Aus der Kinderklinik und Kinderpoliklinik
im Dr. von Haunerschen Kinderspital
Klinik der Ludwig-Maximilians-Universität München
Direktor: Prof. Dr. med. Dr. sci. nat. Christoph Klein

Nonbacterial Osteitis

A Relevant Differential Diagnosis to Bacterial Osteomyelitis

Dissertation
zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

vorgelegt von
Colen Cooper Gore Silier
aus
Clinton, North Carolina, Vereinigte Staaten von Amerika
2019

Mit Genehmigung der Medizinischen Fakultät

der Universität München

Berichterstatterin:	Priv. Doz. Dr. med. Annette Jansson
Mitberichterstatter:	Priv. Doz. Dr. med. Florian Haasters Prof. Dr. med. Uta Behrends
Mitbetreuung durch den promovierten Mitarbeiter:	Dr. med. Veit Grote, MSc
Dekan:	Prof. Dr. med. dent. Reinhard Hickel
Tag der mündlichen Prüfung:	14.11.2019

Eidesstattliche Versicherung

Silier, Colen Cooper Gore

Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema

Nonbacterial Osteitis, A Relevant Differential Diagnosis to Bacterial Osteomyelitis

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 23.01.2019 — Colen Cooper Gore Silier

Ort, Datum — Unterschrift Doktorandin/Doktorand

Table Contents

1. Abbreviations

ANA: Antinuclear Antibodies

BO: Bacterial Osteomyelitis

CARRA: Childhood Arthritis and Rheumatology Research Alliance

CNO: Chronic Nonbacterial Osteitis

CRMO: Chronic Recurrent Multifocal Osteomyelitis

CRP: C-Reactive Protein

CT: Computed Tomography

ESR: Erythrocyte Sedimentation Rate

Hib: Haemophilus Influenzae Type B

HLA: Human Leukocyte Antigen

IBD: Inflammatory Bowel Disease

IL: Interleukin

LPS: Lipopolysaccharide

MTX: Methotrexate

MRI: Magnetic Resonance Imaging

MRSA: Methicillin-Resistant Staphylococcus Aureus

NBO: Nonbacterial Osteitis

PCR: Polymerase Chain Reaction

PPP: Palmoplantare Pustulosis

RANK: Receptor Activator of Nuclear Factor-κB

RANKL: Receptor Activator of Nuclear Factor-κB Ligand

SAPHO**:** Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis

SPSS: Statistical Package for the Social Sciences

TLR: Toll Like Receptor

WB-MRI: Whole-Body Magnetic Resonance Imaging

2. Publication List

Grote V, Silier C, Voit A, Jansson A.F. (2017). Bacterial Osteomyelitis or Nonbacterial Osteitis in Children: A Study Involving the German Surveillance Unit for Rare Diseases in Childhood. *Pediatric Infectious Disease Journal,* 36 (5):451-456.

http://dx.doi.org/10.1097/inf.0000000000001469

Silier C, Greschik J, Gesell I, Grote V, Jansson A.F. (2017). Chronic Nonbacterial Osteitis from the Patient Perspective. *British Medical Journal Open*, 7 (12).

http://dx.doi.org/10.1136/bmjopen-2017-017599

3. Contribution statement

Both studies were conducted through the Department of Rheumatology and Immunology in Dr. von Hauner Children's Hospital, Munich Germany.

Study I: Annette Jansson and Veit Grote conceptualized the study. Colen Silier and Veit Grote reviewed existing literature. Agnes Voit assisted with the initial collection of data, and Veit Grote and Colen Silier collected the data. Control of data quality and data analysis was initially done by Veit Grote with Colen Silier re-validating the data analysis and further contributing. Colen Silier wrote the manuscript with critical revision from Veit Grote. Other co-authors contributed to the manuscript by giving their feedback.

Study II: Annette Jansson developed the idea for the study. Colen Silier and Annette Jansson were involved in the study conception, organization of the patient conference, patient recruiting, preliminary literature review and design of the search strategy and the study protocol/questionnaire. Susanne Gesell and Justina Greschik designed the initial database to record study-inputs and completed initial data input. Colen Silier collected and concluded data input beginning in 2015. Colen Silier and Veit Grote were involved in screening as well as data extraction of papers. Colen Silier reviewed data extraction output and wrote the manuscript, which was critically reviewed and approved by all authors.

Signed copies of the "Author Contribution Statements" can be found with the original publication.

4. Introduction

The term osteomyelitis describes inflammation of the bone and/or bone marrow, which compromises the cortical bone and periosteum and is typically microbial triggered [1, 2]. However in 1972, Giedion et al. described for the first time a form of bone inflammation which appeared to be of a nonbacterial origin and thus, coined the term chronic recurrent multifocal osteomyelitis (CRMO) [3]. In subsequent years, the terms nonbacterial osteitis (NBO) and chronic nonbacterial osteitis would be added. Osteitis conversely describes not only bone marrow inflammation, but inflammation of the bone and surrounding soft tissue [2]. Today the terms osteomyelitis and osteitis are often used as synonyms.

Patients with oncologic diseases, with immune deficiencies, post-injury, or infants are predisposed to bacterial osteomyelitis [4]. But in the ever advancing diagnostics and the increasing usage of WB-MRIs (whole-body magnet resonance imaging), bone lesions are being detected in both pediatric patients as well as adult patients, who otherwise presented and appeared healthy [5, 6]. These radiologically confirmed bone lesions closely resemble those of bacterial osteomyelitis; however, they seem to be of an autoinflammatory origin [7].

Physicians are often confronted with patients presenting with bone pain and lesions, leading many to assume these manifestations to be of bacterial origin, primarily bacterial osteomyelitis, regardless whether an isolated pathogen is found. Therefore, the chief complaint of localized bone pain, which is present in both NBO and BO, can be a diagnostic challenge [6, 8, 9].

The topic of this dissertation and research compared and contrasted nonbacterial osteitis and bacterial osteomyelitis (BO) in a study from July 2006 – July 2011 using the German Surveillance Unit for Rare Diseases in Childhood (Erhebungseinheit für Seltene Paediatrische Erkrankungen in Deutschland (ESPED)). Data was collected in all pediatric hospitals and orthopedic departments nation-wide, capturing NBO cases for the whole time period (5 years) while bacterial osteomyelitis cases were added from July 2009 onwards (2 years).

The second portion of this dissertation gathered, analyzed, and evaluated the impact of chronic nonbacterial osteitis (CNO) from the patient perspective based on surveys from patient conferences held in 2013 and 2015. These questionnaires were developed to include not only the symptoms, diagnostics, and treatment plans but also the social impact that the chronically ill face as well as access to care issues with which patients are confronted. A primary focus in the survey was dedicated to how well the patients were versed in CNO and which difficulties were

encountered. Much emphasis was placed on the socio-economic effect along with the psychosocial aspects of such a disease.

Nonbacterial Osteitis General Information

Nonbacterial osteitis (NBO) is an autoinflammatory bone disease, with or without associated diseases, and can be subdivided into an acute form and a chronic form [10]. The chronic form can be again allocated further into chronic nonbacterial osteitis (CNO) which includes all chronic forms, unifocal and multifocal disease as well as relapsing and persistent osteitis, and chronic recurrent multifocal osteomyelitis (CRMO). CRMO usually represents the most severe subform of CNO [11-15].

CRMO is often regarded to be the pediatric equal of the SAPHO syndrome (Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis), which is better known in adult health care [16-18], and both diseases may include unifocal or multifocal nonpyogenic bone lesions, osteitis, hyperostosis, pustulosis, normal body temperature and good general health [10, 15]. CRMO is often characterized through spontaneous flares and remissions [19, 20].

Pathogenesis

Although the etiology is unknown, recent data, both from patient and mouse models, suggest a genetic component for NBO [18, 20-25]. Through a family based association study, Jansson et al. were able to demonstrate the roll of genetics in the disease emergence with more than one-third of the population's study expressing a rare allele on Chromosome 18 [21].

Most current research has also shown in response to toll like receptor (TLR) 4 with lipopolysaccharide (LPS) that monocytes from NBO patients fail to express or have reduced expression of interleukin 10 (IL-10) and interleukin 19 (IL-19), leading to a significant imbalance between pro-inflammatory and anti-inflammatory signals [25-29]. This downregulation of anti-inflammatory signals, results in increased activity of pro-inflammatory cytokines, especially TNF alpha, interleukin 1β (IL-1β), interleukin 6 (IL-6), and interleukin 20 (IL-20) [25, 27, 30]. The aforementioned pro-inflammatory cytokines lead to an amplified interaction between RANK (receptor activator of nuclear factor-κB) receptors and RANKL (RANK ligand), resulting in induced osteoclast differentiation and activation [25, 31], which therefore results in the typical osteolytic lesions seen in NBO patients.

Ferguson et al. were able to further demonstrate that the lack of functional interleukin 1β (IL-1β) served as a protection factor leading to an attenuated response or complete absence of disease [18].

Epidemiology

To date there has been only one large national study concerning the incidence rates of NBO, which was completed by the Department of Rheumatology and Immunology in Dr. von Hauner Children's Hospital in 2017. The incidence rate in Germany is estimated to be 0.45/100,000 [9]. In the German-wide study, there was a preponderance of females (64%) in the NBO cases and the mean age at time of diagnosis was 11 years old (SD: 3.2 years) [9].

Girschick et al. recently publicized data from an international registry (Eurofever) encompassing 486 patients with NBO, which closely statistically correlates with the national NBO study completed in 2017. The study revealed a likewise 64% female majority with a mean age at time of diagnosis of 10.9 years [28].

Symptoms and Clinical Presentation

While lesions in NBO may appear at any skeletal site and may appear unifocal or multifocal, multiple lesions primarily appear in the pelvis, feet, or metaphyseal in the tibia or femur [10]. However, lesions in the clavicle, vertebrae, mandible, and sternum are all more commonly found in NBO patients in contrast to bacterial osteomyelitis (BO) patients [9, 10, 19]. The chief complaint centers on localized pain with accompanying tenderness, peripheral swelling, and limited range of motion [10, 19].

The average course of chronic NBO (CNO) runs approximately 21-29 months, after which 56% of patients are typically free of complaints [15]. The acute NBO, just like in CNO, is self-limiting but with a course of disease lasting up to six months [15]. There also seems to be a correlation between nonbacterial osteitis and other autoimmune diseases, especially dermatologic disorders [32-34]. Palmoplantar pustolosis has been seen in 15-20% of patients with CRMO [35, 36]. Other cutaneous manifestations such as acne conglobate and acne fulminans [37], pyoderma gangrenosum [38], and Sweet's syndrome [39] have all been associated with sterile multifocal osteomyelitis. In a recent study, circa 20% of patients presented with associated diseases including but not limited to: chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease, celiac disease), inflammatory bowel disease (IBD), rheumatic disease, psoriasis, severe acne and palmoplantar pustulosis (PPP) [11, 15, 40].

Diagnostics

Although no gold standard in the diagnosis for NBO exists, proof of pathogen is usually diagnostic for BO; conversely, NBO is a diagnosis of exclusion. However, it must be noted that approximately half of NBO patients demonstrate and therefore are subsequently diagnosed with a bacterial infection.

With the omission of the chief complaint of bone pain, NBO patients may be overlooked due to an overall good clinical health status. Patients typically present with C-reactive protein (CRP) ≥ 1 mg/dl, mildly elevated erythrocyte sedimentation rate (ESR), a normal blood cell count and a normal body temperature [9, 13-15, 41, 42]. Fever, localized redness, and lymphadenopathy are considered atypical in NBO cases [9, 43]. It has been suggested, based on the above mentioned difficulties, that the incidence rate for NBO is much higher than originally thought and diagnosed [6, 10].

Magnet resonant imaging (MRI), bone scintigraphy, and conventional X-ray are the three most readily used radiologic diagnostic tools, with MRI and the scintigraphy being the most sensitive. In cases with suspected bone destruction, however, MRI is the first choice in radiological diagnostics [11, 44]. Radiologic verified bone lesions exhibit marginal sclerosis, and in the case of NBO, frequently more than one lesion [6]. Today, the recommendation is a whole-body MRI (WB-MRI) due to the ever increasing finding of silent lesions [45]. Clinically silent lesions but radiologically active lesions require treatment; although, the importance of silent lesions is still under discussion [46].

In 2007, Jansson et al. proposed “Major and Minor Diagnostic Criteria of NBO”; hence, NBO can be diagnosed with either two major criteria or one major plus three minor criteria [15]. Presently efforts are being made through CARRA (Childhood Arthritis and Rheumatology Research Alliance) in a joint effort with international partners to establish a databank of diagnosis criteria based on a large patient population [45, 47].

In 2013 Jansson et al. further developed a clinical scoring system for how likely a patient is to have NBO; this scoring system encompassed blood cell counts, radiology findings (+/- osteosclerotic bone lesions), number of bone lesions, symmetry of bone lesions, fever, and CRP levels. The scoring ranges between 0-63, and >35 points indicates a case of NBO. Based on the resulting score, therapy plans can then be developed [48]. The whole-body MRI plays a significant role in this scoring system due to the requirement of finding the total number of lesions and the symmetry of said lesions. Without a WB-MRI, most lesions would go unnoticed [46].

Another factor to consider in the diagnosis, is histology; however, histology is primarily used to distinguish BO from malignancies but not from NBO. The general changes seen in both NBO and BO cases are acute and chronic inflammation. Whereas neutrophils largely characterize BO cases, NBO is often primarily represented in the histology through lymphocytes and plasma cells [44, 49, 50]. Nonetheless, the imbalance of anti-inflammatory and pro-inflammatory cytokines resulting from the monocytes significant reduction or failure to produce IL-10 [8, 9, 18] could eventually be helpful in developing a laboratory marker for NBO.

Furthermore HLA-B27 (Human leukocyte antigen B27) was established in 7.9% of patients tested, as well as elevated ANA titers in 38% [28].

