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Systematic review and meta analysis

Clinical and therapeutic diversity in adult chronic nonbacterial osteomyelitis (CNO) of the sternocostoclavicular region: a meta-analysis

Anne T. Leerling [1,2], Olaf M. Dekkers[1], Natasha M. Appelman-Dijkstra[1,2] and Elizabeth M. Winter [1,2]

Abstract

Objectives. Chronic nonbacterial osteomyelitis (CNO) is a rare inflammatory bone disease. The distinct CNO subtype that affects the anterior chest wall is descriptively named sternocostoclavicular hyperostosis (SCCH) and mainly occurs in adults. Literature on CNO/SCCH is scattered and lacks diagnostic and therapeutic consensus.

Methods. Systematic review and meta-analysis aiming to characterize clinical presentation and therapeutic modalities applied in adult CNO/SCCH patients. Untransformed numerical data and double-arcsine transformed proportional data were pooled in a random effects model in R-4.0.5; proportions were reported with 95% CI.

Results. Forty studies were included, containing data on 2030 and 642 patients for aim 1 and 2, respectively. A female predisposition (67%, 95% CI 60, 73) and major diagnostic delay (5 years 95% CI 3, 7) were noted. Clinical presentation included chest pain (89%, 95% CI 79, 96) and swelling (79%, 95% CI 62, 91). Patients suffered from pustulosis palmoplantaris (53%, 95% CI 37, 68), arthritis (24%, 95% CI 11, 39) and acne (8%, 95% CI 4, 13). Inflammatory markers were inconsistently elevated. Autoantibody and HLA-B27 prevalence was normal, and histopathology unspecific. Increased isotope uptake (99%, 95% CI 96, 100) was a consistent imaging finding. Among manifold treatments, pamidronate and biologicals yielded good response in 83%, 95% CI 60, 98 and 56%, 95% CI 26, 85, respectively.

Conclusion. CNO/SCCH literature proves heterogeneous regarding diagnostics and treatment. Timely diagnosis is challenging and mainly follows from increased isotope uptake on nuclear examination. Biopsies, autoantibodies and HLA status are non-contributory, and biochemical inflammation only variably detected. Based on reported data, bisphosphonates and biologicals seem reasonably effective, but due to limitations in design and heterogeneity between studies the precise magnitude of their effect is uncertain. Fundamentally, international consensus seems imperative to advance clinical care for CNO/SCCH.

Key words: Sternocostoclavicular hyperostosis, SAPHO, pustulotic arthro-osteitis, chronic non-bacterial osteomyelitis, adults, treatment, diagnostics, bisphosphonates, biologicals

CLINICAL SCIENCE

Rheumatology key messages

- Literature on adult CNO/SCCH is highly heterogeneous regarding terminology and classification.
- Timely diagnosis of CNO/SCCH is challenging and mainly follows from combined CT and nuclear imaging.
- Off-label treatments for CNO/SCCH are diverse; bisphosphonates and biologicals seem effective but warrant powered randomized controlled trials.

[1]Department of Internal Medicine, Division of Endocrinology and [2]Center for Bone Quality, Leiden University Medical Center, Leiden, The Netherlands

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Correspondence to: Elizabeth M. Winter, Center for Bone Quality, Leiden University Medical Center, Albinusdreef 2, Postal zone B2-R, 2333 ZA Leiden, The Netherlands. E-mail: e.m.winter@lumc.nl

Introduction

Chronic nonbacterial osteomyelitis (CNO) is an impactful inflammatory bone disease affecting both children and adults. The internal diagnostic classification of the CNO spectrum is poorly resolved, with overlapping or conflicting terminology handled internationally. Essentially, the CNO spectrum contains multiple distinct subtypes, including diffuse sclerosing osteomyelitis of the mandible (DSO), and chronic recurrent multifocal osteomyelitis (CRMO), of which the latter typically affects the long bones rather than the axial skeleton and predominately occurs in children [1–3]. The CNO subtype that is localized in the sternum, clavicles and upper ribs is descriptively named sternocostoclavicular hyperostosis (SCCH). CNO/SCCH is a midlife disease and appears to be associated with a significant diagnostic and therapeutic delay [4–8]. CNO/SCCH can also be one manifestation of the rheumatic entity of SAPHO syndrome, the standing acronym for the combination of synovitis, acne, pustulosis, hyperostosis and osteitis, and of which the latter two comprise CNO/SCCH [9, 10].

In the absence of validated diagnostic criteria, CNO/SCCH may be identified upon osteoarticular involvement of the sternocostoclavicular region, which may or may not be accompanied by other localizations or other SAPHO manifestations [5, 11]. A wide range of off-label treatment modalities have been proposed for CNO/SCCH and SAPHO [5, 6, 10], but currently the choice is physician-dependent. A systematic review on CNO/SCCH in adults has not yet been published, but there is clear need for overview in order to direct future research initiatives and advance clinical care for this highly impacted patient group [12]. We therefore aimed to compile evidence on clinical presentation and treatment modalities applied in adult CNO/SCCH.

