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ORIGINAL ARTICLE

Consensus Treatment Plans for Chronic Nonbacterial Osteomyelitis Refractory to Nonsteroidal Antiinflammatory Drugs and/or With Active Spinal Lesions

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Objective. **To develop standardized treatment regimens for chronic nonbacterial osteomyelitis (CNO), also known as chronic recurrent multifocal osteomyelitis (CRMO), to enable comparative effectiveness treatment studies.**

Methods. **Virtual and face-to-face discussions and meetings were held within the CNO/CRMO subgroup of the Childhood Arthritis and Rheumatology Research Alliance (CARRA). A literature search was conducted, and CARRA membership was surveyed to evaluate available treatment data and identify current treatment practices. Nominal group technique was used to achieve consensus on treatment plans for CNO refractory to nonsteroidal antiinflammatory drug (NSAID) monotherapy and/or with active spinal lesions.**

Results. **Three consensus treatment plans (CTPs) were developed for the first 12 months of therapy for CNO patients refractory to NSAID monotherapy and/or with active spinal lesions. The 3 CTPs are methotrexate or sulfasalazine, tumor necrosis factor inhibitors with optional methotrexate, and bisphosphonates. Short courses of glucocorticoids and continuation of NSAIDs are permitted for all regimens. Consensus was achieved on these CTPs among CARRA members. Consensus was also reached on subject eligibility criteria, initial evaluations that should be conducted prior to the initiation of CTPs, and data items to collect to assess treatment response.**

Conclusion. **Three consensus treatment plans were developed for pediatric patients with CNO refractory to NSAIDs and/or with active spinal lesions. Use of these CTPs will provide additional information on efficacy and will generate meaningful data for comparative effectiveness research in CNO.**

INTRODUCTION

Chronic nonbacterial osteomyelitis (CNO) is an autoinflammatory bone disease that mainly affects children and adolescents. Clinical presentations range from mild and sometimes limited unifocal disease to severe, chronically active or recurrent inflammation of multiple bones. The latter is referred to as chronic recurrent multifocal osteomyelitis (CRMO). Here, we will use the term CNO to refer to the entire spectrum of this disease. CNO can be complicated by vertebral compression fractures, kyphosis, and leg length discrepancy when it is not recognized early or treated adequately. The diagnosis of CNO is made by excluding alternatives in the differential diagnosis, including malignancy (leukemia, lym-

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Significance & Innovations

- Three standardized consensus treatment plans were developed for patients with chronic nonbacterial osteomyelitis (CNO) who have had insufficient response to nonsteroidal antiinflammatory drugs and/or who have active spinal lesions.
- The consensus treatment plans developed by members of the Childhood Arthritis and Rheumatology Research Alliance are the first ever for patients with CNO.
- Use of these treatment plans will allow for evaluation of these medications in patients with CNO in future comparative effectiveness research studies.

phoma, and primary or metastatic bone tumors), Langerhans' cell histiocytosis, and infection. Clinical assessment in conjunction with serum inflammatory parameters and imaging studies, particularly magnetic resonance imaging (MRI), are crucial for the diagnosis and monitoring of disease activity of CNO (1).

Because of significant variation in clinical treatment practices among pediatric rheumatologists, standardized treatment regimens (consensus treatment plans [CTPs]) have been developed within the Childhood Arthritis and Rheumatology Research Alliance (CARRA), a North American organization composed of pediatric rheumatologists and researchers, for systemic juvenile idiopathic arthritis (JIA) (2), polyarticular JIA (3), lupus nephritis (4), juvenile localized scleroderma (5), and juvenile dermatomyositis (6). These CTPs enable progress to be made toward identifying optimal treatment for these diseases through prospective observational studies. The developed CTPs were based on the best available evidence and current treatment practices, and generated through consensus methodology including nominal group techniques. The intention of these CTPs was to limit treatment practice variation in order to enable researchers to conduct comparative effectiveness studies. Because of the variability in the second-line treatment of CNO, we have worked to develop standardized treatment plans and data collection forms and measures for CNO patients with a nonsteroidal antiinflammatory drug (NSAID)-refractory course and/or with active spinal lesions. These CTPs will facilitate future comparative effectiveness studies for CNO. It must be noted that CTPs are not meant to be clinical care guidelines. A treating physician may deviate from the CTP at any time if it is deemed appropriate for the patient's care.

