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Recommendation

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

Elizabeth Winter[1,2,*], Olaf Dekkers[2,3], Caroline Andreasen[4], Salvatore D'Angelo[5], Natasha Appelman-Dijkstra[1,2], Simone Appenzeller[6], Gunter Assmann[7], Judith Bubbear[8], Oana Bulaicon[1,2], Roland Chapurlat[9], Varvara Choida[10,11], Gavin P.R. Clunie[12], Dimitrios Daoussis[13], Torsten Diekhoff[14], Marcel Flendrie[15], Olivier Fogel[16,17], Roba Ghossan[18], Hermann Girschick[19], Femke van Haalen[1], Neveen Hamdy[1,2], Barbara Hauser[20,21], Christian Hedrich[22], Philip Helliwell[23], Kay Geert Hermann[24], Antonella Insalaco[25], Anne Grethe Jurik[26], Mitsumasa Kishimoto[27], Willem Lems[28], Paivi Miettunen[29], Burkhard Muche[30], Ana Navas Cañete[1,31], Natalia Palmou-Fontana[32], Frits Smit[1,33,34], James Teh[35], Charlotte Verroken[36], Kurt de Vlam[37], Daniel Wendling[38], Wei Zhou[39], Hans-Georg Zmierczak[36], Anne Leerling[1,2,3]

[1] *Center for Bone Quality, Leiden University Medical Center, Leiden, The Netherlands*
[2] *Department of Internal Medicine, Division of Endocrinology, Leiden University Medical Center, Leiden, The Netherlands*
[3] *Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands*
[4] *Department of Rheumatology and Internal Medicine, Gødstrup Hospital, Herning, Denmark*
[5] *Department of Health Science, University of Basilicata, Potenza, Italy*
[6] *Departamento de Clínica Médica. Facultade de Ciências Medicas da UNICAMP, Universidade Estadual de Campinas, Campinas, Brazil*
[7] *Department of Rheumatology, Ruhr-Universitat Bochum, Bochum, Germany*
[8] *Department of Rheumatology, Royal National Orthopaedic Hospital, London, UK*
[9] *Service de Rheumatologie et Pathologie osseuse, Hopital Edouard Herriot, INSERM UMR 1033 and University of Lyon, Lyon, France*
[10] *Department of Rheumatology, Homerton Healthcare NHS Foundation Trust, London, UK*
[11] *University College London, London, UK*
[12] *Department of Rheumatology, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK*
[13] *Department of Rheumatology, University of Patras Medical School, Patras, Greece*
[14] *Department of Radiology, Charité Universitätsmedizin Berlin, Berlin, Germany*
[15] *Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands*
[16] *Department of Rheumatology, Paris Saint Joseph Hospital, Paris, France*
[17] *Department of Rheumatology, Cochin Hospital, Paris, France*
[18] *Department of Rheumatology, Hospital Cochin, Paris, France*

*Correspondence to Dr. Elizabeth M. Winter.
E-mail address: e.m.winter@lumc.nl (E. Winter).
Social media: @FogelOlivier (O. Fogel)
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[19] Department of Pediatrics, Vivantes Klinikum im Friedrichshain, Berlin, Germany
[20] Rheumatic Diseases Unit, Western General Hospital, Edinburgh, UK
[21] Centre for Genomic and Experimental Medicine, MRC Institute of Genetics and Cancer, Western General Hospital, Edinburgh, UK
[22] Department of Women's and Children's Health, University of Liverpool, Liverpool, UK
[23] Academic Unit of Musculoskeletal Medicine, University of Leeds, Leeds, UK
[24] Department of Radiology, Charite Universitatsmedizin Berlin, Berlin, Germany
[25] Department of Paediatric Rheumatology, Ospedale Pediatrico Bambino Gesu, Roma, Italy
[26] Department of Radiology, Aarhus University Hospital, Aarhus, Denmark
[27] Department of Nephrology and Rheumatology, Kyorin University, Mitaka, Tokyo, Japan
[28] Department of Rheumatology, Amsterdam University Medical Centres, Amsterdam, The Netherlands
[29] Department of Paediatrics, University of Calgary McCaig Institute for Bone and Joint Health, Calgary, Alberta, Canada
[30] Department of Rheumatology, Charite Universitatsmedizin Berlin, Berlin, Germany
[31] Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands
[32] Department of Rheumatology and Pediatric Rheumatology, Immunology Group, Hospital Universitario Marques de Valdecilla, Santander, Cantabria, Spain
[33] Department of Radiology, Division of Nuclear Medicine, Leiden University Medical Center, Leiden, The Netherlands
[34] Department of Nuclear Medicine, Alrijne Hospital Location Leiderdorp, Leiderdorp, The Netherlands
[35] Department of Radiology, Nuffield Orthopaedic Centre Girdlestone Memorial Library, Oxford, UK
[36] Department of Endocrinology, Unit for Osteoporosis and Metabolic Bone Diseases, Ghent University, Gent, Belgium
[37] Department of Rheumatology, Universitaire Ziekenhuizen Leuven, Leuven, Belgium
[38] Department of Rheumatology, Universite de Franche-Comte, Besancon, France
[39] Department of Rheumatology, Beijing Tiantan Hospital, Beijing, China

