin Immunol* 2023;19:1101–16.
5 Kishimoto M, Taniguchi Y, Tsuji S, *et al*. SAPHO syndrome and pustulotic arthro-osteitis. *Mod Rheumatol* 2022;32:665–74.
6 Ramautar AI, Appelman-Dijkstra NM, Lakerveld S, *et al*. Chronic Nonbacterial Osteomyelitis of the Sternocostoclavicular Region in Adults: A Single-Center Dutch Cohort Study. *JBMR Plus* 2021;5:e10490.
7 Jurik AG, Klicman RF, Simoni P, *et al*. SAPHO and CRMO: The Value of Imaging. *Semin Musculoskelet Radiol* 2018;22:207–24.
8 Rukavina I. SAPHO syndrome: a review. *J Child Orthop* 2015;9:19–27.
9 Sinnappurajar P, Roderick M, Ramanan AV. The neglected and untreated pains of CRMO and SAPHO syndrome. *Rheumatol Sunnyvale* 2022;61:3509–10.
10 Leerling AT, Winter EM. Comment on: The neglected and untreated pains of CRMO and SAPHO syndrome. *Rheumatology (Oxford)* 2022;62:e12–3.
11 Depasquale R, Kumar N, Lalam RK, *et al*. SAPHO: What radiologists should know. *Clin Radiol* 2012;67:195–206.
12 Sonozaki H, Azuma A, Okai K, *et al*. Clinical features of 22 cases with ?Inter-Sterno-Costo-Clavicular Ossification? *Arch Orthop Traumat Surg* 1979;95:13–22.
13 Leerling AT, Navas Cañete A, Winter EM. Chronic non-bacterial osteomyelitis in SAPHO syndrome complicated by subclavian vein obstruction. *Rheumatol (Oxford)* 2023;62:e355–6.
14 Ohida H, Curuk C, Prescher H, *et al*. Thoracic outlet syndrome in a patient with SAPHO syndrome - A case report. *Int J Surg Case Rep* 2021;80:105710.
15 Godot A, Fakih O, Prati C, *et al*. SAPHO syndrome and subclavian thrombosis: Simple fortuitous association? *Eur J Intern Med* 2020;72:103–5.
16 Ramautar A, Appelman-Dijkstra N, Lakerveld S, *et al*. Clinical features of sternocostoclavicular hyperostosis: A large single Center Dutch cohort. *J Bone Miner Res* 2018;33.
17 Brouwers MC, Spithoff K, Kerkvliet K, *et al*. Development and Validation of a Tool to Assess the Quality of Clinical Practice Guideline Recommendations. *JAMA Netw Open* 2020;3:e205535.
18 Leerling AT, Clunie G, Koutrouba E, *et al*. Diagnostic and therapeutic practices in adult chronic nonbacterial osteomyelitis (CNO). *Orphanet J Rare Dis* 2023;18:206.
19 Schünemann HJ, Vist GE, GlasziouP, *et al*. *Cochrane handbook for systematic reviews of interventions version 6.4*. Higgins JPT TJ, Chandler J, Cumpston M, et al, eds. Cochrane, 2023.
20 Colina M, Trotta F. Clinical and radiological characteristics of SAPHO syndrome. *Curr Rheumatol Rev* 2013;9:22–7.
21 Gao S, Deng X, Zhang L, *et al*. The comparison analysis of clinical and radiological features in SAPHO syndrome. *Clin Rheumatol* 2021;40:349–57.
22 Sallés M, Olivé A, Perez-Andres R, *et al*. The SAPHO syndrome: a clinical and imaging study. *Clin Rheumatol* 2011;30:245–9.
23 Himuro H, Kurata S, Nagata S, *et al*. Imaging features in patients with SAPHO/CRMO: a pictorial review. *Jpn J Radiol* 2020;38:622–9.
24 Xu W, Li C, Zhao X, *et al*. Whole-spine Computed Tomography Findings in SAPHO Syndrome. *J Rheumatol* 2017;44:648–54.
25 Yu M, Cao Y, Li J, *et al*. Anterior chest wall in SAPHO syndrome: magnetic resonance imaging findings. *Arthritis Res Ther* 2020;22:216.
26 Ramautar AIE, Navas A, Winter EM, *et al*. Defining the imaging diagnostic criteria for adult chronic non-bacterial osteitis. *JBMR Plus* 2024;8:ziae024.
27 Freyschmidt J, Sternberg A. The bullhead sign: scintigraphic pattern of sternocostoclavicular hyperostosis and pustulotic arthroosteitis. *Eur Radiol* 1998;8:807–12.
28 Cao Y, Li C, Yang Q, *et al*. Three patterns of osteoarticular involvement in SAPHO syndrome: a cluster analysis based on whole body bone scintigraphy of 157 patients. *Rheumatology (Oxford)* 2019;58:1047–55.
29 Okuno H, Watanuki M, Kuwahara Y, *et al*. Clinical features and radiological findings of 67 patients with SAPHO syndrome. *Mod Rheumatol* 2018;28:703–8.
30 Akiyama Y, Sato T, Hanai S, *et al*. SAT0269 The Clinical Features of Sapho Syndrome in Japanese Patients: A Single Center Cohort Study. *Ann Rheum Dis* 2015;74:756.
31 Asano T, Furuya MY, Fujita Y, *et al*. Diagnostic value of ultrasonography in synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome: A case report. *Medicine (Baltimore)* 2018;97:e12725.
32 Aljuhani F, Tournadre A, Tatar Z, *et al*. The SAPHO syndrome: a single-center study of 41 adult patients. *J Rheumatol* 2015;42:329–34.
33 Ralston SH, Scott PD, Sturrock RD. An unusual case of pustulotic arthro-osteitis affecting the leg, and erosive polyarthritis. *Ann Rheum Dis* 1990;49:643–5.
34 Aparicio Rovira M, Aparicio Espinar M, Gifre L, *et al*. AB0738 SAPHO OR PSORIATIC ARTHRITIS?: EVALUATION OF CASPAR CRITERIA IN A COHORT WITH SAPHO. *Ann Rheum Dis* 2020;79:1664–5.
35 Yamamoto T, Hiraiwa T, Tobita R, *et al*. Characteristics of Japanese patients with pustulotic arthro-osteitis associated with palmoplantar pustulosis: a multicenter study. *Int J Dermatology* 2020;59:441–4.
36 Maugars Y, Berthelot JM, Ducloux JM, *et al*. SAPHO syndrome: a followup study of 19 cases with special emphasis on enthesis involvement. *J Rheumatol* 1995;22:2135–41.
37 Hayem G, Bouchaud-Chabot A, Benali K, *et al*. SAPHO syndrome: A long-term follow-up study of 120 cases. *Semin Arthritis Rheum* 1999;29:159–71.
38 Colina M, La Corte R, Trotta F. Sustained remission of SAPHO syndrome with pamidronate: a follow-up of fourteen cases and a review of the literature. *Clin Exp Rheumatol* 2009;27:112–5.
39 Valkema PA, Luymes CH, Witteveen JE, *et al*. High prevalence of autoimmune disease in the rare inflammatory bone disorder sternocostoclavicular hyperostosis: survey of a Dutch cohort. *Orphanet J Rare Dis* 2017;12:20.
40 Carroll MB. Sternocostoclavicular hyperostosis: a review. *Ther Adv Musculoskelet Dis* 2011;3:101–10.
41 Taylor W, Gladman D, Helliwell P, *et al*. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665–73.
42 Zeidler H, Amor B. The Assessment in Spondyloarthritis International Society (ASAS) classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general: the spondyloarthritis concept in progress. *Ann Rheum Dis* 2011;70:1–3.
43 Solau-Gervais E, Soubrier M, Gerot I, *et al*. The usefulness of bone remodelling markers in predicting the efficacy of pamidronate treatment in SAPHO syndrome. *Rheumatology (Sunnyvale)* 2006;45:339–42.
44 Andreasen CM, Jurik AG, Deleuran BW, *et al*. Pamidronate in chronic non-bacterial osteomyelitis: a randomized, double-blinded, placebo-controlled pilot trial. *Scand J Rheumatol* 2020;49:312–22.
45 Armstrong DJ, Wright SA, Coward SM, *et al*. Bone marker response in chronic diffuse sclerosing osteomyelitis treated with intravenous ibandronate [8]. *Ann Rheum Dis* 2006;65:976–7.
46 Cao Y, Li C, Xu W, *et al*. Spinal and sacroiliac involvement in SAPHO syndrome: A single center study of a cohort of 354 patients. *Semin Arthritis Rheum* 2019;48:990–6.
47 Xu T, Ding H, Fan D, *et al*. Prospective Comparison of the Imaging Value of 99mTc-MDP Bone Scan and 68Ga-FAPI-04 PET/CT in Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis Syndrome. *Clin Nucl Med* 2023;48:768–74.
48 Leerling AT, Smit F, Späth Z, *et al*. 18F-Sodium fluoride PET-CT visualizes disease activity in chronic nonbacterial osteitis in adults. *JBMR Plus* 2024;8:ziad007.
49 Przepiera-Będzak H, Brzosko M. SAPHO syndrome: pathogenesis, clinical presentation, imaging, comorbidities and treatment: a review. *Postepy Dermatol Alergol* 2021;38:937–42.
50 Weber U, Lambert RG, Rufibach K, *et al*. Anterior chest wall inflammation by whole-body magnetic resonance imaging in patients with spondyloarthritis: lack of association between clinical and imaging findings in a cross-sectional study. *Arthritis Res Ther* 2012;14:R3.
51 Raptis CA, Ludwig DR, Hammer MM, *et al*. Building blocks for thoracic MRI: Challenges, sequences, and protocol design. *J Magn Reson Imaging* 2019;50:682–701.

52 Khanna L, El-Khoury GY. SAPHO syndrome--a pictorial assay. *Iowa Orthop J* 2012;32:189–95.
53 Leerling AT, Niesters M, Flendrie M, *et al*. Neuropathic and Nociplastic Pain Profiles are Common in Adult Chronic Nonbacterial Osteitis (CNO). *Calcif Tissue Int* 2024;114:603–13.
54 Mendoza T, Mayne T, Rublee D, *et al*. Reliability and validity of a modified Brief Pain Inventory short form in patients with osteoarthritis. *Eur J Pain* 2006;10:353–61.
55 Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol* 2003;30:167–78.
56 Sun X, Li C, Cao Y, *et al*. F-18 FDG PET/CT in 26 patients with SAPHO syndrome: a new vision of clinical and bone scintigraphy correlation. *J Orthop Surg Res* 2018;13:120.
57 Capponi M, Marafon DP, Rivosecchi F, *et al*. Chronic non-bacterial osteomyelitis (CNO): Correlation between clinical and radiological findings. *Arthritis Rheumatol* 2020;72:17–9.
58 Li C, Wang L, Wu N, *et al*. A retrospective study of bone scintigraphy in the follow-up of patients with synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: is it useful to repeat bone scintigraphy for disease assessment? *Clin Rheumatol* 2020;39:1305–14.
59 Takahara M, Hirata Y, Nagato T, *et al*. Treatment outcome and prognostic factors of tonsillectomy for palmoplantar pustulosis and pustulotic arthro-osteitis: A retrospective subjective and objective quantitative analysis of 138 patients. *J Dermatol* 2018;45:812–23.
60 Wang Y, Xiang Y, Cao Y, *et al*. Tonsillectomy Leads to Remission of Bone Marrow Edema and Palmoplantar Pustulosis in Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis Syndrome. *J Clin Rheumatol* 2021;27:S719–20.
61 Xiang Y, Wang Y, Cao Y, *et al*. Tonsillitis as a possible predisposition to synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. *Int J of Rheum Dis* 2021;24:519–25.
62 Yamashita A, Sano T, Iwashita M, *et al*. A Case Report of Improved Palmoplantar Pustulosis following Periodontal Treatment and Possible Association with Diminished Systemic Subclinical Inflammation. *Case Rep Dermatol Med* 2021;2021:5548760.
63 Akazawa H, Nishimura F, Maeda H, *et al*. Regression of pustulosis palmaris et plantaris by periodontal treatment in a subject with severe periodontitis. *Int J Dermatol* 2006;45:1420–2.
64 Kouno M, Nishiyama A, Minabe M, *et al*. Retrospective analysis of the clinical response of palmoplantar pustulosis after dental infection control and dental metal removal. *J Dermatol* 2017;44:695–8.
65 Jung J, Molinger M, Kohn D, *et al*. Intra-Articular Glucocorticosteroid Injection into Sternocostoclavicular Joints in Patients with SAPHO Syndrome. *Semin Arthritis Rheum* 2012;42:266–70.
66 Oray M, Abu Samra K, Ebrahimiadib N, *et al*. Long-term side effects of glucocorticoids. *Expert Opin Drug Saf* 2016;15:457–65.
67 Ramiro S, Nikiphorou E, Sepriano A, *et al*. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis* 2023;82:19–34.
68 Gossec L, Baraliakos X, Kerschbaumer A, *et al*. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;79:700–12.
69 Borzutzky A, Stern S, Reiff A, *et al*. Pediatric chronic nonbacterial osteomyelitis. *Pediatrics* 2012;130:e1190–7.
70 Zhao Y, Wu EY, Oliver MS, *et al*. Consensus Treatment Plans for Chronic Nonbacterial Osteomyelitis Refractory to Nonsteroidal Antiinflammatory Drugs and/or With Active Spinal Lesions. *Arthritis Care Res (Hoboken)* 2018;70:1228–37.
71 Monet M, Prati C, Guillot X, *et al*. Disease modifying anti rheumatic drugs in the treatment of sapho syndrome: systematic literature analysis. *Ann Rheum Dis* 2018;1155–6.
72 Amital H, Applbaum YH, Aamar S, *et al*. SAPHO syndrome treated with pamidronate: an open-label study of 10 patients. *Rheumatology (Oxford)* 2004;43:658–61.
73 Li C, Zhao Y, Zuo Y, *et al*. Efficacy of bisphosphonates in patients with synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: a prospective open study. *Clin Exp Rheumatol* 2019;37:663–9.
74 Delattre E, Guillot X, Godfrin-Valnet M, *et al*. SAPHO syndrome treatment with intravenous pamidronate. Retrospective study of 22 patients. *Joint Bone Spine* 2014;81:456–8.
75 Leerling AT, Cañete AN, Ramautar AIE, *et al*. Sternocostoclavicular Hyperostosis: Positive Clinical and Radiological Response on Pamidronate. *Front Endocrinol (Lausanne)* 2021;12:621604.
76 Galadari H, Bishop AG, Venna SS, *et al*. Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome treated with a combination of isotretinoin and pamidronate. *J Am Acad Dermatol* 2009;61:123–5.
77 Courtney PA, Hosking DJ, Fairbairn KJ, *et al*. Treatment of SAPHO with pamidronate. *Rheumatology (Oxford)* 2002;41:1196–8.
78 Siau K, Laversuch CJ. SAPHO syndrome in an adult with ulcerative colitis responsive to intravenous pamidronate: a case report and review of the literature. *Rheumatol Int* 2010;30:1085–8.
79 Wu N, Zhao Y, Tao W, *et al*. A single cohort, open-label study of the efficacy of pamidronate for palmoplantar pustulosis in synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. *Clin Exp Rheumatol* 2020;38:1263–4.
80 Hayem G, Ben M'BarekR, ToussirotE, *et al*. SAPHO syndrome treated by TNF alpha-blocking agents. Report of 45 cases. *Arthritis Rheum* 2010;2269.
81 Ueno M, Miyagawa I, Miyazaki Y, *et al*. Efficacy and safety of guselkumab and adalimumab for pustulotic arthro-osteitis and their impact on peripheral blood immunophenotypes. *Arthritis Res Ther* 2022;24:240.
82 Ben Abdelghani K, Dran DG, Gottenberg JE, *et al*. Tumor Necrosis Factor-α Blockers in SAPHO Syndrome: Table 1. *J Rheumatol* 2010;37:1699–704.
83 Murgia G, Firinu D, Barca MP, *et al*. Biologics for SAPHO syndrome: A single centre experience. *Allergy Eur J Allergy Clin Immunol* 2015;70:418–9.
84 Abourazzak FE, Hachimi H, Kadi N, *et al*. Etanercept in the treatment of SAPHO syndrome: Which place? *Eur J Rheumatol* 2014;1:125–8.
85 Antoniou C, Nicolaidou E, Moustou AE, *et al*. Palmoplantar pustulosis with arthro-osteitis: successful treatment with etanercept and acitretin. *Acad Dermatol Venereol* 2009;23:854–5.
86 Arias-Santiago S, Sanchez-Cano D, Callejas-Rubio J, *et al*. Adalimumab Treatment for SAPHO Syndrome. *Acta Derm Venerol* 2010;90:301–2.
87 Baisya R, Gavali M, Tyagi M, *et al*. A Case of SAPHO Syndrome Complicated by Uveitis with Good Response to Both TNF Inhibitor and JAKinib. *Case Rep Rheumatol* 2023;2023:6201887.
88 Burgemeister LT, Baeten DLP, Tas SW. Biologics for rare inflammatory diseases: TNF blockade in the SA PHO syndrome. *Neth J Med* 2012;70:444–9.
89 Castellví I, Bonet M, Narváez JA, *et al*. Successful treatment of SAPHO syndrome with adalimumab: a case report. *Clin Rheumatol* 2010;29:1205–7.
90 Crowley EL, O'Toole A, Gooderham MJ. Hidradenitis suppurativa with SAPHO syndrome maintained effectively with adalimumab, methotrexate, and intralesional corticosteroid injections. *SAGE Open Med Case Rep* 2018;6.
91 De Souza A, Solomon GE, Strober BE. SAPHO syndrome associated with hidradenitis suppurativa successfully treated with infliximab and methotrexate. *Bull NYU Hosp Jt Dis* 2011;69:185–7.
92 Hirohata A, Hanafusa T, Kawamoto T, *et al*. Infliximab for Treatment of Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis Syndrome: A Case Report. *Ann Dermatol* 2017;29:131.
93 Iqbal M, Kolodney MS. Acne fulminans with synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome treated with infliximab. *J Am Acad Dermatol* 2005;52:S118–20.
94 Marí A, Morla A, Melero M, *et al*. Diffuse sclerosing osteomyelitis (DSO) of the mandible in SAPHO syndrome: A novel approach with anti-TNF therapy. Systematic review. *J Cranio-Maxillofac Surg* 2014;42:1990–6.
95 Olivieri I, Padula A, Ciancio G, *et al*. Successful treatment of SAPHO syndrome with infliximab: report of two cases. *Ann Rheum Dis* 2002;61:375–6.
96 Sabugo F, Liberman C, Niedmann JP, *et al*. Infliximab can induce a prolonged clinical remission and a decrease in thyroid hormonal requirements in a patient with SAPHO syndrome and hypothyroidism. *Clin Rheumatol* 2008;27:533–5.
97 Saez-Martin LC, Gomez-Castro S, Roman-Curto C, *et al*. Etanercept in the treatment of SAPHO syndrome. *Int J Dermatol* 2015;54:e206–8.
98 Su YS, Chang CH. SAPHO syndrome associated with acne conglobata successfully treated with etanercept. *J Formos Med Assoc* 2015;114:562–4.
99 Vilar-Alejo J, Dehesa L, de la Rosa-del Rey P, *et al*. SAPHO Syndrome with Unusual Cutaneous Manifestations Treated Successfully with Etanercept. *Acta Derm Venerol* 2010;90:531–2.
100 Wagner AD, Andresen J, Jendro MC, *et al*. Sustained response to tumor necrosis factor α–blocking agents in two patients with SAPHO syndrome. *Arthritis & Rheumatism* 2002;46:1965–8.
101 Zhang L, Gao Z. Etanercept in the treatment of refractory SAPHO syndrome. *Am J Clin Exp Immunol* 2016;5:62–6.
102 Hampton SL, Youssef H. Successful treatment of resistant SAPHO syndrome with anti-TNF therapy. *BMJ Case Rep* 2013;2013.
103 Kanda R, Nakano K, Miyagawa I, *et al*. A case of bone destruction caused by chronic non-bacterial osteomyelitis (CNO) successfully repaired with a tumour necrosis factor-α (TNF-α) inhibitor, adalimumab. *Mod Rheumatol Case Rep* 2020;4:196–201.
104 Huber CE, Judex AG, Freyschmidt J, *et al*. Sequential Combination Therapy Leading to Sustained Remission in a Patient with SAPHO Syndrome. *Open Rheumatol J* 2009;3:18–21.
105 Misiak-Galazka M, Jeziorkowska R, Sikorska-Siudek K, *et al*. SAPHO syndrome: Case report. *Postepy Dermatol Alergol* 2012;29:136–8.
106 Jinag C, Zhao Y, Li X, *et al*. Whole-body Bone Scan in the Diagnosis and Treatment of SAPHO Syndrome. *J Coll Physicians Surg Pak* 2022;32:S64–6.
107 Yabe H, Kuroiwa T, Nonaka A, *et al*. Clinical features and treatment results of Japanese patients with sapho (synovitis-acne-pustulosis-hyperostosis-osteitis) syndrome. *Arthritis Rheum* 2012;64:S589–90.
108 Li B, Li GW, Xue L, *et al*. Rapid remission of refractory synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome in response to the Janus kinase inhibitor tofacitinib: A case report. *World J Clin Cases* 2020;8:4527–34.
109 Li Y, Liu G, Zhao Y, *et al*. SAPHO syndrome with pathological fractures of vertebral bodies: a case report. *BMC Musculoskelet Disord* 2019;20:27.

110 Xi Y, Lin Z, Chen N, *et al*. Clavicle fracture in SAPHO syndrome. *Rheumatol (Oxford)* 2024;63:e154–5.
111 Yamamoto H, Taniguchi Y. Pustulotic Arthro-Osteitis–Related Pathological Clavicle Fracture. *J Clin Rheumatol* 2024;30:e123.
112 Murdoch R, Mellar A, Horne AM, *et al*. Effect of a Three-Day Course of Dexamethasone on Acute Phase Response Following Treatment With Zoledronate: A Randomized Controlled Trial. *J Bone Miner Res* 2020;38:631–8.
113 Kennel KA, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. *Mayo Clin Proc* 2009;84:632–7.
114 Fragoulis GE, Nikiphorou E, Dey M, *et al*. 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2023;82:742–53.
115 Brown G, Wang E, Leon A, *et al*. Tumor necrosis factor-α inhibitor-induced psoriasis: Systematic review of clinical features, histopathological findings, and management experience. *J Am Acad Dermatol* 2017;76:334–41.
116 Kodra Y, Weinbach J, Posada-de-la-Paz M, *et al*. Recommendations for Improving the Quality of Rare Disease Registries. *Int J Environ Res Public Health* 2018;15:1644.
117 Ramachandran S, Zhao Y, Ferguson PJ. Update on treatment responses and outcome measure development in chronic nonbacterial osteomyelitis. *Curr Opin Rheumatol* 2023;35:255–64.
118 Russell MD, Dey M, Flint J, *et al*. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. *Rheumatology (Oxford)* 2023;62:e48–88.

AGREE-Recommendation EXcellence (AGREE-REX) Reporting Checklist

This checklist is intended to guide the reporting of clinical practice guideline recommendations.

Manuscripts related to the AGREE-REX are being submitted to peer-reviewed journals for publication. Citations will be added here when they become available.

For more information about the AGREE-REX Reporting Checklist, please visit the AGREE Enterprise website at www.agreetrust.org.

CHECKLIST ITEM	REPORTING CRITERIA	Page #
ITEM 1: CLINICAL APPLICABILITY		
1. Evidence The following criteria are related to the evidence supporting the recommendations.	**To be reported:** ☑ Risk of bias related to the study designs of the supporting evidence ☑ Consistency of the results (i.e., similarity of results across studies) ☑ Directness of evidence to the clinical/health problem (i.e., addresses the exact interventions, populations and outcomes of interest) ☑ Precision of the results (e.g., width of confidence intervals of individual studies or meta-analyses) ☑ Magnitude of the benefits and harms ☑ Likelihood of publication bias ☑ Possibility of confounding variable (if applicable) ☑ Dose-response gradient (if applicable)	S3
2. Applicability to Target Users The following criteria are related to the applicability of the recommendations to target users.	**To be considered during development and reporting of the recommendations and supporting text:** ☑ A clinical/health problem that is relevant to the intended target users ☑ Alignment between the target user's scope of practice and targeted patients/populations ☑ Alignment between the target user's scope of practice and recommended actions ☑ Alignment between the direction of the recommendations (i.e., in favour of or against a particular action) and the trade-offs between harms and benefits ☑ Alignment between the definitiveness or strength of the recommendations and the trade-offs between harms and benefits	5-6 Latter two: Rationale for R1-R16
3. Applicability to Patients/Population The following criteria are related to the applicability of the recommendations to patients/populations.	**To be reported:** ☑ Outcomes relevant to the targeted patients/populations that were considered in the development of evidence base ☑ Recommended actions that have the potential to impact outcomes relevant to patients/populations ☑ How the importance of outcomes to patients was determined ☑ How to tailor recommendations for application to individual (or subsets of) patients or populations (e.g., based on age, sex, ethnicity, comorbidities)	R9, p 18-19 S4 Table 3/4 and 6/7

DOMAIN 2: VALUES AND PREFERENCES		
4. Values and Preferences of Target Users The following criteria are related to the target users' values and preferences.	**To be reported:** ☑ Values and preferences of the target users that were considered in relation to the recommended actions ☑ Factors related to target user acceptability of the recommended actions that were considered (e.g., the acceptability of learning new clinical skills or the need to adapt current routine) ☑ Differentiation between recommended actions for which clinical flexibility and individual patient tailoring is more or less appropriate in the decision-making process ☑ Range of recommended actions that are acceptable in the clinical community, including the preferred option (if relevant), and why it is the preferred choice	R9, p 18-19 S4 Table 4 Table 7 Table 2 and 6
5. Values and Preferences of Patients/Population The following criteria are related to the values and preferences of patients/populations.	**To be reported:** ☑ Values and preferences of the target population (e.g., patients, family, caregivers) that were considered in relation to the recommended actions ☑ Factors related to patient/population acceptability of the recommended actions that with considered (e.g., motivation, ability to achieve outcomes, expectations, perceived effectiveness) ☑ Differentiation between recommended actions for which patient choice and/or values are likely to play a large or small part in the decision-making process ☐ Statement about whether tools for assisting in patient decision-making would be beneficial	Nomenclature; Page10 S4, R9,
6. Values and Preference of Policy/Decision-Makers The following criteria are related to the values and preferences of policy/decision-makers.	**To be reported (if applicable):** ☐ Needs of policy and decision-makers that were considered in the formulation of the recommendations ☐ Impacts of the recommendations on policy and system-level decision-making that were considered in the formulation of recommendations ☐ Impacts of the recommendations on health equities that were considered in the formulation of recommendations ☐ Description of any required changes to policy to align with the recommendations	N/A
7. Values and Preferences of Guideline Developers The following criteria are related to guideline developers' values and preferences and the integration of values and preferences from other stakeholders.	**To be reported:** ☑ Values and preferences that guideline developers brought to the development process ☑ How guideline developer values and preferences influenced their interpretation of the balance between benefits and harms ☑ Methods used to integrate values and preferences, especially when they differ between stakeholders	S4
DOMAIN 3: IMPLEMENTABILITY		

8. Purpose The following criteria are related to the implementation goals and intended impacts of the guideline.	**To be considered during the development and reporting of the recommendations and supporting text:** ☑ Alignment of guideline recommendations with the implementation goals (e.g., for advocacy, policy change) ☑ Anticipated impacts of recommendation adoption on individuals (e.g., patients, populations, target users), organizations, and/or systems	27-28
9. Local Application and Adoption The following criteria are related to the local application and adoption of the recommendations.	**To be reported:** ☑ Types and degree of change required from current practice ☑ Differentiation between recommendations for which local adaptation may be more or less relevant ☑ Factors that are important for successful dissemination ☑ Issues that can influence the adoption of the recommendations and tools and/or advice for implementers, such as: o Advice on how-to tailor recommendations for the local setting o Resources needed to implement the recommendations and their associated costs o Economic analysis o Required competencies or training to implement recommendations o Data required to implement and monitor the adoption of recommended actions o Strategies to overcome barriers related to provider acceptability and/or patient/population and/or policy acceptability of the recommended action(s). o Criteria that can be used to measure recommendation implementation and quality improvement	27-28

Winter EM, *et al. Ann Rheum Dis* 2024;0:1–19. doi: 10.1136/ard-2024-226446

Supplemental material 2: Domains of interest

Note: This domain list was developed prior to the consensus decision to use "adult CNO" and therefore initially referred to "adults with SBI". We have retrospectively updated this designation into "adult CNO" for clarity.

Category	Question
Disease definition and name	1. What are clinical characteristics of adult CNO?
	A. Skeletal distribution pattern
	B. Additional (extra-skeletal) features
	C. Demographics, risk factors, physical exam findings
	2. What are imaging characteristics of adult CNO?
	A. Structural imaging features in early disease and long-term disease
	B. Other diagnostic imaging features
	C. Imaging features related to disease activity
	3. What is the preferred name to use for adult CNO?
Diagnosis	4. Where and how is care for adult CNO preferably organized?
	5. Which laboratory tests are indicated for suspected adult CNO?
	A. Routine laboratory tests
	B. Optional laboratory tests
	6. What type of imaging is preferred for suspected adult CNO?
	A. Imaging preferences for structural characterization of bone lesions
	B. Imaging preferences for assessment of disease activity
	C. Imaging preferences for asymptomatic lesion screening
	7. In what cases is a bone biopsy indicated as part of the diagnostic work-up?
Treatment	8. What are treatment goals in adult CNO?
	9. Which outcome measures should be used for the treatment goals as agreed upon? And what does this imply for treatment indications?
	10. What are considerations regarding contents and duration of step 1 treatment?
	11. What are considerations regarding contents of step 2 treatment?
	12. What are considerations regarding contents of step 3 treatment?
	13. What are considerations regarding ancillary treatments?
	14. What are considerations regarding the treatment of additional (extra-skeletal) features?
	15. What are considerations during patient follow-up?
Research agenda	-- What are research priorities in the near future?

Supplemental material 3: Summary of Evidence

Last update: April 18th 2024

Note: This document was developed prior to the consensus decision to use "adult CNO" and therefore initially referred to "adults with SBI". We have retrospectively updated this designation into "adult CNO" for clarity.

Disease definition and Name

Q1: What are clinical characteristics of adult CNO?

A: Skeletal distribution pattern	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Anterior chest wall	Recent meta-analysis used.	Pooled involvement rate 89%, 95% CI 78-96 (1).	Not queried.	For estimated prevalence of involvement: **Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias)
Spine Cervical Thoracic Lumbar	Recent meta-analysis used. Additionally searched for "lumbar", "thoracic", "cervical".	Pooled involvement rate for spine in general 25%, 95% CI 16-37. Cervical, thoracic and lumbar spine are involved (as defined by increased isotope uptake) in 4.5%, 21% and 33% respectively according to one cohort study (2), and 2.8%, 2.8%, 4.7% according to another (3). Another CT-based study found a predilection for the thoracic vertebrae in patients with spinal involvement (4).	Not queried.	For estimated prevalence of spinal involvement: **Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias) For estimated prevalence of specific spinal level involvement: **Very low** (Due to indirectness, imprecision and inconsistency)
Mandible	Recent meta-analysis used.	Pooled involvement rate 1%, 95% CI 0-3 (1).	Not queried.	For estimated prevalence of involvement: **Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias)
Peripheral bones	Recent meta-analysis used.	Pooled involvement rate 4%, 95% CI 1-10 (1).	Not queried.	For estimated prevalence of involvement: **Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias)
B: Additional (extra-skeletal) features	**Identification of studies**	**Summary of evidence**	**Physician survey results**	**Level of evidence**
Sacroiliitis	Recent meta-analysis used.	Pooled prevalence 12%, 95% CI 6-20 (1).	Not queried.	For estimated prevalence of this feature: **Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias)

Non-erosive/destructive arthritis of peripheral joints	Recent meta-analysis used.	Pooled prevalence 24%, 95% CI 11-39 (1).	Reported as "sometimes/often" seen by 56%.	For estimated prevalence of this feature: **Low** (Due to 6/21 studies included in meta-analysis displaying high risk of bias, and imprecision)
Erosive/destructive arthritis of peripheral joints	**"**erosive arthritis", "erosive synovitis", "destructive arthritis", "peri-articular erosion", "periarticular erosion"	A single report describes a case with erosive peripheral polyarthritis. The authors present the case as unusual, as arthritis is usually non-erosive in adult CNO (5). One case series (n=12) describes the pathogenesis of adult CNO as starting with a destructive sternoclavicular arthritis (6).	Not queried.	For estimated prevalence of this feature: **Very low** (Due to imprecision; only case reports/series)
Dactylitis	"dactylitis", "sausage digit"	Prevalence only reported in one cohort study (n=39), where it was 20% (7). Two case reports describe the co-occurence of dactylitis and adult CNO (8).	Not queried.	For estimated prevalence of this feature: **Very low** (Due to imprecision; few/only one study)
Signs compatible with enthesitis in the peripheral skeleton	"enthesitis", "entheses", "enthesopathy"	Prevalence of peripheral enthesitis was 28% and 20% in two cohort studies (n=67 and n=20 respectively) (9, 10). One case report demonstrates peripheral enthesitis in adult CNO (11). Enthesopathy rather than enthesitis is additionally reported in several case reports/series, as are entheseal abnormalities on ultrasound (12-15).	Not queried.	For estimated prevalence of this feature: **Very low** (Due to imprecision; few/only one study)
Pustulosis palmoplantaris	Recent meta-analysis used.	Pooled prevalence 53%, 95% CI 37-68 (1).	Reported as "sometimes/often" seen by 83%.	For estimated prevalence of this feature: **Low** (Due to 6/21 studies included in meta-analysis displaying high risk of bias, and imprecision)
Psoriasis	Recent meta-analysis used.	Pooled prevalence 8%, 95% CI 4-14 (1).	Reported as "sometimes/often" seen by 78%.	For estimated prevalence of this feature: **Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias)
Severe acne	Recent meta-analysis used.	Pooled prevalence 8%, 95% CI 4-13 (1).	Reported as "sometimes/often" seen by 80%.	For estimated prevalence of this feature: **Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias)
Hidradenitis suppurativa	"hidradenitis"	Limited data on prevalence. Prevalence was 2% in one retrospective study (n=41 patients) (16).	Reported as "sometimes/often" seen by 48%.	For estimated prevalence of this feature: **Very low** (Due to imprecision; few/only one study)
Inflammatory bowel disease	Recent meta-analysis used.	Pooled prevalence 1%, 95% CI 0-3 (1).	Not queried.	For estimated prevalence of this feature: **Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias)

Uveitis	"uveitis", "ocular", "eye"	Limited data on prevalence. A handful case reports describe uveitis in adult CNO (17, 18).	Not queried.	For estimated prevalence of this feature: **Very low** (Due to imprecision; only case reports)
C: Demographics, risk factors, physical exam findings "Adults with sterile bone inflammation…"	**Identification of studies**	**Summary of evidence**	**Physician survey results**	**Level of evidence**
Usually present during midlife (30-50 years of age).	Recent meta-analysis used.	Pooled mean age of onset is 38 95% confidence interval (CI) 29-46 (1).	Not queried.	**Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias)
Are predominately female.	Recent meta-analysis used.	Pooled female predisposition of 67%, 95% CI 60-73 (1).	Not queried.	**Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias)
Mainly present with inflammatory bone pain, which can be chronic or relapsing-remitting.	Recent reviews and large cohort studies used. Alternatively searched for "asymptomatic", "subclinical" and "coincidental" cases.	Pain is a highly prevalent symptom in adult CNO, ranging from 96-100% (3, 19-22). Several fully asymptomatic cases are described in case reports and series, as well as subclinical lesions revealed with whole body imaging, mainly in pediatric patients (6, 23-26).	Median rating of 4.0 (on 5 point Likert scale) regarding importance of this feature to speak of adult CNO.	**Moderate** (Due to indirectness: generally reported as "pain" rather than "inflammatory bone pain" specifically)
Show abnormalities during physical examination e.g. Swelling, local inflammatory signs.	"swelling", "erythema", "redness", "local inflammatory", "local inflammation" *Limited to only larger cohort studies > 100 patients. For fever, recent meta-analysis was used.	Only two large cohort studies have reported exact rates of physical examination findings at presentation, that is 61% bone swelling, 33% acute inflammatory signs (n=213 in total, Dutch cohort) (3) and 39% bone swelling (n=77, United Kingdom cohort) (27). Other studies use descriptive terms like "occasionally", "with or without", "sometimes" (28-30). Swelling seems more pronounced in adult CNO compared to bacterial osteomyelitis in one cohort study of n=156 (exact prevalence not reported) (31). Pooled prevalence of fever 4%, 95% CI 0-14 (1).	Median rating of 3.0 (on 1-5 Likert scale) regarding importance of this feature to speak of adult CNO.	For the estimated prevalence of physical examination abnormalities: **Very low** (Due to inconsistency, imprecision) For estimated prevalence of fever: **Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias)

Are frequently past or active smokers.	"smoking", "tobacco", "intoxication"	Prevalence of past or active smoking is 53%, 59% and 64% in three cohort studies (n=213, n=51, n=164 respectively) (28, 32, 33); two on pustulotic arthro-osteitis (i.e. PPP + sterile bone inflammation), and one on sterile bone inflammation, with or without PPP. The prevalence of active smoking among PPP patients (with or without sterile bone inflammation) has been reported at 71% and 94% in two cohort studies (n=286 and n=136 patients) (34, 35) and adjusted odds ratio of PPP with past or active smoking is 9.5 compared to psoriasis vulgaris and 36 compared to other dermatological conditions in one case control study (n=125) (36).	Not queried.	**Low** (Due to indirectness: two cohorts of patients with pustulotic arthro-osteitis, who form a slightly different population as the smoking-associated feature of PPP is present per definition, and no proper case-control studies performed in adult CNO only)

Q2: What are imaging characteristics of adult CNO?