MATERIALS AND METHODS

The CARRA CNO workgroup of the CARRA Scleroderma, Vasculitis, Autoinflammatory and Rare Diseases (SVARD) subcommittee consists of board-certified pediatric rheumatologists with special interest and expertise in CNO, as well as family representatives. The CARRA CNO workgroup reviewed evidence published between 1966 and April 29, 2015. A literature search was conducted using PubMed with the following medical subject headings (MeSH) terms: SAPHO[all fields] OR (chronic[all fields] AND nonbacterial [all fields] AND ("osteomyelitis"[MeSH terms] OR "osteomyelitis"[all fields])) OR ("chronic recurrent multifocal osteomyelitis"[supplementary concept] OR "chronic recurrent multifocal "osteomyelitis"[all fields] OR "chronic recurrent multifocal osteomyelitis"[all fields]) OR (noninfectious[all fields] AND ("osteomyelitis"[MeSH terms] OR "osteomyelitis"[all fields])) AND (hasabstract[text] AND "humans"[MeSH terms] AND English[lang]).

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In total, 398 articles were screened. A complete list of the results is included in Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23462/abstract. There were no randomized controlled trials or case–control studies in CNO. Therefore, case series, historical cohort studies, and prospective observational studies with at least 3 months of followup data in the pediatric population were included for review. Twenty-one articles met the criteria. Eleven additional articles published between April 29, 2015, and January 1, 2017, were later included. The group formulated clinical scenarios, analyzed survey responses from CNO workgroup members, organized consensus meetings, and finalized treatment plans. Levels of evidence were graded from 2 to 5 according to guidelines established by the Oxford Centre for Evidence-Based Medicine (www.cebm.net).

Planning meetings. Members of the CARRA CNO workgroup initiated the process to develop CTPs at the CARRA 2014 annual meeting. Monthly conference calls within the workgroup were then used to develop a CARRA members' survey and ongoing discussion of the CTPs. The targeted population included patients refractory to NSAID monotherapy and/or with active spinal lesions, because physicians perceived less favorable outcomes and need for additional treatment in such patients. At the planning meeting (April 2015 in Austin, Texas), a survey was sent to the SVARD subcommittee to collect responses of diagnostic, disease monitoring, and therapeutic approaches chosen by CARRA-affiliated pediatric rheumatologists. Further discussion at that meeting outlined the core substance of the planned CTPs. A detailed survey was sent to the CNO group (67% of 34 members responded) asking for comments on summarized plans and proposed options (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23462/abstract). At the American College of Rheumatology Annual Meeting (November 2015 in San Francisco, California), a second meeting was attended by 13 pediatric rheumatologists. Patient characteristics, treatment options, and imaging monitoring were discussed in depth.

Consensus meetings. At the CARRA annual meeting (April 2016 in Toronto, Ontario, Canada), a CNO meeting was attended by 6 family representatives and 30 pediatric rheumatologists, one of whom acted as the facilitator (YZ). The facilitator and family representatives participated in the discussion but were not eligible to vote. Nominal group technique was used to achieve consensus (defined as ≥80% agreement within the group) on all questions considered during the meeting and subsequent conference calls. The facilitator framed the question to be discussed and presented data from the survey relevant to each question. Potential responses to the question were shown based on prior group discussion. Each participant had the opportunity to express his or her opinion for 1–2 minutes without interruption. Potential responses were updated accordingly.

Participants were then given the opportunity to vote for their preferred responses to the questions using a show-of-hands vote. A vote of ≥80% positive or negative was considered a consensus vote. If consensus was not achieved, participants were given the opportunity to speak uninterrupted for 1–2 minutes to share their thought process. After excluding answers that would not result in consensus votes, or after modifying potential responses, another vote was taken. If necessary, this process continued for 2 rounds on each question. If a clear consensus was not reached after 2 rounds, the decision was made to move to the next question.

RESULTS

What standardized disease-assessment tools of CNO have been reported? A literature review of the clinical cohort studies on CRMO, CNO, and pediatric synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome revealed a lack of agreement on a standardized evaluation tool. Two articles have reported standardized assessments with level IV evidence. Beck and colleagues used a PedCNO score (7) to assess prospectively the responses to naproxen in 37 children with CNO. After 12 months of treatment, 54% of patients achieved PedCNO 70 (at least 70% improvement in at least 3 of 5 core variables and no more than 1 of the remaining variables deteriorating by more than 70%). Within the core set, the erythrocyte sedimentation rate (ESR) and the Childhood Health Assessment Questionnaire (C-HAQ) had a floor effect by 3 months, whereas the number of radiologic lesions by MRI, severity of disease estimated by the physician, and severity of disease estimated by the patient or parent continued to improve over 12 months. Zhao and colleagues further described the characteristics of CNO lesions based on MRI findings using a grading system to score the severity of bone edema and soft tissue inflammation as well as the presence of periosteal reaction, hyperostosis, growth plate damage and vertebral compression (8). Applying this scoring tool to 2 retrospective cohorts of patients with CNO, the authors found a significant decrease in the number of nonvertebral lesions and the maximum severity of bone edema in the group receiving aggressive treatment.