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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 nonbacterial 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 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 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

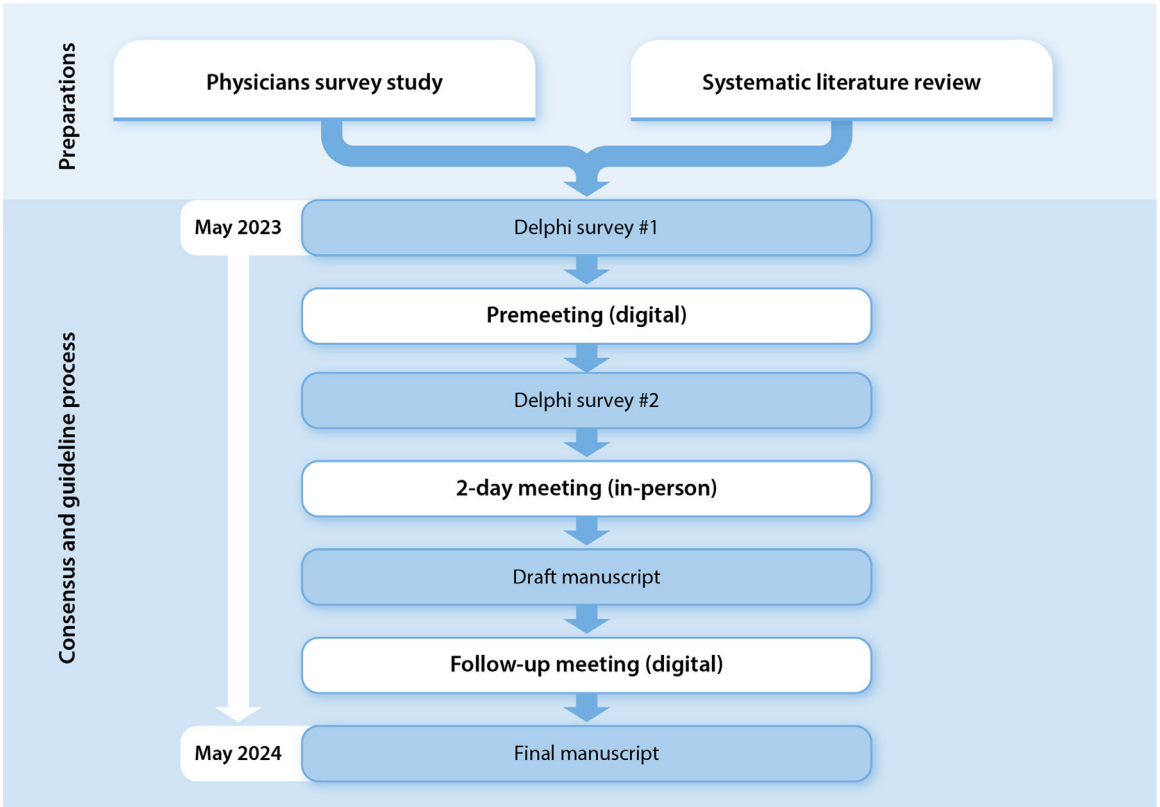

Figure 1. Schematic overview of consensus process.

