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EULAR/American College of Rheumatology Classification Criteria for Pediatric Chronic Nonbacterial Osteomyelitis

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the EULAR Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

Classification criteria are essential in clinical and basic science research because they allow investigators to study relatively homogeneous populations of patients recruited from a single or multiple research sites. In clinical settings, diagnoses are made by health care professionals evaluating an individual patient's symptoms, signs, and results of laboratory and imaging studies in order to guide therapeutic recommendations. Patients diagnosed with a particular disease may or may not fulfill classification criteria for that disease. Classification criteria, in the hands of an experienced clinician with expertise in rheumatology, may inform a diagnostic evaluation, but improperly applied classification criteria may lead to misdiagnosis.

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Objective. To develop and validate classification criteria for pediatric chronic nonbacterial osteomyelitis (CNO) jointly supported by EULAR and the American College of Rheumatology (ACR).

Methods. This international initiative had 4 phases: (1) candidate items were proposed in a survey of pediatric rheumatologists, (2) criteria definition and reduction by Delphi and nominal group technique exercises, (3) criteria weighting using multicriteria decision analysis, and (4) refinement of weights and threshold score in a development cohort of 441 patients and validation in another cohort of 514 patients.

Results. The new EULAR/ACR classification criteria for CNO require typical radiographic or magnetic resonance imaging findings and bone pain as an obligatory entry criterion and exclusion criteria of malignancy, infection, vitamin C deficiency, and hypophosphatasia, followed by additive weighted criteria in 5 clinical (site of bone lesions, pattern of bone lesions, age at onset, coexisting conditions, fever) and 4 pathology/laboratory domains (bone biopsy findings if done, anemia, C-reactive protein level, and erythrocyte sedimentation rate). A total score ≥55 is required for classification as CNO. The new criteria had a sensitivity of 82% and specificity of 98% in the validation cohort.

Conclusion. These new classification criteria for pediatric CNO developed with international input reflect current views about CNO, have high specificity and good sensitivity, and provide a key foundation for future CNO research.

INTRODUCTION

Chronic nonbacterial osteomyelitis (CNO) is a rare autoinflammatory bone disease of unknown cause with an annual incidence of 0.4 to 2.3 per 100,000 children.[1–3] CNO may significantly impact patients' quality of life and result in permanent bone damage, long-term disability, and deformity if left untreated.[4–7] The term chronic recurrent multifocal osteomyelitis is used when multiple bones are affected over time. We use

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CNO throughout this article for consistency. CNO is difficult to characterize and diagnose because of its insidious onset, variable bone location and symptoms at presentation, and lack of high-quality clinical research describing the disease spectrum. These factors, together with limited awareness among physicians about CNO, often result in misdiagnosis[1] and misclassification for research.

There are no previous classification criteria for CNO. Classification criteria are essential to identify homogeneous groups of patients to better characterize the epidemiology and natural history of CNO and to enroll in clinical trials. In the absence of classification criteria, diagnostic criteria proposed for clinical use have been used as inclusion criteria for research in CNO. CNO diagnostic criteria have been proposed by 3 groups: King et al[8] and Manson et al[9], Jansson et al[10], and Roderick et al.[11] These diagnostic criteria were based on clinical experience from single center cohorts with fewer than 100 patients each and have not been validated in independent cohorts. Thus, with the lack of evidence on the validity of these diagnostic criteria, they should not be used as entry criteria for clinical trials or observational studies.

The roles of advanced imaging methods and bone biopsy need to be carefully evaluated in classification criteria for CNO. Previous CNO diagnostic criteria required presence of lytic and/or sclerotic lesions in radiographs or hyperintensity within bone marrow in fluid-sensitive magnetic resonance imaging (MRI) sequences. Symmetric bone lesions and multifocal lesions occur much more frequently than unifocal lesions.[5,10] Whole-body MRI (WBMRI) is a relatively new modality that better defines patterns of lesion distribution and often identifies clinically 'silent' lesions that may affect the vertebral spine, which can impact treatment choice.[2,12–14]

Bone biopsy may be needed to exclude differential diagnoses of CNO, especially infections and malignancy.[10,11] However, there are no pathognomonic biopsy features for CNO. Common histologic findings include acute and chronic inflammation, marrow fibrosis, or osteonecrosis, and sometimes biopsy reveals only normal bone, likely due to sampling error.[10,15–18] Fibrosis in bone biopsy is present in children with prolonged duration of disease.[19] Microbiological investigations including special stains, cultures, or polymerase chain reaction tests are negative for bacteria, fungus, and mycobacteria, except for occasional contaminant organisms.[20] We aimed to develop the first classification criteria for pediatric CNO combining international expert consensus and data-driven methods and including the patient's perspective.[21,22]

METHODS

Study overview. As in prior EULAR/American College of Rheumatology (ACR) classification criteria[23–27], the study had 4 phases: (1) generation of candidate criteria items, (2) item reduction and definition of items, (3) criteria weighting and identification of threshold for CNO classification, and (4) refinement and validation. The data that support the findings of this study are available from the corresponding author (YZ) upon reasonable request.