What evidence of the effectiveness of second-line treatments is there in CNO? Studies focusing on children with CNO who failed to respond to NSAID treatment are limited. Seven articles have reported on pamidronate treatment in CNO with level IV evidence. Kerrison and colleagues reported significant pain relief and improved activity and well-being with pamidronate use in 7 children (3 with spinal lesions) who failed to respond to NSAIDs (9). Simm et al (10) and Miettunen et al (11) demonstrated the effectiveness of pamidronate in children with CNO refractory to NSAIDs. More than 80% of patients had pain relief and more than 90% of patients in Miettunen's study exhibited resolution of bone lesions on MRI after 6 months of treatment. Gleeson and colleagues reported pain relief with pamidronate in 6 of 7 children who failed to respond to NSAIDs (12). Among 5 children with spinal fractures, 3 had followup radiographs showing regression of height loss in affected vertebrae in response to pamidronate therapy. Hospach et al (13) reported complete resolution of hyperintensity signal of active spinal lesions after 3 to 6 cycles of pamidronate and a median interval of 13 months of followup with MRI in 8 of 9 children with CNO refractory to NSAIDs. Roderick et al treated 11 children with CNO refractory to NSAIDs with 4 cycles of

pamidronate at 1 mg/kg/day on 3 consecutive days every 3 months (14). Two patients exhibited a good response, 6 showed a moderate response, 1 had a mild response, and 2 failed to respond based on repeated whole-body MRIs. Schnabel et al described pamidronate to be highly effective in CNO patients refractory to standard treatment with NSAIDs and/or glucocorticoids (15).

Published data on the use of tumor necrosis factor (TNF) inhibitors in CNO are more limited. Eight articles have reported treatment with TNF inhibitors in CNO with level IV evidence. A small cohort study (n = 4) by Eleftheriou et al showed decreased pain in children with CNO after infliximab treatment (n = 3) and anakinra (n = 1, later switched to adalimumab) (16). Borzutzky et al (17) and Wipff et al (18) observed the highest rates of clinical remission (46%) or efficacy (89%) from TNF inhibitors compared to glucocorticoids, methotrexate (MTX), sulfasalazine (SSZ), and NSAIDs. Jansson et al (19) reported disease remission induced by infliximab in 2 patients who failed to respond to NSAIDs, glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and pamidronate. Recently, a combination of infliximab and methotrexate with or without zolendronic acid significantly improved clinical, laboratory, and imaging results in 9 children with CNO (8). However, Kaiser et al found poor response to TNF inhibitors in children with CNO, i.e., only 2 of 7 patients achieved remission (not defined) (20). Conversely, in a small childhood series, etanercept was effective in all 5 patients (21). Anti–interleukin-1 (IL-1) has been reported in fewer pediatric cases (20). In an adult cohort (n = 6), anakinra improved the patient global assessment of disease activity within 1 month in 5 patients (22).

Most of the studies in the literature reported variable success of MTX and SSZ in patients with poor responses to NSAIDs or frequent relapses. Other DMARDs were rarely used. Five articles have reported treatment of DMARDs in CNO with level IV evidence. Jansson et al (19), Catalano-Pons et al (23), and Kaiser et al (20) documented poor responses to SSZ, MTX, and azathioprine in children with CNO. Borzutzky et al (17) and Wipff et al (18) showed relatively lower rates of remission (18–20%) and efficacy (38–41%) in children treated with MTX or SSZ. There was poor tolerance of MTX, and dosing was not reported in most studies.

Currently, there is no consensus on subsequent treatment for patients refractory to NSAID treatment. Based on a survey sent to members of CARRA, 95% of treating physicians (41% response rate) reported the use of NSAIDs as the first-line treatment in children with a new diagnosis of CNO (evidence level V) (24). For patients who failed to respond to NSAID treatment, the most commonly used treatments were reported to be MTX (67%), TNF inhibitors (65%), and bisphosphonates (46%) (24). These results guided the development of CTPs.

