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# BMJ Open

## Chronic Nonbacterial Osteitis from the Patient Perspective

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Chronic Nonbacterial Osteitis from the Patient Perspective

Colen C.G. Silier, MBA<sup>1</sup>; Justina Greschik<sup>2</sup>, Isabella S.Gesell<sup>2</sup>, Veit Grote, MD, MSc<sup>1</sup>,  
Annette F. Jansson, MD<sup>1</sup>

<sup>1</sup> Department of Rheumatology & Immunology, Dr. von Hauner Children’s Hospital, Ludwig-Maximilians-University, Munich, Germany

<sup>2</sup> Department of Orthopaedic Surgery, Physical Medicine and Rehabilitation, Ludwig-Maximilians-University, Munich, Germany

Corresponding Author:

Colen C. G. Silier, MBA, Doctoral Candidate Department of Rheumatology & Immunology,  
Dr. von Hauner Children’s Hospital, Ludwig-Maximilians-University, Munich, Germany  
Email: [colen.silier@campus.lmu.de](mailto:colen.silier@campus.lmu.de)  
Tel: + (49) 89-4400-52811

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## Abstract

**Objective:** Although Chronic Nonbacterial Osteitis (CNO) is an ever increasingly recognized illness in not only the pediatric community but in the adult health care community, a study to assess diagnosing, treatment, and the psychosocial aspect of CNO from a large population pool was not available. We aimed to investigate CNO from the patient perspective.

**Design:** Using a patient survey developed by the LMU Pediatric Rheumatology department, 105 patients from ages 5 to 63 years old were assessed regarding CNO to include epidemiologic data, past and present medical history and treatment, initial symptoms, diagnostic procedures, current symptoms, associated diseases, current treating physicians, absences in school and work due to illness, and the impact of illness on patient, family, and friends.

**Results:** Active CNO was reported in 90% of patients present, with 73% being female and 27% being male. An overwhelming majority (70%) reported being diagnosed within 18 months of onset of symptoms; however, the initial diagnoses were wide-ranged to include malignancies in 36% to bacterial osteomyelitis in 30%, where the majority were treated with an antibiotic and/or were biopsied. When asked about the psychosocial aspect of this illness, 83% reported NBO negatively impacted the family, 79% reported that NBO has negatively affected either school or work, and 56% reported a negative impact on friendships.

**Conclusion:** To our knowledge this is the first study to explore the impact of CNO from the patient perspective. Delay of diagnosis, living with differential diagnoses like malignancies and finding specialists for medical care are a few examples of what leads patients into searching for more information. The negative impact on daily life including family relationships, friendships, and work/school highlight a need for better psychosocial support.

Article Summary

Strengths and limitations of this study

- This is the first study highlighting the impact of chronic nonbacterial osteitis (CNO) from the patient perspective.
- A relative large patient population for CNO was analyzed, which has an incidence rate of 0.45/100,000.
- The explicitness of the needs of CNO patients was examined, while stressing the psychosocial and socio-economic effect of a chronic illness, such as CNO.
- The patient data reflects the current medical literature concerning CNO, therefore further validating the patient information gathered.
- A major limitation lies in the retrospective analysis of different time frames required by our study’s participants.

Osteomyelitis is often assumed to be of bacterial origin even in the absence of a pathogen; however, current research supposes that a leading portion of nonbacterial bone lesions are of an autoinflammatory origin. Furthermore, due to the ever increasing use of magnetic resonance imaging (MRI), bone lesions are increasingly being found in healthy children and adults alike (1, 2).

Nonbacterial osteitis (NBO) can affect one bone or more often, multiple bones; therefore, it is often best known by its most severe manifestation chronic recurrent multifocal osteomyelitis (CRMO) (Figure 1.) with a multifocal sterile osteitis (3-9). The chief complaint of localized bone pain often results in identifying multifocal or unifocal lesions which can appear in all skeletal sites (3-7) and progression can vary widely to include acute, chronic persistent or chronic relapsing (6, 10).

#### Figure 1.

Because chronic nonbacterial osteitis (CNO) is a chronic illness, it was important to be able to assess the psychological and social impact on patients throughout the illness. Maslow et al. studied chronically ill children in regards to social, educational, and vocational outcomes, coming to the conclusion that socially, the pediatric population studied was not discriminated against, but they did have more difficulty with educational and vocational opportunities (11). Chronic illness however, does not only affect the patient, but also the family and support structure; it has been suggested that the adaptation of the patient and the family are closely linked (12, 13).

We assessed patients with diagnosed CNO using a questionnaire that was developed to encompass the onset of symptoms to diagnostics and then on to the social aspect of the chronically ill and access to care issues. Specifically how well is the patient informed about CNO and what does the patient require, not only information-wise but also other needs, were addressed, with emphasis on the psychosocial aspects.

Methods

Study design and study population

In June 2013 and June 2015 the Pediatric Rheumatology department of the Ludwig-Maximilians-University (LMU) Munich hosted a nonbacterial osteitis information day designed for patients, both pediatric and adults, and their relatives. The event was advertised through private practice pediatricians, private practice rheumatologists, websites dedicated to pediatric rheumatology and university clinics throughout Germany. Patients and their families were asked to register in advance, and upon registration they received a survey and a consent form to be filled out and brought with to the conference.

In June 2013, 69 patient surveys were collected, and 38 were collected in 2015- for a total of 107. Patients were asked to not fill out a survey in 2015 if they had previously done so in 2013.

The patient survey consisted of 285 variables per patient and captured important aspects of nonbacterial osteitis to include: Epidemiologic data, age at diagnosis, family history, past medical and treatment history, constitutional symptoms at disease onset, diagnostic procedures, number of lesions, and associated diseases in patients and in family members (parents and siblings). The survey also focused on: who is the consulting physician, how far away is the specialist, physical therapy options, and absences in school or at work due to disease. The psychosocial impact concentrated on the impact of the illness on the patient, friends, and family. We specifically asked in our survey about three initial symptoms: pain, swelling and redness, and pain was rated on a visual analog scale of 1-10, with 10 being maximum pain.

## Statistical Analysis

All data management and analysis was performed using IBM Statistical Package for the Social Science (SPSS) Statistics 23. The Student t test was used to compare quantitative data with P-values below 0.05 considered to be statistically significant. The Pearson's chi-square ( $\chi^2$ ) was used for differences of categorical data.

## Ethics

The study was approved by the ethics committee of the medical faculty at Ludwig-Maximilian University (Munich).

## Results

### General

During the 2-year survey period we received a total of 107 surveys, of these questionnaires, two were incomplete and could not be used for further analysis. Overall, data was collected from 105 patients, 67 from the 2013 conference and 38 from 2015. Active CNO was reported in 90% (n=94) of patients present.

### Epidemiology

From 105 patients, 73% (n=77) were female and 27% (n=28) were male. A total of 18% of the patients living in Germany have a non-German parent (3%) or both parents are of non-German nationality (15%). Eight international patients were also present, residing in other European countries such as Switzerland, Austria, and Sweden. Ages of this collective ranged from 5.5 years old to 63 years old, with an average of age of 16.7 years old (SD 8.5). Thirty-two patients (30.5%) were >18 years old.



Symptom onset occurred at a median of 9.5 years of age, and the median age at time of diagnosis was 10.5 years old, with 86% reporting onset of symptoms between the ages of 6-15 years old.

Clinical Presentation

Our patients were initially referred to a variety of physicians including pediatricians, general practitioners, orthopedic surgeons, rheumatologists (both pediatric and adult), oral and maxillofacial surgeons, dermatologists and ear-nose-throat physicians. The most common first diagnoses are shown in Figure 2, with some receiving multiple first diagnoses. Under malignant tumors/malignant disease, patients listed: unknown: 18%, Ewing Sarcoma: 6%, Leukemia: 3%, Langerhans cell histiocytosis: 2%.

Figure 2.