Investigators. The study was led by a core group (YZ, MSO, AS, EYW, AMH, KCC, HJG, FD, CMH, PJF, RN, and SO) and overseen by a steering committee of 20 members (core group plus AFJ, LP, AVR, AR, SMS, ACT, and LFV) from North America, Europe (including Turkey), and New Zealand (Supplement S1). Steering committee members were nominated based on CNO expertise or methodological experience. In addition to academic pediatric rheumatologists (7 from Europe and 7 from North America), the steering committee included 1 patient with CNO, 1 parent of a patient with CNO, a physical therapist, methodologists, and a biostatistician. The CNO workgroup of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) assisted with item reduction, and additional international collaborators participated by submitting cases of CNO and mimicking conditions used in the development and validation cohorts for the study.

Phase I: Item generation. Candidate items were identified using a free-text survey sent to members of CARRA, the German Society for Pediatric Rheumatology, the Eurofever registry, and the Dr Peter Dent pediatric rheumatology listserv between September 2017 and May 2018. Responders were asked to list features relevant to CNO and individually rank them in order of importance for classification.

Phase II: Item reduction and definition. Candidate items generated from phase I were reduced and defined in a CARRA CNO work group meeting held in Denver, Colorado, in April 2018 followed by a postmeeting survey. Potential items were retained or removed if 80% agreement of all participants at the meeting was achieved using a nominal group technique. In the postmeeting survey, members of the CARRA CNO work group were asked to score each item as follows: +3 (increases the likelihood of CNO the most), +2 (increases the likelihood of CNO moderately), +1 (increases the likelihood of CNO slightly), 0 (no difference), −1 (decreases the likelihood of CNO slightly), −2 (decreases the likelihood of CNO moderately), −3 (decreases the likelihood of CNO the most). Survey results were discussed by the core group, and no threshold was set to include/exclude these items.

The items remaining, and the items in previously proposed diagnostic criteria[10,11], were included in a case report form (CRF; Supplement S2) used to collect data on CNO cases and mimickers to assemble a development and a validation cohort.[10,11] Pediatric rheumatologists in North America, Europe, Australia, Africa, and South America used the CRF to submit cases and mimickers to an online central database using REDCap software.[28] Seattle Children's Hospital Institution Review Board approved the study as the coordination center (#1115),

and each participating site obtained approval from their institutions. Data received between December 2018 and August 2020 formed the development cohort and data received between August 2020 and May 2021 formed the validation cohort. Submitted CNO cases and mimickers were required to have bone pain, ≥1 imaging study (ie, x-ray and/or MRI), and ≥12 months of follow-up (except for mimickers with a confirmed laboratory or pathologic diagnosis) because of the concern of inadequate observation for mistakenly diagnosed CNO or mimickers. Institutional Review Board or ethics committee approval was obtained at each site. Collaborators submitting CRFs had no prior knowledge of the items likely to advance to final consideration as classification criteria and provided an assessment of their degree of confidence in the cases being CNO or a mimicker, rated from +3 to –3.

Once the development cohort was assembled in 2020, candidate items were further reduced using the prevalence ratio (PR) of each item as a predictor of 'CNO.' PRs were calculated using only cases with moderate to high confidence (ie, +2 or +3 or –2 or –3) according to the submitting physicians. PRs >2 or <0.5 suggested distinguishing features for or against CNO, and a P value <0.05 was considered significant.

The core group met every other week for 24 weeks to consider PRs, discuss example cases or mimickers, further define criteria, and group them in domains and levels within a domain. Thirty ambiguous cases from the development cohort with low confidence levels by the submitting physician (ie, –1 to +1 scores) representing as many clinical features as possible were used by the core group to help establish hierarchical levels within each domain in preparation for multicriteria decision analysis (MCDA).

The CNO classification draft domains prepared by the core group were sent to the steering committee. Members were asked to either agree or disagree with each item and level based on the statistical analysis, clinical feasibility, and summary of discussions from the core group. Responses were reviewed at the first steering committee meeting.

