FEEDBACK FOLLOWING PRELIMINARY SEARCH

QUERY REF: Paed-005

Received: 25th September 2014

Feedback to CSG: 15th October 2014 (due), 14th October 2014 (sent)

SEARCH METHODOLOGY

The content of this feedback report refers only to the most relevant material located under each of the evidence headings and is drawn predominantly from author abstracts or research recommendations within guidelines. The question is posed in the context of the use of pamidronate and adalimumab in children with chronic recurrent multifocal osteomyelitis (CRMO). Further details of all the studies included in this report are shown in the appendix, sorted by report section and author name.

Criteria used (PICO):

\[ \text{Who? (population)} \]
Children (and adults) with chronic recurrent multifocal osteomyelitis

\[ \text{What? (intervention/exposure/measure)} \]
Adalimumab and/or pamidronate

\[ \text{Comparison} \]
Each other

\[ \text{What is measured? What are the outcomes?} \]
Improvement in disease e.g. MRI and pain scores

Location and setting
Any

Exclusion Criteria
Non-English language guidelines, recommendations, systematic reviews, overviews and clinical opinions. However, non-English language primary research articles with English abstracts were included if relevant, see Section D: Primary Research.
Databases Searched
CINAHL; Cochrane Library; EMBASE; MEDLINE; ISRCTN Register; UK Clinical Research Network Study Portfolio; NIH records on ClinicalTrials.gov; Nederlands Trial Register; German Clinical Trials Register; Australian New Zealand Clinical Trials Registry; World Health Organization (WHO): International Clinical Trials Registry.

Types of Study
Clinical trials; Observational studies

Keywords searched
Search protocols were designed around the following terms: CRMO AND adalimumab OR pamidronate (e.g. see Appendix 1 for MEDLINE protocol)

Date limits
None

Summary of available evidence

<table>
<thead>
<tr>
<th>EVIDENCE TYPE</th>
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<tbody>
<tr>
<td>A Evidence Summaries</td>
<td>2</td>
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<tr>
<td>B Systematic Reviews &amp; Meta-analyses</td>
<td>4 (5 papers)</td>
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<tr>
<td>C Clinical Trial Registries (Current and Closed)</td>
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<tr>
<td>D Primary Research</td>
<td>82 studies (86 papers)</td>
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<td>E Overviews and expert opinions</td>
<td>n/a</td>
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<tr>
<td>F Intellectual Property Office</td>
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RESULTS

A: Good Quality Evidence Summaries (including guidelines)
Two related consensus statements regarding the use of biological agents including anti-TNFα drugs are included in this review. SAPHO is mentioned but no real detail is provided (Furst, et al., 2005, 2006).

B: Systematic Reviews and Meta-analyses
See Appendix 2, Section B for details of reviews included in this section.
Four systematic reviews, reported in 5 publications, were considered relevant for this evidence review.
Two of these systematic reviews focused on medication and are potentially relevant for this review:

- off-label use of anti-TNFα therapies in dermatology (Alexis and Strober, 2005)
- pamidronate treatment in rheumatology (Slobodin, et al., 2009)

The other two reviews, reported in 3 papers focus on SAPHO syndrome:

- and CRMO treated with anti-TNFα but mention of pamidronate (Moll, et al., 2008)
- in the context of inflammatory bowel disease (Naves, et al., 2013a,b)

C: Clinical Trial Registries

No clinical trials were identified for this report.

D: Primary Research

See Appendix 2, Section D for details of studies included in this section.

Eighty six primary research articles, reporting 82 studies were identified for this review, including 2 intervention studies, 1 prospective observational studies (2 articles), 1 cross-sectional observation study and 78 retrospective observational studies (81 articles).

**Intervention studies (section 2.D.1)**

Two intervention studies were identified, both uncontrolled, single group assignment:

- Adult with SAPHO given pamidronate (Solau-Gervais, 2006)
- Children with CNO treated with bisphosphonate pamidronate (Hofmann, et al., 2014)

**Observational studies (section 2.D.2)**

**Prospective**

One paediatric prospective observational study, reported in two papers, was identified (Miettunen, et al., 2009; Miettunen, Wei, Reslan and Kaura, 2010 [conference abstract])

**Cross-sectional**

One adult cross-sectional observational study (Witt, et al., 2014)

**Retrospective**

Seventy eight retrospective observational studies, across 81 papers, were identified. These have been categorised below according to age and type of article.
Adult

30 adult studies, reported in 31 papers, were found; these were predominantly case studies. This included 22 studies as peer-reviewed articles (23 papers), 2 conference abstracts and 6 letters reporting cases.

- Conference abstracts (Conway and Khan, 2011; Spacey, et al., 2014).

Paediatric

Forty paediatric studies, reported in 42 papers, were found; these were predominantly case studies. This included 21 studies as peer-reviewed articles, 19 conference abstracts (17 studies) and 2 letters reporting cases.


Mixed i.e. adult and paediatric

Four studies reporting both adults and paediatric patients were identified; this included 2 peer-reviewed articles, 1 conference abstracts and 1 letter.
**Age unclear**

Four studies were identified in which the age to the patient(s) was unclear; this included 3 peer-reviewed articles and 1 conference abstract.

- Peer reviewed articles (Ben Abdelghani, et al., 2010; Guignard, Job-Deslandre, Sayag-Boukris and Kahan, 2002; Kuhn, Fehr and Stoll, 2007).
- Conference abstract (Firinu, et al., 2014).

A number of studies were identified, where it was unclear from the abstract if they were relevant but could not be accessed. These have been excluded from the appendix, but are included here for completeness:

- Retrospective studies
  - Child (Alenazi, et al., 2012; Hosalkar, Barroeta, Torbert and Lackman, 2006; Tingley, et al., 2001)
  - Adult (Kwon, et al., 2005)
  - Age unclear (Anic, et al., 2014; Araujo, et al., 2011; Collange, Brantus, Sidot and Meunier, 1996; Zhao, Li, Zhao and Li, 2011)
- Other studies (Leirisalo-Repo, 1995; Patel, et al., 2011)

**E: Overviews and Expert Opinions**

Not relevant to this report.

**F: Intellectual Property Office**

Not relevant to this report.

**CONCLUSION**

Primary research comprises the majority of studies included in this report (82/88) with no clinical trials on-going or recently completed and unpublished identified. Observational studies represented 97.5% (80/82) of the primary research, of which 78 studies were retrospective observational studies. Only two intervention studies were found, these were both uncontrolled studies using pamidronate. In addition, 2 related consensus statements and 4 systematic reviews were pertinent to this review.

Overall, this report identifies a large body of case studies regarding the use of pamidronate and/or adalimumab in the treatment of paediatric or adult chronic recurrent multifocal
ostemyelitis (CNO, SAPHO, CRMO), however, whilst two intervention studies were identified these we both uncontrolled. These findings concur with those reported in the systematic reviews and consensus statements included in this evidence review. In general, it appears that pamidronate and adalimumab are beneficial, at least in some cases; however, there is a paucity of well designed controlled trials to substantiate these findings and future trials are therefore warranted.

**Abbreviations**

- CNO: Chronic non-bacterial osteomyelitis
- CRMO: Chronic recurrent multifocal osteomyelitis
- SAPHO: Synovitis, acne, pustulosis, hyperostosis, osteitis
- TNF: Tumor necrosis factor

**References**


Arias-Santiago, S., Sanchez-Cano, D., Callejas-Rubio, J. L., Fernandez-Pugnaire, M. A. and


**APPENDIX 1**

MEDLINE search protocol (ran 06.10.14)  Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