A: Structural imaging features in early disease and long-term disease	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Osteosclerosis	Studies were not selected systematically through key words. Included were studies reporting imaging data for ≥40 adult patients, and reviews on imaging features of adult CNO published from 2010 onwards.	Osteosclerosis in adult CNO is described to evolve over time as a healing response to active osteitis. While osteosclerosis represents chronic inflammatory change, patients usually present with a radiologic picture that has accumulated over years (of note: mean diagnostic delay in adult CNO is 5 years (1)), which then already includes osteosclerosis (37-40). Sclerotic changes usually progress over time and complete resolution is rare, though has been reported (37, 41). Sclerosis also differentiates CNO patients from non-CNO patients (42).	Scored as typical imaging feature by 64% of physicians (not stratified for early vs. Long-term disease).	For general association of this feature with adult CNO: **Moderate** (Due to indirectness: no comparative studies between adult patients and controls) For prevalence estimates of these features: **Low** (Prevalence could not be pooled in recent meta-analysis due to heterogeneity and selective reporting of data)
Osteolysis		In adult CNO, early disease may be characterized by lytic bone destruction in medullary areas. This has been reported for different localizations of adult CNO, including the clavicle, mandible, and spine (9, 37, 40, 43, 44). The healing (in long-term disease) process may also display a mixed lytic/sclerotic image (37, 40). It should be noted that a substantial part of the evidence on osteolysis as an imaging feature in the cited reviews pertains to paediatric CNO.	Scored as typical imaging feature by 39% of physicians (not stratified for early vs. Long-term disease).	
Bone erosions		Cortical bone erosions may develop as a result of both osteitis or arthritis in early stages of adult CNO (40, 45). In the spine, these occur mostly at the anterior vertebral end plates (4, 39, 46).	Scored as typical imaging feature by 22% of physicians (not stratified for early vs. Long-term disease).	
Soft tissue calcification/ossification		Prolonged inflammation may give rise to paravertebral or ligamentous ossification in adult CNO, in contrast to paediatric patients where this feature is not seen (4, 39, 47). Ossification of the costal cartilage is also common (48), as is calcification of the costoclavicular ligaments in patients with anterior chest wall involvement (42).	Scored as typical imaging feature by 10% of physicians (not stratified for early vs. Long-term disease).	
Hyperostosis		Hyperostosis, reflected as endosteal and periosteal thickening, is another chronic inflammatory change occurring in longstanding adult CNO (9, 38, 40). However, similar to osteosclerosis, hyperostosis may already be a key feature detected at presentation as radiologic changes may already have evolved during the period between onset and diagnosis (1, 37). In spinal adult CNO, hyperostosis may manifest as anterior bony bridges over discovertebral junctions (37), whereas in the anterior chest wall, hyperostosis may occur at the costosternal transitions (49). Hyperostotic	Scored as typical imaging feature by 78% of physicians (not stratified for early vs. Long-term disease).	

		changes are generally irreversible (37). Hyperostosis also differentiates CNO patients from non-CNO patients (42).		
Ankylosis		Ankylosis may occur in later stages of disease, mostly in the axial skeleton (sternoclavicular joints, sacroiliac joints, sternocostal joints, costochondral areas, manubriosternal joint or pubic symphysis) (39, 46, 47). A recent MRI-based study found ankylosis in the anterior chest wall in 80% of patients (48).	Scored as typical imaging feature by 10% of physicians (not stratified for early vs. Long-term disease).	
B: Other <u>diagnostic</u> imaging features	**Identification of studies**	**Summary of Evidence**	**Physician survey results**	**Level of evidence**
Bone marrow oedema (BMO)	Studies were not selected systematically through key words. Included were studies reporting imaging data for ≥40 adult patients, and reviews on imaging features of adult CNO published from 2010 onwards.	Bone marrow oedema (BMO) is a frequent observation during the acute phase of osteitis in adult CNO (39, 44). BMO was found in 89% (n=71) in a recent cohort study of MRI-findings of adult CNO of the anterior chest wall (48). BMO, altogether, appears as a sensitive imaging finding, but is also nonspecific due to its broad range of causes .	BMO scored as typical imaging feature by 58% of physicians.	For general association of this feature with adult CNO: **Moderate** (Due to indirectness: no comparative studies between adult patients and controls) For prevalence estimate of this feature: **Moderate** (Prevalence could not be pooled in recent meta-analysis due to heterogeneity and selective reporting of data, but more recent study has assessed BMO prevalence exhaustively)
Increased isotope uptake on nuclear imaging		99% (95% CI 96-100) of adult CNO patients display increased isotope uptake on nuclear imaging at sites of bone inflammation, suggesting high *sensitivity* of this finding. Increased isotope uptake also shows good correlation with abnormalities on CT (45). However, increased uptake is also known to lack *specificity* as it is associated with various differential diagnoses. The characteristic bull-head sign, representing increased uptake of the medial clavicles and manubrium sterni is only present in 8% (95% CI 1-10) (1). Key clinical and radiologic features or a highly typical distribution pattern therefore remain important for diagnosis of adult CNO (50).	Not queried.	For general association of this feature with adult CNO: **Moderate** (Due to indirectness: no comparative studies between adult patients and controls) For prevalence estimate: **Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias)
C: Imaging features related to disease activity	**Identification of studies**	**Summary of Evidence**	**Physician survey results**	**Level of evidence**
Bone marrow oedema (BMO)	Studies were not selected systematically	BMO and soft tissue oedema assessed by MRI can aid the differentiation between acute and chronic disease (40) and is incorporated in the MRI scoring tool proposed for paediatric CNO (51). One paediatric study	Not queried.	**Very low** (Due to indirectness, inconsistency, imprecision; few studies performed in

	through key words. Included were studies reporting imaging data for ≥40 adult patients, and reviews on imaging features of adult CNO published from 2010 onwards.	demonstrated a good correlation between clinical symptoms (biochemical, functional impairment and physician assessment) and MRI score at baseline, but not at 6 and 12 months follow-up (52). A pilot trial in mainly adult CNO patients demonstrated the significant decrease BMO after therapy with pamidronate (53). However, it remains unknown to what degree BMO resolves in response to disease remission, and what the prognostic value of residual BMO in asymptomatic patients is.		adult patients, disease activity indices remain to be validated)
Increased isotope uptake on nuclear imaging		For technetium labelled hydroxymethylene diphosphonate bone scintigraphy, it has been demonstrated that increased isotope uptake will persist despite remission of inflammatory activity of bone lesions (54), and therefore is limitedly helpful to differentiate active from non-active disease. PET can theoretically differentiate active from silent lesions (37, 49, 55). PET demonstrated moderate to substantial agreement with CT and bone scintigraphy in a study in 26 patients. Uptake on PET did not correlate well with clinical symptoms (55). This poor correlation resulted partly from a large number of patients reporting pain in specific musculoskeletal regions, without PET revealing increased uptake at these sights, and a substantial proportion of patients with subclinical lesions. It therefore remains unknown if tracer uptake is a proper indicator of disease activity.		**Very low** (Due to indirectness (for PET: no longitudinal study so no information on responsivity of PET in relation to changed clinical parameters), and imprecision (only 1 study per modality).

Q3: What is the preferred name of the clinical entity of "adults with sterile bone inflammation"?

"The preferred name for the clinical entity of "adults with sterile bone inflammation" is…"	**Identification of studies**	**Summary of evidence**	**Physician survey results**	**Level of evidence**
Chronic nonbacterial osteomyelitis (**CNO**) Synovitis, acne, pustulosis, hyperostosis, osteitis (**SAPHO**)-syndrome Synovitis, acne, pustulosis, hyperostosis, osteitis (**SAPHO**)-syndrome: **complete or incomplete** Chronic nonbacterial osteomyelitis/synovitis, acne, pustulosis, hyperostosis, osteitis (**ADULT CNO**) Sternocostoclavicular hyperostosis (**SCCH**). Pustulotic arthro-osteitis or pustolotic arthro-osteopathy (**PAO**). Chronic recurrent multifocal osteomyelitis (**CRMO**).	Recent meta-analysis and reviews published from 2010 onwards discussing terminology used.	The nomenclature surrounding adult CNO is diverse. A geographical preference was seen in a recent meta-analysis, where it was found that Chinese, Italian and French studies tend to refer to SAPHO, whereas Japanese studies use PAO. Dutch, German, Belgian and Scandinavian studies generally use CNO or SCCH (1). Many more terms (>50) to describe subsets of or related entities to adult CNO are encountered in current literature including condensing osteitis of the clavicle, inter-costo-sternal ossification, acquired hyperostosis syndrome (21). The term CRMO appears to be reserved for paediatric disease mostly, infrequently occurring as a label in adult literature. In clinical practice, physicians tend to use different labels according to disease phenotype (e.g. CNO in cases with isolated bone involvement, SCCH in case of anterior chest wall involvement, SAPHO in case of dermatitis or synovitis, CRMO in patients who have alternating locations or have presented at young age). Various authors believe that CNO, SAPHO, CRMO, SCCH and PAO are part of the same clinical spectrum chiefly characterized by autoinflammatory bone lesions (with or without extra-skeletal symptoms) (56).	Physicians use the following terms (alone, or in combination with others): CNO: 36% SAPHO: 36% CNO or SAPHO according to clinical picture: 50% SCCH: 31% PAO: 3% CRMO: 36%	N/A

Diagnosis

Q4: Where and how is care for adults with CNO preferably organized?

Organization of care	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Preferred physician to provide care for adults with CNO.	"specialist", "physician", "department", "dermatologist", "rheumatologist", "orthopedic", "internist", "clinical care''	No available literature on the question which physicians ideally see patients with adult CNO. However, the vast majority of studies on adult CNO derive from rheumatology departments. One retrospective study (n=25) compared the clinical management of adult CNO between rheumatologists and dermatologists, and found marked differences in therapeutic preference, but overall no difference in therapeutic outcome (57).	Not specifically queried, but responding physicians were rheumatologists (n=31), endocrinologists (2), and orthopedic surgeon (n=1).	**Very low** (Due to imprecision: only one study evaluating differences in patient outcomes between different medical specialties).
Preferred location/centre type to provide care for adults with CNO.	"center", "centre", "specialized", "expert", "referral"	No available literature on the question where care adult CNO is ideally situated, or whether care at an expert centre leads to better patient outcomes.	Most responding physicians were situated at university medical centres (86%), suggesting ADULT CNO care may be primarily situated here.	**Very low** (Due to indirectness: no studies evaluating differences in patient outcomes at regular versus expert referral centres).

Q5: Which laboratory tests are indicated for suspected adult CNO?

A: <u>Routine</u> laboratory tests	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Generic inflammation markers (full blood count with leucocyte differentiation, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)).	Recent meta-analysis used.	ESR and CRP are raised in 43%, 95%CI 27-59 and 54%, 95% CI 34-73 of patients. Elevation of ESR and CRP is mostly mild to moderate (1).	Inflammation markers are often/always determined by 86% of physicians. Of note, the survey did not query how often these markers were elevated according to physician's experience.	For prevalence estimate of raised markers: **Low** (Due to 6/21 studies included in meta-analysis displaying high risk of bias, and imprecision) For diagnostic value/clinical utility: **Very low** (Due to indirectness; clinical utility and diagnostic value of inflammation markers not studied in adults)
Alkaline-phosphatase (ALP)	Recent meta-analysis used.	ALP (generic) is elevated in 17%, 95%CI 7-31 of patients (1), but may also be used to evaluate the differential diagnosis of other high bone turnover diseases like Paget's disease and osteomalacia.	Not queried.	For prevalence estimate of raised markers: **Low** (Due to 6/21 studies included in meta-analysis displaying high risk of bias, and imprecision) For diagnostic value/clinical utility: **Very low** (Due to indirectness; clinical utility and diagnostic value of this marker not studied in adults)
Serum calcium, phosphate, parathyroid hormone.	"calcium", "phosphate", "parathyroid", "PTH"	Practically no data on abnormal calcium/phosphate homeostasis in adult CNO, apart from a recent case study reporting transient hypercalcemia in adult CNO patient (58). Alternatively, calcium, phosphate and parathyroid hormone might be used to evaluate the differential diagnosis of metabolic bone disorders.	Not queried.	For prevalence estimate of raised markers: **Very low** (Due to indirectness; no studies performed) For diagnostic value/clinical utility: **Very low** (Due to indirectness; clinical utility and diagnostic value of these markers not studied in adults)

B: <u>Optional</u> laboratory tests	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Bone markers osteocalcin, serum procollagen type I N propeptide (P1NP) and C-terminal telopeptide (CTx).	"bone marker", "P1NP", "ctx", "beta-crosslaps", "procollagen type I N propeptide", "osteocalcin", and "C-terminal telopeptide"	In a cohort study of n=213 patients, mean concentration of P1NP and CTx was normal at diagnosis (3). Similar results were found in a pilot randomized controlled trial in n=12 patients, with normal CTx, osteocalcin and P1NP levels at baseline (53). Another study of n=58 patients found that CTx is elevated (but not exceeding normal range) in patients with active as compared to stable disease, and that CTx is positively correlated with pain scores, while osteocalcin was not (59). A prospective study evaluating the utility of bone turnover markers in predicting the efficacy of bisphosphonate therapy found that 7/13 patients had elevated CTx at baseline, and that elevated CTx was a predictor of clinical response to treatment with intravenous pamidronate (60). Lastly, one case series evaluating the change in bone markers after bisphosphonate therapy demonstrated increased osteocalcin in 2/3 patients, and increased CTx in 2/3 patients at baseline (61). There are limited data on the utility of following up on bone turnover markers. Available data derive mostly from studies evaluating the efficacy of bisphosphonate therapy, in which bone markers show decrease as a result of treatment. It is yet unclear whether decrease in bone markers is associated with clinical improvement, i.e. What the clinical relevance of bone markers at follow-up is (53, 61).	Bone markers are often/always used by 42% of physicians but were not regarded useful for diagnosis. Of note, the survey did not query how often these markers were elevated according to physician's experience. Generally regarded unhelpful to monitor disease course.	For prevalence estimate of raised markers: **Low** (Due to inconsistency, indirectness (mean markers reported instead of % raised)) For diagnostic value/clinical utility: **Very low** (Due to imprecision; only one small study evaluating the prognostic value of bone turnover markers, and indirectness; diagnostic value of determining bone markers not studied in adults)
Anti-citrullinated protein antibodies (anti-CCP) and rheumatoid factor (RF).	For RF: NA, recent meta-analysis used For anti-CCP: "anti-CCP", "Anti-citrullinated protein antibodies"	RF is present in 3%, 95%CI 1-6 of patients (no higher prevalence than found in general population) (1), but is a key diagnostic in the evaluation of the differential diagnosis of rheumatoid arthritis, which may be considered in case of peripheral synovitis (62). Anti-CCP antibodies were evaluated in one cohort study only, and elevated in 0% of patients (n=90) (63).	Not queried.	For prevalence estimates: **Moderate** (Due to 6/21 studies included in meta-analysis displaying high risk of bias) For diagnostic value/clinical utility: **Very low** (Due to indirectness; not studied, though its limited diagnostic value may be inferred from its normal prevalence)
Anti-nuclear antibodies (ANA) and immunofluorescence pattern.	Recent meta-analysis used.	ANA is positive in 5%, 95%CI 0-13 of patients (no higher prevalence than found in general population) (1).	Not queried.	

Human Leucocyte Antigen (HLA)-B27.	Recent meta-analysis used.	HLA-B27 is present in 5%, 95% CI 3-6 of patients (no higher prevalence than found in general population) (1), but is a key diagnostic in the evaluation of the differential diagnosis of spondylarthritis, which may be considered in case of inflammatory back pain.	Not queried.	
Fecal calprotectin.	"calprotectin", "calgranulin"	No data found, but estimated prevalence of inflammatory bowel disease in adult CNO is 1%, see Q1C.	Not queried.	For evidence of the prevalence estimate of inflammatory bowel disease, see Q1C. For diagnostic value/clinical utility: **Very low** (Due to indirectness: prevalence, clinical utility and diagnostic value not studied)
Serum angiotensin-converting enzyme (ACE) and soluble IL-2 receptor levels.	"angiotensin", "soluble", "sarcoid", "sarcoidosis", "granulomatous", "granuloma"	No data found for the use of these markers in the diagnostic work-up for adult CNO, addressing sarcoidosis as a differential. However, musculoskeletal manifestations of sarcoidosis are well-described and estimated to occur in 25-30% of patients. They may form a differential of adult CNO if skeletal lesions are located at sights typical for both diseases (64).	Not queried.	**Very low** (Clinical utility and diagnostic value of these markers not studied)

Q6: What type of imaging is preferred for suspected adult CNO?

A: Imaging preferences for structural characterization of bone lesions	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Computed tomography (CT)	Studies were not selected systematically through key words. Included were studies reporting imaging data for ≥40 adult patients, and reviews on imaging features of adult CNO	CT is especially sensitive in revealing chronic structural changes like sclerosis, hyperostosis, bone expansion (hyperostosis), new bone formation (ossification of ligaments, ankylosis (37, 44). These changes are well-appreciated by CT (37, 38, 44, 47). While many of these features can be visualized on plain X-rays too, CT is superior in evaluating subtle abnormalities, as well as their extent (37, 49). CT seems preferred over MRI for imaging the anterior chest wall specifically, due to its superior ability to detect subtle structural bone changes (37) and the fact that MRI of the anterior chest wall is associated with high artefact risk due to breathing motions (65). Notwithstanding,	Used "always/often" by 42%, preferred by 8% (not stratified per treatment goal or localization).	Regarding the superiority of one imaging modality over the other: **Very low** (Due to indirectness: larger head-to-head studies comparing different modalities against each other in adult CNO not performed but in one study; utility of modalities based on theory, clinical experience, and extrapolation from other diseases)

	published from 2010 onwards.	few to no comparative studies in adult CNO have been performed to compare CT against MRI for this region. In a pilot randomized trial in adult CNO patients treated with pamidronate or placebo, the anterior chest wall was scanned with both modalities at baseline, and CT revealed more lesions than MRI (53).		
Magnetic resonance imaging (MRI)		MRI can detect early acute (inflammatory) changes like BMO or soft tissue oedema and structural (chronic) changes like accumulated fatty metaplasia in adult CNO (37, 44, 49). MRI is specifically preferred for the evaluation of the sacroiliac region in patients with suspected sacroiliitis (50, 66, 67). In the anterior chest wall, MRI visualizes enthesitis, osteitis and synovitis, but structural characterization of the lesions remains better appreciated by CT (48). Whole body MRI is an exhaustive imaging modality capturing multifocal bone involvement and can also reflect subclinical lesions (25, 40, 68). It can also capture the evolvement or resolution of lesions and has a distinct advantage of not imposing radiation (25, 40, 68-71).	Used "always/often" by 64% and also preferred by 47% (not stratified per treatment goal or localization).	
Plain X-Ray		Plain X-rays may be negative in 80% of patients in the first 3 months of disease according to one study (72); other studies have underscored the low sensitivity of plain X-rays in early disease too (40). Plain X-rays can detect hyperostosis, sclerosis, and osteolysis, but mostly in advanced disease as subtle changes are often not visualized (37, 46, 50).	Used "almost always/often" by 53%, only preferred by 3%.	
B: Imaging preferences for assessment of disease activity	**Identification of studies**	**Summary of evidence**	**Physician survey results**	**Level of evidence**
Magnetic resonance imaging (MRI)	Studies were not selected systematically through key words. Included were studies reporting imaging data for ≥40 adult patients, and reviews on imaging features of adult CNO published from 2010 onwards.	See also Q2C. BMO and soft tissue oedema assessed by MRI can aid the differentiation between acute and chronic disease (40). Various paediatric and adult studies have evaluated MRI-derived disease activity indices and their correlation with clinical outcome measures and proposed standardized scoring systems for their assessments to be validated in further studies (25, 51, 71, 73, 74). In adults, an MRI-score assessing the axial skeletal disease activity improved after therapy and correlated with biochemical and clinical parameters of disease activity at baseline and at follow-up (74). One paediatric study demonstrated a good correlation between clinical symptoms (biochemical, functional impairment and physician assessment) and the CROMRIS MRI score at baseline, but not at 6 and 12 months follow-up (52).	Used "always/often" by 64% and also preferred by 47% (not stratified per treatment goal or localization).	**Low** (Due to imprecision and indirectness; very few studies addressing the specific question, none evaluate head-to-head against other modalities)
Diffusion weighted magnetic resonance imaging (DW-MRI)		Limited data yet available. Change in apparent diffusion coefficient was evaluated as an outcome measure in adult CNO using data from a randomized pilot trial, and demonstrated to be feasible in terms of assessment time; correlations with clinical parameters of disease activity were not reported in this proof-of-concept study (75).	Not queried.	**Very low** (Due to imprecision and indirectness; only one study and correlation with clinical activity not reported)

Whole body bone scintigraphy (WBBS)/Technetium labeled hydroxymethylene diphosphonate single positron emission computed tomography ([^{99m}tc]Tc-HDP SPECT/CT)		WBBS can detect changes in osteoblastic activity which may result from inflammation, and displays the complete skeleton in one investigation. However, WBBS does not differentiate active and chronic lesions as both give increased isotope uptake (37), and may underestimate abnormalities in the anterior vertebrae due to insufficient spatial resolution (46). When directly combined with CT ([^{99m}tc]Tc-HDP SPECT/CT) the sensitivity increases due to superior anatomical orientation (46), but it still lacks the ability to differentiate active from non-active lesions (37). The value of follow-up imaging with WBBS/[^{99m}tc]Tc-HDP SPECT/CT has been evaluated in one study, which found the increased tracer uptake to persist despite clinical remission, following a so-called imprinting pattern (54).	WBBS alone "almost/often" used by 44%, preferred by 14% (not stratified per treatment goal or localization). Direct combination with CT ([^{99m}tc]Tc-HDP SPECT/CT) "almost/often" used by 25%, preferred by 14% (not stratified per treatment goal or localization).	**Very low** (Due to indirectness; only one studies performed on value of this technique as a follow-up disease activity evaluator)

Positron emission tomography (PET) with CT (PET/CT)	"positron emission tomography", "PET", "PET/CT"	**Fluorodeoxyglucose (FDG)-PET/CT:** FDG-PET/CT is comparable to ^{99m}tc]Tc-HDP SPECT/CT in detecting osteitis lesions in adult CNO and also has the ability to differentiate acute and chronic lesions according to several case reports (37, 49, 55). One study evaluated 18F-FDG PET/CT in adult CNO and found similar capacity in revealing bone lesions compared to [^{99m}tc]Tc-HDP SPECT/CT, but the agreement between uptake on PET and clinical symptoms was poor (55). However, this poor correlation resulted partly from a large number of patients reporting pain in specific musculoskeletal regions, without PET revealing increased uptake at these sights, and a substantial proportion of patients with subclinical lesions. **Sodium fluoride positron emission tomography with CT ([18F]NaF-PET/CT):** Current evidence on the role of [18F]NaF-PET/CT in adult CNO is limited. However, [18F] NaF -PET/CT generates higher resolution images in shorter scanning time and with less radiation exposure compared to [^{99m}tc]Tc-HDP SPECT/CT and is suited to differentiate acute and chronic lesions in similar fashion as FDG-PET/CT (40, 76). Also, [18F] NaF-PET/CT yields quantitative parameters of bone turnover that correlate with biochemical measures of inflammation in adult CNO, and also visualizes the process of new bone formation as NaF precipitates in young osteoid (76). **Fibroblast-activation-protein inhibitors (FAPIs)-based PET/CT (68 Ga-FAPI-04 PET/CT):** One study has compared the value of 68 Ga-FAPI-04 PET/CT against conventional [^{99m}tc]Tc-HDP SPECT/CT, in which it was slightly more sensitive in identifying osteoarticular lesions. Another study compared 68 Ga-FAPI-04 PET/CT against FDG-PET/CT and observed higher sensitivity and better correlation with clinical symptoms (77).	FDG-PET/CT Used "almost/often" by 17%, preferred by 14 (not stratified per treatment goal or localization) Other PET/CT modalities not queried.	**For FDG-PET/CT and ([18F]NaF-PET/CT):** **Very low** (Due to imprecision; only one study per modality, and indirectness: no longitudinal data) **For 68 Ga-FAPI-04 PET/CT:** **Low** (Due to imprecision: only two studies, and indirectness: no longitudinal data)
C: Imaging preferences for asymptomatic lesion screening	**Identification of studies**	**Summary of evidence**	**Physician survey results**	**Level of evidence**
Whole body magnetic resonance imaging (WB-MRI)	Studies were not selected systematically through key words. Included were studies reporting imaging data for ≥40 adult	See Q6A/B for general advantages and disadvantages of this technique.	Used "always/often" by 64% and also preferred by 47% (not stratified per treatment goal or localization).	Regarding the prevalence of asymptomatic lesions: **Low** (Due to imprecision, inconsistency) Regarding the clinical value of asymptomatic lesion screening,

Whole body bone scintigraphy (WBBS)/ Technetium labeled hydroxymethylene diphosphonate single positron emission computed tomography ([^{99m}tc]Tc-HDP SPECT/CT)	patients, and reviews on imaging features of adult CNO published from 2010 onwards.	See Q6B for general advantages and disadvantages of this technique. WBBS/[^{99m}tc]Tc-HDP SPECT/CT can reveal subclinical lesions, which are estimated to be present in up to 67% of patients (38, 40, 46, 78).	WBBS alone "almost/often" used by 44%, preferred by 14% (not stratified per treatment goal or localization). Direct combination with CT ([^{99m}tc]Tc-HDP SPECT/CT) "almost/often" used by 25%, preferred by 14% (not stratified per treatment goal or localization).	irrespective of the modality used: **Very low** (Due to indirectness: prognostic value of asymptomatic lesions and herewith the utility of screening yet unknown)
Positron emission tomography (PET) with CT (PET/CT)		See Q6B for general advantages and disadvantages of this technique and specific tracers. FDG-PET/CT and 68 Ga-FAPI-04 PET/CT have been shown to identify asymptomatic lesions (55, 77, 79). For [18F]NaF-PET/CT, this has not been reported but in theory, this modality should visualize subclinical lesions in like manner.	Used "almost/often" by 17%, preferred by 14 (not stratified per treatment goal or localization).	

Q7: In what cases is a bone biopsy indicated as part of the diagnostic work-up?

Subtopic	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Role of bone biopsies in suspected adult CNO.	"biopsy", "histopathological", "histopathology", "mimicking", "mimick", "mimicker", "masquerade", "masquerading", "malignancy", "infection", "infectious osteomyelitis", "bacterial osteomyelitis"	Bone biopsies are performed in 24%, 95% CI 16-32 of adult patients and reveal nonspecific inflammation in 97%, 95% CI 89-100 of cases, with negative cultures in practically all except for 1%, 95% CI 0-9 positive for proprionibacterium acnes (1). There are numerous case reports describing suspected infectious or malignant disease excluded at histological level, before diagnosis of adult CNO was made (80-93). As clinical and radiologic understanding of adult CNO has improved over time, recent reviews and opinion papers generally assert that a biopsy – which is also associated with patient burden and local complications like periosteal thickening (94) - is no longer standard in the diagnostic work-up. Rather, biopsies may be considered in cases clinically suspect for malignancy or infection. One case report describes a patient with malignant bone lesions which were clinically diagnosed as adult CNO. Here, not performing a biopsy would have led to a missed diagnosis of severe pathology (95). In pediatric CNO bone biopsies are generally reserved for cases with unifocal disease, constitutional symptoms and nocturnal bone pain (1, 56, 96, 97). The specific indications for a bone biopsy in adult CNO are still less well-defined.	Bone biopsies are performed differentially (never/rarely by 55%, sometimes/often by 42%, always by 3%). Biopsies are regarded a "very useful" or "essential" diagnostic by 30% of physicians, remaining 70% scored as "little useful", "not useful". 65% of physicians do not regard it essential to exclude malignancy at histological level, 35% do. 57% of physicians do not regard it essential to exclude infection at histological level, 43 % do.	**Very low** (Due to indirectness; diagnostic accuracy studies evaluating non-invasive diagnostics like imaging against biopsies have not been performed)

Treatment

Q8: What are treatment goals in adult CNO?

Proposed treatment goals	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
To relieve patient symptoms.	No literature search performed.		Decrease/absence of pain selected by 65% and 35% respectively as a relevant treatment goal and by 100% as a criterium for remission.	N/A
To help maintain/regain functional capacity.			Functional improvement/full physical recovery selected by 70% and 13% respectively as a relevant treatment goal. Improved/free range of motion selected by 65% and 13% respectively as a relevant treatment goal. Restored functioning selected by by 68% of physicians as a criterium for remission.	N/A
To reduce inflammation to the lowest level possible.			Decrease/normalization of radiologic inflammation selected by 57% and 4% respectively as a relevant treatment goal. Decrease/normalization of bone turnover selected by 22% and 9% respectively as a relevant treatment goal. Absence of inflammatory signs at physical examination selected by 59% of physicians as a criterium for remission. Normalization of previously raised inflammation markers selected by 59% of physicians as a criterium for remission. Absence of strongly increased uptake on “nuclear imaging” selected by 42% of physicians as a criterium for remission; not stratified for specific modality.	N/A
To prevent structural bone and joint damage.			Stabilization of structural changes selected by 56%, and prevention of complications selected by 35% as relevant treatment goals.	N/A

Q9: Which outcome measures should be used for the treatment goals as agreed upon?

A: Potential outcome measures for relieving CNO-related symptoms	**Identification of studies**	**Summary of evidence**	**Physician survey results**	**Level of evidence**
Overall pain.	No literature search performed, regarded as generic part of follow-up. Pain scores are recommended in the paediatric CNO consensus treatment plan as a follow-up measure (98).		Patient-reported pain (not specifically queried if this should include a numerical score) is monitored by 96% of physicians.	N/A
Pain with emphasis on inflammatory bone pain.	"neuropathic pain", "widespread pain", "fibromyalgia", "sensitization"	One study has found a prevalence of comorbid fibromyalgia in adult CNO of 18% (99), which was also associated with worse patient reported outcomes. Likewise, fibromyalgia, sensitization and also neuropathic pain are frequent contributors to total pain in axial spondylarthritis (100-102). Pain stratification may therefore be relevant during follow-up, as different pain types warrant different therapeutic approaches.	Not queried.	Regarding the prevalence of alternative pain phenotypes: Very low (Due to imprecision; only one study performed) Regarding the value of pain stratification in evaluation of disease activity: **Very low** (Due to indirectness: no studies performed with this question)
B: Potential outcome measures for maintaining or regaining functional capacity	**Identification of studies**	**Summary of evidence**	**Physician survey results**	**Level of evidence**
Range of motion of joints surrounding lesion areas.	No literature search performed, regarded as generic part of follow-up.		Not queried, but likely implied by "Functional capacity" (see below)	N/A
Functional capacity.	No literature search performed, regarded as generic part of follow-up.		Monitored by 96% of physicians.	N/A
Fatigue	No literature search performed, regarded as generic part of follow-up.		Not queried.	N/A
C: Potential outcome measures for reducing inflammation	**Identification of studies**	**Summary of evidence**	**Physician survey results**	**Level of evidence**
Signs of active inflammation at physical examination, if previously present.	No literature search performed, regarded as generic part of follow-up.		Monitored by practically all physicians.	N/A
Inflammation markers (blood count/ESR/CRP).	No literature search performed, regarded as generic part of follow-up.	ESR/CRP are also recommended in the paediatric CNO consensus treatment plan as a follow-up measure (98).	Generally regarded unhelpful to monitor disease course, but	Regarding the estimated prevalence of raised markers: **see Q5**.

			nevertheless collected by 61%.	
Signs of active inflammation on imaging like bone marrow oedema, joint effusion, increased isotope uptake.	Studies were not selected systematically through key words. Included were studies reporting imaging data for ≥40 adult patients, and reviews on imaging features of adult CNO published from 2010 onwards.	See also Q2 for a review on this topic. For WBBS and SPECT, the value of follow-up imaging has been evaluated in one study, which found the increased tracer uptake to persist despite clinical remission, following a so-called imprinting pattern (54). It follows that WBBS and SPECT might not be informative to monitor disease course in adult CNO, as they do not differentiate chronic from acute disease (37). However, it should be noted that numerous case reports describe the marked decrease in uptake on WBBS or SPECT after therapy, suggesting that clinically meaningful differences can be detected. PET has the ability to differentiate active from silent lesions (37, 49, 55), so may candidate as a follow-up imaging tool. Likewise, MRI can visualize signs of active inflammation (bone marrow oedema, soft tissue oedema, joint effusion) which also show (partial) resolution after treatment (25, 40, 68). Various paediatric and adult studies have evaluated MRI-derived disease activity indices which include BMO, soft tissue oedema, joint effusion (25, 51, 71, 73, 74). The paediatric CNO consensus treatment plan recommends these signs to be included in therapeutic monitoring (98)	22% of physicians use follow-up nuclear imaging, either WBBS, SPECT or PET. 22% of physicians use follow-up nuclear imaging, either WBBS, SPECT or PET. 52% of physicians use follow-up MRI.	Regarding the issue whether follow-up imaging adequately reflects disease activity (and may therefore be used as a readout) **See Q2**
D: Potential outcome measures for preventing structural bone and joint damage	**Identification of studies**	**Summary of evidence**	**Physician survey results**	**Level of evidence**
Structural abnormalities like sclerosis, hyperostosis, erosions as assessed by imaging	No additional literature search performed, see Q2 for literature review of imaging during the disease course of adult CNO.	The number of radiologic lesions are also recommended in the paediatric CNO consensus treatment plan as a follow-up measure (98).	52% of physicians use follow-up MRI to track radiologic disease course.	**Very low** (Due to indirectness: absence of studies evaluating the utility of following structural progression of disease by imaging)
E: Remaining considerations	**Identification of studies**	**Summary of evidence**	**Physician survey results**	**Level of evidence**
Use of standardized methods or surveys to evaluate PROMs like pain, functioning, and fatigue in clinical	No systematic literature search performed.	In axial spondylarthritis, disease activity measurements generally make use of NRS-11 scales to score pain and functioning, and there are	Not queried.	**Very low** (Due to indirectness: absence of studies

practice (e.g. Visual Analogue Scale (VAS) or numerical rating scale (NRS), SF or RAND-36).		specifically validated quality of life instruments for the condition (103).		evaluating the validity and utility of standardized measuring tools for proms)
Treatment indications and considerations for patients without clinical symptoms, but radiologic disease activity.	"asymptomatic", "indication", "subclinical", "disease course", "follow-up"	Over a follow-up period of 12 years, 53% of adult patients develop new bone lesions according to one study (72). However, there is no literature at current that resolves whether disease progression or extension can be effectively prevented with treatment in asymptomatic patients.	18% of physicians would start treatment in asymptomatic patients, who, e.g. display radiologic signs of inflammation. The remaining 72% would only initiate treatment in presence of pain.	**Very low** (Due to indirectness: absence of studies addressing the prognostic relevance of asymptomatic lesions on patient outcomes)

Q10: What are considerations regarding contents and duration of step 1 treatment?
*Treatment domain focusses on the treatment of sterile bone inflammation in adult CNO. Treatment of additional (extra-skeletal) features is addressed in Q14.

Subtopic	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Use of non-steroidal anti-inflammatory drugs (NSAIDs)/ cyclooxygenase-2 inhibitors (COXIBs) in treatment-naive adult CNO patients.	Recent meta-analysis used, and also sought for "NSAID", "non steroidal anti inflammatory drugs", "cyclooxygenase-2 inhibitor", "COXIB". EULAR recommendations for axial spondylarthritis were additionally consulted.	Step 1 treatment with NSAIDs/COXIBs yields good response in 14% (95% CI 0-42) of patients, and partial response in 60% of patients (total n=488) (1). There are limited studies that compare the clinical outcomes between NSAIDs/COXIBs versus direct step 2 therapies in adults. In paediatric patients, direct step 2 treatments (infliximab, methotrexate with/without single-shot zoledronic acid) yield better clinical results than step 1 NSAIDs/COXIBs, in which NSAIDs/COXIBs also did not prevent structural tissue damage in 1 patient (104). Another paediatric study of n=70 patients found that NSAIDs/COXIBs were less likely to induce clinical improvement than direct step 2 therapy (105). Contrarily, NSAIDs/COXIBs were reasonably effective in another paediatric cohort as step 1 therapy (69). In the consensus treatment plan for paediatric CNO, NSAIDs/COXIBs are the common step 1 treatment, except in patients with spinal involvement (98). In axial spondylarthritis, NSAID/COXIB monotherapy is recommended in all patients if it can sufficiently control symptoms. NSAIDs/COXIBs should only be administered with the attempt to control symptoms, and not to prevent structural disease progression over time (66). As for long-term NSAID/COXIB use in general, it is known that discontinuation due to intolerance of maximum dosage is common and frequently a reason for step-up therapy to be initiated (106).	83% of physicians apply nsaids as first-line treatment (but 17% directly applied other agents: bisphosphonates or sulfasalazine)	**Very low** (Due to risk of bias, imprecision, inconsistency and indirectness)
Preferred duration of NSAIDs/COXIBs therapy (at maximum approved and tolerated dosage).	Recent meta-analysis used, and also sought for "NSAID", "non steroidal anti inflammatory drugs", "cyclooxygenase-2 inhibitor", "COXIB". EULAR recommendations for axial spondylarthritis	No literature evaluating the preferred duration of NSAIDs/COXIBs therapy in adult CNO, nor the need for NSAIDs/COXIBs rotation. In general guidelines for axial spondylarthritis, response to NSAIDs/COXIBs is determined after 2-4 weeks, after which a second course of a different NSAID/COXIB is considered. Similarly, for psoriatic arthritis evaluation of NSAID/COXIB first-line therapy is recommended after 4 weeks (66, 107).	Not queried.	**Very low** (Due to indirectness: absence of studies on the preferred duration)
Necessity of an NSAID/COXIB rotation before step-up.				**Very low** (Due to indirectness: total absence of studies on the added value of NSAID rotation)

	were additionally consulted.			
Direct step-up treatment in patients with active spinal lesions.	"fracture", "spinal", "spine", "vertebrae", "vertrebral"	No studies available on the prognostic value of spinal bone lesions, and whether more aggressive (step 2) treatment leads to better outcomes in these patients. However, spinal lesions form an indication for direct step 2 treatment with pamidronate in the consensus diagnosis and treatment plan for paediatric CNO, in order to minimize the risk of pathological fractures (98). In adults, pathological fractures in osteitis areas have been reported too, in the clavicle (108-112) as well as vertebrae (113, 114). However, whether complications like fractures can be prevented with more aggressive treatment from the start is yet unknown.	Not queried.	**Very low** (Due to indirectness: no studies in adults on prognostic relevance of this characteristic and whether direct step-up improves patient outcomes)
Direct step-up treatment in patients with significant skeletal damage attributable to sterile bone inflammation/osteitis.	"NSAID", "non steroidal anti inflammatory drugs", "cyclooxygenase-2 inhibitor", "COXIB", "step-up", "step-down", also studies covering treatment in cohorts of >10 patients were reviewed.	No studies available on the prognostic value of significant skeletal damage, and whether more aggressive (step 2) treatment leads to better outcomes in such patients.	Not queried.	
Direct step-up treatment in patients with pronounced systemic inflammation (e.g. High ESR/CRP) attributable to sterile bone inflammation/osteitis.	"NSAID", "non steroidal anti inflammatory drugs", "cyclooxygenase-2 inhibitor", "COXIB", "step-up", "step-down", also studies covering treatment in cohorts of >10 patients were reviewed.	No studies available on the prognostic value of pronounced systemic inflammation, and whether more aggressive (step 2) treatment leads to better outcomes in such patients.	Not queried.	