Pediatric Rheumatologists diagnosed in 57% the CNO cases present. Overall rheumatologists and pediatricians made the diagnosis in 69% of all patients. Only 6% were diagnosed after consultation with one physician, and 69% consulted with 2-5 physicians before receiving the final diagnosis. One patient was referred to a total of 15 different physicians before receiving the diagnosis of chronic nonbacterial osteitis.

At the time of survey, the median length of CNO symptoms was 3.92 years, and the median length from the time of diagnosis was 2.17 years.

Pain was reported as the number one initial symptom (97%), followed by swelling at 60% and redness at 25%. Fever of unknown origin was reported in 17%. An overwhelming majority of patients (65%) reported being in constant pain at the start of this syndrome with peak-pain times being in the evening (36%). 20% rated pain on a VAS (0-10) as an 8, 23% at a 9, and 23% at a 10 at initial presentation. Patients rated current pain levels to be significantly lower; approximately 55% of patients rated pain to be a 4 or below and 81% as a 6 or below.

Former or current elevated inflammation parameters (CRP and ESR) were reported in 45% of patients.

A precipitating event or illness is believed to be the cause of CNO in 45% (n=47) of patients. From the 47 patients, 14 (30%) believe this trigger to be a bacterial infection and 9 (19%) believe this to be viral. A trauma, which was directly related to the emergence of CNO, was reported in 53% of cases. Trauma encompassed both physical traumas, such as a fall (n=11, 20%), and psychological traumas. Physical traumas (n=18, 32%) included not only falls but also dog bites, fractures, intravenous needles, and others. Psychological traumas (n=7, 13%) comprised of bullying and familial and school problems.

### Number of lesions and localizations

At first manifestation the median number of lesions was 2-5 in 50% of the self-reported CNO cases, and 23% reported 5-10 lesions. During the course of disease, further lesions were confirmed in 51% of CNO cases, with 21% being located within 6 months from initial diagnosis. The distribution of lesions can be found in Figure 3. Most lesions were in the metaphyses of long bones, pelvis, lower extremities and feet. Vertebral lesions were found in 30% of cases in the first step of diagnosis. In 30% of cases, the patients' chief complaint was back pain, which led to further diagnostics focusing on the vertebrae. Approximately 11% already had a vertebrae plana at first diagnosis. Further lesions in the spinal column were diagnosed during the course of the disease in 18% of patients without initial vertebral lesions; lesions in the cervical spine were reported in 16% of patients, in the thoracic spine 28%, in the lumbar spine 18%, and in the sacrum and coccyx 18%.

Circa 20% of patients reported a unifocal lesion.

### Figure 3.

**Treatment**

Differing initial diagnoses (bone malignancies) resulted in 3 patients receiving chemotherapy for approximately 12 months.

NSAIDs such as ibuprofen (61%), naproxen (50%), indometacin (23%), diclofenac (20%) were prescribed in 95% of all patients, and NSAIDs and steroids (33%) were the most commonly prescribed therapy after the CNO diagnosis. Forty-six percent of all patients answered the question, what NSAID provided the best relief of symptoms. Sixty-five percent of this group reported naproxen as the NSAID with the most beneficial impact and ibuprofen at 35% as the second most beneficial.

Although NSAIDs and steroids were the most commonly prescribed drugs for CNO, bisphosphonates and biologics were frequently used in patients with severe courses of disease. Bisphosphonates made up 21% (n=22) of the therapeutic agents, with pamidronate (n=18) as the most commonly prescribed. From the 22 patients that were receiving a bisphosphonate, 68% (n=15) had vertebral lesions. Over 14% of patients received a biologic agent: 9.5% etanercept, 2% adalimumab, 2% infliximab, and 1% golimumab. Of the 14% of patients which received biologics, 7/15 had lesions on the pelvis, 7/15 on the clavicle, 5/15 in the mandible, and 5/15 on the spinal column. Most of these patients had multiple lesions, with one patient being affected throughout the entire spinal column (cervical, thoracic and lumbar), clavicle, pelvis, and feet.

**Associated Diseases**

CNO-related diseases were present in 28% (30/105) of this patient population.

Of the associated diseases, skin disorders dominated with 67% including palmoplantar pustulosis (9/30), psoriasis (5/30), and severe acne (6/30). Other reported associated diseases included arthritis (9/30; 33% adjacent to lesion) and Crohn's disease (n=1).

Associated diseases in family members were revealed in 16/105 (15%) fathers and 16/105 (15%) mothers. Again, the skin lesions such as psoriasis (34%) and palmoplantar pustulosis and psoriasis (13%) were predominant. Other rheumatic diseases like chronic polyarthritis were reported in 10/16 females and 3/16 males. Crohn's disease (2/16) and ulcerative colitis (1/16) were diagnosed in fathers of our patients.

### Patient Care

From the pediatric population, 96% were being treated by a pediatric rheumatologist or an orthopedic surgeon, whereas with the adult population only 62% were being treated by a specialist (defined by rheumatologist or orthopedic surgeon) and 16% by a general practitioner (Figure 4.) From the 32 patients >18 y/o, 22% had no treating physician; from these patients with no treating physician, 4/7 no longer had an active disease at time of survey and 7/7 patients were between the ages of 18-28 years old.

### Figure 4.

The distance to the treating physician varied widely; however, 45% had to travel 25 kilometers (km) or less and 86% traveled 100 km or less, and one patient traveled up to 300 km to a specialist. Patients were asked how well cared for do they feel from their specialists, and on a visual analog scale from 1-10, >50% responded with an 8 or higher. Patients were often referred to or specifically asked for a referral to see a physical therapist in 64% of cases.

CNO had reported negative effects in 44% of cases on the entire family, with another 39% reporting a partial effect on the family. Not only were close family members affected by CNO, also friendships, school, and work-life. From patients which reported difficulty in friendships, 56% described, at minimum, a partial negative affect on relationships. In comparison however, due to this disorder, 79% reported that CNO has negatively affected either school or work.

Seventy-five percent of all patients received no type of psychosocial guidance, although 49% would have liked to have consultation with a guidance counselor or psychologist. These numbers correlate with the 51% of patients and family members which felt uninformed regarding the nonbacterial osteitis diagnosis and the course of disease.

Periods of absences from school or work did not vary widely between before the diagnosis and afterwards. The largest change in the number of days absent per year due to CNO, was in the 6-20 day category; before the diagnosis, patients reported absences at 22% and afterwards at 31%. However, absences greater than 20 days saw a 5% drop after the diagnosis, from 30% to 25%.

Patients were also questioned as to what they would most like to learn and hear about at the information day. Specifically: more general information to CNO, information to prognosis, practical tips, contact to physicians with CNO expertise, contact to other patients, and building of self-help groups (Figure 5.)

**Figure 5.**

Other topics of interest ranged from typical side effects of medications to pregnancy to nutrition and alternative therapy options. Many of the pediatric patients and family members were concerned with the transition into adulthood and what effect CNO would have later in life.

**Discussion**

To our knowledge this is the first health services research to assess diagnosing, treatment, and the psychosocial aspect of CNO from a patient perspective with such a large population pool.

## Medical data

Overall the patient derived information concerning their own illness matches the current medical literature. The number of lesions, localization of lesions, therapy plan, inflammation parameters and imagery used (data not shown) is comparable to previous scientific literature (6, 14-18). This leads to the conclusion that the group of patients in attendance on the two conference days were well informed, have read about CNO and were seeking further information.

## Delay of diagnosis

Patients reported long lag times from onset of symptoms until diagnosis. Approximately 70% of the patients were diagnosed within 18 months from the onset of symptoms, but still 7% had to wait more than five years. These lag times lead to not only patient stress, both physical and emotional, but unnecessary testing and treatment. Delays in the diagnosis may lead to prolonged use of antibiotics, multiple surgeries, repeated bone biopsies, and excessive radiation exposure. Another contributing factor to the long lag times in diagnoses and treatment is the distance to specialists. In Germany, most pediatric rheumatologists are located in larger cities and at university hospitals, and adult rheumatologists often have long wait-lists. Therefore, patients often resort to being treated either by a general practitioner or a pediatrician.