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### APPENDIX 2 – FULL TEXT

### SECTION B – SYSTEMATIC REVIEWS & META-ANALYSES

<table>
<thead>
<tr>
<th>Title</th>
<th>Abstract [The following text is verbatim]</th>
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<tr>
<td>Alexis and Strober (2005). Off-label dermatologic uses of anti-TNF-a therapies.</td>
<td>BACKGROUND: Tumor necrosis factor-alpha (TNF-a) is a proinflammatory cytokine that plays an immunomodulatory role in a variety of systemic and dermatologic diseases. Currently, three anti-TNF-a drugs are available in North America: infliximab (approved in the U.S. for the treatment of rheumatoid arthritis, Crohn’s disease, ankylosing spondylitis, ulcerative colitis, and psoriatic arthritis), etanercept (approved in the U.S. for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and psoriasis), and adalimumab (approved for the treatment of rheumatoid arthritis and psoriatic arthritis). OBJECTIVE: To review the current literature supporting alternative (and currently off-label) dermatologic uses of TNF-a antagonists. METHODS: A MEDLINE search (1966-March 2005) was conducted using the keywords “infliximab,” “etanercept,” “adalimumab,” “TNF inhibitors,” and “off-label” to identify published reports of off-label dermatologic uses of TNF-a inhibitors. RESULTS: Anti-TNF-a therapies have been reported in the following dermatologic diseases: sarcoidosis, hidradenitis suppurativa, cicatricial pemphigoid, Behcet’s disease, pyoderma gangrenosum, multicentric reticulohistiocytosis, apthous stomatitis, Sneddon-Wilkinson disease, SAPHO syndrome, pityriasis rubra pilaris, eosinophilic fasciitis, panniculitis, Crohn’s disease, necrobiosis lipoidica diabetorum, dermatomyositis, and scleroderma. The vast majority of these reports are in the form of individual case reports and small case series. Only two published randomized controlled trials involving the off-label use of a TNF inhibitor were found. CONCLUSIONS: A growing number of published reports suggest that anti-TNF-a therapies may be effective in the treatment of numerous inflammatory skin diseases outside their currently approved indications.</td>
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<td>Moll, et al. (2008). Ilium Osteitis as the Main Manifestation of the SAPHO Syndrome: Response to Infliximab Therapy and Review of the Literature.</td>
<td>Objective: To analyze the clinical efficacy of anti-tumor necrosis factor (TNF)-alpha therapy in the SAPHO (synovitis, acne, pustulosis, hyperostosis, ostitis) syndrome. We describe 2 new cases with ilium osteitis as the main SAPHO syndrome feature and review reported cases treated with anti-TNF-alpha. Methods: A literature search of SAPHO syndrome cases treated with TNF-alpha blocking therapy with special emphasis on osteoarticular and skin responses was performed. Results: Eighteen cases were identified: 17 SAPHO syndrome and 1 chronic recurrent multifocal osteomyelitis, a juvenile variant of SAPHO syndrome. Sixteen were reported cases and 2 were nonreported cases seen in our arthritis unit. Sixteen patients received infliximab and 2 received etanercept, with an early, sustained clinical improvement in most cases. Conclusions: Anti-TNF-alpha therapies are effective treatment for patients with refractory SAPHO syndrome, not only for cutaneous lesions but also for persistent bone lesions such as osteitis. 2008 Elsevier Inc. All rights reserved.</td>
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<td>Naves, et al. (2013a). A systematic review of SAPHO syndrome and inflammatory bowel disease association Also: Naves, et al. (2013b).</td>
<td>Background: The association between inflammatory bowel disease (IBD) and synovitis, acne, pustulosis, hyperostosis, ostitis syndrome (SAPHO syndrome) was first reported in 1992. To date, only case reports and short series have been published. Aims: The purpose of this study was to report new cases and systematically review the literature on this association. Materials and Methods: All patients with concomitant diagnosis of SAPHO syndrome and IBD were identified from the databases of the rheumatology and gastroenterology departments of our institution. In addition, we systematically searched for published full articles in Medlars Online International Literature via PubMed. Relevant information of each positive match was collected and all authors were contacted for additional clinical data. Results: Three patients sharing both SAPHO syndrome and IBD were identified among the 62 patients with SAPHO syndrome (4.8 % of the SAPHO cohort) and the 1,309 patients with IBD (0.2 % of the IBD cohort) from our hospital database. After a systematic review, a total of 39 reported patients with concomitant diagnosis of SAPHO syndrome and IBD were identified. There was a female predominance and most had Crohn’s disease with colonic involvement.</td>
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<td>Slobodin, Rosner,</td>
<td>Pamidronate, along with other bisphosphonates, has been used for treatment of bone pain secondary to malignant involvement or metastatic disease for years. Some data, however, have also accumulated on the utility of pamidronate in a variety of benign conditions frequently handled by rheumatologists. This study aims to review the available published data regarding the potential use of pamidronate in rheumatology practice. Methods include the review of relevant articles retrieved by a PUBMED search utilizing the index term &quot;pamidronate&quot;. All available randomized control trials, open trials, and case series, as well as properly reported case studies evaluating usage of pamidronate in rheumatic disorders, have been included in the literature review. The efficacy of pamidronate in patients with spondyloarthopathies; synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome; hypertrophic osteoarthropathy; osteoporotic vertebral fractures; chronic back pain due to disk disease or spinal stenosis; Charcot arthropathy; transient osteoporosis; and complex regional pain syndrome-1, has been demonstrated in more than 40 reports, the majority of which, however, were not controlled studies. In some of reviewed conditions, aside from providing analgesic relief, pamidronate may also have disease-modifying properties. While used in different doses in a variety of rheumatic disorders, pamidronate was generally reported to be well tolerated with an overall good safety profile. Pamidronate may represent an effective and safe choice for a spectrum of rheumatic patients, suffering from intractable musculoskeletal pain, unresponsive to traditionally recommended therapies. Large randomized, controlled studies examining the efficacy of pamidronate in the rheumatic conditions are urgently needed. [References: 56]</td>
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<td>Feld, Rimar,</td>
<td>Introduction: SAPHO syndrome is an inflammatory disorder including axial and peripheral skeletal manifestations frequently associated with different forms of skin pustulosis and other neutrophilic dermatosis. Despite a triggering role of an infectious agent emerging, aetiopathogenesis remains obscure. As a consequence its treatment is still empirical. Non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and classical disease-modifying anti-rheumatic drugs s are all used in the treatment of SAPHO syndrome with different results. In refractory cases bisphosphonates (pamidronate) and biological agents, namely anti-TNF-alpha and anti-IL-1, could also be effective in association. Antibiotics may also play a relevant role, especially in the early phases of the disease. Areas covered: A computerised search was conducted using Medline, PubMed, EMBase and Cochrane Central Register of Controlled Trials (CENTRAL) for articles published in English (up to July 2013) applying the MeSH terms and keywords 'SAPHO syndrome', 'bisphosphonates', 'antibiotics', 'anti-TNF-alpha agents' and 'autoinflammatory diseases'. Boolean operators (NOT; AND; OR) were used in succession to narrow and widen the search. Expert opinion: To prevent new bone formation, continuous NSAID therapy could be explored considering the results obtained in spondyloarthritides, but cardiovascular and gastrointestinal risks have to be taken into account. Furthermore, no experience exists with the new anti-TNF-alpha agents golimumab and certolizumab pegol. Also, the new anti-IL-1 agent canakinumab deserves to be tried, due to the mechanism of action and suitable dosage regimen. Finally, following the hypothesis of a triggering infectious agent, prolonged and repeated courses of antibiotic therapy may be an option. 2013 Informa UK, Ltd.</td>
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<td>Rozenbaum, Boulman</td>
<td>Conclusions: The association of SAPHO syndrome and IBD seems to be rare among IBD patients but not so among SAPHO patients. SAPHO could be underdiagnosed because of the similarity of its clinical manifestations and some more common extraintestinal manifestations or drug-related side effects in IBD. 2013 Springer Science+Business Media New York.</td>
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<td>Trotta, Ciancio and</td>
<td>Introduction: SAPHO syndrome is an inflammatory disorder including axial and peripheral skeletal manifestations frequently associated with different forms of skin pustulosis and other neutrophilic dermatosis. Despite a triggering role of an infectious agent emerging, aetiopathogenesis remains obscure. As a consequence its treatment is still empirical. Non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and classical disease-modifying anti-rheumatic drugs s are all used in the treatment of SAPHO syndrome with different results. In refractory cases bisphosphonates (pamidronate) and biological agents, namely anti-TNF-alpha and anti-IL-1, could also be effective in association. Antibiotics may also play a relevant role, especially in the early phases of the disease. Areas covered: A computerised search was conducted using Medline, PubMed, EMBase and Cochrane Central Register of Controlled Trials (CENTRAL) for articles published in English (up to July 2013) applying the MeSH terms and keywords 'SAPHO syndrome', 'bisphosphonates', 'antibiotics', 'anti-TNF-alpha agents' and 'autoinflammatory diseases'. Boolean operators (NOT; AND; OR) were used in succession to narrow and widen the search. Expert opinion: To prevent new bone formation, continuous NSAID therapy could be explored considering the results obtained in spondyloarthritides, but cardiovascular and gastrointestinal risks have to be taken into account. Furthermore, no experience exists with the new anti-TNF-alpha agents golimumab and certolizumab pegol. Also, the new anti-IL-1 agent canakinumab deserves to be tried, due to the mechanism of action and suitable dosage regimen. Finally, following the hypothesis of a triggering infectious agent, prolonged and repeated courses of antibiotic therapy may be an option. 2013 Informa UK, Ltd.</td>
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### 2.D.1: Intervention studies