Q11: What are considerations regarding contents of step 2 treatment?
*Treatment domain focusses on the treatment of sterile bone inflammation in adult CNO. Treatment of additional (extra-skeletal) features is addressed in Q14.

Step 2 treatment: options	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) like methotrexate, sulfasalazine, leflunomide.	"methotrexate", "MTX", "sulfasalazine", "salazopyrine", "SSA", "leflunomide", "LFN"	A recent systematic literature review reported a response rate of 47% for csDMARDs (methotrexate, sulfasalazine, or leflunomide). A meta-analysis found a good response rate of 8% and partial response rate of 55% (methotrexate or sulfasalazine, total n=204) (1, 115). Several case reports assert the efficacy of methotrexate in patients with adult CNO. These patients were usually also suffering from arthritis or cutaneous symptoms. Methotrexate is applied either as monotherapy or combination therapy with NSAIDs/COXIBs, prednisolone, sulfasalazine, TNF-alpha inhibitors (TNFi) or bisphosphonates and is reported to improve articular and cutaneous symptoms (12, 116-118). In one cohort study on n=41 patients, 4 received methotrexate and only 2 achieved partial clinical response. One retrospective study reports the use of csDMARDs in general (either sulfasalazine or methotrexate) and found pain relief in only 4/14 patients who received these agents (119). For sulfasalazine, scarce reports indicate a partial efficacy of monotherapy in 1/6 patients (16, 116), and several reports discuss the failure of sulfasalazine (29, 120). Combined therapy with sulfasalazine and methotrexate has been reported with favorable outcomes (116, 121). Leflunomide has specifically been reported to improve nail involvement in adult CNO (122). Methotrexate or sulfasalazine are included in one of the consensus treatment plans for paediatric CNO (98) as csDMARD monotherapy.	22% of physicians use methotrexate as step 2 treatment.	**Very low** (Due to risk of bias, imprecision, inconsistency, indirectness, suspected publication bias)
Intravenous bisphosphonates.	"bisphosphonates", "pamidronate", "APD", "pamidronic acid" "zoledronate", "zoledronic acid", "ibandronate", "ibandronic acid", "risedronate", "risedronic acid", "neridronate", "neridronic acid",	**Pamidronate:** A relatively high number of studies describe the efficacy of intravenous pamidronate in adult CNO, containing one *pilot double-blinded randomized controlled trial showing radiologic and clinical improvement as compared to placebo (n=6 patients per arm) (53). Two recent literature reviews found response rates of 88% and 83% (good) and 9% (partial) (total n=112) (1, 115). Besides, multiple prospective and retrospective studies and case reports demonstrated clinical and radiologic response in the majority of patients. One study also demonstrated an association with clinical response and increased CTx at baseline, and another described its positive effects on PPP-lesions in specific too (16, 41, 60, 123-130). Pamidronate is mostly administered in 3-month intervals (either 3x30	42% of physicians use bisphosphonates as step 2 treatment; 28% use pamidronate, 14% use other bisphosphonates. 19% use bisphosphonates (not specified which) as step 3 treatment.	**Very low** (Due to risk of bias, imprecision, inconsistency, indirectness, suspected publication bias) *The one RCT still demonstrates high risk of bias as assessed by ROB-2.

		mg on consecutive days, 60 mg, or 90 mg per cycle), or in monthly intervals with 1 mg/kg or 60 mg as standard dosage. **Zoledronate:** Positive clinical and radiological response has also been described for intravenous zoledronate in several case reports (131-134), with regimen ranging 4-5 mg per 6 months. In a small cohort study, intravenous zoledronate (0.025 mg/kg every 3 months) was compared with pamidronate (1 mg/kg/month; first dose administered over 3 consecutive days) in 16 children with CNO, leading to similar clinical outcomes in both groups, while zoledronate allows for a more convenient dosage and logistics (135). One report in adults compared 30 patients treated with zoledronate to other studies treating similar patients with pamidronate, yielding similar clinical improvements at 3-days after treatment as well (136). **Others:** Intravenous ibandronate, risedronate and neridronate led to clinical improvement in several cases (61, 137-139) (140). Data on the use of oral bisphosphonates are scarce; only one report depicts successful treatment of adult CNO of the mandible with oral alendronate (141). **General:** A retrospective study in 34 patients found quicker disease control with bisphosphonates than with immunosuppressive drugs(142). Bisphosphonates are included in one paediatric CNO consensus treatment plan, recommending either pamidronate (1mg/kg every month, max. 60 mg) or zoledronate (1 mg/kg/dose for 3 consecutive days every 3 months) (98)/ In comparison with TNFi, pamidronate seems to lead to faster radiologic response in paediatric patients. However, response seems less durable, as more flares were observed under pamidronate than under TNFi (143).		
Tumor necrosis factor alpha inhibitors (TNFi).	**"**TNF", "tumor necrosis factor", "adalimumab", "infliximab", "etanercept", "certolizumab"	A recent systematic review and meta-analysis report response rates of 85%, and 94% (57% good; 37% partial) (total n=76 for the meta-analysis) (1, 115). A recent prospective study comparing the safety and efficacy of guselkumab and adalimumab in adult CNO found comparable clinical response rates with significant improvement in both groups, a continuation rate of 9/13 patients at 6-months for adalimumab, and a 39% incidence of adverse events (144). In a retrospective study of n=45 multi-step refractory patients treated with tnfi, etanercept, adalimumab and infliximab yielded partial response or remission in 21/30, 22/22, and 10/18 patients respectively (145). Several case series assert the (partial) effectiveness of TNFi on clinical,	19% of physicians use TNFi as direct step 2 treatment. 56% of physicians use TNFi as step 3 treatment.	**Very low** (Due to risk of bias, imprecision, inconsistency, indirectness, suspected publication bias)

		biochemical, and dermatological parameters in adult CNO, with response favouring adalimumab over infliximab and etanercept (12, 17, 120, 146-164). TNFi has been reported to improve ocular complications (165). Certolizumab has been evaluated in one case report, with improvement on osteoarticular and skin symptoms(166). Several reports are less positive, indicating TNFi (specifically infliximab) indicating that radiologic osteitis may persist or even expand under TNFi treatment (16, 167, 168) and TNFi can induce paradoxical psoriatic skin lesions (145, 146, 150, 169-172). TNFi is commonly combined with csDMARDs and NSAIDs/COXIBs (12, 152, 168, 169, 173). In paediatric CNO, TNFi (either etanercept, adalimumab, infliximab) is recommended as one of the three consensus treatment plans, either as monotherapy or in combination with methotrexate (98).		
Step 2 treatment: specific subtopics	**Identification of studies**	**Summary of evidence**	**Physician survey results**	**Level of evidence**
Specific preference for intravenous in patients with active spinal bone lesions, so as to minimize risk of pathological fractures.	"fracture", "spinal", "spine", "vertebrae", "vertrebral"	Spinal lesions form an indication for direct step 2 treatment with pamidronate in the consensus diagnosis and treatment plan for paediatric CNO, in order to minimize the risk of pathological fractures. (98) In adults, pathological fractures in osteitis areas have been reported in the clavicle (108-112) as well as vertebrae (113, 114).	Not queried.	**Very low** (Due to indirectness: no studies addressing the efficacy of bisphosphonates against other medications in these patients)
Specific preference for TNFi in patients with a history of uveitis or inflammatory bowel disease.	No systematic literature search performed, EULAR recommendations for axial spondylarthritis consulted.	For patients with axial spondylartritis with manifestations of uveitis or inflammatory bowel disease, there is superior evidence for the efficacy of specific TNFi than for other biologics (66). Extrapolating to adult CNO, which may also co-present with uveitis or enteropathy, patients with these features might benefit from specific TNFi as a specific biologic most.	Not queried.	**Low** (Due to indirectness: no studies assessing this strategy in adult CNO)
Specific preference to initiate TNFi as step 2 treatment, and not a csDMARD, in patients presenting with axial disease and overlapping features	No systematic literature search performed, EULAR recommendations for axial spondylarthritis consulted.	Patients with an overlapping phenotype of axial spondylarthritis and adult CNO may benefit most from therapies that have already been found effective in axial spondylarthritis, like TNFi, which could steer choice for biologic therapy (66). A similar line of reasoning is upheld for paediatric CNO, in which patients with sacroiliitis are preferably treated with TNFi (96).	Not queried.	**Low** (Due to indirectness: no studies assessing this strategy in adult CNO)

with axial spondylarthritis.				
Maintenance of NSAID/COXIB or csDMARD aside from biologic/antiresorptive therapy if the drug has been partly helpful.	"combination", "monotherapy", "add-on" EULAR recommendations for axial spondylarthritis and psoriatic arthritis were additionally consulted.	For adult CNO, there is no proper evidence directly comparing combination therapy of NSAIDs/COXIBs and csDMARDs with biologics or antiresorptives versus monotherapy. However, several reports assert the effectiveness of combination therapies and report cases in which it was superior to a biologic or bisphosphonate alone (10, 19, 174-176). In psoriatic arthritis, it is currently recommended to continue the csDMARD of methotrexate when adding a biologic, whilst there is no conclusive evidence that this combination therapy is preferred over biologic monotherapy (107). Methotrexate may be reduced in dosage if patients clinically respond to biologic treatment. In the paediatric CNO consensus treatment plan, methotrexate is suggested in addition to TNFi either as intended combination therapy, or to suppress the generation of antichimeric anti-TNF antibody production (98).	Not queried.	**Very low** (Due to risk of bias, imprecision, inconsistency, suspected publication bias). In psoriatic arthritis, there is also no conclusive evidence that combination therapy is more effective than biologic monotherapy).

Q12: What are considerations regarding contents of step 3 treatment?
*Treatment questions focus on the treatment of sterile bone inflammation in adult CNO. Treatment of additional (extra-skeletal) features is addressed in Q14.

Step 3 treatment: options	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Interleukin-17 inhibitors (IL-17i)	"secukinumab", "ixekizumab", "brodalumab", "IL-17", "interleukin 17", "IL-17A", "interleukin 17A"	Increased Th17-lymphocyte numbers and elevation of Th17-related cytokines in bone lesions have been found in adult CNO patients, prompting the hypothesis that this pathway is a key disease driver, and blockage might improve symptoms (177, 178). Secukinumab was effective in reducing (radiologic) osteitis, patient reported health, and skin symptoms in two series of n=12 and n=4 patients, and response seemed associated with increased numbers of Th17-lymphocytes at baseline in the former study (179, 180). Various case reports confirm the efficacy of both secukinumab and brodalumab (172, 181-184). One study showed poor clinical effects of secukimab in adult CNO and two others reported paradoxical psoriatic skin lesions induced by therapy, particularly in patients with PPP (185-187).	6% of physicians use IL-17i as step 3 treatment.	**Very low** (Due to risk of bias, imprecision, inconsistency, suspected publication bias).
Interleukin-23 inhibitors	"IL-23", "interleukin 23", "guselkumab", "tidrakizumab", "risankizumab"	Guselkumab has been shown effective in improving osteoarticular and dermatologic manifestations for adult CNO in a prospective study (n=12), a retrospective study (n=5), in an exploratory analysis of a randomized placebo-controlled trial* (n=45), and a case report (144, 188-190). Risankizumab has been described as inducing sustained remission in two case reports (191, 192).	Not selected by any of the physicians as step 2 or 3 treatment.	**Very low** (Due to risk of bias, imprecision, inconsistency, suspected publication bias). * The RCT still poses high risk of bias as assessed with to rob-2
Interleukin-12/23 inhibitors (IL-12/23i)	"IL-12", "interleukin 12", "IL-23", "interleukin 23", "ustekinumab"	Ustekinumab was evaluated in a series of 3 patients, but was ineffective for osteoarticular symptoms, partly effective for PPP, but caused a paradoxical flare of psoriasis in one patient (185). Two other case reports describe conflicting results, one demonstrating overall little efficacy for osteoarticular symptoms and one reporting significant improvement of both osteoarticular and skin manifestations (193, 194).	Not selected by any of the physicians as step 2 or 3 treatment.	**Very low** (Due to risk of bias, imprecision, inconsistency, suspected publication bias).
Interleukin-6 inhibitors	"IL-6", "interleukin 6", "tocilizumab", "sarilumab"	Tocilizumab has been reported to give clinical and radiologic improvement in adult CNO in one case report, but also failed in two others (195, 196). Treatment with tocilizumab was complicated by the development of an aseptic subcutaneous abscess in the anterior chest wall in one patient with adult CNO and secondary amyloid A amyloidosis (197).	3% of physicians use IL-6i as step 3 treatment.	**Very low** (Due to risk of bias, imprecision, inconsistency, suspected publication bias).
Interleukin-1 inhibitors	"IL-1", "interleukin 1", "canakinumab", "anakinra"	Three studies (2 case reports and series of n=6) have reported the efficacy of anakinra on clinical, biochemical and radiologic disease activity (198-200), but one reported failure (201). Canacinumab was evaluated in one case report of a paediatric CNO patient and found	Not selected by any of the physicians as step 2 or 3 treatment.	**Very low** (Due to risk of bias, imprecision, inconsistency,

		effective in the short term to control bone and skin manifestations, but not in inducing long-term remission of skeletal symptoms (202).		suspected publication bias).
Janus kinase (JAK)-inhibitors	"janus kinase", "JAK", "baricitinib", "tofacitinib"	Multiple case reports have asserted the efficacy of the JAKi tofacitinib (almost exclusively as monotherapy) in adult CNO, with improvement of osteoarticular symptoms in most patients (17, 113, 203-209). Tofacitinib has also been reported to improve dermatological manifestations in adult CNO in a prospective study of n=13 patients and case reports (186, 209-211), and paradoxical psoriatic skin lesions induced by other therapies like IL-17i (187). Two retrospective studies (n=13 and n=12) showed efficacy of tofacitinib on pain, radiologic inflammation assessed by MRI and skin lesions (212, 213). A case series of 5 patients treated with baricitinib reported improvement in inflammation indices and led to clinical remission in 4 (214).	3% of physicians use JAKi as a step 2 treatment.	**Very low** (Due to risk of bias, imprecision, inconsistency, suspected publication bias).
Surgical intervention (in cases of unifocal involvement or hyperostotic complications)	"surgery", "surgical", "resection", "curettage", "operative"	In general, there are very limited data on operative management of adult CNO. In a case series of 4 patients with unifocal osteitis of the clavicle, extended curettage caused improvement of symptoms (215). Other surgical reports pertain to mandibular osteitis mostly, where resection of the affected bone shows favourable outcomes but also high recurrence rate (216-218). Curettage improved symptoms and prevented spinal destruction in one patient with spondylitis, but did not in a case with femoral involvement (219, 220). The potential of remodelling surgery after remission of mandibular CNO has also been reported (221).	3% of physicians use surgery as a step 3 treatment.	**Very low** (Due to risk of bias, imprecision, inconsistency, suspected publication bias).

Q13: What are considerations regarding ancillary treatment?

Potential ancillary treatments	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Intra-articular glucocorticoids (in case of local disease activity, e.g. in sternoclavicular joint or in cases of peripheral mono/oligoarthritis).	"intra-articular" "injection", "articular injection" In addition, (ASAS)-EULAR recommendations for axial spondylarthritis and psoriatic arthritis were consulted.	One prospective study evaluated the efficacy of intra-articular glucocorticoid injections in the sternoclavicular joint in adult CNO, without improvement of osteitis in MRI and patient health assessment (222). Another retrospective study found clinical improvement in 17 out of 27 patients treated with intra-articular injections (29). Intra-articular glucocorticoids may be considered as adjunctive therapy for psoriatic arthritis and axial spondylarthritis in cases to treat local joint inflammation (66, 107).	8% of physicians administer glucocorticoid injections as step 2 treatment.	**Very low** (Due to risk of bias, imprecision, inconsistency, suspected publication bias).
Short (not long) courses of oral prednisolone.	No systematic literature search performed; ASAS-EULAR recommendations for axial spondylarthritis and psoriatic arthritis were consulted.	In axial spondylarthritis, systemic glucocorticoids are only recommended for short-term use in case of purely axial disease. Data on long-term use are absent, while the adverse effects of systemic glucocorticoids are well-established and should prompt cautious use. In psoriatic arthritis, systemic glucocorticoids are not recommended for purely axial disease (66, 107). Extrapolating these recommendations for adult CNO, systemic glucocorticoids may be considered for short-term use, mostly in patients with peripheral disease. Systemic glucocorticoids may cause flares of psoriasis, but recent studies have indicated that this risk is much lower than traditionally presumed (223).	3% of physicians use oral prednisolone as step 2 treatment.	**Very low** (Due to indirectness: no studies performed in adult CNO)
Intramuscular methylprednisolone acetate.			6% of physicians use intramuscular methylprednisolone as step 2 treatment.	
Physiotherapy	"physiotherapy", "physical therapy", "rehabilitation", "exercise"	One case report describes the role of physical therapy and rehabilitation in the treatment of adult CNO (224). In axial spondylarthritis, the positive effects of exercise programmes are well-established and it is recommended to consider physiotherapy in all patients (66, 225).	61% of physicians recommend physiotherapy to adult CNO patients.	**Very low** (Due to indirectness: no studies performed in adult CNO)
Smoking cessation	"smoking", "tobacco", "intoxication"	No specific data on the prognostic benefit of smoking cessation in adult CNO. However, (see Q1D), prevalence of active smoking among adult CNO patients is high, its association with PPP is well-established, and, obviously, smoking cessation has important general health benefits irrespective of diagnosis of adult CNO.	70% of physicians discuss the importance of smoking cessation.	**Very low** (Due to indirectness: no studies performed in adult CNO)

Q14: What are considerations regarding treatment of additional (extra-skeletal) features?

Subtopic	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Treatment alterations in case of additional (extra-skeletal) features; adherence to established treatment protocols, and preferably alignment with treatment for sterile bone inflammation/osteitis if possible.	No systematic literature search performed.		Not specifically queried, but data indicate that physicians try to optimize therapy according to the combination of manifestations, using multi-angled therapy where possible.	N/A

Q15: What are considerations during patient follow-up in adult CNO?

Subtopic	Identification of studies	Summary of evidence	Physician survey results	Level of evidence
Necessity of long-term follow-up	"Long-term", "longterm", "follow-up", "clinical course", "disease course"	Existing evidence highlights that adult CNO may have a chronic disease course, with both persistence of presenting features and the development of new manifestations. During long-term follow-up (5-23 years in the cited studies), an important proportion of patients develop bone lesions or arthritis at new localizations (29, 72, 125), supporting patient instruction to be mindful of similar but also different symptoms in the future.	Not queried.	Regarding the incidence of new bone or joint lesions during long-term follow-up: **Moderate** (Due to imprecision, indirectness) Regarding the clinical utility of long-term follow-up: **Low** (Due to indirectness: never studied whether this improves patient outcomes)
Patient education on recurrence of symptoms.			Not queried.	
Complication awareness: vertebral fractures in patients with spinal involvement.	"fracture"	Pathological fractures form an important complication of spinal CNO in paediatric patients (98). In adults, pathological fractures in osteitis vertebrae have been reported too (113, 114), as well as fractures at other involvement sites such as the clavicle (226, 227).	Not queried.	**Very low** (Due to imprecision: only several case reports available)
Complication awareness: neurovascular obstruction due to hyperostotic compression in patients with anterior chest wall involvement, (thoracic outlet syndrome or subclavian vein obstruction).	"venous", "obstruction", "thrombosis", "vascular", "thoracic outlet", "subclavian"	Numerous publications report the complication of neurovascular obstruction in adult CNO, usually caused by hyperostotic mechanic compression (121, 228-244). Compression may be asymptomatic, but may also case thrombosis and be a presenting feature. Nerve compression may cause numbness or paraesthesia in the ipsilateral arm. In severe cases, neurovascular obstruction may warrant surgical intervention. A recent cohort study in MRI-findings in the anterior chest wall found a prevalence of 18% for venous stenosis in adult CNO patients (48).	Not queried.	**Low** (Due to imprecision; only several case reports and one cohort study available)

References (in order of appearance)

1. Leerling A, Dekkers O, Appelman-Dijkstra N, Winter E. Clinical and therapeutic diversity in adult chronic nonbacterial osteomyelitis (CNO) of the sternocostoclavicular region: a meta-analysis. Rheumatology (Oxford). 2022.
2. Cao Y, Li C, Yang Q, Wu N, Xu P, Li Y, et al. Three patterns of osteoarticular involvement in SAPHO syndrome: a cluster analysis based on whole body bone scintigraphy of 157 patients. Rheumatology. 2019;58(6):1047-55.
3. Ramautar AI, Appelman-Dijkstra NM, Lakerveld S, Schroijen MA, Snel M, Winter EM, et al. Chronic Nonbacterial Osteomyelitis of the Sternocostoclavicular Region in Adults: A Single-Center Dutch Cohort Study. JBMR Plus. 2021;5(5):e10490.
4. Xu W, Li C, Zhao X, Lu J, Li L, Wu N, et al. Whole-spine Computed Tomography Findings in SAPHO Syndrome. J Rheumatol. 2017;44(5):648-54.
5. Ralston SH, Scott PD, Sturrock RD. An unusual case of pustulotic arthro-osteitis affecting the leg, and erosive polyarthritis. Ann Rheum Dis. 1990;49(8):643-5.
6. Fritz P, Baldauf G, Wilke HJ, Reitter I. Sternocostoclavicular hyperostosis: its progression and radiological features. A study of 12 cases. Annals of the Rheumatic Diseases. 1992;51(5):658-64.
7. Aparicio Rovira M, Aparicio Espinar M, Gifre L, Holgado S, Martinez-Morillo M, Riveros A, et al. SAPHO or psoriatic arthritis?: Evaluation of caspar criteria in a cohort with SAPHO. Annals of the Rheumatic Diseases. 2020;79 (SUPPL 1):1664-5.
8. Jiang H, Lv L, Lin Z, Li C. SAPHO syndrome can cause sausage finger lesions. RMD Open. 2023;9(3).
9. Okuno H, Watanuki M, Kuwahara Y, Sekiguchi A, Mori Y, Hitachi S, et al. Clinical features and radiological findings of 67 patients with SAPHO syndrome. Modern rheumatology. 2018;28(4):703-8.
10. Akiyama Y, Sato T, Hanai S, Kamata Y, Nagatani K, Iwamoto M, et al. The clinical features of SAPHO syndrome in Japanese patients: A single center cohort study. Annals of the Rheumatic Diseases. 2015;74:756.
11. Asano T, Furuya MY, Fujita Y, Matsuoka N, Sato S, Kobayashi H, et al. Diagnostic value of ultrasonography in synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome: A case report. Medicine (Baltimore). 2018;97(41):e12725.
12. De Souza A, Solomon GE, Strober BE. SAPHO syndrome associated with hidradenitis suppurativa successfully treated with infliximab and methotrexate. Bull NYU Hosp Jt Dis. 2011;69(2):185-7.
13. Jurik AG, Helmig O, Graudal H. Skeletal disease, arthro-osteitis, in adult patients with pustulosis palmoplantaris. Scand J Rheumatol Suppl. 1988;70:3-15.
14. Jirik FR, Stein HB, Chalmers A. Clavicular hyperostosis with enthesopathy, hypergammaglobulinemia, and thoracic outlet syndrome. Ann Intern Med. 1982;97(1):48-50.
15. Queiro R, Alonso S, Alperi M, Fernandez M, Tejon P, Riestra JL, et al. Entheseal ultrasound abnormalities in patients with SAPHO syndrome. Clin Rheumatol. 2012;31(6):913-9.
16. Aljuhani F, Tournadre A, Tatar Z, Couderc M, Mathieu S, Malochet-Guinamand S, et al. The SAPHO syndrome: a single-center study of 41 adult patients. J Rheumatol. 2015;42(2):329-34.
17. Baisya R, Gavali M, Tyagi M, Devarasetti PK. A Case of SAPHO Syndrome Complicated by Uveitis with Good Response to Both TNF Inhibitor and JAKinib. Case Rep Rheumatol. 2023;2023:6201887.

18. Ozyemisci-Taskiran O, Bolukbasi N, Gogus F. A hidradenitis suppurativa related SAPHO case associated with features resembling spondylarthropathy and proteinuria. Clin Rheumatol. 2007;26(5):789-91.
19. Zhao M, Wu D, Yu K, Shen M. Clinical and Genetic Features of Chinese Adult Patients With Chronic Non-Bacterial Osteomyelitis: A Single Center Report. Front Immunol. 2022;13:860646.
20. Li C, Zuo Y, Wu N, Li L, Li F, Zhang W, et al. Synovitis, acne, pustulosis, hyperostosis and osteitis syndrome: a single centre study of a cohort of 164 patients. Rheumatology. 2016;55(6):1023-30.
21. Carroll MB. Sternocostoclavicular hyperostosis: a review. Therapeutic advances in musculoskeletal disease. 2011;3(2):101-10.
22. Buch K, Thuesen ACB, Brons C, Schwarz P. Chronic Non-bacterial Osteomyelitis: A Review. Calcified Tissue International. 2019;104(5):544-53.
23. Carr F. The 'hidden' SAPHO syndrome. BMJ Case Rep. 2014;2014.
24. Takizawa Y, Murota A, Setoguchi K, Suzuki Y. Severe inflammation associated with synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome was markedly ameliorated by single use of minocycline. Mod Rheumatol. 2014;24(6):1015-8.
25. Arnoldi AP, Schlett CL, Douis H, Geyer LL, Voit AM, Bleisteiner F, et al. Whole-body MRI in patients with Non-bacterial Osteitis: Radiological findings and correlation with clinical data. Eur Radiol. 2017;27(6):2391-9.
26. Pyrgioti M, Mahaira E, Papagiannakis G, Syrou A, Alexandris IH, Kyriakidis AV, et al. The "sapho" syndrome: A case report of a patient with an accidental finding of hyperostosis in plain x-rays of thorax. Journal of Musculoskeletal Research. 2008;11(1):29-35.
27. Gill T, Bubbear J, Keen R. Non-bacterial osteitis syndromes: Characterising an adult population. Rheumatology (United Kingdom). 2020;59 (Supplement 2):ii90-ii1.
28. Yamamoto T, Hiraiwa T, Tobita R, Hirano H, Masuda-Kuroki K, Ishii M, et al. Characteristics of Japanese patients with pustulotic arthro-osteitis associated with palmoplantar pustulosis: a multicenter study. Int J Dermatol. 2020;59(4):441-4.
29. Hayem G, Bouchaud-Chabot A, Benali K, Roux S, Palazzo E, Silbermann-Hoffman O, et al. SAPHO syndrome: a long-term follow-up study of 120 cases. YSARH. 1999;29(3):159-71.
30. Colina M, Govoni M, Orzincolo C, Trotta F. Clinical and radiologic evolution of synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: a single center study of a cohort of 71 subjects. Arthritis and rheumatism. 2009;61(6):813-21.
31. Jiang N, Zhang P, Hu WR, Yao ZL, Yu B. Similarities and Differences between Clavicular Bacterial Osteomyelitis and Nonbacterial Osteitis: Comparisons of 327 Reported Cases. J Immunol Res. 2021;2021:4634505.
32. Kondo N, Sakai Y, Kakutani R, Netsu T, Kijima Y, Kudo N, et al. Clinical characteristics and treatment status of pustulotic arthro-osteitis: A single-center study involving 51 cases. J Dermatol. 2021;48(11):1724-30.
33. Ramautar A, Appelman-Dijkstra N, Lakerveld S, Valkema P, Snel M, Schroijen M, et al. Clinical features of sternocostoclavicular hyperostosis: A large single Center Dutch cohort. Journal of Bone and Mineral Research. 2018;33(Supplement 1):180.
34. Hiraiwa T, Yamamoto T. Comorbidities of Japanese patients with palmoplantar pustulosis: a report from a single center. Int J Dermatol. 2018;57(7):e40-e1.
35. Takahara M, Hirata Y, Nagato T, Kishibe K, Katada A, Hayashi T, et al. Treatment outcome and prognostic factors of tonsillectomy for palmoplantar pustulosis and pustulotic arthro-osteitis: A retrospective subjective and objective quantitative analysis of 138 patients. J Dermatol. 2018;45(7):812-23.

36. Miot HA, Miot LD, Lopes PS, Haddad GR, Marques SA. Association between palmoplantar pustulosis and cigarette smoking in Brazil: a case-control study. J Eur Acad Dermatol Venereol. 2009;23(10):1173-7.
37. Jurik AG, Klicman RF, Simoni P, Robinson P, Teh J. SAPHO and CRMO: The Value of Imaging. Semin Musculoskelet Radiol. 2018;22(2):207-24.
38. Colina M, Trotta F. Clinical and radiological characteristics of SAPHO syndrome. Curr Rheumatol Rev. 2013;9(1):22-7.
39. Gao S, Deng X, Zhang L, Song L. The comparison analysis of clinical and radiological features in SAPHO syndrome. Clin Rheumatol. 2021;40(1):349-57.
40. Depasquale R, Kumar N, Lalam RK, Tins BJ, Tyrrell PN, Singh J, et al. SAPHO: What radiologists should know. Clin Radiol. 2012;67(3):195-206.
41. Leerling AT, Canete AN, Ramautar AIE, Appelman-Dijkstra NM, Winter EM. Sternocostoclavicular Hyperostosis: Positive Clinical and Radiological Response on Pamidronate. Front Endocrinol (Lausanne). 2021;12:621604.
42. Ramautar AIE, Navas A, Winter EM, Kroon HM, Smit F, Vriens D, et al. Defining the imaging diagnostic criteria for adult chronic non-bacterial osteitis. JBMR Plus. 2024;8(5):ziae024.
43. Schaub S, Sirkis HM, Kay J. Imaging for Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis (SAPHO) Syndrome. Rheum Dis Clin North Am. 2016;42(4):695-710.
44. Cao Y, Li C, Xu W, Wu X, Sun X, Zhang W, et al. Spinal and sacroiliac involvement in SAPHO syndrome: A single center study of a cohort of 354 patients. YSARH. 2019;48(6):990-6.
45. Salles M, Olive A, Perez-Andres R, Holgado S, Mateo L, Riera E, et al. The SAPHO syndrome: a clinical and imaging study. Clin Rheumatol. 2011;30(2):245-9.
46. Himuro H, Kurata S, Nagata S, Sumi A, Tsubaki F, Matsuda A, et al. Imaging features in patients with SAPHO/CRMO: a pictorial review. Jpn J Radiol. 2020;38(7):622-9.
47. Depasquale R, Kumar N, Lalam RK, Tins BJ, Tyrrell PNM, Singh J, et al. SAPHO: What radiologists should know. Clin Radiol. 2012;67(3):195-206.
48. Yu M, Cao Y, Li J, Zhang Y, Ye Y, Wang L, et al. Anterior chest wall in SAPHO syndrome: magnetic resonance imaging findings. Arthritis Res Ther. 2020;22(1):216.
49. Khanna L, El-Khoury GY. SAPHO syndrome--a pictorial assay. Iowa Orthop J. 2012;32:189-95.
50. Przepiera-Bedzak H, Brzosko M. SAPHO syndrome: pathogenesis, clinical presentation, imaging, comorbidities and treatment: a review. Postepy Dermatol Alergol. 2021;38(6):937-42.
51. Zhao Y, Sato TS, Nielsen SM, Beer M, Huang M, Iyer RS, et al. Development of a Scoring Tool for Chronic Nonbacterial Osteomyelitis Magnetic Resonance Imaging and Evaluation of its Interrater Reliability. J Rheumatol. 2020;47(5):739-47.
52. Capponi M, Marafon DP, Rivosecchi F, Pardeo M, De Benedetti F, Insalaco A. Chronic non-bacterial osteomyelitis (CNO): Correlation between clinical and radiological findings. Arthritis and Rheumatology. 2020;72 (Supplement 1):17-9.
53. Andreasen CM, Jurik AG, Deleuran BW, Horn HC, Folkmar TB, Herlin T, et al. Pamidronate in chronic non-bacterial osteomyelitis: a randomized, double-blinded, placebo-controlled pilot trial. Scand J Rheumatol. 2020;49(4):312-22.
54. Li C, Wang L, Wu N, Cao Y, Sun X, Zhang W, et al. A retrospective study of bone scintigraphy in the follow-up of patients with synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: is it useful to repeat bone scintigraphy for disease assessment? Clinical Rheumatology. 2019.

55. Sun X, Li C, Cao Y, Shi X, Li L, Zhang W, et al. F-18 FDG PET/CT in 26 patients with SAPHO syndrome: a new vision of clinical and bone scintigraphy correlation. J Orthop Surg Res. 2018;13(1):120.
56. Rukavina I. SAPHO syndrome: a review. J Child Orthop. 2015;9(1):19-27.
57. Ikumi N, Hayama K, Terui T, Kitamura N, Takei M, Fujita H. Retrospective study of the differences in the management for pustulotic arthro-osteitis in patients with palmoplantar pustulosis between dermatologists and rheumatologists. J Dermatol. 2021.
58. Yoshida T, Oya M. Transient hypercalcemia in a patient with SAPHO syndrome. J Gen Fam Med. 2022;23(1):44-6.
59. Li C, Shuo Z, Jinhe L. Relationship analysis between disease activity and osteocalcin, b-CTX in SAPHO syndrome. Int J Rheum Dis. 2016;19 (Supplement 2):32.
60. Solau-Gervais E, Soubrier M, Gerot I, Grange L, Puechal X, Sordet C, et al. The usefulness of bone remodelling markers in predicting the efficacy of pamidronate treatment in SAPHO syndrome. Rheumatology. 2006;45(3):339-42.
61. Armstrong DJ, Wright SA, Coward SM, Finch MB. Bone marker response in chronic diffuse sclerosing osteomyelitis treated with intravenous ibandronate [8]. Annals of the Rheumatic Diseases. 2006;65(7):976-7.
62. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology (Oxford). 2012;51 Suppl 6:vi5-9.
63. Grosjean C, Hurtado-Nedelec M, Nicaise-Roland P, Ferreyra-Dillon R, Bollet C, Quintin E, et al. Prevalence of autoantibodies in SAPHO syndrome: a single-center study of 90 patients. J Rheumatol. 2010;37(3):639-43.
64. Kucharz EJ. Osseous manifestations of sarcoidosis. Reumatologia. 2020;58(2):93-100.
65. Raptis CA, Ludwig DR, Hammer MM, Luna A, Broncano J, Henry TS, et al. Building blocks for thoracic MRI: Challenges, sequences, and protocol design. J Magn Reson Imaging. 2019;50(3):682-701.
66. Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis. 2023;82(1):19-34.
67. Walsh JA, Magrey M. Clinical Manifestations and Diagnosis of Axial Spondyloarthritis. J Clin Rheumatol. 2021;27(8):e547-e60.
68. Jurik AG. Quantification of Disease Activity in Chronic Nonbacterial Osteomyelitis by Whole-body Magnetic Resonance Imaging. J Rheumatol. 2020;47(5):646-9.
69. Beck C, Morbach H, Beer M, Stenzel M, Tappe D, Gattenlohner S, et al. Chronic nonbacterial osteomyelitis in childhood: prospective follow-up during the first year of anti-inflammatory treatment. Arthritis Res Ther. 2010;12(2):R74.
70. Reiser C, Klotsche J, Hospach A, Berendes R, Schnabel A, Jansson AF, et al. First-year follow-up of children with chronic nonbacterial osteomyelitis-an analysis of the German National Pediatric Rheumatologic Database from 2009 to 2018. Arthritis Res Ther. 2021;23(1):281.
71. Capponi M, Pires Marafon D, Rivosecchi F, Zhao Y, Pardeo M, Messia V, et al. Assessment of disease activity using a whole-body MRI derived radiological activity index in chronic nonbacterial osteomyelitis. Pediatr Rheumatol Online J. 2021;19(1):123.
72. Maugars Y, Berthelot JM, Ducloux JM, Prost A. SAPHO syndrome: a followup study of 19 cases with special emphasis on enthesis involvement. J Rheumatol. 1995;22(11):2135-41.
73. Kieninger A, Schafer JF, Tsiflikas I, Moll M, Kummerle-Deschner J, Kraus MS, et al. Early diagnosis and response assessment in chronic recurrent multifocal osteomyelitis: changes in lesion volume and signal intensity assessed by whole-body MRI. Br J Radiol. 2022;95(1130):20211091.

