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Factors associated with treatment response in chronic nonbacterial osteomyelitis at a single center: a retrospective cohort study

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Abstract

Background NSAIDs are commonly used as first line therapy in chronic nonbacterial osteomyelitis (CNO) but are not effective for all patients. The objective of this study was to identify clinical variables associated with NSAID monotherapy response versus requiring second-line medication in a single-center cohort of patients with CNO.

Methods The charts of children with CNO who attended a CNO clinic at a quaternary care center between 1/1/05 and 7/31/21 were retrospectively reviewed. Patients were divided into 3 groups: NSAID-short (NSAID monotherapy for 3 to < 7 months), NSAID-long (NSAID monotherapy for ≥ 7 months), or second-line treatment. Patients were also categorized by which bodily regions were affected by CNO. Multiple linear and logistic regression models were constructed to predict total NSAID monotherapy days and the odds of needing second-line treatment, respectively. These models were optimized using variable combinations that minimized multicollinearity and maximized predictive power, as indicated by minimized AIC values.

Results One-hundred-sixty-four patients fulfilled inclusion criteria. Thirty-two patients were in the NSAID-short group, 62 in the NSAID-long group, and 70 in the second-line treatment group. Comparing the two NSAID groups showed that patients with unifocal disease at diagnosis required 47% fewer days of NSAIDs than those with multifocal disease. Results from logistic regression indicated that for each additional region affected, the odds of needing second line treatment increased by 1.94 times ($p = 0.01$) and that patients with symmetric bone lesions were 6.86 times more likely to require second-line treatment ($p < 0.001$).

Conclusions Patients with unifocal CNO involvement at diagnosis were more likely to require shorter NSAID treatment. Patients with more regions affected and those with symmetric bone lesions were more likely to require second-line treatment.

Keywords Magnetic resonance imaging, Methotrexate, Nonsteroidal anti-inflammatory drugs, Osteomyelitis, Pamidronate, TNF-inhibitors

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Background

Chronic Nonbacterial Osteomyelitis (CNO) is an inflammatory condition characterized by sterile bone lesions [1–3]. CNO may develop in any part of the skeleton but has a predilection for the metaphysis of long bones, clavicles, and vertebrae, particularly in the skeletally immature [4–11]. In its mildest form, CNO manifests as a self-limited and unifocal disease. In contrast, the form of CNO sometimes referred to as Chronic Recurrent Multifocal Osteomyelitis (CRMO), causes chronic, recurrent, and multifocal bone lesions [12, 13]. Diagnosis of CNO is often delayed since the disease typically presents in an indolent manner [3]. Multiple diagnostic criteria have been proposed including those by Jansson and Bristol, but none are universally accepted [2, 14].

Severity of the disease at onset, presence of comorbidities such as inflammatory bowel disease (IBD) or juvenile idiopathic arthritis (JIA), and involvement of high-risk sites, namely vertebrae which are at risk of compression fracture, impact initial treatment decisions for patients with CNO [3, 6, 11, 15, 16]. In cases with inflammatory comorbidities, treatment with immunosuppressive therapy, typically a tumor necrosis factor alpha inhibitor (TNFi) is considered to treat both conditions. In cases with active spinal lesions, patients are generally treated with bisphosphonates or a TNFi [5, 9–11, 17, 18].

In patients without inflammatory comorbidities or spinal involvement, nonsteroidal anti-inflammatory drugs (NSAIDs) remain the mainstay of first-line treatment [4, 6, 8–11, 15, 18–22]. NSAIDs have been proven to resolve pain and radiologic evidence of disease activity in 13–83% of patients [6, 9–11, 14, 19–22]. Ninety-five percent of surveyed North American pediatric rheumatologists in 2015 reported using NSAIDs as first-line treatment for CNO [23]. The treatment duration varies widely from several months to one or more years after the disease is controlled due to the lack of evidence [11, 24]. Since long-term use of NSAIDs can be complicated by gastrointestinal side effects including gastritis and intestinal ulcer formation, it is preferable to avoid unnecessarily prolonged treatment [25].

For patients who fail to respond sufficiently to NSAIDs or who have active spinal lesions, the Childhood Arthritis and Rheumatology Research Alliance provides consensus treatment plans for the following treatments: 1) methotrexate or sulfasalazine, [2] TNFi with optional use of methotrexate, and [3] bisphosphonates [24]. It is advantageous to identify which patients will require second-line treatments as early as possible, however, it remains unclear which disease features are associated with the need for second-line treatment. In this study we aimed to determine which clinical variables are associated with response to NSAID monotherapy versus requiring a second-line medication through retrospective review of the largest single-center North American cohort reported to date.

Methods

Ethical approval and patient selection

Ethical approval for this study was obtained from the Colorado Multiple Institutional Review Board (#12–1557 and #13–0099). Children and adolescents with a diagnosis of CNO made before 18 years of age who attended the multidisciplinary (orthopedics and rheumatology) CNO clinic at the Children's Hospital of Colorado in Aurora, Colorado were invited to enroll in a registry. The medical records of those enrolled in the registry between January 1, 2005 and July 31, 2021 were retrospectively reviewed through January 31, 2022. The diagnosis of CNO was made by a pediatric rheumatologist (JS) and/or pediatric orthopedic surgeon (ND) with expertise in the condition based on the presence of unifocal or multifocal inflammatory bone lesions identified by imaging in the setting of historical and physical exam findings consistent with the diagnosis.