Phase III: Criteria definition and weighting. Ten virtual consensus meetings of the steering committee were held between March 2021 and October 2023 to refine the draft prepared by the core group and assign preliminary weights using MCDA facilitated by 1000minds software (1000minds decision-making and conjoint analysis software, https://www.1000minds.com). The steering committee was presented with hypothetical pairs of cases contrasting 2 domains at a time (Supplement S3) and asked to decide individually and anonymously which case of the pair they were more likely to classify as CNO. Importantly voters were to assume the 2 cases were equal in all other features.

The participants then reviewed the tally of votes together. One hundred percent agreement was considered consensus without further discussion. Incomplete agreement prompted further discussion, moderated by a methodologist (AMH), to achieve consensus as to which case was more likely to be classified as CNO. Discussion was encouraged and facilitated until all members reached consensus. Complex choices in which consensus was not readily achieved were deferred for additional voting rounds. As a result of these forced choices between the alternative pairs, candidate items were weighted and ranked using 1000minds decision-making software.

Threshold identification. The draft weights derived from MCDA were applied to each case of the development cohort. A different set of 30 CNO cases and mimickers that covered the entire range of confidence from very likely to very unlikely CNO, based on the opinion of the submitting clinician, were selected by the statistician, and the case/mimicker status was confirmed by a 3-expert group (SO, AS, and YZ). The total scores for these 30 cases and mimickers were used to examine the performance of the draft weights and to determine a threshold for classification.

The submitting physician's diagnosis was considered the gold standard unless there was disagreement from the 3-expert group. This contrary opinion and its rationale were shared with the submitting physician and they were asked to review their diagnosis. The submitting physician's subsequent diagnosis after review of the expert commentary became the final diagnosis.

An initial threshold score for CNO was identified by examining the additive scores of all cases ranked from high to low. A receiver operating characteristic (ROC) curve analysis was conducted using the additive scores for all cases in the development cohort. This process identified an optimal threshold to distinguish CNO cases from mimickers.

Phase IV: Refinement and validation. The final criteria domains were examined by the steering committee based on the misclassified cases to ensure the clarity of the definitions for the differentially weighted classification system. The updated definitions with minimal change aimed to enhance the ease of application, sensitivity, and specificity of the classification system.

The final criteria were then applied to every CNO case or mimicker confirmed by adjudicators in the validation cohort to obtain their final score and their classification as CNO or not, relative to the agreed threshold. Adjudicators consisted of 5 rheumatologists who did not participate in the steering committee or submit any cases. They adjudicated 600 to 660 cases to ensure triple coverage of each case to verify the diagnosis of cases within the development cohort and exclude disagreed cases from the validation cohort. Sensitivity and specificity of the criteria were calculated and contrasted with the sensitivity and specificity of previously proposed diagnostic criteria.[10,11] Because the original criteria by Jansson et al[10] did not include MRI findings, we tested a version of the Jansson et al criteria modified by adding 'typical MRI findings' defined in the same way as for the new EULAR/ACR classification criteria.

Patient and public involvement. Caregivers of children with CNO and adults who were pediatric patients of CNO were involved in setting the research question and they were intimately involved in design and consensus meetings.

RESULTS

Phase I: Item generation. Overall, 259 of 865 (30%) of surveyed international pediatric rheumatologists responded and provided candidate items for CNO classification. Among responders, 132 (51%) practiced in North America, 77 (30%) in Europe, and 50 (19%) in other continents (South America 9, Asia 8, Australia/New Zealand 9, and other 14). A total of 138 responders (53%) had >10 years of practicing experience, and 108 (42%) had diagnosed and treated >10 CNO patients. The 33 items proposed in free-text survey responses were categorized into 6 domains (clinical presentation, physical examination, laboratory findings, imaging findings, bone biopsy, and treatment response). This is a smaller number of items than in recent criteria for other rheumatic disorders.[24,27] The following 8 items were ranked most important by survey respondents: (1) exclusion of malignancy and infection by bone biopsy, (2) multifocal bone lesions, (3) presence of bone pain or swelling, (4) signs of fibrosis or inflammation in bone biopsy, (5) bone lesions in typical locations (clavicle, metaphysis of long bones, mandible, vertebra), (6) presence of CNO-related comorbidities, (7) normal or mildly elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), and (8) MRI findings 'typical' of CNO.

