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

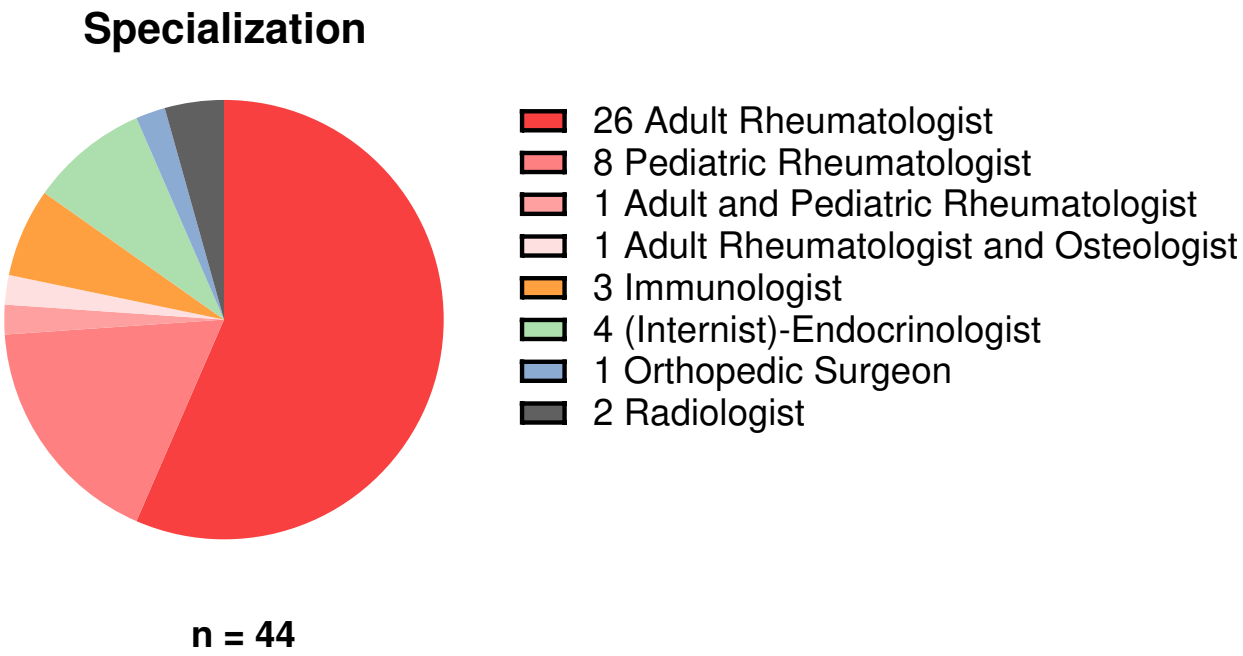
- All open text comments are listed below the pertaining question
- Subgroup analysis was performed according to number of patients under clinical care (<10 vs. ≥10) and remarkable differences in scoring are discussed as appropriate, indicated with *
- Bipolarity analysis was performed by visual inspection 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 ***

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

Results

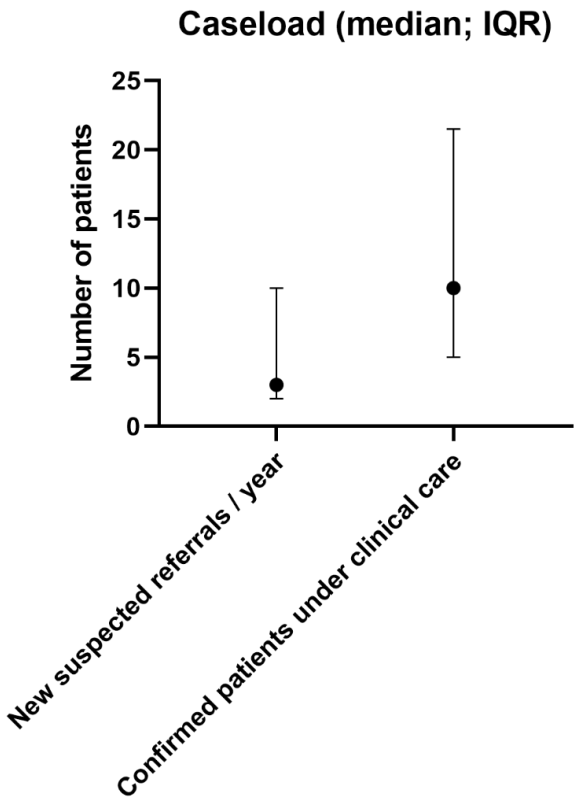
Number of completed responses: 44

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**

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

"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"		

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

"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)"		

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

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."		

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

"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."		

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

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."		

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

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."		

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

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."		

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

"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."		

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

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**

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

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."		

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

"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).	

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

"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."

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

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."		

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

"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”.

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

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)."		

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

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!"		

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

"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."		

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

"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."		

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

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**

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

	** 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."		

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

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	

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

	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."		

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

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."		

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

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."		

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

"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"		

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

"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"		

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

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."		

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

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"		

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

"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"		

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

"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."		

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

"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	

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

	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."""	

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

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?"		