In addition, diseases such as Hepatitis B and C as well as Tuberculosis should be excluded before the definitive diagnosis is made and eventually treated. Tuberculosis is especially an important differential diagnosis in the case of unifocal lesions [47].

Therapy

There are no authorized therapeutic agents for the sole treatment of CNO; therefore, the therapy of choice lies with the treating physicians and is considered an "off-line" therapy [47]. Additionally there is no established definition for CNO therapy response so far, merely protocols, and it is left to the treating physician to classify the response as remission, partial response, or no response [28, 45, 47].

According to many experts in the field, first-line therapy for pediatric NBO patients without spinal lesions are NSAIDs (nonsteroidal anti-inflammatory drugs), which have an 80% response rate [19, 45, 47, 51]. As escalation therapy, steroids should be considered; although, in the case of vertebral fractures, steroid usage should be avoided [19]. If no relief is found with NSAIDs or steroids, immunosuppressant drugs (e.g. sulfalazin, methotrexate), TNF-α antagonists and bisphosphonates are to be considered, with the latter two being most successful [19, 52-56]. Treatment with methotrexate (MTX) and sulfalazin demonstrated lower remission rates and in the case of MTX, poor tolerance [54, 55].

Complementary measures to the pharmaceutical treatment of CNO should also be considered. These include but are not limited to physical therapy to help avoid contractures and aid in muscle strength, cyro- and thermotherapy for symptomatic relief, orthopedic and medical aids for better mobility, vitamin D supplements and psychosocial support [47, 57].

A complication of therapy, is the continued use of antibiotics in NBO cases. This highlights the uncertainty surrounding the therapy protocol for NBO; therefore, a step-by-step guide was developed by Jansson et al. in 2009 to alleviate any ambiguity [52], and in 2018 a treat-to-target strategy was further developed into a therapy protocol to be used as an interventional strategy with flexible application by Schwarz et al. in a joint effort with Childhood Arthritis and Rheumatology Research Alliance (CARRA) in North America [45, 47]. Therapy recommendations have been standardized recently (2018) in the form of the aforesaid therapy protocols both on a national and international level [45, 47].

Recommended follow-up and if needed, escalation therapy or treatment modification, is recommended at the three month assessment appointment. The treatment duration is recommended as a minimum of 12 months to achieve the best results and avoid later complications [45].

Complications

Approximately 20% of patients do not respond well to initial therapy and/or have multiple relapses. Furthermore they can develop therapy resistance, osseous changes, vertebral fractures, hyperostosis, scoliosis and kyphosis. These complications highlight the urgent need for timely and effective therapy [14, 19, 42]. In an orthopedic follow-up study of CNO in Melbourne, Australia 5/12 patients showed a leg-length discrepancy of $\geq$1.5 cm (mean = 3.2 cm), and 50% of these patients showed a difference in muscle girth varying between 1.5 cm and 4 cm [58].

Because NBO is typically chronic, the psychosocial aspect of chronic nonbacterial osteitis (CNO) plays a large role in the day-to-day lives of patients. The burden of disease often impairs familial relationships and friendships [9, 59]. Therefore, it is important for the physician as well as for the patient's support structure to educate and empower the patient to prevent negative long-term effects.

Bacterial Osteomyelitis General Information

In practice, bacterial osteomyelitis (BO) is the most common differential diagnosis to NBO, and until 1972, assumed to be the only form of osteomyelitis [3]. Bacterial osteomyelitis can be classified in to three categories: primary acute hematogenous osteomyelitis, secondary osteomyelitis through trauma or surgical intervention, and secondary osteomyelitis through vascular insufficiency [19]. In children, the primary acute form is by far the most prevalent, approximately 90% [19, 60, 61]. Generally in pediatrics the long bones of the lower extremities, especially the metaphyses of the femur and the tibia, are most frequently affected [9, 21, 62].

Pathogenesis

Based on the duration of symptoms, BO can be categorized into: acute with a duration under two weeks, sub-acute with a duration of two weeks to three months, and chronic with a duration longer than three months [4, 63]. The most common pathogen of bacterial osteomyelitis is dependent on age, susceptibility factors of the host, and microbial etiology. Newborns are most commonly infected with *Streptococcus agalactiae* and *Escheria coli*; whereas, in school-aged children *Staphylococcus aureus*, *Streptococcus pyogenes* and *Haemophilus influenza* are predominantly found. *Haemophilus influenza* Type B (HiB) is not as prevalent as in the past due the increasing number of HiB immunizations [64].

Kingella kingae is also taking on an ever increasing role in children, especially under four years old [4, 65-67]; however, this pathogen is difficult to identify in blood cultures and bodily fluid cultures (e.g. synovial fluid) [68]. Evidence suggests that with real-time polymerase chain reaction (PCR), the proof of pathogen yield is much higher for K. kingea [67-69]; nonetheless, it is not common practice for most practitioners to use PCR without K. kingea suspicion.

Staphylococcus aureus, the most typical causative pathogen responsible for not only the acute form but also for the chronic osteomyelitis, forms a biofilm. This can lead to antimicrobial resistance and the further expression of virulence factors [70]. Many multiple resistant strains, not only found in a hospital setting, but also community-acquired strains, may result in a delay in therapy which increases the risk of disease chronification. The prevalence of methicillin resistant staphylococcus aureus (MRSA) and K. kingae vary significantly from location to location [4, 62].

Epidemiology

The incidence rate for osteomyelitis has shown large variations. In 2008 in Norway, the incidence rate was estimated to be 13/100,000 [71] and in Belgium in 2005 1/5,000[60]. Based on a study from 2009 to 2011 in Germany, the bacterial osteomyelitis incidence rate is estimated to be 1.2 (-5)/100,000 [9]. The average age at diagnosis in BO cases is 6.6 years old [72, 73], with 50% of cases occurring in children under five years old [74, 75] and one-third of patients being under 24 months old [75]. Males are more often afflicted than females at a ratio of 2:1[74-76].

Symptoms and Clinical Presentation

The symptoms of osteomyelitis vary and are dependent upon the age of the child, localization of the infection, the virulence of the pathogen as well as the bodily defenses of the organism. The beginning is often accompanied with sudden onset of bone pain and fever [60, 74]. Children exhibit declining range of motion in the affected bone/extremity so that limited mobility

or pseudoparalysis appears [77]. In the case of the lower extremities, a limp may accompany the localized pain, swelling, warmth and redness, which may or may not be present as well [61, 74]. Newborns are more likely to show restlessness and a refusal to drink or eat [19, 74].

Diagnostics

Blood cultures in 20 - 40% of the cases and biopsies in 60% of the cases can help specify the causative agent [11, 20, 60, 65, 78]. Biopsy indications include but are not limited to: unifocal lesions, B symptoms, and unclear findings [52]. Frequently the decision for further diagnostic measures are unspecific. In 85% of cases a leukocytosis is present, in 70% an elevated erythrocyte sedimentation rate (ESR), and in 42% is the C-reactive protein (CRP) elevated [60, 79].

A conventional X-ray can in 85% of cases validate an osteomyelitis; however, osseous changes are usually not recognized until two to three weeks after the beginning of disease activity [19]. BO tends to present as a unifocal lesion; however, in the case of newborns, BO can and often does present multifocal [77, 80]. The first changes to be seen in radiology are soft tissue swelling, thickening of the periosteum and a sub-periosteum fluid retention. In the later stages, bone density is affected and bone destruction is evident [19].

A bone scintigraphy with technetium-99m also helps endorse the suspicion of an osteomyelitis, especially in the early stages when the disease is active in other areas of the body outside of the long bones. Computed tomography (CT) demonstrates the bone destruction, but the magnet resonance imaging (MRI) is still the first choice in diagnostic imaging for bacterial osteomyelitis due to the radiation exposure in pediatric patients [19].

Therapy

All empiric therapies must take into account the local prevalence of organisms, local antimicrobial sensitivities, and underlying conditions. A penicillinase resistant penicillin or cephalosporin (cefuroxime) are the two most recommended antibiotics in pediatric osteomyelitis. But due to the rising cases of MRSA, clindamycin and vancomycin have been added [62, 81]. Some have suggested that new regimens should include MRSA coverage if more than 10% of the *S. aureus* cases are in fact methicillin resistant [62, 78], and Peltola et al. recommended that therapy be guided by CRP and ESR levels [82]. Due to the ever rising resistance in the K. kingae, caution should be used when administering clindamycin [62].

Traditionally, acute osteomyelitis was treated four to six weeks long with broad spectrum antibiotics [83-85]. New research suggests in children older than three months of age that three to

four days of parenteral antibiotics and then transitioning to oral antibiotics for three weeks is as effective as a lengthy antibiotic regimen. The recommendation for neonates remains unchanged with antibiotics given exclusively parenterally for four weeks [62].

Complications

With adequate and timely antibiotic therapy, the risk of BO developing into a chronic bacterial osteomyelitis drops dramatically. BO leads to permanent damage in 6 -50% of the cases in newborns including lack of growth, leg length discrepancies, arthritis, fractures, and gait abnormalities [19]. If the disease cannot be treated appropriately with antibiotics and results in chronic bacterial osteomyelitis, the therapy recommendation is radical surgical debridement down to living bone [4, 70]. Therefore, being able to better differentiate between NBO and BO should help patients and physicians alike to refrain from delay of diagnosis, over treatment, and unnecessary treatment.

Study I

Beginning in July 2006 through July 2011 using German Surveillance Unit for Rare Diseases in Childhood (Erhebungseinheit für Seltene Paediatrische Erkrankungen in Deutschland (ESPED)) treating physicians in pediatric hospitals and pediatric orthopedic departments were asked to report newly diagnosed NBO cases and later BO cases. NBO cases were defined as children >18 months and <18 years of age with newly diagnosed NBO. BO cases were later added in July 2009, so that a total study period of two years was achieved. The treating physicians in the corresponding hospitals and wards were asked to fill in the detailed clinical information on a corresponding report card with the assistance of ESPED representatives at each site.

At the beginning of the study, each ESPED representative was provided with information about nonbacterial osteitis, to include a case definition. The study was also announced in the German Pediatric Society's board journal. The journal additionally provided a timely review article on this issue which was linked to the surveillance to assist in the collection of data.

All centers were asked to report children >18 months and <18 years of age who had been in the previous month newly diagnosed with NBO, CRMO, CNO, SAPHO syndrome, bacterial osteomyelitis or other inflammatory bone lesions. The primary diagnosis of nonbacterial osteitis or bacterial osteomyelitis was made by the treating physician. Children with previous chronic illnesses, trauma, surgery, and immunosuppression were excluded from the study, and no distinction was made between inpatients and outpatients. The children recruited for the study had to have at least one X-ray- or MRI-verified osteolytic/sclerotic or osteosclerotic bone lesion.

Each report contained a detailed, two-page report filled in by the treating physicians. After the addition of the bacterial osteomyelitis cases in July 2009, minimal changes were introduced to the questionnaire. Every form contained the following information:

Category	**Details**
General Information	Gender, birth date, age at diagnosis, age at onset, associated diseases
Clinical Presentation	Including associated symptoms: fever, weight loss, lack of appetite, enlarged lymph nodes
Laboratory Values	blood count anomalies, leukocytosis with or without left shift, CRP, ESR, ANA titers
Radiology Findings	Scintigraphy, X-ray, MRI, CT with documentation of the number of lesions
Localization of Bone Lesions	Symmetry? Specific localization
Microbiology Results	Bacterial pathogen?
Therapy	Before and after the diagnosis
Complications	i.e. hyperostosis, vertebrae fractures, vertebra plana, scoliosis, etc.

Good clinical condition was defined as absence of fever, absence of enlarged lymph nodes, absence of weight loss and a healthy appetite. CRP > 1 mg/dl, ESR >15 mm/h and ANA titers >1:80 were considered to be elevated.

The collected data was analyzed using Statistical Package for the Social Sciences (SPSS). The study highlighted the difficulties in differentiating between NBO and BO and led to the conclusion that NBO could be significantly underdiagnosed. This study further defined the clinical presentation and confirmed the epidemiological data regarding both diseases. The most effective therapies were further investigated as well.

Study II

The Pediatric Rheumatology department of the Ludwig-Maximilians-University (LMU) Munich hosted CNO patient conferences in June 2013 and again in June 2015. The intended audience was to encompass not only the pediatric patients, but adult patients and relatives of patients as well. Once registration was completed, patients received a twelve page questionnaire, which was to be turned in at the aforementioned conference. From the 134 patients in attendance, 107 completed the survey and were hence collected (2013: 69 and 2015: 38).

The patient survey captured 285 variables per patient and focused on important aspects of nonbacterial osteitis to include but not limited to:

Category	Details
General Information	Age at onset and diagnosis, , past medical and treatment history, family history and associated disease in patients and family members
CNO Symptoms and Diagnostics	Symptoms at onset and at time of survey, diagnostic procedures used, total number of lesions
Patient and Family Satisfaction	With consulting physician, treatment plan, treatment options, explanation of disease
Psychosocial Impact	On patient, friends, and family
Absences Due to Disease	At school, work, social functions

The data was analyzed using SPSS helping to highlight areas for improvement, such as the need for international standardized diagnostic procedures, better transition of care models, and enhanced psychosocial and socio-economical support. The conclusion of this study furthermore validated the medical literature concerning CNO regarding initial symptoms, clinical presentation, and the most effective therapy plans.

5. Summary

The diagnosis of nonbacterial osteitis (NBO) is gaining ground not only in the pediatric community but in adult health care as well. The topic of the dissertation presented, firstly aimed to compare and contrast nonbacterial osteitis and bacterial osteomyelitis (BO). The second portion gathered, analyzed and evaluated the impact of chronic nonbacterial osteitis from the patient perspective based on questionnaires from patient conferences.