What patient characteristics should be included for this CTP? The initial intent was to include all children with CNO. However, through further workgroup discussion, it was agreed that NSAIDs were generally considered first-line treatment for all newly diagnosed patients without active spinal lesions. Therefore, our attention turned to a more defined subset: patients refractory to NSAIDs and/or with active spinal lesions. The definition of "refractory to NSAIDs" was debated among group members, and the duration of the initial NSAID trial was set at a minimum of 4 weeks. Based on the physician's discretion and the disease severity, further treatment may be initiated. The rationale of including active spinal lesions as a patient characteristic is the perceived significance of increased risk of vertebral fracture (11–13). The age limit for the CTP was set to 21 years, because children and adults younger than 21 years of age are commonly seen and followed in children's hospitals. Patients with malignancy, infectious osteomyelitis, or other contraindications to the proposed treatment agents were not eligible for the CTP. Characteristics of the patients are shown in detail in Table 1.

What standardized data should be collected at the initial evaluation? Each patient should undergo a complete clinical assessment, including comprehensive musculoskeletal exam, since clinically active lesions are defined by findings of focal

Table 1. Patient characteristics for pediatric chronic nonbacterial osteomyelitis refractory to NSAID monotherapy and/or with active spinal lesions*

Enrolled patients should have:
Age at enrollment 21 years or younger
Presence of bone edema on STIR or T2 fat saturation sequence on MRI within 12 weeks of enrollment
Whole-body imaging evaluation (either whole-body MRI or bone scintigraphy)†
Active disease after failing at least 4 weeks of NSAIDs and/or presence of active spinal lesions, regardless of NSAID trial‡
Bone biopsy to exclude infection or malignancy unless bone lesions follow typical distribution or there is IBD, psoriasis, or palmar plantar pustulosis§
Enrolled patients should NOT have:
History of or current malignancy
Current infectious osteomyelitis
Contraindication to the selected treatment agent

* NSAID = nonsteroidal antiinflammatory drug; STIR = short tau inversion recovery sequence; MRI = magnetic resonance imaging; IBD = inflammatory bowel disease.
† Suggested protocol includes STIR or fat saturation sequences of coronal views of whole body and sagittal view of total spine. Some patients may require dedicated views of hands or feet when lesions in these areas are present. Gadolinium is not required.
‡ Active disease defined as persistent pain with focal tenderness and/or warmth and/or persistence of bone edema on MRI in at least 1 lesion site. Active spinal lesions are defined as bone edema within at least 1 vertebral body of the cervical, thoracic, or lumbar spine.
§ Typical distribution of lesions includes the clavicle or symmetrical lesions in long bones at metaphysis/epiphysis.

tenderness, and/or swelling, and/or warmth, in addition to the patient's report of pain. Active joint counts with arthritis and enthesitis are important to record because of reported overlap between enthesitis-related arthritis (ERA) and CNO. Due to the lack of validated CNO-specific patient-reported outcomes, both the C-HAQ and Patient-Reported Outcomes Measurement Information System (PROMIS) should be administered. Based on the previously published CNO diagnostic criteria (19,25) and results from physician surveys (24), a bone biopsy is recommended, unless typical lesions including the clavicle or symmetrical lesions at metaphysis/epiphysis of long bones, or comorbidities such as inflammatory bowel disease, palmoplantar pustulosis, or psoriasis, are present. All participants agreed that whole-body imaging is required to identify all bone lesions. Whole-body MRI is preferred (26). A suggested protocol is included in Table 1. Bone scintigraphy is considered an adequate alternative if whole-body MRI is not available. The total number of bone lesions is recorded as per the radiologist's report. A baseline MRI (whole body or regional) is required to define active bone lesions based on the presence of bone marrow edema from short tau inversion recovery (STIR) or T2 fat saturation sequences, as the MRI findings are important to guide treatment decisions and to monitor disease activity (8,11,13,24,27). The normal range of bone marrow signal on MRI has not been established yet. Therefore, distinguishing abnormal marrow signal is subject to the experience of the radiologist reading the image. The size and severity of bone edema and/or soft tissue inflammation is determined by the radiologist based on previous description (8). Bony expansion, growth plate damage, and vertebral compression were considered disease damage and not active inflammation (8). In children treated with bisphosphonates, a linear hyperintense signal should not be mistaken for active lesions. Laboratory data, including complete blood cell counts, ESR, and C-reactive protein (CRP) level, are required for disease monitoring. Alkaline phosphatase at baseline is required to screen for metabolic bone disease. HLA–B27 has been reported to be associated with cutaneous diseases in CNO and to have a strong association with ERA. Thus, participants agreed to include HLA–B27 testing.