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<td><strong>Paediatric</strong>&lt;br&gt;Hofmann, et al. (2014). A standardized clinical and radiological follow-up of patients with chronic non-bacterial osteomyelitis treated with pamidronate.</td>
<td>OBJECTIVES: Chronic non-bacterial osteomyelitis (CNO) is an autoinflammatory disorder of the skeletal system. Treatment with NSAIDs is generally effective in the majority of patients, however, a sizeable proportion of patients have persistent disease and subsequent treatment strategies are required. The aim of this study was to characterise the clinical and radiological disease course in CNO patients treated with the bisphosphonate pamidronate (PAM). METHODS: Eight CNO patients refractory to NSAIDs, glucocorticoids and sulfasalazine were treated with 6 cycles of PAM in four-weekly intervals. The disease course was assessed by clinical examination and whole-body (WB) MRI at standardised time points during the treatment phase and in a 6 months follow-up. RESULTS: Seven patients were in complete clinical remission after 6 applications of PAM. WB MRIs showed regression of inflammatory lesions in 7 patients with complete remission in only one patient and partial remission in 6 patients. One patient developed radiological progression despite a marked improvement of clinical symptoms. In the follow-up after PAM therapy, 3 patients developed MRI confirmed relapse. Additional applications of PAM induced a sustained clinical remission and partial radiological response in two of them. Mild temporary adverse effects were noted in 5 patients. CONCLUSIONS: Our study highlights that PAM is effective in controlling clinical symptoms (e.g. pain) in CNO patients. However, subclinical bone inflammation was still detectable by MRI in most of the patients and disease progression was noticed in some patients after cessation of PAM.</td>
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<td><strong>Adult</strong>&lt;br&gt;Solau-Gervais, et al. (2006). The usefulness of bone remodelling markers in predicting the efficacy of pamidronate treatment in SAPHO syndrome.</td>
<td>OBJECTIVES: Pamidronate has recently been used in SAPHO syndrome due to its anti-osteoclastic effect. The aim of this study is to determine the usefulness of bone remodelling markers for determining the efficacy of pamidronate treatment. METHODS: Thirteen patients with SAPHO syndrome were treated with pamidronate. The treatment evaluation was done using a visual analogue scale (VAS) and also erythrocyte sedimentation rate, C-reactive protein, serum crosslaps (sCTX) and osteocalcin initially and after 3 months. A relevant clinical response was defined as an improvement in VAS of at least 40%. RESULTS: At 3 months, 7 of 13 patients had a good clinical response, as previously defined. Five of the seven patients maintained the good response over 6 months. Before the first perfusion 6 of the 13 patients had increased sCTX (upper 3250 pmol/l). In this small cohort we tried to analyse whether the increase in bone remodelling markers was associated with a good clinical response. In the responders group the mean levels of sCTX and osteocalcin at baseline were 6783.17 and 24.66, respectively, and in the non-responders group the levels were 2152 and 11.8, respectively. There was a significant difference in sCTX between the responders and the non-responders (P = 0.0044). CONCLUSION: Infusion of pamidronate is effective in SAPHO in some patients. Increased sCTX might be a prognostic marker for a good clinical response but results have to be confirmed in a larger cohort.</td>
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### 2.D.2: Observational studies

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| Al Hajry, Al Jumah and Almayouf (2012). Chronic recurrent multifocal osteomyelitis: a first report from Saudi Arabia. | **Retrospective; Paediatric**  
BACKGROUND AND OBJECTIVES: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare, systemic, aseptic, inflammatory disorder that involves different sites. Pathogenesis of chronic recurrent multifocal osteomyelitis is currently unknown. To our knowledge, there are no reports of CRMO from Saudi Arabia. We describe the clinical and laboratory features and treatment of a cohort of children with CRMO.  
DESIGN AND SETTING: Retrospective, patients referred to pediatric rheumatology clinic at a tertiary care center in Riyadh, Saudi Arabia.  
PATIENTS AND METHODS: The diagnosis of CRMO was based on evidence of recurrent osteomyelitis with radiographic evidence of chronic osteomyelitis involving at least two sites in the absence of infectious cause in a child less than 14 years old. RESULTS: Ten patients (9 female, 1 male) with CRMO; 2 patients presented in infancy. The referral diagnosis was inaccurate in all patients. All of them presented with pain and 8 of them had associated swelling and were found to have multifocal lesions. Imaging studies showed findings consistent with chronic osteomyelitis. Histopathological and microbiological examination confirmed the diagnosis in 9 patients. Cyclic pamidronate infusions induced good improvement in 6 patients. CONCLUSION: This report indicates that CRMO may be overlooked in our community. Early diagnosis and treatment are required to avoid potential complications. |
| Aladbe, et al. (2014). Childhood autoinflammatory disorders (AID) in Qatar. also Aladbe, et al. (2013). | **Retrospective; Paediatric [Conference abstract]**  
Introduction: The multi-ethnic population in Qatar is characterized by high rates of consanguinity. Reporting AID in this population will enhance our knowledge regarding genetic profile and clinical phenotypes in our region. Objective: To report the clinical and genetic profile of children with AID in Qatar. Methods: A retrospective review of children 14-years old or younger. Results: FMF: 32 symptomatic children and 9 asymptomatic carriers with equal gender predilection were Arabic (28), Persian (8), Turkish/Arabic (4), and Turkish (1). Clinical manifestations included recurrent abdominal pain and fever (32), arthralgia/arthritis (19), chest pain (4), oral aphthouses (3), thyroid disease (2), erysipelas (1), and membranoproliferative glomerulonephritis (1). Partial response to colchicine was uncommon and attributed mostly to poor compliance. Out of the expected 42 MEFV mutant alleles (21 probands), only 31 were identified as following: M694V (10), R202Q (5), E148Q (5), M694I (4), V726A (3), and M680I, E167D, F479L, and N599D (1 each). Overlap AID: one Arabic female with FMF (V726A/- MEFV) had clinical and radiological manifestations of CRMO (LPIN2 in process). Another Arabic brother and sister presented with overlap of FMF and HIDS manifestations were homozygote for V377I MVK mutation with complex MEFV mutations. PAPA: One Arabic boy presented with recurrent episodes of pyogenic arthritis and skin abscesses since 6 months of age had a de novo and novel D246N mutation of PSTPIP1. He responded well to courses of prednisone during disease flare. CRMO: Seven Arabic patients presented with arthralgia/arthritis (10), anemia (5), abnormal gait (4) back pain (2), compression fractures of the spine (1), and/or psoriasis (1). A brother and sister homozygote for S734L LPIN2 mutation had milder manifestations. Treatments included naproxen, infliximab, pamidronate, and canakinumab. Conclusion: Clinical manifestations can be variable for similar AID mutations even among the same family. Concurrent mutations in different AID genes can be present. |
| Amital, et al. (2004). SAPHO syndrome treated with pamidronate: an open-label study of 10 patients. | **Retrospective; Adult**  
BACKGROUND: In recent years the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and ostitis) has been encountered more frequently. However, clinical evidence indicating superiority of a specific therapeutic modality is still absent. Pamidronate, a second-generation bisphosphonate, has a pronounced effect on bone metabolism by suppressing bone resorption. We report our clinical experience with intravenous pamidronate in SAPHO syndrome. METHODS: Between the years 1999 and 2003 we treated 10 patients with the SAPHO syndrome who did not respond to NSAIDs, oral corticosteroids, colchicine, methotrexate, sulphasalazine or infliximab. All patients were treated with 60 mg pamidronate, given intravenously within an hour. In cases of no response a subsequent dose was given within a month and if there was a partial response an additional infusion was given after 4 months. The primary |
endpoint was the disappearance of recurrent bouts of bone pain, osteitis or hyperostosis, or recurrent synovitis. Reduction of the frequency of attacks by 50% was regarded as a partial response. RESULTS: Seven of the patients were females and three were males. The age at diagnosis ranged from 26 to 68 yr. All patients had axial or peripheral arthritis and cutaneous involvement; three had severe acne, eight had pustulosis and two had concomitant psoriasis vulgaris. Hyperostosis of the anterior chest wall involving either sternocostal or sternoclavicular joints, as seen on technetium 99 bone scintigraphy, was detected in all patients. Complete remission was observed following therapy in six patients, three others partially responded and only one patient had no response. Two patients needed four cycles of pamidronate infusion, one patient needed three, six needed two infusions and one patient remitted following a single pamidronate infusion. In all but one patient pamidronate was effective in preventing recurrent bouts of pustulosis. CONCLUSION: Pamidronate seems to be a very effective mode of therapy for patients with the SAPHO syndrome, by promoting remission in all components of the disorder, such as bone, joint and skin involvement, and ceases the bouts that characterize this disorder.