Nonbacterial osteitis is an aseptic, autoinflammatory bone disorder, which can present at all ages and in all skeletal sites [10]. It can present as acute, chronic persistent, or chronic recurrent as well as unifocal or multifocal. NBO is most often known by its most severe form: chronic recurrent multifocal osteomyelitis (CRMO) [11-15]. The most common differential diagnoses are bacterial osteomyelitis and malignancies (Ewing-sarcoma, osteosarcoma, leukemia, histiocytosis) [13, 52].

The chief complaint of patients is localized bone pain in both NBO and BO, which can lead to a diagnostic challenge [19, 86]. However, NBO patients tend be female with a median age of 11 years (SD: 3.2 years) and present typically in general good health with multifocal bone lesions. In contrast, BO patients tend to be male, younger, and present with unifocal lesions, fever, high inflammation markers, and localized redness.

Whereas proof of pathogen is usually diagnostic for BO, bacterial infections can be verified in only half of the patients; conversely, NBO is a diagnosis of exclusion. While a gold standard for the diagnosis of NBO does not yet exist, the goal of the first portion of this dissertation (ESPED study) was to better differentiate between NBO and BO and to prevent unnecessary antibiotic treatments. Timely diagnoses and targeted therapy reduce patient stress and reduce the burden on the German healthcare system. This study was the first prospective German-wide study concerning the first manifestation of NBO in childhood and the first prospective German-wide study concerning first manifestation of BO in childhood. Through a five-year national study, 279 NBO patient data were collected, and in the last 2 years of the study, 378 BO patient data were additionally collected -leading to the largest study of NBO patients up until this point in time.

The goal of study number two was to gain a better understanding of chronic nonbacterial osteitis (CNO) from the patient perspective. Thereby it was important to investigate how well the patients were informed regarding CNO, the psychosocial impact was explored, and the approach to betterment of treatment and patient care was discussed. Through two patient conferences (2013

and 2015) a total of 107 patients attended and provided us with reliable data through our surveys. This data lead to the first study world-wide concerning the impact of chronic nonbacterial osteitis from the patient perspective.

6. Zusammenfassung

Die Diagnose nichtbakterielle Osteitis (NBO) wird zunehmend nicht nur in der Pädiatrie, sondern auch in der Erwachsenenmedizin gestellt. Das Thema der vorliegenden Dissertation beinhaltet erstmals den Vergleich von nichtbakterieller Osteitis und ihrer häufigsten Differenzialdiagnose, der bakteriellen Osteomyelitis (BO). Im zweiten Teil wurden mithilfe von Erhebung durch Fragebögen im Rahmen von Patiententagungen die Auswirkungen der chronischen nichtbakteriellen Osteitis aus der Patientenperspektive gesammelt, analysiert sowie evaluiert.

Die nichtbakterielle Osteitis ist eine aseptische, autoinflammatorische Knochenentzündung, die in jedem Alter und an jeder Lokalisation auftreten kann [10]. Dabei kann sie sich unifokal oder multifokal präsentieren sowie akute, chronisch persistierende und chronisch rekurrierende Formen ausbilden. Die NBO ist am besten bekannt durch ihre schwerste Verlaufsform, die chronisch-rezidivierende multifokale Osteomyelitis (CRMO) [11-15]. Die häufigsten Differenzialdiagnosen stellen bakterielle Osteomyelitis und Malignome (Ewing-Sarkom, Osteosarkom, Leukämie, Histiozytose) dar [13, 52].

Bei NBO sowie bei BO ist das Leitsymptom der lokale Schmerz, was eine besondere Herausforderung für die Diagnosestellung darstellt [19, 86]. Jedoch präsentieren sich Patienten mit einer NBO erfahrungsgemäß in einem guten Allgemeinzustand, mit multiplen Knochenherden, sind dabei meistens weiblich und haben ein Medianalter von 11 Jahren (SD: 3,2 Jahre). Auf der anderen Seite sind Patienten mit einer BO häufig männlich, jünger und weisen vorwiegend unifokale Knochenläsionen sowie Fieber, hohe Entzündungszeichen und lokale Rötungen auf.

Während ein Erregernachweis für eine BO spricht, jedoch nur in etwa der Hälfte der bakteriellen Infektionen nachgewiesen werden kann, handelt es sich bei einer NBO um eine Ausschlussdiagnose. Da keine standardisierten Diagnosekriterien für NBO existierten, war es das Ziel des ersten Teiles dieser Dissertation (ESPED-Studie) die Differenzierung zwischen NBO und BO zu verbessern und somit unnötige antibiotische Therapien zu vermeiden. Zeitgerechte Diagnosestellung und gezielte Behandlung reduzieren die Belastung der Patienten und des Gesundheits-Systems. Diese Studie ist die erste prospektive deutschlandweite Erhebung zur Erstmanifestation der NBO im Kindesalter und die erste prospektive deutschlandweite Erhebung zur Erstmanifestation der BO im Kindesalter. Über fünf Jahre wurden 279 Patienten mit NBO erfasst sowie über 2 Jahre 378 Patienten mit BO. Dies stellt zu diesem Zeitpunkt das größte publizierte Kollektiv von NBO Fällen dar.

Das Ziel der zweiten Untersuchung war es, ein besseres Verständnis der chronisch-nichtbakteriellen Osteitis (CNO) aus der Patientenperspektive zu erlangen. Dabei war es wichtig, in wie weit Betroffene über ihre Erkrankung informiert waren, die psychosoziale Auswirkung erfragt sowie Ansätze zur Verbesserung der Behandlung und Betreuung diskutiert wurden. An zwei Patienteninformationsveranstaltungen (2013 und 2015) waren insgesamt 107 Patienten anwesend, welche an unserer Erhebung teilnahmen. Die erhobenen Daten stellen die erste Untersuchung weltweit bezüglich der Auswirkung von CNO aus der Patientenperspektive dar.

7. Published scientific works

7.1 Bacterial Osteomyelitis or Nonbacterial Osteitis in Children: A Study Involving the German Surveillance Unit for Rare Diseases in Childhood

Pediatric Infectious Disease Journal

DOI: 10.1097/INF.0000000000001469

Published in print: Volume 36, Issue 5, pp. 451-456

First published online: May 2017

Impact Factor: 2.305

Presented at “4th International Meeting on Autoinflammatory Bone Diseases and Chronic Nonbacterial Osteomyelitis (CNO)” in Würzburg, Germany on 9 June 2017

Bacterial Osteomyelitis or Nonbacterial Osteitis in Children: A Study Involving the German Surveillance Unit for Rare Diseases in Childhood

Veit Grote, MD, MSc, Colen C. G. Silier, MBA, Agnes M. Voit, and Annette F. Jansson, MD

Background: Although bacterial osteomyelitis (BO) is a commonly recognized diagnosis in pediatrics, it is often difficult to distinguish from nonbacterial osteitis (NBO). The goal of our study was to distinguish between the 2 disease entities and better define NBO.

Methods: Using the German Surveillance Unit for Rare Diseases in Childhood (Erhebungseinheit für Seltene Paediatrische Erkrankungen in Deutschland), this prospective study during a 5-year period captured 657 patients at first diagnosis of either BO (n = 378) or NBO (n = 279) while analyzing epidemiologic, clinical and radiologic data.

Results: BO was reported in 1.2 per 100,000 children with a higher prevalence in younger male patients (58%), and NBO was reported in 0.45 per 100,000 children. BO patients tended to present with fevers (68%), elevated inflammation markers (82%) and local swelling (62%) but a shorter course of symptoms than NBO patients. NBO patients presented in good general health (86%) and were more likely to have multifocal lesions (66%). *Staphylococcus aureus* was the most prominent pathogen (83%), with only one methicillin-resistant *S. aureus* reported. Complications ranged from arthritis adjacent to the lesion to hyperostosis and vertebral fractures.

Conclusions: BO and NBO can be distinguished based on symptoms, associated diseases and inflammation markers. NBO should always be considered in pediatric patients presenting with bone lesions and pain, especially in young female patients presenting with good general health, minimal inflammation markers and multifocal lesions in the vertebrae, clavicle and sternum.

Key Words: bacterial osteomyelitis, nonbacterial osteitis, chronic, recurrent, multifocal osteomyelitis CRMO, SAPHO syndrome, epidemiology, Germany

(*Pediatr Infect Dis J* 2017;36:451–456)

Localized bone pain in children can be a diagnostic challenge. Bacterial osteomyelitis (BO) is a well-known differential diagnosis of localized bone pain, and nonbacterial osteitis (NBO) is an important differential diagnosis of BO.[1] BO in otherwise healthy children older than 12 months has been observed to be rare,[1,2] and we speculated previously that NBO might be as prevalent as BO in children of this age group.[3]

NBO is an autoinflammatory bone disorder accompanied or unaccompanied with associated diseases and can present at all skeletal sites and in all ages.[4–8] Recent data from mouse models and from patients support a genetic basis for NBO.[9–14] Its leading symptom is localized (bone) pain, with acute, chronic, unifocal and multifocal forms being described.[7] It is best known by its most severe manifestation, the chronic recurrent multifocal osteomyelitis (CRMO). By some authors, CRMO is regarded to be a pediatric subset of the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis).[15,16] The two disease entities share similar features to include "osteitis, unifocal or multifocal presentation, pustulosis, hyperostosis and a good general state of health without spiking fever, organomegaly, weight loss or fatigue".[7]

Disease entities with sterile osteitis as comorbidity such as chronic inflammatory bowel disease, severe acne and arthritis should be delineated as different entities, as they usually differ in diagnostic findings and therapeutic approaches. The most important differential diagnoses are malignancies (osteosarcoma, Ewing-sarcoma, leukemia, histiocytosis) and BO.[17,18]

In practice, BO is the most often considered differential diagnosis. It is a supposedly well-defined disease, which requires immediate attention and appropriate therapy.[19] However, a bacterial agent is usually found in only approximately 40% of patients without a bone biopsy and in about 60% of patients with a bone biopsy.[9,19–21] Patients experiencing a chronic course of the disease with the absence of a bacterial agent are often suspected of being infected by slowly growing organisms with fastidious growth requirements.[22] For instance, *Kingella kingae* has been recently described to be a major causative agent of BO in young children.[23,24]

There is no existing gold standard in the diagnosis for BO and NBO yet. Although the proof of a pathogen is usually diagnostic for BO, the diagnosis in all other cases usually is a diagnosis of exclusion. Because of a considerable overlap in clinical signs and laboratory parameters, the differentiation of bacterial and nonbacterial osteomyelitis can be difficult.

Histology is usually not revealing and can only be used to differentiate osteitis from other diagnoses like malignancies.[7,18] The problem lays within the inability, based on histology alone, to distinguish between the 2 entities. Both show unspecific changes with acute and/or chronic inflammation. These unspecific changes tend to be infiltrated with lymphocytes, plasma cells, histiocytes and neutrophil granulocytes, with neutrophils being the predominant cell type in early stages.[25–27] Macrophages were also abundant in the infiltrate, whereas in a small sample population, mild lymphocytic and granulocytic infiltrates were also found.[25] A NBO hallmark, however, includes the failure of monocytes to produce IL-10, which in turn results in an imbalance between proinflammatory and antiinflammatory cytokines.[27,28]

Also radiologically, NBO resembles BO.[3,29] Magnetic resonance imaging (MRI) diagnostics without further information may not be able to differentiate between osteomyelitis and other differential diagnoses as Langerhans cell histiocytosis, childhood hypophosphatasia, sarcoidosis[18,30–32] or malignancy. Conventional radiography can be very helpful concerning peripheral bone lesions and could be sufficient in the follow-up of unifocal lesions. In the case of expected bone destruction, however, especially in the vertebrae, MRI is the first choice, although computed tomography (CT) might be helpful in particular cases.[3,27] In patients with silent

Accepted for publication September 12, 2016.
From the Department of Rheumatology and Immunology, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University, Munich, Germany.
V.G. and C.C.G.S. contributed equally.
Funded by the foundation Kindness for Kids (Munich, Germany).
The authors have no conflicts of interest to disclose.
Address for correspondence: Veit Grote, MD, MSc, Department of Rheumatology and Immunology, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University, Munich 80539, Germany. E-mail: Veit.grote@med.uni-muenchen.de.

ISSN: 0891-3668/17/3605-0451
DOI: 10.1097/INF.0000000000001469

lesions and those assumed to be in clinical remission, lesions are often only discovered through whole-body MRI (WB-MRI). In case of clinical silent but radiologically active vertebral lesions, treatment should be initiated to avoid long-term damage.[33] However, it also might lead to overtreatment, as the importance of silent lesions is still under discussion.

National incidence data and a comparison between the clinical and diagnostic findings in these 2 differential diagnoses using the same assessment tools are still lacking at this point of time. We, therefore, assessed children with a newly diagnosed NBO or BO in a national survey using the same questionnaire to estimate the incidence rate and to better delineate both disease entities in otherwise healthy children. Being able to better differentiate BO and NBO cases should help to avoid unnecessary antibiotic therapies, diagnostic procedures and even surgeries.

METHODS

Study Design and Study Population

The study was conducted from July 1, 2006 through July 31, 2011 using the German Surveillance Unit for Rare Diseases in Childhood (Erhebungseinheit für Seltene Paediatrische Erkrankungen [ESPED] in Deutschland) in all pediatric hospitals and orthopedic departments nation-wide. Although newly diagnosed NBO cases were captured for the whole time period (5 years), BO cases were added from July 2009 onwards (2 years). Data from the first 1.5 years of surveillance were published previously.[3]

ESPED is a pediatric hospital surveillance system, which has been successfully used for many epidemiologic investigations of rare diseases in childhood.[34,35] The study population included all German children and adolescents >18 months and <18 years of age (13,134,352 children in 2011; German Federal Statistical Office, Germany, 2016).

The ESPED study center sent out report cards (mostly by email) to each pediatric hospital or department (about 350) and orthopedic department every month. There is an ESPED representative designated at each site to assist in collecting the data. The reports are returned with the number of cases observed, and for every reported patient, the coordinating center contacted the respective hospital physician to obtain a questionnaire with detailed clinical information.