What are the most important therapies to include? We reviewed the literature for medications with reported efficacy in CNO refractory to NSAIDs, including nonbiologic DMARDs, TNF inhibitors, and bisphosphonates (8–14,17,18,20,28,29). There are no head-to-head comparisons among these treatments, even though current data suggested higher remission rates in children treated with TNFi than those treated with DMARDs (17,18). Among CARRA physicians, MTX, TNF inhibitors, and bisphosphonates were the most commonly used medications in children with CNO who failed to respond to NSAIDs (24).

Table 2. Consensus treatment plans for the first 6–12 months*

Treatment plan A: nonbiologic DMARDs
Methotrexate (oral or subcutaneous): 15 mg/m^2 (maximum 25 mg/dose) weekly
OR
Sulfasalazine (oral): 50 mg/kg/day (maximum 1,500 mg/dose) divided twice daily
Treatment plan B: TNF inhibitors with or without methotrexate
Adalimumab (subcutaneous): 20 mg every other week for body weight 15–30 kg; 40 mg every other week for body weight ≥30 kg. May increase to weekly.
OR
Etanercept (subcutaneous): 0.8 mg/kg (maximum 50 mg/dose) weekly. May split into twice a week.
OR
Infliximab (intravenous): 5–10 mg/kg (maximum 1,000 mg/dose) at week 0, 2, and 6, then every 4–8 weeks
OR
Other TNF inhibitor at discretion of treating physician
Optional: concomitant methotrexate (do not need to follow treatment protocol; may use lower dosing, i.e., 5–10 mg/m^2)
Treatment plan C: bisphosphonates
Pamidronate (intravenous)
Option 1: 1 mg/kg/dose (maximum 60 mg/dose) every month†
Option 2: 1 mg/kg/dose for 3 consecutive days every 3 months†
OR
Zolendronic acid (intravenous): initial dose 0.0125–0.025 mg/kg every 6 months. May increase dose to 0.05 mg/kg/dose (maximum 4 mg/dose)
All options allow concurrent use of
NSAIDs‡
Glucocorticoids: up to a total of 6 weeks of treatment with or without tapering, with an upper limit of 2 mg/kg/day (equivalent dosing of prednisone, maximum 60 mg daily)

* With the exception of bisphosphonates (minimum 3–6 months), the minimum treatment duration should be 12 months. DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor; NSAID = nonsteroidal anti-inflammatory drug.
† A lower dose of 0.5 mg/kg may be used at initiation of treatment. Both options should continue for a minimum duration of 3 months. Maximum cumulative dose is 11.5 mg/kg/year.
‡ For details on dosing, see Supplementary Appendix C, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23462/abstract.

Consensus was reached to include the 3 most commonly applied combinations of medications in the final CTPs. There was a discussion about whether concomitant NSAIDs and/or oral glucocorticoid "bursts" were allowed. The group decided on the optional use of both, with limits on the allowable duration of glucocorticoids due to their known side effects. Glucocorticoid "bursts" were defined as glucocorticoids (equivalent dosing of prednisone) up to 2 mg/kg/day (maximum daily dose of 60 mg) for up to a total of 6 weeks of treatment with or without tapering. Chosen strategies were in agreement with current practice echoed by participants. In patients treated with TNF inhibitors, concomitant MTX was allowed to suppress the formation of human antichimeric anti-TNF antibody production (particularly with infliximab) as well as for combination therapy (Table 2).