Circa 20% of patients reported a unifocal lesion. However, from the 21 patients reporting one lesion, only 5 (24%) received a whole-body MRI and 6 (29%) a bone scan. This often led to a different differential diagnosis, mostly bacterial osteomyelitis, and a different therapy plan. This resulted in another delay in diagnosis.

**Therapy**

With 27% continuing with antibiotic therapy after diagnosis, there must be still uncertainty in the medical community regarding the CNO diagnosis and the proper treatment plan once recognized. A step-wise guide for the therapeutic treatment of CNO was developed to alleviate pain and prevent further degeneration; the plan highlights the use of NSAIDs in the first-line treatment of CNO (19). Currently there are national and international efforts to establish validated treatment protocols for chronic nonbacterial osteitis.

The long lag times in diagnosis and the continuation of antibiotic therapy among other factors, leads to the conclusion that there is a need for better clarification and education regarding nonbacterial osteitis.

**Psychosocial and socio-economic aspects**

As with most chronically ill patients, absences from school and work are of great importance. These absences have an effect on school performance, promotions, and the emotional well-being of the patient. When comparing the number of absences before and after the diagnosis, there is very little difference. Which leads to the questions, is the medical therapy successful or does pain amplification play a significant role in the patient group in attendance at the conference? However, according to the patients, most had seen a significant pain level drop when comparing onset to current conditions, with most patients starting with a median pain level of 9/10 and dropping to 4/10 after treatment.

On the other hand, not only pharmacological therapy, but psychosocial aspects have a great influence on well-being and quality of life. Three quarters of all patients did not receive psychosocial support. Half of all patients would have liked to have consultation with a guidance counselor or psychologist.

More than 80% reported that CNO has had a negative influence on family life. Physicians caring for chronically ill patients should be aware how this illness not only affects



especially young patients, but also other family members and members of the support structure. In Germany, unfortunately, interdisciplinary care can only be offered in specialized medical centers.

### Transition and adult patients

From the adult population in attendance, 22% were not seeing a specialist and had no treating physician for CNO. These patients vary in ages between 18 – 28 years old. This highlights the need for a better transition model from pediatric care to adult care, as all of these patients were diagnosed as children with CNO.

Especially in anglo-american countries, there are transition clinics where the needs of chronically ill young adults are met (20-22). In Germany a transition model for patients with chronic rheumatic illnesses was developed (20, 23). This model helps patients coordinate care transitioning from the pediatric community into the adult community and works together with both communities to assure a seamless transition. Once transition is complete this is followed up to ascertain and highlight any needs for improvement. Although such models exist in Germany, this transition care is not widespread, and leaves many patients without a healthcare provider for chronic illnesses after the age of eighteen.

A large portion of the study's population felt uninformed regarding this illness. This was the top reason for visiting the conference, patients needed and wanted more information about CNO (98%). Practical tips and information to prognosis were also important topics. With such small percentages of patients with CNO, attendance at our conference represented the thirst for information that these chronically ill patients have.

### Conclusion

To our knowledge this is the first study highlighting the impact of CNO from the patient perspective. Delay of diagnosis, living with differential diagnoses like malignancies



and finding specialists for medical care drives patients to search for more information. Interested patients were able to report their disease precisely, so that patient data matched medical literature concerning CNO very well. Nevertheless this survey shows very clearly that psychosocial and socio-economic aspects need to be addressed. Negative impact on family, work and friendships seems to influence partaking in daily life. Support is especially necessary in adolescents and young adults, who often dropped out of medical attendance.

For the incidence rate of this disease, 0.45/100000 (14), 105 patients is large but a relative snapshot in time. Therefore, prospective evaluations of independent patient populations would give more insight.

**Limitations**

As with most health services research, patient subjectivity remains to be a problem. Some of the surveys were either not completely filled in or answers were given that did not match the question-which often led to the participant’s answer being disregarded. Often patients were diagnosed years previously with CNO und neither the patient nor the parents could recall initial symptoms, pain levels, etc. Patients in attendance were typically patients with a more severe course of disease and patients that were very well informed about this disease. This could also explain why the patients’ data was very comparable to previous research.

## Funding

The study was funded by the non-profit organizations Kinder-Rheumhilfe Muenchen e.V. and Kindness for Kids, Munich.

Through financial pledges, both organizations provided the necessary capital for the two patient conferences. In addition, Kinder-Rheumhilfe Muenchen also organized the two conferences.

The study itself and the work thereafter were unfunded.

## Conflict of Interests

The authors have no conflicts of interest to disclose.

## Data Sharing

All available data can be obtained by contacting the corresponding author.

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**Figure Legend:**

Figure 1. Terminology of Nonbacterial Osteitis

Figure 2. First Diagnoses

Figure 3. Distribution of Lesions in Chronic Nonbacterial Osteitis

Figure 4. Current Treating Physician for Chronic Nonbacterial Osteitis

Figure 5. Patient Wishes from CNO Conference

**Author Contribution:**

Contributor Annette Jansson (AJ) developed the idea for the study. Colen Silier (CS) and AJ were involved in the study conception, preliminary literature review and design of the search strategy and the study protocol. Isabella Gesell (IS) and Justina Greschik (JG) designed the initial data base to record study-inputs and completed initial data input. CS concluded data input. CS and Veit Grote (VG) were involved in screening and data extraction of papers. CS, AJ and VG reviewed data extraction output. CS drafted the report, which was critically reviewed and approved by all authors.

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Figure 1. Terminology of Nonbacterial Osteitis

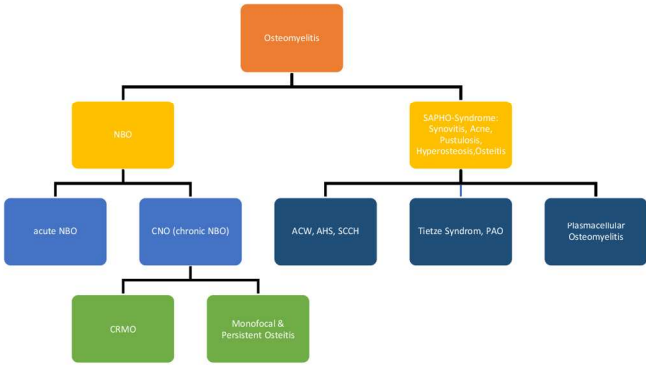


Figure 1. Terminology of Nonbacterial Osteitis

210x297mm (200 x 200 DPI)

Figure 2. First Diagnoses

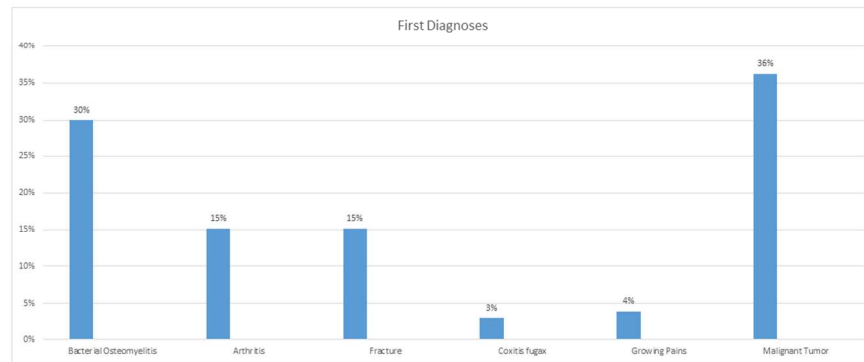


Figure 2. First Diagnoses

338x190mm (96 x 96 DPI)