Phase II: Item reduction and definition. At the 2018 CARRA CNO workgroup meeting, 39 pediatric rheumatologists (35 from North America, 4 from Europe) and 7 parents of patients with CNO participated in item reduction. Twelve of the 33 items were thoroughly discussed, and the rest deferred to a postmeeting survey. Consensus was reached to exclude 8 items (antinuclear antibody, human lymphocyte antigen B27, lactate dehydrogenase (LDH), uric acid, and alkaline phosphatase (ALP) tests, fever, arthritis, and good clinical response to nonsteroidal anti-inflammatory drugs). LDH, low ALP, and fever were reconsidered in phase III. Physical examination findings were split into 3 items, and ESR and CRP values were expanded from 2 to 6 items to capture the range more accurately. Thus, the total number of items was only modestly reduced from 33 to 31.

In the postmeeting survey of all members of the CARRA CNO work group, 77 of 82 members (94%) scored the 31 items from +3 (increases the likelihood of CNO the most) to –3 (decreases the likelihood of CNO the most). Respondents included 62 pediatric rheumatologists, 9 pediatric rheumatology trainees, 2 adult rheumatologists, and 2 patient/parent representatives. Seventy percent of practitioners had >6 years of experience, and 34% managed >10 CNO patients every year. Supplement S4 shows the average scores for the 31 items. The items with the highest scores were 'multifocal lesions on imaging,' 'ruling out malignancy and infection by biopsy,' and 'typical location on imaging.' The item with the lowest scores (decreases likelihood of CNO the most) was 'CRP and ESR >3 times upper limit of normal.' Results were presented to the steering committee at their first meeting.

CNO cases and mimickers. Demographic information for cases included in the development and validation cohorts is summarized in Table 1. The diagnoses of mimicker cases are reported in Table 2. Among 441 CRFs included in the development cohort, 264 of 285 (93%) CNO cases and 145 of 156 (93%) mimickers had moderate or greater confidence in the diagnosis reported by the submitting physician and were used for calculation of PRs (Supplement S5). Adjudicators disagreed with the diagnosis of 2 CNO cases and 2 mimicker cases that were included in PR calculations. Data missing rates were also assessed. CNO cases more frequently had intermittent pain, clavicular swelling, symmetric bone lesions, and involvement of the thoracic spine, clavicle, sternum/manubrium, pelvic bones, bilateral femur, bilateral tibia, unilateral fibula, and foot bones. Mimickers more frequently had continuous pain, fever, active arthritis (examination findings or imaging findings of arthritis), or imaging findings suggesting infection or malignancy. Finally, complete and sustained response to antibiotic treatment was more frequent in mimickers.

Based on the calculated PRs and discussions of ambiguous cases by the core group (those cases with less than moderate confidence in the diagnosis as reported by the submitting physician, n = 30), candidate criteria were further reduced from 31 to 14, and the levels or options within each domain were defined. Findings from physical exams, disease durations, and pain patterns were among the 17 items removed after reviewing PRs, which were between 0.5 and 2. LDH, fever, and axial arthritis as part of coexisting conditions were added back to the criteria because of their PRs and incidence of >5% in the total population.

Phase III: Criteria definition and weighting. *Phase IIIa: Criteria definition.* Based on discussions by the steering committee, further refinements were made to the definitions for bone lesion pattern and distribution with consensus. The most specific bone sites were determined as the mandible and clavicle, and the least specific sites for CNO were the skull and hands. LDH levels were removed from the classification domains and 'pathological LDH concerning for malignancy' was added as exclusion criteria instead. Although an LDH >700 international units/L had a significant PR of <0.5 to distinguish CNO and mimickers, there was variability across laboratory reporting systems and a lack of expert agreement to establish a cutoff value. Platelet levels were also removed from the classification domains and 'platelets <100,000/mm3' was added as exclusion criteria instead due to concerns for malignancy. Family history of associated conditions, defined as reported axial arthritis, inflammatory bowel disease,

Table 1. Demographic, clinical, and laboratory characteristics of subjects included in development and validation cohorts*