Retrospective; Adult [Letter]
No abstract


Retrospective; Mixed
Introduction: Primary chronic osteomyelitis of the jaw is a rare, non-suppurative, chronic inflammatory disease of unknown aetiology. To date, classification is confusing due to a non-uniform terminology. The aim of this study was to establish a simple (clinical) classification based on patient data from our clinic. Methods: Retrospective analysis revealed 30 cases of which clinical course, radiology, pathology, therapy and outcome were analysed. Results: Both sexes were equally represented. The mean age at onset of disease was 35 years (range 5-76 years). Onset of disease revealed two peaks of incidence, one in adolescence and one after age 50 years. While clinical symptoms were similar in all cases, an increased intensity of these symptoms was noted in younger individuals as well as in the early stages of the disease. Five adults and one adolescent presented with additional non-facial bone, joint and skin manifestations consistent with the diagnosis of SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome, or chronic recurrent multifocal osteomyelitis. Radiology demonstrated sclerosis, osteolysis and periosteal reaction in variable stages in all cases. However, findings were more extensive in younger patients. Histology revealed different stages of chronic inflammation in all cases. Microabscess formation was noted in 11 cases, six of which were children/adolescents. Therapy consisted mainly of surgery, antibiotics and hyperbaric oxygen therapy. At the end of the follow up period, 11 patients demonstrated complete remission, while in 14 cases amelioration and in 5 no significant improvement was noted. Conclusion: Based on differences in age at presentation, clinical appearance and course, radiology and histology, a subclassification into early and adult onset primary chronic osteomyelitis has been established. Cases with purely mandibular involvement should further be distinguished from cases associated with other syndromes. 2003 European Association for Cranio-Maxillofacial Surgery.


Retrospective; Paediatric [Conference abstract]
Background Chronic recurrent multifocal osteomyelitis (CRMO) is a non-infectious inflammatory bone disease of unknown etiology that predominantly affects children and young adults. It is characterized by multifocal inflammatory bone lesions with swelling and pain and an unpredictable course of exacerbations and spontaneous resolution. The goal of treatment is to relieve clinical symptoms. There is no known cure. Objectives To determine the clinical outcome of children with chronic recurrent multifocal osteomyelitis (CRMO). Methods We conducted a retrospective evaluation of children, under the age of sixteen, diagnosed with CRMO at the Department of Pediatrics, Aarhus University Hospital Skejby between January 2001 and June 2011. We found the patients by searching the database with the keyword chronic recurrent multifocal osteomyelitis (CRMO) and the ICD-code M86.3; and reviewed clinical, radiological and bone biopsy data registered in the patient's file. Results Thirty-

OBJECTIVE: To analyze the clinical efficacy of anti-tumor necrosis factor-alpha (TNF-
alpha) therapy in treatment of synovitis, acne, pustulosis, hyperostosis, osteitis
(SAPHO) syndrome, we describe cases of refractory SAPHO syndrome and review
cases treated with anti-TNF-alpha reported in the literature. METHODS: We describe
6 cases of patients with SAPHO syndrome treated with anti-TNF-alpha between 2004
and 2008. Therapeutic response was evaluated according to improvement in pain
score, amelioration of disease activity, and improvement in function. The efficacy
of treatment was considered to be reduced need for analgesics and/or antiinflammatory
therapy. RESULTS: In our series, 4 patients received infliximab, 1 etanercept, and 1
adalimumab. These treatments brought clinical response in 4 patients (66.6%):
response was sustained with infliximab in 1 case for 7 months; with adalimumab in
another case for 22 months; and with etanercept in 2 cases for 1 and 42 months,
respectively. In contrast, 2 other patients showed no response to infliximab.
Improvement was initially temporary after infusions 1 and 2, then pain recurred at
Week 14. Skin lesions were healed in 3 of 4 cases, but recurred or worsened in 2
cases, after infusion 2 of infliximab. Treatment was generally well tolerated.
Paradoxical psoriasis was noted in 2 cases and urticaria in 1. CONCLUSION: Given
our results and those from the literature, TNF-alpha blockers should be considered in
the therapeutic strategy of refractory cases of SAPHO syndrome, despite their effect
seeming less impressive than in other spondyloarthropathies.

Boiu, et al. (2013). P03-018 diversity in presenting manifestations of AUTOINFL.
and Boiu, et al. (2012).

Retrospective; Paediatric [Conference abstract].

Introduction: The autoinflammatory diseases (AID) include monogenic and polygenic
disorders characterized by primary dysfunction of the innate immune system.
Objectives: To describe the clinical spectrum, genetic background and therapy in a
cohort of AID patients followed in a reference Pediatric Rheumatology center.
Methods: Medical records of AID patients followed between May 2007 and November
2010 and entered in the Eurofever Registry were studied. Results: Fifty six patients
were included: 17 Cryopyrin-Associated Periodic Syndromes (CAPS), 4 TNF-
Receptor-Associated Periodic fever Syndrome (TRAPS), 5
Hyperimmunoglobulinaemia D with periodic fever Syndrome (HIDS), 18 Familial


Retrospective; Paediatric BACKGROUND AND OBJECTIVES: Little information is available concerning the natural history and optimal treatment of chronic nonbacterial osteomyelitis (CNO). We conducted a retrospective review to assess the clinical characteristics and treatment responses of a large cohort of pediatric CNO patients. METHODS: Children diagnosed with CNO at 3 tertiary care centers in the United States between 1985 and 2009 were identified. Their charts were reviewed, and clinical, laboratory, histopathologic, and radiologic data were extracted. RESULTS: Seventy children with CNO (67% female patients) were identified. Median age at onset was 9.6 years (range 3-17), and median follow-up was 1.8 years (range 0-13). Half of the patients had comorbid autoimmune diseases, and 49% had a family history of autoimmunity. Patients with comorbid autoimmune diseases had more bone lesions ($P < .001$), higher erythrocyte sedimentation rate ($P < .05$), and higher use of second line therapy ($P = .02$). Treatment response to nonsteroidal antiinflammatory drugs (NSAIDs), sulfasalazine, methotrexate, tumor necrosis factor a inhibitors, and corticosteroids was evaluated. The only significant predictor of a positive treatment response was the agent used ($P < .0001$). Estimated probability of response was 57% for NSAIDs, 66% for sulfasalazine, 91% for methotrexate, 91% for tumor necrosis factor alpha inhibitors, and 95% for corticosteroids. CONCLUSIONS: In a US cohort of 70 children with CNO, coexisting autoimmunity was a risk factor for multifocal involvement and treatment with immunosuppressive agents. Disease-modifying antirheumatic drugs and biologics were more likely to lead to clinical improvement than NSAIDs. Copyright 2012 by the American Academy of Pediatrics.

Burgemeister, Baeten and Tas (2012). Biologics for rare inflammatory diseases: TNF blockade in the SAPHO syndrome.

Retrospective; Adult Introduction: SAPHO is an invalidating syndrome characterised by Synovitis, Acne, Pustulosis, Hyperostosis and Ostitis. The low prevalence and heterogeneous presentation often leads to a significant diagnostic delay. Here, we provide an up-to-date overview of current insights into the pathogenesis and different treatment options. In addition, we describe the effects of anti-TNF treatment in three refractory cases. Case reports: Patient A is a 25-year-old female with hidradenitis suppurativa, inflammatory back pain and painful joints. After diagnosis, anti-TNF treatment was started resulting in clinical improvement. Patient B is a 44-year-old woman who presented with acne, palmoplantar pustulosis and anterior chest wall pain. Bone scintigraphy showed increased uptake at the anterior chest wall. Treatment with bisphosphonates resulted in temporary improvement and subsequent treatment with
anti-TNF induced long-term clinical improvement. Patient C is a 37-year-old woman with palmoplantar psoriasis, relapsing hidradenitis and inflammatory back pain. MRI revealed osteitis of the pubic bone. Anti-TNF was started for SAPHO syndrome. However, despite a clinical response, our patient discontinued treatment, resulting in rapid deterioration. Anti-TNF treatment was re-introduced followed by clinical improvement. Conclusion: These case reports illustrate, consistent with the current literature, that TNF blockers can be considered for treatment of refractory SAPHO syndrome. Van Zuiden Communications B.V.


Retrospective; Adult
SAPHO syndrome is a disorder involving the skin, bone and joints. The underlying causes of SAPHO are poorly understood, and treatment is, therefore, directed towards the individual symptoms. However, many patients are refractory to treatment, and new treatment options are needed. Herein, we describe a 28-year-old patient with SAPHO syndrome and palmoplantar pustulosis seen at our hospital. Treatment was initiated with non-steroidal anti-inflammatory drugs, but clinical improvement was poor. The addition of sulfasalazine and oral alendronate also failed to alleviate symptoms. We subsequently commenced treatment with adalimumab 40 mg every 15 days and suspended bisphosphonates. Following 4 weeks' treatment with adalimumab, there was clear articular improvement and disappearance of palmoplantar pustulotic lesions. Nocturnal inflammatory lumbar pain and global disease assessment were also improved. To our knowledge, this is the first report on the use of adalimumab for SAPHO. More studies are required to confirm our findings.


Retrospective; Paediatric
At initial presentation, chronic recurrent multifocal osteomyelitis may mimic acute hematogenous osteomyelitis; however, cultures of affected bone are sterile. Nuclear scintigraphy identifies additional foci of involvement that present concurrently or sequentially. Unlike acute bacterial osteomyelitis, chronic recurrent multifocal osteomyelitis seems unaffected by antibiotic therapy and typically responds to treatment with anti-inflammatory drugs. Surgical decortication has been reported for refractory cases. The case presented here illustrates the rare involvement of the mandible after initial presentation in the spine of a 4-year-old girl and the refractory nature of the disease over 6 years despite treatment with various medical and surgical therapies.