Materials and methods

A review protocol was submitted to Prospero on 26 January 2021 and to the Open Science Framework on 3 March 2021, and was later updated upon the decision to perform meta-analyses. A PRISMA guideline checklist is provided in Supplementary Data S1, available at *Rheumatology* online. A literature search was conducted for Pubmed, Embase, Emcare, Web of Science and Cochrane (final search string attached in Supplementary Data S2, available at *Rheumatology* online).

Selection of studies

Reviews, letters, editorials, quizzes, imaging rubrics, meeting abstracts, non-peer-reviewed work, and work without full texts available in English were excluded for both aims. For aim 1 (characterizing clinical presentation), we included studies that:

- reported on >15 subjects age 18 or above sampled on the diagnosis of CNO/SCCH based on: (i) clinical characteristics: presence of (relapse remitting) pain, optionally with redness and/or swelling in sternocostoclavicular (SCC) region; and (ii) radiologic characteristics: osteitis, sclerosis or hyperostosis around SCC region on CT-imaging, X-ray or MRI and/or increased uptake around SCC region on skeletal scintigraphy. Of note, this diagnostic definition includes both isolated CNO/SCCH, and CNO/SCCH accompanied by bone lesions outside the SCC region, or arthritis and skin manifestations as seen in SAPHO syndrome; and
- focused on the clinical presentation and/or diagnostic process.

For aim 2 (compiling treatment modalities plus response) we included studies that:

- reported on >5 subjects age 18 or above with diagnosis of CNO/SCCH (as described above); and
- focused on therapy for the SCC lesion with systematic evaluation of treatment response

Study selection was done by A.L. In case of doubtful fulfilment of criteria, studies were also independently assessed by E.W. Upon conflicting assessment, eventual selection was consensus-based.

Data extraction and synthesis

The final data extraction form is attached in Supplementary Data S3, available at *Rheumatology* online. Numerical data were extracted only when presented in means, excluding medians. Missing numerical data were calculated if possible. As several studies were conducted in the same centre, we contacted authors to inquire about cohort overlap, or assessed potential overlap ourselves (see Supplementary Table S1, available at *Rheumatology* online).

Non-numerical data were categorized to generate proportions per study. Data categories were defined by A.L. and E.W. (see Supplementary Data S4 for detailed definitions, available at *Rheumatology* online). For treatment response, 'good response' was defined as any description indicating major reduction of pain, disease remission, or improvement of pain on a visual analogue scale (VAS) of >50%. 'Partial response' was defined as some, but incomplete improvement pain, or improvement of pain on VAS of 20–50%. 'No response' was scored in case of no pain reduction, worsening of symptoms, or whenever a switch to another treatment modality was necessary.

Statistical analysis

All analyses were performed in R-4.0.5. Untransformed means were meta-analysed using the inverse variance method, in a random effects model. For binary data, the weighted proportions from individual studies were double-arcsine transformed and meta-analysed into summary proportions in a random effects model. The method of restricted maximum likelihood (REML) was used to assess heterogeneity between studies as expressed as I^2 and Tau^2. No meta-analytical pooling was conducted for data items that were either incidentally reported (not for total cohorts) or in fewer than four studies. Stratified analyses for CNO/SCCH diagnosed as

a separate entity and CNO/SCCH diagnosed as part of SAPHO syndrome were performed as indicated.

Risk of bias analysis

Studies were categorized into trials (i.e. the intervention was imposed as aim of the study [13]; non-randomized or randomized), cohort studies and cross-sectional studies. For non-randomized and randomized trials, the ROBINS-I tool and RoB-2 tool were used respectively for appraisal [14, 15]. Cohort studies [13] were assessed by the Newcastle Ottawa Scale [16]. For cross-sectional, the AXIS appraisal tool was used [17]. Assessment was performed by A.L. and checked with E.W.