Variables	Development cohort		Validation cohort	
	CNO (n = 285)	Mimickers (n = 156)	CNO (n = 382)	Mimickers (n = 132)
Age at onset (y)	9.5 (3.3)	8.6 (5.1)	9.2 (3.3)	7.3 (5.5)
Time to diagnosis (mo)	13.0 (21.1)	4.6 (8.0)	13.6 (20.5)	6.1 (17.3)
Male sex at birth	115 (40.4%)	96 (61.5%)	159 (42.1%)	84 (63.6%)
Geographic locations				
North America	141 (49.5%)	94 (60.3%)	216 (56.5%)	74 (56.1%)
South America	0 (0%)	0 (0%)	13 (3.4%)	0 (0%)
Europe	117 (41.1%)	59 (37.8%)	147 (38.5 %)	55 (41.7%)
Asia	18 (6.3%)	1 (0.6%)	1 (0.3%)	1 (0.8%)
Africa	0 (0%)	0 (0%)	3 (0.8%)	1 (0.8%)
Oceania	9 (3.2%)	2 (1.3%)	0 (0%)	1 (0.8%)
Other	0 (0%)	0 (0%)	2 (0.5%)	0 (0%)
Race/ethnicity				
Asian	12 (4.2%)	8 (5.1%)	21 (5.5%)	6 (4.5%)
Black	5 (1.8%)	8 (5.1%)	9 (2.4%)	6 (4.5%)
Hispanic/Latino	6 (2.1%)	8 (5.1%)	9 (2.4%)	4 (3.0%)
Middle Eastern/North African	5 (1.8%)	4 (2.6%)	6 (1.6%)	2 (1.5%)
Native American	0 (0%)	4 (2.6%)	3 (0.8%)	1 (0.8%)
Native Hawaiian/Pacific Islander	0 (0%)	0 (0%)	0 (0%)	2 (1.5%)
White	246 (86.3%)	105 (67.3%)	310 (81.2%)	100 (75.8%)
Multiracial	5 (1.8%)	3 (1.9%)	10 (2.6%)	3 (2.3%)
Unknown	6 (2.1%)	16 (10.3%)	14 (3.7%)	8 (6.1%)
Bone biopsy results available	187 (65.6%)	93 (59.6%)	241 (63.1%)	114 (86.4%)
Hemoglobin (g/dL)	12.5 (11.8-13.2)	11.6 (10.3-13.0)	12.3 (11.4-13.2)	11.6 (10.0-12.9)
Platelets (10^9/L)	345 (293-414)	333 (255-427)	330 (275-395)	300 (253-395)
ESR (mm/h)	21 (11-44)	33 (15-73)	24 (10-43)	25 (10-47)
C-reactive protein (mg/L)	8 (3-16)	12 (6-44)	8 (5-15)	12 (3-44)

* Variables are presented as mean (SD), median (median interquartile range), or n (%). The development cohort included 3 CNO cases and 3 mimicker cases that adjudicators disagreed with submitting physicians. The validation cohort excluded 5 CNO cases that adjudicators disagreed with submitting physicians. CNO, chronic nonbacterial osteomyelitis; ESR, erythrocyte sedimentation rate.

psoriasis in a first-degree relative, and an ESR/platelet ratio ≥0.2 (relative thrombocytopenia during inflammation) were later removed due to insignificant weight relative to the other criteria. The remaining criteria were hierarchically organized, and definitions for the domains and their levels were further refined by the steering committee. The final 9 domains include sites of bone lesions and distribution patterns of these lesions based on imaging, bone biopsy pathological findings, age at the onset of symptoms, coexisting conditions, hemoglobin level, associated fever history, ESR, and CRP (Table 3).

The steering committee reached consensus on entry and exclusion criteria to be applied before scoring the 9 domains (5 clinical and 4 pathology/laboratory domains) (Table 3). Entry criteria are as follows: (1) aged <18 years at symptom onset, (2) presence of bone pain and/or functional musculoskeletal limitation for ≥6 weeks, and (3) abnormal radiographic or MRI imaging findings at nonarthritic bone sites. Nonarthritic bone sites refer to bones whose endings, if forming a joint, do not demonstrate signs of arthritis on physical examination or imaging (ie, no synovial thickening, contrast enhancement, or moderate to large joint effusions). Exclusion criteria are as follows: (1) confirmatory evidence of mutually exclusive mimicker diseases such as malignancy, infection, scurvy, or hypophosphatasia; (2) pathological LDH concerning for malignancy; (3) platelets <100,000/mm3; and (4) complete and sustained clinical and laboratory response to antimicrobial treatment alone.

Phase IIIb: Criteria weighting. During 8 virtual consensus meetings of the steering committee, 59 MCDA pairwise trade-off decisions were made. Criteria weights were calculated by the 1000minds software based on these decisions. The final list of criteria and their assigned weighted scores are shown in Table 3.