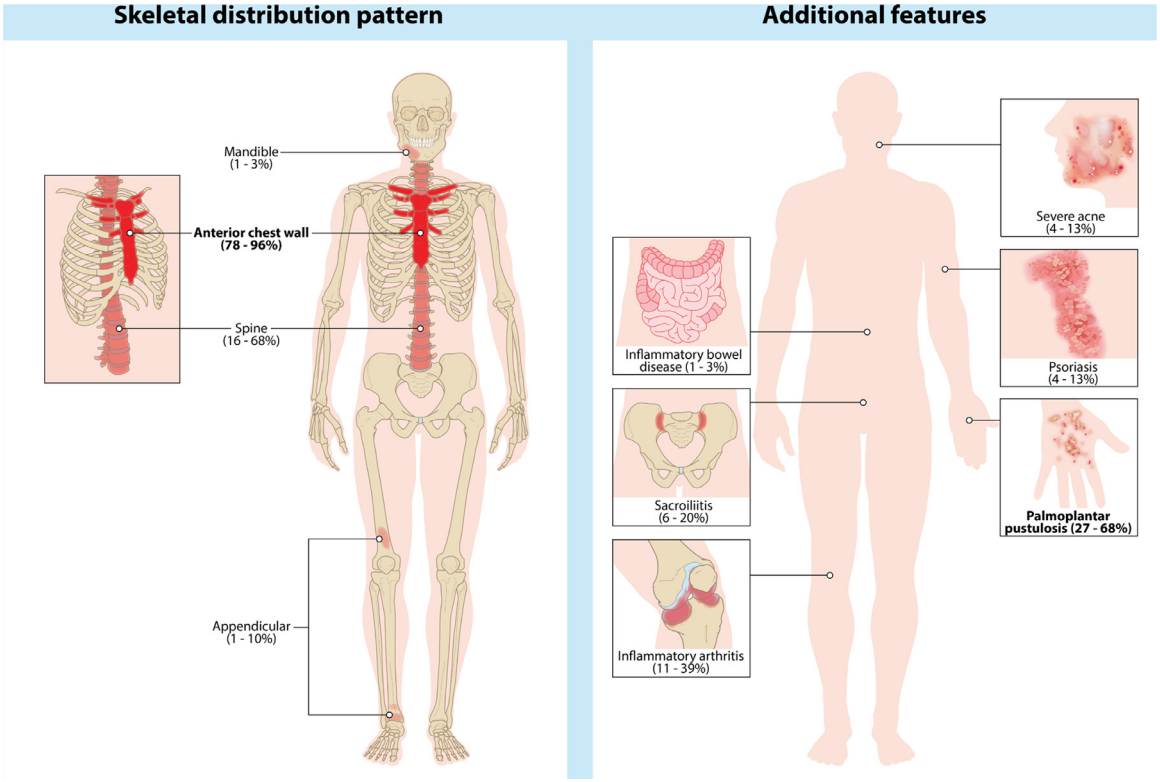

Figure 2. Visual representation of disease definition of adult CNO; skeletal distribution pattern of osteitis (left) and additional (extra)-skeletal features (right). Reported as 95% CI.

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. 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,

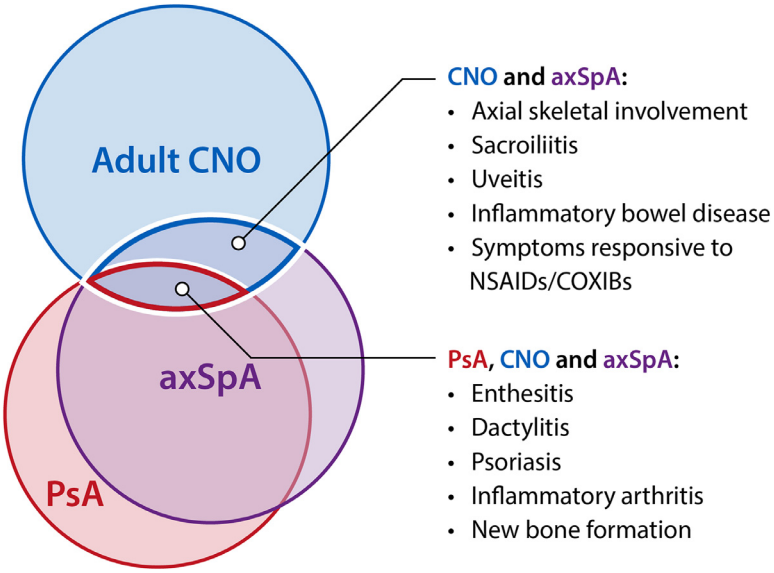

Figure 3. Venn diagram displaying conceptual overlap between adult chronic non-bacterial osteitis (CNO) and axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) based on features seen in the multiple conditions. COXIB, cyclooxygenase-2 inhibitor; NSAID, non-steroidal anti-inflammatory drug.