What dose/route/frequency should be used for each medication in the CTPs? The most commonly used DMARD by physician members in the CARRA survey was MTX (34%) (24). However, within the CNO group, members reported that SSZ was commonly used based on personal experience. Thus, only these 2 DMARDs were included in the protocol. TNF inhibitors reported for use in CNO were limited to etanercept, adalimumab, and infliximab. The frequency of using these TNF inhibitors among surveyed CARRA physician members was 26% with adalimumab and infliximab, and 17% with etanercept (24). Thus, all 3 were included in the protocol. Other TNF inhibitors may be used by the treating physician with discretion. Mandatory tuberculosis screening is required prior to the initiation of a TNF inhibitor. The dosing of DMARDs and TNF inhibitors followed standard JIA treatment regimens as reported in the literature and clinical practice (Table 2). Pamidronate was the most commonly reported bisphosphonate (9–15), whereas zolendronic acid was only reported as concomitant treatment in a single study (8). However, both were used by physicians within CARRA (pamidronate 79%, zolendronic acid 21%) (24). Therefore, in the bisphosphonate arm, pamidronate and zolendronic acid were both included in the protocol. The dosing of bisphosphonates was based on the pediatric endocrinology literature and has been utilized in case series of CNO and SAPHO patients (Table 2). Suggested toxicity monitoring and immunizations are included in Supplementary Appendix C, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23462/abstract.

What criteria should be used to determine treatment failure? Various parameters have been used to define treatment response in CNO, including the PedCNO score (7), total number of clinically active bone lesions, and severity of bone edema and soft tissue inflammation on MRI (8). After discussion, group consensus was reached to use a composite score similar to the JIA core set based on significant variation of symptoms and a high incidence of pain amplification (pain in the absence of inflammatory activity) among CNO patients. Various items were proposed by group members, and after in-depth discussion, the group identified the top 6 individual items. These treatment response criteria are considered expert opinion (evidence level IV). Thus a modified composite score was proposed by replacing the C-HAQ and severity of disease estimated by patient or parent with the size and severity of bone marrow edema and/or soft tissue inflammation in the MRI and the total count of clinically active lesions. These criteria have not been validated and are merely suggestions for physicians to consider during their clinical management of children with CNO. As shown in Table 3, a combination of criteria for treatment failure include the following: patient pain, as measured by visual analog scale (VAS), total number of clinically active lesions (defined as focal tenderness, and/or swelling, and/or warmth in addition to patient's report of pain at a known CNO lesion site), physician evaluation of disease activity as measured on a 10-cm Likert scale (VAS), number of radiologic lesions by whole-body MRI or bone scintigraphy, maximum severity of marrow edema of CNO lesions on imaging, and abnormal ESR and/or CRP level after exclusion of other potential causes. The C-HAQ was not included because of its floor effect and lack of applicability to the majority of CNO patients according to CNO group members' experience. Treatment failure at 3 months was defined as no improvement in at least 4 of the 6 criteria, or no improvement in ≥50% of applicable criteria if not all were available. Treatment success (complete resolution) was defined as resolution of pain, normalization of ESR and CRP level, and resolution of bone marrow edema in MRI, as reported previously (17–19).

Management of CNO patients at followup visits will depend on the overall assessment of disease activity by the physician, because there are no validated criteria at this time.

Table 3. Criteria for treatment failure at 3 months (when a patient fails to improve on at least 4 of 6 of the criteria or on >50% of applicable criteria)*

1)	Patient pain as measured by VAS
2)	Total number of clinically active lesions†
3)	Number of radiologic lesions by whole-body MRI or bone scintigraphy
4)	Size and degree of bone marrow edema of CNO lesions and/or presence of soft tissue swelling/inflammation related to CNO lesion on imaging
5)	Physician VAS
6)	Abnormal ESR and/or CRP level after exclusion of other potential causes‡

* VAS = visual analog scale; CNO = chronic nonbacterial osteomyelitis; MRI: magnetic resonance imaging; ESR = erythrocyte sedimentation rate; CRP = C- reactive protein.
† Defined as a body part with focal tenderness, and/or swelling, and/or warmth in addition to patient's report of pain at a known CNO lesion site.
‡ Abnormal ESR defined as ≥20 mm/hour and abnormal CRP as ≥1 mg/dl.

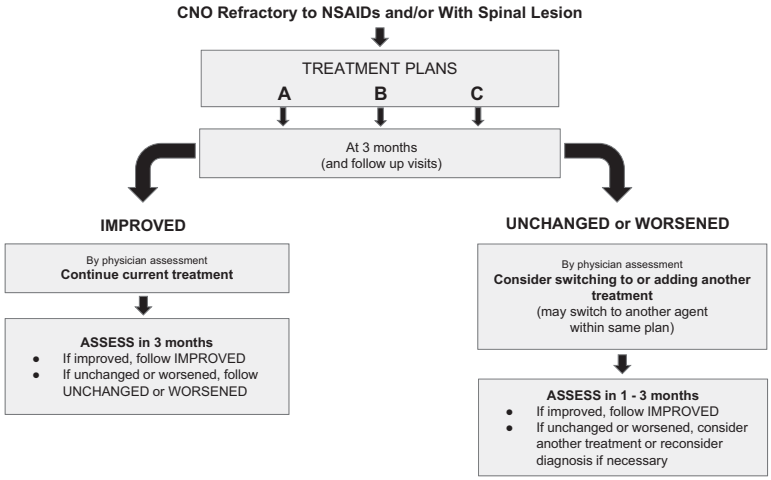

Figure 1. Summary of protocols. CNO = chronic nonbacterial osteomyelitis; NSAID = nonsteroidal antiinflammatory drug.