Figure 3. Distribution of Lesions in Chronic Nonbacterial Osteitis

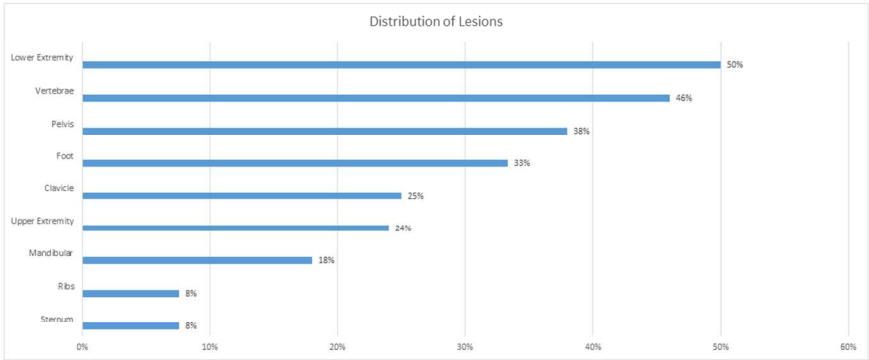


Figure 3. Distribution of Lesions in Chronic Nonbacterial Osteitis

338x190mm (96 x 96 DPI)

Figure 4. Current Treating Physician for Chronic Nonbacterial Osteitis

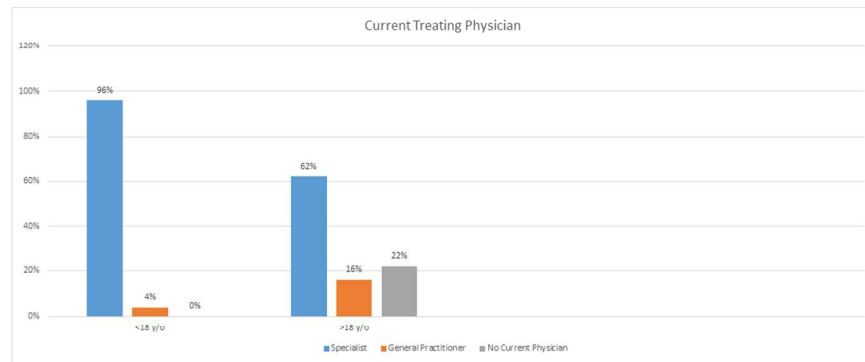


Figure 4. Current Treating Physician for Chronic Nonbacterial Osteitis

338x190mm (96 x 96 DPI)

Figure 5. Patient Wishes from CNO Conference

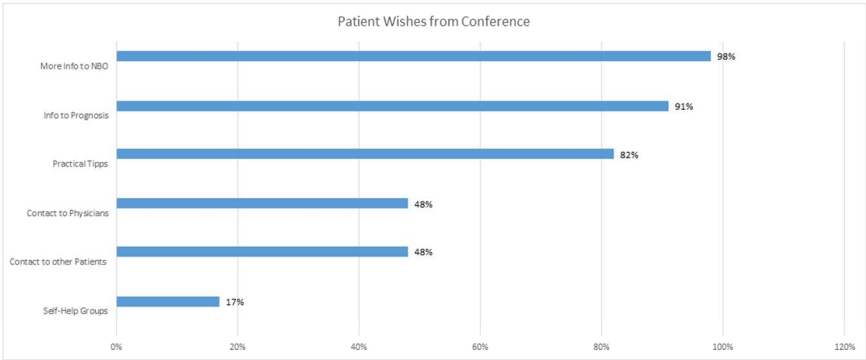


Figure 5. Patient Wishes from CNO Conference

338x190mm (96 x 96 DPI)

## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
✓ <b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract <a href="#">pg. Abstract "Design" and pg. 2</a> (b) Provide in the abstract an informative and balanced summary of what was done and what was found <a href="#">pg. Abstract "Design" and "Results"</a>
<b>Introduction</b>		
✓ Background/rationale <a href="#">pg. Abstract "Objective" and pg. 1</a>	2	Explain the scientific background and rationale for the investigation being reported
✓ Objectives <a href="#">pg. 1</a>	3	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
✓ Study design <a href="#">pg. 2</a>	4	Present key elements of study design early in the paper
✓ Setting <a href="#">pg. 2</a>	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
✓ Participants <a href="#">pg. 2, 3</a>	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
✓ Variables <a href="#">pg. 1, 3-8</a>	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
✓ Data sources/ measurement <a href="#">pg. 2-8</a>	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
✓ Bias <a href="#">pg. 1, 12</a>	9	Describe any efforts to address potential sources of bias
✓ Study size <a href="#">pg. 2</a>	10	Explain how the study size was arrived at
✓ Quantitative variables <a href="#">pg. 1, 2</a>	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
✓ Statistical methods <a href="#">pg. 2, 3</a>	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

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**Results**

✓ Participants pg. 3, 4, 12	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
✓ Descriptive data pg. 3, 4, 12	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
✓ Outcome data pg. 3	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
✓ Main results pg. 3-8	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
✓ Other analyses N/A	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

**Discussion**

✓ Key results pg. 9, 10, 11	18	Summarise key results with reference to study objectives
✓ Limitations pg. 12	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
✓ Interpretation pg. 11, 12	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
✓ Generalisability pg. 12	21	Discuss the generalisability (external validity) of the study results

**Other information**

✓ Funding pg. 13	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
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\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Chronic Nonbacterial Osteitis from the Patient Perspective: A Health Services Research through Data Collected from Patient Conferences

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Complete List of Authors:	Silier, Colen; Ludwig-Maximilians University Munich, Department of Pediatric Rheumatology and Immunology, Dr. von Hauner Children's Hospital, Ludwig-Maximilians University Greschik, Justina; Ludwig-Maximilians-Universitat Munchen, Department of Orthopaedic Surgery, Physical Medicine and Rehabilitation Gesell, Susanne; Ludwig-Maximilians-Universitat Munchen, Department of Orthopaedic Surgery, Physical Medicine and Rehabilitation Grote, Veit; Ludwig-Maximilians-University Muenchen, Department of Pediatric Rheumatology and Immunology, Dr. von Hauner Children's Hospital, Ludwig-Maximilians University Jansson, Annette; Ludwig-Maximilians-University-Muenchen, Department of Pediatric Rheumatology and Immunology, Dr. von Hauner Children's Hospital, Ludwig-Maximilians University
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Keywords:	Chronic Nonbacterial Osteitis (CNO), Nonbacterial Osteitis (NBO), Chronic Recurrent Multifocal Osteomyelitis (CRMO), Germany, SAPHO Syndrom (Synovitis, acne, pustolosis, hyperostosis, osteomyelitis)

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**Chronic Nonbacterial Osteitis from the Patient Perspective: A Health Services Research  
through Data Collected from Patient Conferences**

Colen C.G. Silier, MBA<sup>1</sup>; Justina Greschik<sup>2</sup>, Susanne Gesell<sup>2</sup>, Veit Grote, MD, MSc<sup>1</sup>, Annette  
F. Jansson, MD<sup>1</sup>

<sup>1</sup> Department of Rheumatology & Immunology, Dr. von Hauner Children’s Hospital, Ludwig-  
Maximilians-University, Munich, Germany

<sup>2</sup> Department of Orthopaedic Surgery, Physical Medicine and Rehabilitation, Ludwig-  
Maximilians-University, Munich, Germany

**Corresponding Author:**

Colen C. G. Silier, MBA, Doctoral Candidate Department of Rheumatology & Immunology,  
Dr. von Hauner Children’s Hospital, Ludwig-Maximilians-University, Munich, Germany  
Email: [colen.silier@campus.lmu.de](mailto:colen.silier@campus.lmu.de)  
Tel: + (49) 89-4400-52811

**Running Title:** CNO from the Patient Perspective

**Keywords:** Chronic Nonbacterial Osteitis (CNO), Nonbacterial Osteitis (NBO), chronic  
recurrent multifocal osteomyelitis (CRMO), SAPHO syndrome (Synovitis, acne, pustolosis,  
hyperostosis, osteomyelitis), Germany

**Word Count:** 3291



## Abstract

**Objective:** Although Chronic Nonbacterial Osteitis (CNO) is an ever increasingly recognized illness in not only the pediatric community but in the adult health care community, a study to assess diagnosing, treatment, and the psychosocial aspect of CNO from a large population pool was not available. We aimed to investigate CNO from the patient perspective.