Phase IV: Refinement and validation. During the initial weighting, LDH, response to antibiotics, family history, and ESR/platelet ratio were included. LDH and complete response to antibiotics were moved to exclusion criteria due to the difficulty to define absolute threshold and >50% missing data. The latter 2 domains were removed due to low weight (1%–2%). The optimal threshold for CNO classification, based on Youden index of the ROC curve analysis in the development cohort (Supplement S6), was identified as 55 of a maximum of 100 when inclusion criteria and the composite domain score were applied. Cases that would have met exclusion criteria were kept in the pool for the exercise of threshold setting. There was a mixed cluster of CNO cases and mimicker cases in the development cohort with weighted scores between 52 and 54. These CNO cases did not have a bone biopsy, and it was probable that

Table 2. Detailed distribution of mimicker cases within development and validation cohorts*

Mimicker diagnosis	Development (n = 156)	Validation (n = 32)
Infection	49 (31%)	57[a] (43%)
Malignancy	61 (39%)	61 (46%)
Inflammatory arthritis	21 (13%)	4 (3%)
Other mimickers	25 (16%)	10 (8%)
Vitamin C deficiency	10	2
Benign bone tumor	7	4
Hypophosphatasia	1	2
Amplified pain syndrome	2	0
Fracture	1	0
Hyperostosis hypophosphatemia	1	0
NEMO deficiency syndrome	1	0
Traumatic injury	1	0
Unicameral bone cyst	1	0
Other autoinflammatory disease	0	1
Vascular malformation	0	1

* The development cohort included 1 case of inflammatory arthritis, 1 case of hyperostosis hypophosphatemia, and 1 case of amplified pain syndrome that adjudicators disagreed with submitting physician. NEMO, nuclear factor kappa B essential modulator.
[a] Includes 33 patients with bone tuberculosis.

biopsy findings could have moved their weighted score above the threshold for classification. After discussion, the steering committee agreed that a patient should be classified as having CNO if their score was ≥55. This cutoff value corresponded to a sensitivity of 92% and a specificity of 99% in the development cohort.

The final CNO criteria were then applied to the validation cohort to determine their performance. Given that no previous CNO classification criteria exist, their performance was compared to proposed diagnostic criteria by Jansson et al[10] and Roderick et al.[11] The demographic information of the validation cohort (n = 382 CNO patients) is summarized in Table 1, and the distribution of mimickers (n = 132) is presented in Table 2. The new EULAR/ACR CNO classification criteria had a sensitivity of 82% (95% confidence interval [CI], 78-86) and specificity of 98% (95% CI, 94-100) in the validation cohort. Two false positive cases had benign bone tumors. Sensitivity compared favorably to the Roderick et al diagnostic criteria (63%) and similarly to the modified Jansson et al criteria (85%) while specificity was similar to the Roderick et al criteria and superior to the Jansson et al criteria (Table 4).[10,11] Since all 3 criteria include bone biopsy results, a bone biopsy showing evidence of infection or malignancy is considered an exclusion for all 3 criteria, ie, the case is not classified as CNO if such evidence is found. However, the other exclusions given in Table 3 are only applied to the EULAR/ACR classification criteria because they are not specified as exclusions in the other 2 criteria. In our dataset, confirmatory evidence of mutually exclusive mimicker diseases was based on vitamin C measurement, bone marrow aspiration biopsy, blood culture, and test for tuberculosis or atypical mycobacteria, in addition to bone biopsy, which was the source of such evidence in most mimicker cases. In the validation cohort, 88% of mimicker cases met one of the exclusion criteria in Table 3, including 69% with a bone biopsy showing evidence of infection or malignancy. That said, a bone biopsy is not required to apply the classification criteria, and approximately one-third of all CNO cases had no bone biopsy.

DISCUSSION

The EULAR/ACR endorsed classification criteria for pediatric CNO presented here represent a milestone in CNO care and research. Through a 4-phase, iterative process, an international collaborative group defined weighted criteria to classify CNO, distinguishing it from mimicker conditions. The excellent specificity (98%) and sensitivity (82%) of these criteria will help define homogenous CNO cohorts for research studies. A key strength of the criteria is that patients can be classified accurately as having CNO, even in the absence of bone biopsies. However, it is important to reiterate that classification criteria are not diagnostic criteria and that biopsies may be essential in certain settings to exclude differential diagnoses of CNO.

These EULAR/ACR pediatric CNO classification criteria were built on a robust and widely recognized multiphase methodological approach that defined entry and exclusion criteria. The absolute exclusion criteria cover important mimickers of pediatric CNO such as malignancy, infection, and metabolic bone disease. Scurvy and hypophosphatasia can be diagnosed via laboratory testing and may present with a clinical picture resembling CNO, and it is important for researchers to exclude these 2 conditions prior to classifying a patient as CNO. In prospective use of the criteria to select subjects for future studies, exclusion criteria are to be applied during case review before attempting to add criteria weights. If confirmatory evidence of an alternative diagnosis such as malignancy or vitamin C deficiency is already available, if the patient had received monotherapy with antibiotics that fully resolved the symptoms, or if thrombocytopenia or marked elevation of LDH are documented, the patient should not be classified as CNO. These exclusion criteria do not mean that every subject needs to have bone biopsies or have received full courses of antibiotics before they can be classified as CNO. If none of these is documented, then proceed to add criteria weights.