Data collection

Demographic details recorded included sex at birth, age at symptom onset, age at the time of diagnosis, race, and ethnicity. Clinical characteristics including comorbid conditions (inflammatory arthritis, psoriasis, and IBD), family history of inflammatory arthritis, IBD, and psoriasis in first degree relatives, laboratory studies (total white blood cell count, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) and bone biopsy reports were also recorded. Imaging findings were extracted from radiology reports, and it was noted whether bone lesions identified by magnetic resonance imaging (MRI) were evident on initial plain radiographs. Whether the patient had unifocal or multifocal disease at the time of diagnosis based on available imaging, each patient's total number of whole-body MRIs (WB-MRI), the sites of CNO lesions, and if the patient had symmetric bone lesions at any point in their disease were also recorded. The presence of symmetric bone lesions in long bones was defined as symmetric CNO lesions involving the same end of the long bone bilaterally (e.g. both right and left distal tibias, but not right proximal tibia and left distal tibia). To characterize the distribution of CNO lesions, it was recorded whether a patient ever had CNO involvement in each of the following six regions: 1) head and face, 2) upper torso (clavicle, scapula, sternum, ribs), 3) upper extremities, 4) neck and back (cervical, thoracic, and lumbar spine), 5) lower torso (sacrum and pelvis), and 6) lower extremities. Disease complications were recorded including

development of amplified pain and vertebral compression fractures.

Treatment protocol

Patients were treated per the algorithm outlined in Fig. 1. Unless a patient had spinal involvement or a comorbidity such as JIA or IBD, patients were initially treated with an NSAID. Response to NSAIDs was defined as resolution of symptoms as well as when applicable, resolution of physical examination findings, elevations in inflammatory markers, and/or imaging changes consistent with active CNO. Typically, a patient needed to fail at least two NSAIDs before a second-line agent was prescribed. Patients who responded to NSAIDs were treated for approximately six months before discontinuing treatment if the patient's disease became inactive while on NSAID treatment. If the patient's symptoms recurred after treatment discontinuation, then the discontinued NSAID was resumed. If the patient's disease became inactive, the NSAID was continued for an additional year and then discontinued again. If the patient experienced a return of CNO symptoms after the second time discontinuing the NSAID, then the NSAID would either be resumed, or a second-line agent was started. If a patient developed comorbidities or active spinal lesions at any point in treatment, then second-line medications were reconsidered. Treatment features noted in this study included medications used, dates of use, as well as the date of and reason for discontinuation when applicable.

Categorization of treatment requirement outcomes

To determine which clinical variables were associated with an increased likelihood of a patient requiring a second-line treatment versus NSAID monotherapy, patients were categorized into three groups. The first group, NSAID-short, was composed of patients who were treated with one or more NSAIDs at routine anti-inflammatory dosing for at least three months, but less than seven months. The second group, NSAID-long, was composed of patients who were treated with NSAIDs for a total of seven months or longer due to persistent disease activity (determined by history and exam, and/or imaging) or because they experienced a return of symptoms following a trial of stopping NSAIDs. The third group of patients were those treated with one or more second-line CNO treatments at any time point. This third group included patients who failed or were intolerant of NSAID-monotherapy as well as those had active spinal involvement or a comorbidity that prompted use of a second-line agent.

Statistical analysis

A multiple linear regression model was constructed to model the relationship between total NSAID monotherapy days and relevant clinical variables. Multiple logistic regression was used to model the odds of needing a second-line treatment when considering those same variables. The variables included in both models were: female sex, age at symptom onset, interval from symptom onset to treatment initiation, positive family history, unifocal

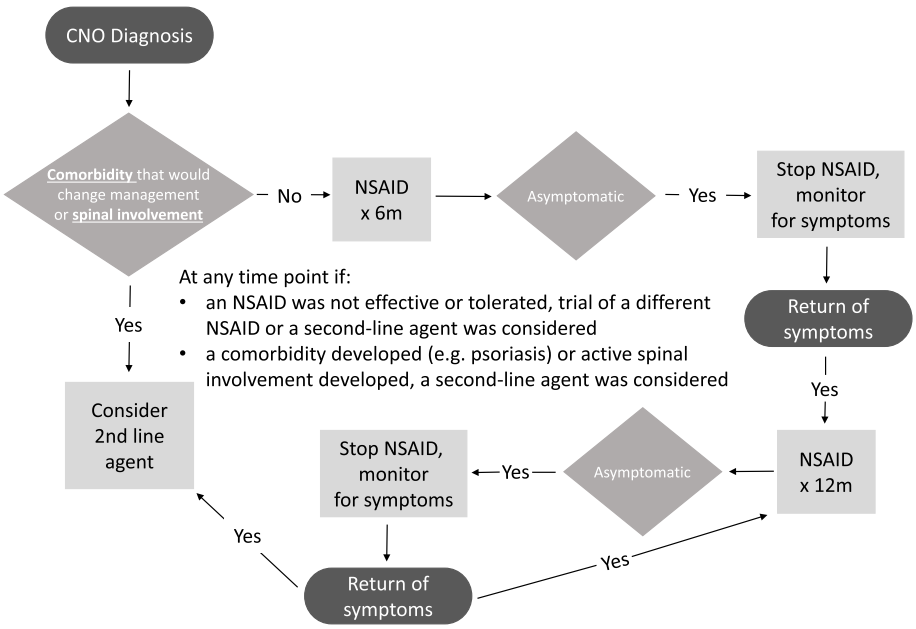

Fig. 1 CNO treatment algorithm followed at this institution's CNO multi-disciplinary clinic