**Design:** Health services research, patient survey

**Setting:** LMU Pediatric Rheumatology department CNO conferences held in June 2013 and June 2015.

**Participants:** Using a patient survey developed by the LMU Pediatric Rheumatology department, 105 patients from ages 5 to 63 years old were assessed regarding CNO to include epidemiologic data, past and present medical history and treatment, initial symptoms, diagnostic procedures, current symptoms, associated diseases, current treating physicians, absences in school and work due to illness, and the impact of illness on patient, family, and friends.

**Results:** Active CNO was reported in 90% of patients present, with 73% being female and 27% being male. An overwhelming majority (70%) reported being diagnosed within 18 months of onset of symptoms; however, the initial diagnoses were wide-ranged to include malignancies in 36% to bacterial osteomyelitis in 30%, where the majority were treated with an antibiotic and/or were biopsied. When asked about the psychosocial aspect of this illness, 83% reported NBO negatively impacted the family, 79% reported that NBO has negatively affected either school or work, and 56% reported a negative impact on friendships.

**Conclusion:** Delay of diagnosis, living with differential diagnoses like malignancies and finding specialists for medical care are a few examples of what leads patients into searching for more information. The negative impact on daily life including family relationships, friendships, and work/school highlight a need for better psychosocial support such as

guidance counseling or psychological support due to three-quarters of patients receiving no such said support.

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## Article Summary

### Strengths and limitations of this study

- This is the first study highlighting the impact of chronic nonbacterial osteitis (CNO) from the patient perspective.
- A relative large patient population for CNO was analyzed, which has an incidence rate of 0.45/100,000.
- The explicitness of the needs of CNO patients was examined, while stressing the psychosocial and socio-economic effect of a chronic illness, such as CNO.
- The patient data reflects the current medical literature concerning CNO, therefore further validating the patient information gathered.
- A major limitation lies in the retrospective analysis of different time frames required by our study's participants.

Osteomyelitis is often assumed to be of bacterial origin even in the absence of a pathogen; however, current research supposes that a leading portion of nonbacterial bone lesions are of an autoinflammatory origin. Furthermore, due to the ever increasing use of magnetic resonance imaging (MRI), bone lesions are increasingly being found in healthy children and adults alike (1, 2).

Nonbacterial osteitis (NBO) can affect one bone or more often, multiple bones; therefore, it is often best known by its most severe manifestation chronic recurrent multifocal osteomyelitis (CRMO) (Figure 1.) with a multifocal sterile osteitis (3-9). The chief complaint of localized bone pain often results in identifying multifocal or unifocal lesions which can appear in all skeletal sites (3-7) and progression can vary widely to include acute, chronic persistent or chronic relapsing (6, 10).

**Figure 1.**

Because chronic nonbacterial osteitis (CNO) is a chronic illness, it was important to be able to assess the psychological and social impact on patients throughout the illness. Maslow et al. studied chronically ill children in regards to social, educational, and vocational outcomes, coming to the conclusion that socially, the pediatric population studied was not discriminated against, but they did have more difficulty with educational and vocational opportunities (11). Chronic illness however, does not only affect the patient, but also the family and support structure; it has been suggested that the adaptation of the patient and the family are closely linked (12, 13).

We assessed patients with diagnosed CNO using a questionnaire that was developed to encompass the onset of symptoms to diagnostics and then on to the social aspect of the chronically ill and access to care issues. Specifically how well is the patient informed about CNO and what does the patient require, not only information-wise but also other needs, were addressed, with emphasis on the psychosocial aspects.

## Methods

### Study design and study population

In June 2013 and June 2015 the Pediatric Rheumatology department of the Ludwig-Maximilians-University (LMU) Munich hosted a nonbacterial osteitis information day designed for patients, both pediatric and adults, and their relatives. The event was advertised through private practice pediatricians, private practice rheumatologists, websites dedicated to pediatric rheumatology and university clinics throughout Germany. Patients and their families were asked to register two weeks in advance, and upon registration they received a survey and a consent form to be filled out and brought with to the conference.

In total, 134 patients were in attendance, with 107 patients completing the survey. In June 2013, 69 patient surveys were collected, and 38 were collected in 2015. Patients were asked to not fill out a survey in 2015 if they had previously done so in 2013. There were thirteen patients which visited both conference days, and therefore did not repeat the survey. However, fourteen patients did not respond due to appearing without prior registration or registering after the two week deadline.

The patient survey consisted of 285 variables per patient and captured important aspects of nonbacterial osteitis to include: Epidemiologic data, age at diagnosis, family history, past medical and treatment history, constitutional symptoms at disease onset, diagnostic procedures, number of lesions, and associated diseases in patients and in family members (parents and siblings). The survey also focused on: who is the consulting physician, how far away is the specialist, physical therapy options, and absences in school or at work due to disease. The psychosocial impact concentrated on the impact of the illness on the patient, friends, and family. We specifically asked in our survey about three initial symptoms: pain, swelling and redness, and pain was rated on a visual analog scale of 1-10, with 10 being maximum pain.

**Statistical Analysis**

All data management and analysis was performed using IBM Statistical Package for the Social Science (SPSS) Statistics 23. Continuous variables were expressed in means with standard deviation or – if skewed – as medians with interquartile ranges (IQR: 25th, 75th percentiles). The Student t test was used to compare quantitative data with P-values below 0.05 considered to be statistically significant. The Pearson’s chi-square ( $\chi^2$ ) was used for differences of categorical data.

**Ethics**

The study was approved by the ethics committee of the medical faculty at Ludwig-Maximilian University (Munich).

**Results**

**General**

During the 2-year survey period we received a total of 107 surveys, of these questionnaires, two were incomplete and could not be used for further analysis. Overall, data was collected from 105 patients, 67 from the 2013 conference and 38 from 2015. Active CNO was reported in 90% (n=94) of patients present.

**Epidemiology**

From 105 patients, 73% (n=77) were female and 27% (n=28) were male. A total of 18% of the patients living in Germany have a non-German parent (3%) or both parents are of non-German nationality (15%). Eight international patients were also present, residing in other European countries such as Switzerland, Austria, and Sweden. Ages of this collective ranged from 5.5 years old to 63 years old, with an average of age of 16.7 years old (SD 8.5). Thirty-two patients (30.5%) were >18 years old.

Symptom onset occurred at a median of 9.5 years of age (IQR: 7.5; 12), and the median age at time of diagnosis was 10.5 years old (IQR: 8.5; 13.5), with 86% reporting onset of symptoms between the ages of 6-15 years old.

## Clinical Presentation

Our patients were initially referred to a variety of physicians including pediatricians, general practitioners, orthopedic surgeons, rheumatologists (both pediatric and adult), oral and maxillofacial surgeons, dermatologists and ear-nose-throat physicians. The most common first diagnoses are shown in Figure 2, with some receiving multiple first diagnoses. Under malignant tumors/malignant disease, patients listed: unknown: 18%, Ewing Sarcoma: 6%, Leukemia: 3%, Langerhans cell histiocytosis: 2%.

### Figure 2.

Pediatric Rheumatologists diagnosed in 57% the CNO cases present. Overall rheumatologists and pediatricians made the diagnosis in 69% of all patients. Only 6% were diagnosed after consultation with one physician, and 69% consulted with 2-5 physicians before receiving the final diagnosis. One patient was referred to a total of 15 different physicians before receiving the diagnosis of chronic nonbacterial osteitis.

At the time of survey, the median length of CNO symptoms was 3.92 years (IQR: 1.83; 6.83), and the median length from the time of diagnosis was 2.17 years (IQR: 0.92; 5.08).

Pain was reported as the number one initial symptom (97%), followed by swelling at 60% and redness at 25%. Fever of unknown origin was reported in 17%. An overwhelming majority of patients (65%) reported being in constant pain at the start of this syndrome with peak-pain times being in the evening (36%). 20% rated pain on a VAS (0-10) as an 8, 23% at a 9, and 23% at a 10 at initial presentation. Patients rated current pain levels to be

significantly lower; approximately 55% of patients rated pain to be a 4 or below and 81% as a 6 or below.

Former or current elevated inflammation parameters (CRP and ESR) were reported in 45% of patients.