Some patients with a clinical diagnosis of pediatric CNO will not fulfill classification criteria. We focused classification criteria development efforts on patients with 'typical' and 'common' manifestations with the goal of enrolling homogeneous populations into observational studies and clinical trials. As reported here, some patients with a diagnosis of CNO without bone biopsy did not accrue sufficient points to be classified as CNO. It is possible that if a biopsy was performed, those patients would have had sufficient points for classification. That said, in the hands of experienced clinicians, biopsy may not be necessary in all cases.

Table 3. EULAR/ACR classification criteria for pediatric chronic nonbacterial osteomyelitis*

Step 1, Verify entry criteria (ALL should be present):	
1. Bone pain and/or musculoskeletal functional limitation ≥6 wk	
2. Age of onset <18 y	
3. Abnormal findings from radiograph and/or advanced imaging including MRI, CT, bone scintigraphy at nonarthritic bone sites[a]	
Step 2, Verify exclusion criteria (NONE should be present):	
1. Confirmatory evidence of mutually exclusive mimicker diseases[b]	
2. Platelet <100,000/mm3	
3. Pathological LDH concerning for malignancy[c]	
4. Complete and sustained clinical and laboratory response to antimicrobial treatment alone	
Step 3, Add the scores: Add the highest value from each of the 9 domains below. A score of ≥55 is required to classify a patient as having CNO.	
Criteria domains/levels	
Bone biopsy[d]	Score
• Signs of inflammation[e] AND fibrosis	17
• Signs of fibrosis only	11
• Signs of inflammation only	9
• No signs of inflammation or fibrosis	0
Age at the onset of symptoms	
• ≥3 y	17
• <3 y	0
Sites of bone lesions based on imaging	
• Clavicle and/or mandible	16
• Sites other than clavicle, mandible, skull, or hand	9
• Skull or hand without clavicle or mandible	0
Distribution pattern of bone lesions based on imaging	
• Multifocal lesions (in ≥2 bones) with symmetrical pattern (bilateral involvement of at least one bone)	9
• Multifocal without any symmetrical pattern of bone involvement	7
• Unifocal without whole-body imaging such as WBMRI, PET/CT performed	3
• Unifocal with whole-body imaging performed	0
Coexisting conditions prior to the diagnosis of CNO	
• Inflammatory bowel disease (IBD)	9
• Cutaneous condition[f] without IBD	8
• Axial arthritis[g] without cutaneous condition or IBD	5
• None	0
Hemoglobin (normal range varies by age)	
• ≥10 g/dL	8
• <10 g/dL	0
Fever (oral/temporal temperature above 38°C and not related to common infections)	
• Absence of fever	8
• Presence of fever	0
Erythrocyte sedimentation rate (normal range: 0-20 mm/h)	
• <60 mm/h	8
• ≥60 mm/h	0
C-reactive protein (normal range: 0-10 mg/L)	
• <30 mg/L	8
• ≥30 mg/L	0

* Fever is defined as temperature >38°C without common infections including clinical symptoms of upper airway infection or urinary tract infection or abscess. It does not need to be present throughout 6 wk but any stage between the onset and the diagnosis. ACR, American College of Rheumatology; CNO, chronic nonbacterial osteomyelitis; CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET, positron emission tomography; WBMRI, whole-body MRI.
[a] Typical imaging findings include but are not limited to lytic, sclerotic lesions with or without periosteal reaction, hyperostosis on radiograph or CT, bone marrow edema or hyperintensity in a fluid-sensitive sequence of MRI. Nonarthritic bone sites refer to bones whose joint-forming ends do not demonstrate imaging signs of arthritis including synovial thickening, enhancement, and/or moderate to large joint effusions. See Supplement S7.
[b] Primary or metastatic malignancy in bone, leukemia, lymphoma, neuroblastoma, infectious osteomyelitis, metabolic bone disease, vitamin C deficiency, hypophosphatasia, and monogenic bone diseases including Majeed or deficiency of interleukin-1 receptor antagonist (DIRA).
[c] Due to differences in laboratory assays across institutions, no absolute threshold is defined. Levels ≥700 IU or >2 times the upper normal limit may be considered pathological.
[d] Bone biopsy is not required before applying these criteria.
[e] Defined as the presence of immune cells including neutrophils, monocytes, lymphocytes, and/or plasma cells.
[f] Cutaneous conditions include psoriasis, palmoplantar pustulosis, pyoderma gangrenosum, acne fulminans, and hidradenitis suppurativa.
[g] Axial arthritis is defined as imaging confirmation of inflammation within the sacroiliac joint or intervertebral joint.