We made a major effort to assure ascertainment by providing information at the beginning of the study about NBO to each ESPED representative, by providing the case definition on each report card, and, additionally, the study was announced in the German Pediatric Society's board journal. The journal additionally provided a timely review article on this issue, which was linked to the surveillance.

Case Definition

Centers were asked to report all children >18 months and <18 years of age who had been in the previous month newly diagnosed with SAPHO syndrome, NBO, CNO, CRMO, other inflammatory bone lesions or BO. The primary diagnosis of NBO or BO was made by the treating physician. Children with previous chronic illnesses, trauma, surgery and immunosuppression were excluded from the study, and no distinction was made between inpatients and outpatients. The children recruited for the study had to have at least one radiograph- or MRI-verified osteolytic/sclerotic or osteosclerotic bone lesion.

Data Assessment

Each report contained a detailed, 2-page questionnaire filled in by the treating physicians. After the addition of the BO cases in July 2009, minimal changes were introduced to the questionnaire. Every form contained the following information:

1. General information regarding birth date, gender, age at diagnosis, age at onset and associated diseases in first-degree relatives and in patient (palmoplantar pustulosis [PPP], severe acne, psoriasis, Crohn's disease or ulcerative colitis, NBO/CRMO, others)
2. Clinical presentation, including associated symptoms such as fever, lack of appetite, enlarged lymph nodes and weight loss
3. Laboratory values (C-reactive protein [CRP], blood count anomalies including anemia, leukocytosis, left shift, erythrocyte sedimentation rate [ESR, 1st hour], and antinuclear antibodies titers [ANA])
4. Findings using radiological tools (i.e., Scintigraphy, X-ray, MRI), with documentation of the number of lesions
5. Localization of bone lesions, with documentation of symmetry
6. Microbiologic results
7. Therapy before and after the diagnosis of NBO
8. Complications at first diagnosis (hyperostosis, fractures of the vertebral body or vertebra plana with [out] consecutive scoliosis/kyphosis >10°, other fractures and other complications).

To resolve unclear or incomplete information, the treating physician was contacted.

Data Management and Statistics

Good clinical condition was defined as absence of fever, absence of enlarged lymph nodes, absence of weight loss and a healthy appetite. CRP > 1 mg/dL, ESR > 15 mm/h and ANA titers > 1:80 were considered to be elevated.

Continuous variables were expressed as means with standard deviation or – if skewed – as medians with interquartile ranges (IQR: 25th, 75th percentiles). Pearson's χ^2 test was used for statistical comparison of categorical data. For the comparison of continuous variables, either a *t*-test or a Kruskal-Wallis rank test was used.

When it proved to be appropriate *P*-values below 0.05 were considered to be statistically significant.

All data management and analysis were performed using Stata 12.2 (StataCorp, Texas).

Ethics

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

RESULTS

General

During the 5-year survey, we received 939 reports from ESPED, of these 282 were without further information or were invalid. Reason for exclusion or invalidity were as follows: ESPED representatives did not respond (n = 64) or could not identify the reported case/reported cases twice (n = 73); age was not adequate (n = 75); chronic disease, trauma or absent radiologic lesion (n = 35); children had other diagnosis than originally thought (n = 29) to include: 6 BO (in the period where only NBO cases were assessed), 3 malignancies (2 ALL, 1 histiocytosis), 9 with arthritis (septic and others) and 11 children with other diagnosis, many unspecified, like aseptic bone necrosis, bone cysts and osteoid osteoma. Questionnaires of 6 children were incomplete so that they could not be used for further analysis. Overall, we had data from 657 children, 378 diagnosed with BO and 279 with NBO. The majority of the reports (87%) were from pediatric hospitals and wards; 61 (16%) of BO patients were from surgical departments and 18 (6%) of NBO patients from pediatric orthopedic departments.

Epidemiology

There were approximately 50–60 NBO cases and about 150 BO cases reported per year; thus resulting in an average of 0.45 pediatric NBO cases per 100,000 children under 18 years of age and an average of 1.2 BO cases per 100,000. Within the German states, several had incidences around 1/100,000 and others with markedly lower incidences, whereas BO incidence rates were more evenly distributed.

Clinical Presentation

Patients with BO were significantly younger than those with NBO: 8.7 (SD 4.2) versus 11.0 (SD 3.2) years ($P < 0.001$). Only 8 (3%) NBO patients were between 18 and 24 months of age and 14 (5%) were under 5 years of age, but there were 49 children (13%) between 18 and 24 months and 90 children (24%) under 5 years old diagnosed with BO. There was preponderance of girls in NBO (64%) and of boys (58%) in BO patients ($P < 0.001$) (Table 1). Interestingly, girls were generally younger, especially in the BO group (data not shown).

NBO patients were, in 86% of the cases, in good general health and very few presented with typical inflammatory markers such as a low grade fever (21%), redness (21%) and peripheral swelling (53%). This is in stark contrast to the BO cases where only 63% of patients were in good health, 68% presented with fever, 43% with local redness and 62% with localized swelling (Table 2).

Diagnostics

In almost all children, 96% (629/657), MRI and in about 75%, conventional X-ray was conducted. A skeletal scintigraphy was performed in 15% (55/377) of BO and 50% (139/278) of NBO children ($P < 0.001$). WB-MRI was applied only once in the BO cases in comparison to 35/94 (37%) NBO cases, and from the NBO patient pool only 6 (6/35) (17%) had unifocal lesions and 83% (29/35) presented with multifocal lesions.

Overall it was reported that in 333/377 (88%) BO and 161/279 (58%) NBO patients microbiological testing was completed, blood cultures in 71% and 35% of BO and NBO patients, respectively. In only 48% (29/61) of children with BO admitted to a surgical ward was a blood culture done. A biopsy, on the contrary, was more often performed in patients diagnosed with NBO, 50% (140/278), than those with suspected BO, 32% (119/376), and was most often performed in patients on a surgical ward (64%).

A pathogen was found in 164 children (43%) with BO, less often in girls ($P < 0.001$) (Table 2). Blood cultures were found to be positive in 38% of the girls and in 48% of the boys. If a biopsy was performed taking in to account the age differences, there was a significant increase in the positive bone biopsies in the age category 7–12 years old, up to 64%, in comparison to the much younger and much older pediatric patients. A gender difference was also observed, in that girls received more often a biopsy in both NBO and BO cases (151/333 − 45%) than boys (102/314 − 32%) ($P = 0.001$).

Isolated pathogens were *Staphylococcus aureus* (136/164 − 83%), *S. pyogenes* (6.1%), bacteria of the skin flora (5.5%) and others (5.5%), such as *Pseudomonas aeruginosa*, *Salmonella* sp., *Mycobacteria*, *K. kingae*, *Propionibacterium acnes* and *Peptostreptococcus* sp. Only one methicillin-resistant *S. aureus* (MRSA) was reported.

TABLE 1. Basic Characteristics of 378 Children With Bacterial Osteomyelitis and 279 Children With Nonbacterial Osteitis

	Bacterial Osteomyelitis N = 378		Nonbacterial Osteitis N = 279	
Number of lesions	1 N = 300 (79%)	≥2 N = 78 (21%)	1 N = 96 (34%)	≥2 N = 183 (66%)
Girls	42%	42%	62%	65%
Bone biopsy	28%	16%	36%	31%
Mean age in years (SD)	8.7	9.4	11.1 (3.1)	10.9 (3.2)
First symptoms >4 wk	7.75%	9.5%	51%	69%
ESR median (25%–75%)	45 (26–72)		26 (12–50)	
CRP median (25%–75%)	5.05 (1.59–11.5)		0.6 (0–2.57)	

TABLE 2. Clinical Features and Laboratory Values

	BO N = 378			
Characteristics	No pathogen N = 214 (57%)	With pathogen N = 164 (43%)	NBO N = 279	*P*-value BO vs. NBO
CRP > 1 mg/dL	78% (166)	87% (141)	41% (111)	$P < 0.001$
ESR > 30 mm/h	64% (128)	69% (93)	44% (109)	$P < 0.001$
Fever	62% (132)	75% (122)	21% (57)	$P < 0.001$
Local swelling	62% (130)	62% (101)	53% (70)	$P = 0.079$
Local redness	42% (88)	45% (72)	21% (28)	$P < 0.001$
CRP > 5 mg/dL	40% (84)	64% (103)	12% (32)	$P < 0.001$
Leukocytosis	18% (38)	27% (44)	8% (20)	$P < 0.001$
Left shift	14% (29)	30% (49)	4% (11)	$P < 0.001$
Anemia	15% (33)	18% (29)	7% (18)	$P = 0.001$
Pustulosis, acne or psoriasis	0%	0%	13% (35)	$P < 0.001$

Number of Lesions and Localization

The median number of lesions was 1 in BO and 2 in NBO with 79% and 34%, respectively. Up to 8 lesions were detected in BO patients and up to 17 lesions in NBO patients, with 30% of the NBO patients having more than 3 lesions. One child diagnosed with BO presented without an isolated pathogen and showed multiple lesions including those in vertebral bodies. The distribution of lesions can be found in Figure 1. Most lesions were in the metaphyses of long bones, pelvis and the lower extremities and feet. NBO children showed a higher than proportional number of lesions in the mandible, upper extremities, clavicle, sternum and vertebral bodies.

Approximately 25% of the children diagnosed with NBO were treated with antibiotics before diagnosis. The median duration of antibiotic treatment for patients diagnosed with BO was between 15 days and 6 weeks. Forty one percent of NBO patients received antibiotic therapy between 15 days and 6 weeks and 21% were treated longer than 6 weeks. Clindamycin (39% of BO cases) and cephalosporin of the 2nd (31% of BO cases) and 3rd generations (13% of BO cases) were the preferred choice.

Complications reported in BO cases included para lesion arthritis, abscesses, myositis, hyperostosis, vertebral fractures. In BO children, approximately 25% reported an arthritis that developed next to the lesion, far outweighing other complications. In NBO children, the most frequent complications noted were hyperostosis (8%) and vertebral fractures (7%).

DISCUSSION

To our knowledge, this is the first prospective epidemiologic investigation concerning the incidence of nonbacterial

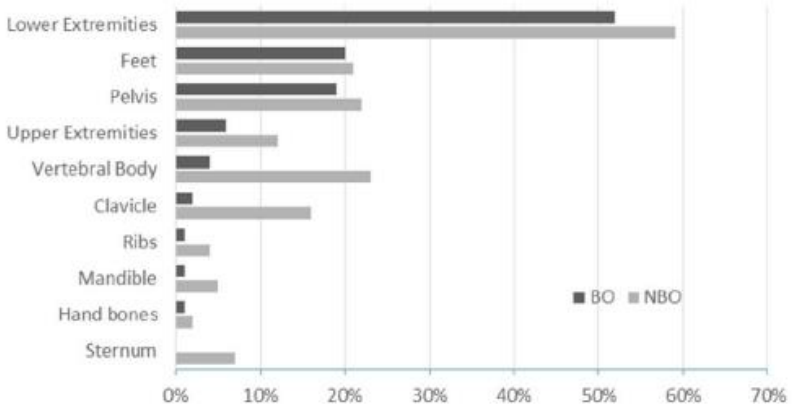

FIGURE 1. Distribution of lesions in bacterial osteomyelitis and nonbacterial osteitis.

osteomyelitis, which was expanded to include the important differential diagnosis of BO.

In Germany, the reported incidence of BO in children is estimated around 1.2/100.000 and has a 3 times higher incidence than nonbacterial osteomyelitis. However, the estimate of the BO incidence is considerably lower than those found in other studies like in Norway, where the incidence was estimated at 13/100,000 children.[36] However, one has to consider that we only included healthy children and excluded children below 1½ years of age when the incidence is highest. As most practitioners are much better acquainted with BO, we expected that NBO might substantially be underdiagnosed. The observed regional differences in incidence point to the possibility that the number of BO and NBO cases might be similar. In our own experience, the incidence of BO and NBO seems to be comparable in otherwise healthy children, apart from infancy.

In this prospective analysis of children newly diagnosed with NBO or BO, our findings emphasize that the clinical presentation of NBO patients and BO patients tend to be significantly different. Children with BO are significantly younger than those with NBO, are more frequently boys and present with a shorter clinical history. They more often present with fever, local redness, elevated inflammation parameters and leukocytosis with left shift, especially when a bacterial agent is found. Concerning the number of lesions, BO patients showed most frequently one lesion, as expected. Nevertheless, more than one lesion was reported quite frequently and, interestingly, half of them were girls without a proven bacterial agent. NBO patients are more frequently girls, 1–2 years older and with a clinical history longer than 4 weeks. Blood count was normal in most NBO patients. Associated diseases such as PPP, acne or psoriasis were reported only rarely. These findings are consistent with the literature concerning BO and NBO.[10,26,37,38]

Radiologic diagnostic tools play an important role in the diagnosis of both NBO and BO.[5,33,39] Magnet resonance imaging (MRI) is the most often used in both entities, followed by conventional radiographs and bone scintigraphy. Between 2006 and 2011, WB-MRI was not a diagnostic standard as it is recommended today, although it was commonly available in university hospitals. In a recent study, only 26 patients from 53 presented with multifocal lesion complaints; however, the WB-MRI detected multifocal lesions in 52 of the 53 patients (so-called silent lesions), including 75% with bilateral lesions.[32,33]

Although MRI is highly sensitive, it is not very specific, resulting in difficulty distinguishing between NBO and BO.[29] Microbiologic testing was done in nearly all BO patients and in half of the NBO patients. On the one hand, blood cultures were not as often done on surgical wards compared with pediatric wards; on the other hand, bone biopsies were more often done there. Bone biopsies were performed more frequently in NBO patients and in girls. Simultaneous histologic investigations for exclusion of other differential diagnoses might be the reason for these procedures. As expected, bone biopsies in BO were more frequently positive than blood cultures.[20,40,41] Interestingly, blood cultures were found to be more often positive in boys than in girls, and the same is true for bone biopsies, which were positive in about two thirds of BO cases found in boys. These observations may be another hint that NBO, in our collective, is underdiagnosed (or BO over diagnosed). Although bone biopsies were much more commonly performed in girls than in boys, the cultures might be negative in girls, as there might be no pathogen.