A precipitating event or illness is believed to be the cause of CNO in 45% (n=47) of patients. From the 47 patients, 14 (30%) believe this trigger to be a bacterial infection and 9 (19%) believe this to be viral. A trauma, which was directly related to the emergence of CNO, was reported in 53% of cases. Trauma encompassed both physical traumas, such as a fall (n=11, 20%), and psychological traumas. Physical traumas (n=18, 32%) included not only falls but also dog bites, fractures, intravenous needles, and others. Psychological traumas (n=7, 13%) comprised of bullying and familial and school problems.

**Number of lesions and localizations**

At first manifestation, 20% reported 1 lesion, 50% reported 2-5 lesions and 27% reported more than 5 lesions. During the course of disease, further lesions were confirmed in 51% of CNO cases, with 21% being located within 6 months from initial diagnosis. The distribution of lesions can be found in Figure 3. Most lesions were in the metaphyses of long bones, pelvis, lower extremities and feet. Vertebral lesions were found in 30% of cases in the first step of diagnosis. In 30% of cases, the patients' chief complaint was back pain, which led to further diagnostics focusing on the vertebrae. Approximately 11% already had a vertebrae plana at first diagnosis. Further lesions in the spinal column were diagnosed during the course of the disease in 18% of patients without initial vertebral lesions; lesions in the cervical spine were reported in 16% of patients, in the thoracic spine 28%, in the lumbar spine 18%, and in the sacrum and coccyx 18%.

Circa 20% of patients reported a unifocal lesion.

**Figure 3.**



## Treatment

Differing initial diagnoses (bone malignancies) resulted in 3 patients receiving chemotherapy for approximately 12 months.

NSAIDs such as ibuprofen (61%), naproxen (50%), indometacin (23%), diclofenac (20%) were prescribed in 95% of all patients, and NSAIDs and steroids (33%) were the most commonly prescribed therapy after the CNO diagnosis. Forty-six percent of all patients answered the question, what NSAID provided the best relief of symptoms. Sixty-five percent of this group reported naproxen as the NSAID with the most beneficial impact and ibuprofen at 35% as the second most beneficial.

Although NSAIDs and steroids were the most commonly prescribed drugs for CNO, bisphosphonates and biologics were frequently used in patients with severe courses of disease. Bisphosphonates made up 21% (n=22) of the therapeutic agents, with pamidronate (n=18) as the most commonly prescribed. From the 22 patients that were receiving a bisphosphonate, 68% (n=15) had vertebral lesions. Over 14% of patients received a biologic agent: 9.5% etanercept, 2% adalimumab, 2% infliximab, and 1% golimumab. Of the 14% of patients which received biologics, 7/15 had lesions on the pelvis, 7/15 on the clavicle, 5/15 in the mandible, and 5/15 on the spinal column. Most of these patients had multiple lesions, with one patient being affected throughout the entire spinal column (cervical, thoracic and lumbar), clavicle, pelvis, and feet.

## Associated Diseases

CNO-related diseases were present in 28% (30/105) of this patient population. Of the associated diseases, skin disorders dominated with 67% including palmoplantar pustulosis (9/30), psoriasis (5/30), and severe acne (6/30). Other reported associated diseases included arthritis (9/30; 33% adjacent to lesion) and Crohn's disease (n=1).

Associated diseases in family members were revealed in 16/105 (15%) fathers and 16/105 (15%) mothers. Again, the skin lesions such as psoriasis (34%) and palmoplantar pustulosis and psoriasis (13%) were predominant. Other rheumatic diseases like chronic polyarthritis were reported in 10/16 females and 3/16 males. Crohn’s disease (2/16) and ulcerative colitis (1/16) were diagnosed in fathers of our patients.

**Patient Care**

From the pediatric population, 96% were being treated by a pediatric rheumatologist or an orthopedic surgeon, whereas with the adult population only 62% were being treated by a specialist (defined by rheumatologist or orthopedic surgeon) and 16% by a general practitioner (Figure 4.) From the 32 patients >18 y/o, 22% had no treating physician; from these patients with no treating physician, 4/7 no longer had an active disease at time of survey and 7/7 patients were between the ages of 18-28 years old.

**Figure 4.**

The distance to the treating physician varied widely; however, 45% had to travel 25 kilometers (km) or less and 86% traveled 100 km or less, and one patient traveled up to 300 km to a specialist. Patients were asked how well cared for do they feel from their specialists, and on a visual analog scale from 1-10, >50% responded with an 8 or higher. Patients were often referred to or specifically asked for a referral to see a physical therapist in 64% of cases.

CNO had reported negative effects in 44% of cases on the entire family, with another 39% reporting a partial effect on the family. Not only were close family members affected by CNO, but also friendships, school, and work-life. From patients which reported difficulty in friendships, 56% described, at minimum, a partial negative affect on relationships. In comparison however, due to this disorder, 79% reported that CNO has negatively affected either school or work.

Seventy-five percent of all patients received no type of psychosocial guidance, although 49% would have liked to have consultation with a guidance counselor or psychologist. These numbers correlate with the 51% of patients and family members which felt uninformed regarding the nonbacterial osteitis diagnosis and the course of disease.

Periods of absences from school or work did not vary widely between before the diagnosis and afterwards. The largest change in the number of days absent per year due to CNO, was in the 6-20 day category; before the diagnosis, patients reported absences at 22% and afterwards at 31%. However, absences greater than 20 days saw a 5% drop after the diagnosis, from 30% to 25%.

Patients were also questioned as to what they would most like to learn and hear about at the information day. Specifically: more general information to CNO, information to prognosis, practical tips, contact to physicians with CNO expertise, contact to other patients, and building of self-help groups (Figure 5.)

#### **Figure 5.**

Other topics of interest ranged from typical side effects of medications to pregnancy to nutrition and alternative therapy options. Many of the pediatric patients and family members were concerned with the transition into adulthood and what effect CNO would have later in life.

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**Discussion**

To our knowledge this is the first health services research to assess diagnosing, treatment, and the psychosocial aspect of CNO from a patient perspective with such a large population pool.

**Medical data**

Overall the patient derived information concerning their own illness matches the current medical literature. The number of lesions, localization of lesions, therapy plan, inflammation parameters and imagery used (data not shown) is comparable to previous scientific literature (6, 14-18). This leads to the conclusion that the group of patients in attendance on the two conference days were well informed, have read about CNO and were seeking further information.

**Delay of diagnosis**

Patients reported long lag times from onset of symptoms until diagnosis. Approximately 70% of the patients were diagnosed within 18 months from the onset of symptoms, but still 7% had to wait more than five years. These lag times lead to not only patient stress, both physical and emotional, but unnecessary testing and treatment. Delays in the diagnosis may lead to prolonged use of antibiotics, multiple surgeries, repeated bone biopsies, and excessive radiation exposure. Another contributing factor to the long lag times in diagnoses and treatment is the distance to specialists. In Germany, most pediatric rheumatologists are located in larger cities and at university hospitals, and adult rheumatologists often have long wait-lists. Therefore, patients often resort to being treated either by a general practitioner or a pediatrician.

Circa 20% of patients reported a unifocal lesion. However, from the 21 patients reporting one lesion, only 5 (24%) received a whole-body MRI and 6 (29%) a bone scan. This

often led to a different differential diagnosis, mostly bacterial osteomyelitis, and a different therapy plan. This resulted in another delay in diagnosis.

## Therapy

With 27% continuing with antibiotic therapy after diagnosis, there must be still uncertainty in the medical community regarding the CNO diagnosis and the proper treatment plan once recognized. A step-wise guide for the therapeutic treatment of CNO was developed to alleviate pain and prevent further degeneration; the plan highlights the use of NSAIDs in the first-line treatment of CNO (19). Currently there are national and international efforts to establish validated treatment protocols for chronic nonbacterial osteitis.

The long lag times in diagnosis and the continuation of antibiotic therapy among other factors, leads to the conclusion that there is a need for better clarification and education regarding nonbacterial osteitis.