Results

Literature search and study selection

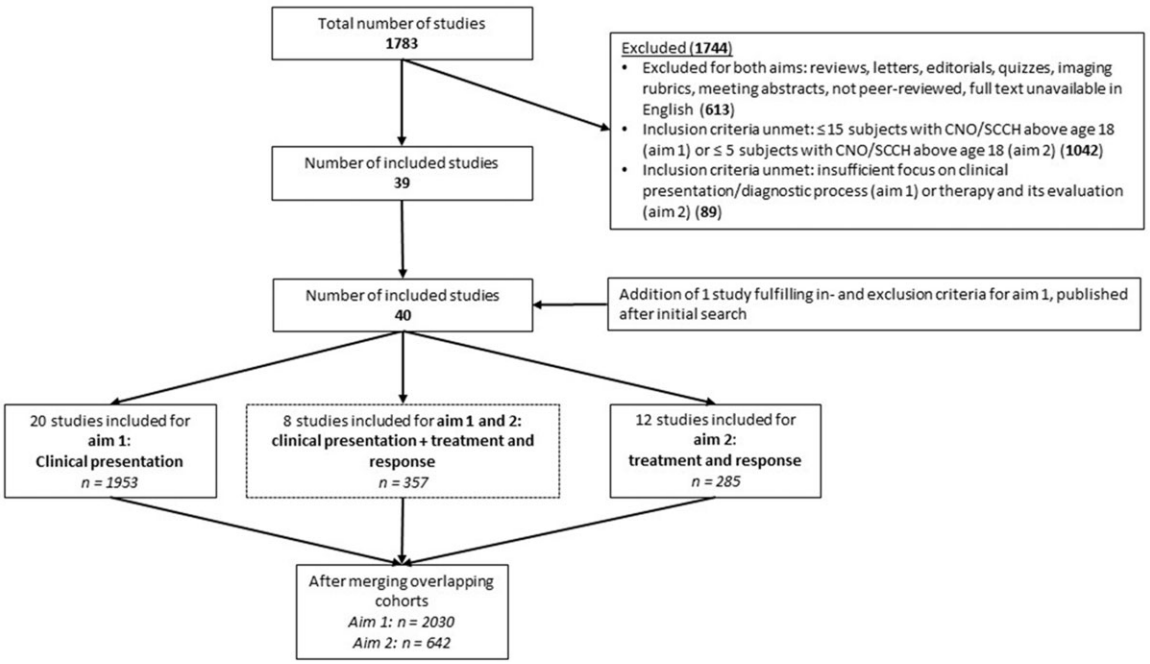
The search yielded 1783 unique publications (February 2021). A total of 613 were excluded due to publication type, 1042 due to unmet cohort criteria, and 89 due to insufficient focus (see Fig. 1). One eligible publication was published in full-text after the last search, and was considered of main importance; it was therefore manually added to the final selection. In total, 40 publications were included (see Supplementary Table S2 for core study details, available at *Rheumatology* online), published between 1979 and 2021 [6–9, 11, 18–52]. After merging overlapping cohorts, 2030 patients were analysed for aim 1 and 642 for aim 2.

There was substantial nomenclatural diversity across the included studies; an overview of the terms encountered to describe CNO/SCCH is provided in Supplementary Data S5, available at *Rheumatology* online. Consequentially, cases of CNO/SCCH were found under different diagnostic criteria. Studies sampled their cohorts on specific diagnosis of CNO/SCCH, (i.e. requiring SCC involvement) (10 studies), on diagnosis of SAPHO syndrome as defined by Kahn *et al.* or Benhamou *et al.* (22 studies) [53, 54], on diagnosis of pustulotic arthro-osteitis (PAO, one study) [42], or on diagnosis of general CNO (one study) [25]. For these latter three, SCC involvement is not a prerequisite, and including these cohorts meant including some patients without SCC involvement in the final analysis. This was accepted because 89% of subjects still displayed SCC involvement, and excluding individual data of those without was not feasible.

Risk of bias analysis

Assessment details are provided in Supplementary Data S6, available at *Rheumatology* online. The one randomized controlled trial (RCT) with placebo control [25] displayed a high risk of bias, mainly because of the dropout of two patients (14.2% of total) on an already small sample size. The other seven trials all displayed 'serious' risk of bias mainly due to absence of (placebo) control. The AXIS tool did not produce a summarizing qualifying score for cross-sectional studies, but 15/21 studies scored positively on recruiting a representative

Fig. 1 Overview of study selection



Forty studies were included for the final analyses: 20 for aim 1 (clinical presentation), 12 for aim 2 (treatment modalities and response) and eight for both.

sample, interpreted as reasonable quality. All cohort studies displayed poor quality on the Newcastle–Ottawa scale, primarily because none had a control group.

General and clinical characteristics

Data on general patient characteristics revealed a clear female preponderance, with a pooled estimate of 67%, 95% CI 60, 73 (see Table 1). Mean age of onset was 37.6 years, 95% CI 29, 46 and a mean 5.3 years, 95% CI 3, seven passed between onset and eventual diagnosis. Comorbidity in the form of autoimmune thyroid or inflammatory bowel disease was present in 2%, 95% CI 0, 6 and 1%, 95% CI 0, 3 respectively. In five studies (data not shown), information of diagnosis made prior to diagnosis of CNO/SCCH was provided; 'rheumatic disease or osteoarthritis' ($n = 63$) and 'functional or psychosomatic disorder' ($n = 27$) appeared most frequently, but severe diagnoses, such as 'cardiac event' or 'malignancy' were also made in 19 and 13 patients.

In total, the SCC region was radiologically involved in 89%, 95% CI 78, 96 of patients. In a sub-analysis of studies that diagnosed CNO/SCCH as a part of SAPHO or PAO (not necessarily requiring SCC involvement), 76%, 95% CI 65, 85 had SCC involvement (data not shown). Only two studies exhaustively reported involvement for all possible SCC osteoarticular localizations, thus data were not pooled. From these two studies, ribs 1 and 2 prevailed as most frequently involved, followed by the sternoclavicular joint(s) [29, 30]. The clavicle was involved in only 8%, which contrasted other large cohorts reporting 76% and 42% [7, 43] (data not shown). Osteoarticular lesions outside the SCC region were reported more methodically, and were mostly found in the spine (25%, 95% CI 1637) and sacroiliac joint (12%, 95% CI 6, 20). Involvement of the peripheral bones was noted in 4%, 95% CI 1–10 and of the mandible in 1%, 95% CI 0, 3.