Clivati Brandt, et al. (2009). Multiple pustules on trunk, face, oral mucosa, genital area, palms and soles, arthralgia and anterior chest wall osteitis.

Retrospective; Adult
The article discusses the case study of a 51-year-old Brazilian man with multiple pustules on the trunk, palms, soles, face, oral mucosa and genital area, which is progressive for 5 months. High C-reactive protein level and erythrocyte sedimentation rate were detected by laboratory investigations. Intraepidermal and dermal pustules were seen in a biopsy taken from the cutaneous lesions. The diagnosis was SAPHO syndrome, wherein SAPHO stands for five morbid changes.


Retrospective; Paediatric
UNLABELLED: Chronic recurrent multifocal osteitis (OCRM) is a rare condition in children, of unknown aetiology, which may be misdiagnosed as osteomyelitis, arthritis or tumour. PATIENTS AND METHODS: We present a retrospective multicentric study of 17 patients (five boys and 12 girls) with an average follow-up of 7.5 years (six months-25 years). RESULTS: A spectrum of presenting features is possible, ranging from bone lesions alone to lesions combined with arthritis, palmoplantar pustulosis or psoriasis. The diagnosis was delayed from two weeks to five years. Roentgenographic evaluation was often normal at the beginning of the disease or showed nonspecific bone reactions. Radioisotope bone scans assisted in establishing the diagnosis and in identifying lesions that were initially clinically silent. Bone biopsies were performed in seven cases. Histopathological examination showed only mild inflammatory nonspecific changes. Microbiological cultures were always negative. Treatments were different according to the evolution of the disease and the hospital. There was no response to antibiotics in seven patients. The response to nonsteroidal anti-inflammatory agents and steroids was moderate and often transient. Salazopyrine and pamidronate treatment used in two patients allowed a durable remission. We lost sight of four patients, pain persisted in three in spite of treatment, it
disappeared in two with treatment, mild pain persisted in five without treatment and remission occurred in three without treatment. CONCLUSION: This study clarifies the clinical and radiologic features of chronic recurrent multifocal osteomyelitis. The recognition of this rare entity is often delayed and difficulties in patient management sometimes emerge from its usual protracted course.

**Colina, Govoni, Orzincolo and Trotta (2009). Clinical and radiologic evolution of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome: A single center study of a cohort of 71 subjects.**

**Retrospective; Paediatric**

Objective: To assess the basic features and outcomes of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. Methods: We identified all patients seen in our unit between 1990 and 2008 diagnosed according to the proposed inclusion criteria with SAPHO syndrome, who had a followup of at least 2 years. Results: Seventy-one patients (48 women, 23 men) with SAPHO syndrome were identified. The median disease duration at the end of followup was 10 years (interquartile range [IQR] 7–15 years), and the median followup duration was 11 years (IQR 6–11.5 years). Six patients were diagnosed with Crohn's disease. Fourteen patients had never had cutaneous involvement, but 8 patients presented >1 skin manifestation. Nine patients (13%) presented a limited (<6 months) monophasic disease course, 25 cases (35%) had a relapsing–remitting course, and 37 patients (52%) had an acute painful phase with a prolonged course lasting >6 months. A total of 4% of the patients were HLA–B27 positive. Female sex (odds ratio [OR] 7.2, 95% confidence interval [95% CI] 2.2–22.9) and the presence at onset of anterior chest wall (ACW) involvement (OR 5.7, 95% CI 1.8–18.1), peripheral synovitis (P = 0.0036), skin involvement (OR 10.3, 95% CI 3.4–31.1), and high values of acute-phase reactants (OR 7.7, 95% CI 2.7–22) were correlated with a chronic disease course and involvement of new osteoarticular sites. Conclusion: A chronic course is the more common evolution of SAPHO syndrome. Female sex, elevated erythrocyte sedimentation rate and C-reactive protein values, ACW involvement, peripheral synovitis, and skin involvement at the onset seem to be associated with a chronic course.

**Colina, La Corte and Trotta (2009). Sustained remission of SAPHO syndrome with pamidronate: a follow-up of fourteen cases and a review of the literature.**

**Retrospective; Paediatric**

OBJECTIVE: To evaluate the efficacy of intravenous (i.v.) pamidronate in patients with SAPHO syndrome refractory to first line treatments and to review the available literature on pamidronate for this indication. METHODS: We report 14 cases of SAPHO syndrome refractory to non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease modifying anti-rheumatic drugs (DMARDs) treated with i.v. pamidronate. All patients received i.v. 60 mg pamidronate/day for 3 consecutive days. The primary evaluation criterion was the disappearance of bone pain, considered as the reduction in the visual analogic scale for pain (VAS) greater than 50%. RESULTS: Ten patients were females and 4 were males. The mean age at onset was 40.4 years old. Ten patients presented a relapsing–remitting course, while in 4 cases the disease followed a prolonged course. In all cases anterior chest wall involvement occurred early in the disease. In 2 cases there was also a peripheral monoarthritis. Eleven patients experienced several flares of palmo-plantar pustulosis, while severe acne was present in 2. In one case there was no cutaneous involvement. Twelve of the 14 patients had a good response after 3 infusions and in 8 of these patients a sustained remission was observed. The recurrence of skin manifestations does not seem to be influenced by pamidronate. CONCLUSIONS: Pamidronate appears to be an effective treatment in the osteo-articular manifestations of SAPHO syndrome. As far as cutaneous lesions are concerned, evidence of efficacy is not so impressive.

**Compeyrot-Lacassagne, Babyn and Laxer (2007). Pamidronate treatment of chronic noninfectious inflammatory lesions of the mandible in**

**Retrospective; Paediatric**

Noninfectious inflammatory lesions of the mandible occur in chronic recurrent multifocal osteomyelitis (CRMO). Diffuse sclerosing osteomyelitis of the mandible (DSOM) is a condition thought to be a localized form of CRMO. Recently, bisphosphonate therapy, and particularly intravenous pamidronate, has been proposed as a treatment for patients with both CRMO and DSOM who do not improve with nonsteroidal antiinflammatory drug treatment. We report our experience using pamidronate in 2 children with chronic noninfectious osteomyelitis affecting the mandible. We describe the clinical and radiographic features and the treatment, side effects, and clinical and radiographic responses. Our experience suggests that pamidronate is an effective second-line therapy.
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<th>Reference</th>
<th>Study Design</th>
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<td>Conway and Khan (2011). Chronic recurrent multifocal osteomyelitis diagnosed in an adult</td>
<td>Retrospective; Adult [Conference abstract]</td>
<td>Aim/Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare autoinflammatory disorder of unknown origin. It is characterized by recurrent sterile multifocal bone lesions. CRMO classically presents in children. We present a case of CRMO first diagnosed in a 39 year old man. To our knowledge, this is the first report of newly diagnosed CRMO in an adult. Method: He gave a history of episodic pain in both hips and his lower back since childhood. He had been diagnosed with ankylosing spondylitis at the age of 18 and was lost to follow up until this review. He had a left total hip replacement at the age of 22 and a pyoderma gangrenosum at 38. He had persistently elevated inflammatory markers over the years, his latest ESR was 76 mm/h, CRP 73 mg/L, haemoglobin 10.2 g/dL and platelets 596 x 10^9/L. Serum protein electrophoresis revealed a polyclonal gammopathy. Alkaline phosphatase was elevated at 161 IU/L. Plain radiography revealed sclerosis in the left hemipelvis. Isotope bone scan demonstrated increased activity in the left hemipelvis. 2 previous bone biopsies were reported as showing non-specific focal inflammatory changes. Results: An MRI and repeat bone biopsy of the left sacrum were performed. MRI demonstrated marked osteitis in the left hemipelvis. Sacral biopsy demonstrated changes consistent with osteomyelitis. Microscopy and cultures including TB cultures were negative. A diagnosis of CRMO was made. Treatment with NSAID’s and pamidronate was commenced with marked symptomatic and biochemical improvement. Conclusions: In conclusion our case demonstrates the need for awareness of the possibility of the diagnosis of CRMO in adults.</td>
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<td>Davies, et al. (2014). Bilateral pulmonary consolidation associated with chronic recurrent multifocal osteomyelitis.</td>
<td>Retrospective; Paediatric [Conference abstract]</td>
<td>Aims A nine-year-old girl with Chronic Recurrent Multifocal Osteomyelitis (CRMO) developed asymptomatic bilateral pulmonary consolidation that was thought to be part of the CRMO disease process. Approximately 25% of patients with CRMO have another inflammatory disorder; usually of the skin or gastrointestinal tract. The association of CRMO with pulmonary lesions has been reported only twice in the literature. This case is the first reported in which lung infiltrates were successfully treated with azithromycin. Methods The patient presented with nine-months of right leg pain. MRI showed an area of high signal in the right femoral diaphysis. Biopsy was negative for pathogens and malignancy. She developed painful swelling of the right clavicle and spinal discomfort. An isotope bone scan showed abnormal uptake in both clavicles and one vertebral body and CMRO was diagnosed. She responded to...</td>
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ibuprofen but symptoms returned. Repeat isotope bone scan showed improved appearances at the bony sites, however low resolution CT scan performed as part of this showed bilateral pulmonary infiltrates. Chest radiographs showed left mid-zone consolidation. After four months this resolved but new infiltrates were seen in the left apex and right upper-zone. There were no clinical features of infection, serum C-reactive protein and white cell count were normal. She was given azithromycin for 4 weeks in view of its known anti-inflammatory properties; in one study seven of thirteen patients with CRMO showed a rapid clinical improvement in bone lesions when given azithromycin[1]. Results Radiographs taken 2 and 6 months after azithromycin found near complete resolution of the pulmonary abnormalities. She received eight pamidronate infusions and symptoms resolved except for clavicular discomfort. Inflammatory bone lesions resolved on pelvic MRI. The two previous cases of pulmonary involvement in CRMO received prolonged antibiotics for two [2] and six months [3]. (A) Axial proton density MRI image through right thigh showing cortical high signal lesion (arrow) with evidence of marrow oedema. (B) Clinical photograph demonstrating bony prominence of the medial ends of each clavicle. (C) Coronal CT image of the thorax demonstrating bilateral pulmonary infiltrates. (D) Anterior view only from isotope bone scan showing increased activity arising from both clavicles. The right femoral lesion can just be appreciated. (E) Chest radiograph showing left midzone infiltrate. (F) Chest radiograph demonstrates new infiltrates at left apex and right mid zone (G) Chest radiograph taken two months following completion of azithromycin therapy demonstrating near complete resolution of the pulmonary infiltrates. Conclusions Our observations of pulmonary involvement add to the understanding that CRMO is a heterogeneous disease; it is likely that such prolonged and atypical pulmonary changes are part of the disease process of CRMO. Pulmonary consolidation is a rare complication of CRMO, should be looked for in patients with refractory disease and may respond to azithromycin. (Figure Presented).