## Psychosocial and socio-economic aspects

As with most chronically ill patients, absences from school and work are of great importance. These absences have an effect on school performance, promotions, and the emotional well-being of the patient. When comparing the number of absences before and after the diagnosis, there is very little difference. Which leads to the questions, is the medical therapy successful or does pain amplification play a significant role in the patient group in attendance at the conference? However, according to the patients, most had seen a significant pain level drop when comparing onset to current conditions, with most patients starting with a median pain level of 8/10 (IQR: 6.5; 9) and dropping to 4/10 (IQR: 1.5; 6) after treatment. On the other hand, not only pharmacological therapy, but psychosocial aspects have a great influence on well-being and quality of life. Three quarters of all patients did not receive

psychosocial support. Half of all patients would have liked to have consultation with a guidance counselor or psychologist.

More than 80% reported that CNO has had a negative influence on family life. Physicians caring for chronically ill patients should be aware how this illness not only affects especially young patients, but also other family members and members of the support structure. In Germany, unfortunately, interdisciplinary care can only be offered in specialized medical centers.

**Transition and adult patients**

From the adult population in attendance, 22% were not seeing a specialist and had no treating physician for CNO. These patients vary in ages between 18 – 28 years old. This highlights the need for a better transition model from pediatric care to adult care, as all of these patients were diagnosed as children with CNO.

Especially in Anglo-American countries, there are transition clinics where the needs of chronically ill young adults are met (20-22). In Germany a transition model for patients with chronic rheumatic illnesses was developed (20, 23). This model helps patients coordinate care transitioning from the pediatric community into the adult community and works together with both communities to assure a seamless transition. Once transition is complete this is followed up to ascertain and highlight any needs for improvement. Although such models exist in Germany, this transition care is not widespread, and leaves many patients without a healthcare provider for chronic illnesses after the age of eighteen.

A large portion of the study’s population felt uninformed regarding this illness. This was the top reason for visiting the conference, patients needed and wanted more information about CNO (98%). Practical tips and information to prognosis were also important topics. With such small percentages of patients with CNO, attendance at our conference represented the thirst for information that these chronically ill patients have.

## Conclusion

To our knowledge this is the first study highlighting the impact of CNO from the patient perspective. Delay of diagnosis, living with differential diagnoses like malignancies and finding specialists for medical care drives patients to search for more information. Interested patients were able to report their disease precisely, so that patient data matched medical literature concerning CNO very well. Nevertheless, this survey shows very clearly that psychosocial and socio-economic aspects need to be addressed. Negative impact on family, work and friendships seems to influence partaking in daily life. Support is especially necessary in adolescents and young adults, who often dropped out of medical attendance.

For the incidence rate of this disease, 0.45/100000 (14), 105 patients is large but a relative snapshot in time. Therefore, prospective evaluations of independent patient populations would give more insight.

## Limitations

As with most health services research, patient subjectivity remains to be a problem. Some of the surveys were either not completely filled in or answers were given that did not match the question-which often led to the participant's answer being disregarded. In an attempt to restrain the time and burden on patients, the questionnaire was kept short; therefore limiting the information which could be collected. Often patients were diagnosed years previously with CNO and neither the patient nor the parents could recall initial symptoms, pain levels, etc. In attendance were typically patients with a more severe course of disease and that were very well informed about this disease. This could also explain why the patients' data was very comparable to previous research.

**Funding**

The study was funded by the non-profit organizations Kinder-Rheumhilfe Muenchen e.V. and Kindness for Kids, Munich. Through financial pledges, both organizations provided the necessary capital for the two patient conferences. In addition, Kinder-Rheumhilfe Muenchen also organized the two conferences. The study itself and the work thereafter were unfunded.

**Conflict of Interests**

The authors have no conflicts of interest to disclose.

**Data Sharing**

All available data can be obtained by contacting the corresponding author.



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**Figure Legend:**

Figure 1. Terminology of Nonbacterial Osteitis

Figure 2. First Diagnoses

Figure 3. Distribution of Lesions in Chronic Nonbacterial Osteitis

Figure 4. Current Treating Physician for Chronic Nonbacterial Osteitis

Figure 5. Patient Wishes from CNO Conference

**Author Contribution:**

Contributor Annette Jansson (AJ) developed the idea for the study. Colen Silier (CS) and AJ were involved in the study conception, preliminary literature review and design of the search strategy and the study protocol. Susanne Gesell (SG) and Justina Greschik (JG) designed the initial data base to record study-inputs and completed initial data input. CS concluded data input. CS and Veit Grote (VG) were involved in screening and data extraction of papers. CS, AJ and VG reviewed data extraction output. CS drafted the report, which was critically reviewed and approved by all authors.

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**Figure 1.** Terminology of Nonbacterial Osteitis

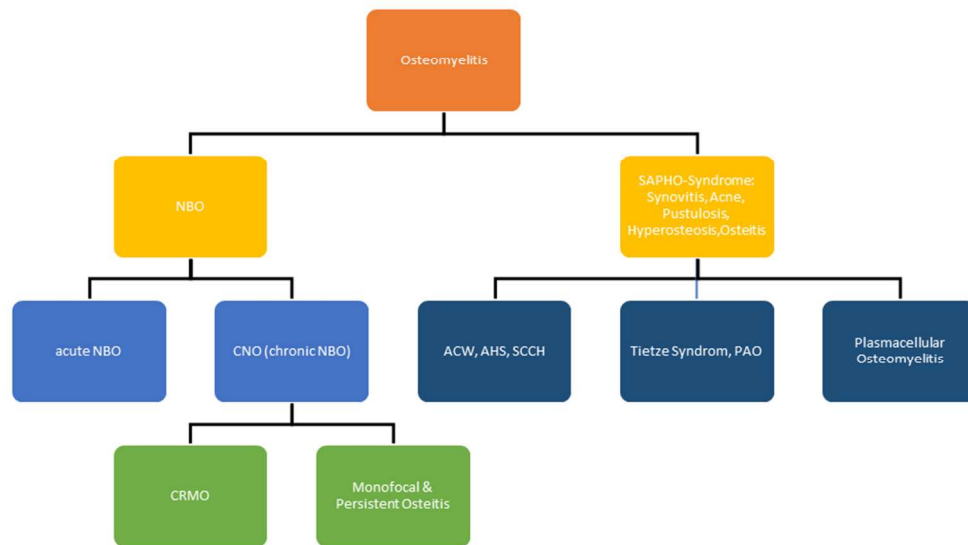


Figure 1. Terminology of Nonbacterial Osteitis

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**Figure 2.** First Diagnoses

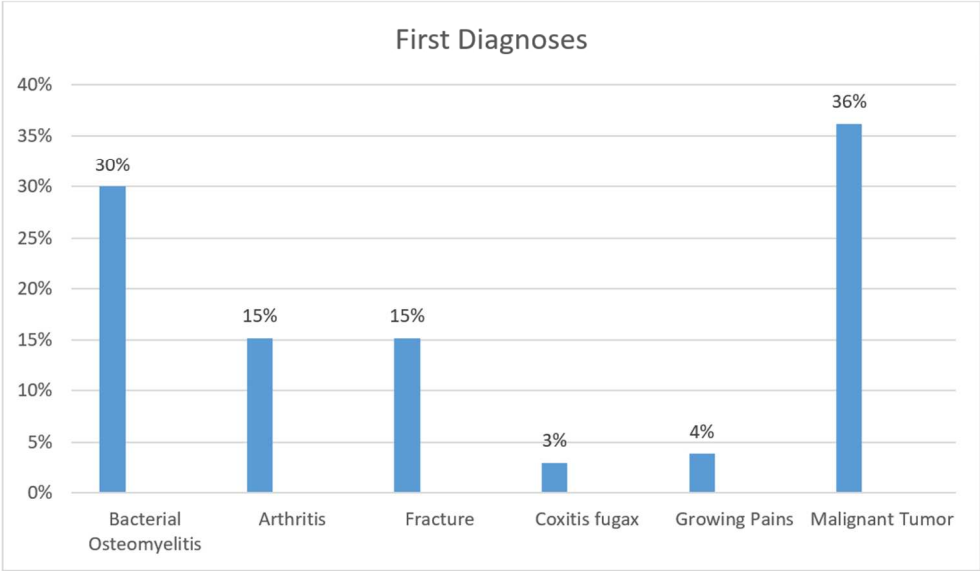


Figure 2. First Diagnoses

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**Figure 3.** Distribution of Lesions in Chronic Nonbacterial Osteitis