The most common pathogen in BO patients was *S. aureus* at 83%. In the United States, the most common pathogen is *S. aureus* (80%) as well,[42] but where a large portion of pathogens reported are MRSA (40%–50% of *S. aureus* osteomyelitis incidences),[43] which has a distinct more serious course of disease and requires much longer therapy.[19,44,45] The antibiotic recommendations from Peltola and Paakkonen[19] may not be as useful in the USA in comparison with Europe, which has rarely an osteomyelitis of MRSA origin; in our case 0.26%. In addition to antibiotic treatment for MRSA, supplementary medications need to be given, primarily nonsteroidal antiinflammatory drugs (NSAIDs) to prevent deep-vein thrombosis and septic pulmonary emboli, both of which are characteristic in MRSA osteomyelitis cases.[19] If polymerase chain reaction (PCR) is conducted or if the sample is grown on a slow-growing medium, the yield for a positive proof of pathogen is much higher.[46] Recent research shows that in the age group ≤4 years of age, *K. kingae* is taking on an ever increasing role, and this pathogen is often overlooked when doing the routine blood, synovial fluid and bone exudate cultures, but with the quantitative polymerase chain reaction (qPCR) assays, the yield for positive proof of pathogen was significantly higher.[47] In our study we asked whether PCR technique and mycobacteria diagnostics were performed, and in less than 10% of the cases, such diagnostics were performed.

A large number of NBO patients were treated with antibiotics before the final diagnosis was rendered, and despite the final diagnosis of NBO, still a significant number was continued on antibiotic therapy. This leads to the conclusion that there is still uncertainty in the pediatric medical community regarding the NBO

TABLE 3. BO vs. NBO

	Bacterial Osteomyelitis (BO)	Nonbacterial Osteitis (NBO)
Incidence	1.2 (–5)/100.000 significantly younger patients	0.45 (1)/100.000
Bacterial agent	*Staphylococcus aureus* (83%)	None
Clinical presentation	Short course of disease, fever, local redness, high inflammation markers	Most in good health
Localization	Monofocal	Multifocal (symmetrical), vertebral, clavicle, sternum, mandible foci
Complications	Arthritis adjacent to lesion, abscesses, myositis	Vertebral lesions, hyperostosis

diagnosis and the proper treatment plan for NBO once recognized. A step-wise guide for the therapeutic treatment of NBO was developed to alleviate pain and prevent further destruction.[17] Regarding treatment of BO, antibiotics are CRP and ESR guided as recommended by Peltola et al,[48] but still there is a wide range of variation to be found, as we also see in our population.

Limitations

The estimated prevalence is certainly an underestimation. Generally, ESPED studies are encouraged to use a second source for case ascertainment to estimate the underreporting rate. However, an appropriate second source was not found for our disease entities. Thus, the true rate of underreporting for the present study is not known. Based on other studies, underreporting can be as low as 20% for diseases such as diabetes type 1[49] or invasive pneumococcal disease,[50] or as high as 40% for Kawasaki disease[51] or multiple sclerosis.[52] Furthermore, we cannot exclude the possibility that underreporting was affecting both entities, NBO and BO to a different extent. As the diagnosis of NBO is more likely delayed and the diagnosis is less well acknowledged, we assume that underreporting is more likely for NBO cases. Furthermore, there are indications that a proportion of reported BO cases might have been NBO cases.

Because there is no standardized diagnostic procedure for NBO, it is often a diagnosis of exclusion and only reflects current practice. Patients may have been overlooked and all facets of the disease may have not been captured. Reports in ESPED are typically filed within approximately 6 weeks after the diagnosis is rendered,[53] leaving usually enough time to exclude typical differential diagnoses that have to be considered. This is also reflected in that after the initial report of NBO, some cases were later relabeled to be leukemia or other typical differential diagnosis.

We cannot rule out that the self-reported fevers were due to intercurrent infections, which might have triggered first NBO manifestation. Furthermore, in our study we simply asked whether the patient had a fever, failing to define the term and failing to document who measured the fever, although others have reported similar numbers regarding NBO patients presenting with fever.

Based on our study, we were able to differentiate NBO versus BO with the following traits (Table 3). Although previous diagnostic criteria for NBO have been published, NBO cases are still poorly recognized but should always be taken in to consideration with pediatric patients presenting with bone lesions and pain.

ACKNOWLEDGMENTS

The authors thank their colleagues at the German Surveillance Unit for Rare Diseases in Childhood (Erhebungseinheit für Seltene Paediatrische Erkrankungen [ESPED] in Deutschland) and all of the reporting pediatricians for their support and assistance in the collection of data for this study. The study was supported by the Kindness for Kids foundation.

REFERENCES

1. Jansson AF, Müller TH, Gliera L, et al. Clinical score for nonbacterial osteitis in children and adults. *Arthritis Rheum*. 2009;60:1152–1159.
2. Schnabel A, Berner R, Hedrich CM. Chronic nonbacterial and bacterial osteomyelitis. *Monatsschrift Kinderheilkunde*. 2016;164:505–519.
3. Jansson AF, Grote V; ESPED Study Group. Nonbacterial osteitis in children: data of a German Incidence Surveillance Study. *Acta Paediatr*. 2011;100:1150–1157.
4. Ferguson PJ, El-Shanti HI. Autoinflammatory bone disorders. *Curr Opin Rheumatol*. 2007;19:492–498.
5. Girschick HJ, Zimmer C, Klaus G, et al. Chronic recurrent multifocal osteomyelitis: what is it and how should it be treated? *Nat Clin Pract Rheumatol*. 2007;3:733–738.
6. El-Shanti HI, Ferguson PJ. Chronic recurrent multifocal osteomyelitis: a concise review and genetic update. *Clin Orthop Relat Res*. 2007;462:11–19.
7. Jansson A, Renner ED, Ramser J, et al. Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. *Rheumatology (Oxford)*. 2007;46:154–160.
8. King SM, Laxer RM, Manson D, et al. Chronic recurrent multifocal osteomyelitis: a noninfectious inflammatory process. *Pediatr Infect Dis J*. 1987;6:907–911.
9. Jansson A, Golla A, Schneider K, et al. Chronic recurrent multifocal osteomyelitis (CRMO). Review and first results of a genetic study. *Monatsschrift Kinderheilkunde*. 2002;150:477–489.
10. Golla A, Jansson A, Ramser J, et al. Chronic recurrent multifocal osteomyelitis (CRMO): evidence for a susceptibility gene located on chromosome 18q21.3-18q22. *Eur J Hum Genet*. 2002;10:217–221.
11. Majeed HA, Kalaawi M, Mohanty D, et al. Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet syndrome in two siblings. *J Pediatr*. 1989;115(5 Pt 1):730–734.
12. Aksentijevich I, Masters SL, Ferguson PJ, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *N Engl J Med*. 2009;360:2426–2437.
13. Cassel SL, Janczy JR, Bing X, et al. Inflammasome-independent IL-1β mediates autoinflammatory disease in Pstpip2-deficient mice. *Proc Natl Acad Sci USA*. 2014;111:1072–1077.
14. Ferguson PJ, Laxer RM. New discoveries in CRMO: IL-1β, the neutrophil, and the microbiome implicated in disease pathogenesis in Pstpip2-deficient mice. *Semin Immunopathol*. 2015;37:407–412.
15. Kahn MF. Current status of the SAPHO syndrome. *Presse Med*. 1995;24:338–340.
16. Anderson SE, Heini P, Sauvain MJ, et al. Imaging of chronic recurrent multifocal osteomyelitis of childhood first presenting with isolated primary spinal involvement. *Skeletal Radiol*. 2003;32:328–336.
17. Jansson AF, Borte M, Hospach A, et al. Diagnostik und Therapie der nichtbakteriellen Osteitis. *Monatsschrift Kinderheilkunde*. 2014;162:539–545.
18. Girschick HJ, Mornet E, Beer M, et al. Chronic multifocal non-bacterial osteomyelitis in hypophosphatasia mimicking malignancy. *BMC Pediatr*. 2007;7:3.
19. Peltola H, Pääkkönen M. Acute osteomyelitis in children. *N Engl J Med*. 2014;370:352–360.
20. De Boeck H. Osteomyelitis and septic arthritis in children. *Acta Orthop Belg*. 2005;71:505–515.

21. Kaplan SL. Osteomyelitis in children. *Infect Dis Clin North Am*. 2005;19:787–797, vii.
22. Schultz C, Holterhus PM, Seidel A, et al. Chronic recurrent multifocal osteomyelitis in children. *Pediatr Infect Dis J*. 1999;18:1008–1013.
23. Chometon S, Benito Y, Chaker M, et al. Specific real-time polymerase chain reaction places Kingella kingae as the most common cause of osteoarticular infections in young children. *Pediatr Infect Dis J*. 2007;26:377–381.
24. Ferroni A. Epidemiology and bacteriological diagnosis of paediatric acute osteoarticular infections. *Arch Pediatr*. 2007;14(suppl 2):S91–S96.
25. Girschick HJ, Huppertz HI, Harmsen D, et al. Chronic recurrent multifocal osteomyelitis in children: diagnostic value of histopathology and microbial testing. *Hum Pathol*. 1999;30:59–65.
26. Jansson A, Borte M, Boschow G, et al. Non-bacterial osteitis in children and adults. Consensus statement of the 8th Worlitz Expert Meeting 2005, for the German Society for Paediatric and Adolescent Rheumatology. *Monatsschrift Kinderheilkunde*. 2006;154:831–833.
27. Hedrich CM, Hahn G, Girschick HJ, et al. A clinical and pathomechanistic profile of chronic nonbacterial osteomyelitis/chronic recurrent multifocal osteomyelitis and challenges facing the field. *Expert Rev Clin Immunol*. 2013;9:845–854.
28. Hofmann SR, Kubasch AS, Ioannidis C, et al. Altered expression of IL-10 family cytokines in monocytes from CRMO patients result in enhanced IL-1β expression and release. *Clin Immunol*. 2015;161:300–307.
29. Khanna G, Sato TS, Ferguson P. Imaging of chronic recurrent multifocal osteomyelitis. *Radiographics*. 2009;29:1159–1177.
30. Zimmerli W. Clinical practice. Vertebral osteomyelitis. *N Engl J Med*. 2010;362:1022–1029.
31. Whyte MP, Wenkert D, McAlister WH, et al. Chronic recurrent multifocal osteomyelitis mimicked in childhood hypophosphatasia. *J Bone Miner Res*. 2009;24:1493–1505.
32. von Kalle T, Heim N, Hospach T, et al. Typical patterns of bone involvement in whole-body MRI of patients with chronic recurrent multifocal osteomyelitis (CRMO). *Rofo*. 2013;185:655–661.
33. Voit AM, Arnoldi AP, Douis H, et al. Whole-body magnetic resonance imaging in chronic recurrent multifocal osteomyelitis: clinical long term assessment may underestimate activity. *J Rheumatol*. 2015;42:1455–1462.
34. von Kries R, Heinrich B, Hermann M. German paediatric surveillance unit (ESPED). *Monatsschr Kinderheilk*. 2001;149:1191–1193.
35. Grenier D, Elliott EJ, Zurynski Y, et al. Beyond counting cases: public health impacts of national Paediatric Surveillance Units. *Arch Dis Child*. 2007;92:527–533.
36. Riise ØR, Kirkhus E, Handeland KS, et al. Childhood osteomyelitis-incidence and differentiation from other acute onset musculoskeletal features in a population-based study. *BMC Pediatr*. 2008;8:45.
37. Girschick HJ, Raab P, Surbaum S, et al. Chronic non-bacterial osteomyelitis in children. *Ann Rheum Dis*. 2005;64:279–285.
38. Carr AJ, Cole WG, Roberton DM, et al. Chronic multifocal osteomyelitis. *J Bone Joint Surg Br*. 1993;75:582–591.
39. Jansson A. Nichtbakterielle Osteitiden. Aktueller Wissensstand und Therapieoptionen. *Arthritis und Rheuma*. 2013;33:371–376.
40. Fritz JM, McDonald JR. Osteomyelitis: approach to diagnosis and treatment. *Phys Sportsmed*. 2008;36:nihpa116823.
41. Saavedra-Lozano J, Mejias A, Ahmad N, et al. Changing trends in acute osteomyelitis in children: impact of methicillin-resistant Staphylococcus aureus infections. *J Pediatr Orthop*. 2008;28: 569–575.
42. Ellington JK, Harris M, Hudson MC, et al. Intracellular Staphylococcus aureus and antibiotic resistance: implications for treatment of staphylococcal osteomyelitis. *J Orthop Res*. 2006;24:87–93.
43. Narasimhan R. Pediatric osteoarticular infections. *Indian J Orthop*. 2013;47:321–321.
44. Harik NS, Smeltzer MS. Management of acute hematogenous osteomyelitis in children. *Expert Rev Anti Infect Ther*. 2010;8:175–181.
45. Martínez-Aguilar G, Avalos-Mishaan A, Hulten K, et al. Community-acquired, methicillin-resistant and methicillin-susceptible Staphylococcus aureus musculoskeletal infections in children. *Pediatr Infect Dis J*. 2004;23:701–706.
46. Ilharreborde B, Bidet P, Lorrot M, et al. New real-time PCR-based method for Kingella kingae DNA detection: application to samples collected from 89 children with acute arthritis. *J Clin Microbiol*. 2009;47:1837–1841.
47. Ceroni D, Cherkaoui A, Combescure C, et al. Differentiating osteoarticular infections caused by Kingella kingae from those due to typical pathogens in young children. *Pediatr Infect Dis J*. 2011;30:906–909.
48. Peltola H, Pääkkönen M, Kallio P, et al.; Osteomyelitis-Septic Arthritis Study Group. Short-versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: prospective, randomized trial on 131 culture-positive cases. *Pediatr Infect Dis J*. 2010;29:1123–1128.
49. Rosenbauer J, Icks A, Giani G. Incidence and prevalence of childhood type 1 diabetes mellitus in Germany–model-based national estimates. *J Pediatr Endocrinol Metab*. 2002;15:1497–1504.
50. Rückinger S, van der Linden M, Reinert RR, et al. Reduction in the incidence of invasive pneumococcal disease after general vaccination with 7-valent pneumococcal conjugate vaccine in Germany. *Vaccine*. 2009;27:4136–4141.
51. Jakob A, Whelan J, Kordecki M, et al. Kawasaki disease in Germany: a prospective, population-based study adjusted for underreporting. *Pediatr Infect Dis J*. 2016;35:129–134.
52. Reinhardt K, Weiss S, Rosenbauer J, et al. Multiple sclerosis in children and adolescents: incidence and clinical picture - new insights from the nationwide German surveillance (2009-2011). *Eur J Neurol*. 2014;21:654–659.
53. Liese JG, Grote V, Rosenfeld E, et al.; ESPED Varicella Study Group. The burden of varicella complications before the introduction of routine varicella vaccination in Germany. *Pediatr Infect Dis J*. 2008;27:119–124.