disease at diagnosis, presence of symmetric bone lesions, and cumulative number of regions affected. For both modeling techniques, the final model was selected based on the best subsets combination of variables that resulted in the smallest Akaike Information Criteria (AIC) using the MASS library in R version 4.2.2 [26]. This technique is commonly used to identify the most important predictors of the dependent variable, while controlling for overfitting and the inclusion of irrelevant variables [27]. Summaries of continuous variables are presented as means and standard deviation, and categorical variables as counts and percentages. *P*-values in summary tables correspond to a one-way analysis of variance for continuous variables and chi-squared test for categorical variables. The total NSAID monotherapy days in the multiple linear regression model was log-transformed to maintain the assumption of normality of errors. Additionally, odds ratios (OR) from the logistic regression model were exponentiated to reflect percent change in the text but remain as log-odds in tables and 95% confidence intervals.

Results

Diagnosis and clinical characteristics

We reviewed the medical records of 236 children with a clinical diagnosis of CNO enrolled in our registry. As detailed in Fig. 2, 72 patients were excluded, and 164 patients were included in the final analysis. Demographic and clinical characteristics of the cohort overall and of the three treatments groups are summarized in Table 1. Thirty-two patients were in the NSAIDs-short group. All patients in this group stopped treatment at least 5 months before the study end date. Sixty-two patients were in the NSAID-long group. Seventeen of these patients (27.4%) were still on NSAID monotherapy at the time of the study end date and all other patients in this group stopped NSAID treatment a minimum of sixty days prior to the study end date. All patients in the NSAID-long group were trialed off treatment after approximately 6 months of therapy or there was documentation of some degree of disease activity (either symptoms or imaging findings) that prompted ongoing NSAID use without a treatment discontinuation trial. Seventy patients were in the second-line treatment group and the treatments they received are depicted in Fig. 3.

The average age at symptom onset was 8.87 years (±3.5) and was similar between groups (Table 1). The average interval between symptom onset and diagnosis date (time to diagnosis) was 263 days overall but was significantly different between groups ($p=0.02$). The time to diagnosis was shortest in the NSAID-short group 119 days (±211) and longest in the second-line treatment group 324 days (±403). The overall average follow-up duration was 2.89 years (±2.3) and increased between the NSAID-short, NSAID-long, and second-line treatment groups. Thirteen patients (7.9%) developed amplified pain and 22 patients (13%) were found to have one or more vertebral compression fractures (76% of those with neck and back involvement).

Laboratory studies

Laboratory studies were not uniformly obtained at diagnosis, but the available data revealed mild elevations of ESR (22.8 mm/hr ± 20.5) and CRP (1.83 mg/dL ± 3.8). However, it is notable that CRP was undetectable (i.e. below the lower limit of normal) in 36.9% of the 130 patients in which this value was checked at the time of diagnosis. The average ESR and CRP were the highest in the second-line treatment group, but these differences were not statistically significant. Eighty-two percent of patients underwent at least one bone biopsy. Significantly, more patients in the second-line treatment group ($n=66$, 94.3%) underwent a bone biopsy compared to the

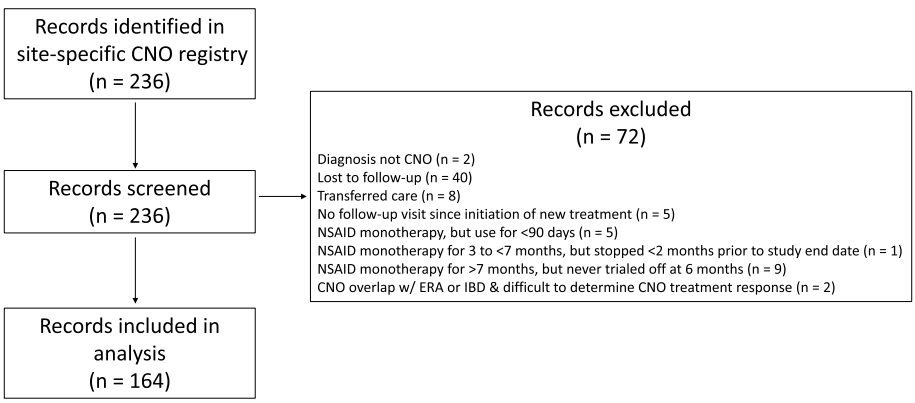

Fig. 2 Exclusion criteria. CNO: chronic nonbacterial osteomyelitis. NSAID: non-steroidal anti-inflammatory drug. ERA: enthesitis-related arthritis. IBD: inflammatory bowel disease