74. Gu Z, Li C, Xu W, Xiang Y, Gao C, Wu N, et al. Disease activity in patients with synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome: the utility of the SPARCC MRI scoring system for assessment of axial spine involvement. Clin Exp Rheumatol. 2021.
75. Moller JM, Andreasen CM, Buus TW, Pedersen SJ, Ostergaard M, Thomsen HS, et al. Diffusion-weighted MR imaging in chronic non-bacterial osteitis: Proof-of-concept of the apparent diffusion coefficient as an outcome measure. Acta Radiol Open. 2021;10(9):20584601211044478.
76. Leerling AT SF, Späth Z, Navas Cañete A, De Geus-Oei LF, Van de Burgt A, Dekkers OM, Van der Bruggen W, Appelman-Dijkstra NM, Vriens D, Winter EM. 18F-sodium fluoride PET-CT visualizes disease activity in adult chronic nonbacterial osteomyelitis/synovitis, acne, pustulosis, hyperostosis, osteitis syndrome (CNO/SAPHO). Submitted. 2023.
77. Wang P, Li C, Hou G, Li Z, Jing H, Zhang W, et al. Comparison of 68Ga-DOTA-FAPI-04 and 18F-FDG PET/CT in Patients With SAPHO Syndrome. Clin Nucl Med. 2023;48(9):781-4.
78. Freyschmidt J, Sternberg A. The bullhead sign: scintigraphic pattern of sternocostoclavicular hyperostosis and pustulotic arthroosteitis. Eur Radiol. 1998;8(5):807-12.
79. Xu T, Ding H, Fan D, Shu Q, Liu G, Zhang S, et al. Prospective Comparison of the Imaging Value of 99m Tc-MDP Bone Scan and 68 Ga-FAPI-04 PET/CT in Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis Syndrome. Clin Nucl Med. 2023;48(9):768-74.
80. Sampelean D, Adam M, Muntean V, Hanescu B, Domsa I. Pancreatic hamartoma and SAPHO syndrome: a case report. J Gastrointestin Liver Dis. 2009;18(4):483-6.
81. Kubo Y, Ito K, Fujiwara Y, Yoshida T, Kusumoto M. Case Report: SAPHO Syndrome Mimicking Bone Metastases During Treatment With Pembrolizumab for Non-small Cell Lung Cancer. Front Med (Lausanne). 2021;8:679111.
82. Zacharia B, Udupa HH. Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO), and chronic recurrent multifocal osteomyelitis (CRMO): A tale of two cases. Egyptian Rheumatologist. 2020.
83. Yacoub AT, Khwaja SI, Greene JN. Chronic recurrent multifocal osteomyelitis mimicking infection. Infectious Diseases in Clinical Practice. 2014;22(4):e93-e4.
84. Xu T, Huang Y, Zhao Y, Wang P, Chen Y. 68Ga-DOTA-FAPI-04 PET/CT Imaging in a Case of SAPHO Syndrome. Clin Nucl Med. 2022;47(3):246-8.
85. Watanuki M, Hatori M, Kokubun S. SAPHO syndrome with a tumour-like bony proliferative lesion in distal femur. A case report. Ups J Med Sci. 2006;111(2):243-8.
86. Waghmode A, Soman N, Gupta A. A Case of Sterile Osteomyelitis: Chronic Recurrent Multifocal Osteomyelitis (CRMO). Cureus. 2022;14(6):e26370.
87. Theumann NH, So A, Mouhsine E, Spoletini P, Hoesli P, Boubaker E, et al. SAPHO syndrome masquerading as metastatic bone disease. Australas Radiol. 2005;49(5):418-21.
88. Pahlavan PS, Leslie WD. Multiple imaging findings in SAPHO syndrome. Clin Nucl Med. 2008;33(12):912-5.
89. Mann B, Shaerf DA, Sheeraz A, Skinner JA, Saifuddin A. SAPHO syndrome presenting as widespread bony metastatic disease of unknown origin. Rheumatol Int. 2012;32(2):505-7.
90. Malik D, Handa R, Petraszko A, Tejwani S. SAPHO Syndrome Masquerading as Metastatic Breast Cancer. Case Rep Rheumatol. 2018;2018:3168452.
91. Hong CW, Hsiao EC, Horvai AE, Link TM. Chronic recurrent multifocal osteomyelitis with an atypical presentation in an adult man. Skeletal Radiol. 2015;44(9):1359-64.

92. Court C, Charlez C, Molina V, Clerc D, Miquel A, Nordin JY. Isolated thoracic spine lesion: is this the presentation of a SAPHO syndrome? A case report. Eur Spine J. 2005;14(7):711-5.
93. Bracamonte JD, Roberts CC. Chronic Recurrent Multifocal Osteomyelitis Mimicking Osteosarcoma. Radiol Case Rep. 2006;1(2):42-6.
94. Verbruggen LA, Shahabpour M, De Geeter F, Van Tiggelen R. Femoral periosteal thickening in pustulotic arthroosteitis, including 3-year followup by magnetic resonance imaging. J Rheumatol. 1993;20(10):1793-800.
95. Ni J, Tang P. An Unusual Bone Metastasis Mimicking SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis) Syndrome on Bone Scintigraphy. Clin Nucl Med. 2016;41(2):173-5.
96. Zhao Y, Laxer RM, Ferguson PJ. Treatment Advances in Chronic Non-Bacterial Osteomyelitis and Other Autoinflammatory Bone Conditions. Current Treatment Options in Rheumatology. 2017;3(1):17-32.
97. Zhao Y, Dedeoglu F, Ferguson PJ, Lapidus SK, Laxer RM, Bradford MC, et al. Physicians' Perspectives on the Diagnosis and Treatment of Chronic Nonbacterial Osteomyelitis. Int J Rheumatol. 2017;2017:7694942.
98. Zhao Y, Wu EY, Oliver MS, Cooper AM, Basiaga ML, Vora SS, et al. Consensus Treatment Plans for Chronic Nonbacterial Osteomyelitis Refractory to Nonsteroidal Antiinflammatory Drugs and/or With Active Spinal Lesions. Arthritis Care Res (Hoboken). 2018;70(8):1228-37.
99. Xiang Y, Jiao R, Cao Y, Yu Y, Zhang W, Liang D, et al. Fibromyalgia in patients with synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome: prevalence and screening. Clin Rheumatol. 2021;40(4):1559-65.
100. Zhou L, Li T, Wu X, Lu HJ, Lin L, Ye LY, et al. Assessment of Neuropathic Pain in Ankylosing Spondylitis: Prevalence and Characteristics. Pain and Therapy. 2021;10(2):1467-79.
101. Borman P, Kaygisiz F, Yaman A. Neuropathic component of low back pain in patients with ankylosing spondylitis. Mod Rheumatol. 2021;31(2):462-7.
102. Baraka E, Balata M, Ahmed S, El-Blbehisy M, Elattar E. Concomitant Diagnosis of Fibromyalgia and Ankylosing Spondylitis: Relation to Clinical Features and Plasma Pentraxin -3 Level. Curr Rheumatol Rev. 2021;17(3):331-41.
103. He Q, Luo J, Chen J, Yang J, Yao C, Xu C, et al. The validity and reliability of quality of life questionnaires in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and meta-analysis. Health Qual Life Outcomes. 2022;20(1):116.
104. Zhao Y, Chauvin NA, Jaramillo D, Burnham JM. Aggressive Therapy Reduces Disease Activity without Skeletal Damage Progression in Chronic Nonbacterial Osteomyelitis. J Rheumatol. 2015;42(7):1245-51.
105. Borzutzky A, Stern S, Reiff A, Zurakowski D, Steinberg EA, Dedeoglu F, et al. Pediatric chronic nonbacterial osteomyelitis. Pediatrics. 2012;130(5):e1190-7.
106. Wong RSY. Disease-Modifying Effects of Long-Term and Continuous Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Spondyloarthritis. Adv Pharmacol Sci. 2019;2019:5324170.
107. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis. 2020;79(6):700-12.
108. Kuroda T, Ehara S, Murakami H. Stress fracture of the clavicle associated with sternocostoclavicular hyperostosis. Skeletal Radiol. 2005;34(7):424-6.
109. Lagier R, Arroyo J, Fallet GH. Sternocostoclavicular hyperostosis. Radiological and pathological study of a specimen with ununited clavicular fracture. Pathol Res Pract. 1986;181(5):596-603.

110. Mittal D. Sternoclavicular hyperostosis with pathological fracture of the clavicle--a case report. Injury. 2004;35(6):634; author reply
111. Miyamoto S, Otsuka M, Hasue F, Fujiyoshi T, Kamiya K, Kiuchi H, et al. Stress fracture of the midshaft clavicle associated with sternocostoclavicular hyperostosis-Case report. Int J Surg Case Rep. 2019;58:121-6.
112. Raja S, Goel A, Paul A. Sternoclavicular hyperostosis with pathological fracture of the clavicle--a case report. Injury. 2003;34(6):464-6.
113. Li B, Li GW, Xue L, Chen YY. Rapid remission of refractory synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome in response to the Janus kinase inhibitor tofacitinib: A case report. World Journal of Clinical Cases. 2020;8(19):4527-34.
114. Li Y, Liu G, Zhao Y, Luo Y, Lu T. SAPHO syndrome with pathological fractures of vertebral bodies: a case report. BMC Musculoskelet Disord. 2019;20(1):27.
115. Monet M, Prati C, Guillot X, Sondag M, Verhoeven F, Aubin F, et al. Disease modifying anti rheumatic drugs in the treatment of Sapho syndrome: Systematic literature analysis. Annals of the Rheumatic Diseases. 2018;77 (Supplement 2):1155-6.
116. Huber CE, Judex AG, Freyschmidt J, Feuerbach S, Scholmerich J, Muller-Ladner U. Sequential Combination Therapy Leading to Sustained Remission in a Patient with SAPHO Syndrome. Open Rheumatol J. 2009;3(1):18-21.
117. Misiak-Galazka M, Jeziorkowska R, Sikorska-Siudek K, Wolska H. SAPHO syndrome: Case report. Postepy Dermatologii i Alergologii. 2012;29(2):136-8.
118. Jinag C, Zhao Y, Li X, Hu H, Li C. Whole-body Bone Scan in the Diagnosis and Treatment of SAPHO Syndrome. J Coll Physicians Surg Pak. 2022;32(4):S64-S6.
119. Yabe H, Kuroiwa T, Nonaka A, Tsutsumi T, Sakurai T, Moriguchi M, et al. Clinical features and treatment results of Japanese patients with sapho (synovitis-acne-pustulosis-hyperostosis-osteitis) syndrome. Arthritis and Rheumatism. 2012;64(SUPPL. 10):S589-S90.
120. Castellvi I, Bonet M, Narvaez JA, Molina-Hinojosa JC. Successful treatment of SAPHO syndrome with adalimumab: a case report. Clin Rheumatol. 2010;29(10):1205-7.
121. Rosero A, Ruano R, Martin M, Hidalgo C, Garcia-Talavera J. Acute venous thrombosis as complication and clue to diagnose a SAPHO syndrome case. A case report. Acta Reumatol Port. 2013;38(3):203-6.
122. Li Z, Liu S, Liu Y, Ma M, Li L, Li C. Successful treatment of nail involvement using leflunomide in a patient with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. Australas J Dermatol. 2023;64(1):156-7.
123. Amital H, Applbaum YH, Aamar S, Daniel N, Rubinow A. SAPHO syndrome treated with pamidronate: an open-label study of 10 patients. Rheumatology. 2004;43(5):658-61.
124. Li C, Zhao Y, Zuo Y, Zhou Y, Zhang F, Liu S, et al. Efficacy of bisphosphonates in patients with synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: a prospective open study. Clinical and experimental rheumatology. 2019;37(4):663-9.
125. Colina M, La Corte R, Trotta F. Sustained remission of SAPHO syndrome with pamidronate: a follow-up of fourteen cases and a review of the literature. Clinical and experimental rheumatology. 2009;27(1):112-5.
126. Delattre E, Guillot X, Godfrin-Valnet M, Prati C, Wendling D. SAPHO syndrome treatment with intravenous pamidronate. Retrospective study of 22 patients. Joint Bone Spine. 2014;81(5):456-8.
127. Galadari H, Bishop AG, Venna SS, Sultan E, Do D, Zeltser R. Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome treated with a combination of isotretinoin and pamidronate. Journal of the American Academy of Dermatology. 2009;61(1):123-5.

128. Courtney PA, Hosking DJ, Fairbairn KJ, Deighton CM. Treatment of SAPHO with pamidronate. Rheumatology. 2002;41(10):1196-8.
129. Siau K, Laversuch CJ. SAPHO syndrome in an adult with ulcerative colitis responsive to intravenous pamidronate: a case report and review of the literature. Rheumatology international. 2010;30(8):1085-8.
130. Wu N, Zhao Y, Tao W, Wu Z, Li C, Li L. A single cohort, open-label study of the efficacy of pamidronate for palmoplantar pustulosis in synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. Clin Exp Rheumatol. 2020;38(6):1263-4.
131. Kopterides P, Pikazis D, Koufos C. Successful treatment of SAPHO syndrome with zoledronic acid. Arthritis Rheum. 2004;50(9):2970-3.
132. Just A, Adams S, Brinkmeier T, Barsegian V, Lorenzen J, Schilling F, et al. Successful treatment of primary chronic osteomyelitis in SAPHO syndrome with bisphosphonates. [German, English]. JDDG - Journal of the German Society of Dermatology. 2008;6(8):657-60.
133. Gorecki P, Stockmann P, Distler JHW, Wuest W, Schmidt D, Neukam FW, et al. Implication of bisphosphonate use in the treatment of SAPHO syndrome: Case report and discussion of current literature. Journal of Medical Hypotheses and Ideas. 2015;9(2):72-8.
134. Wang CR, Tsai YS, Whang-Peng J. Zoledronic acid monotherapy improves osteoarticular involvement in SAPHO syndrome. Scand J Rheumatol. 2020;49(5):419-21.
135. Gonzalez Vazquez E, Martin Pedraz L, Galindo Zavala R, Diaz-Cordoves Rego G, Nunez Cuadros E. Is zoledronate a safe and effective treatment option in chronic nonbacterial osteomyelitis? An Pediatr (Engl Ed). 2023;98(2):142-5.
136. Liu S, Yin D, Lin Z, Wei S, Li C. Short-term efficacy of zoledronic acid in the treatment of 30 cases of SAPHO syndrome. Clin Exp Rheumatol. 2024;42(1):205-6.
137. Ringe JD, Faber H, Farahmand P. Rapid pain relief and remission of sternocostoclavicular hyperostosis after intravenous ibandronate therapy. J Bone Miner Metab. 2005;24(1):87-93.
138. Soyfoo MS, Gangji V, Margaux J. Successful treatment of SAPHO syndrome with ibandronate. J Clin Rheumatol. 2010;16(5):253.
139. Otto S, Troeltzsch M, Burian E, Mahaini S, Probst F, Pautke C, et al. Ibandronate treatment of diffuse sclerosing osteomyelitis of the mandible: Pain relief and insight into pathogenesis. J Craniomaxillofac Surg. 2015;43(9):1837-42.
140. Fassio A, Adami G, Boninsegna E, Mansueto G, Guglielmi G, Giollo A, et al. A case of adult chronic recurrent multifocal osteomyelitis successfully treated with neridronate. Clinical Cases in Mineral and Bone Metabolism. 2019;16(1):75-9.
141. Ikeda A, Yamachika E, Matsumura T, Mizutani M, Matsui Y, Iida S. A case of diffuse sclerotic osteomyelitis of the mandible associated with SAPHO syndrome successfully treated with an oral bisphosphonate. J Oral Maxillofac Surg Med Pathol. 2015;27(6):858-61.
142. Brevet P, Michelin P, Marcelli C, Alcaix D, Lequerre T, Vittecoq O. Association between treatment type and therapeutic response according to clinical form of SAPHO syndrome in adults from a multicentre retrospective cohort study. Clin Exp Rheumatol. 2024.
143. Schnabel A, Nashawi M, Anderson C, Felsenstein S, Lamoudi M, Poole-Cowley J, et al. TNF-inhibitors or bisphosphonates in chronic nonbacterial osteomyelitis? - Results of an international retrospective multicenter study. Clin Immunol. 2022;238:109018.
144. Ueno M, Miyagawa I, Miyazaki Y, Hanami K, Fukuyo S, Kubo S, et al. Efficacy and safety of guselkumab and adalimumab for pustulotic arthro-osteitis and their impact on peripheral blood immunophenotypes. Arthritis Res Ther. 2022;24(1):240.
145. Hayem G, Ben M'Barek R, Toussirot E, Compaore C, Pham T, Houvenagel E, et al. SAPHO syndrome treated by TNF alpha-blocking agents. Report of 45 cases. Arthritis and Rheumatism. 2010;10):2269.

146. Ben Abdelghani K, Dran DG, Gottenberg JE, Morel J, Sibilia J, Combe B. Tumor necrosis factor-alpha blockers in SAPHO syndrome. J Rheumatol. 2010;37(8):1699-704.
147. Murgia G, Firinu D, Barca MP, Peralta MM, Manconi PE, Del Giacco SR. Biologics for SAPHO syndrome: A single centre experience. Allergy: European Journal of Allergy and Clinical Immunology. 2015;70:418-9.
148. Abourazzak FE, Hachimi H, Kadi N, Berrada K, Tizniti S, Harzy T. Etanercept in the treatment of SAPHO syndrome: Which place? Eur J Rheumatol. 2014;1(3):125-8.
149. Antoniou C, Nicolaidou E, Moustou AE, Stratigos A, Katsambas A. Palmoplantar pustulosis with arthro-osteitis: successful treatment with etanercept and acitretin. J Eur Acad Dermatol Venereol. 2009;23(7):854-5.
150. Arias-Santiago S, Sanchez-Cano D, Callejas-Rubio JL, Fernandez-Pugnaire MA, Ortego-Centeno N. Adalimumab treatment for SAPHO syndrome. Acta Derm Venereol. 2010;90(3):301-2.
151. Burgemeister LT, Baeten DLP, Tas SW. Biologics for rare inflammatory diseases: TNF blockade in the SA PHO syndrome. Neth J Med. 2012;70(10):444-9.
152. Crowley EL, O'Toole A, Gooderham MJ. Hidradenitis suppurativa with SAPHO syndrome maintained effectively with adalimumab, methotrexate, and intralesional corticosteroid injections. SAGE Open Med Case Rep. 2018;6:2050313x18778723.
153. Hirohata A, Hanafusa T, Kawamoto T, Ikegami R. Infliximab for treatment of synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: A case report. Annals of Dermatology. 2017;29(1):131-3.
154. Iqbal M, Kolodney MS. Acne fulminans with synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome treated with infliximab. J Am Acad Dermatol. 2005;52(5 Suppl 1):S118-20.
155. Mari A, Morla A, Melero M, Schiavone R, Rodriguez J. Diffuse sclerosing osteomyelitis (DSO) of the mandible in SAPHO syndrome: a novel approach with anti-TNF therapy. Systematic review. J Craniomaxillofac Surg. 2014;42(8):1990-6.
156. Olivieri I, Padula A, Ciancio G, Salvarani C, Niccoli L, Cantini F. Successful treatment of SAPHO syndrome with infliximab: report of two cases. Annals of the Rheumatic Diseases. 2002;61(4):375-6.
157. Sabugo F, Liberman C, Niedmann JP, Soto L, Cuchacovich M. Infliximab can induce a prolonged clinical remission and a decrease in thyroid hormonal requirements in a patient with SAPHO syndrome and hypothyroidism. Clin Rheumatol. 2008;27(4):533-5.
158. Saez-Martin LC, Gomez-Castro S, Roman-Curto C, Palacios-Alvarez I, Fernandez-Lopez E. Etanercept in the treatment of SAPHO syndrome. Int J Dermatol. 2015;54(6):e206-8.
159. Su YS, Chang CH. SAPHO syndrome associated with acne conglobata successfully treated with etanercept. J Formos Med Assoc. 2015;114(6):562-4.
160. Vilar-Alejo J, Dehesa L, de la Rosa-del Rey P, Novoa-Medina J, Valeron Almazan P, Santana Medina N, et al. SAPHO syndrome with unusual cutaneous manifestations treated successfully with etanercept. Acta Derm Venereol. 2010;90(5):531-2.
161. Wagner AD, Andresen J, Jendro MC, Hülsemann JL, Zeidler H. Sustained response to tumor necrosis factor alpha-blocking agents in two patients with SAPHO syndrome. Arthritis and rheumatism. 2002;46(7):1965-8.
162. Zhang L, Gao Z. Etanercept in the treatment of refractory SAPHO syndrome. Am J Clin Exp Immunol. 2016;5(4):62-6.
163. Hampton SL, Youssef H. Successful treatment of resistant SAPHO syndrome with anti-TNF therapy. BMJ Case Rep. 2013;2013.

164. Kanda R, Nakano K, Miyagawa I, Iwata S, Nakayamada S, Tanaka Y. A case of bone destruction caused by chronic non-bacterial osteomyelitis (CNO) successfully repaired with a tumour necrosis factor-α (TNF-α) inhibitor, adalimumab. Mod Rheumatol Case Rep. 2020;4(2):196-201.
165. Iwahashi C, Itami T, Sakamoto M, Kusaka S. Retinal Vasculitis Associated with SAPHO Syndrome Responding to Treatment with Adalimumab. Ocul Immunol Inflamm. 2023:1-4.
166. Daoussis D, Konstantopoulou G, Kraniotis P, Sakkas L, Liossis S-N. Biologics in SAPHO syndrome: A systematic review. YSARH. 2019;48(4):618-25.
167. Fruehauf J, Cierny-Modre B, Caelen LE-S, Schwarz T, Weinke R, Aberer E. Response to infliximab in SAPHO syndrome. BMJ Case Rep. 2009;2009(may19 1):bcr1020081145-bcr.
168. Garcovich S, Amelia R, Magarelli N, Valenza V, Amerio P. Long-term treatment of severe SAPHO syndrome with adalimumab: case report and a review of the literature. Am J Clin Dermatol. 2012;13(1):55-9.
169. Anic B, Padjen I, Baresic M, Tezak S. The lobster sign in SAPHO syndrome: unusually extensive osteitis of the anterior chest wall partially responsive to infliximab. Rheumatol Int. 2014;34(2):281-2.
170. Li C, Wu X, Cao Y, Zeng Y, Zhang W, Zhang S, et al. Paradoxical skin lesions induced by anti-TNF-alpha agents in SAPHO syndrome. Clin Rheumatol. 2019;38(1):53-61.
171. Massara A, Cavazzini PL, Trotta F. In SAPHO syndrome anti-TNF-alpha therapy may induce persistent amelioration of osteoarticular complaints, but may exacerbate cutaneous manifestations. Rheumatology (Oxford). 2006;45(6):730-3.
172. Fan D, Li F, Liu Z, Tang Z, Lv S. Successful Treatment of Refractory Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis (SAPHO) Syndrome and Paradoxical Psoriasis with Secukinumab: A Case Report. Clin Cosmet Investig Dermatol. 2024;17:547-52.
173. Vekic DA, Woods J, Lin P, Cains GD. SAPHO syndrome associated with hidradenitis suppurativa and pyoderma gangrenosum successfully treated with adalimumab and methotrexate: a case report and review of the literature. Int J Dermatol. 2018;57(1):10-8.
174. Huang H, Zhang Z, Zhao J, Hao Y, Zhou W. The effectiveness of treatments for patients with SAPHO syndrome: a follow-up study of 24 cases from a single center and review of literature. Clin Rheumatol. 2020.
175. Gil F, Mariano P, Silva S, Gil J, Eufémia Calmeiro M. SAPHO syndrome: the value of classic drugs in the era of biologics. Dermatol Online J. 2020;26(5).
176. Slouma M, Bettaieb H, Rahmouni S, Litaiem N, Dhahri R, Gharsallah I, et al. Pharmacological Management of Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis Syndrome Syndrome: A Proposal of a Treatment Algorithm. J Clin Rheumatol. 2022;28(2):e545-e51.
177. Li C, Shi X, Xu W, Gong M, Zhang W, Zhang S. Letters to the editor: Refractory SAPHO syndrome with positive Th17-related pathway immunohistochemistry staining. European Journal of Inflammation. 2018;16:1-5.
178. Firinu D, Barca MP, Lorrai MM, Perra S, Cabras S, Muggianu E, et al. TH17 cells are increased in the peripheral blood of patients with SAPHO syndrome. Autoimmunity. 2014;47(6):389-94.
179. Assmann G, Bittenbring T, Wagner AD, Schreiber M, Christofyllakis K, Hueffmeier U, et al. Impact of interleukin 17 blocking agent on clinical outcome in sapho patients. Annals of the Rheumatic Diseases. 2019;78 (Supplement 2):875-6.
180. Wang L, Sun B, Li C. Clinical and Radiological Remission of Osteoarticular and Cutaneous Lesions in SAPHO Patients Treated With Secukinumab: A Case Series. J Rheumatol. 2021;48(6):953-5.

181. Ji Q, Wang Q, Pan W, Hou Y, Wang X, Bian L, et al. Exceptional response of skin symptoms to secukinumab treatment in a patient with SAPHO syndrome: Case report and literature review. Medicine (Baltimore). 2022;101(33):e30065.
182. Funabiki M, Tahara M, Kondo S, Ayuzawa N, Yanagida H. SAPHO Syndrome Complicated by Lesions of the Central Nervous System Successfully Treated with Brodalumab. Case Rep Rheumatol. 2023;2023:6005531.
183. Sun B, Cao Y, Wang L, Wang M, Li C. Successful treatment of refractory mandibular lesions in SAPHO syndrome with secukinumab. Rheumatology (Oxford). 2021;60(1):473-4.
184. Tu W, Nie D, Chen Y, Wen C, Zeng Z. Successful Treatment of SAPHO Syndrome Complicated with Ankylosing Spondylitis by Secukinumab: A Case Report. J Pers Med. 2023;13(3).
185. Wendling D, Aubin F, Verhoeven F, Prati C. IL-23/Th17 targeted therapies in SAPHO syndrome. A case series. Joint Bone Spine. 2017;84(6):733-5.
186. Luan L, Lv C. Secukinumab-induced paradoxical skin lesions,but successful treatment with tofacitinib in SAPHO syndrome: a case report. J Dermatolog Treat. 2023:1-16.
187. Li Y, Meng F, Jiang H, Peng Q, Fu J, Yin D, et al. Paradoxical skin lesions induced by IL-17 inhibitors in SAPHO syndrome. J Dermatolog Treat. 2024;35(1):2295239.
188. Ikumi N, Fujita H, Terui T. Guselkumab improves joint pain in patients with pustulotic arthro-osteitis: A retrospective pilot study. J Dermatol. 2020.
189. Yamamoto T. Effects of guselkumab on ankylosing spondylitis-type pustulotic arthro-osteitis in a patient with palmoplantar pustulosis. Dermatol Ther. 2020;33(6):e14088.
190. Yamamoto T, Fukuda K, Morita A, Kimura T, Morishima H, Goto R, et al. Efficacy of guselkumab in a subpopulation with pustulotic arthro-osteitis through week 52: an exploratory analysis of a phase 3, randomized, double-blind, placebo-controlled study in Japanese patients with palmoplantar pustulosis. J Eur Acad Dermatol Venereol. 2020;34(10):2318-29.
191. Flora A, Holland R, Smith A, Frew JW. Rapid and sustained remission of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome with IL-23p19 antagonist (risankizumab). JAAD Case Rep. 2021;14:33-6.
192. Ferraioli M, Fiannacca L, Greco E, Cela E, Fatica M, Bergamini A, et al. Risankizumab Efficacy in Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis (SAPHO) Remission: A Case Report on Rheumatologic and Dermatologic Disease Manifestations with Literature Review. Case Reports Immunol. 2024;2024:9076852.
193. Adamo S, Nilsson J, Krebs A, Steiner U, Cozzio A, French LE, et al. Successful treatment of SAPHO syndrome with apremilast. Br J Dermatol. 2018;179(4):959-62.
194. Firinu D, Murgia G, Lorrai MM, Barca MP, Peralta MM, Manconi PE, et al. Biological treatments for SAPHO syndrome: an update. Inflamm Allergy Drug Targets. 2014;13(3):199-205.
195. Sato H, Wada Y, Hasegawa E, Nozawa Y, Nakatsue T, Ito T, et al. Adult-onset Chronic Recurrent Multifocal Osteomyelitis with High Intensity of Muscles Detected by Magnetic Resonance Imaging, Successfully Controlled with Tocilizumab. Intern Med. 2017;56(17):2353-60.
196. Sun XC, Liu S, Li C, Zhang S, Wang M, Shi XH, et al. Failure of tocilizumab in treating two patients with refractory SAPHO syndrome: a case report. J Int Med Res. 2018;46(12):5309-15.

197. Fujita S, Kosaka N, Mito T, Hayashi H, Morita Y. Development of aseptic subcutaneous abscess after tocilizumab therapy in a patient with SAPHO syndrome complicated by amyloid A amyloidosis. Int J Rheum Dis. 2015;18(4):476-9.
198. Colina M, Pizzirani C, Khodeir M, Falzoni S, Bruschi M, Trotta F, et al. Dysregulation of P2X7 receptor-inflammasome axis in SAPHO syndrome: successful treatment with anakinra. Rheumatology. 2010;49(7):1416-8.
199. Wendling D, Prati C, Aubin F. Anakinra treatment of SAPHO syndrome: short-term results of an open study. Annals of the Rheumatic Diseases. 2012;71(6):1098-100.
200. Adam Z, Sediva A, Zeman D, Fojtik Z, Petrasova H, Diatkova J, et al. Successful treatment of SAPHO syndrome (chronic nonbacterial osteomyelitis and acne) with anakinra and denosumab. Case report and review of therapy. Vnitr Lek. 2023;69(E-5):4-14.
201. Sundqvist M, Christenson K, Wekell P, Bjornsdottir H, Dahlstrand Rudin A, Sanchez Klose FP, et al. Severe chronic non-bacterial osteomyelitis in combination with total MPO deficiency and responsiveness to TNFalpha inhibition. Front Immunol. 2023;14:1233101.
202. Acierno S, Angrisani F, Marino A, Caporali RF, Cimaz R, Giani T. Canakinumab treatment in a young girl with refractory chronic recurrent multifocal osteomyelitis associated with pyoderma gangrenosum. Int J Rheum Dis. 2022;25(11):1333-8.
203. Cao F, Hou X, Kang T, Shi X, Ma W, Zhang Y, et al. SAPHO syndrome complicated with relapsing polychondritis: A case report. Int J Rheum Dis. 2023.
204. Lanis A, Van Den Bogaerde S, Zhao Y. Chronic recurrent multifocal osteomyelitis and tofacitinib: a case series. Rheumatology (Oxford). 2022.
205. Liu Y, Wu X, Cao Y, Liu S, Ma M, Li C. Synovitis, acne, pustulosis, hyperostosis and osteitis syndrome with mandibular involvement: Would surgical operation help? Int J Rheum Dis. 2023;26(3):563-7.
206. Ru C, Qian T, Liu X, Wang C, Li W, Hou X, et al. SAPHO syndrome with Takayasu arteritis successfully treated with tofacitinib. Int J Rheum Dis. 2023.
207. Yang Q, Zhao Y, Li C, Luo Y, Hao W, Zhang W. Case report: successful treatment of refractory SAPHO syndrome with the JAK inhibitor tofacitinib. Medicine (Baltimore). 2018;97(25):e11149.
208. Yang J, Yuan C, Zhou S, Teng Z, Li M. Successful Treatment of Refractory Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis (SAPHO) Syndrome with Baricitinib, a Janus Kinase Inhibitor. Clin Cosmet Investig Dermatol. 2024;17:529-37.
209. Sarikaya Solak S, Yelgen Ilyas H. Tofacitinib: a successful treatment option for SAPHO syndrome. Int J Dermatol. 2024.
210. Li C, Li Z, Cao Y, Li L, Li F, Li Y, et al. Tofacitinib for the Treatment of Nail Lesions and Palmoplantar Pustulosis in Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis Syndrome. JAMA Dermatol. 2021;157(1):74-8.
211. Yuan F, Luo J, Yang Q. SAPHO Syndrome Complicated by Ankylosing Spondylitis Successfully Treated With Tofacitinib: A Case Report. Front Immunol. 2022;13:911922.
212. Li Y, Huo J, Cao Y, Yu M, Zhang Y, Li Z, et al. Efficacy of tofacitinib in synovitis, acne, pustulosis, hyperostosis and osteitis syndrome: a pilot study with clinical and MRI evaluation. Ann Rheum Dis. 2020;79(9):1255-7.
213. Xie W, Huang H, Zhang Z. Off-label use of tofacitinib: a potential treatment option for SAPHO syndrome. Ann Rheum Dis. 2020.
214. Liu S, Yu Y, Liu Y, Ma M, Li C. Efficacy of baricitinib in synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: A case series. Joint Bone Spine. 2023;90(5):105587.
215. Jamshidi K, Heidari M, Bagherifard A, Mirzaei A. Favorable outcome of extended curettage for the treatment of unifocal chronic sclerosing osteomyelitis of clavicle: a case series. J Shoulder Elbow Surg. 2020;29(5):954-60.

216. Rustemeyer J, Siegmund BJ, Okcu Y, Busch A. Total mandibular reconstruction following diffuse sclerosing osteomyelitis. Oral Maxillofac Surg. 2019;23(1):95-9.
217. Suei Y, Tanimoto K, Miyauchi M, Ishikawa T. Partial resection of the mandible for the treatment of diffuse sclerosing osteomyelitis: report of four cases. J Oral Maxillofac Surg. 1997;55(4):410-4; 4-5.
218. Park YY, Park B. Aesthetic Mandibular Angloplasty to Improve Patient Quality of Life in Chronic Recurrent Multifocal Osteomyelitis. Plast Reconstr Surg Glob Open. 2024;12(4):e5718.
219. Takigawa T, Tanaka M, Nakahara S, Sugimoto Y, Ozaki T. SAPHO syndrome with rapidly progressing destructive spondylitis: two cases treated surgically. Eur Spine J. 2008;17 Suppl 2:S331-7.
220. Bianchi G, Marinelli A, Frizziero A, Mercuri M. Hyperostosis and osteitis in Sapho syndrome: conservative or surgical treatment. Chir Organi Mov. 2004;89(1):45-9.
221. Meent MM, Ende RP, Pichardo SE, Merkesteyn JP. Remodelling surgery with 3D printed patient specific surgical guides in patients with chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible, a case series. Med Oral Patol Oral Cir Bucal. 2024.
222. Jung J, Molinger M, Kohn D, Schreiber M, Pfreundschuh M, Assmann G. Intra-articular glucocorticosteroid injection into sternocostoclavicular joints in patients with SAPHO syndrome. YSARH. 2012;42(3):266-70.
223. Gregoire ARF, DeRuyter BK, Stratman EJ. Psoriasis Flares Following Systemic Glucocorticoid Exposure in Patients With a History of Psoriasis. JAMA Dermatol. 2021;157(2):198-201.
224. Sachdeva S, Pawaria S. Role of Physical Therapy and Rehabilitation in a Rare Condition SAPHO Syndrome. JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH. 2021;15(3).
225. JS SDR. Physiotherapy for Ankylosing Spondylitis: Systematic Review and a Proposed Rehabilitation Protocol. Curr Rheumatol Rev. 2017;13(2):121-5.
226. Xi Y, Lin Z, Chen N, Hou X, Zhu Y, Li C. Clavicle fracture in SAPHO syndrome. Rheumatology (Oxford). 2023.
227. Yamamoto H, Taniguchi Y. Pustulotic Arthro-Osteitis-Related Pathological Clavicle Fracture. J Clin Rheumatol. 2024.
228. Sanges S, Ducoulombier V, Sivery B, Delhaye N, Haffner C, Houvenagel E. Thrombosis of the subclavian vein complicating a SAPHO syndrome: An observation. Revue du Rhumatisme (Edition Francaise). 2015;82(1):61-2.
229. Suzuki M, Kanazawa H, Shinozaki T, Sugimoto H. Radiologists need to be aware of secondary central venous stenosis in patients with SAPHO syndrome. Eur Radiol. 2017;27(11):4532-7.
230. van Holsbeeck M, Martel W, Dequeker J, Favril A, Gielen J, Verschakelen J, et al. Soft tissue involvement, mediastinal pseudotumor, and venous thrombosis in pustulotic arthro-osteitis. A study of eight new cases. Skeletal Radiol. 1989;18(1):1-8.
231. Bolukbas N, Bolukbas S, Erel A, Tali ET. Sapho syndrome associated with acne fulminans and prominent acromioclavicular joint involvement. Scand J Rheumatol. 1996;25(3):180-2.
232. Godot A, Fakih O, Prati C, Wendling D, Verhoeven F. SAPHO syndrome and subclavian thrombosis: Simple fortuitous association? European journal of internal medicine. 2019.
233. Goetti P, Pham C, Gallusser N, Becce F, di Summa PG, Vauclair F, et al. Total clavicle reconstruction with free peroneal graft for the surgical management of chronic nonbacterial osteomyelitis of the clavicle: a case report. BMC Musculoskelet Disord. 2019;20(1):211.

234. Gorospe L, Moran-Alvarez P, Velasco D, Cabanero-Sanchez A, Moreno-Mata N, Gallego-Rivera JI, et al. Left Subclavian Vein Occlusion in a Patient With SAPHO Syndrome. J Clin Rheumatol. 2018:1.
235. Haenel LC, Bradway WR, Costantini PJ. Thrombophlebitis complicating sternocostoclavicular hyperostosis. Postgrad Med. 1980;68(5):113-5, 7-8.
236. Hallas J, Olesen KP. Sterno-costo-clavicular hyperostosis. A case report with a review of the literature. Acta Radiol. 1988;29(5):577-9.
237. Inoue E, Hiroumi S, Sato S, Hayashi M, Konaka H, Tsuji S, et al. Palmoplantar pustulosis and pustulotic arthro-osteitis associated with multiple venous occlusion: A case report and literature review. J Dermatol. 2023.
238. Ishizuka M, Yamamoto Y, Yamada S, Maemura S, Nakata R, Motozawa Y, et al. Bilateral subclavian vein occlusion in a SAPHO syndrome patient who needed an implantable cardioverter defibrillator: An unusual cause of lead access failure. International Heart Journal. 2016;57(3):380-2.
239. Kawabata T, Morita Y, Nakatsuka A, Kagawa H, Kawashima M, Sei T, et al. Multiple venous thrombosis in SAPHO syndrome. Ann Rheum Dis. 2005;64(3):505-6.
240. Kohler H, Uehlinger E, Kutzner J, West TB. Sternocostoclavicular hyperostosis: painful swelling of the sternum, clavicles, and upper ribs. Report of two new cases. Ann Intern Med. 1977;87(2):192-7.
241. Lazzarin P, Punzi L, Cesaro G, Sfriso P, De Sandre P, Padovani G, et al. Thrombosis of the subclavian vein in SAPHO syndrome - A case-report. Rev Rhum. 1999;66(3):173-6.
242. Ohida H, Curuk C, Prescher H, Stegemann E, Bürger T. Thoracic outlet syndrome in a patient with SAPHO syndrome - A case report. Int J Surg Case Rep. 2021;80:105710.
243. Okuno S, Nunokawa T, Chinen N, Sogabe S. SAPHO Syndrome Accompanied by Thoracic Outlet Syndrome. Intern Med. 2022.
244. Leerling AT, Navas Canete A, Winter EM. Chronic non-bacterial osteomyelitis in SAPHO syndrome complicated by subclavian vein obstruction. Rheumatology (Oxford). 2023;62(12):e355-e6.