**Retrospective; Paediatric [Conference abstract]**

Background. There are no guidelines for the treatment of SAPHO (Synovitis, Acne, Pustulosis, Osteitis, Hyperostosis) syndrome, particularly in the situation of inadequate response to NSAIDs. Bone involvement (hyperostosis, osteitis) may legitimate the therapeutic use of bisphosphonates. Objectives The aim of this study was to evaluate efficacy and tolerance of intravenous (IV) pamidronate in patients with SAPHO. Methods Open monocentric retrospective study including patients with SAPHO syndrome (Benhamou "criteria") and treated with IV pamidronate. Main characteristics of the disease and the treatments were recorded. Pamidronate was administered IV, 60 or 120 mg (one or 2 infusions), eventually repeated every 4 weeks. Efficacy was assessed by global patient VAS, % of improvement, physician’s judgment and biologic parameters (ESR, CRP). Side effects were recorded. Results 22 patients were evaluable: 19 women, mean age 48 years, mean disease duration 5.8 years. Skin involvement was present in 18 patients, 22 patients had osteitis, 4 hyperostosis and 13 a sterno clavicular involvement. Initial CRP was 16+22 mg/l, ESR 25 and VAS 67+21 mm. The mean number of infusions was 5.6 (1 to 23). A significant improvement is obvious at month 1 (VAS 44+18; p=0.01), no more significative at month 2 (p=0.06). Physician's judgment was: efficacy (n=13), partial or transient efficacy (n=8), inefficacy (n=1). In case of efficacy, the mean duration of efficacy under treatment was 7 months. A non significant decrease in ESR was observed at month 1 (25 to 14 mm). Side effects were noted in 11 cases: flu-like syndrome (N=5), fever (3), hypocalcemia, conjunctivitis, headache, vein inflammation. No predictive factor for good response could be found in these patients. Conclusions This study suggests a modest global efficacy, variable and transitory, of IV pamidronate treatment in SAPHO syndrome. Analysis of the results remains difficult in the absence of validated response criteria in this heterogeneous disease.

Docquier, Mousny, Malghem and Rombouts (2006). Chronic osteomyelitis of clavicle as primary

**Retrospective; Paediatric**

Four cases of chronic osteomyelitis of clavicle as primary manifestation of synovitis, acne, pustulosis, hyperostosis, osteomyelitis (SAPHO) are reported in adolescents. In all cases a typical radiographical evolution had been observed with progressive slow migration of sclerotic area from medial to lateral side of clavicle. Long-term evolution was alternation of remission and exacerbation but none of the patients healed. 2006 Elsevier Masson SAS. All rights reserved.

**Retrospective; Paediatric**

Objective: To date there is no uniformly effective treatment for either chronic recurrent multifocal osteomyelitis (CRMO) or synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. We report on our clinical experience of using biologics to treat children with these conditions. Methods: Retrospective descriptive case series of four children with refractory disease treated with biologics. Disease activity was assessed at predetermined time points (T =0, T = 6 weeks and T = 12 months after the start of biologic therapy, and at latest follow-up) using a combination of clinical examination and radiological findings: a 10 cm pain and physician visual analogue scale; the Childhood Health Assessment Questionnaire as an assessment of disability; and changes in markers of systemic inflammation. Results: There was an initial improvement in all parameters assessed for all three children treated with TNF-alpha blockade, although the third case had to discontinue the therapy due to a suspected (but unconfirmed) fungal skin infection. Anakinra treatment alleviated the symptoms in the fourth patient at 6 weeks, but there was no sustained response to treatment at 1-year follow-up. Conclusion: We present our preliminary experience of using biological therapies to treat children with CRMO and SAPHO in conjunction with other immunosuppression. Further studies are needed to establish the role of these therapies in refractory CRMO and SAPHO. The Author 2010.


**Retrospective; Paediatric**

AIM: To report and describe a series of four cases of chronic recurrent multifocal osteomyelitis (CRMO) and to discuss therapeutic options, particularly bisphosphonate therapy. METHODS: Retrospective review of four CRMO cases in two Pediatric Units in Lisbon, between 2005 and 2010. RESULTS: Median age of first CRMO symptoms was 11.3 years (range 9-13). The more affected sites were the metaphysis of the long bones, pelvis and coxofemoral joints. Median number of initial bony lesions for each patient was 2.3 (range 1-3) at onset and 3.8 (range 2-6) during the disease course. All patients failed to respond to NSAIDs therapy. Two patients received corticosteroids, with clinical disease remission in only one of them. All patients received bisphosphonates (alendronate in two and pamidronate in two), all with good clinical response and induction of clinical remission in two of them. After a median follow-up period of 4.3 years (range 4-5), three patients are clinically asymptomatic and one patient remains with chronic residual pain. CONCLUSIONS: The treatment of CRMO is not standardized. Bisphosphonate therapy can be of benefit to patients with relapsing symptoms. Randomized controlled multicentric trials are needed to provide better evidence for universal recommendation and definition of bisphosphonate therapy protocol.


**Retrospective; Age unclear [Conference abstract]**

Background: Autoinflammatory diseases (AIDs) are a group of disorders with a heterogeneous clinical spectrum that is characterised by recurring episodes of fever and systemic inflammatory symptoms, affecting the serosal surfaces, joints, skin and eyes. Most of them are caused by mutations in specific genes that lead to the dysregulation of innate immune system. Within these disorders are included among AIDs of the bone, including chronic recurrent multifocal osteomyelitis (CRMO)-most common in children-and Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis (SAPHO) syndrome, that is the most common in adults. Method: We report the features of patients with AIDs observed at our department between 2009 and 2013. Results: Fourteen patients were diagnosed as periodic fever. All cases did not satisfy criteria for familial Mediterranean fever (FMF) and had a negative screening for MEFV, TNFRSF1A and MVK genes mutations. Three of them had Periodic fever, Aphthous stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome, two had atypical adult-onset Still's disease, and one patient had both periodic fever and Xlinked thrombocytopenia. Five cases were responsive to colchicine. Ten patients were diagnosed with SAPHO and one with CRMO. In the SAPHO group, chronic...
Inflammatory disorders of the skin were observed in 9/10 patients, palmo-plantar pustulosis in 7/9 and psoriasis vulgaris in 2/9. Sternoclavicular osteitis was present in all cases, sacro-ileitis in 5/10 and Spondylodiscitis in 2/10 cases. Corticosteroids, common immunosuppressive drugs and pamidronate were unsuccessful in 9/10 patients. They were treated with biological drugs, including anti-TNFalpha agents, anti-IL1 agents and ustekinumab achieving total or partial remission. Conclusion: Interestingly, all our patients with autoinflammatory diseases have a negative genetic screening and we observed a good response to colchicine. Furthermore, biological drugs showed to be effective in almost all SAPHO and CRMO cases.