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]. 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 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

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.

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

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.

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 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 ([^{99}mTc]Tc-HDP SPECT/CT) and positron emission tomography (PET)/CT with a boneseeking 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 [^{99}mTc] 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 [^{99}mTc]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 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

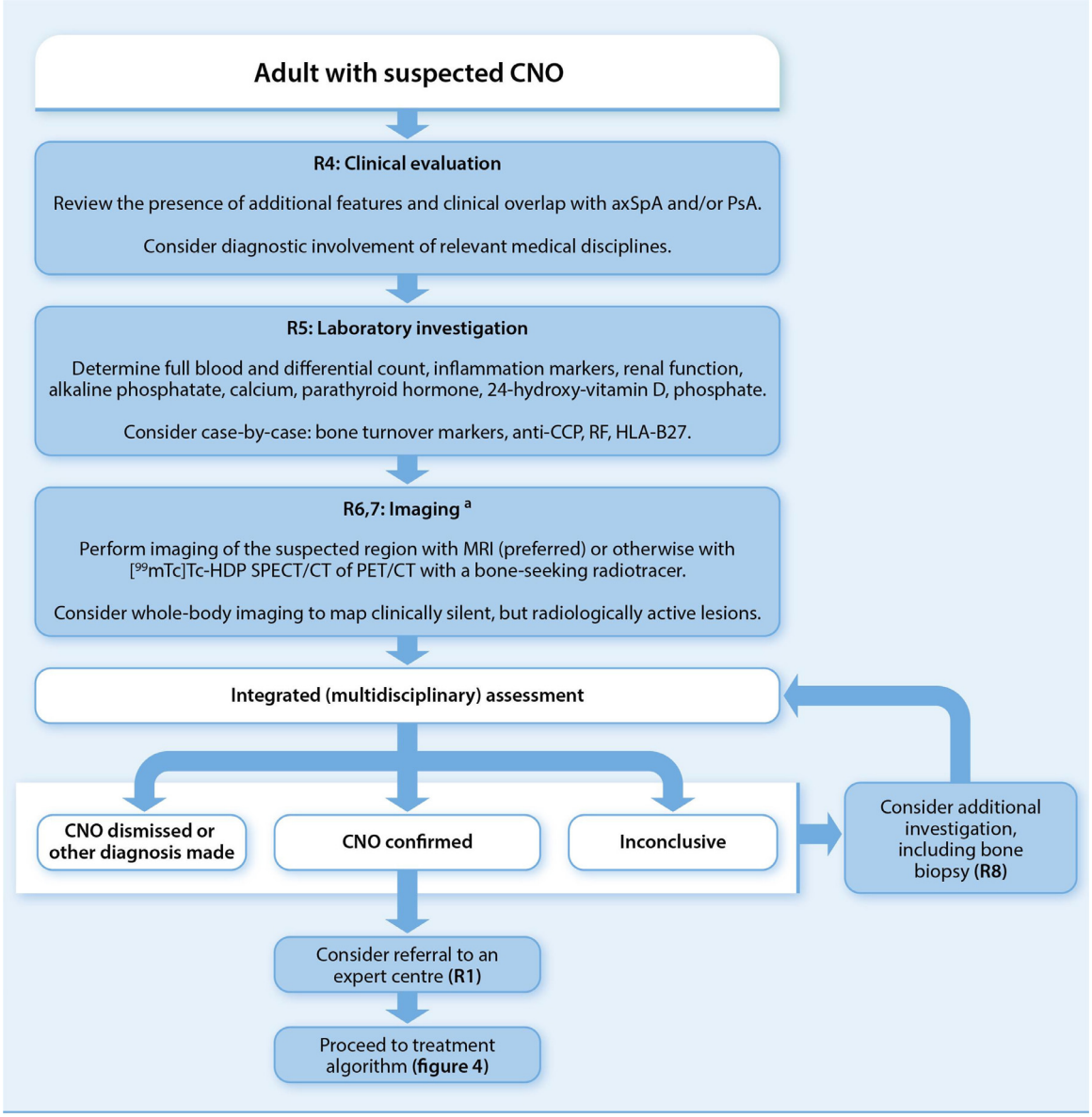

Figure 4. Diagnostic algorithm for adult CNO. ANA, antinuclear antibody and immunofluorescence pattern; anti-CCP, anticitrullinated protein antibodies; CNO, chronic non-bacterial osteitis; HLA-B27, human leucocyte antigen B27 typing; PET, positron emission tomography; RF, rheumatoid factor; [^{99}mTc]Tc-HDP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

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

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.