Supplemental material 4: Detailed methods for consensus process

Systematic literature review: data collection

The systematic literature review addressed the domains of interest (see S2), covering the disease definition, name, organization of care, diagnostics and treatment. A search was conducted for Embase, Emcare, Web of Science, and Cochrane (initial search February 2021) and Pubmed (initial search May 11th 2023, last update April 18th 2024) The search string (see below) aimed to retrieve literature on the full spectrum of CNO, also including pediatric studies. In total, n=1385 papers were retrieved, excluding duplicates. Per domain of interest, papers were selected by searching title, abstract, and full text for key words (specified in the summary of evidence). Relevance of identified papers was assessed by reading full text by ATL. For several themes, the search was limited at the discretion of ATL, EMW and OMD to recent (systematic) reviews or studies with larger patient numbers only, as specified in the summary of evidence. The summary of evidence focused mainly on literature for adult CNO. When evidence from pediatric studies was considered relevant , this is explicitly mentioned in the text. In addition, the current European Alliance of Associations for Rheumatology (EULAR) recommendations for axial spondylarthritis (axSpA) and psoriatic arthritis (PsA) were consulted as these patients populations bear some clinical resemblance to adult CNO. Relevant considerations are embedded in the summary of evidence, with explicit mentioning that they were conceived for axSpA or PsA as appropriate. Lastly, for several domains that surpass the domain of CNO in specific (e.g. on differential diagnoses), supportive evidence was added manually. Current clinical practice standards were derived from a physician survey study that has been published previously (1).

Systematic literature review: full search string

(("Hyperostosis, Sternocostoclavicular"[majr] OR "sterno-costo-clavicular hyperostosis"[ti] OR "sternocostoclavicular hyperostosis"[ti] OR "sterno costoclavicular hyperostosis"[ti] OR "sternocosto clavicular hyperostosis"[ti] OR ("SCCH"[ti] AND "hyperostosis"[ti]) OR "SAPHO"[ti] OR "Acquired Hyperostosis Syndrome"[majr] OR "acquired hyperostosis syndrome"[ti] OR "Acquired Hyperostosis"[ti] OR "Acute pseudoseptic arthritis and palmoplantar pustulosis"[ti] OR "Aseptic osteomyelitis"[ti] OR "Bilateral clavicular osteomyelitis"[ti] OR "CRMO"[ti] OR "Chronic mandibular osteomyelitis"[ti] OR "chronic multifocal osteomyelitis"[ti] OR "Chronic multifocal symmetrical osteomyelitis"[ti] OR "chronic non bacterial osteomyelitis"[ti] OR "chronic non hematogenous osteomyelitis"[ti] OR "chronic recurrent multifocal osteomyelitis"[ti] OR "Chronic recurrent osteomyelitis"[ti] OR "Chronic sclerosing osteitis"[ti] OR "Chronic symmetric osteomyelitis"[ti] OR "Clavicular hyperostosis"[ti] OR "Clavicular periosteal new bone formation"[ti] OR "Condensing osteitis of the clavicle"[ti] OR "Diffuse sclerosing osteomyelitis"[ti] OR "Hyperostosis Syndrome"[ti] OR "Intersternocostoclavicular ossification"[ti] OR "Multifocal chronic osteomyelitis"[ti] OR "Multifocal sterile osteomyelitis"[ti] OR "Musculoskeletal syndromes associated with acne"[ti] OR

"non bacterial osteitis"[ti] OR "non bacterial osteomyelitis"[ti] OR "nonbacterial osteitis"[ti] OR "nonbacterial osteomyelitis"[ti] OR "Non-infectious osteitis"[ti] OR "Osteomyelitis of the bilateral clavicles"[ti] OR "pustulotic arthritis"[ti] OR "Pustulotic arthro-osteopathy"[ti] OR "Recurrent hyperostosis of the clavicle"[ti] OR "Sclerosis and hyperostosis of the manubrium sterni"[ti] OR "Spondylarthropathy with hidradenitis suppurativa and acne conglobata"[ti] OR "sternocostoclavicular osteoarthritis"[ti] OR "sternocostoclavicular pain"[ti] OR "sternocostoclavicular syndrome"[ti] OR "Subacute and chronic symmetrical osteomyelitis"[ti] OR "pustulotic arthro-osteitis"[ti] OR "pustulotic arthroosteitis"[ti] OR "sternocostoclavicular arthro-osteitis"[ti] OR "sternocostoclavicular arthroosteitis"[ti] OR "inter-sterno-costo-clavicular ossification"[ti] OR "intersterno costoclavicular ossification"[ti] OR "intersternocostoclavicular ossification"[ti] OR ("arthro-osteitis"[ti] AND "pustulosis"[ti])) AND english[la]

Systematic literature review: methods for appraising level of evidence

An appraisal of the quality of evidence was evaluated using the GRADE approach as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (2). GRADE was performed by ATL and checked with EMW and OMD.

- For each statement or outcome in this Summary of Evidence, level of evidence is rated as “very low”, “low”, “moderate”, or “high”.
- Level of evidence may differ per clinical context. For example, for a certain laboratory marker, we may have “high” level of evidence on how often or how much it is increased, but we have no studies (“very low”) level of evidence on whether the evaluation of this marker improves diagnostic certainty or patient outcomes. Similarly, we may have a fair estimate on the prevalence of asymptomatic lesions (“moderate”), yet no studies on whether screening for them has clinical consequence or improves patient outcomes (“very low”). In such cases, the level of evidence is based on clinical utility to improve patient outcomes. This is specified in the summary of evidence where relevant.
- Evidence deriving from observational studies pertaining to clinical features in CNO/SAPHO was initially categorized as “high” level of evidence as for prevalence estimates randomization does not increase the validity.
- Evidence deriving from randomized controlled trials (RCTs) was initially categorized as “high” level of evidence.
- Evidence deriving from non-randomized studies of intervention (NRSIs) was initially categorized as “low” level of evidence
- Level of evidence was lowered in the presence of the following factors:

    - Significant risk of bias due to e.g.: confouding (NRSIs), absence of allocation concealment or absence of blinding (RCTs), loss to follow-up, selective reporting of outcomes.
    - Inconsistency in findings across studies (heterogeneity)
    - Indirectness (poor applicability of study results to the population of adult CNO/SAPHO)
    - Imprecision (large uncertainty in effect estimates, or few/only one study)
- Level of evidence was decreased by one level for each factor that prompted "serious concerns", or by two levels for each factor that prompted "very serious" concerns.
    - If only one/very few studies were available for the question at hand, level of evidence was marked as "very low" on the base of very serious imprecision.
    - Due to the general scarcity of literature in adult CNO/SAPHO, the presence of publication bias, which traditionally also lowers the level of evidence, could not be properly assessed.
- Level of evidence was increased one level for each of the following factors:
    - Particularly large effect sizes
    - Presence of dose-response relationships
    - Plausible residual opposing confounding

Expert panel constitution

To assemble a diverse expert panel, several strategies were employed (see also **figure A**). Firstly, individuals who had participated in the physician survey study were invited. These individuals had been approached via European Alliance of Associations for Rheumatology (EULAR), Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases Network (ERN RITA), European Reference Network on Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET), European Reference Network on Rare Bone Disorders (ERN BOND), European Society of Endocrinology (ESE), European Calcified Tissue Society (ECTS), Rare Bone Disease Action Group, South East Asia and Pacific Area League Against Rheumatism (APLAR), Japan College of Rheumatology (JCR), American Society for Bone and Mineral Research (ASBMR), International Osteoporosis Foundation (IOF), International Federation of Musculoskeletal Research Societies (IFMRS)) (n=32) (1). Simultaneously, invitations were sent to first and last authors of CNO-related publications from the past 5 years, if not participated in the survey study already (n=46, total number of invited participants n=78). Moreover, the consensus initiative was disseminated via the aforementioned networks, with the addition of Childhood Arthritis and Rheumatology Research Alliance (CARRA), the American College of Rheumatology (ACR), Paediatric Rheumatology European Society (PRES), European Association of Nuclear Medicine (EANM) and the professional networks of EMW. This led to spontaneous applications from associated experts (n=21 in total). Recognizing the scarcity of expertise in CNO, the

initiative remained open to participants even after its formal commencement. ATL, OMD, and OB fulfilled the tasks of research fellow, supervising methodologist and chair, and minutes secretary respectively and were not eligible to formally vote.

Formulation of the expert consensus recommendations

A schematic overview of the process for the development of the recommendations is presented in Figure 1. A two-survey Delphi process was started in May 2023. Both Delphi surveys were executed using the General Data Protection Regulation-compliant system of Calibrum (Surveylet); as only participant's opinions were assessed, no personal details of individual patients were gathered. Statements for the first Delphi were derived from the Summary of Evidence by ATL, EMW and OMD, and piloted by two collaborators who had previously participated in the preparatory physician survey study (GC and HGZ) (see **S5** for Delphi survey 1, including data overview). Experts were invited to provide anonymous ratings for each statement on a 9-point Likert scale, along with the opportunity for free-text commentary, such as suggestions for reformulations or additional content.

In total, 44 experts completed Delphi survey 1, of whom 36 were invited and 8 had volunteered via relevant networks (see above). Consensus on a specific statement was defined as a median score of at least 7/9 (indicating positive agreement with the statement), with an interquartile range (IQR) no larger than 25% of the total scale (indicating acceptable spread of scores). Group median scores, degree of spread, bipolarity assessments, and stakeholder group differences were analysed with SPSS Statistics version 25, IBM corp.

The results, plus a compilation of free-text comments, were made available before the first digital pre-meeting (June 2023, attended by n=39/44 survey completers). This meeting involved a structured discussion on the results of the first Delphi survey, with emphasis on dissent items.

Afterwards, a second Delphi survey was developed (see **S6** for the survey, including data overview). At this point, 2 experts withdrew from the project due to time constraints, and 13 more had self-applied via relevant networks. Of the total of 55 enrolled experts, n=43 completed the second Delphi survey in August 2023.

Following similar analysis strategies, the results of the second Delphi survey set the framework for a two-day in-person meeting held in October 2023, attended by 36 out of 55 panel members. This meeting incorporated in-depth discussions across all domains of interest, including a session featuring presentations from imaging experts (ANC, TD, FS, JT), a session with representatives from the Dutch CNO patient association, and a round-table session on a future research agenda.

Of note that after the second Delphi round, we transitioned from formal level of agreement metrics to a more open discussion format. The discussions were thematically organized around key topics such as disease definition, naming conventions, diagnostics, and treatment strategies. Each session began with an overview of the data from both Delphi rounds to inform the discussions, which were led by an independent methodologist. In most cases, the panel was able to reach unanimous consensus on the text presented in the final manuscript. However, in instances of differing opinions, votes were held to capture the majority viewpoint while addressing opposing perspectives as considerations within the recommendations. Minutes were kept to be able to reiterate panel member's individual viewpoints in follow-up meetings and during manuscript revisions.

Synthesizing all information from the Summary of Evidence, the two Delphi surveys, and the two meetings, a draft recommendations were prepared and circulated for feedback. A digital follow-up meeting was held in February 2024 to resolve remaining points of discussion. Subsequently, a revised version of the document was circulated and amended. Eventually, the final recommendations were also rated by the full panel on a 0-10 Likert scale, with 0 indicating no agreement and 10 indicating full agreement. Level of agreement metrics are displayed in the recommendation tables with mean score and standard deviation, as well as the proportion of the panel rating the recommendation 8/10 or higher. Authorship on the eventual manuscript was determined based on active participation, meeting attendance, and adherence to the International Committee of Medical Journal Editors (ICMJE) authorship guidelines.

References cited in this supplement:

1. Leerling AT, Clunie G, Koutrouba E, Dekkers OM, Appelman-Dijkstra NM, Winter EM. Diagnostic and therapeutic practices in adult chronic nonbacterial osteomyelitis (CNO). Orphanet J Rare Dis. 2023;18(1):206.
2. Schünemann HJ HJ, Vist GE, Glasziou P, Akl EA, Skoetz N, Guyatt GH. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor: Cochrane; 2023.

2023 Consensus Initiative For Diagnosis and Management of Chronic Nonbacterial Osteomyelitis (CNO)/Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO)-Syndrome in Adults

Delphi round 1 – Analysis

Date: June 18th 2023

2023 consensus initiative for diagnosis and treatment of adult CNO-SAPHO

Methods for data analysis

- Consensus was assessed per statement by calculating medians and interquartile ranges of the 1-9 point Likert scale (1 representing total disagreement, 9 representing total agreement) and labelled as follows:

	Consensus	Median ≥ 7 with IQR ≤ 2.25 (25% of total scale)
	Near consensus	Median ≥ 7 with IQR ≤ 3 (30% of total scale)
	Negative consensus	Median ≤ 3 with IQR ≤ 2.25
	Near negative consensus	Median ≤ 3 with IQR ≤ 3
	Consensus at another level	Median 4-6, and IQR ≤ 2.25
	Near consensus at another level	Median 4-6, and IQR ≤ 3
	Dissent	Any median, and IQR > 3

- All open text comments are listed below the pertaining question
- Subgroup analysis was performed according to number of patients under clinical care (<10 vs. ≥10) and remarkable differences in scoring are discussed as appropriate, indicated with *
- Bipolarity analysis was performed by visual inspection of histograms and comparison of median and mode, and remarkable bipolarity is discussed as appropriate, indicated with **
- Conditional questions were further evaluated by comparing paired responses or correlations between related questions and discussed as appropriate, indicated with ***

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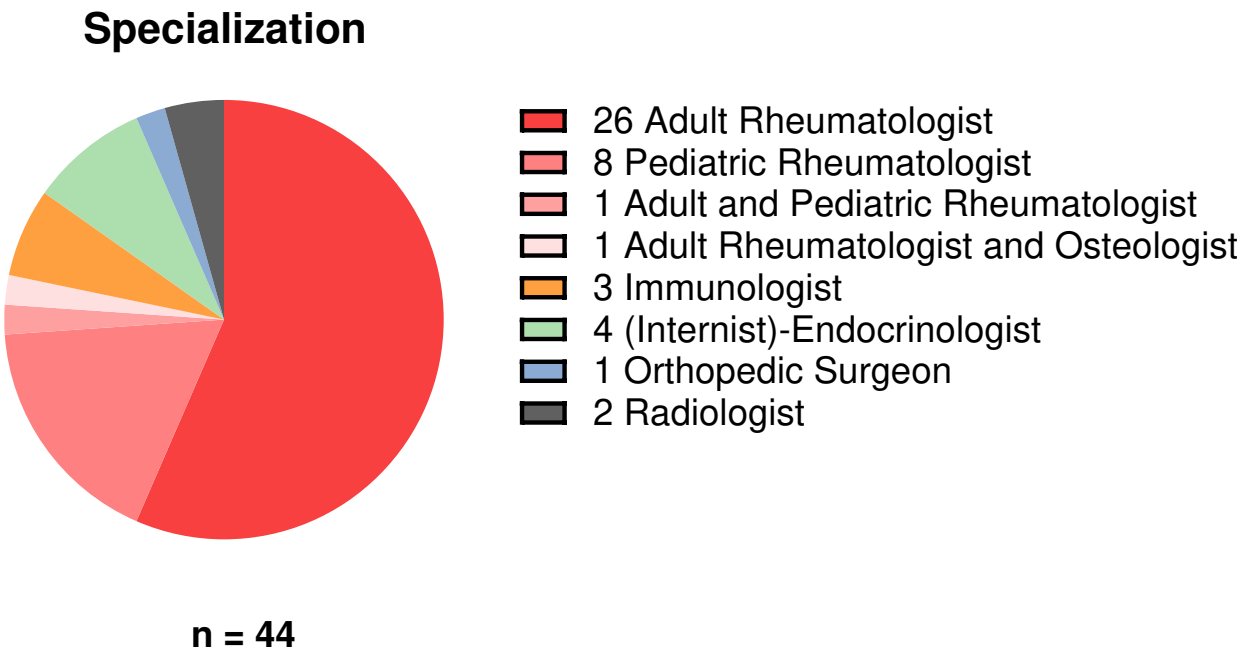
Results

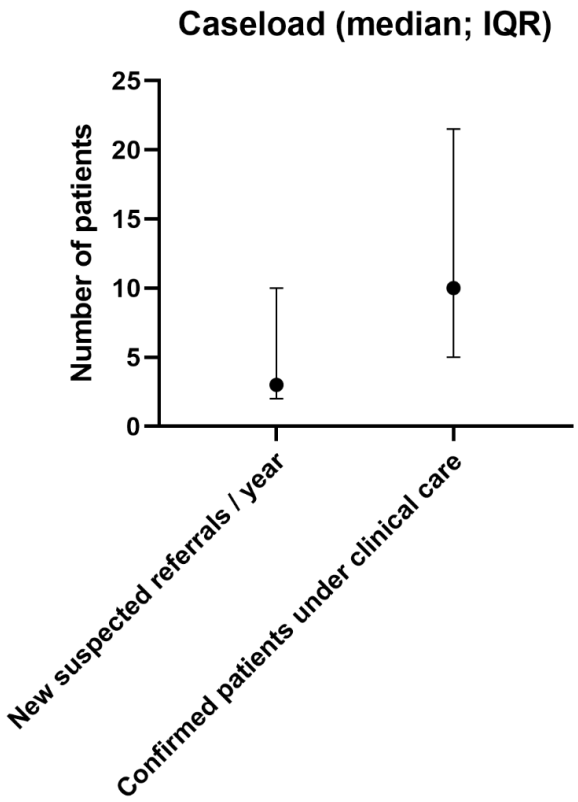
Number of completed responses: 44

Q0: What is your medical specialty?



2023 consensus initiative for diagnosis and treatment of adult CNO-SAPHO

Q0: How many patients do you have under your clinical care (new cases and follow-up?)



2023 consensus initiative for diagnosis and treatment of adult CNO-SAPHO

Theme 1: Disease (spectrum) definition

Q1. What are key clinical characteristics of "**adults with sterile bone inflammation**"?

Statement **"Adults with sterile bone inflammation, in our experience…"**	**Median (IQR)**	**Consensus assessment**
1. Usually present during midlife (30-50 years of age).	7.00 (6.50-8.00)	**Near consensus**
"Age at diagnosis is most often situated between 30 and 50 years of age. This is only descriptive and not important for diagnosis nor has to reflect onset"		
2. Are predominately female.	7.00 (5.00-8.00)	**Near consensus**
"Is descriptive but not relevant for diagnosis nor necessarily correct. Can be due to confounders, misdiagnosis, different disease expression or activity" "In my experience, at onset males are usually younger than females, and severe acne and/or hidradenitis suppurativa is their main skin involvement" "I confirm: not exclusively women, I did care for 3 men in the past, so in my situation I guess w:m 3:1 to 4:1"		
3. Mainly present with inflammatory bone pain, which can be chronic or relapsing-remitting.	8.00 (7.75-9.00)	**Consensus**
"Patients have pain in the back, at different locations of the appendicular skeleton. But how do you distinguish bone pain from other pain? It's redundancy, post hoc the pain is attributed to bone pain (usually after imaging). It can be a one episode event, relapsing-remitting or chronic. This is also of main interest for giving the condition a correct name. Bad terminology has extremely bad consequences on short and long term" "In my experience, the most frequent localizations of bone pain are the anterior chest wall and the dorso-lumbar spine"		
4. Often suffer from other auto-inflammatory comorbidities (general).	5.00 (3.00-7.00)	**Dissent**
"But no autoimmunity disorders" "Is important in giving the condition a correct name. Sterile -bone inflammation facultative + a, b, c" "Auto-inflammation syndromes are rare, maybe wording should be changed into auto-immune diseases" "There is overlap with clinical features of spondylo-arthritis in a proportion of patients" "We would clarify what does other auto-inflammatory comorbidities mean"		
5. May have/have had/develop sacroiliitis.	7.00 (5.00-8.25)	**Dissent**

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"In Japan and Report from China, Axial involvement is common in SAPHO especially in PAO (Pustulo-arthro osteitis), seen about 40%" "At least with most of the generally accepted definitions. Not sure that the SI-joint really is involved or whether is only / mainly the surrounding bone"		
6. May have/have had/develop peripheral synovitis.	7.00 (5.00-8.00) *Tended to be scored less positively by physicians caring for ≥10 patients vs. < 10 patients: median 6.00 (4.00-7.50) vs. median 7.00 (5.50-9.00), p=0.071.	**Near consensus**
"General problem of definitions of conditions with different possible features. Some persons which clearly can be classified as psoriatic arthritis have sterno-clavicular arthritis. Some persons only have real sterno-clavicular arthritis and no known other joint involvement; most with sterno-clavicular complaints have no arthritis but degenerative or ligament or no locomotoric conditions. The SC joint has a synovium, so nothing special" "Might be as an overlap to pure psoriatic arthritis" "Clinically apparent arthritis is not always peripheral synovitis" "Peripheral synovitis may be further specified if it is synovitis related to peripheral joint or also joint related to the anterior chest wall eg. sternoclavicular joint."		
7. May have/have had/develop peripheral erosive synovitis.	5.00 (3.00-7.00)	**Dissent**
"Only in cases which also meet the PsA criteria" "May also have spinal involvement: bony vertebral, spondylodiscitis" "Depends on definition of conditions" "Never saw a case of peripheral destructive synovitis" "Usually seen in SC joints/Sterno-coracoid joints" "Erosive if related to joints in the anterior chest wall. Not related to peripheral joints."		
8. May have/have had/develop dactylitis.	5.00 (3.00-6.00)	**Dissent**
"Only in cases which also meet the PsA criteria" "Is mainly tenosynovitis. Part of the spectrum or not? If psoriasis and palmar, plantar pustulosis are in, it has to be in too"		

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"If you add PsA in SAPHO, answer is yes, but we rarely see dactylitis in SAPHO/PAO"		
9. May have/have had/develop peripheral enthesitis.	5.50 (4.00-7.00)	**Dissent**
"If you add PsA in SAPHO, answer is yes, but we rarely see peripheral enthesitis in SAPHO/PAO" "Will be extremely difficult to distinguish from bone inflammation and even just mechanic stress. May have / had signs compatible with ..." "Definition of and detection of enthesitis is sometimes debatable...."		
10. May have/have had/develop pustulosis palmoplantaris.	8.00 (6.00-9.00)	**Near consensus**
"Is a part of disease definition, that's why commonly seen (self-fulfilling prophecy)" "More than 80% of SAPHO are PAO in Japan and China"		
11. May have/have had/develop psoriasis.	6.00 (6.00-8.00)	**Consensus at another level**
"Yes, but how to distinguish from PsA?" "In PPP/PAO in Japan, psoriasis is a rare in PPP patients. As for the term PPP in Japan, we believe it is classified into PPP Type A and Type B: PPP in Japan is pustular bacterid of the hands and feet proposed by Andrews and is classified as a type of pustulosis. We often see this lesions with concomitant local infection such as periodontal disease(eg, apical abscess) or/and recurrent tonsilitis. However, in Europe and the United States, pustular psoriasis of extremities reported by Barber is often considered to be PPP. PPP (or PPPP) as used in Western articles is often used as an abbreviation for palmo-plantar pustular psoriasis (part of psoriasis, not with concurrent infections), and together with acrodermatitis continua Hallopeau, as categorized into localized pustular psoriasis. The former is sometimes referred to as Andrews' Type A and the latter as Barber's Type B."		
12. May have/have had/develop severe acne.	7.00 (5.00-8.00)	**Near consensus**
"It is only 10-20% of total SAPHO in Japan (report in GRAPPA survey conducted in 2021)"		
13. May have/have had/develop hidradenitis suppurativa.	5.50 (3.00-7.00)	**Dissent**
"Very rarely seen" "Also other neutrophilic dermatoses" "Never saw a case of both diseases, but maybe..." "It is only 10-20% of total SAPHO in Japan (report in GRAPPA survey conducted in 2021)"		

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14. May have/have had/develop inflammatory bowel disease.	4.00 (3.00-6.00)	**Consensus at another level**
"Only relevant if prevalence exceeds prevalence in the general population (plus wrong sterile bone inflammation diagnosis)" "Could be, if CNO/SAPHO is seen as a special subgroup of spondylarthropathies, but I did not see a case" "Our GI department follows >1000 IBD patients. We really see IBD+SAPHO".		
15. May have/have had/develop uveitis.	3.00 (2.75-5.00)	**Consensus at another level**
"Could be, if CNO/SAPHO is seen as a special subgroup of spondylarthropathies, but I did not see a case" "I have never seen it"		
16. Show abnormalities during physical examination at presentation, e.g. swelling, local inflammatory signs.	8.00 (6.00-9.00)	**Near consensus**
"May show…"		
17. Are frequently past or active smokers.	5.00 (3.00-6.00)	**Near consensus at another level**
"Not relevant for diagnosis. May be a modulating factor. Kids usually don't smoke and can get CRMO." "As far as I remember my cases, all were non-smokers" "In patients with PPP its a known association, unclear what it is in patients without PPP, SCCH for instance" "High ex/current Smoking rate in PAO/SAPHO is seen in Japan"		

2023 consensus initiative for diagnosis and treatment of adult CNO-SAPHO

Q2: What are key imaging characteristics of "**adults with sterile bone inflammation**"?

Statement **"Adults with sterile bone inflammation, in our experience…"**	**Median (IQR)**	**Consensus assessment**
1. Display osteosclerosis on imaging <u>at presentation.</u>	7.00 (5.00-7.75)	**Near consensus**
"Depends on time of onset of symptoms until specialists evaluation, which can be many months to years" "Since bone marrow edema (acute osteitis) is the active/early signs of the disease, sclerosis is somewhat later stage"		
2. Display osteosclerosis on imaging <u>during follow-up.</u>	8.00 (7.00-9.00)	**Consensus**
"Since bone marrow edema (acute osteitis) is the Active/early signs of the disease, sclerosis is somewhat later stage"		
3. Display osteolysis on imaging <u>at presentation.</u>	6.00 (4.00-7.00)	**Near consensus at another level**
"But typical erosions for example in SCCH" "May display osteolysis on imaging"		
4. Display osteolysis on imaging <u>during follow-up.</u>	6.00 (5.00-7.00)	**Consensus at another level**
"May display osteolysis on imaging" "May display, in axial disease?"		
5. Display hyperostosis on imaging <u>at presentation.</u>	6.00 (5.00-7.75)	**Near consensus at another level**
"Many patients present with hyperostosis at presentation, but in many cases the diagnosis is several years later than the onset" "If it is delayed diagnosis, hyperostosis is seen at presentation" "May display hyperostosis on imaging"		
6. Display hyperostosis on imaging <u>during follow-up.</u>	8.00 (6.25-9.00)	**Near consensus**
"May? Probably minimal hyperostosis in most cases."		
7. Display specific signs in bone on MRI on fat suppression sequences <u>at presentation.</u>	8.00 (6.00-8.00)	**Consensus**
"By no means specific."		

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"Specific? better typical, because tumorous infiltration or bacterial infection may look alike in MRI" "Display increased signal within the bone marrow on fluid-sensitive images" "Bone marrow edema(acute osteitis), STIR(T2 Fat suppression) high, T1 Low lesion"		
8. Display specific signs in bone on MRI on fat suppression sequences during follow up.	7.00 (5.00-8.00)	**Near consensus**
"The MRI findings seem to be less typical during longterm disease in my experience" "Display increased signal within the bone marrow on fluid-sensitive images" "Consider to ask questions that both relate to active and chronic signs of bone inflammation" "Fat-deposition , STIR(T2 Fat suppression) low, T1 high lesion. and hyperostosis/ankylosis/osteolytis lesions can be seen during follow up"		
9. Display increased uptake/diffusion on quantitative imaging techniques like nuclear imaging or diffusion weighted Magnetic Resonance Imaging (MRI) at presentation.	8.00 (6.00-8.75)	**Near consensus**
"Not in inactive disease" "Display increased tracer uptake on bone scintigraphy. (The DWI can be covered on the MRI section above as it is a different imaging modality to nuclear medicine)" "May specify if increased uptake is at presentation or during follow up. Increased uptake is in this case scored at presentation."		

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Q3. What is the preferred name of the clinical entity?

Note: henceforth, the name CNO/SAPHO is used throughout this document for the sake of clarity, but this name is subject to change according to the outcome of Q2.

Statement **"The preferred name for the clinical entity of "adults with sterile bone inflammation" is…"**	**Median (IQR)**	**Consensus assessment**
1. Chronic nonbacterial osteomyelitis (CNO) in all patients.	6.00 (3.00-8.00) ** Bipolarity in responses observed: n=17 scored as 1-3 (strong disagreement) and n=19 as 7-9 (strong agreement).	**Dissent**
"This might be used as an umbrella term with subsets, maybe like SLE / lupus nephritis." "I would prefer one grouping term with needs to: - adequately describe the main feature of the disease - comprehend all possible subclasses and phenotypes - is acceptable by the current medical community 'it rings a bell'. So maybe CNO/SAPHO might be better at the moment, with a review in x years."		
2. Chronic nonbacterial osteomyelitis (CNO) in case of sterile bone inflammation only, but synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO)-syndrome in case of bone plus skin and/or joint inflammation.	7.00 (3.00-9.00) ** Some bipolarity in responses observed: n=13 scored as 1-3 (strong disagreement) and n=24 as 7-9 (strong agreement).	**Dissent**
"CNO is a more pathologic entity, whereas SAPHO is a more clinical diagnosis." "CNO or CRMO if only bone is involved - that's my current wording :-) sometimes even incomplete SAPHO syndrome." "Also, you can say incomplete SAPHO, in case of osteitis, hyperostosis, and synovitis, without skin involved." "This could be useful to discriminate the two forms (isolated bone inflammation from joint and skin disease) for clinical or translational studies."		
3. Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO)-syndrome in all patients.	3.00 (1.00-5.00)	**Dissent**
"Most of the cases are incomplete SAPHOs." "If only bone is involved, I would miss other features of a syndrome - one might probably solve this with wording 'incomplete SAPHO syndrome'." "It's easier in routine care and covers the entire spectrum, but not appropriate for studies."		

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4. Chronic nonbacterial osteomyelitis/synovitis, acne, pustulosis, hyperostosis, osteitis (CNO/SAPHO) in all patients.	4.50 (1.00-8.00) ** Bipolarity in responses observed: n=17 scored as 1-3 (strong disagreement) and n=15 as 7-9 (strong agreement).	**Dissent**
"A main problem is that many terms are used, and this creates confusion. An effort should be made to establish a term that replaces all previously used terms. The combined term CNO/SAPHO is probably the term that could be used to describe all cases." "This combination is not currently used."		
5. Sternocostoclavicular hyperostosis (SCCH) in all patients.	1.00 (1.00-3.75)	**Near negative consensus**
"This would only allow such patients into the definition"		
6. Pustulotic arthro-osteitis or pustolotic arthro-osteopathy (PAO) in all patients.	1.00 (1.00-2.00)	**Negative consensus**
7. Chronic recurrent multifocal osteomyelitis (CRMO) in all patients.	3.00 (1.00-5.00) *Tended to be scored less positively by physicians caring for ≥10 patients vs. < 10 patients: median 2.00 (1.00-4.00; near negative consensus) vs. median 4.00 (2.00-7.50), p=0.073.	**Dissent**
"In Germany, a widely used name." "A commonly used term, but this wording requires multifocality, while some patients have clinical symptoms only in one bone region." "This entity is more frequent in children."		

2023 consensus initiative for diagnosis and treatment of adult CNO-SAPHO

Q4. What physicians preferably see and treat adult CNO/SAPHO?

Statement **"Patients should preferably be under treatment of a…"**	**Median (IQR)**	**Consensus assessment**
1. Bone-oriented specialist, specifically rheumatologist, internist, endocrinologist, immunologist or osteologist.	8.00 (7.00-9.00)	**Consensus**
2. Any bone-oriented specialist, those with surgical background like orthopedic surgeon trauma surgeon included.	3.00 (1.00-5.25)	**Dissent**
	*Tended to be scored less positively by physicians caring for ≥10 patients vs. < 10 patients: median 3.00 (1.00-4.50) vs. median 4.00 (2.50-6.50), p=0.074.	
3. Any specialist, not necessarily bone-oriented, dermatologists included.	2.50 (1.00-3.50)	**Near negative consensus**
4. Preferably a rheumatologist.	8.00 (6.75-9.00)	**Consensus**
"From a patients perspective one specialist is preferred in cases of a rare chronic disease to bundle expertise. From a disease perspective having rheumatologists and endocrinologists working together with other specialists is preferable as multiple organs can be targeted."		

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Theme 2: Preferred diagnostics

Q5: Which laboratory investigations are indicated for suspected adult CNO/SAPHO?

Statement **"The laboratory diagnostic work-up of suspected adult CNO/SAPHO should include…"**	**Median (IQR)**	**Consensus assessment**
1. Generic inflammation markers (full blood count with leucocyte differentiation, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)).	9.00 (8.00-9.00)	**Consensus**
"Although not all patient have elevated APR"		
2. (Bone-specific) alkaline-phosphatase (bsALP).	7.00 (5.00-9.00)	**Dissent**
"Very stable marker, which (if increased value seen at diagnosis) can be a good marker during follow-up." "Sclerosis + increased APh may also point to Paget's disease, so important for differential diagnosis."		
3. Serum calcium, phosphate, parathyroid hormone.	8.00 (6.00-9.00)	**Near consensus**
"I think a hyperparathyroidism is a clinically different disease but maybe not? Never heard of an association." "For differential diagnosis" "Because of treatment with bisphosphonates"		
4. Bone markers osteocalcin, serum procollagen type I N propeptide (P1NP) and C-terminal telopeptide (CTx).	5.00 (3.00-6.25)	**Dissent**
"Maybe for research purposes." "Pre-analytic difficulties, that's why I would give a modest recommendation..." "Unclear to me what is known about the diagnostic and prognostic value of CTx and other markers in clinical practice." "It could be optime but these kinds of analyses are not available in many centers."		
5. Anticyclic citrullinated peptide antibodies (anti-CCP) and rheumatoid factor (RF).	3.00 (1.00-5.00)	**Dissent**
"If associated synovitis." "Only in cases with an unclassified peripheral synovitis. The clinical image is often very different in my opinion."		

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"If the patient has synovitis in SC/sterno-coracoid joints." "Only with peripheral synovitis, which is infrequent."		
6. Anticyclic citrullinated peptide antibodies (anti-CCP) and rheumatoid factor (RF), only if presentation includes peripheral synovitis.	7.00 (3.75-9.00)	**Dissent**
"This would routinely be done in a rheumatologic first contact for every joint inflammation patient for differential diagnosis, but I would not insist on this for the diagnosis of SAPHO." "Peripheral synovitis/arthralgia." "Still depending on the other presenting features, i.e., axial features."		
7. Anti-nuclear antibodies and differentiation.	3.00 (1.00-5.00)	**Dissent**
"Will be commonly done at rheumatologists' first visit, but not needed for the diagnosis of SAPHO." "In adult rheumatology, ANA-positive autoimmune disorders do not resemble CNO/SAPHO, but in the work-up of younger patients, it might have some value." "Not mandatory" "Before anti-TNF."		
8. HLA-B27.	5.50 (4.00-8.25)	**Dissent**
"Only in case of axial involvement." "Will be commonly done at rheumatologists' first visit, especially in inflammatory back pain or sacroiliitis in imaging, but not needed for the diagnosis of SAPHO." "Ambivalent because axial spondyloarthritis is considered in the differential diagnosis and HLA-B27 is part of the ASAS spondyloarthritis criteria. Nevertheless, it adds only diagnostic value in doubtful cases and has little diagnostic value on its own. Screening in all inflammatory back pain reduces sensitivity of SpA criteria and results in a substantial part of misclassification of regional back pain syndromes. In my opinion, if SpA is obvious from imaging, I don't have to test HLA-B27. And likewise, if SpA is unlikely from a clinical point of view, it doesn't add enough diagnostic value to change the diagnosis." "Not mandatory."		

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9. HLA-B27, only if presentation includes inflammatory back pain.	6.00 (3.00-8.25)	**Dissent**
"30% of patients with PsA are asymptomatic" "Ambivalent because axial spondyloarthritis is considered in the differential diagnosis and HLA-B27 is part of the ASAS spondyloarthritis criteria. Nevertheless, it adds only diagnostic value in doubtful cases and has little diagnostic value on its own. Screening in all inflammatory back pain reduces sensitivity of SpA criteria and results in a substantial part of misclassification of regional back pain syndromes. In my opinion, if SpA is obvious from imaging, I don't have to test HLA-B27. And likewise, if SpA is unlikely from a clinical point of view, it doesn't add enough diagnostic value to change the diagnosis."		
10. Fecal calprotectin.	3.00 (1.75-6.00)	**Dissent**
11. Fecal calprotectin, only if presentation includes enteropathic symptoms suggestive of IBD.	8.00 (5.00-9.00)	**Dissent**
12. Serum angiotensin-converting enzyme (ACE) and soluble IL-2 receptor levels.	2.00 (1.00-3.25)	**Negative consensus**
"I prefer to use only the sIL2-R, not ACE." "I think the diagnostic value of these tests needs to be revised or will be revised in the near future because they do not perform so well in cases of sarcoidosis."		
13. Serum angiotensin-converting enzyme (ACE) and soluble IL-2 receptor levels, only if presentation includes symptoms suggestive of sarcoidosis.	7.00 (5.00-8.00)	**Near consensus**

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Q6: What type of diagnostic imaging is preferred for suspected adult CNO/SAPHO?

Statement **"In suspected adult CNO/SAPHO, the preferred imaging modality is…"**	**Median (IQR)**	**Consensus assessment**
1. Computed tomography (CT)	5.50 (3.00-7.75)	**Dissent**
	** Bipolarity in responses observed: n=12 scored as 1-3 (strong disagreement) and n=20 as 7-9 (strong agreement).	
"It depends on manifestation/localization." "Perhaps early in the diagnostic odyssey if malignancy is suspected." "If contraindication for MRI." "I think the preferred imaging modality is ideally the one with the best predictive properties. Do we know and what is the gold standard then? Also, availability plays a part as PET-CT is not always available. Fluor-PET is only in a few centers available, as is Whole-body MRI. We only have CT and MRI in our center, which results in a work-up that is maybe not the preferred work-up. When PCTechnetium-labeled hydroxymethylene diphosphonate single photon emission computed tomography. When PCT-CT is unavailable, CT + SPECT/WBBS is a good starting point, maybe whole body MRI as an alternative if available." "Good for a targeted (painful) region."		
2. Whole body bone scintigraphy (WBBS).	5.00 (3.00-7.75	**Dissent**
"Adequate for screening multiple osteitis lesions." "If MRI not available." "Commonly used."		
3. Technetium labeled hydroxymethylene diphosphonate single positron emission computed tomography ([^{99m}Tc]Tc-HDP SPECT/CT)	5.00 (3.00-7.00)	**Dissent**
"I have no experiences." "Limited access." "If to detect subclinical localizations to establish monostotic or polyostotic forms."		