At the 3-month followup visit, an escalation of treatment, such as switching medications within an arm or switching to a different arm is recommended if there is worsening of the disease or no improvement based on the treating physician's assessment (Figure 1). Otherwise, maintaining current treatment is recommended. With the exception of bisphosphonates (3–6 months), minimum treatment duration should be 12 months based on the chronic nature of CNO, poor response to previous NSAID treatment, and the risk of vertebral compression fractures.

At what intervals should patients be followed for the purposes of data collection? Consensus was reached to follow intended CNO patients a minimum of every 3 months for the first year. The followup visit may occur earlier if the physician has concerns about the clinical course and/or treatment response. In addition to routine history, physical examinations, and laboratory testing, MRI is strongly recommended to objectively assess disease activity at 6 and 12 months after adjusting therapy. Additional imaging is recommended in suspected disease flares or persistent activity despite treatment escalation. Whole-body MRI is generally preferred, but regional MRI of known sites is acceptable in unifocal disease or if whole-body MRI is not available.

Data collection at followup and final approval of the CTP by CARRA members. Consensus was reached to minimize data collection for practicability using a standardized form. The clinical parameters, imaging tests, and laboratory tests considered essential for CNO followup assessment are shown in Table 4. A final survey was sent to 337 active voting members of CARRA in April 2017 (see Supplementary Appendix D, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23462/abstract). A total of 275 responses were received, for a response rate of 82%. Of the respondents, 254 were attending pediatric rheumatologists in North America who have cared for children with CNO. Of these 254 respondents, a total of 216 (85%) completed the entire survey. Most respondents (70%) had 1–4 patients with CNO who either failed to respond to NSAID treatment or had active spinal lesions over the last 12 months, whereas 14% had none and 16% had 5 or more.

The survey results showed that more than 90% of respondents agreed with the patient characteristics, treatment plans, and definition of treatment failure. Within the treatment plans, 78%, 90%, and 50% of 228 responders use DMARDs, TNF inhibitors, or bisphosphonates, respectively, on children who fail to respond to NSAIDs; 62%, 94%, and 73% of 221 responders are willing to use these respective treatment plans on children with active spinal lesions.

DISCUSSION

To our knowledge, these are the first CTPs developed for children with CNO by members of a professional society. Our work demonstrates the feasibility of achieving consensus in treatment plans and data collection for a rare and understudied pediatric rheumatic disease using a combination of surveys, a comprehensive literature search, and nominal group technique.

Lack of validated criteria for classification and followup, as well as standardized treatment, has hindered the progress of comparative effectiveness research in CNO. Current approaches are solely based on small case series, personal experience, and expert opinion (1). Our work is one step forward toward standardizing applied treatment regimens based on existing data and collection of a minimal set of data. This may allow objective evaluation of the effectiveness of different treatments. In addition, consistent imaging data collection will provide important corroboration with patient-reported outcomes and the physician's clinical assessment.

The CTPs presented here reflect the current clinical practice of CARRA members. Thus, they are highly applicable and more likely to be adopted in daily practice by practitioners. The intent behind these CTPs is to reduce the variation of applied treatment options so that meaningful data from as many patients as possible can be collected in an observational study.

Of note, the proposed treatment plans are standardized regimens without strong evidence of which treatment is optimal. They are not to be misinterpreted as guidelines, as

Table 4. Suggested minimum data collection and assessment intervals to be used with treatment plans*