The most prevalent symptom of CNO/SCCH proved anterior chest pain and swelling, reported in 89%, 95% CI 79, 96 and 79%, 95% CI 62, 91, respectively. Pain elsewhere in the body was mainly reported for the shoulder (53%, 95% CI 26, 76) and back (40%, 95% CI21–61), though with much more variety. When stratifying for CNO/SCCH diagnosed as a separate entity *vs* CNO/SCCH as part of SAPHO or PAO, the latter showed lower prevalence of shoulder pain (31%, 95% CI 10, 55 *vs* 87%, 95% CI 60, 100 for CNO/SCCH), but a higher prevalence of back pain (45%, 95% CI 22, 69 *vs* 29%, 95% CI 0, 76) and peripheral arthritis (32%, 95% CI 27, 36, $Tau^2 = 0$ *vs* 15%, 95% CI 0, 42). As for skin manifestations, pustulosis palmoplantaris (PPP)

Table 1 General and clinical characteristics of CNO/SCCH patients

	Proportion (pooled estimate)	I^2	Tau^2	No. of studies (subjects)
Gender, female	67%, 95% CI 60, 73	86%	0.02 ($P < 0.01$)	22 (1775)
Mean age of onset (years)	37.6, 95% CI 29, 46	98%	69.9 ($P < 0.01$)	4 (609)
Mean diagnostic delay (years)	5.3, 95% CI 3, 7	87%	3.9 ($P < 0.01$)	5 (520)
Mean age at diagnosis (years)	43.4, 95% CI 39, 47	91%	18.9 ($P < 0.01$)	5 (638)
Concomitant thyroid autoimmune disease	2%, 95% CI 0, 6	80%	0.01 ($P < 0.01$)	8 (620)
Concomitant inflammatory bowel bisease	1%, 95% CI 0, 3	58%	0.004 ($P = 0.02$)	8 (620)
Sites of bone lesions				
SCC involvement	89%, 95% CI 78, 96	96%	0.06 ($P < 0.01$)	14 (1375)
Spine	25%, 95% CI 16, 37	96%	0.07 ($P < 0.01$)	20 (1638)
Sacroiliac region	12%, 95% CI 6, 20	94%	0.05 ($P < 0.01$)	20 (1638)
Mandible	1%, 95% CI 0, 3	81%	0.01 ($P < 0.01$)	20 (1638)
Peripheral bones	4%, 95% CI 1, 10	95%	0.06 ($P < 0.01$)	20 (1638)
Presenting symptoms				
Anterior chest pain	89%, 95% CI 79, 96	96%	0.07 ($P < 0.01$)	18 (1574)
Anterior chest swelling	79%, 95% CI 62, 91	93%	0.66 ($P < 0.01$)	10 (541)
Shoulder pain	53%, 95% CI 26, 76	97%	0.15 ($P < 0.01$)	8 (506)
Back pain	40%, 95% CI 21, 61	96%	0.12 ($P < 0.01$)	11 (1058)
Peripheral arthritis	24%, 95% CI 11, 39	94%	0.05 ($P < 0.01$)	8 (722)
Fever	4%, 95% CI 0, 14	92%	0.04 ($P < 0.01$)	6 (514)
Skin manifestations				
PPP[a]	53%, 95% CI 37, 68	97%	0.10 ($P < 0.01$)	17 (1095)
Acne	8%, 95% CI 4, 13	91%	0.03 ($P < 0.01$)	16 (1496)
PV	8%, 95% CI 4, 14	91%	0.03 ($P < 0.01$)	16 (1114)
None	11%, 95% CI 3, 22	93%	0.04 ($P < 0.01$)	7 (680)

[a]The study of Yamamoto *et al.* (50) was excluded from this analysis due to its sampling criterium of PPP. CNO: chronic nonbacterial osteomyelitis; PPP: pustulosis palmoplantaris; PV: psoriasis vulgaris; SCC: sternocostoclavicular; SCCH: sternocostoclavicular hyperostosis.

was present in 53%, 95% CI 37, 68. Importantly, most studies did not specify their diagnostic criteria for PPP. Acne was found in 8%, 95% CI 4, 13. 11%, 95% CI 3, 22 of patients did not present with skin manifestations, though most studies did not report exact numbers. One study described obstructive complications of CNO/SCCH including compression of vessels or nerves, which occurred in two out of 120 cases (data not shown) [9]. Work absence was reported in two studies, the largest sample yielding 27% full or partial absence due to symptoms (data not shown) [7].