Retrospective; Adult
Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a clinically heterogeneous entity, encompassing a variety of debilitating conditions that have in common inflammation of the skeletal system and skin. To date, there is a paucity of documented efficacious treatment options. We report a 48-year-old man with skeletal and cutaneous signs and symptoms who improved dramatically after treatment with a combination of isotretinoin and pamidronate. This report provides an alternative treatment regimen for SAPHO that addresses the possible underlying pathophysiology of this likely underdiagnosed syndrome.


Retrospective; Paediatric [Conference abstract]
Background Chronic recurrent multifocal osteomyelitis (CRMO) is a rare autoinflammatory disease in children. First-line treatments used are nonsteroidal anti-inflammatory drugs (NSAIDS). Secondary treatments after NSAIDS in case of refractory CRMO are not standardized and have been few evaluated. Biphosphonates, in particular pamidronate, have been used off label in a limited number of patients. Objectives A retrospective survey and chart review to evaluate the reasons for use, the efficacy and the tolerability of IV pamidronate in 13 patients with difficult CRMO. Methods Thirteen of the 30 patients followed in the pediatric rheumatology unit at Bicetre hospital, were analyzed retrospectively. Pamidronate treatment was documented as follows: reasons for its use, administration scheme, clinical efficacy (pain was evaluated by visual analog scale (VAS) and tolerability. Radiological changes were evaluated where available. Results Thirteen patients (4M, 9F) were treated by pamidronate from November, 2004. The median age at treatment was 10 years (6-14 years). Pamidronate was administered, on demand, intravenously by cycles of 3 consecutive days (0.5 mg/kg at J1, then 1 mg/kg at J2 and J3), following the protocol for osteogenesis imperfecta. Eleven patients received from a single cycle, 1 patient received 4 cycles and 1 patient 6 cycles. Pain resistant to oral and IV NSAIDS was the main reason for all the patients. VAS was 6/10 before pamidronate, and 0/10 36 hours after pamidronate infusion for 11/13 patients. Pain persisted for 1 patient and disappeared after 3 weeks for another one. The clavicle swelling disappeared in 1/5 patients and clearly decreased in 4/5 patients. The median duration of symptom-free intervals between 2 crises was 10 months (1-21.6). Five patients had a MRI after pamidronate treatment, which showed a decrease of the number of the lesions for 4 of them. The main side effects of pamidronate infusions were mild and transient: fever (n=9) with 5 flu-like symptoms, hypocalcaemia (>2mM, n=6; 2 mM, n=5, and 2 were symptomatic). Conclusions Our observations show that about 1/3 of patients with CRMO may present difficult to treat acute attacks of bone pain. In these cases, pamidronate appears to be the best pain relieving treatment with a rapid time of response and with limited side effects.


Retrospective; Adult
SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome defines an association of inflammatory cutaneous disorders with osteoarticular manifestations and represents a clinical and therapeutic challenge. We report a case of severe SAPHO syndrome with acne conglobata and a diffuse involvement of the anterior chest wall and sacroiliac joints that required treatment with isotretinoin and adalimumab, a new fully human anti-tumor necrosis factor (TNF)-alpha monoclonal antibody. Combination treatment determined a complete clinical remission of cutaneous and osteoarticular manifestations after 48 weeks. Despite maintenance of clinical remission, follow-up imaging studies after 24 months of adalimumab monotherapy revealed osteoarticular disease progression, with features of...
inflammatory osteitis. TNFalpha antagonists have been used as third-line therapy for SAPHO syndrome in single case reports or case series, but these lack consistent long-term follow-up. SAPHO syndrome can present an intermittent-favorable course in the majority of cases as well as a chronic-progressive course, the latter requiring aggressive combination treatment with TNFalpha antagonists and conventional systemic agents.

**Gerheim Machado, et al. (2005).** [Pamidronate treatment in SAPHO syndrome.][Portuguese]

**Retrospective; Paediatric**

Although relatively rare and still not frequently diagnosed, SAPHO syndrome has specific features that originated the acronym: Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis. Diagnosis is made possible through a combination of clinical manifestations, laboratory findings, and radiological exams, with bone scintigraphy playing a prominent role. Pamidronate is a second-generation bisphosphonate that affects bone turnover and exhibits anti-inflammatory properties, being a treatment option for this entity. With this case report, we aim to draw attention to SAPHO syndrome and the use of Pamidronate for its treatment.

**Gleeson, et al. (2008).** Childhood chronic recurrent multifocal osteomyelitis: pamidronate therapy decreases pain and improves vertebral shape.

**Retrospective; Paediatric**

OBJECTIVE: Chronic relapsing multifocal osteomyelitis (CRMO) results in significant morbidity, especially in those with vertebral collapse. Symptomatic benefit with intravenous pamidronate (PAM) has been shown; however, few studies have demonstrated radiological benefit. We describe clinical and radiological data on 7 pediatric cases of CRMO treated with PAM. METHODS: Retrospective chart review on all children with CRMO treated with PAM. Response to PAM was measured by subjective reports and radiology including vertebral morphometry. RESULTS: Seven patients (1 male) presented with bone pain at a median age of 8 years (range 5-14). Symptoms had been present for a median of 18 months (range 11-51) before PAM therapy. All patients had involvement of multiple nonspinal sites, 5 children had spinal involvement with vertebral fractures, and 5 had joint involvement. Six cases had symptomatic improvement within 6 months of starting PAM, which was sustained during PAM therapy (median 26 mo, range 6-41) and persisted in the 4 cases who had ceased treatment for the duration of followup (27 mo, range 18-51). The least benefit was seen in the 3 cases with synovial joint involvement. The 3 cases with spinal radiological followup showed modeling of vertebral fractures and in one patient improvement in kyphosis. No radiological improvement in nonspinal lesions was seen. CONCLUSION: PAM therapy was associated with symptomatic improvement and vertebral modeling in children with CRMO. We suggest that children with bone pain and/or spinal involvement be considered for PAM therapy early after diagnosis.


**Retrospective; Age unclear**

OBJECTIVE: Pamidronate is usually administered because of its antiosteoclastic effects but seems to have anti-inflammatory properties also. SAPHO syndrome is characterized by both increased bone remodeling and inflammatory osteitis, indicating that it may respond favorably to pamidronate's dual mechanism of action. PATIENTS AND METHODS: We report five cases of SAPHO syndrome refractory to standard treatments. All patients were taking nonsteroidal anti-inflammatory drugs, either alone or in combination with analgesics, glucocorticoids, and/or second-line drugs. We used intravenous pamidronate during exacerbations of the disease. The primary evaluation criterion was the reduction in the visual analog scale (VAS) score for pain, and a response was defined as a greater than 50% reduction. RESULTS: Four of the five patients had a response after 1 week. Two of these four patients still met the response criterion after 3 months. Four of the five patients were able to reduce the dosage of their usual medications. In one patient, pamidronate therapy was associated with an increase in the intervals between exacerbations. Joint Bone

**Habibi, Thompson, Thyagarajan and Ramanan (2013).** Unusual presentation of spinal involvement in a child with chronic recurrent