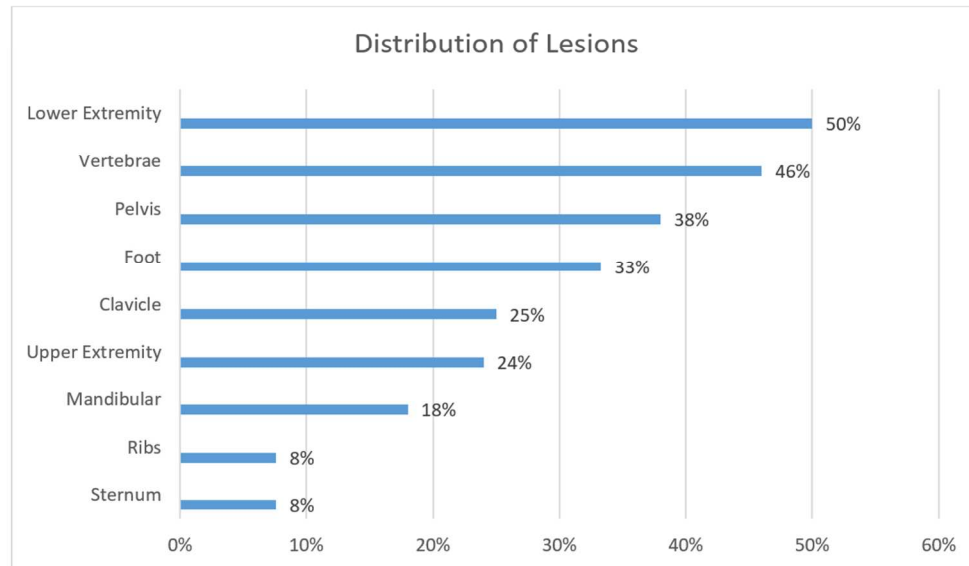


Figure 3. Distribution of Lesions in Chronic Nonbacterial Osteitis

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**Figure 4.** Current Treating Physician for Chronic Nonbacterial Osteitis

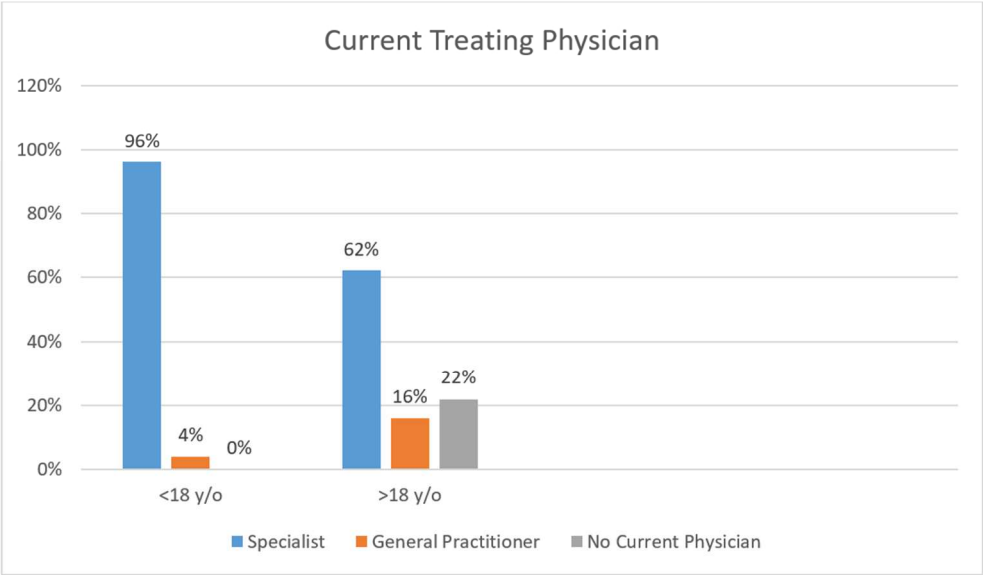


Figure 4. Current Treating Physician for Chronic Nonbacterial Osteitis

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**Figure 5.** Patient Wishes from CNO Conference

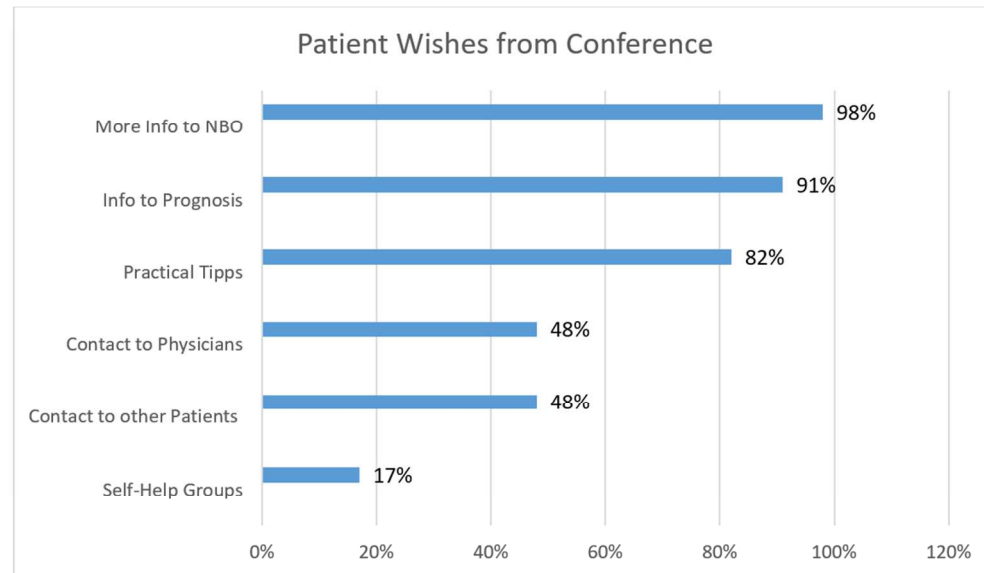


Figure 5. Patient Wishes from CNO Conference

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
✓ Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract <a href="#">pg. Abstract “Design” and pg. 2</a> (b) Provide in the abstract an informative and balanced summary of what was done and what was found <a href="#">pg. Abstract “Design” and “Results”</a>
<b>Introduction</b>		
✓ Background/rationale <a href="#">pg. Abstract “Objective” and pg. 1</a>	2	Explain the scientific background and rationale for the investigation being reported
✓ Objectives <a href="#">pg. 1</a>	3	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
✓ Study design <a href="#">pg. 2</a>	4	Present key elements of study design early in the paper
✓ Setting <a href="#">pg. 2</a>	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
✓ Participants <a href="#">pg. 2, 3</a>	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
✓ Variables <a href="#">pg. 1, 3-8</a>	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
✓ Data sources/ measurement <a href="#">pg. 2-8</a>	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
✓ Bias <a href="#">pg. 1, 12</a>	9	Describe any efforts to address potential sources of bias
✓ Study size <a href="#">pg. 2</a>	10	Explain how the study size was arrived at
✓ Quantitative variables <a href="#">pg. 1, 2</a>	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
✓ Statistical methods <a href="#">pg. 2, 3</a>	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

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<b>Results</b>		
✓ Participants pg. 3, 4, 12	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
✓ Descriptive data pg. 3, 4, 12	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
✓ Outcome data pg. 3	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
✓ Main results pg. 3-8	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
✓ Other analyses N/A	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
<b>Discussion</b>		
✓ Key results pg. 9, 10, 11	18	Summarise key results with reference to study objectives
✓ Limitations pg. 12	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
✓ Interpretation pg. 11, 12	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
✓ Generalisability pg. 12	21	Discuss the generalisability (external validity) of the study results
<b>Other information</b>		
✓ Funding pg. 13	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).