Table 1 Cohort characteristics

	NSAID-short (*n* = 32)	NSAID-long (*n* = 62)	Second-line (*n* = 70)	*P* value	Overall (*N* = 164)
Mean age at symptom onset, years (SD)	8.46 (4.4)	8.94 (S3.1)	8.99 (3.4)	0.76	8.87 (3.5)
Mean interval from symptom onset to treatment onset, days (SD)	124 (210)	269 (333)	293 (388)	**0.06**	251 (343)
Mean interval from symptom onset to diagnosis, days (SD)	119 (211)	270 (327)	324 (S403)	**0.02**	263 (351)
Mean follow-up, years (SD)	1.21 (S1.5)	2.70 (2.1)	3.83 (2.3)	**< 0.001**	2.89 (2.3)
Female sex, n (%)	17 (53.1%)	37 (59.7%)	42 (60%)	0.77	96 (59%)
Race and ethnicity, n (%)					
Asian	1 (3.1%)	0 (0%)	1 (1.4%)	0.71	2 (1.2%)
Black	1 (3.1%)	1 (1.6%)	1 (1.4%)		3 (1.8%)
Multiracial	0 (0%)	2 (3.2%)	3 (4.3%)		5 (3.0%)
Native American	0 (0%)	0 (0%)	1 (1.4%)		1 (0.6%)
White	29 (90.6%)	56 (90.3%)	59 (84.3%)		144 (87.8%)
Other	0 (0%)	1 (1.6%)	4 (5.7%)		5 (3.0%)
Unknown	0 (0%)	1 (1.6%)	0 (0%)		1 (0.6%)
Missing	1 (3%)	1 (1.6%)	1 (1.4%)		3 (1.8%)
Ethnicity, n (%)					
Hispanic	0 (0%)	6 (9.7%)	11 (15.7%)	0.08	17 (10.4%)
Non-Hispanic	31 (96.9%)	54 (87.1%)	58 (82.9%)		143 (87.2%)
Unknown	0 (0%)	1 (1.6%)	0 (0%)		1 (0.6%)
Missing	1 (3.1%)	1 (1.6%)	1 (1.4%)		3 (1.8%)
Family history, n (%)					
Inflammatory arthritis	0 (0%)	3 (4.8%)	5 (7.1%)	0.27	8 (4.9%)
Inflammatory Bowel Disease	0 (0%)	0 (0%)	2 (2.9%)	0.36	2 (1.2%)
Psoriasis	0 (0%)	1 (1.6%)	1 (1.4%)	> 0.99	2 (1.2%)
Mean ESR at presentation, mm/hr (SD)	19.7 (18.5)	19.6 (19.6)	27.6 (25.3)	0.09	22.8 (20.5)
Missing ESR, n (%)	3 (9.4%)	13 (21%)	17 (24.3%)		33 (20.1%)
Mean CRP at presentation, mg/dL (SD)	1.57 (3.0)	0.950 (2.1)	2.69 (4.9)	0.060	1.83 (3.8)
Missing CRP, n (%)	3 (9.4%)	16 (25.8%)	15 (21.4%)		34 (20.7%)
Biopsy performed, n (%)	22 (68.8%)	46 (74.2%)	66 (94.3%)	**0.003**	134 (81.7%)
CNO lesion apparent on plain radiographs at presentation, n (%)	19 (59.4%)	36 (58.1%)	31 (44.3%)	0.23	86 (52.4%)
Missing, n (%)	1 (3.1%)	0 (0%)	2 (2.9%)		3 (1.8%)
Unifocal disease at diagnosis, n (%)	23 (71.9%)	29 (46.8%)	29 (41.4%)	**0.02**	81 (49.4%)
Total number of whole-body MRIs, n (%)					
0	28 (87.5%)	51 (82.3%)	29 (41.4%)	**< 0.001**	106 (64.6%)
1	4 (12.5%)	8 (12.9%)	16 (22.9%)		28 (17.1%)
2	0 (0%)	3 (4.8%)	8 (11.4%)		11 (6.7%)
≥ 3	0 (0%)	0 (0%)	17 (24.3%)		17 (10.4%)
Patients with affected regions, n (%)					
Head & face	0 (0%)	0 (0%)	3 (4.3%)	0.23	3 (1.2%)
Neck and back	2 (6.3%)	9 (14.5%)	18 (25.7%)	**0.05**	29 (17.7%)
Upper torso	3 (9.4%)	8 (12.9%)	9 (12.9%)	0.90	20 (12.2%)
Upper extremity	4 (12.5%)	11 (17.7%)	22 (31.4%)	**0.05**	37 (22.6%)
Lower torso	7 (21.9%)	19 (30.6%)	33 (47.1%)	**0.03**	59 (36.0%)
Lower extremity	23 (71.9%)	34 (54.8%)	59 (84.3%)	**< 0.001**	116 (70.7%)
Mean number out of 6 regions affected (SD)	1.22 (0.6)	1.31 (0.6)	2.06 (1.0)	**< 0.001**	1.61 (0.9)
Symmetric bone lesions, n (%)	5 (15.6%)	14 (22.6%)	51 (72.9%)	**< 0.001**	70 (42.7%)
Mean days on NSAID monotherapy, days (SD)	175 (26.5)	725 (512)	441 (536)	< **0.001**	497 (511)