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

British Medical Journal Open

DOI: 10.1136/bmjopen-2017-017599

First published online: 26 December 2017

Impact Factor: 2.413

Presented at “4th International Meeting on Autoinflammatory Bone Diseases and Chronic Nonbacterial Osteomyelitis (CNO)” in Würzburg, Germany on 9 June 2017

BMJ Open

Chronic non-bacterial osteitis from the patient perspective: a health services research through data collected from patient conferences

Colen Cooper Gore Silier,[1] Justina Greschik,[2] Susanne Gesell,[2] Veit Grote,[1] Annette F Jansson[1]

To cite: Silier CCG, Greschik J, Gesell S, *et al*. Chronic non-bacterial osteitis from the patient perspective: a health services research through data collected from patient conferences. *BMJ Open* 2017;**7**:e017599. doi:10.1136/bmjopen-2017-017599

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-017599).

Received 9 May 2017
Revised 8 September 2017
Accepted 16 October 2017

[1]Department of Rheumatology and Immunology, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University, Munich, Germany
[2]Department of Orthopaedic Surgery, Physical Medicine and Rehabilitation, Ludwig-Maximilians-University, Munich, Germany

Correspondence to
Mrs. Colen Cooper Gore Silier; colen.silier@campus.lmu.de, colen.silier@gmail.com

ABSTRACT

Objective Although chronic non-bacterial osteitis (CNO) is an ever-increasingly recognised illness in the paediatric community and the adult healthcare 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 Ludwig-Maximilians-University (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 were assessed regarding CNO to include epidemiological data, 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 women and 27% being men. 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 that non-bacterial osteitis (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 highlights a need for better psychosocial support such as guidance counselling or psychological support due to three-quarters of patients receiving no such said support.

Strengths and limitations of this study

- This is the first study highlighting the impact of chronic non-bacterial osteitis (CNO) from the patient perspective.
- A relatively large patient population for CNO was analysed, which has an incidence rate of 0.45/100 000.
- The explicitness of the needs of patients with CNO was examined, while stressing the psychosocial and socioeconomic effect of a chronic illness, such as CNO.
- The patient data reflect 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.

INTRODUCTION

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 non-bacterial bone lesions are of an autoinflammatory origin. Furthermore, due to the ever-increasing use of MRI, bone lesions are increasingly being found in healthy children and adults alike.[1 2]

Non-bacterial 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 localised 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]

Because chronic non-bacterial 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 paediatric population studied was

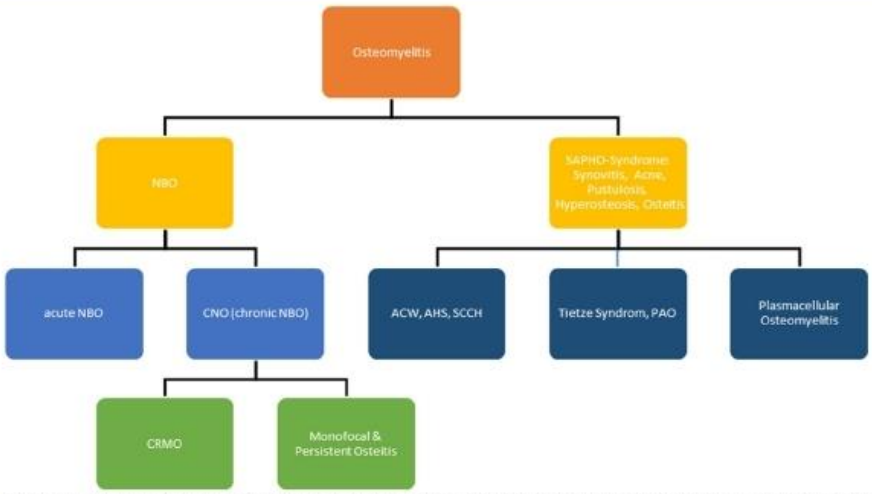

Figure 1 Terminology of NBO. ACW, Anterior Chest Wall Syndrome; AHS, Acquired Hyperostosis Syndrome; CRMO, chronic recurrent multifocal osteomyelitis; NBO, non-bacterial osteitis; PAO, Pustulotic arthro-osteitis; SCCH, Sternocostoclavicular Hyperostosis.

not discriminated against, but they did have more difficulty with educational and vocational opportunities.[10] Chronic illness, however, does affect the patient and the family and support structure; it has been suggested that the adaptation of the patient and the family is closely linked.[11 12]

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 (information-wise and 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 Munich hosted an NBO information day designed for patients, both paediatric and adults, and their relatives. The event was advertised through private practice paediatricians, private practice rheumatologists, websites dedicated to paediatric rheumatology and university clinics throughout Germany. Patients and their families were asked to register 2weeks in advance, and on 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 13 patients which visited both conference days, and therefore did not repeat the survey. However, 14 patients did not respond due to appearing without prior registration or registering after the 2-week deadline.

The patient survey consisted of 285 variables/patient and captured important aspects of NBO to include: epidemiological data, age at diagnosis, family history, 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 Analogue Scale (VAS) of 1–10, with 10 being maximum pain.

Statistical analysis

All data management and analysis were performed using IBM SPSS Statistics V.23. Continuous variables were expressed in means with SD or—if skewed—as medians with IQRs (IQR: 25th–75th percentiles). The Student's t-test was used to compare quantitative data with P values below 0.05 considered to be statistically significant. The Pearson's χ^2 test was used for differences of categorical data.

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 were

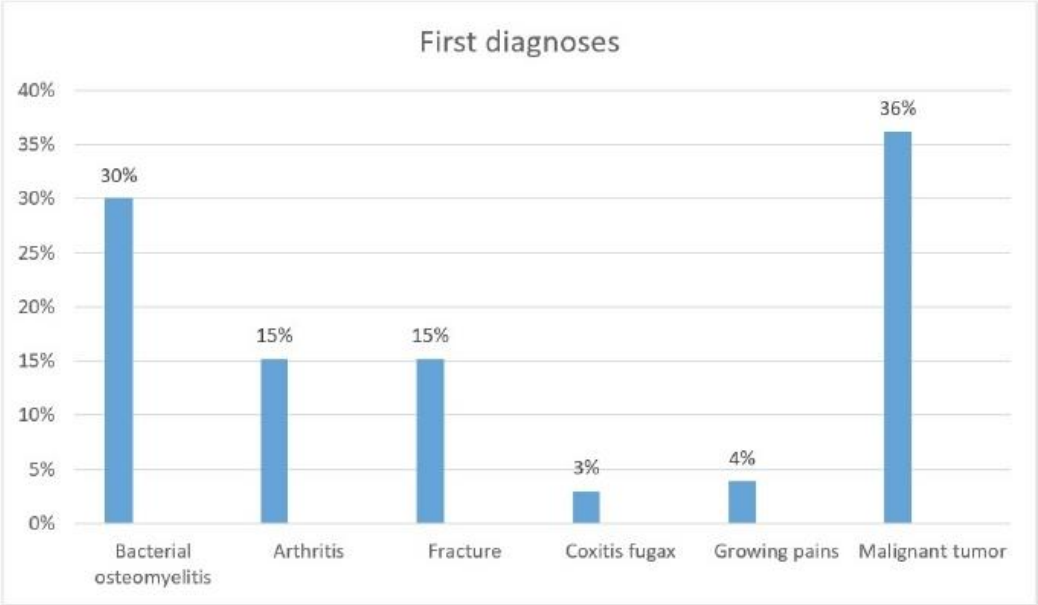

Figure 2 First diagnoses.

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 to 63 years, with an average of age of 16.7 years (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 the time of diagnosis was 10.5 years (IQR: 8.5–13.5), with 86% reporting onset of symptoms between the ages of 6 and 15 years.

Clinical presentation

Our patients were initially referred to a variety of physicians including paediatricians, general practitioners, orthopaedic surgeons, rheumatologists (both paediatric 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 tumours/malignant disease, patients listed—unknown: 18%, Ewing's sarcoma: 6%, leukaemia: 3% and Langerhans cell histiocytosis: 2%.

Paediatric rheumatologists diagnosed in 57% of the CNO cases present. Overall rheumatologists and paediatricians 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 CNO.

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%). At initial presentation, 20% rated pain on a VAS (0–10) as an 8, 23% at a 9 and 23% at a 10. 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 (C reactive protein (CRP) and erythrocyte sedimentation rate (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,

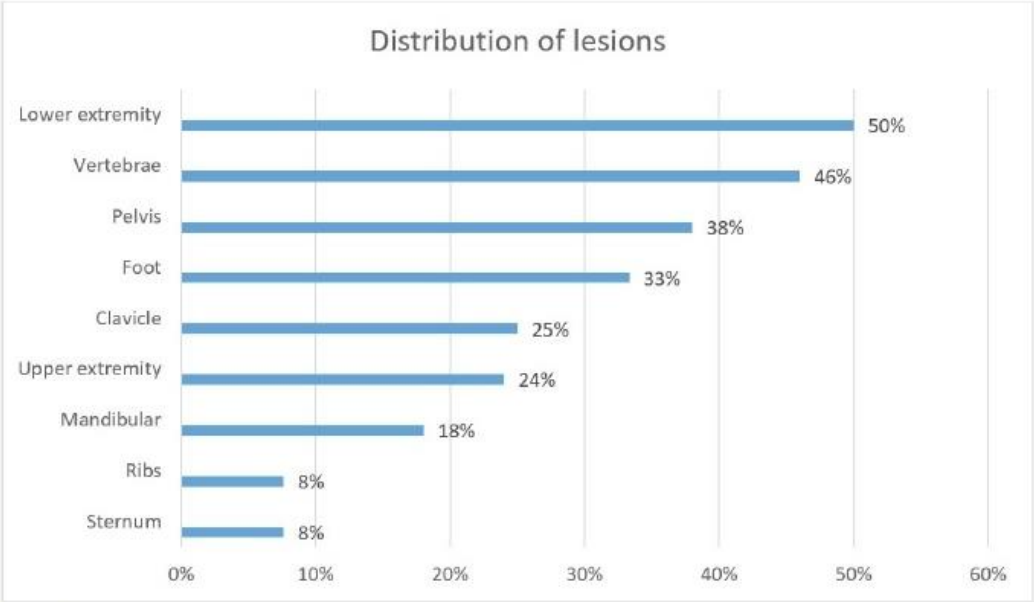

Figure 3 Distribution of lesions in chronic non-bacterial osteitis.

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 bullying, and familial and school problems.

Number of lesions and localisations

At first manifestation, 20% reported one lesion, 50% reported two to five lesions and 27% reported more than five 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.

Treatment

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

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (61%), naproxen (50%), indometacin (23%) and 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 per cent of all patients answered the question, what NSAID provided the best relief of symptoms. Sixty-five per cent 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 who 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.

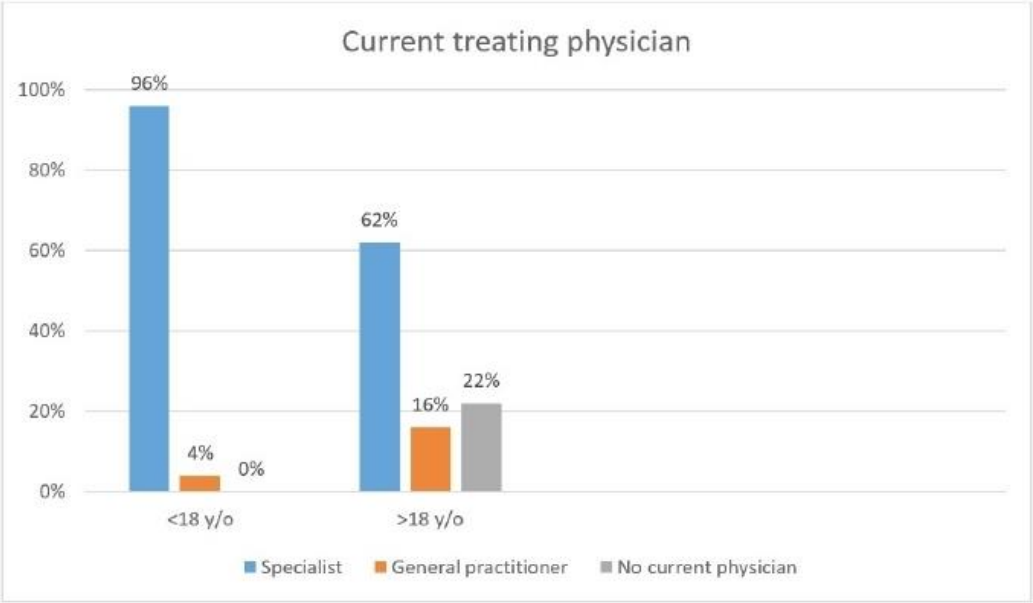

Figure 4 Current treating physician for chronic non-bacterial osteitis.