Biochemical and histopathological characteristics

ESR and CRP showed variable rates of elevation (see Table 2), with pooled estimates of 43%, 95% CI 27, 59 and 53%, 95% CI 34, 73. For the latter, several studies used high-sensitive CRP, which was elevated more frequently (68%, 95% CI 62, 74). HLA-B27 was present in 5%, 95% CI 3, 6, RF in 3%, 95% CI 1, 6, and ANA in 5%, 95% CI 0, 13. Markers of bone turnover were usually unreported, exempting alkaline phosphatase, showing elevation in 17%, 95% CI 7, 31 of patients. During the diagnostic process, 24%, 95% CI 16, 32 underwent a bone biopsy, yielding nonspecific inflammatory characteristics in 97%, 95% CI 89, 100. Cultures were almost exclusively negative.

Imaging techniques applied in CNO/SCCH

The imaging features of bone lesions in the SCC region were so erratically reported that meta-analytical pooling was not possible. Radiographs were performed in 93% of patients, 95% CI 70, 100 (see Table 3). On these, mainly ossification of ligaments or other soft tissue, and sclerosis, hyperostosis and erosions were described. Interestingly, three studies reported SCCH cases with normal radiographs, though with great variation. CT imaging was performed in 77%, 95% CI 55, 93 of cases, and mainly displayed hyperostosis and sclerosis, erosions, and in lesser extent the (beginning) joint ankylosis. MRI was performed in 36%, 95% CI 12, 65. The presence of bone marrow oedema, specifically detectable with MRI, was present in 6/71 patients it was reported for [43]. Nuclear imaging was the second most frequently performed imaging modality (79%, 95% CI 62, 92) and revealed local increase of isotope uptake in practically all cases. The presence of the 'bullhead sign', indicating symmetrically increased uptake in the manubrium sterni, medial clavicles and first medial ribs, was present in 8%, 95% CI 3, 15.

Treatment modalities and effects

An abundance of treatments were applied in trials and cohort studies (see Fig. 2). NSAIDs were most commonly prescribed and were mainly partially effective. DMARDs (mostly methotrexate and sulfasalazine) yielded good response in only 8%, 95% CI 0, 26. Least effective were antibiotics (good response in only 1%, 95% CI 0, 9). Higher good response rates were seen in bisphosphonates, mainly IV pamidronate (83%, 95% CI 60, 97). Both oral and intra-articular corticosteroids appeared reasonably effective. Biologicals (almost exclusively TNF-α inhibitors) gave good response in 56%, 95% CI 26, 85. Other treatment agents included colchicine ($n = 43$), opioids ($n = 19$), and surgical resection of bone ($n = 9$).

Non-pooled results of intervention trials only are outlined in Table 4. Pamidronate was both effective in non-randomized trials and the sole RCT, in which pain decreased with 54% compared with an increase of 4% in the placebo group [18, 20, 21, 25]. Antibiotics gave clinical improvement in one study, but pain recurred after discontinuation [24]. In other studies, *Tripterygium wilfordii* and tonsillectomy (in patients with concomitant tonsillitis) caused significant improvement of bone pain [22, 23].

Table 2 Biochemical and histopathological characteristics of CNO/SCCH patients

	Proportion (pooled estimate)	I^2	Tau^2	No. of studies (subjects)
ESR ↑[a]	43%, 95% CI 27, 59	96%	0.08 ($P < 0.01$)	13 (897)
CRP ↑[a]	54%, 95% CI 34, 73	97%	0.11 ($P < 0.01$)	11 (782)
HLA-B27 +	5%, 95% CI 3, 6	64%	0.0069 ($P < 0.01$)	15 (1046)
RF +	3%, 95% CI 1, 6	67%	0.0068 ($P < 0.01$)	11 (666)
ANA +	5%, 95% CI 0, 13	85%	0.02 ($P < 0.01$)	8 (548)
Alkaline phosphatase ↑[a]	17%, 95% CI 7, 31	79%	0.02 ($P < 0.01$)	5 (318)
Biopsy performed	24%, 95% CI 16, 32	87%	0.03 ($P < 0.01$)	14 (963)
(Nonspecific) chronic inflammation	97%, 95% CI 89, 100	70%	0.03 ($P < 0.01$)	12 (207)
Sclerosis/fibrosis	93%, 95% CI 58, 100	90%	0.15 ($P < 0.01$)	5 (93)
Cultures + for *P. acnes*	1%, 95% CI 0, 9	66%	0.03 ($P < 0.01$)	9 (165)
Cultures –	100%, 95% CI 93, 100	68%	0.03 ($P < 0.01$)	9 (165)