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"The best for mapping/found asymptomatic lesions."		
4. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) with CT (FDG-PET/CT)	3.00 (2.00-5.00)	**Near negative consensus**
"I have no experience with PET-CT personally." "Rarely available/reimbursed."		
5. Sodium fluoride positron emission tomography with CT ([18F]NaF-PET/CT)	4.00 (2.00-6.00)	**Dissent**
"Probably a good or better alternative to Tc-SPECT/CT but not widely available." "Limited access in some countries." "We only do it for research; however, I consider whole body MRI the best option." "Rarely available/reimbursed." "But not available in my center." "This might become the best in the future, but limited availability and difficult protocol/logistics around the fluoride." "Might be useful but needs more studies (many aspecific lesions) and requires an experienced reader."		
6. (Whole body) Magnetic Resonance Imaging (MRI).	8.00 (5.00-9.00)	**Dissent**
"Current routine is clinically focused, not whole body." "Regional MRI of areas with suspected CNO. Whole-body MRI can be used to screen for asymptomatic lesions or in patients with multiple suspected sites of CNO." "Good, but the access to this imaging could be difficult in routine care. As CT, it should be used for a targeted/painful body region." “Suggest also to ask question about MRI of the anterior chest wall”		
7. Diffusion weighted (whole body) Magnetic Resonance Imaging (DW-MRI).	5.00 (3.00-7.00)	**Dissent**
	** Bipolarity in responses observed: n=13 scored as 1-3 (strong disagreement) and n=18 as 7-9 (strong agreement).	

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"Not always available."

"It's very difficult to propose a preferred imaging method. We don't have comparative studies or detailed descriptions of the value of bone inflammation for most of the mentioned techniques. 99Tc scintigraphy without SPECT-CT, however, is only an option if SPECT-CT isn't available. CT alone is excellent for imaging hyperostosis or bone condensation but doesn't capture activity. MRI and FDG PET can capture extra-skeletal features but are less easily available, and reading all images carefully and correctly is difficult. Imaging will depend on the scope. What may be needed in therapy studies most often will not be needed in clinical practice."

"Not aware whether in use in my region."

"It is a good imaging technique, but it isn't available."

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Q7: Are there other specific imaging considerations in adult CNO/SAPHO?

Statement:	**Median (IQR)**	**Consensus assessment**
1. CT (either alone or with PET/SPECT) is preferred over MRI for imaging the anterior chest wall.	5.50 (3.25-8.00)	**Dissent**
	** Bipolarity in responses observed: n=11 scored as 1-3 (strong disagreement) and n=20 as 7-9 (strong agreement).	
"Undecided - radiologists' task ;-)" "Combination can be very also useful, as MRI adds information on active inflammation. Note that new CT and MRI imaging techniques are rapidly developing, and both techniques will become better in the near future for combining information on structural lesions and active inflammation."		
2. Plain X-rays have no value in the work-up of suspected CNO/SAPHO.	5.00 (2.00-7.00)	**Dissent**
	*Tended to be scored more positively by physicians caring for ≥10 patients vs. < 10 patients: median 5.00 (3.00-7.00) vs. median 4.00 (1.00-5.50), p=0.039.	
"They are usually what brings the patient into the clinic in the first place." "They still have value to see damage, but sensitivity and specificity are low." "Because easily accessible, they are still often used. Maybe helpful in spinal involvement (typical sclerosis of one or more complete vertebrae) or sacroiliitis." "They can be useful for easy access for the evaluation of sacroiliac involvement." "In case of delayed diagnosis patients, the answer is yes."		
3. Whole body imaging (WBBS, PET/CT, whole body MRI, whole body CT) is advisable in all patients (even if presenting with seemingly limited disease).	8.00 (5.25-9.00)	**Dissent**
“I tend to do whole body imaging, but I doubt what the added value is in the mature patients with only sternal complaints”		
4. Axial skeletal imaging with MRI should be done in patients with a history of inflammatory back and/or posterior pelvis and/or neck pain.	8.00 (7.00-9.00)	**Consensus**
"Not with a history of it, it may be useful in patients who still complain about it."		

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"Unless conventional radiology already has shown SpA features. MRI is the second step in case of doubt."
"Axial involvement is common."
“Axial skeletal imaging should be specified also to include question about MRI of SI-joints”.

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Q8: In what cases is a bone biopsy indicated as part of the diagnostic work-up?

Statement **"Bone biopsies.."**	**Median (IQR)**	**Consensus assessment**
1. Are indicated in all suspected CNO/SAPHO patients to rule out malignancy or infection.	2.50 (1.00-5.25)	**Dissent**
"Never had a case with malignancy in the differential diagnosis, but they may exist." "In GRAPPA survey, 80% of specialists do not perform biopsy upon diagnosis."		
2. Should be considered in difficult CNO/SAPHO where suspicion of malignancy or infection is high.	9.00 (8.00-9.00)	**Consensus**
"Where suspicion of malignancy or infection is high, always consider it in an early stage." "Mainly for unifocal bone lesion."		

Theme 3: Treatment

Q9: What are treatment goals in adult CNO/SAPHO?

Statement **"Treatment goals in adult CNO/SAPHO are…"**	**Median (IQR)**	**Consensus assessment**
1. To relieve patient symptoms.	9.00 (8.75-9.00)	**Consensus**
2. To help maintain/regain functional capacity.	9.00 (8.00-9.00)	**Consensus**
3. To reduce inflammation to the lowest level possible.	8.00 (7.00-9.00)	**Consensus**
"Don't treat lab values, treat patients." "My first aim is the pain of the patient/quality of life. 'Lowest level possible' sounds to me like a marketing slogan for pharmaceutical companies producing costly biologicals." "It is the assumption that statement one and two follow from disease control (statement three and four) in diseases like rheumatoid arthritis. It is important to take patients' preferences into account. We do a lot of research on patient preferences in rheumatic diseases."		
4. To prevent structural bone and joint damage.	8.00 (7.00-9.00)	**Consensus**
"Structural bone and joint damage for most patients is secondary. But nearly all want to be free of pain and be able to function." "A core set of outcome variables should be defined for research questions regarding interventions/therapy. I would think all of the above + possible additional quality of life and/or imaging outcomes (inflammation next to structural damage)."		

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Q10: Which patient reported, biochemical and radiological measures do we recommend to be collected to monitor disease course?

Statement **"Follow up in adult CNO/SAPHO should include … to monitor disease course"**	**Median (IQR)**	**Consensus assessment**
1. Overall pain scores.	9.00 (7.00-9.00)	**Consensus**
"The scores are useless in individual patients but useful in studies." "A patient panel interview or study is warranted in case this exercise is to determine relevant outcome measures for CNO patients."		
2. Pain scores stratified for inflammatory bone pain, mechanic pain, and overall pain.	7.00 (3.25-9.00)	**Dissent**
	** Bipolarity in responses observed: n=11 scored as 1-3 (strong disagreement) and n=24 as 7-9 (strong agreement).	
"Most patients are not distinguishing." "Many patients cannot differentiate inflammatory vs. mechanical pain. Maybe better to ask for pain during exercise/the day vs. also suffering from pain at rest/at night." "It would be difficult to ask patients to differentiate between the two types of pain. There could be additional scores for morning discomfort/stiffness, night pain, and physician's disease activity assessment." "I doubt if this is instructable on a larger scale. An alternative could be using index joints/areas in study settings."		
3. Range of motion of joints surrounding lesion areas.	7.00 (5.00-8.75)	**Dissent**
"Where possible." "It can be helpful on an individual basis but not for general monitoring."		
4. Functional capacity.	8.00 (7.00-9.00)	**Consensus**
"How do you evaluate this correctly? Scores like HAQ or BASDAI / BASFI don't work for individual patients but are useful in comparative studies if the groups are big enough."		
5. Inflammation markers (blood count/ESR/CRP).	8.00 (7.00-9.00)	**Consensus**
"CRP!"		

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"If increased in the beginning, it might be helpful markers during follow-up. If very high, it may point to infection. However, maybe 50% of patients have normal CRP and ESR. Blood count is normally unremarkable in SAPHO, but it may point to the differential diagnosis of bacterial infection (including procalcitonin)."		
6. (Bone specific) Alkaline phosphatase (bsALP).	5.00 (3.25-6.00)	**Near consensus at another level**
	***Positively correlated to score of Q5.2 (is bsALP indicated for suspected adult CNO/SAPHO?); Spearman's rho 0.431, p=0.004.	
"We do not have these exams widely accessible." "Probably not reliable for assessing outcomes but relevant for safety." "If increased at the time point of starting a therapy, then helpful for monitoring. If normal at the beginning, no use." "I do not know its value."		
7. Bone markers osteocalcin, serum procollagen type I N propeptide (P1NP) and C-terminal telopeptide (CTx).	4.50 (3.00-5.00)	**Consensus at another level**
	***Positively correlated to score of Q5.3 (are P1NP and CTx indicated for suspected adult CNO/SAPHO?); Spearman's rho 0.463, p=0.002.	
"Probably not very reliable for outcomes but relevant in studies." "Selected cases only. Difficult pre-analytical situation." "I do not know its value."		
8. Imaging: modality that can monitor structural changes resulting from inflammation (e.g. hyperostotic changes, erosive changes).	7.00 (5.00-8.00)	**Near consensus**
"In studies or if doubts in diagnosis or treatment results." "Not needed in easy cases with very successful treatment." "Regional MRI or WB-MRI preferred."		

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"Only if it informs shared decision-making regarding disease-modifying therapies. So in case primary or patient-related outcome measures are not reached." "MRI once a year."		
9. Signs of acute inflammatory activity assessed by WBBS or SPECT.	5.00 (3.00-6.00)	**Near consensus at another level**
	***Positively correlated to score of Q6.2 (is WBBS preferred as diagnostic imaging for adult CNO/SAPHO?); Spearman's rho 0.528, p<0.001.	
"In studies or doubts on treatment results." "Might be discussed in cases with new pain/regions involved. Not very useful for general follow-up." "Only if it informs shared decision-making regarding disease-modifying therapies." "Radiation exposure."		
10. Signs of acute inflammatory activity assessed by PET, MRI, or DW-MRI.	7.00 (5.00-8.00)	**Near consensus**
"In studies or if doubts on diagnosis or treatment results." "Not needed in easy-going cases." "Signs of acute inflammation on imaging, preferably MRI." "WB-MRI preferred (with STIR images)." "Only if it informs shared decision-making regarding disease-modifying therapies."		

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Q11: Which of these measures determine treatment success or failure?

Statement	**Median (IQR)**	**Consensus assessment**
1. Overall pain scores.	8.00 (7.00-9.00)	**Consensus**
2. Pain scores stratified for inflammatory bone pain, mechanic pain, and overall pain.	7.00 (5.25-8.75)	**Dissent**
	***Positively correlated to score of Q11.2 (should these stratified parameters be collected during follow-up?); Spearman's rho 0.908, p<0.001.	
"Additional scores such as morning discomfort/stiffness, night pain could be used in addition to pain scores to capture symptoms due to inflammation (versus mechanical pain or pain sensitisation)."		
3. Range of motion of joints surrounding lesion areas.	7.00 (5.00-8.00)	**Near consensus**
4. Functional capacity.	7.50 (6.00-9.00)	**Near consensus**
"How to assess?"		
5. Inflammation markers (blood count/ESR/CRP).	7.00 (5.00-9.00)	**Dissent**
"CRP"		
6. (Bone specific) Alkaline phosphatase (bsALP).	4.00 (2.00-6.00)	**Dissent**
"Influenced by bishosphonates whether they worded or not."		
7. Bone markers osteocalcin, serum procollagen type I N propeptide (P1NP) and C-terminal telopeptide (CTx).	4.00 (2.00-5.00)	**Near consensus at another level**
"Influenced by bishosphonates whether they worded or not."		
8. Imaging: modality that can monitor structural changes resulting from inflammation (e.g. hyperostotic changes, erosive changes).	7.00 (5.00-8.00)	**Near consensus**
"Only in studies" "The possibility of reaching significant improvement on pain and functional PRO is likely to be influenced of the presence of structural lesions and the location of these lesions (for instance SC-abnormalities can have a high impact). This needs to be taken into account when determining treatment goals in RCTs and in clinical practice."		
9. Signs of acute inflammatory activity assessed by WBBS or SPECT.	5.00 (3.00-7.00)	**Dissent**

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	** Bipolarity in responses observed: n=12 scored as 1-3 (strong disagreement) and n=15 as 7-9 (strong agreement).	
"Only in studies"		
10. Signs of acute inflammatory activity assessed by PET, MRI, or DW-MRI.	7.00 (5.00-8.00)	**Near consensus**
"Only in studies" "Signs of acute inflammatory activity assessed by imaging, preferably MRI." "Bone marrow edema on MRI can be regarded as a sign of inflammation, but it is also frequently found in osteoarthritis and other structural lesions (like those found in CNO/SAPHO/SCCH) and also after 'normal' or physiological mechanical stress (sports, etc.). Not always easy to determine the relevance." "Only for treatment failure in routine care. Not recommended to confirm treatment success. Maybe for assessing treatment efficacy for studies."		

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Q12: Is step 1 treatment with non-steroidal anti-inflammatory drugs (NSAIDs) reasonable in all patients?

Statement **"NSAIDs are reasonable as a step 1 treatment…"**	**Median (IQR)**	**Consensus assessment**
1. In all patients, irrespective of disease extent or severity, in absence of contra-indications (CIs).	8.00 (5.75-9.00)	**Dissent**
"I think the next comments can be summarized to extra-bone manifestations, and yes, they have to be treated separately. They reduce pain in most patients and can therefore even help to sustain the diagnosis or not." "...and used in high to maximal doses for at least 2-4 weeks (clinically comparable to axial spondyloarthritis). Please use NSAIDs/coxibs because some people still tend to differentiate both." "I tend to favor this approach unless robust scientific evidence points to a much better outcome in case of strategy Q12-2 and/or Q12-3. Even in SpA both axial and peripheral NSAIDs are still first-line and are advised for at least two courses with adequate duration (total of 4 weeks minimum)."		
2. Generally in all patients, but those with spinal lesions warrant step 2 treatment from the start.	7.00 (5.00-9.00)	**Dissent**
"Will depend of the extend of spinal lesions" "As far as I know, there are no data" "Step 2 treatment covers many agents and approaches and is a very broad group. May need to consider discussing what is the next step after NSAID. Options include traditional DMARD, biological DMARD (TNFi vs non-TNF), and IV bisphosphonate."		
3. Generally in all patients, but those with significant synovitis warrant step 2 treatment from the start.	7.00 (5.00-8.25)	**Dissent**
"As far as I know, there are no data" "I would discriminate oligo- (try NSAID) to polyarthritis (go for step 2)"		
4. Generally in all patients, but those with dactylitis warrant step 2 treatment from the start.	7.00 (5.00-8.00)	**Near consensus**
	*Scored more positively by physicians caring for ≥10 patients vs. < 10 patients: median 7.00 (5.50-8.50; near consensus) vs. median 5.00 (4.00-7.50), p=0.047.	
5. Generally in all patients, but those with marked biochemical inflammation warrant step 2 treatment from the start.	5.00 (3.75-7.00)	**Dissent**
	**Some bipolarity in responses observed: n=10 scored as 1-3 (strong	

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	disagreement) and n=17 as 7-9 (strong agreement).	
"As far as I know, there are no data" "Unless it is a proven better strategy in achieving remission or preventing structural damage."		
6. Generally in all patients, but those already presenting with significant bone/joint damage warrant step 2 treatment from the start.	7.00 (5.00-9.00)	**Dissent**
"If bisphosphonates or RANK-L inhibition prove to be effective in reduction of bone damage I would combine this with NSAIDs from the start."		
7. After failure of one NSAID, a second trial with another NSAID should be considered before initiating step 2 treatment.	3.50 (2.00-6.00)	**Dissent**
"Depends on the NSAID or COXIB used. If Ibuprofen (most often underdosed use), Diclofenac, Meloxicam, Piroxicam full dose, or Etoricoxib at ankylosing spondylitis dose should be tried." "Another NSAID or COXIB." "After the failure of one NSAID, a second trial with another NSAID could be considered in patients with disease limited to few sites and/or mild symptoms." "To try a second NSAID is okay, as long as there are no features of more severe disease and/or spine involvement." "The time period for both trials as well as the total period after which effectiveness can be determined should be defined."		

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Q13: How long should patients preferably be treated with NSAIDs before considering step 2 treatment?

Statement **"NSAID treatment (for one agent) should last…before declaring NSAID-refractory disease and considering step 2 treatment."**	**Median (IQR)**	**Consensus assessment**
1. 1 week	2.00 (1.00-6.00)	**Dissent**
"I prefer a trial period of 2 weeks in higher to maximal approved dose" "For one NSAID."		
2. 1 month	8.00 (4.75-8.25)	**Dissent**
	*Scored more positively by physicians caring for ≥10 patients vs. < 10 patients: median 8.00 (6.50-9.00; near consensus) vs. median 5.00 (2.00-8.00), p=0.047.	
"At least 2 weeks of treatment per NSAID." "With NSAID rotation in this period."		
3. 3 months	5.00 (2.00-7.00)	**Dissent**
	** Bipolarity in responses observed: n=15 scored as 1-3 (strong disagreement) and n=15 as 7-9 (strong agreement).	
"This is only acceptable if pain is reduced significantly (e.g., >50%). If there is no real improvement, I would not like my patients with severe symptoms to suffer." "This is a difficult question in the light of absence of evidence. It is determined by: When is a first effect to be expected? When is maximum effect to be expected? What time is needed for development of structural lesions? What is the total window of opportunity? Experience and analogy to SpA say one might examine the effect after one month and then decide to switch in case of nonresponse and continue in case of partial response with another evaluation after 3 months. Maybe this is one for the research agenda." "Corticosteroids could be recommended for reducing short recurrent flare-ups, but it might be too long of a duration for a single painful lesion."		

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Q14: What are treatment considerations for step 2 and 3 treatment in NSAID-refractory adult CNO/SAPHO?

Statement **General preferences** **"In absence of contraindications or specific indications for another treatment…"**	**Median (IQR)**	**Consensus assessment**
1. Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) like methotrexate, sulfasalazine, leflunomide are the preferred treatment.	5.00 (3.00-7.00)	**Dissent**
"In case of associated arthritis, methotrexate is a recommended treatment option. However, it has to be dosed high enough, as there may have been underdosing in the reports. Leflunomide is not the first choice but may be used in some situations. Sulfasalazine may be added on if there is concurrent inflammatory bowel disease." "This will strongly depend of the extend of the disease. and distribution of bone lesions. Eg if only synovitis in one sternoclavicular joint." "Methotrexate is recommended only if peripheral joints are involved." "In Asia, we also use igratimod as a conventional synthetic disease-modifying antirheumatic drug (csDMARD)."		
2. Intravenous bisphosphonates are the preferred treatment..	7.00 (5.00-9.00)	**Dissent**
"In case of predominantly bone involvement, bisphosphonates can be helpful for bone-related symptoms. They could be considered as a second-line treatment option specifically for bone involvement. Zoledronate is generally more convenient to use compared to pamidronate." "Yes, bisphosphonates are relatively cheap and effective in many patients, but they are not specifically approved for this particular use. Therefore, there may be bureaucratic hurdles involved in prescribing them." "In cases of osteitis, I would prefer bisphosphonates over immunomodulation. If there is synovitis or clinical arthritis present, I would also consider starting a disease-modifying antirheumatic drug (DMARD). In situations of uncertainty, I might choose to use both treatments. It's important to note that case reports and case series have limitations and may be subject to reporting bias, with relatively short follow-up periods of up to one year. Some cases of treatment failure with bisphosphonates have been reported in patients who subsequently tried TNF inhibition."		
3. Tumor necrosis factor alpha inhibitors (TNFi) are the preferred treatment.	7.00 (6.00-8.00)	**Consensus**
"yes, but not in cases of severe PPP" "in third line after bisphosphonates" "If cs DMARDs fail or in mainly axial inflammation after NSAIDs - COXIBs failed."		

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"IMHO, equally effective to bisphosphonates, but much more costly and no clear idea, how long to treat, which doses to be used, number of relapses after treatment cessation. For reimbursement. those patients are coded as axSpA or PsA, so no additional bureaucracy...." "If treatment with biphosphonate isn't effective, it is better to start with anti-tnf or both of them, depending on the structural lessons and the bone oedema and response of treatment" "Third line in case of arthritis/synovitis"		
4. Interleukin-17 inhibitors (IL-17i) are the preferred treatment.	6.00 (3.00-7.00) ** Bipolarity in responses observed: n=12 scored as 1-3 (strong disagreement) and n=12 as 7-9 (strong agreement).	**Dissent**
"step 3 in case of skin involvement" "Case reports describe some good results. May be after TNFi and failure." "maybe preferred in cases with skin involvement, but low level of experience" "if it is not response to anti-TNF and also is related to spondyloarthritis and PsA is a good option use il12-23 and il17 inhibitor" "on biological basis an option in individual cases"		
5. Interleukin-12/23 inhibitors (IL-12/23i) are the preferred treatment.	4.00 (2.75-6.00)	**Dissent**
"step 3 in case of skin involvement" "case reports not very convincing" "no experiences, may not be effective in the axial skeleton as in spondyloarthritis." "In addition, IL23 inhibitor including risankizumab and guselkumab were both approved in Japan for PPP/PAO treatment"		
6. Interleukin-6 inhibitors are the preferred treatment.	2.00 (1.00-4.00)	**Near negative consensus**
"Not at present. Less safe than anti-TNFs. Lack of data. May be interesting, regarding the inflammatory cytokine pathway." "It depends on the pathology; if is an anti-inflammatory syndrome, probable it response to antiIl1"		

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"I don't see how this works but can be my shortage of knowledge"		
7. Interleukin-1 inhibitors are the preferred treatment.	4.00 (2.00-5.00)	**Dissent**
"Only in phenotype of autoinflammatory activity/phenotype" "Not at present. Less safe than anti-TNFs. Lack of data. May be interesting, regarding the inflammatory cytokine pathway; may be a 4th step." "I would like to add another drug, which was not available for a long time and is now quite costly: calcitonine (I did have a couple of patients between 2002- ~2012, who were extremely well with relatively short courses of calcitonine while failing with TNFi and i.v. bisphosphonates at that time." "NOT approved in Japan for PPP/PAO"		
Preferences for specific patient groups **"In absence of contraindications…"**		
8. Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) like methotrexate, sulfasalazine, leflunomide are specifically preferred in patients with significant peripheral synovitis.	7.00 (5.75-8.25)	**Near consensus**
"Methotrexate is also working for bone and skin. Should always be considered. If handled correctly it's very save. More active than sulfasalazine. Saver than leflunomide."		
9. Intravenous bisphosphonates are specifically preferred in patients with spinal bone lesions.	7.00 (6.00-9.00)	**Near consensus**
"Not preferred but should be considered. Don't do nothing for extra-skeletal."		
10. Within the class of intravenous bisphosphonates, intravenous pamidronate is the bisphosphonate of choice.	7.00 (5.00-9.00)	**Dissent**
"Zoledronate." "would give no written preference --- and personally use zoledronic acid (cheaper, higher bone affinity - so longer and better effect expected - but very limited data); others used ibandronate or clodronate instead" "Zolendronic acid is easier to administer in outpatient setting." "I use mostly zoledronate" "Based on body of evidence and lesser body of evidence of ibandronate? Biologically both should work." "We often use oral BP"		

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11. In patients with a history of uveitis or inflammatory bowel disease, TNFi is specifically preferred as biologic.	8.00 (7.75-9.00)	**Consensus**
"Maybe those patients suffer primarily from axSpA with one/few additional features of SAPHO" "Needs to be specified as not all are equal for both diseases!" "But rarely develop uveitis"		
12. In patients with prominent psoriasis, IL-17i or IL-12/23i are specifically preferred as biologic.	6.00 (5.00-8.00)	**Near consensus at another level**
"No. First try TNFi in adjunction to MTX. If this isn't efficient enough, next step could be IL-17i or IL12/23i." "maybe from theoretical point of view but need more data" "IL23 is also the choice"		
13. In patients presenting with axial disease and overlapping features with axial spondylarthritis, direct step 2 treatment with TNFi or IL-17i is preferred over a csDMARD like methotrexate.	8.50 (7.75-9.00)	**Consensus**
"There may be some arguments for this but mainly if diagnosis is in doubt."		
14. Intra-articular glucocorticoids can be considered in case of local disease activity (e.g. in sternoclavicular joint or in cases of peripheral mono/oligoarthritis).	7.00 (5.00-9.00)	**Dissent**
"but this normally would not relieve bone pain...." "yes, for symptom relief but is not a replacement/alternative in my opinion, this needs to be very clear"		
15. Janus kinase (JAK)-inhibitors may be considered in multi-step refractory CNO/SAPHO.	7.00 (5.00-8.00)	**Near consensus**
"I would like to see this tested in a prospective, randomized clinical trial!!!" "Yes, possibly the next option in refractory cases (step 4)"		
16. Surgical intervention may be considered in cases of local osteitis/hyperostotic complications or in multi-step refractory disease.	3.50 (2.00-6.00)	**Dissent**
"Yes, but only if pharmacological therapy has failed or for extra-skeletal complications of hyperostosis. The indication shouldn't be made by the surgeon alone." "very, very last resort." "Depends on the case; severity, location, disease control, expected outcome."		

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Considerations on sequentiality and combination therapy		
17. Specific biologic therapy should be chosen based on spectrum of clinical symptoms, any contraindications to specific therapy, costs and logistics, and patient preference.	8.00 (7.00-9.00)	**Consensus**
"Leave out patient preferences. It's a typical expensive word. Medicine shouldn't be a self-service shop. You certainly have to take patients preferences in to account if reasonable but it's the society who pays thousands of EUR yearly for the treatment and it's not fair to waste money just for preferences without presumed objective surplus value."		
18. If a csDMARD has been partly helpful, it should be retained if a biologic treatment/antiresorptive treatment is started in addition.	7.00 (6.00-9.00)	**Near consensus**
"At least as overlapping treatment" "At least at the beginning" "NSAIDs only at the start, as it may take weeks before the biologic agent works. Methotrexate should be retained but dose reduction should be considered once disease is under control." "But can/should be reduced after achieving a good clinical and biological response"		
19. Most biologic therapies should generally be considered in multi-step refractory patients (e.g. to NSAIDs, csDMARDs, local glucocorticoids, bisphosphonates).	7.00 (5.00-8.25)	**Dissent**
"If signs of active synovitis, SAPHO are present" "Not sure about bisphosphonates. Depends on the whole spectrum."		
20. TNFi are a good option as step 2 treatment, directly following NSAIDs.	7.00 (5.00-8.00)	**Near consensus**
	*Tended to be scored more positively by physicians caring for ≥10 patients vs. < 10 patients: median 8.00 (6.50-8.50; consensus) vs. median 7.00 (4.50-8.00), p=0.092.	
"But careful use highly active PPP" "We shouldn't ruin health care systems by making useless costs." "Only higher than IL17i due to longer/more experience" "It depends on clinical and if the pathology is associated with spondylarthritis"		

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"In osteitis I would prefer bisphosphonates or direct combination" "IL23 first in Japan since it is approved"		
21. IL-17i are a good option as step 2 treatment, directly following NSAIDs.	5.00 (3.00-6.25) ** Some bipolarity in responses observed: n=13 scored as 1-3 (strong disagreement) and n=10 as 7-9 (strong agreement).	**Dissent**
"We shouldn't ruin health care systems by making useless costs." "I would think about anti-IL1 agent prior to anti-IL17" "Less evidence, but on theoretical ground effective"		
Considerations on ancillary treatments		
22. Short courses of oral prednisolone can be helpful in the management of CNO/SAPHO.	5.50 (3.00-7.00) ** Bipolarity in responses observed: n=13 scored as 1-3 (strong disagreement) and n=16 as 7-9 (strong agreement).	**Dissent**
"Can be helpful to give csDMARDs or bDMARDs the time to work. Should definitely not be a long-term strategy." "The duration is short and the dose range might be mentioned in recommendations, even if this is only expert opinion. (e.g. 0.5-1.0 mg/kg prednisolone with fast tapering to zero within 4-6 weeks)" "Not for long time"		
23. Intramuscular methylprednisolone acetate periodically offers a better option to short courses of oral prednisolone.	3.00 (2.00-5.00) *Scored less positively by physicians caring for ≥10 patients vs. < 10 patients: median 2.00 (1.50-3.50; negative consensus) vs. median 5.00 (2.50-5.00), p=0.047.	**Near negative consensus**
"No own experience"		

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"Less side effects, lower cumulative dose, frequently used in our practice for all inflammatory rheumatological diseases and osteoarthritis"		
24. Long-term use of oral prednisolone should be avoided.	9.00 (8.00-9.00)	**Consensus**
"There is absence of evidence, no clear recommendation besides 'we don't really know the effects'"		
25. Physiotherapy should be considered in all patients to optimize physical capacity.	8.00 (6.00-9.00)	**Near consensus**
"Sounds useful, but i guess, no robust evidence..."		
26. Smoking cessation should be recommended to all patients.	9.00 (7.75-9.00)	**Consensus**
"Given some similarities with axSpA and PsA, I would strongly recommend stopping smoking." "This is just a waste of time. All smokers know that it isn't healthy. You then should also waste your time on recommending the obese with skin disease to lose weight until they are normal weight. And to stop drinking alcohol. And to move enough. And so on and so on. Avoid recommendations with extremely low chances of success."		

Q15: How do we define remission in adult CNO/SAPHO?

Statement **"For adult CNO/SAPHO, remission should include…"**	**Median (IQR)**	**Consensus assessment**
1. Resolution of inflammatory bone pain.	9.00 (8.00-9.00)	**Consensus**
"Or substantial improvement (= no disturbed sleep due to pain, pain VAS </= 3/10)" "Pain should be included in the 'core set', and the threshold should be subject of investigation." "Doesn't account for extra-skeletal symptoms. Most patients don't distinguish inflammatory pain from pain or even feeling bad from whatever reasons. You should specify: by the judgment of the treating physician."		
2. Restored functioning to previous or acceptable level.	8.00 (6.00-8.00)	**Consensus**
"There might be other patient-related experiences living with SAPHO-CNO that might need to be targeted: fatigue, sleep, mental health, chronic widespread pain/AMPS. Need to study PRO measures to understand this." "You can't restore damaged joints. Remission could be: no objectable signs of inflammation and extra-skeletal symptoms. You clearly have to distinguish damage from disease activity. Functioning can be determined by inflammation, by damage, by not disease related other conditions, and very importantly by coping and mindset."		

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"Restored functioning is difficult as: - we mostly do not know functioning before the onset of disease, and functional scores themselves are: - it is dependent on disease duration and age. - it is sometimes used as an outcome for validation of remission criteria."		
3. Absence of signs of active inflammation at musculoskeletal examination (e.g. bone swelling with soft tissue involvement, joint swelling)	8.50 (8.00-9.00)	**Consensus**
"Yes, active inflammation indicates a state of non-remission." "Works only for peripheral joint involvement and extra-skeletal. Bone deformation is damage, not activity."		
4. Normalisation of previously raised systemic inflammatory markers.	8.00 (7.00-9.00)	**Consensus**
"... and not attributed to other causes. Should however regarded as only one among other parameters."		
5. Absence of strongly increased uptake on WBBS or SPECT.	5.00 (4.25-7.00)	**Dissent**
"Should be no increased uptake at the regions of interest. Probably, in general, you should assess clinical remission from the absence of any objective symptoms. May be low or very low disease activity could be considered." "Yes, but: - Clinical signs and symptoms should prevail - Whole-body bone scintigraphy (WBBS)/PET/MRI might be combined into one criterion with a scoring chart/system (0 to 4, for instance). It should be investigated what the prognostic value is of residual inflammation on imaging in those patients in clinical remission, on functional capacity and structural damage, to know the additional value of including this. So maybe a clinical/biochemical score + the strong wish for an additional imaging score, the latter being a research agenda question."		
6. Absence of strongly increased uptake on PET.	6.00 (5.00-7.00)	**Consensus at another level**
	***Positively correlated to score of 10.10 (should signs of active inflammation on e.g. PET or MRI be followed-up in adult CNO/SAPHO?; Spearman's rho 0.353, p=0.019.	
"Should I be happy with normal PET/MRI, if patient still complains significant pain? Otherwise, do I have to adjust therapy, if patient feels well??? I usually treat symptoms and diseases of patients, and not images." "Should be no increased uptake at the regions of interest. Probably, in general, you should assess clinical remission from the absence of any objective symptoms. May be low or very low disease activity could be considered."		
7. Absence of bone marrow edema, soft tissue edema or joint effusion on MRI.	7.00 (5.00-8.75)	**Dissent**
	***Positively correlated to score of 10.10 (should signs of active inflammation on e.g. PET or MRI be	

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	followed-up in adult CNO/SAPHO?; Spearman's rho 0.378, p=0.011.
"Only if MRI is performed." "In detail, follow-up MRI for one target lesion (osteitis)." "Yes, but only for bone and joint." "Regional or whole-body MRI is the preferred modality used to track bone lesions." "Improvement of acute osteitis lesion by MRI may be delayed after resolution of symptoms and signs." "May be interesting for studies." "Often also during the phase of remission of the disease, when the patient is fine without any pain, sign, or symptoms, MRI shows soft bone marrow edema."""	

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Q16: What are considerations during patient follow-up in CNO/SAPHO?

Statement	**Median (IQR)**	**Consensus assessment**
1. Long-term follow up is important in CNO/SAPHO, due to the temporal dissociation of different clinical features.	9.00 (7.00-9.00)	**Consensus**
"I would stop follow up in successfully treated patients with the wording: maybe its gone forever, but sometimes there are relapses, please feel free to make a new appointment if symptoms recur"		
2. Patients should be advised, after end of follow up, that their condition might return with similar clinical features at some time in the future.	8.50 (8.00-9.00)	**Consensus**
3. Patients should be advised, after end of follow up, that their condition might return with different clinical features at some time in the future.	8.00 (7.00-9.00)	**Consensus**
"Would prefer previous wording"		
4. Patients with spinal involvement should be monitored for pathological vertebral fractures.	7.00 (6.00-9.00)	**Near consensus**
"I guess, there are no data on that or only few case reports... Would not be my current practice as osteologist..." "I agree, if monitoring is coupled with a treatment advice"		
5. Patients with anterior chest wall involvement should be monitored for neurovascular obstruction due to hyperostotic compression (thoracic outlet syndrome, v. subclavia obstruction, etc.)	6.00 (5.00-8.00)	**Near consensus at another level**
"They shouldn't be monitored in general but should be investigated if they have compatible complaints and / or clinical signs." "Only if clinically presented, but no regular rule to follow." "What are treatment implications in case of venous stenosis? Do we switch therapy? What is the number needed to monitor to prevent one thrombotic event?"		

The 2023 consensus initiative for the diagnosis and management of CNO/SAPHO in adults

Integrated data overview
Delphi round #1, digital pre-meeting, and Delphi round #2
September 2023

Organizing committee:
Elizabeth M. Winter, Associate Professor, Internist-Endocrinologist (*initiator*)
Olaf M. Dekkers, Professor of Research Methodology (*methodologist*)
Natasha M. Appelman-Dijkstra, Internist-Endocrinologist
Anne T. Leerling, MD-PhD Candidate (*fellow*)
Oana Danila-Bulaicon, MD-PhD Candidate (*minutes secretary*)

Leiden University Medical Center

Centre for Bone Quality
Leiden University Medical Center

Initiative endorsed by:

Domains of interest

Disease (spectrum) definition

1. What are the clinical characteristics of adults with "sterile bone inflammation"?
    A. Skeletal distribution pattern
    B. Additional (extra-skeletal) features)
    C. Demographics, risk factors, physical exam findings
2. What are imaging characteristics of "adults with sterile bone inflammation"?
    A. Structural imaging features in early disease and long-term disease
    B. Other diagnostic imaging features
    C. Imaging features related to disease activity
3. What is the preferred name of the clinical entity?
4. Which physicians preferably see and treat adults with CNO/SAPHO?

Diagnostics

5. Which laboratory tests are indicated for suspected adult CNO/SAPHO?
    A. Routine laboratory tests
    B. Optional laboratory tests
6. What type of imaging is preferred for suspected adult CNO/SAPHO?
    A. Imaging preferences for the identification of structural changes in bone lesions
    B. Imaging preferences for assessment of disease activity
    C. Imaging preferences for asymptomatic lesion screening
7. When is a bone biopsy indicated as part of the diagnostic work-up?

Treatment

8. What are the treatment goals in adult CNO/SAPHO?
9. What are the treatment goals?
    A. Relieve patient symptoms
    B. Maintain/regain functional capacity
    C. Reduce inflammation to the lowest level possible
    D. Prevent structural bone and joint damage
    E. Other considerations
10. What is the best option as a first-line treatment (step 1) and what should be its duration?
11. What is the best option as a second-line treatment (step 2), and what should be its duration?
12. What is the best option as a third-line treatment (step 3), and what should be its duration?
13. Whichancillary treatments should be considered in adults with CNO/SAPHO?
14. What are the treatment considerations for patients with CNO and extra-skeletal features?
15. What are the follow-up considerations for adults with CNO/SAPHO?

Methods

Commented [MOU1]: When and how? It would be best to explain the process

In Delphi round 2, we assessed the level of agreement between participants for each question answered as outlined in Table 1... The level of agreement ranged from dissent to consensus, based on predefined criteria specific to question type. Theparticipants could add open-text comments below each question. Comments with similar content were grouped for clarity and conciseness.