Table 1 (continued)

	NSAID-short ($n=32$)	NSAID-long ($n=62$)	Second-line ($n=70$)	*P* value	Overall ($N=164$)
Number of NSAIDs Trialed, n (%)					
0	0 (0%)	0 (0%)	2 (2.9%)	**<0.001**	2 (1.2%)
1	30 (93.8%)	28 (45.2%)	17 (24.3%)		75 (45.7%)
2	2 (6.3%)	32 (51.6%)	45 (64.3%)		79 (48.2%)
3 or more	0 (0%)	3 (4.8%)	6 (8.6%)		8 (4.9%)
Patients with complications, n (%)					
Vertebral height loss	0 (0%)	8 (13%)	14 (20%)	**0.02**	22 (13%)
Amplified pain	0 (0%)	3 (5%)	10 (14%)	**0.02**	13 (8%)

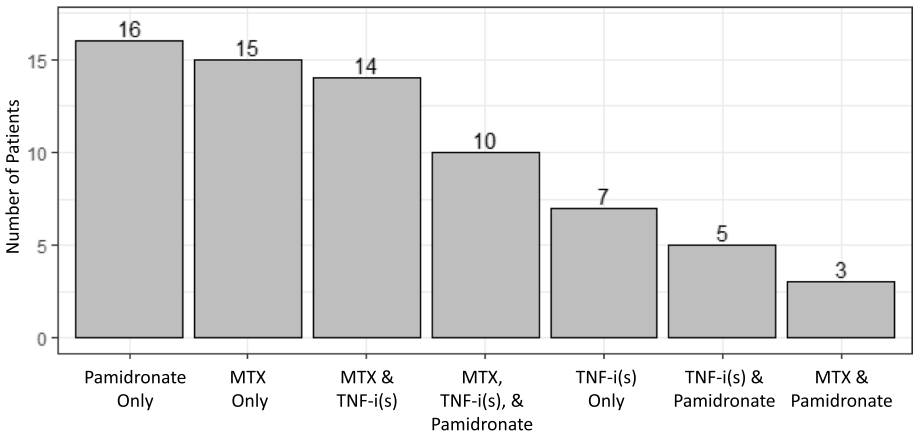

Fig. 3 Distribution of medications used in the second-line treatment group

NSAID short ($n=22$, 68.8%) and NSAID-long ($n=46$, 74.2%) groups ($p=0.003$).

Imaging results and disease distribution

As listed in Table 1, 75 (45.7%) patients had normal plain radiographs at the time of presentation. The presence of radiographically apparent lesions at the time of diagnosis was not statistically different between groups. MRI was performed for all patients. The use of WB-MRI became more prevalent over the course of the study period, but 106 patients (64.6%) did not undergo WB-MRI (Table 1). Patients in the second-line treatment group underwent more WB-MRIs than the NSAID treatment groups. Specifically, 12.5% of the NSAID-short and 17.7% of the NSAID-long group patients underwent WB-MRI, while 58.6% of the second-line treatment group patients underwent WB-MRI. Based on available imaging data, 99 (60.4%) patients had CNO lesions limited to just one of the defined six regions. There was a statistically significant difference in the proportion of patients having multi-regional CNO lesions among treatment groups ($p<0.001$) with the greatest in the second-line treatment group. The lower extremity and the lower torso (i.e. sacrum and pelvis) were the most frequently involved regions. Only three patients in this cohort had lesions in the head and face region while the neck and back region were affected in 29 patients (17.7%). Significantly more patients in the second-line treatment group (72.9%) had symmetric bone involvement when compared to the NSAID treatment groups ($p<0.001$).

Variables associated with treatments received

Results from linear regression analysis of the NSAID-short and NSAID-long groups with AIC-based variable selection can be found in Table 2. When controlling for the variables listed in Table 2, there is statistically significant evidence that having unifocal disease at diagnosis in this cohort had a negative effect on the total number of NSAID monotherapy days ($p=0.03$). On average, patients with unifocal disease at diagnosis required 47.1% fewer days of total NSAID monotherapy treatment than patients with multifocal disease at diagnosis.

Results of the logistic model with AIC-based variable selection can be found in Table 3. This model showed that when controlling for the listed variables, the number of regions affected by CNO had a positive effect on the

Table 2 Linear regression modeling *log(days of NSAID monotherapy)* with IC-based variable selection comparing the NSAID-short and NSAID long groups

	Coefficient	Std. Error	*t*-value	*p*-value	95% CI
(Intercept)	6.37	0.26	24.35	< 0.001	[5.85—6.89]
Unifocal Disease at Diagnosis	−0.39	0.17	−2.22	0.03	[−0.73 to −0.04]
Number of Regions Affected	−0.22	0.15	−1.49	0.14	[−0.53 to 0.08]
Onset to Treatment Interval	$4.0e^{-4}$	$3.0e^{-4}$	1.41	0.16	[$-1.5e^{-4}$ to $9.1e^{-4}$]

Table 3 Logistic regression modeling of the odds of requiring second-line treatment with IC-based variable selection