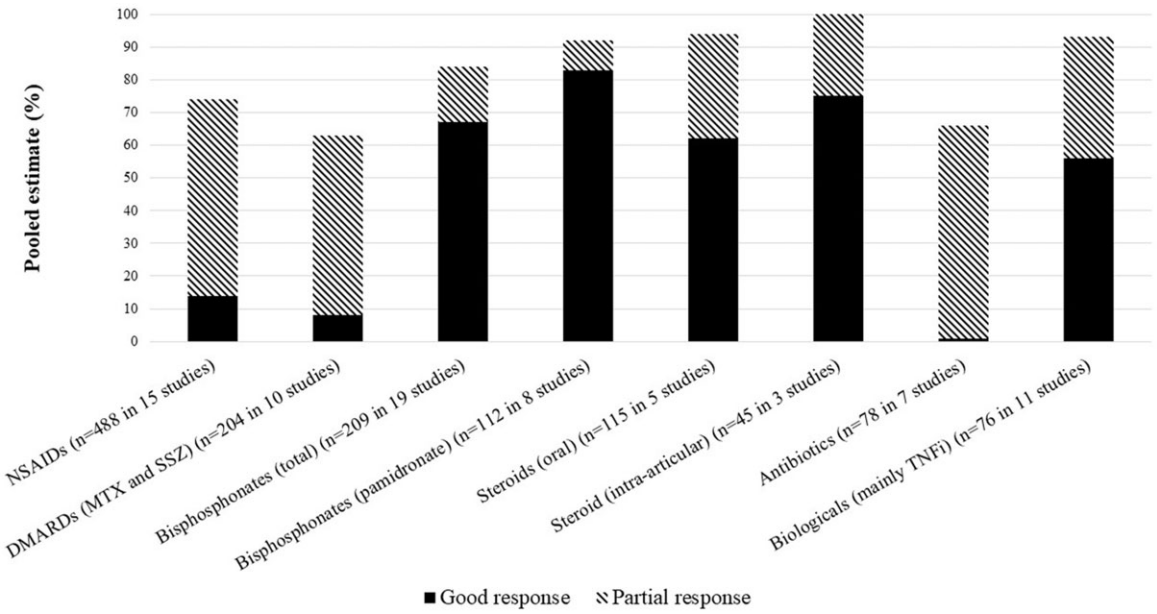
[a]Parameters reported as elevated by original study, or classified as elevated in case of exceeding 20 mm/h for ESR, 5 mg/L for CRP and 98 U/L for alkaline phosphatase. +: positive; –: negative; ↑: elevated above reference values; CNO: chronic nonbacterial osteomyelitis; HLA-B27: human leucocyte antigen B27; Lb: lower bound; *P. acnes*: *Proprionibacterium acnes*; SCCH: sternocostoclavicular hyperostosis; ub: upper bound.

Table 3 Imaging techniques applied in CNO/SCCH patients

	Proportion (pooled estimate)	I^2	Tau^2	No. of studies (total *n*)
Radiography performed	93%, 95% CI 70, 100	98%	0.23 ($P < 0.01$)	10 (659)
CT performed	77%, 95% CI 55, 93	97%	0.12 ($P < 0.01$)	9 (646)
MRI performed	36%, 95% CI 12, 65	98%	0.18 ($P < 0.01$)	9 (894)
Nuclear imaging performed	79%, 95% CI 62, 92	96%	0.10 ($P < 0.01$)	12 (823)
Increased isotope uptake	99%, 95% CI 96, 100	76%	0.01 ($P < 0.01$)	13 (907)
Bullhead sign[a]	8%, 95% CI 3, 15	67%	0.007 ($P = 0.03$)	4 (321)
Other lesion sites[b]				
Spine	25%, 95% CI 16, 37	96%	0.07 ($P < 0.01$)	20 (1638)
Sacroiliac region	12%, 95% CI 6, 20	94%	0.05 ($P < 0.01$)	20 (1638)
Mandible	1%, 95% CI 0, 3	81%	0.01 ($P < 0.01$)	20 (1638)
Peripheral bones	4%, 95% CI 1, 10	95%	0.06 ($P < 0.01$)	20 (1638)

[a]The study by Freyschmidt *et al.* (29) was excluded as a bullhead sign was required for inclusion. [b]As detected by any form of imaging. CNO: chronic nonbacterial osteomyelitis; SCC: sternocostoclavicula; SCCH: sternocostoclavicular hyperostosis.

Fig. 2 Treatment modalities applied in CNO/SCCH and pooled response rates (cohort and intervention trials combined)



Bisphosphonates, steroids and biologicals appear most effective. TNFi: TNF-α inhibitors.

Discussion

First, this review shows that CNO/SCCH as a CNO subtype is insufficiently defined in the present medical literature and cases are found under a variety of names and classifications. Chinese, Italian and French studies consequently refer to SAPHO syndrome, Japanese studies use PAO, and Dutch and Scandinavian studies generally use CNO/SCCH. Clinical, biochemical, histopathological and imaging characteristics as well as treatment modalities and effects were diverse, and differentially reported and interpreted, as also reflected in the statistical pooling of data. This diversity is a key observation as it seriously hampers insight in the disease of CNO/SCCH. We found a mean diagnostic delay of 5.3 years, regardless of whether CNO/SCCH was diagnosed as a manifestation of SAPHO or PAO or as a separate entity. The delay may therefore not fully be caused by the absence of diagnostic criteria, as these are available for SAPHO syndrome [53, 55]. In any case, this substantial delay is problematic, for it has been associated with irreversible tissue damage and impaired quality of life (QoL) [12]. Following from our data, the major drawback for fast diagnosis is CNO/SCCH's unspecific presentation.