Table 1: Definition of consensus levels per question type

Type of questions	**Consensus**	**Near-consensus**	**Negative consensus**	**Dissent**
1-9 point Likert scale for prevalence	Any median with IQR ≤ 2.25	Any median with IQR ≤ 3	N.A.	Any median, and IQR > 3
1-9 point Likert scale for agreement	Median ≥ 7 with IQR ≤ 2.25	Median ≥ 7 with IQR ≤ 3	Median ≤ 3 with IQR ≤ 2.25	Any median, and IQR > 3
Agree/Disagree questions	≥67% "agree"	56-67% "agree"	≤33% "agree"	33-55% "agree"
> 2 option questions	One option selected by ≥67%	One option selected by 56-67%	One option selected by ≤33%	Other
Symbolized with:	●	♦	●	X

Consensus initiative: panel group member characteristics

Table 1: Delphi response rate, medical specialty, caseload and country of residence of consensus initiative members (n=58 total)

Medical specialization (n (%))		
Adult rheumatologist	31 (53%)	
Pediatric rheumatologist	8 (14%)	
Adult + pediatric rheumatologist	1 (2%)	
Adult rheumatologist + osteologist	1 (2%)	
Immunologist	3 (6%)	
(Internist)-endocrinologist	4 (7%)	
Orthopedic surgeon	1 (2%)	
Radiologist	7 (12%)	
Nuclear medicine physician	1 (2%)	
Dermatologist	1 (2%)	
Adult CNO/SAPHO caseload (median (IQR))		
New referrals/year	4 (2-10)	
Confirmed cases under care	10 (5-22)	
Country of residence (n (%))		
United Kingdom	12 (21%)	
Netherlands	9 (16%)	
France	6 (10%)	
Italy	5 (9%)	
Germany	5 (9%)	
Belgium	4 (7%)	
United States	4 (7%)	
Denmark	2 (3%)	
Spain	2 (3%)	
Japan	1 (2%)	
New Zealand	1 (2%)	
Brazil	1 (2%)	
Russia	1 (2%)	
Tunisia	1 (2%)	
China	1 (2%)	
Canada	1 (2%)	
Greece	1 (2%)	
Israel	1 (2%)	
Survey response rate (n (%))	**Delphi Round #1**	**Delphi Round #2**
Registered participants at survey launch	47	58
Completed survey responses	44 (94%)	43 (74%)

1. Disease (spectrum) definition

1.1 Clinical characteristics of "adults with sterile bone inflammation"

In both Delphi round #1 and the digital pre-meeting, the disease definition of adult CNO/SAPHO syndrome was recognized as complex. This initiative regards "adults with sterile bone inflammation" as a starting concept. This concept specifically excludes genetic syndromes such as Majeed syndrome and Deficiency of IL-1 Receptor Antagonist (DIRA), and also excludes pediatric CNO.

1.1A: Skeletal distribution pattern

According to group discussions, "adults with sterile bone inflammation" form a clinically diverse population, with various skeletal distribution patterns. These were further evaluated in Delphi Round #2, as shown in figure 1.1A.

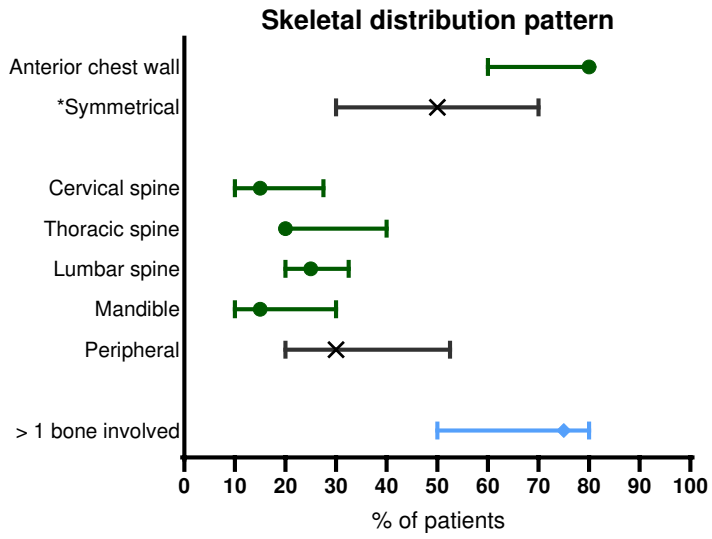


Figure 1.1A: Skeletal distribution pattern as seen by respondents in adults with sterile bone inflammation (presented as median, interquartile range). ●: consensus, ♦: near-consensus, X: dissent

Skeletal distribution pattern: free-text comments (clustered if appropriate)

Sites of involvement:

"Anterior chest wall: sometimes in relation to spondyloarthritis or psoriatic arthritis"

"Cervical spine: No idea. Is probably often missed."

"Mandible is not frequently seen in adults presenting with SAPHO/CNO i.m.h.o"

Commented [MOU2]: What does this mean?

"Peripheral bones: also more frequently in CRMO/younger patients, can transfer to adult age however."

Diagnostic evaluation:

"I think it is really dependant of the way of recruitment and specialty; multifocal disease may present to rheumatologist/internist, unifocal disease may present at orthopedic surgeon" (n=3)

"It is usually lesions in a typical distribution that lead to a suspected diagnosis, so involvement of the anterior chest wall is likely prevalent as it prompts diagnosis." (n=2)

"Above percentage may change if we would screen everyone with whole body imaging" (n=2)

Regarding the definition of "multifocal":

"Multifocal involvement means more than two manifestations" (n=2)

Commented [MOU3]: Two or more bone sites involved

Regarding the definition of "symmetrical":

"By symmetrical I understand both sides (bilateral), rather than involved to the same degree of severity at both sides." (n=3)

Regarding the classification and terminology of skeletal distribution:

"Does bilateral anterior chest wall involvement (SCCH) fall under 'unifocal' or 'multifocal'? Might consider a specific note on this in a classification proposal."

"For clarity's sake, I suggest these questions regarding skeletal involvement, instead of those about unifocal and multifocal involvement: - One or more lesions isolated to the sternocostoclavicular region (separate ORPHANET code 178311 for Isolated SCCH) - Lesions in the SCC region + other axial localisations (mandible/spine/pelvis) - Unifocal axial lesion, no involvement of SCC region (mandible? pelvis) In my experience, unifocal lesions are rarely seen in isolation at presentation, except for the mandible, probably because of the natural history of the disorder and the still prevalent delay in diagnosis, thus missing the early stages of the disease."

"It may be considered to define the term peripheral bones or to use the term the appendicular skeleton instead"

"For me, there seem to be different patient subsets, some with full blown SAPHO, some only axial +/- thoracic or sternoclavicular inflammation, others more or less only (mostly proximal) long bone inflammatory activity."

"Do we include DSO as CNO?"

"Pelvis in occasionally involved - considered axial skeletal"

1.1B: Additional (extra-skeletal) features

According to group discussions, "adults with sterile bone inflammation" form a clinically diverse population, with various additional (extra-skeletal) features. The group prefers to describe additional (extra-skeletal) features as additions to the primary disease characteristic of "sterile bone inflammation", and not to make strict diagnostic subcategories according to these features. Features were evaluated once more in Delphi Round #2, as depicted in figure 1.1B.

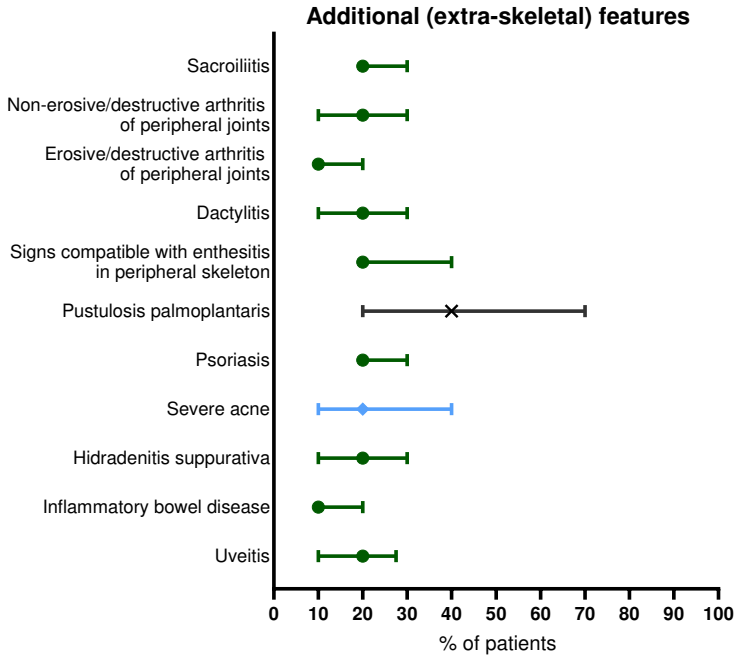


Figure 1.1B: Additional (extra-skeletal) features as seen by respondents in adults with sterile bone inflammation (presented as median, interquartile range). ●: consensus, ♦: near-consensus, X: dissent

Additional (extra-skeletal) features: free-text comments (clustered if appropriate)
"Iliitis 70%. Sacroiliitis as in SpA <10%."
"Sacroillitis in 10% of all patients, 30% of those with only /preferably central disease"
"If new diagnosis and treated 0% erosive, 0% destructive."
"Pustulosis palmoplantaris: This is a feature strongly pointing to the diagnosis, so may be overrepresented"
"History of psoriasis/acne should also count" (n=2)
"Hidradenitis: Maybe underreported, I do not perform complete skin search, do not explicitly ask for it (only asking for psoriasis and pustulosis)"

1.1C: Demographics, risk factors, physical exam findings

In Delphi Round #1, consensus was already achieved on the main presenting symptom of adults with sterile bone inflammation, that is inflammatory bone pain, which can be chronic or relapsing-remitting. Other demographics, risk factors, and physical exam findings were further queried in Delphi Round #2 and are depicted in figure 1.1C.

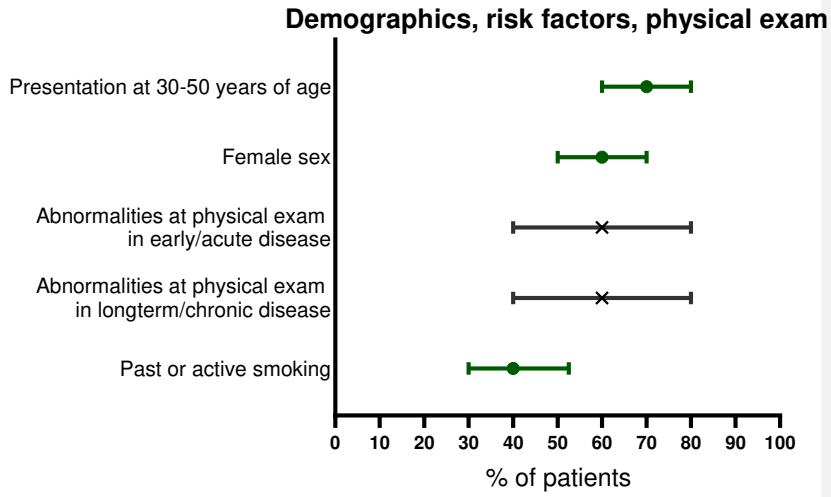


Figure 1.1C: Demographics, risk factors, physical exam findings as seen by respondents in adults with sterile bone inflammation (presented as median, interquartile range). ●: consensus, ♦: near-consensus, X: dissent

Demographics, risk factors, physical exam findings: free-text comments (clustered if appropriate)

"CNO/SAPHO seems to be rare in elderly (or misdiagnosed..)"

"For physical exam findings: not so impressive, that I would remember it."

"Number given for those with thoracic involvement. Depends, no chronic bone swelling in patients with mostly long bone inflammation"

1.2 Imaging characteristics of "adults with sterile bone inflammation"

1.2A Structural imaging features in early and long-term disease

Delphi Round #1 contained questions about imaging features at theirinitial presentation and during follow-up, in order to understand which features are considered prominent in early vs. long-term stages of the disease. However, group comments emphasized that the time of presentation in adult CNO/SAPHO depends on diagnostic delay and, therefore, does not necessarily represent early disease. Also, more distinguishment was needed between structural features that develop over time, and features that may fluctuate with disease activity. For the latter, it was noted that imaging features representing disease activity do not always correlate with clinical symptoms. These nuances have now been addressed in Delphi Round #2.

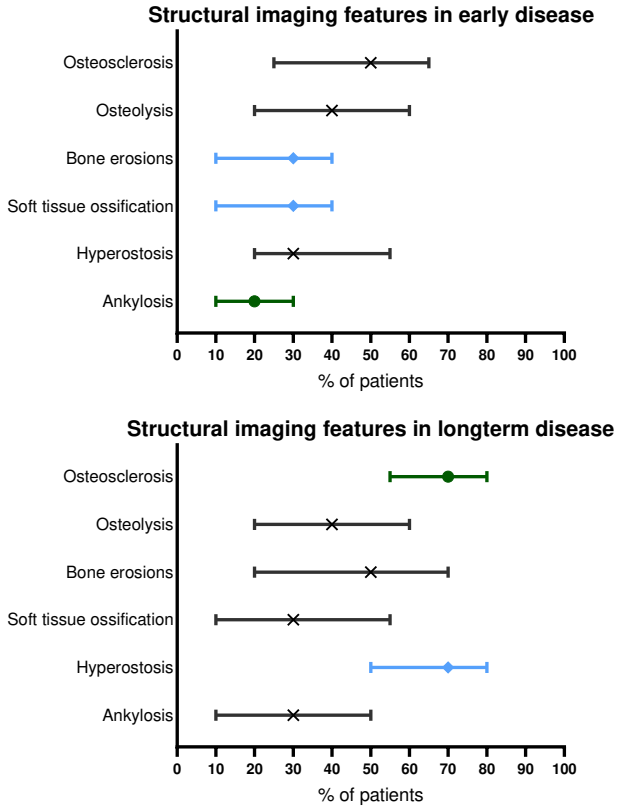


Figure 1.2A: Structural imaging features in early (upper) and long-term (lower) disease as seen by respondents in adults with sterile bone inflammation (presented as median, interquartile range). ●: consensus, ♦: near-consensus, X: dissent

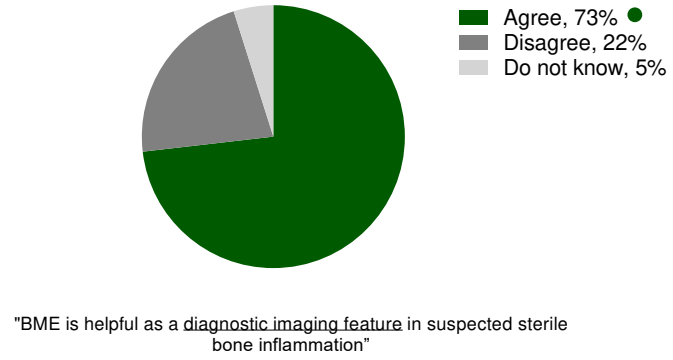
Structural imaging features: free-text comments (clustered if appropriate)

"It is difficult to define early disease, as opposed to disease on initial presentation due to diagnostic delay" (n=2)

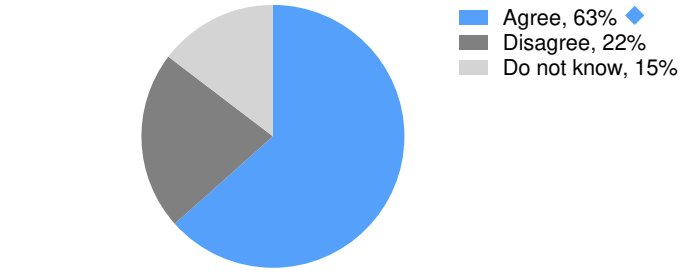
"Osteolysis and erosions, particularly around the sternoclavicular joints, and in long-term disease, depends on therapy."

"Osteosclerosis is a typical feature of long-standing disease."

1.2B Other diagnostic imaging features



"BME is helpful as a diagnostic imaging feature in suspected sterile bone inflammation"



"Increased isotope uptake on nuclear imaging is helpful as a diagnostic imaging feature in suspected sterile bone inflammation"

Figure 1.2B: Respondent's opinion on the utility of bone marrow edema (BME) and increased isotope uptake on nuclear imaging as diagnostic imaging features in suspected sterile bone inflammation. ●: consensus, ♦: near-consensus

Commented [MOU4]: In the main manuscript it is referred as BMO

Other diagnostic imaging features: free-text comments (clustered if appropriate)

Regarding BME:

“BME reflects the inflammatory process” (n=9)

“BME is too nonspecific to be diagnostic (has a broad differential diagnosis)” (n=14)

“BME is mainly helpful in combination with specific localizations (within bone itself, e.g. not exclusively in subchondral bone, and within skeleton) or other typical clinical or imaging features” (n=8)

“BME is helpful and therefore makes MRI the preferred imaging tool in CNO/SAPHO” (n=6)

“BME may be less useful in chronic disease due to delayed improvement” (n=3)

"BME can be masked on MRI due to the presence of associated sclerosis/hyperostosis and can be missed in small anatomical parts such as costochondral articulations due to the worse anatomical definition of MRI with respect to CT in the evaluation of the chest wall (main point of affectation of this disease)”

Regarding isotope uptake:

“Diagnostic value of isotope uptake depends on the tracer used” (n=2)

“Diagnostic value of isotope uptake depends on the distribution” (n=5)

“Isotope uptake is too nonspecific to be diagnostic” (n=11)

“Only if MRI is not available: MRI is more specific” (n=6)

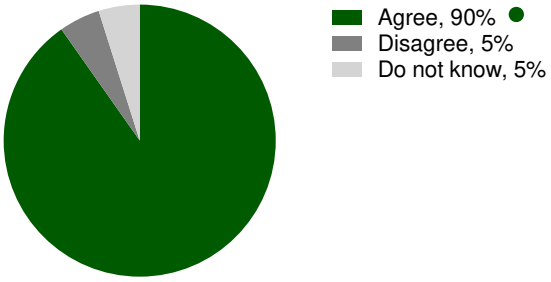
“Very helpful, sensitive feature” (n=8)

"SPECT-CT should always be added to WBBS if available."

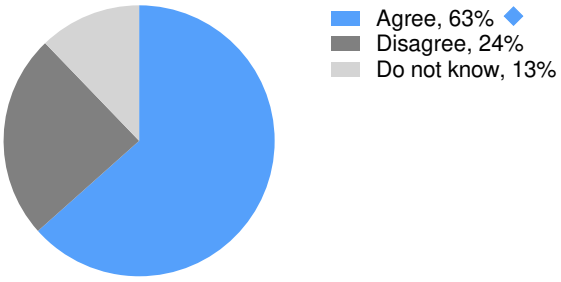
“Does not necessarily correlate with clinical symptoms” (n=2)

“Convenient technique: scans whole body, can detect asymptomatic lesions” (n=2)

1.2C Imaging features related to disease activity



"Bone marrow edema (BME) is helpful to differentiate active from non-active disease"



"Increased isotope uptake on nuclear imaging is helpful to differentiate active from non-active disease"

Figure 1.2C: Respondent's opinion on the utility of bone marrow edema (BME) and increased isotope uptake on nuclear imaging as reflectors of disease activity in adults with sterile bone inflammation. ●: consensus, ♦: near-consensus

Imaging features relating to disease activity: free-text comments (clustered if appropriate)

Regarding BME:

"BME represents tissue changes (like e.g. vascularization) that we would expect in acute or subacute bone inflammation" (n=19)

"Bone marrow edema (BME) like changes can persist weeks/months after resolution of the symptoms, and they are not always well correlated with inflammatory markers." (n=6)

"BME can have other causes than active bone inflammation as well" (n=4)

"BME can be an objective disease activity marker (in the way that clinical complaints not always can)

"BME is frequently associated with pain in my patients, and similar to other diseases such as SpA or bone fracture."

"In two cohorts we applied an MRI score (synovitis/effusion/edema and more) with the goal to assess the disease activity in a more scientific way, but it seems to be difficult."

"Yes, but only informative if BME is substantial"

"This may be relevant in particular for lesser weight-bearing bones, i.e., clavicle."

Regarding isotope uptake:

"Active inflammation implies increased vascularization and/or osteoblastic activity and thereby result in increased isotope uptake, so isotope uptake is useful to monitor activity" (n=8)

"Isotope uptake is not specific for active inflammation" (n=4)

"Captures active bone formation. Does not capture osteolysis without any formation. No hypercaptation in silent disease."(n=2)

"Increased uptake also persists despite clinical improvement with some tracers" (n=4)

"Good measure of activity is MRI is not available" (n=7)

"Should not be used routinely to evaluate disease activity due to radiation" (n=2)

"In my opinion, isotope uptake is very helpful in the evaluation of this disease. It provides information before structural changes are present (such as sclerosis/hyperostosis) and can monitor (from the quantitative and qualitative point of view) the disease. Quantitative assessment is not possible with MRI."

"I agree, but there are some remarks to take into consideration. False positive signals in and around joints are seen more often since scanning techniques have been improved over recent years, maybe also true for bones? Don't know if data is present. [18F]fluorodeoxyglucose (FDG)-PET might also reflect bone formation more than active osteitis, as has been shown for ankylosing spondylitis."

1.3 Preferred name for the spectrum of "adults with sterile bone inflammation"

The importance of a uniform and appropriate name for the entity of "adults with sterile bone inflammation" is broadly felt. In the pre-meeting, it was emphasized that the name should reflect the core characteristic of the disease, i.e. sterile bone inflammation; the core name may then be supplemented with additional features as appropriate. Continuity in naming children and adults was advocated, to ensure that children transitioning to adulthood do not receive a different label for their condition. The term "SAPHO" was deemed very broad since the vast majority of patients do not exhibit all the features of the SAPHO acronym (incomplete representation). It was recognized that patients should be able to communicate their naming preferences, as they are the ones who eventually carry the label. In Delphi Round #2, responders were asked to allocate 100 points freely among the naming options below, reflecting their preference.

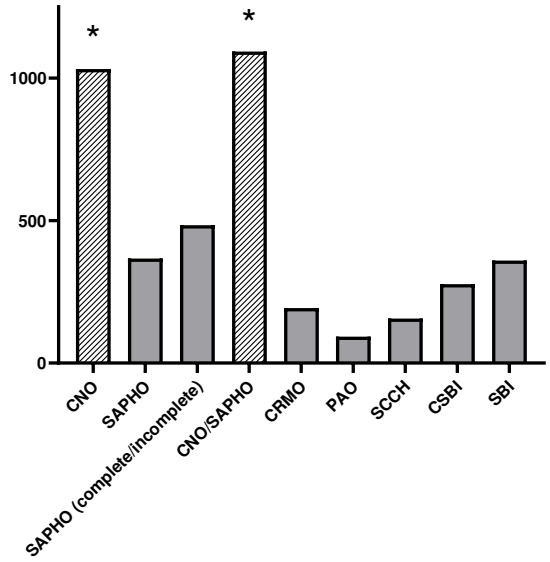


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Figure 1.3: Preferred name for the clinical spectrum of "adults with sterile bone inflammation" (represented by total number of points received). CNO = Chronic nonbacterial osteomyelitis. SAPHO = Synovitis, acne, pustulosis, hyperostosis, osteitis – syndrome, CRMO = chronic recurrent multifocal osteomyelitis, PAO = pustulotic arthro-osteopathy, SCCH = sternocostoclavicular hyperostosis, CSBI = chronic sterile bone inflammation, SBI = sterile bone inflammation. * representing the two highest total scores.

Nomenclature: free-text comments (clustered if appropriate)

In favour of CNO/SAPHO:

"It is best to use a term that shows that CNO/CRMO and SAPHO are essentially part of the same syndrome, and should be studied together in future clinical trials."

"CNO/SAPHO is useful because it is broad and the terms are well-known" (n=4)

"It is important to keep the entity SAPHO in the title as it englobes many features that could or not be all present (complete or incomplete) and add an entity for patients who only have osteitis which is chronic and sterile (CNO)."

"SAPHO remains relevant because it is a common occurrence in medicine that patients affected by a classical syndrome do not exhibit all features of the syndrome. The value of SAPHO relies on the fact that features are well summarized in an easy-to-remember name."

In favour of CNO:

"It is important to use the same name for children and adults, and CNO is now used in pediatric patients too." (n=4)

"CNO is the most inclusive term; includes both unifocal and multifocal disease, describes the core disease, additional features may be added" (n=4)

"SAPHO is a helpful label in patients with other features in the syndrome, but not as an overarching diagnostic label as very few fulfil all symptoms. " (n=3)

Regarding (C)SBI:

"Introducing a new name for the disease such as CSBI or SBI will cause even more confusion and unclarity" (n=5)

"SBI might be a good descriptive option and encompasses the core feature, but it can also be too general and unspecific." (n=3)

Other:

"Essentially there is no need to use the wording chronic in the name, there may also be single episodes; for these patients the word "chronic" is misleading" (n=3)

"I struggle with lumping monogenic disease together with CNO and SAPHO. An improvement may be mendelian autoinflammatory bone disease versus what you are trying to define here. Some rare CNO cases may have monogenic causes."

"Proposing a nomenclature change is really challenging. It can only be successful if adapted by the medical community, both physicians and patients. It might be a good subject for a focus group study amongst patients and a broader survey amongst physicians."

"My preference goes for combining CNO and SCCH in adults into CNO/SCCH for the following reasons. The term chronic nonbacterial osteomyelitis (or osteitis) has been widely adopted as a distinct disease entity in paediatric patients over a decade and a half ago, and its use in adults has widely followed suit over the past decade. Second, just as CRMO is by far the most common clinical presentation in paediatric CNO, and the disorder is named by paediatric consensus CNO/CRMO in this population, it is my view that since SCCH is the most common presentation of CNO in adults, we should follow the same logic and consequently name the disorder CNO/SCCH in adults. We could also consider adopting the nomer CNO/SAPHO but only for the few patients with CNO/SCCH demonstrating the full spectrum of the originally described components of the SAPHO syndrome"

"PAO is commonly used for pregnancy-associated osteoporosis."

1.4 Clinical care aspects

The group already agreed on the recommendation to have adult CNO/SAPHO patients be seen by a bone-oriented specialist, with a preference for rheumatologists. There was no consensus regarding the inclusion of specialists with surgical background in this recommendation. Two newly formulated statements were evaluatedin Delphi Round #2 (see figure 1.4).

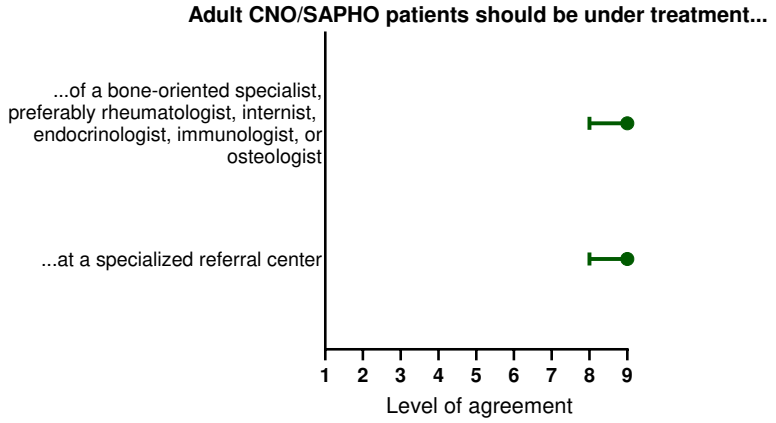


Figure 1.4: Recommendations regarding clinical care aspects in adult CNO/SAPHO (presented as median level of agreement, interquartile range). ●: consensus

Clinical care aspects: free-text comments (clustered if appropriate)

"A hub and spoke model can work well, e.g., annual review at a specialist centre, but also local care for the management of drugs such as DMARDs/biologics. This may be cost-effective and patient-friendly" (n=2)

"Rheumatologists are more familiar with the use of DMARDs and are able to prescribe them. Other specialists might not be able to prescribe and monitor treatment with biologics."

"Not sure whether an immunologist belongs in the list, but might be hospital/center-dependent."

"Since we do not know much about this disease and the studies in the literature are scarce, I believe that patients should be referred to specialist centers. Since there are no guidelines, rheumatologists tend to treat SAPHO at their discretion, mostly by extrapolating SpA guidelines on SAPHO. By referring patients to expert rheumatologists at designated centers, a database would be easy to create, and this is an important thing to consider."

"Really not always possible but doesn't mean it couldn't be an ideal, but expertise needs to be shared, treatment is challenging and once-in-a-lifetime cases may not get excellent care."

"Maybe it's easier to name a bone specialist than a referral center with specific expertise."

2. Diagnostics

2.5 Laboratory evaluation of suspected CNO/SAPHO

Generally, the diagnosis of adult CNO/SAPHO seems not to be heavily reliant on blood tests. There was (near) consensus on the use of generic inflammation markers and serum calcium, phosphate, and parathyroid hormone as standard part of the diagnostic process. Regarding other markers, it was noted that they lack specificity for adult CNO/SAPHO but may be conducted to explore differential diagnoses. Several markers were deemed useful to determine before the start of specific treatments (e.g. bone markers before treating with bisphosphonates, or ANA and differentiation before treating with anti-TNFa). Particular markers were found useful only upon indication, and not for routine evaluation (e.g. HLA-B27).

In Delphi Round #2, routine versus optional tests were stratified, and results are depicted below.

2.5A: Routine laboratory tests

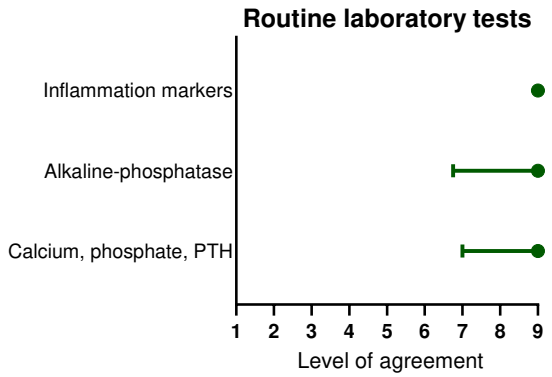


Figure 2.5A: Recommendations regarding routine laboratory investigations in suspected adult CNO/SAPHO (presented as median level of agreement, interquartile range). ●: consensus

Routine laboratory tests: free text comments (clustered if appropriate)
"ESR should be left out."
"PTH should be left out. Should only be measured if s-Ca is abnormal." (n=2)
"VitD and renal tests should be done routinely commensurate with bone profile tests - many levels of reasons why!"

2.5B: Optional laboratory tests

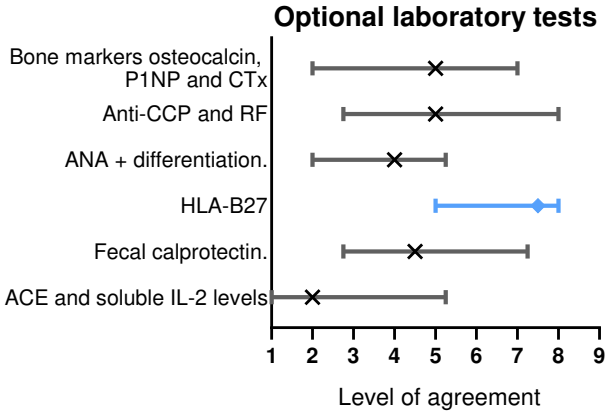


Figure 2.5B: Recommendations regarding routine laboratory investigations in suspected adult CNO/SAPHO (presented as median level of agreement, interquartile range) ●: consensus, ♦: near-consensus, X: dissent.

Optional laboratory tests: free-text comments (clustered if appropriate)

"Any test should be considered if there is an indication - these are all reasonable." (n=3)

“For all these extra optional markers it is questionable whether the bone specialist should perform these laboratory tests, or the preferred specialist like an stomach/intestine/liver doctor for fecal calprotectin and a pulmonologist for ACE/IL2” (n=2)

“Anti-CCP and RF only in case of arthritis/synovitis” (n=2)

"ANA doesn't add anything to the diagnosis or differential diagnoses; limited use as a screening test." (n=2)

"ANA can be done before anti-TNF." (n=2)

"HLA-B27 in the case of axial involvement only."

"Fecal calprotectin only in case of suspicion of associated IBD." (n=2)

"Bone markers only if future monitoring is suspected (e.g., bisphosphonates treatment)." (n=2)

2.6 Imaging preferences in adult CNO/SAPHO

Imaging plays a crucial role in the diagnosis and monitoring of adult CNO/SAPHO. The main outcome of Delphi Round #1 and the digital pre-meeting was that there is no "one-size-fits-all scan". The preferred modality likely depends on the specific goal, patient characteristics, and availability at the treating center. While some techniques may be considered optimal, others may be acceptable. So far, MRI emerges as the preferred diagnostic and follow-up imaging technique. Nevertheless, it was emphasized by the participating radiologists that CT provides superior images compared to MRI when imaging the anterior chest wall, a frequently involved site in adult CNO/SAPHO. Hence, the anterior chest wall may be best structurally visualized with CT, combined with a modality that informs about disease activity like MRI or nuclear imaging. Delphi Round #2 addressed these nuances in the imaging-related questions. Results are displayed below.

2.6A: Imaging preferences for structural characterization of bone lesions

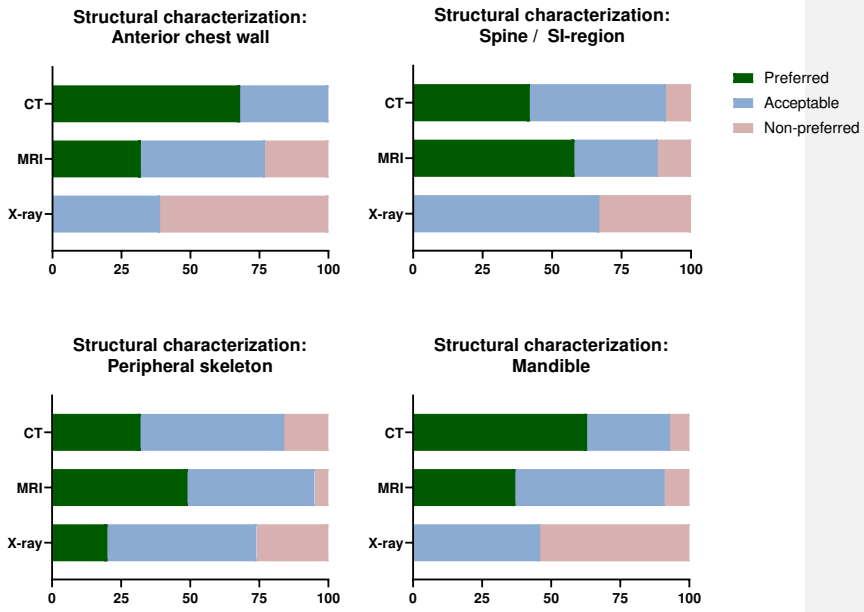


Figure 2.6A: Preferred, acceptable, and non-preferred imaging modalities for structural characterization of bone lesions in adult CNO/SAPHO, stratified per skeletal region. No consensus evaluation performed yet.

Imaging preferences for structural characterization: free-text comments (clustered if appropriate)

Reported advantages of CT as compared to MRI (general)
- Better structural characterization of lesions
- Visualizes more specific features
- Suitable to evaluate bone compression/neurovascular complications

- Better spatial resolution
- Faster than MRI

Reported disadvantages of CT as compared to MRI (general)
- CT entails radiation exposure, especially if low-dose CT is not available
- It is questionable whether the structural evaluation that CT is better at providing has any therapeutic consequence
- No information on disease activity (e.g. with bone marrow edema)
- Poorer assessment of soft tissue inflammation

Regarding the anterior chest wall:
“CT is superior as it is less influences by motion artefacts” (n=2)

“For the anterior chest wall, combination of CT and MRI may be preferred" (n=2)

" X-rays are not sensitive for early disease" (n=4)

“X-rays may be helpful as a screening tool” (n=2)

“All are acceptable, despite differences in predictive value." (n=5)

Regarding the spine/SI-region:

"MRI allows you to assess for sacroiliitis, which may mean I can get funding for biologics through my healthcare system."

"MRI is good for the purpose of structural characterization of bone lesions in the spine/SI joints and is not subject to radiation.” (n=3)

"In AxSpA diagnosis, we, ASAS, recommend MRI to detect both acute and structural lesions in the spine and SI joints."

"X-rays can be fine for the SI-region." (n=2)

"Ideally, one would like to have one modality with good visualization of both structural lesions and bone marrow edema/inflammation”

"MRI is not good for axial bone structural lesions but may be used for the SI region (especially if ZTE sequences are done)."

"Lumbar spine and overall SI joints are well seen with each modality. All may have value, but with the specific question CNO/SAPHO, I'd suggest MRI > CT (> plain X-ray)."

Regarding peripheral skeleton:

"Of course, MRI may pick up erosion earlier than plain x-ray, but we always use XR first to follow RA patients (easily accessible, low cost)"

"Plain X-rays can give valuable information in addition to MRI; i.e., OA changes may be better visible on plain X-rays."

"MRI is better for peripheral arthritis (more sensitive). I think osteitis will be best investigated with MRI, as is arthritis. Hyperostosis/sclerosis can be seen on plain x-rays." (n=2)

"MRI will allow us to characterize the bone lesions but also surrounding tissue, i.e., on the presence of enthesitis or synovitis."

"For peripheral joints, ultrasound is preferred."

Regarding the mandible:

"I preferred CT because you get good information in a fast way, but MRI is also good for the evaluation of the jaw, especially in early disease" (n=3)

"MRI has no radiation exposure, and it picks up both acute and structural lesions. Not suitable with braces, in these cases tomography is preferred. With mandibular CNO/SAPHO, there is often soft tissue involvement that can be better appreciated by MRI." (n=3)

"MSK radiology specialists should advise here." (n=2)

"X-rays of the mandible are very difficult to interpret and do not describe soft tissue involvement or activity." (n=3)

2.6B: Imaging preferences for assessment of disease activity

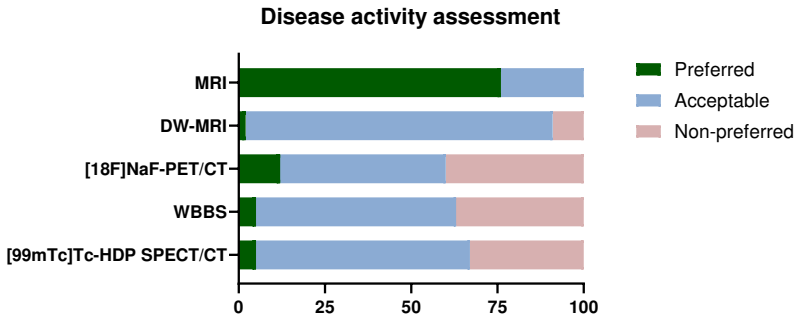


Figure 2.6B: Preferred, acceptable, and non-preferred imaging modalities for disease activity assessment in adult CNO/SAPHO. MRI= Magnetic resonance imaging, DW-MRI=Diffusion weighted magnetic resonance imaging, [18F]NaF-PET/CT= Sodium fluoride positron emission tomography with CT, WBBS=Whole body bone scintigraphy, ([99mTc]Tc-HDP SPECT/CT =Technetium labeled hydroxymethylene diphosphonate single positron emission computed tomography. No consensus evaluation performed yet.
*18F-FDG PET/CT was already regarded a non-preferred imaging technique in Delphi Round #1, so was not included in further Delphi questions of round 2.