	Coefficient	Std. Error	*t*-value	*p*-value	95% CI
(Intercept)	−2.54	0.47	−5.46	< 0.001	[−3.50 to −1.67]
Symmetric Bone Lesions	1.93	0.42	4.56	< 0.001	[1.11—2.78]
Number of Regions Affected	0.66	0.27	2.51	0.01	[0.16—1.21]
Positive Family History	1.33	0.84	1.58	0.11	[−0.27 to 3.08]
Onset to Treatment Interval	$9.0e^{-4}$	$5.0e^{-4}$	1.57	0.13	[$-1.9e^{-4}$ to $1.97e^{-3}$]

odds of a patient requiring second-line therapy ($p = 0.01$). For each additional region affected by CNO, the odds of needing second-line therapy increased by a factor of 1.94 on average (OR = 0.66, 95% CI [0.16, 1.21]). In addition, ever-having symmetric bone lesions increased the odds of needing a second-line therapy ($p < 0.001$). On average, patients with symmetric bone lesions were 6.86 times more likely to require second-line therapy than patients without symmetric bone lesions (OR = 1.93, 95% CI [1.11, 2.78]).

Discussion

This study describes the largest reported single center cohort of patients with CNO in North America and identifies clinical variables which may be useful in determining which treatment course, NSAID monotherapy or a second-line agent, a patient will require. Demographic characteristics including the percentage of female patients, mean age at symptom onset and mean interval from symptom onset to diagnosis of patients in this cohort were similar to other reported cohorts [6, 7, 9, 14, 21, 28–30]. In this cohort, the average ESR and CRP were modestly elevated, which is comparable to the values reported in other cohorts [2, 6, 9, 15, 21, 30]. While the average CRP was mildly elevated, it is notable that CRP was undetectable in 36.9% of the 130 patients for whom this value was checked at diagnosis. The ESR and CRP levels in our cohort underscore that many patients with CNO have no signs of systemic inflammation. Our center routinely performs bone biopsies in the workup for suspected CNO to rule out disease mimickers, particularly before starting second-line CNO treatments. The bone biopsy rate in our cohort is comparable to other reported CNO cohorts [2, 5, 10, 14, 19, 22].

Just under half of patients in our cohort had normal plain radiographs at the time of initial presentation but were found to have characteristic CNO lesions by MRI. This finding is consistent with previous reports describing the insensitivity of plain radiographs in CNO and reinforces the value of advanced imaging in CNO workup [31]. As in other described cohorts, most patients in this study had lower extremity involvement (70.7%) [6, 9, 10, 15, 29, 32]. The percentage of patients with the neck and back region (i.e. spine) affected by CNO (17.7% overall) was also similar to other reports [5–7, 10, 29]. The frequency of head and face involvement in this cohort (1.2%) was similar to studies by Kaut et al., Kostik et al., and Wipff et al., but considerably lower than other reports which describe head and face involvement ranging from 6 to 21% [5, 6, 9, 10, 20, 29]. This is likely due to the fact that patients with CNO predominantly involving the jaw at our center were seen in rheumatology clinic and not the multidisciplinary CNO clinic in which the patients in this cohort were followed. Symmetric bone involvement is a hallmark of CNO, although not uniformly present. Jansson et al. identified symmetric CNO lesions in 20 out of 89 (22%) in their cohort [14]. Seventy patients (42.7%) in our cohort had symmetric CNO lesions during the course of their follow-up and presence of symmetric CNO lesions was significantly different between groups.

Given the heterogeneity of CNO with some patients having unifocal, monophasic disease and others with multifocal, chronic and/or recurrent disease, it is not

surprising that there are variable response rates to treatment. Thus, an ongoing challenge in the management of patients with CNO is predicting which treatment will be efficacious and how long treatment is likely to be necessary. In this cohort, just over half of patients were treated with NSAID monotherapy [11, 22]. Patients in the NSAID-short group were treated for an average of 6 months. This suggests that a subset of CNO patients only require relatively short courses of NSAID treatment. When we modeled the relationship between NSAID monotherapy days and potential associated clinical variables in the NSAID responsive patients (NSAID-short and NSAID-long), we found that patients with clinically unifocal disease at presentation were significantly more likely to require a shorter course of NSAIDs than those with clinically multifocal disease at presentation. Specifically, patients with clinically unifocal disease at diagnosis required nearly half the number of days of total NSAID monotherapy treatment compared to patients with multifocal disease. Catalono-Pons et al. similarly found that NSAID-non-responders had statistically more lesions at disease onset [33].

Multiple groups have described their cohorts of CNO patients and the clinical characteristics associated with the need for a second-line treatment. In a similarly sized ($n=178$) cohort of patients with CNO, the factors associated with severe disease and an increased likelihood of being treated with a bisphosphonate and/or TNFi included male sex, multifocal disease, extra-rheumatologic manifestations, family history of associated disease, and CRP greater than 1 mg/dL [5]. In our cohort, the only statistically significant factors associated with an increased odds of receiving second-line treatment were two or more regions ever affected by CNO and the presence of symmetric bone lesions ever in the treatment course. Further studies will be needed to confirm these findings.