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.

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.

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 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.**
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

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 ondemand 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, reevaluate 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.

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.

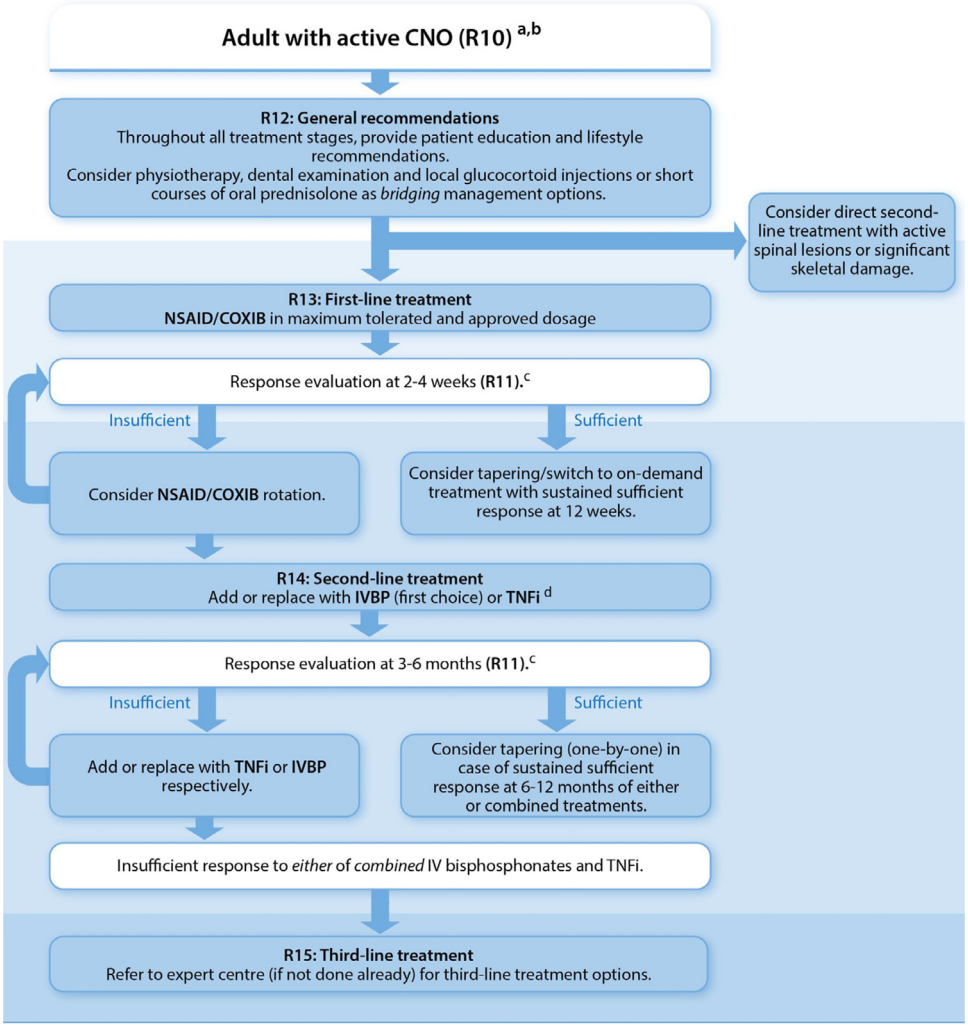

Figure 5. Treatment algorithm for adult CNO. axSpA, axial spondyloarthritis; CNO, chronic non-bacterial osteitis; COXIB, cyclooxygenase-2 inhibitor; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IVBP, intravenous bisphosphonates; NSAID, non-steroidal anti-inflammatory drug; PsA, 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.

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:

- **Provide patient education and lifestyle recommendations**
- **Consider physiotherapy and dental examination**
- **Consider short courses of oral prednisolone or intraarticular 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 antiinflammatory 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 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

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.

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/COX-IBs. 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

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.

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 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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Contributors

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Supplementary materials

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Orcid

Elizabeth Winter: http://orcid.org/0000-0002-0119-1588

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