Imaging preferences for disease activity assessment: free-text comments (clustered if appropriate)

Regarding MRI:

"Very sensitive for BME/inflammation and therefore preferred to monitor activity" (n=13)

“Activity monitoring requires low radiation exposure burden, therefore only MRI is feasible” (n=6)

"The resolution of DW-MRI is typically not as good as standard MRI protocols and therefore not suited to assess structural changes" (n=2)

“T2W Fat saturated MRI is good enough to show active inflammation of the skeletal system.”

“DW-MRI needs the cooperation of radiologist”

Regarding nuclear imaging:

“PET/CT is preferred if you want to rule out infection”

"Nuclear imaging evaluates the inflammatory process. 99mTc-HDP SPECT/CT usually is easily available, radiation exposure is relatively low. Whole-body images are easy to read. SPECT-CT gives indications of structural changes if compared to previous images and damage”

"Bone scintigraphy using NaF PET (-CT) is relatively new compared to the classical 99mTc based bone scintigraphy. Indications largely coincide with the indications for classical 99mTc based bone scintigraphy. Fluoride can have certain advantages compared to 99mTc labeled tracers. The incorporation or binding is faster, so the scan can be performed after a shorter incubation period, and generally the PET (-CT) scanner has higher sensitivity and spatial resolution compared to planar gamma cameras or even SPECT (-CT). The dose used, and with that, the absorbed dose to the patient is lower than with 99mTc labeled tracers. Imaging is always 3D, and often the accompanying CT will offer attenuation correction and anatomical information. Also the signal is (semi-) quantitative. My second best is Technetium labeled hydroxymethylene diphosphonate single positron emission computed tomography ([99mTc]Tc-HDP SPECT/CT)."

"WBBS can be used as a diagnostic tool but it is not ideal for follow-up as it can remain abnormal for a prolonged period of time." (n=2)

"I am not sure if head-to-head diagnostic and monitoring has been done, but [18F]NaF-PET/CT is a promising tool, though we don't have one."

"Regarding 18F-PET/CT: Not invasive, complete. Superior performance over 99mTC bone scintigraphy.”

Regarding availability/logistics/radiation:

"A localized lesion is easy to assess by MRI, but in case of a multifocal disorder, whole-body scintigraphy or PET will be advantageous unless whole-body MRI is a possibility."

“PET-CT is more expensive than MRI and increases radiation exposure."

"[18F]NaF-PET/CT is probably limitedly available." (n=3)

"PET/CT is limitedly available compared to MRI." (n=2)

“Nuclear imaging is more available in clinical practice compared to MRI” (n=2)

"Availability and costs need be considered” (n=2)

2.6C: Imaging preferences for asymptomatic lesion screening

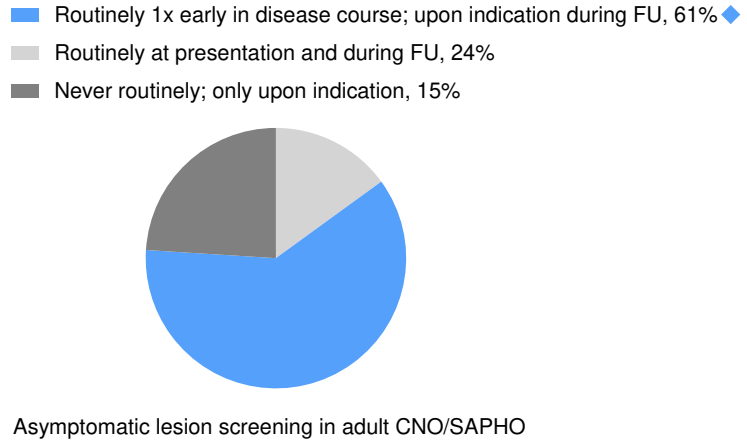


Figure 2.6C: Respondent's opinion regarding the need for asymptomatic lesion screening in adult CNO/SAPHO. FU=follow up.

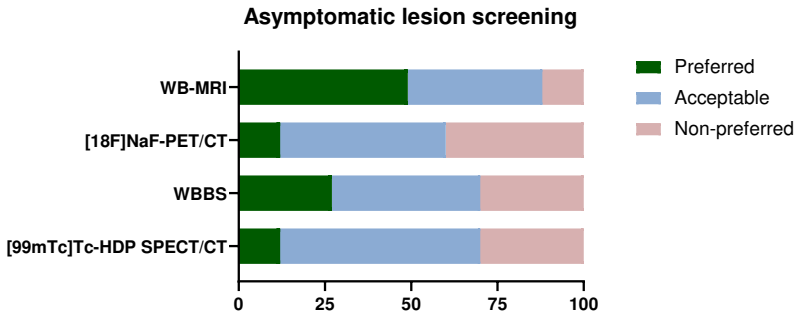


Figure 2.6C (continued): Preferred, acceptable, and non-preferred imaging modalities for asymptomatic lesion screening in adult CNO/SAPHO. WB-MRI= Whole Body Magnetic resonance imaging, [18F]NaF-PET/CT= Sodium fluoride positron emission tomography with CT, WBBS=Whole body bone scintigraphy, ([99mTc]Tc-HDP SPECT/CT =Technetium labeled hydroxymethylene diphosphonate single positron emission computed tomography

*18F-FDG PET/CT was already regarded a non-preferred imaging technique in Delphi Round #1, so was not included in further Delphi questions of round 2.

Asymptomatic lesion screening: free-text comments (clustered if appropriate)

"Screening is useful for mapping bone lesions. Help for diagnosis." (n=2)

"Spinal lesions may arise late and without symptoms."

"Availability and radiation and cost should be considered." (n=2)

"I would consider it if there are multiple symptomatic areas."

"I think it should be routinely done, although we are not able to do it."

"While there is controversy regarding whether asymptomatic lesions represent active disease, it is important to gather prospective data, and only by regular MRIs is one able to have a better idea re: clinical correlation of asymptomatic lesions."

"Treatment of the diseases includes treatment of asymptomatic lesions."

"One can debate about screening upon diagnosis. It will have no added value if the patient and doctor have already agreed upon starting therapy. Only if asymptomatic lesions require treatment and there is a high rate of therapeutic success, for instance prevention of structural damage, then we should screen."

Regarding the preferred screening modality:

"MRI confers no radiation (which is particularly important for screening purposes) and will display silent lesions." (n=8)

"Availability and radiation and cost should be considered." (n=5)

"WBBS is simple and available for screening as compared to MRI, and has lower radiation than SPECT/CT." (n=5)

"[18F]NaF-PET/CT might be more promising but is not widely available and maybe too academic" (n=6)

"Downside of WBBS is that it can show uptake in degenerative disease whereas MRI can discriminate better between CNO and degenerative disease."

"Sodium Fluoride PET/CT I think it's better, also with 18Ga."

2.7 Bone biopsies

In Delphi Round #1, there was already agreement about the role of bone biopsies in suspected adult CNO/SAPHO. These should not be performed routinely, but should be considered in difficult cases where suspicion of malignancy or infection is high. Red flags include lesionswith unifocal involvement and/or rapidly growing,, evidence of cortical destruction on imaging, systemic symptoms like weight loss and fever, or other clinical signs that favour thediagnosis of malignancy or infection.

3. Treatment

3.8 Treatment goals

In Delphi Round #1, there was already group consensus on several treatment goals for CNO/SAPHO, which include relieving symptoms, maintaining/regaining functional capacity, preventing structural bone and joint damage, and reducing inflammation to the lowest possible level. Regarding "reducing inflammation", there is uncertainty within the group regarding the relevance and prognostic value of residual inflammatory signs on imaging. Whether these signs should influence treatment decisions remains unclear. Overall, the group prioritizes patient symptoms over laboratory and radiological findings as treatment goals, and also acknowledges the need to develop andvalidate patient-centred outcomes,.

3.9 Readout parameters for specified treatment goals

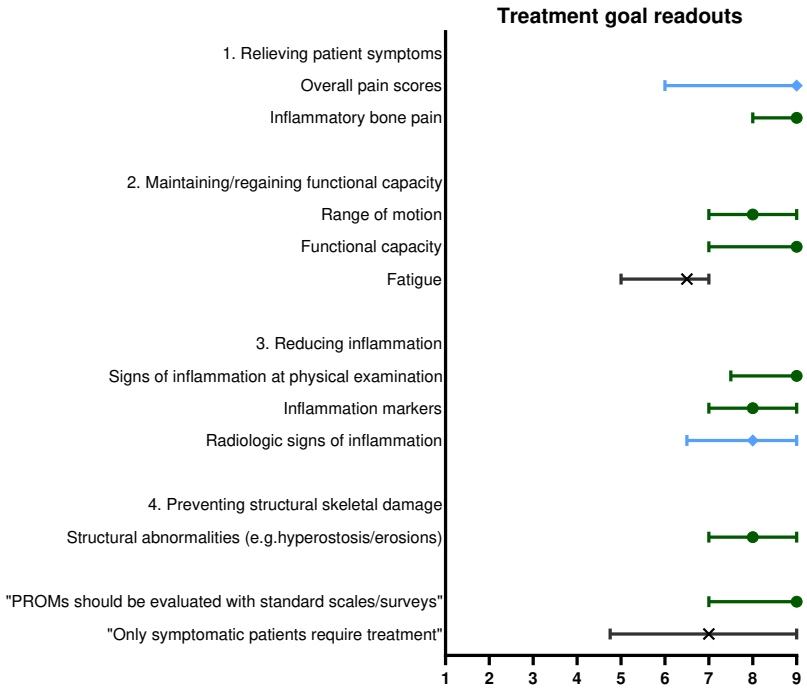


Figure 3.9: Respondent's opinion on readouts per specified treatment goal (presented as median level of agreement, interquartile range) ●: consensus, ♦: near-consensus, X: dissent

Readouts for treatment goals: free-text comments (clustered if appropriate)

Regarding patient-reported outcomes:

"Overall pain can be frequent in CNO. It should be addressed, but only inflammatory pain is a sign of active disease" (n=2)

"Fatigue is a non-specific symptom, important for the patient, but with multiple mechanisms and endless confounding factors." (n=5)

"It is unclear how to define inflammatory bone pain" (n=3)

"Health Assessment Questionnaire - Disability Index (HAQ-DI) can be used. Ability to work."

"Standardized surveys for PROMs are only useful in comparative studies. They are time-consuming and less useful for clinical practice." (n=2)

"Improving range of motion is a valid treatment goal, but will be reflected in functional capacity and symptom relief and QOL scales."

"I would not categorize fatigue under functional capacity. I would involve patient preferences in the choice of clinical outcome parameters."

"VAS on what location, for how long, last day/last week?"

"Not sure whether SF36 will be used in daily routine for an individual patient, but might be a good tool to compare groups (e.g., before and after specific therapy) as we have no validated specific questionnaire (and I doubt whether we would need this due to the relatively broad spectrum of disease features...)"

Regarding radiologic inflammation and structural damage:

"Importance of radiologic inflammatory signs depends on where - spine MUST be without edema, other areas may not be as worrisome, e.g., long bones."

"Radiologic inflammation is not always coupled with clinical symptoms or biologic markers of inflammation. Importance of residual inflammation is unknown." (n=3)

"Radiologic inflammation can be used if the clinical picture is unclear, for example, if not sure if persistent symptoms are due to persistent inflammation.

"I prefer the patient's opinion over some STIR signal without clinical signs... But would like to have this information and lab tests at some time of follow-up."

"Prevention of structural damage won't be possible if already present at diagnosis, so maybe rephrase into 'no progression'."

Regarding treatment initiation in asymptomatic patients:

"Unfortunately, we do not know if treatment prevents structural damage." (n=3)

"Treatment should be started immediately when the patient has lesions to prevent structural changes as well as pain."

"Some asymptomatic lesion may require treatment, especially in the spine. This may justify preventive treatment to avoid evolution, and should be discussed with the patient." (n=7)

"SCCH with slow growth can affect veins and more, a follow-up without treatment, but reevaluation by imaging to exclude/detect increasing SCCH seems to me necessary."

"Like in Paget's it depends on location."

3.10 Step 1 treatment considerations

The group input so far revealed two key concerns regarding management. First, the diverse clinical presentation of adult CNO/SAPHO makes it challenging to formulate uniform treatment approaches. For all treatment questions, it was therefore decided to focus on the treatment of **sterile bone inflammation** (being the core feature of the disease spectrum). Second, treatment recommendations for adult CNO/SAPHO will be largely eminence-based as there is a lack of robust evidence. Regarding step 1 treatment, the group generally opts for NSAIDs/COXIBs in the majority of patients. There was little agreement on indications to skip NSAID/COXIB treatment and advance with step 2 treatment directly. There was also insufficient agreement on the need for NSAID/COXIB rotation, and the total duration of NSAID/COXIB therapy. Delphi Round #2 addressed these issues in more detail, yielding the results shown below. Of note, for step 1 treatment, fully treatment-naïve patients were assumed for sake of clarity.

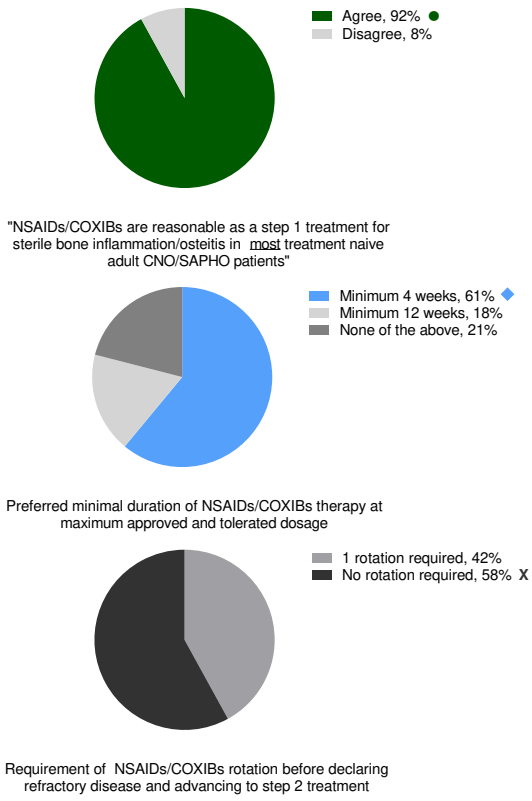


Figure 3.10: Respondent's opinion on the role, duration, and rotation of NSAIDs/COXIBs as step 1 treatment in most treatment naïve CNO/SAPHO patients. ●: consensus, ♦: near-consensus, X: dissent

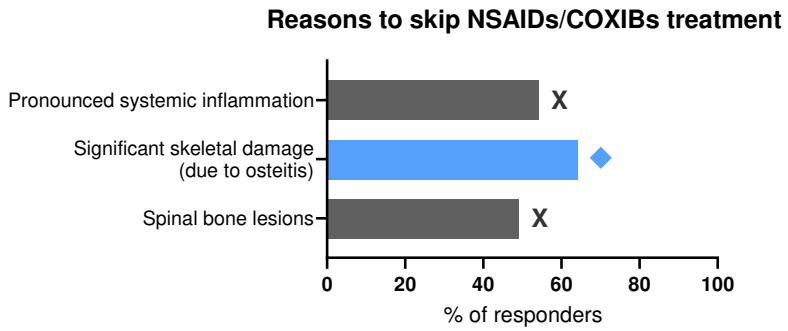


Figure 3.10 (continued): Reasons to skip NSAIDs/COXIBs treatment and advance to step 2 treatment. ●: consensus, ♦: near-consensus, X: dissent

Step 1 treatment: free text comments (clustered if appropriate)

"In most treatment-naive patients, this will not suffice to obtain substantial pain decrease." (n=2)

"We do strongly recommend Non-Pharmacological treatment as a 1st line conjunctive treatment such as management of focal infection eg, periodontal infection/tonsillitis/sinusitis if it is indicated and smoking cessation. Since in Japan, 85% of SAPHO are PPP related osteo-arthritis (PAO) (we reported in 2020 in Rheumatol Ther 2020, 883-891). Similarly, reports from China agree that >80% of SAPHO patients have PPP lesions (Yu et al. Arthritis Res & Ther 2020, 22, 216). PPP exacerbated by focal infection was first described by Andrews as Pustular bacterid,(Andrews GC, Machacek GF: Pustular bacterid of the hands and feet, Arch Dermatol, 1935; 32: 837–847.) and the majority of our patients with PPP (>80%) are this character, reported from Yamamoto et al (Pustulotic arthro-osteitis associated with palmoplantar pustulosis, J Dermatol, 2013; 40: 857–863). Furthermore, PAO was first described by Dr. Sonozaki in 1979 (Arch Orthop Trauma Surg 1979;95:13-22) followed by case series in 1981 (Ann Rheum Dis 1981, 40, 547-553) before SAPHO definition by Prof. Khan in 1987."

"I don't have experience with newly diagnosed CNO/SAPHO, but I can imagine that, even in light of the moderate results (pooled response is 'good' in 14%) in clinical studies, a 4-week NSAID course in a treatment-naive patient, repeated for another 4 weeks in case of a partial response, before stepping up is a valid approach. There is analogy in that approach to inflammatory arthritis (rheumatoid arthritis, spondyloarthritis). In practice, most patients will already have been given an NSAID trial by their GP or specialist, although often not in the optimal dosage and sufficiently long period."

"If there are no signs of multifocal destructive disease (i.e., peripheral erosive polyarthritis)."

Treatment duration:

"If the patient continues with pain, we have to start bisphosphonate monthly during 6 months to be well-tolerated."

"If taken at the full dose each day, then steady-state drug levels are reached in 3-5 days, and so judgment on therapeutic effects will be known within 1-2 weeks." (n=2)

"If the patient fails to respond in 4 weeks, it is unlikely that long-term treatment will be of any value." (n=2)

"For peripheral CNO/SAPHO 4 weeks may be reasonable but often the patients come to a physician with a long duration of pain and a likely pre-trial with NSAIDs. I would vote for 2-3 weeks duration."

"Depends on symptoms, as needed, may also be longer" (n=2)

"Coming from axial spondyloarthritis, it might be helpful to say at least two different NSAIDs at maximal doses over one month - but I think no studies exist here. Every one of my patients had been treated with at least one NSAID, many even with 2 or 3 different substances (either OTC or prescribed by GP or orthopedist in private practices) before being sent to a specialist."

Second trial of NSAID/COXIB:

"Long-term NSAIDs are a greater risk than some of the other options." (n=2)

"The possibility of a meaningful response upon a second NSAID (following a complete lack of response to the first one) is low." (n=3)

"If piroxicam, meloxicam, diclofenac, or etoricoxib are used for more than one week at full dose without sufficient effect, no other NSAID / COXIB step is needed. If lower doses than full dose of the above-mentioned or if ibuprofen or celecoxib are used, an additional NSAID / COXIB trial of at least one week should be performed."

"But not more than two different ones."

"It depends on the severity of the symptoms and the extent of the disease. If the symptoms are more manageable and the disease is limited then a second NSAID would be considered first, but it should not be considered a necessary step for every patient." (n=2)

"In general in rheumatology, I recommend 2 rotations (i.e., x3 NSAIDs tried) - chance of side effects on one / chance of inefficacy on one / taking into consideration the known idiosyncratic therapeutic effect."

"Same as AxSpA treatment, ASAS/EULAR AxSpA treatment recommendation updated in 2022. I believe you are talking about patients having received sufficient doses at an appropriate frequency. While a high dose of naproxen (and others) is necessary to see improvement in pediatric CNO, UK colleagues are frequently using insufficiently low doses."

"For example, one short half-life and a long half-life drug."

"I guess the advice to use at least two NSAIDs can be challenged. I cannot easily find the literature that supports, for instance, the ASAS-EULAR guideline on AS, which states that one should rotate. But maybe there is data on the subject. Regarding step 1: In DCP, there is a distinction between the effect on pain and on inflammation, and there is a distinction between non-responders and partial-responders. This can be taken into account when making a statement. In DCP, I personally don't see large improvements from a second NSAID course in non-responders. Disease-specific features or targeted organs (skin, joints) may also have a role in a step-up versus combination therapy-approach."

Indications for treatment escalation (step 2):

"Spinal lesions form an indication only if there was evidence of vertebral collapse"

"Patients with extended disease and high inflammatory burden are unlikely to respond to NSAIDs alone"

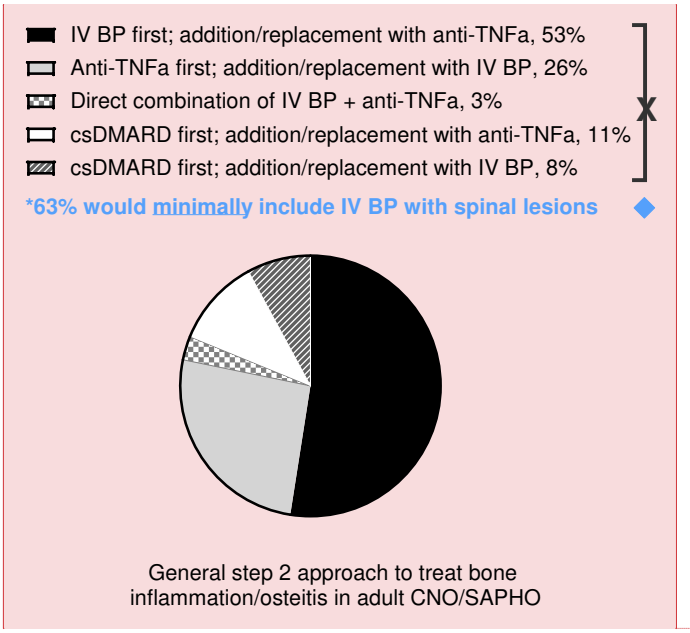
"Pain is also a step-up criterium"

"Or active MRI findings in long standing diseases"

"The patients with pronounced systemic inflammation but no spinal lesions or damage might actually be the ones who benefit from NSAIDs. In Ax-SpA CRP is a prognostic marker for NSAID response."

3.11 Step 2 treatment considerations

For step 2 treatment, not one "preferred" approach could yet be formulated, as choices are dependent on numerous patient and contextual factors. Overall, it seems like intravenous bisphosphonates and anti-TNF alpha are most frequently used as step 2 agents, but their preferred order (or direct combination) is not yet clear. Delphi Round #2 attempted to identify the global preferences regarding step 2 treatment, proposing several strategies that were frequently mentioned in earlier discussions (figure 3.11). Of note, for step 2 treatment, patients refractory to NSAIDs/COXIBs, or those with indications for direct step 2 treatment as identified by the group were assumed.



Commented [MOU5]: TNF alpha or TNFα

Figure 3.11: Respondent's preferred approach in step 2 treatment of bone inflammation/osteitis in adult CNO/SAPHO. IV BP=intravenous bisphosphonates, Anti-TNF alpha=Tumour Necrosis Factor-alpha inhibitors, csDMARD=conventional synthetic disease-modifying anti-rheumatic drug, "addition/replacement" signifying addition of the second drug, of full replacement with the second drug if the first drug yields insufficient response.
** Not chosen by any : "Direct combination of csDMARD and IV BP" and "Direct combination of csDMARD and anti-TNFa" and "none of the above"

Step 2 treatment considerations: free-text comments (clustered if appropriate)

Choice remains highly dependent on the skeletal distribution (unifocal or multifocal) and the presence of additional features (n=8)

"Preference for BP in spinal lesions depends on the feature of the lesions."

Anti-TNF alpha agents:

"Prescription of anti-TNF alpha drugs is limited by healthcare system to those with specific features leading to reimbursement" (n=2)

"With spinal lesions, BPs should be given together with anti-TNF alpha" (n=3)

"If there is many lesions or enthesitis of the spine, I would go for anti-TNF."

"What is non-response, in case of secondary failure, because of antibodies, start another anti-TNF. In difficult casus IL17 blocker, particular with eg sacroiliac involvement."

"Anti-TNF is possible to be effective to nearly all domains of adult CNO/SAPHO, other medicine could be add-on when the response of anti-TNF is not sufficient, but change to other biologics or targeted medicines in case no response at all."

"In women of reproductive age, anti-TNF alpha agents would be preferable over bisphosphonates."

"Even though BPs appear effective based on published evidence we should acknowledge that most of these data are relatively old, prior to biologics, when treatment options were extremely limited. In my mind anti-TNF appear as the most robust tools for sterile bone inflammation and are a reasonable step 2 treatment option."

Conventional syntheticDMARDs (csDMARDs):

"Generally methotrexate (MTX) first. Efficient, cheap, very few serious side effects in the hands of MTX well-educated and experienced medical healthcare providers (not too much influenced by pharmaceutical companies) if the patient takes it correctly."

"In my cohorts 80% of patients reach a remission of CNO only bDMARDs (preferentially TNFi), however, 20% already on cDMARDs (MTX, other) with/without bisphosphonates, therefore I recommend the escalation starting from three months csDMARDs followed by bisphosphonate add-on (before bDMARDs). Single patients with high level of painful disease (concerning mandibula, clavivula or others) also need for a few weeks glucorticosteroids (after NSAR failure)."

"I tend to avoid csDMARDs unless strong sense this is PsA spectrum disease with peripheral skeletal phenotype."

"There are two RCT (strong evidence) to suggest IL23 inhibitor improve PPPASI (some patients have PAO in the studies), eg, Risankizumab and Guselkumab. So I do recommend replacing TNFi to bDMARDs including TNFi,IL23i and perhaps IL17i."

3.12 Step 3 treatment considerations

Delphi Round #2 evaluated which treatments/interventions may be considered in multi-step refractory adults with CNO/SAPHO to manage sterile bone inflammation/osteitis (see figure 3.12).

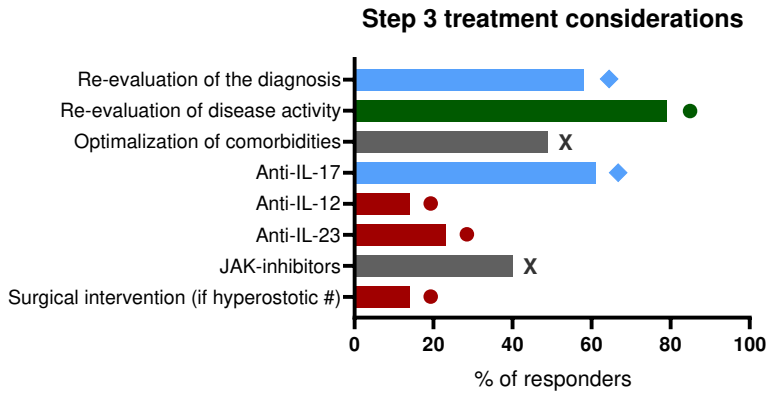


Figure 3.12: Considerations for step 3 treatment of bone inflammation/osteitis in adult CNO/SAPHO. IL=interleukin, JAKi=janus kinase inhibitors, #: complication, ●: (negative) consensus, ♦: near-consensus, X: dissent

Step 3 treatment considerations: free-text comments (clustered if appropriate)

"Consider anti-IL-1 treatment; there is some evidence in children and usually permitted." (n=3)

"Anti IL-17 and anti IL-23 may be considered particularly in case of skin involvement." (n=2)

"At present I'm hesitant regarding IL-17, IL-12, IL-23, and JAKs. I would consider these only if nothing else helps or had to be stopped, but this is not very likely. Anti-IL23 and JAKi could be discussed but I would say in the next step (not same level as anti-IL17)."

"I have doubts about anti-IL17 but I would suggest a very formal approach for this initiative. State the present evidence regarding pathophysiological mechanisms and case-reports/series with bDMARDs/tsDMARDs, and refrain from speculations."

"Surgical intervention: I have good experience in two cases with synovectomy in the manifestation of osteitis/synovitis in the region of SCCH."

" Please change IL12 to IL12/23 inhibitor which is Ustekinumab. Then I choose Yes for IL12/23. Anti-23s (Guselkumab and Risankizumab as stated above) remain the important selections as well."

"Anti-IL-12/23 is not available so far in our hospital, I have no idea about them."

"JAKi in younger patients <65 years."

3.13 Ancillary treatment considerations

Delphi Round #2 evaluated which treatments/interventions may be considered as ancillary treatments in adult CNO/SAPHO (see figure 3.13).

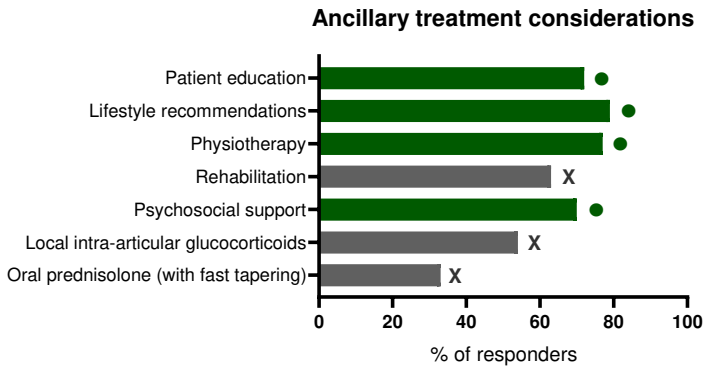


Figure 3.12: Considerations for ancillary treatments in adult CNO/SAPHO. ●: consensus, X: dissent

Ancillary treatment options: free-text comments (clustered if appropriate)

"Lifestyle recommendations (smoking cessation, physical activity, weight control, etc.): You can talk about it but they all already know and the result of bothering the patient will be very close to zero."

"I avoid steroids. Can be of limited therapeutic impact and risk of rebound psoriasis issue if palmar-planta pustulosis."

"I think all can play a role in adequate management, especially in difficult-to-treat cases, which are many. Again, patient-preferences would be interesting to study on these subjects."

3.14 Treatment considerations for additional (extra-skeletal) features

The questions above have concentrated on treatment of **sterile bone inflammation/osteitis** in adult CNO/SAPHO, as recommended during group discussions. However, this core manifestation of adult CNO/SAPHO can be accompanied by additional (extra-skeletal) features, which may warrant different treatments. These treatments may complement the treatments for sterile bone inflammation/osteitis (e.g. CNO/SAPHO + clinically apparent arthritis may be treated with intravenous bisphosphonates + methotrexate), or one agent may conveniently target multiple features. (e.g. CNO/SAPHO + features compatible with axSpA like sacro-iliitis or uveitis may be jointly treated with anti-TNFa.)

As apparent from Delphi Round #2, there is **unanimous consensus (100% agreement)** about including the statement below (or a slightly modified version) in the final recommendations to address this issue. This way, the final recommendations leave room for clinicians to optimize treatments according to specific patient phenotype.

"In case of additional (extra-skeletal) features, follow established treatment protocols accordingly. Align or combine with treatment for sterile bone inflammation/osteitis if applicable.

Features may include: psoriasis, pustulosis palmoplantaris, hidradenitis suppurativa, dactylitis, arthritis, sacro-iliitis, uveitis, inflammatory bowel disease"

Treatment considerations for additional (extra-skeletal) features : free-text comments (clustered if appropriate)

"This is what I do. If there are further features then I can get different drugs."

"Fully agree. it has been done the same for axial SpA. As there is no strong evidence for one treatment rather than another, extraosseous manifestations can be very useful in choosing the appropriate treatment."

"In my experience at least 50% (or even more) of the CNO patients meets the criteria of PsA or AS diagnosis, I think, for treatment choice an relevant aspect"

"Topical treatment (skin: acne, psoriasis, pustulosis), systemic treatment with retinoids for acne if necessary"

"In many patients, especially younger males hidradenitis suppurativa strongly affect quality of life. Uveitis, especially if recurrent, and IBD are not ancillary problems"

"I think it would add largely to the practical use of the initiative, and thereby the adaptation/implementation. Any thought on how to implement it the end result?"

"Long sentence reads difficult. In case of extra-skeletal features (e.g. at the skin) one might consider to use combination therapy (e.g. bisphosphonate plus methotrexate) or initial choice of advanced treatments (e.g. TNF inhibitors or others) to target all structures with one drug."

3.15 Follow-up

The group agreed in Delphi Round #1 that long-term follow-up is important due to the temporal dissociation of different clinical features. In that regard, patients should be advised that after the end of follow-up, their condition might return with similar or different clinical features in the future. Complication monitoring was further evaluated in Delphi Round #2, yielding the results as shown below.

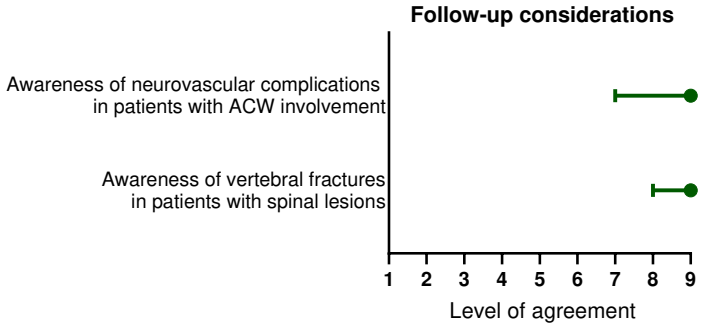


Figure 3.15: Respondent's opinion regarding follow-up considerations (presented as median, interquartile range). ●: consensus

Follow-up: free-text comments:

"Neurovascular complication is not something that I have personally encountered." (n=2)

"Neurovascular complication does not need to be mentioned here. I think this is very rare and doesn't need to be mentioned in a guideline"

Supplemental material 7: Minimal dataset for patient registry for adult CNO

Generic data elements: consent, date of birth, sex at birth, current gender, country at birth, country of residence, follow-up status, date of death if applicable, first contact with centre, clinician responsible, date of first clinical manifestations, how diagnosis was reached, date of diagnosis, biobank samples available for research.

Of note: The form is filled out at initial referral, and subsequently during follow-up with either periodic consultation depending on local protocols (minimally every 2 years), or with a major treatment switch or change in clinical picture. The data system should capture differences between the initial form and follow-up forms as representing changes in clinical course and management (e.g. new additional features, treatment switches). The form may be potentially be supplemented with patient reported outcomes (PROs) and patient reported outcome measures (PROMs), which can be filled out by the patient directly. PROMs relevant to CNO include, among others, Brief Pain Inventory Short Form and EQ-5D.

Data elements for condition specific module for adult CNO

Variable	Response type & options	Comments
Type of imaging performed	Checkbox - Magnetic Resonance Imaging (local) - Magnetic Resonance Imaging (total body) - Computed Tomography (local) - Computed Tomography (total body) - ([^{99}mTc]Tc-HDP SPECT/CT - PET/CT (if checked; specify tracer in free text) - Plain X-ray	Automatically deduces whether total body imaging has been performed
Localization of CNO bone lesions	Checkbox Total-body skeleton image with zoom-in possibility in typical regions such as: - Clavicles (left/right) - Ribs (left/right, including level) - Sternum - Spine (including vertebral level) - Mandible (left/right) - Ilium (left/right) - Other (specify)	Automatically yields total number of bone lesions

Radiologic activity of CNO bone lesions	Severe/moderate/mild/none	Defined by bone marrow oedema or increased radiotracer uptake, will be assessed by central review of images
Skeletal damage (erosions hyperostosis, ankylosis, soft tissue ossification) due to CNO	Yes/no, if yes, checkbox for specification	Exact definitions of erosions, hyperostosis, ankylosis and soft tissue ossification including typical localizations given in field instruction.
Bone biopsy performed	Radio buttons Yes/no	
Additional features (history or current)	Checkbox - Arthritis - Sacro-iliitis - Enthesitis - Dactylitis - Palmoplantar pustulosis - Psoriasis - Hidradenitis suppurativa - Severe acne - Uveitis - Inflammatory bowel disease	
Other auto-inflammatory features (history or current)	Radio buttons Yes/no, if yes, free-text specification	
Smoking habit	Dropdown Past/current/never	
Work participation	Full absence from (paid) work due to CNO/partial absence from (paid) work due to CNO/no absence from (paid) work due to CNO	
Positive family history (1st degree relatives) for autoinflammatory/autoimmune disease	Radio buttons Yes/no	List of autoinflammatory/autoimmune diseases is provided.
Bone pain at CNO lesion site	Radio buttons Yes/no, if yes, specify Numerical Rating Scale (NRS) for pain if available	
Focal inflammatory signs at physical examination	Radio buttons Yes/no	E.g. erythema, warmth, soft tissue swelling

Erythrocyte sedimentation rate	Numeric (mm/h)	
C-reactive protein	Numeric (mg/L)	
Treatment history for CNO or CNO-related symptoms	Checkbox - NSAID/COXIB - csDMARD - Bisphosphonates (IV) - Bisphosphonates (oral) - TNFi - Other biologic DMARD - Glucocorticoids (systemic) - Glucocorticoids (intra-articular) - Opioids - Surgery - Physical therapy - Other (free text)	Include treatment for osteitis AND treatment for additional features, if present.
Current treatment for CNO	Checkbox - NSAID/COXIB - csDMARD - Bisphosphonates - TNFi - Other biologic DMARD - Glucocorticoids (systemic) - Glucocorticoids (intra-articular) - Opioids - Surgery - Physical therapy - Other (free text) All that all selected prompt a follow-up question for type, administration route, and dose	Include treatment for osteitis AND treatment for additional features, if present.
Indication for current treatment	Checkbox - Bone pain at CNO lesion site - To improve functioning or quality of life - Prevention of complications	Complications may include: vertebral collapse Structural skeletal damage secondary to inflammation may include: erosions, hyperostosis, ankylosis, soft tissue ossification

	- Prevention of structural skeletal damage secondary to inflammation - Additional features (if selected, specify which based on previous entry)	
Adverse effects of current treatment	Free text	