A limitation of our study was the relatively infrequent use of imaging and in particular WB-MRI. Since WB-MRIs were not routinely obtained at baseline, some patients with multifocal disease may have been misclassified as unifocal disease. Another limitation is that the variables of symmetric bone lesions and number of regions affected reflect disease involvement over each patient's clinical course, which means that the results of our statistical modeling cannot be used to evaluate baseline characteristics and predict response to treatment. A strength, however, is that patients included in this cohort were those seen in our multidisciplinary CNO clinic based on a protocolized approach, which made for a more homogenous group of patients managed in a more consistent manner.

Conclusions

In summary, our data suggest that it may be reasonable to trial short NSAID courses in NSAID-responders especially those who have confirmed unifocal disease by WB-MRI. Patients with symmetric CNO involvement or multiregional disease may be more likely to require second-line treatments. Future multisite studies are needed to confirm these findings.

Abbreviations

CNO	Chronic Nonbacterial Osteomyelitis
CRMO	Chronic Recurrent Multifocal Osteomyelitis
IBD	Inflammatory Bowel Disease
JIA	Juvenile Idiopathic Arthritis
TNFi	Tumor Necrosis Factor alpha inhibitor
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
ESR	Erythrocyte Sedimentation Rate
CRP	C-reactive Protein
MRI	Magnetic Resonance Imaging
WB-MRI	Whole Body MRI
NSAID-short	Patients on NSAID(s) monotherapy for less than 7 months
NSAID-long	Patients on NSAID(s) monotherapy for 7 months or longer
AIC	Akaike Information Criteria
OR	Odds Ratio

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Authors' contributions

KN was the researcher principally responsible for study conception, design, data collection, interpretation of results and manuscript preparation. NR contributed substantially to study conception, design, data collection, interpretation of results as well as manuscript preparation. CK performed the statistical analysis and contributed to the methods section. ND helped revise the manuscript. JS contributed to data interpretation and revision of the manuscript. YZ contributed to study design, interpretation of results and manuscript revision. All authors read and approved the final manuscript.

Authors' information

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board of record of records, the Colorado Multiple Institutional Review Board (COMIRB) approved the collection of data for this study (#12–1557 and #13–0099). Informed consent and assent were obtained from all individual participants enrolled in this study after January 1, 2018 as data was collected prospectively (although prospective data was not included in this report), but consent was waived for those patients enrolled prior to January 1, 2018 given the retrospective nature of data collection for these patients.

Consent for publication

Not applicable.

Competing interests
YD received research funding from Bristol-Myers Squibb, Rheumatology Research Foundation, Consortium for Technology & Innovation in Pediatrics, Childhood Arthritis & Rheumatology Research Alliance, royalties from UpToDate and consulting fees from Novartis in 2020.