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 (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 paediatric population, 96% were being treated by a paediatric rheumatologist or an orthopaedic surgeon, whereas with the adult population only 62% were being treated by a specialist (defined by a rheumatologist or an orthopaedic surgeon) and 16% by a general practitioner (figure 4.) From the 32 patients>18 years old, 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 and 28 years.

The distance to the treating physician varied widely; however, 45% had to travel 25 km or less and 86% travelled 100 km or less, and one patient travelled up to 300 km to a specialist. Patients were asked how well cared for do they feel from their specialists, and on a VAS from 1 to 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. CNO affected close family members, and friendships, school and work life. From patients which reported difficulty in friendships, 56% described, at minimum, a partial negative effect on relationships. In comparison, however, due to this disorder, 79% reported that CNO has negatively affected either school or work.

Seventy-five per cent of all patients received no type of psychosocial guidance, although 49% would have liked to have consultation with a guidance counsellor or psychologist. These numbers correlate with the 51% of patients and family members which felt uninformed regarding the NBO 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

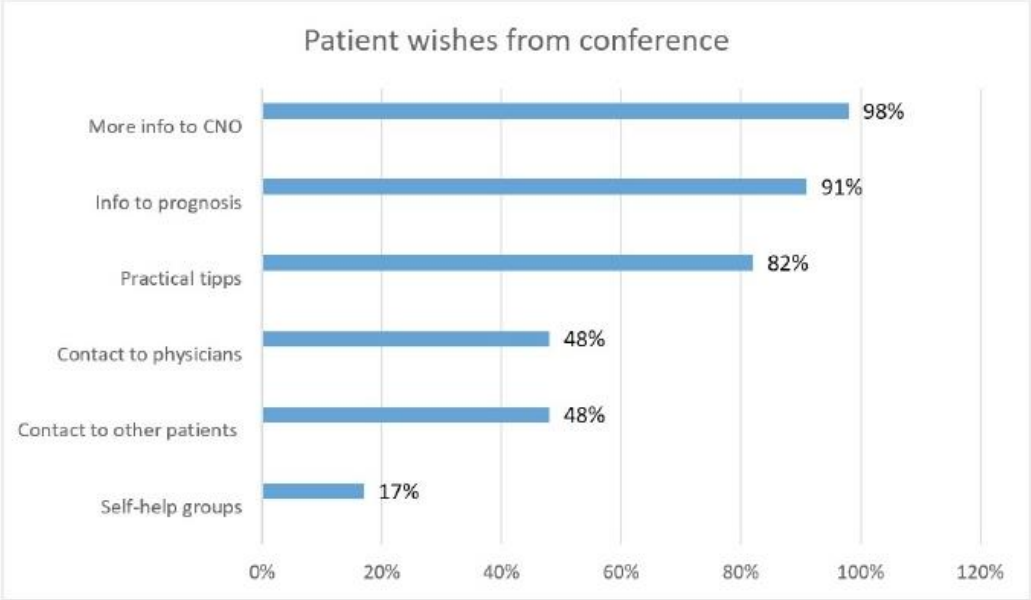

Figure 5 Patient wishes from CNO conference. CNO, chronic non-bacterial osteitis; info, information; NBO, non-bacterial osteitis.

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.)

Other topics of interest ranged from typical side effects of medications to pregnancy to nutrition and alternative therapy options. Many of the paediatric 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, localisation of lesions, therapy plan, inflammation parameters and imagery used (data not shown) is comparable to previous scientific literature.[6 13–17] 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 the 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 5 years. These lag times lead to patient stress, both physical and emotional, and 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 paediatric 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 paediatrician.

Circa 20% of patients reported a unifocal lesion. However, from the 21 patients reporting 1 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 recognised. A stepwise 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.[18] Currently, there are national and international efforts to establish validated treatment protocols for CNO.

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

Psychosocial and socioeconomic 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, pharmacological therapy and 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 counsellor 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 affects especially young patients, and other family members and members of the support structure. In Germany, unfortunately, interdisciplinary care can only be offered in specialised medical centres.

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 and 28 years old. This highlights the need for a better transition model from paediatric 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.[19–21] In Germany, a transition model for patients with chronic rheumatic illnesses was developed.[19 22] This model helps patients coordinate care transitioning from the paediatric 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 18.

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 drive 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 socioeconomic 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, 0.45/100 000,[13] 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 or pain levels. 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 were very comparable with previous research.

Contributors AFJ developed the idea for the study. CCGS and AFJ were involved in the study conception, preliminary literature review and design of the search strategy and the study protocol. SG and JG designed the initial database to record study inputs and completed initial data input. CCGS concluded data input and drafted the report, which was critically reviewed and approved by all authors. CCGS and VG were involved in screening and data extraction of papers. CCGS, AFJ and VG reviewed data extraction output.

Funding The study was funded by the non-profit organisations Kinder-Rheumahilfe Muenchen e.V., Edith-Haberland-Wagner-Stiftung and Kindness for Kids, Munich. Through financial pledges, all three organisations provided the necessary capital for the two patient conferences. In addition, Kinder-Rheumahilfe Muenchen also organised the two conferences. The study itself and the work thereafter were unfunded.

Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval Ethics committee of the medical faculty at Ludwig-Maximilian University (Munich).

Provenance and peer review Not commissioned; externally peer reviewed.

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

REFERENCES

1. Hayem G, Bouchaud-Chabot A, Benali K, *et al*. SAPHO syndrome: a long-term follow-up study of 120 cases. *Semin Arthritis Rheum* 1999;29:159–71.
2. Jansson AF, Müller TH, Gliera L, *et al*. Clinical score for nonbacterial osteitis in children and adults. *Arthritis Rheum* 2009;60:1152–9.
3. Ferguson PJ, El-Shanti HI. Autoinflammatory bone disorders. *Curr Opin Rheumatol* 2007;19:492–8.
4. Girschick HJ, Zimmer C, Klaus G, *et al*. Chronic recurrent multifocal osteomyelitis: what is it and how should it be treated? *Nat Clin Pract Rheumatol* 2007;3:733–8.
5. El-Shanti HI, Ferguson PJ. Chronic recurrent multifocal osteomyelitis: a concise review and genetic update. *Clin Orthop Relat Res* 2007;462:11–19.
6. Jansson A, Renner ED, Ramser J, *et al*. Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. *Rheumatology* 2007;46:154–60.
7. King SM, Laxer RM, Manson D, *et al*. Chronic recurrent multifocal osteomyelitis: a noninfectious inflammatory process. *Pediatr Infect Dis J* 1987;6:907–11.
8. Kahn MF. [Current status of the SAPHO syndrome]. *Presse Med* 1995;24:338–40.
9. Anderson SE, Heini P, Sauvain MJ, *et al*. Imaging of chronic recurrent multifocal osteomyelitis of childhood first presenting with isolated primary spinal involvement. *Skeletal Radiol* 2003;32:328–36.
10. Maslow GR, Haydon A, McRee AL, *et al*. Growing up with a chronic illness: social success, educational/vocational distress. *J Adolesc Health* 2011;49:206–12.
11. Shapiro J. Family reactions and coping strategies in response to the physically ill or handicapped child: a review. *Soc Sci Med* 1983;17:913–31.
12. Northam EA. Psychosocial impact of chronic illness in children. *J Paediatr Child Health* 1997;33:369–72.
13. Grote V, Silier CC, Voit AM, *et al*. Bacterial osteomyelitis or nonbacterial osteitis in children: a study involving the German surveillance unit for rare diseases in childhood. *Pediatr Infect Dis J* 2016. doi: 10.1097/INF.0000000000001469 [Epub ahead of print 13 Dec 2016].
14. Peltola H, Pääkkönen M, Kallio P, *et al*. Short- versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: prospective, randomized trial on 131 culture-positive cases. *Pediatr Infect Dis J* 2010;29:1123–8.
15. Jansson A, Grote V. Non-bacterial osteitis and bacterial osteomyelitis. *Monatsschrift Kinderheilkunde* 2009;157:718–9.
16. Copley LA, Kinsler MA, Gheen T, *et al*. The impact of evidence-based clinical practice guidelines applied by a multidisciplinary team for the care of children with osteomyelitis. *J Bone Joint Surg Am* 2013;95:686–93.
17. Jorge LS, Chueire AG, Rossit AR. Osteomyelitis: a current challenge. *Braz J Infect Dis* 2010;14:310–5.
18. Jansson AF, Borte M, Hospach A, *et al*. Diagnostics and therapy of non-bacterial osteitis. Consensus statement of the 16th Worlitz expert meeting 2013 for the Deutsche Gesellschaft fur Kind- und Jugendrheumatologie. *Monatsschrift Kinderheilkunde* 2014;162:539–45.
19. Foster HE, Minden K, Clemente D, *et al*. EULAR/PReS standards and recommendations for the transitional care of young people with juvenile-onset rheumatic diseases. *Ann Rheum Dis* 2017;76:639–46.
20. McDonagh JE. Transition of care from paediatric to adult rheumatology. *Arch Dis Child* 2007;92:802–7.
21. McDonagh JE, Southwood TR, Shaw KL. The impact of a coordinated transitional care programme on adolescents with juvenile idiopathic arthritis. *Rheumatology* 2007;46:161–8.
22. Schalm S, Jansson AF. [Transitional care in rheumatology in Germany]. *Internist* 2012;53:1054–62.

BMJ Open

Chronic non-bacterial osteitis from the patient perspective: a health services research through data collected from patient conferences

Colen Cooper Gore Silier, Justina Greschik, Susanne Gesell, Veit Grote and Annette F Jansson

*BMJ Open*2017 7:
doi: 10.1136/bmjopen-2017-017599

8. References

1. Jundt, G., *Pathologie*. 5 ed, ed. H.D. W. Böcker, Ph. U. Heitz, G. Höfler, H. Kreipe, H. Moch. 2012, Munich: Urban & Fischer Verlag/Elsevier GmbH. 1092.
2. Tiemann, A.H. and G.O. Hofmann, *Principles of the therapy of bone infections in adult extremities : Are there any new developments?* Strategies Trauma Limb Reconstr, 2009. **4**(2): p. 57-64.
3. Giedion, A., et al., *[Subacute and chronic "symmetrical" osteomyelitis].* Ann Radiol (Paris), 1972. **15**(3): p. 329-42.
4. Carek, P.J., L.M. Dickerson, and J.L. Sack, *Diagnosis and management of osteomyelitis.* Am Fam Physician, 2001. **63**(12): p. 2413-20.
5. Hayem, G., et al., *SAPHO syndrome: a long-term follow-up study of 120 cases.* Semin Arthritis Rheum, 1999. **29**(3): p. 159-71.
6. Jansson, A.F., et al., *Clinical score for nonbacterial osteitis in children and adults.* Arthritis Rheum, 2009. **60**(4): p. 1152-9.
7. Jansson, A.F., et al., *Clinical score for nonbacterial osteitis in children and adults.* Arthritis and Rheumatism, 2009. **60**(4): p. 1152-9.
8. Schnabel, A., R. Berner, and C.M. Hedrich, *Chronic nonbacterial and bacterial osteomyelitis.* Monatsschrift Kinderheilkunde, 2016. **164**(6): p. 505-519.
9. Grote, V., et al., *Bacterial Osteomyelitis or Nonbacterial Osteitis in Children: A Study Involving the German Surveillance Unit for Rare Diseases in Childhood.* The Pediatric Infectious Disease Journal, 2017. **36**(5): p. 451-456.
10. Khanna, G., T.S. Sato, and P. Ferguson, *Imaging of chronic recurrent multifocal osteomyelitis.* Radiographics, 2009. **29**(4): p. 1159-77.
11. Jansson, A.F. and V. Grote, *Nonbacterial osteitis in children: data of a German Incidence Surveillance Study.* Acta Paediatrica, 2011. **100**(8): p. 1150-7.
12. Ferguson, P.J. and H.I. El-Shanti, *Autoinflammatory bone disorders.* Curr Opin Rheumatol, 2007. **19**(5): p. 492-8.
13. Girschick, H.J., et al., *Chronic recurrent multifocal osteomyelitis: what is it and how should it be treated?* Nat Clin Pract Rheumatol, 2007. **3**(12): p. 733-8.
14. El-Shanti, H.I. and P.J. Ferguson, *Chronic recurrent multifocal osteomyelitis: a concise review and genetic update.* Clin Orthop Relat Res, 2007. **462**: p. 11-9.
15. Jansson, A., et al., *Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients.* Rheumatology (Oxford), 2007. **46**(1): p. 154-60.
16. Kahn, M.F., *Current status of the SAPHO syndrome.* Presse Med, 1995. **24**(7): p. 338-40.
17. Anderson, S.E., et al., *Imaging of chronic recurrent multifocal osteomyelitis of childhood first presenting with isolated primary spinal involvement.* Skeletal Radiol, 2003. **32**(6): p. 328-36.
18. Ferguson, P.J. and R.M. Laxer, *New discoveries in CRMO: IL-1beta, the neutrophil, and the microbiome implicated in disease pathogenesis in Pstpip2-deficient mice.* Semin Immunopathol, 2015. **37**(4): p. 407-12.
19. Jansson, A., V. Jansson, and A. von Liebe, *Pediatric osteomyelitis.* Orthopade, 2009. **38**(3): p. 283-294.
20. Jansson, A., et al., *Chronic recurrent multifocal osteomyelitis (CRMO). Review and first results of a genetic study.* Monatsschrift Kinderheilkunde, 2002. **150**(4): p. 477-489.
21. Golla, A., et al., *Chronic recurrent multifocal osteomyelitis (CRMO): evidence for a susceptibility gene located on chromosome 18q21.3-18q22.* Eur J Hum Genet, 2002. **10**(3): p. 217-21.
22. Majeed, H.A., et al., *Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet syndrome in two siblings.* Journal of Pediatrics, 1989. **115**(5 Pt 1): p. 730-4.