Differential weighting of criteria represents their relative contribution to an individual child's classification as having CNO. For CNO, having a lesion at a typical site, such as the mandible and clavicle, in the absence of lesions at rarely affected sites, such as the skull and hands, carries the most weight. While the clavicle was proposed as a pathognomonic site by Roderick et al[11], based on

Table 4. Sensitivity and specificity of EULAR/ACR classification criteria compared to previously published diagnostic criteria using validation cohort data*

Criteria	Sensitivity	Specificity
EULAR/ACR classification criteria	82% (78%-86%)	98% (94%-100%)
Modified Jansson et al diagnostic criteria[a]	85% (81%-89%)	80% (72%-87%)
Roderick et al diagnostic criteria[b]	63% (58%-68%)	95% (89%-98%)

* ACR, American College of Rheumatology.
[a] Jansson et al diagnostic criteria require 2 of 4 major criteria or 1 of 4 major criteria and 3 of 6 minor criteria to diagnose chronic non-bacterial osteomyelitis.[10]
[b] Roderick et al diagnostic criteria require the presence of typical clinical findings and typical radiological findings and 1 of 2 criteria depending on bone sites and the number of lesions as well as the level of C-reactive protein.[11]

the personal experience of steering committee members, mimicker diseases, such as Langerhans cell histiocytosis and primary bone malignancy, may also present with clavicular lesions.[29] For this reason, clavicular lesions were not chosen as a sufficient criterion to classify as CNO. Mandibular CNO lesions have been reported extensively by oral maxillofacial surgeons[30–37], and it is important to recognize their usefulness for classifying an individual as having CNO.

The pattern of bone lesions (unifocal, multifocal, symmetrical) is also very important for CNO classification. Unifocal lesions confirmed by whole-body imaging are not characteristic of CNO. If whole-body imaging was not performed, multifocal or symmetrical lesions may be missed. Bone biopsy findings are not sufficient by themselves for CNO classification. This may suggest consideration of obtaining WBMRI before deciding on a bone biopsy.

Several items that may be useful for recognizing CNO in clinical practice, such as family history of associated diseases and ESR/platelet ratio, were not included in the criteria because they carried very low weight in the 1000minds exercise. Coexisting conditions such as inflammatory arthritis may pose a challenge in classifying CNO. Some children with inflammatory arthritis may subsequently develop CNO, and future longitudinal studies may help determine the prevalence of such occurrence by applying our CNO criteria.

Our study has several strengths. First, a large cohort of nearly 1000 patients with CNO or a mimicking condition was assembled by an international group of investigators. These criteria can be generalized to patients worldwide regardless of racial composition. Second, the experts involved in the consensus exercise and decision analysis (MCDA) also had international representation.

While it represents a significant step forward in planning randomized controlled trials and improving the quality of clinical and laboratory studies, this study also has limitations. First, the laboratory, imaging, and pathological findings were not measured or confirmed centrally, and detailed imaging findings were not available. Second, not all the cases had received all diagnostic tests considered within the inclusion criteria, including ESR, CRP, and hemoglobin. Therefore, the authors had to score 'not available' as '0.' Finally, ascorbic acid (vitamin C) deficiency, benign bone tumors, and hypophosphatasia are difficult to distinguish from CNO without applying exclusion criteria, which highlights the importance of obtaining appropriate history and laboratory results prior to applying classification criteria. The sensitivity and specificity results should be interpreted cautiously for 3 reasons. First, there is no true gold standard; the sensitivity and specificity presented reflect how well each of the classification rules agrees with the diagnosis given by the physician who submitted the case and confirmed by independent adjudicators. Second, specificity may be different if different mimicking conditions are included; the results presented here apply to the mix of mimicker conditions in our data and may be different with a different mix. Third, patients who had incomplete data may have been misclassified.

These EULAR/ACR endorsed classification criteria for pediatric CNO are the first criteria set developed through international collaboration using large development and validation cohorts and rigorous methodology. The criteria had excellent specificity (98%) and good sensitivity (82%). These criteria are easy to apply in a pediatric population because clinical, laboratory, and imaging findings are incorporated into the classification without the absolute requirement for a bone biopsy. The criteria will help researchers to easily identify a homogeneous study population for future clinical and laboratory studies.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Zhao confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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