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References

1. Zhao Y, Ferguson PJ. Chronic Nonbacterial Osteomyelitis and Chronic Recurrent Multifocal Osteomyelitis in Children. Pediatr Clin North Am. 2018;65(4):783–800.
2. Roderick MR, Shah R, Rogers V, Finn A, Ramanan AV. Chronic recurrent multifocal osteomyelitis (CRMO) - advancing the diagnosis. Pediatr Rheumatol Online J. 2016;14(1):47.
3. Ferguson PJ, Sandu M. Current understanding of the pathogenesis and management of chronic recurrent multifocal osteomyelitis. Curr Rheumatol Rep. 2012;14(2):130–41.
4. Girschick H, Finetti M, Orlando F, Schalm S, Insalaco A, Ganser G, et al. The multifaceted presentation of chronic recurrent multifocal osteomyelitis: a series of 486 cases from the Eurofever international registry. Rheumatology (Oxford). 2018;57(7):1203–11.
5. Wipff J, Costantino F, Lemelle I, Pajot C, Duquesne A, Lorrot M, et al. A large national cohort of French patients with chronic recurrent multifocal osteitis. Arthritis Rheumatol. 2015;67(4):1128–37.
6. Borzutzky A, Stern S, Reiff A, Zurakowski D, Steinberg EA, Dedeoglu F, et al. Pediatric chronic nonbacterial osteomyelitis. Pediatrics. 2012;130(5):e1190–7.
7. Walsh P, Manners PJ, Vercoe J, Burgner D, Murray KJ. Chronic recurrent multifocal osteomyelitis in children: nine years' experience at a statewide tertiary paediatric rheumatology referral centre. Rheumatology (Oxford). 2015;54(9):1688–91.
8. Bhat CS, Anderson C, Harbinson A, McCann LJ, Roderick M, Finn A, et al. Chronic non bacterial osteitis- a multicentre study. Pediatr Rheumatol Online J. 2018;16(1):74.
9. Kostik MM, Kopchak OL, Chikova IA, Isupova EA, Mushkin AY. Comparison of different treatment approaches of pediatric chronic non-bacterial osteomyelitis. Rheumatol Int. 2019;39(1):89–96.
10. O'Leary D, Wilson AG, MacDermott EJ, Lowry C, Killeen OG. Variability in phenotype and response to treatment in chronic nonbacterial osteomyelitis; the Irish experience of a national cohort. Pediatr Rheumatol Online J. 2021;19(1):45.
11. Beck C, Morbach H, Beer M, Stenzel M, Tappe D, Gattenlöhner S, et al. Chronic nonbacterial osteomyelitis in childhood: prospective follow-up during the first year of anti-inflammatory treatment. Arthritis Res Ther. 2010;12(2):R74.
12. Zhao DY, McCann L, Hahn G, Hedrich CM. Chronic nonbacterial osteomyelitis (CNO) and chronic recurrent multifocal osteomyelitis (CRMO). J Transl Autoimmun. 2021;4: 100095.
13. Girschick HJ, Raab P, Surbaum S, Trusen A, Kirschner S, Schneider P, et al. Chronic non-bacterial osteomyelitis in children. Ann Rheum Dis. 2005;64(2):279–85.
14. Jansson A, Renner ED, Ramser J, Mayer A, Haban M, Meindl A, et al. Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. Rheumatology (Oxford). 2007;46(1):154–60.
15. Concha S, Hernández-Ojeda A, Contreras O, Mendez C, Talesnik E, Borzutzky A. Chronic nonbacterial osteomyelitis in children: a multicenter case series. Rheumatol Int. 2020;40(1):115–20.
16. Laxer RM, Shore AD, Manson D, King S, Silverman ED, Wilmot DM. Chronic recurrent multifocal osteomyelitis and psoriasis–a report of a new association and review of related disorders. Semin Arthritis Rheum. 1988;17(4):260–70.
17. Gleeson H, Wiltshire E, Briody J, Hall J, Chaitow J, Sillence D, et al. Childhood chronic recurrent multifocal osteomyelitis: pamidronate therapy decreases pain and improves vertebral shape. J Rheumatol. 2008;35(4):707–12.
18. Beck NA, Roudnitsky E, Nuzzi LC, Padwa BL, Dedeoglu F. How Have the Diagnosis and Treatment of Chronic Recurrent Multifocal Osteomyelitis Changed Over Time? J Oral Maxillofac Surg. 2023;81(2):238–47.
19. Kaiser D, Bolt I, Hofer M, Relly C, Berthet G, Bolz D, et al. Chronic nonbacterial osteomyelitis in children: a retrospective multicenter study. Pediatr Rheumatol Online J. 2015;13:25.
20. Kaut S, Van den Wyngaert I, Christiaens D, Wouters C, Noppe N, Herregods N, et al. Chronic nonbacterial osteomyelitis in children: a multicentre Belgian cohort of 30 children. Pediatr Rheumatol Online J. 2022;20(1):41.
21. Reiser C, Klotsche J, Hospach A, Berendes R, Schnabel A, Jansson AF, et al. First-year follow-up of children with chronic nonbacterial osteomyelitis-an analysis of the German National Pediatric Rheumatologic Database from 2009 to 2018. Arthritis Res Ther. 2021;23(1):281.
22. Schnabel A, Range U, Hahn G, Berner R, Hedrich CM. Treatment Response and Longterm Outcomes in Children with Chronic Nonbacterial Osteomyelitis. J Rheumatol. 2017;44(7):1058–65.
23. Zhao Y, Dedeoglu F, Ferguson PJ, Lapidus SK, Laxer RM, Bradford MC, et al. Physicians' Perspectives on the Diagnosis and Treatment of Chronic Nonbacterial Osteomyelitis. Int J Rheumatol. 2017;2017:7694942.
24. Zhao Y, Wu EY, Oliver MS, Cooper AM, Basiaga ML, Vora SS, et al. Consensus Treatment Plans for Chronic Nonbacterial Osteomyelitis Refractory to Nonsteroidal Antiinflammatory Drugs and/or With Active Spinal Lesions. Arthritis Care Res (Hoboken). 2018;70(8):1228–37.
25. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol. 2020;180: 114147.
26. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria2018.
27. W. N. Venables BDR. Modern Applied Statistics with S. 4 ed. New York, NY: Springer; 2010. 498 p.
28. Jansson AF, Grote V. Nonbacterial osteitis in children: data of a German Incidence Surveillance Study. Acta Paediatr. 2011;100(8):1150–7.
29. Ma L, Liu H, Tang H, Zhang Z, Zou L, Yu H, et al. Clinical characteristics and outcomes of chronic nonbacterial osteomyelitis in children: a multicenter case series. Pediatr Rheumatol Online J. 2022;20(1):1.
30. Ziobrowska-Bech A, Fiirgaard B, Heuck C, Ramsgaard Hansen O, Herlin T. Ten-year review of Danish children with chronic non-bacterial osteitis. Clin Exp Rheumatol. 2013;31(6):974–9.
31. Fritz J, Tzaribatchev N, Claussen CD, Carrino JA, Horger MS. Chronic recurrent multifocal osteomyelitis: comparison of whole-body MR imaging with radiography and correlation with clinical and laboratory data. Radiology. 2009;252(3):842–51.
32. Huber AM, Lam PY, Duffy CM, Yeung RS, Ditchfield M, Laxer D, et al. Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up. J Pediatr. 2002;141(2):198–203.
33. Catalano-Pons C, Comte A, Wipff J, Quartier P, Faye A, Gendrel D, et al. Clinical outcome in children with chronic recurrent multifocal osteomyelitis. Rheumatology (Oxford). 2008;47(9):1397–9.

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