Table 4 Treatment modalities in intervention trials and their effects

Trial	Design	Intervention	*n*	Follow-up	Reported effects
Amital *et al.* (2004) [18]	Non-randomized trial	Pamidronate IV, 60 mg Second infusion at 1 month or 4 months depending on response. Additional infusions at 4-monthly intervals as necessary	10	24 months	Complete remission ($n = 6$) Partial remission ($n = 3$) No response ($n = 1$)
Andreasen *et al.* (2020) [25]	Randomized controlled trial	Pamidronate IV (1 mg/kg/day, max. 60 mg, 3 consecutive days at 3-monthly intervals) *vs* placebo	6 per arm	36 weeks	VAS for pain decreased by 54% in pamidronate group and increased by 4% in the placebo group ($P = 0.11$)
Assmann *et al.* (2009) [24]	Non-randomized trial	Azythromycin, clindamycin, or doxycylin for 16 weeks	27	28 weeks	Health assessment score (including pain) decreased from 3.3–2.1 ($P = 0.01$) but increased after discontinuation of treatment 2.2–3.3 ($P = 0.02$)
Li *et al.* (2019) [20]	Non-randomized trial	Pamidronate IV (1 mg/day, 3 consecutive days at 0 and 3 months)	30	51 weeks	Decrease in VAS for bone pain (5.70 ± 1.62 *vs* 2.30 ± 1.29 cm for the first treatment, 4.03 ± 1.88 *vs* 2.17 ± 1.23 cm for the second treatment) ($P < 0.05$)
Jung *et al.* (2012) [19]	Non-randomized trial	Corticosteroid injection in SC or CS joint (20 mg triamcinolone acetonide in 1 ml)	10	12 weeks	Mean disease activity score decreased from 4.2–3.2 ($P = 0.062$).
Solau-Gervais *et al.* (2006) [21]	Non-randomized trial	Pamidronate IV, 60 mg over 3 days	13	24 weeks	Good response ($n = 7$) Partial response ($n = 2$) No response ($n = 4$)
Wang *et al.* (2021) [22]	Randomized non-controlled trial	Post-meal Tripterygium Wilfordii arm 1: 1.0 mg/kg/day arm 2: 1.5 mg/kg/day for the first 4 weeks, then reducing gradually to 1.0 mg/kg/day at 12 weeks	15 per arm	12 weeks	Decrease in VAS for global osteoarticular pain ($P < 0.05$) in both groups.
Xiang *et al.* (2021) [23]	Non-randomized trial	Tonsillectomy in patients with concomitant tonsillitis	7	8–18 weeks	Decrease in VAS for bone pain (5 *vs* 3, $P = 0.034$)

CS: costosternal; IV: intravenous; SC: sternoclavicular; VAS: visual analogue scale.

Symptom-wise, pain of the anterior chest wall and shoulder were ascribed to a wide range of alternative diagnosis, many of which are self-limiting and would not require referral, especially not at the relatively young age of presentation [56]. Co-occurrence with pustulosis, a highly particular manifestation found in 53% should theoretically steer towards CNO/SCCH, but it is known that osteoarticular and skin manifestations generally do not flare simultaneously [9]. Another delaying factor is that step-one imaging techniques such as plain X-rays often do not show clear changes; one study found normal X-rays in 36/54 patients [6]. Hence, CT scans or nuclear imaging are often needed to detect key abnormalities. The most consistent finding was the strongly increased isotope uptake on nuclear imaging, reported for over 99%. The essential role of nuclear imaging in the diagnostic process is herewith confirmed. MRI, which is preferred in paediatric CNO/CRMO to prevent radiation exposure, was performed less frequently in this adult population and bone marrow oedema as an early sign of inflammation was only reported in one study [25, 57]. The combined CT and nuclear imaging prove the diagnostic tools of choice; they are easily performed simultaneously, they detect early signs of inflammation and soft tissue involvement, and also assess bone turnover. Laboratory investigation was also unspecific for CNO/SCCH. Biochemical inflammation (ESR or CRP rise) was only found in approximately half of the patients.

Interestingly, one study found that CNO/SCCH patients with PPP and CNO/SCCH patients with other axial localizations demonstrate (significantly) higher levels of ESR and CRP [7], suggesting that biochemical inflammation may be limited to those with more extensive disease. Alternatively, as CRP elevation was also more prevalent in studies using high-sensitive (hs) CRP, the detection of low-grade inflammation might require more sensitive markers than generic CRP and ESR. Indeed, in RA, hs-CRP has shown to be a better predictor of disease activity compared with ESR [58]. The utility of sensitive markers to diagnose and monitor CNO/SCCH should therefore be addressed in future research [5]. Also relevant in this context is that infection (like tonsillitis or sinusitis) was found in 156/363 patients of four studies total [37, 40, 42, 59], tempting speculation whether molecular mimicry might trigger CNO/SCCH, as proposed for other rheumatic diseases too [60] and supported by the positive clinical effects of tonsillectomy in SAPHO patients [23, 61].