Proposed variables	Baseline	Followup
History		
Demographics		
Date of birth	x	
Sex	x	
Race and ethnicity	x	
Clinical symptoms		
Fever	x	x
Rash	x	x
Gastroenterological symptoms	x	x
Bone pain	x	x
Limitation of motor functions†	x	x
Pre-enrollment treatment history for CNO	x	
Family history of CNO-associated conditions‡	x	
Past medical history/concurrently CNO-associated conditions‡	x	x
Current medications and doses	x	x
Patient-reported outcomes and global assessments		
Pain	x	x
Health-related quality of life	x	x
Physical function (C-HAQ, PROMIS)	x	x
Parent/patient global assessment of disease activity	x	x
Physician global assessment of disease activity	x	x
Physical examination		
Height and weight	x	x
Clinically active CNO lesion count	x	x
Active joint counts	x	x
Enthesitis	x	x
Rash	x	x
Imaging findings		
MRI (whole body preferred if available)	x	x
Bone scintigraphy if whole-body MRI not available	x	
Radiograph if done	x	x
CT if done	x	x
DXA if done	x	x
Laboratory findings		
CBC with differential	x	x
C-reactive protein level	x	x
Erythrocyte sedimentation rate	x	x
Alkaline phosphatase	x	
HLA–B27	x	
Bone biopsy findings§		
Bacterial, fungal, and AFB culture	x	
Pathology	x	
Treatment plan–related items		
Serious adverse events or important medical event		x
If plan discontinued, rationale		x
Number of glucocorticoid burst, if any		x

* Data are collected at baseline and at followup visits every 2–3 months. CNO = chronic nonbacterial osteomyelitis; C-HAQ = Childhood Health Assessment Questionnaire; PROMIS = Patient-Reported Outcomes Measurement Information System; MRI: magnetic resonance imaging; CT = computed tomography; DXA = dual-energy X ray absorptiometry; CBC = complete blood cell count.
† Prolonged school/daycare absences, limited use of upper body, difficulty bearing weight, requiring crutches, bedridden from spinal/leg pain.
‡ Psoriasis, inflammatory bowel disease, celiac disease, inflammatory arthritis, or spondyloarthropathy.
§ Needed when bone lesions do not follow typical distribution (clavicle or symmetrical lesions in long bones at metaphysis/epiphysis) in the absence of CNO-associated conditions.

their intention is to enable further study to identify optimal treatment. These CTPs currently do not include any biologic treatments other than TNF inhibitors, because of the rarity of their use in CNO and a lack of support by the available literature. However, these CTPs may be revised in the future to include other potentially effective forms of treatment as more evidence becomes available.

Bone biopsy was not required for all children with CNO (18,25). However, other diagnoses must be excluded prior to using these plans based on the treating physician's thorough

evaluation. These plans should only be used when physicians are confident of the diagnosis. Since whole-body MRI offers the most thorough imaging evaluation for CNO without exposure to radiation, it should be considered the gold standard. However, regional MRIs (or a series of multiple regional MRIs) are considered reasonable when whole-body MRI is not available. Other whole-body imaging, such as bone scintigraphy, is considered an alternative one-time baseline assessment whenever whole-body MRI is not available.

The CTP presented here has limitations. First, this CTP does not extend beyond 12 months of treatment. Second, this CTP does not include biologic treatments other than TNF inhibitors. Third, validated disease monitoring scoring tools are lacking, and the proposed criteria of treatment failure need further evaluation and validation.

In conclusion, 3 standardized CTPs were developed for patients with CNO with insufficient response to NSAIDs and/or the presence of active spinal lesions. Use of these treatment plans will provide an opportunity to generate meaningful data for future prospective observational studies to evaluate their effectiveness in children with CNO.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Zhao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Zhao, Wu, Oliver, Cooper, Basiaga, Vora, Lee, Fox, Amarilyo, Stern, Dvergsten, Hausmann, Miettunen, Barron, Hollander, Lapidus, Li, Girschick, Laxer, Dedeoglu, Hedrich, Ferguson.

Acquisition of data. Zhao, Wu, Oliver, Cooper, Basiaga, Vora, Lee, Fox, Amarilyo, Stern, Dvergsten, Haines, Rouster-Stevens, Onel, Cherian, Hausmann, Miettunen, Cellucci, Nuruzzaman, Taneja, Barron, Hollander, Lapidus, Li, Ozen, Girschick, Laxer, Dedeoglu, Hedrich, Ferguson.

Analysis and interpretation of data. Zhao, Wu, Oliver, Cooper, Basiaga, Vora, Lee, Fox, Amarilyo, Stern, Dvergsten, Haines, Rouster-Stevens, Onel, Cherian, Hausmann, Miettunen, Cellucci, Nuruzzaman, Taneja, Barron, Hollander, Lapidus, Li, Ozen, Girschick, Laxer, Dedeoglu, Hedrich, Ferguson.

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