23. Aksentijevich, I., et al., *An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist.* N Engl J Med, 2009. **360**(23): p. 2426-37.
24. Cassel, S.L., et al., *Inflammasome-independent IL-1beta mediates autoinflammatory disease in Pstpip2-deficient mice.* Proc Natl Acad Sci U S A, 2014. **111**(3): p. 1072-7.
25. Hofmann, S.R., et al., *Chronic Recurrent Multifocal Osteomyelitis (CRMO): Presentation, Pathogenesis, and Treatment.* Curr Osteoporos Rep, 2017. **15**(6): p. 542-554.
26. Hofmann, S.R., et al., *Altered expression of IL-10 family cytokines in monocytes from CRMO patients result in enhanced IL-1beta expression and release.* Clin Immunol, 2015. **161**(2): p. 300-307.
27. Hofmann, S.R., et al., *Attenuated TLR4/MAPK signaling in monocytes from patients with CRMO results in impaired IL-10 expression.* Clin Immunol, 2012. **145**(1): p. 69-76.
28. Girschick, H., et al., *The multifaceted presentation of chronic recurrent multifocal osteomyelitis: a series of 486 cases from the Eurofever international registry.* Rheumatology (Oxford), 2018. **57**(8): p. 1504.
29. Hofmann, S.R., et al., *Chronic Nonbacterial Osteomyelitis: Pathophysiological Concepts and Current Treatment Strategies.* J Rheumatol, 2016. **43**(11): p. 1956-1964.
30. Cox, A.J., Y. Zhao, and P.J. Ferguson, *Chronic Recurrent Multifocal Osteomyelitis and Related Diseases-Update on Pathogenesis.* Curr Rheumatol Rep, 2017. **19**(4): p. 18.
31. Hofmann, S.R., et al., *Serum biomarkers for the diagnosis and monitoring of chronic recurrent multifocal osteomyelitis (CRMO).* Rheumatol Int, 2016. **36**(6): p. 769-79.
32. Bousvaros, A., et al., *Chronic recurrent multifocal osteomyelitis associated with chronic inflammatory bowel disease in children.* Digestive Diseases and Sciences, 1999. **44**(12): p. 2500-7.
33. Pelkonen, P., et al., *Chronic Osteomyelitis-Like Disease with Negative Bacterial Cultures.* American Journal of Diseases of Children, 1988. **142**(11): p. 1167-1173.
34. Jansson A, B.B., Golla A, Borelli C, Plewig G, *Nichtbakterielle Osteitiden, Akne und andere Hautmanifestationen*, in *Fortschritte der praktischen Dermatologie und Venerologie*. 2005. p. 259 - 268.
35. Kozlowski, K., et al., *Multifocal, chronic osteomyelitis of unknown etiology. A further report.* Rofo, 1985. **142**(4): p. 440-6.
36. Rajka, G., *Immunology of pustulosis palmoplantaris.* Acta Derm Venereol Suppl (Stockh), 1979. **87**: p. 31-2.
37. Laasonen, L.S., S.L. Karvonen, and T.L. Reunala, *Bone disease in adolescents with acne fulminans and severe cystic acne: radiologic and scintigraphic findings.* AJR Am J Roentgenol, 1994. **162**(5): p. 1161-5.
38. Wallace, R.G., et al., *Familial expansile osteolysis.* Clin Orthop Relat Res, 1989(248): p. 265-77.
39. Edwards, T.C., et al., *Sweet's syndrome with multifocal sterile osteomyelitis.* Am J Dis Child, 1986. **140**(8): p. 817-8.
40. Kaiser, D., et al., *Chronic nonbacterial osteomyelitis in children: a retrospective multicenter study.* Pediatr Rheumatol Online J, 2015. **13**: p. 25.
41. Beretta-Piccoli, B.C., et al., *Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome in childhood: a report of ten cases and review of the literature.* Eur J Pediatr, 2000. **159**(8): p. 594-601.
42. Huber, A.M., et al., *Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up.* J Pediatr, 2002. **141**(2): p. 198-203.
43. Jansson, A. and D. Reinhardt, *Bone pain.* Monatsschrift Kinderheilkunde, 2009. **157**(7): p. 645-646.
44. Hedrich, C.M., et al., *A clinical and pathomechanistic profile of chronic nonbacterial osteomyelitis/chronic recurrent multifocal osteomyelitis and challenges facing the field.* Expert Rev Clin Immunol, 2013. **9**(9): p. 845-54.

45. Zhao, Y., et al., *Consensus Treatment Plans for Chronic Nonbacterial Osteomyelitis Refractory to Nonsteroidal Antiinflammatory Drugs and/or With Active Spinal Lesions.* Arthritis Care Res (Hoboken), 2018. **70**(8): p. 1228-1237.
46. Voit, A.M., et al., *Whole-body Magnetic Resonance Imaging in Chronic Recurrent Multifocal Osteomyelitis: Clinical Longterm Assessment May Underestimate Activity.* J Rheumatol, 2015. **42**(8): p. 1455-62.
47. Schwarz, T., et al., *Protokolle zur Klassifikation, Überwachung und Therapie in der Kinderrheumatologie (PRO-KIND): Chronisch nicht-bakterielle Osteomyelitis (CNO).* Arthritis und Rheuma, 2018. **38**(04): p. 282-288.
48. Jansson, A.F., *Nichtbakterielle Osteitiden. Aktueller Wissensstand und Therapieoptionen.* Arthritis und Rheuma, 2013. **33**(6): p. 371-376.
49. Girschick, H.J., et al., *Chronic recurrent multifocal osteomyelitis in children: diagnostic value of histopathology and microbial testing.* Hum Pathol, 1999. **30**(1): p. 59-65.
50. Jansson, A., et al., *Non-bacterial osteitis in children and adults. Consensus statement of the 8th Worlitz Expert Meeting 2005, for the German Society for Paediatric and Adolescent Rheumatology.* Monatsschrift Kinderheilkunde, 2006. **154**(8): p. 831-833.
51. Beck, C., et al., *Chronic nonbacterial osteomyelitis in childhood: prospective follow-up during the first year of anti-inflammatory treatment.* Arthritis Res Ther, 2010. **12**(2): p. R74.
52. Jansson, A.F., et al., *Diagnostics and therapy of non-bacterial osteitis. Consensus statement of the 16th Worlitz expert meeting 2013 for the Deutsche Gesellschaft fur Kind- und Jugendrheumatologie.* Monatsschrift Kinderheilkunde, 2014. **162**(6): p. 539-545.
53. Miettunen, P.M., et al., *Dramatic pain relief and resolution of bone inflammation following pamidronate in 9 pediatric patients with persistent chronic recurrent multifocal osteomyelitis (CRMO).* Pediatr Rheumatol Online J, 2009. **7**: p. 2.
54. Borzutzky, A., et al., *Pediatric chronic nonbacterial osteomyelitis.* Pediatrics, 2012. **130**(5): p. e1190-7.
55. Wipff, J., et al., *A large national cohort of French patients with chronic recurrent multifocal osteitis.* Arthritis Rheumatol, 2015. **67**(4): p. 1128-37.
56. Schnabel, A., et al., *Treatment Response and Longterm Outcomes in Children with Chronic Nonbacterial Osteomyelitis.* J Rheumatol, 2017. **44**(7): p. 1058-1065.
57. Silier, C.C.G., et al., *Chronic non-bacterial osteitis from the patient perspective: a health services research through data collected from patient conferences.* BMJ Open, 2017. **7**(12).
58. Duffy, C.M., et al., *Chronic recurrent multifocal osteomyelitis: review of orthopaedic complications at maturity.* J Pediatr Orthop, 2002. **22**(4): p. 501-5.
59. Oliver, M., et al., *Disease burden and social impact of pediatric chronic nonbacterial osteomyelitis from the patient and family perspective.* Pediatr Rheumatol Online J, 2018. **16**(1): p. 78.
60. De Boeck, H., *Osteomyelitis and septic arthritis in children.* Acta Orthopaedica Belgica, 2005. **71**(5): p. 505-515.
61. McCarthy, J.J., et al., *Musculoskeletal infections in children: basic treatment principles and recent advancements.* Instr Course Lect, 2005. **54**: p. 515-28.
62. Howard-Jones, A.R. and D. Isaacs, *Systematic review of duration and choice of systemic antibiotic therapy for acute haematogenous bacterial osteomyelitis in children.* J Paediatr Child Health, 2013. **49**(9): p. 760-8.
63. Bohndorf, K., *Infection of the appendicular skeleton.* Eur Radiol, 2004. **14 Suppl 3**: p. E53-63.
64. Jorge, L.S., A.G. Chueire, and A.R. Rossit, *Osteomyelitis: a current challenge.* Braz J Infect Dis, 2010. **14**(3): p. 310-5.
65. Peltola, H. and M. Paakkonen, *Acute osteomyelitis in children.* N Engl J Med, 2014. **370**(4): p. 352-60.
66. Ferroni, A., *Epidemiology and bacteriological diagnosis of paediatric acute osteoarticular infections.* Arch Pediatr, 2007. **14 Suppl 2**: p. S91-6.

67. Ceroni, D., et al., *Differentiating osteoarticular infections caused by Kingella kingae from those due to typical pathogens in young children.* Pediatr Infect Dis J, 2011. **30**(10): p. 906-9.
68. Principi, N. and S. Esposito, *Kingella kingae infections in children.* BMC Infect Dis, 2015. **15**: p. 260.
69. Chometon, S., et al., *Specific real-time polymerase chain reaction places Kingella kingae as the most common cause of osteoarticular infections in young children.* Pediatr Infect Dis J, 2007. **26**(5): p. 377-81.
70. Lew, D.P. and F.A. Waldvogel, *Osteomyelitis.* Lancet, 2004. **364**(9431): p. 369-79.
71. Riise, O.R., et al., *Childhood osteomyelitis-incidence and differentiation from other acute onset musculoskeletal features in a population-based study.* BMC Pediatr, 2008. **8**: p. 45.
72. Dodwell, E.R., *Osteomyelitis and septic arthritis in children: current concepts.* Curr Opin Pediatr, 2013. **25**(1): p. 58-63.
73. Dartnell, J., M. Ramachandran, and M. Katchburian, *Haematogenous acute and subacute paediatric osteomyelitis: a systematic review of the literature.* J Bone Joint Surg Br, 2012. **94**(5): p. 584-95.
74. Karmazyn, B., *Imaging approach to acute hematogenous osteomyelitis in children: an update.* Seminars in Ultrasound, CT and MR, 2010. **31**(2): p. 100-6.
75. Blickman, J.G., C.E. van Die, and J.W. de Rooy, *Current imaging concepts in pediatric osteomyelitis.* European Radiology, 2004. **14 Suppl 4**: p. L55-64.
76. Pineda, C., A. Vargas, and A.V. Rodriguez, *Imaging of osteomyelitis: current concepts.* Infect Dis Clin North Am, 2006. **20**(4): p. 789-825.
77. Offiah, A.C., *Acute osteomyelitis, septic arthritis and discitis: differences between neonates and older children.* Eur J Radiol, 2006. **60**(2): p. 221-32.
78. Kaplan, S.L., *Osteomyelitis in children.* Infectious Disease Clinics of North America, 2005. **19**(4): p. 787-97, vii.
79. Saavedra-Lozano, J., et al., *Changing trends in acute osteomyelitis in children: impact of methicillin-resistant Staphylococcus aureus infections.* J Pediatr Orthop, 2008. **28**(5): p. 569-75.
80. Kothari, N.A., D.J. Pelchovitz, and J.S. Meyer, *Imaging of musculoskeletal infections.* Radiol Clin North Am, 2001. **39**(4): p. 653-71.
81. Copley, L.A., et al., *The impact of evidence-based clinical practice guidelines applied by a multidisciplinary team for the care of children with osteomyelitis.* J Bone Joint Surg Am, 2013. **95**(8): p. 686-93.
82. Peltola, H., et al., *Short- Versus Long-term Antimicrobial Treatment for Acute Hematogenous Osteomyelitis of Childhood: Prospective, Randomized Trial on 131 Culture-positive Cases.* Pediatric Infectious Disease Journal, 2010.
83. Isaacs, D., et al., *Osteomyelitis and Septic Arthritis*, in *Evidence-based Pediatric Infectious Diseases*. 2008, Blackwell Publishing Ltd. p. 156-165.
84. Nelson, J.D., et al., *Evaluation of new anti-infective drugs for the treatment of acute hematogenous osteomyelitis in children. Infectious Diseases Society of America and the Food and Drug Administration.* Clin Infect Dis, 1992. **15 Suppl 1**: p. S162-6.
85. Overturf, G.D., *Chapter 8 - Bacterial Infections of the Bones and Joints A2 - Remington, Jack S*, in *Infectious Diseases of the Fetus and Newborn Infant (Sixth Edition)*, J.O. Klein, C.B. Wilson, and C.J. Baker, Editors. 2006, W.B. Saunders: Philadelphia. p. 319-333.
86. Schnabel, A., et al., *Unexpectedly high incidences of chronic non-bacterial as compared to bacterial osteomyelitis in children.* Rheumatol Int, 2016. **36**(12): p. 1737-1745.

9. Acknowledgments

First and foremost, I would like to thank Dr. Annette Jansson, who gave me the opportunity to delve into a world that was not only unknown to me but exciting as well. Her patience and guidance always softly directed me to find the right path.

Dr. Veit Grote, I would like to thank, who read and re-read what seemed like 1,000 drafts of my articles and offered insight and shared knowledge that every author so desperately needs.

I would also like to thank all of the co-authors who laid the groundwork for what we have accomplished.

I especially would like to thank my family for always standing behind me every step of the way, and especially my husband, whose eternal support with which I could not do without.