HLA-B27, RF and ANA prevalence were all lower compared with the general population [62–64]. Hence, they are non-contributory to diagnosis of CNO/SCCH but may be used to exclude other rheumatic diagnoses whenever arthritis or inflammatory back pain are presenting symptoms. Bone biopsies were also nonspecific and mainly performed to exclude malignancy or infection. However, both the clavicle and the sternum are rare localizations for bone tumors (the latter making up for 0.65%), they are mostly metastatic [65, 66], and exhibit typical imaging features [65]. Invasive bone biopsies should therefore be reserved for cases highly suspect for malignancy and do not contribute to diagnosis of CNO/SCCH in adults *per se*.

As for treatment, this review again highlights the absence of proper trials and evidence-based therapeutic guidelines. NSAIDs were generally the first-line treatment, mostly with partial effect on osteoarticular pain. Antibiotics were conceivably prescribed upon the postulate that infection with *Propionibacterium acnes* plays a part in CNO/SCCH pathophysiology, but cultures were only positive in a pooled 1%. This considered, the effect of antibiotics was higher than expected, possibly explained by a strong placebo effect or by an indirect effect via the aforementioned co-infections. Oral and intra-articular corticosteroids both proved effective in relieving pain, though for intra-articular steroids the high efficacy mainly resulted from two studies presenting good results for a cohort, without individual data [9, 19]. Oral steroids may be effective at reducing inflammation, but considering that CNO/SCCH is a female-dominated, chronic, relapse-remitting disease, they may not be the preferred treatment option given their major side-effects, glucocorticoid-induced osteoporosis specifically [67, 68]. The best treatment effects were seen in bisphosphonates (reducing the characteristically increased bone turnover) and biologicals, reducing the inflammation that triggers this turnover cascade [10].

While the pooled treatment response data are instructive, it should be noted that they are subject to multiple limitations. First, the data derive from studies that were heterogeneous in terms of design and methodological quality. Due to the scarcity of evidence for CNO/SCCH, the selection of studies for the analysis of treatment response could not be limited to the mere two randomized controlled trials, posing serious risk of overestimation of treatment effect and bias. On top, response definitions varied between studies, or response was merely described in words, necessitating *a posteriori* categorization for the purpose of this meta-analysis. Moreover, the sequential use of different treatments could not always be distilled from the studies, but may affect the results too. Generally, CNO/SCCH is treated first-line with NSAIDs. In that respect, patients requiring second-line treatments are likely to be more severely affected. However, as the second-line treatments are physician-dependent rather than sequential, the groups receiving DMARDs, bisphosphonates, steroids, antibiotics and biologicals are reasonably comparable. In sum, the treatment response data should be interpreted in the context of their limitations and should be more conservatively estimated due to the almost complete lack of placebo control. Still, the pooled data combined with the response data from intervention trials separately provide an informative overview of treatments adopted in CNO/SCCH: some clearly show superior effects than others. In that respect, the data rather steer towards the medications that have most potential to prove their efficacy in future trials. Most studies that were included to characterize clinical presentation reported on fairly representative patient samples, making their pooled data on demographics, symptomatology, and biochemical and histological profile useful for clinical practice. Still, heterogeneity between studies was generally high. On one hand, methodological issues, publication bias, and missing data might partly contribute to this. On the other hand, the fact that CNO/SCCH cases were found under a variety of different diagnoses suggests there are true clinical differences between these patient populations too. For example, SAPHO patients more frequently had concomitant peripheral arthritis, and PAO patients had palmoplantar pustulosis per definition contrary to patients with CNO/SCCH. Therefore, CNO/SCCH that is diagnosed as part of SAPHO or PAO may truly have different clinical presentation than CNO/SCCH that is diagnosed in isolation. This observation is relevant in the ongoing debate whether CNO/SCCH should be classified separately from SAPHO syndrome. Our review chose CNO/SCCH as a starting position, implying osteitis and hyperostosis of the anterior chest wall. Our data indicate that 53% of CNO/SCCH patients also suffered from PPP, 24% from synovitis and 8% from acne. In reverse, 76% of patients included upon the broader criteria of SAPHO, PAO or CNO (general), displayed CNO/SCCH. These numbers show how not all CNO/SCCH patients have other manifestations of the SAPHO acronym, but SAPHO syndrome (and arthro-osteitis and general CNO) frequently entail a sternocostoclavicular osteitis with hyperostosis.

In conclusion, the controversy around CNO/SCCH classification, diagnosis and treatment is major. Notwithstanding, this review points out several persistent characteristics of CNO/SCCH in adults which are relevant for clinical use. Considering clinical presentation, CNO/SCCH initial symptomatology seems unspecific and step one investigations (routine laboratory parameters, X-rays) may be negative. Diagnosis requires a combination of CT and nuclear imaging, the latter being highly consistent, whereas autoantibodies, HLA profiling, and biopsies are not directly indicated. Treatment modalities are manifold, and bisphosphonates and biologicals appear effective. However, there is great need for powered, randomized and (placebo)-controlled research with standardized measures of response to affirm their potential.

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Data availability statement

Data are available on request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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