**Retrospective; Paediatric [Letter]**
<table>
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<th><strong>multifocal osteomyelitis.</strong></th>
<th><strong>Retrospective; Paediatric</strong></th>
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<td>Handly, et al. (2013). Bisphosphonate therapy for chronic recurrent multifocal osteomyelitis.</td>
<td>This patient was diagnosed with chronic multifocal recurrent osteomyelitis of the ankle approximately 4 years prior to the presented images. Multiple treatments were administered, most notably monthly intravenous pamidronate, a therapy that was continued for 17 months, until recrudescent disease prompted a change in therapy. At the time of the presented images, the patient had not received bisphosphonate therapy for 2 years.</td>
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<td>Hayem, et al. (2010). SAPHO syndrome treated by TNF alpha-blocking agents. Report of 45 cases.</td>
<td><strong>Retrospective; Mixed [Conference abstract]</strong> Objectives: To evaluate the efficacy and safety of TNF-alpha-blocking agents in SAPHO syndrome. Methods: A retrospective study was conducted by the &quot;Club Rhumatismes et Inflammation&quot; (depending from the French Society of Rheumatology) to find and analyse all the case records from patients suffering from SAPHO syndrome, who had been treated with at least one of the three following TNFalpha-blocking agents: adalimumab (ADA), etanercept (ETN), or infliximab (IFX). Demographic and clinical data were collected, including previous treatments and incident side effects. The efficacy of anti-TNFalpha treatment was evaluated at last follow-up visit, based on the decrease of SAPHO syndrome-related symptoms, appreciated by each patient on a visual analogic scale (VAS). A score decrease of more than 80% was considered as a remission. An improvement comprised between 50 and 79% indicated a partial efficacy and a reduction less than 50% was interpreted as a lack of response. Results: The case records of 45 patients (33F/12M; mean age 45) were available for analysis. The mean age at disease onset was 31 years (range 11-61). In all patients, SAPHO syndrome was previously considered as refractory to at least three of the five following types of treatments: non steroidal anti-inflammatory drugs, corticosteroids, antibiotics (various regimens), synthetic disease modifying anti-rheumatic drugs (methotrexate or sulfasalazin), and bisphosphonates. Forty-four patients also had active cutaneous manifestations when TNF-alpha-blocking agent was started. Thirty patients received ETN (25 mg biw or 50 mg qw SC; first biologic to be used in 17 patients; follow-up: 3-60 months). Remission was observed in 11 patients, and partial efficacy in 10. Twenty-two patients were treated with ADA (40 mg SC eow; first biologic in 7 patients; follow-up: 2 to 17 months). Remission and partial efficacy were registered in 12 and 2 patients, respectively. IFX was administered to 18 patients (5 mg/kg, infusions at week 0, 2 and 6, then every 8 weeks; first biologic in 12 patients; follow-up: 3-65 months). Remission and partial efficacy were noted in 5 and 5 patients, respectively. The treatment with TNF-alpha-blocking agents was stopped 11 times for a side effect, in 9 patients: 3 times with ETN (1 papillomavirus cutaneous and genital infection, 1 psoriasis vulgaris, 1 optic neuritis); 4 times with ADA (2 allergic reactions, 1 pyelonephritis, 1 hidradenitis suppurativa of the breast) and 4 times with IFX (1 psoriasis vulgaris, 1 flare of palmoplantar pustulosis, 1 hidradenitis suppurativa of the breast and 1 peritonitis). Conclusion: TNF-alpha-blocking agents seem to represent an interesting therapeutic option in refractory cases of SAPHO syndrome, without unpredicted side effects.</td>
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<tr>
<td>Henriques, Sousa, Panarra and Riso (2011). The dark side of SAPHO syndrome.</td>
<td><strong>Retrospective; Adult</strong> SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) is a relatively rare entity. The therapeutic approach of patients with SAPHO syndrome has included multiple drugs with varying success and incoherence responses. The therapy is still empirical today. SAPHO syndrome is commonly treated with non-steroidal anti-inflammatory drugs, bisphosphonates and non-biologic disease modifying antirheumatic drugs. Recent reports showed successful treatment with tumour necrosis factor alpha (TNF alpha) antagonists, but there is still a dark side of SAPHO syndrome including a subgroup of patient's refractory to all the treatments that have been empirically experienced. A clinical report of a patient with SAPHO syndrome with 12 years of evolution is described. All the therapeutic approaches, including anti TNF alpha therapy, have not prevented the clinical and radiographic progression of the disease. Given that the disease affects mostly younger patients, new therapeutic strategies are necessary in order to avoid potentially irreversible joint and bone lesions. Copyright 2011 BMJ Publishing Group. All rights reserved.</td>
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<td>Hess, et al. (2011). Life-</td>
<td><strong>Retrospective; Paediatric</strong> Life-threatening disseminated tuberculosis developed in a 17-year-old girl who was</td>
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treated with the TNF-alpha blocker adalimumab for refractory SAPHO syndrome. The patient presented to the emergency department with dyspnea and somnolence and within 2 h developed the clinical picture of a septic shock. In addition to this unusual presentation, she showed a complicated course with increasing cerebral granuloma formation in spite of adequate antimycobacterial treatment. Immune reconstitution after discontinuation of TNF blockade may contribute to this "paradoxical reaction." Possible implications for screening, diagnosis, and treatment of tuberculosis in children and adolescents receiving anti-TNF treatment are discussed.

**Hospach, et al. (2010). Spinal involvement in chronic recurrent multifocal osteomyelitis (CRMO) in childhood and effect of pamidronate.**

*Retrospective; Paediatric*

There are only a few studies that address the frequency and type of spinal involvement in patients with chronic recurrent multifocal osteomyelitis (CRMO) as well as the outcome of these patients treated with pamidrone (PAM). We performed a retrospective study on patients with CRMO and analyzed clinical and pain assessments as well as regional and whole body MRI findings and compared with posttreatment findings. Of 102 children and adolescents with CRMO, 27 (26%) had involvement of the spine. Vertebral deformities were seen in 14 of these 27 patients, scoliosis or kyphosis in 6. After routine whole body MRI, 19 complained of back pain, whereas eight were asymptomatic with spinal lesions detected incidentally. A total of 72 spinal lesions were detected, thoracic vertebrae being the most commonly affected. Seven patients were treated with PAM; all of whom had vertebral deformities and ongoing back pain. Pain resolution was achieved within 3 months of PAM treatment in every case. One patient subsequently developed a pain amplification syndrome. Repeat MRI performed at a mean interval of 13 months revealed partial or complete resolution of vertebral hyperintensities in every patient. Improvement of vertebral height was seen in a total of three vertebrae in two patients. Severe side effects were not observed. In conclusion, we demonstrated that spinal involvement and associated vertebral deformities with or without kyphoscoliosis are not rare in CRMO, and PAM appears to be an effective and safe treatment for this condition. Although controlled studies are urgently needed, the use of PAM for refractory CRMO with extended spinal involvement (vertebral deformities, kyphosis, and scoliosis) should be considered, especially after failing of conventional therapy.

**Kerrison, Davidson, Cleary and Beresford (2004). Pamidronate in the treatment of childhood SAPHO syndrome.**

*Retrospective; Paediatric*

**BACKGROUND:** SAPHO syndrome is increasingly recognized within the paediatric population. Conventional therapeutic approaches have often not been effective. Pamidronate is a second-generation bisphosphonate that affects bone turnover and demonstrates anti-inflammatory properties. In small case series it has given symptomatic relief to adults with this condition. **OBJECTIVES:** To report the clinical experience with pamidronate in childhood SAPHO syndrome. **METHODS:** A retrospective observational study of all children with SAPHO syndrome treated with pamidronate between 1996 and 2003 at a tertiary rheumatology centre. The standard dosing regime for pamidronate was 1 mg/kg to a maximum of 30 mg, administered daily for three consecutive days, repeated 3-monthly as required. Response to treatment was determined by clinical observation, patient subjective response and reduction in other treatments. **RESULTS:** Seven girls were treated, with a median (range) age at diagnosis of 11 yr (9-15 yr). All patients demonstrated a beneficial clinical response, with relief of pain, increased activity and improved well-being. Subsequent courses of pamidronate were used in all patients. Other medications including corticosteroids and methotrexate could subsequently be stopped. Transient symptoms were associated with the initial course of pamidronate in some patients. No serious adverse events were reported. **CONCLUSIONS:** Pamidronate was associated with a marked improvement in function and well-being, and a reduction of pain and use of other medications in all patients, with no significant adverse effects. This study represents preliminary clinical data. A prospective multicentre study is necessary to assess the role and long-term safety of pamidronate in the management of childhood SAPHO syndrome.
**Presentation of chronic non-bacterial osteomyelitis.**


**Retrospective; Adult**

Chronic recurrent multifocal osteomyelitis (CRMO) is a chronic, relapsing, inflammatory, non-infectious disorder of the skeletal system and is of unknown origin. Early diagnosis of the disease is essential to exact treatment. The relationship between inflammatory bowel disease and CRMO is understood as extraintestinal rheumatic manifestations. CRMO associated with ulcerative colitis (UC) is very rarely reported. This case is first report of sternocostal involvement in CRMO associated with UC.

Korczowski, Lonc, Dabrowska and Guz (2010). [Chronic recurrent multifocal osteomyelitis - Diagnostic problems.] [Polish]

**Retrospective; Paediatric**

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare disease of presumptive autoimmune etiology, characterized by aseptic inflammation of osseous tissue. CRMO is the most severe form of sterile inflammation of bone in children. Diagnostic problems in two girls suffering from severe form of CRMO are presented. To differentiate CRMO from neoplastic process was the main diagnostic challenge. Treatment with antibiotics and non-steroidal antiinflammatory drugs were not effective. Intravenous infusions with sodium Pamidronate were introduced resulting in clinical improvement. 2010 by Polskie Towarzystwo Pediatryczne.


**Retrospective; Paediatric [Conference abstract]**

Introduction: Pediatric chronic nonbacterial osteomyelitis (CNO) is a sterile inflammatory bone disorder in which innate and adaptive immunity dysfunction involved. Unifocal and multifocal disease courses are known. The modern treatment modalities include non-steroid antiinflammatory drugs (NSAIDs), steroids, sulfasalazine (SSZ), methotrexate (MTX), bisphosphonates and biologic drugs - TNFalpha and ILbeta-antagonists, with limited data. Objectives: The aim of our study was to assess children with CNO and to evaluate efficacy of treatment modalities. Methods: Our cohort of CNO patients included 22 children, 8 boys and 14 girls. Monofocal disease course was in 9/22 children (40.9), multifocal in 13/22 (59.1) with mean 6 foci per patient. Histological confirmation was made in 13/22. Repeated MRI, CT and bone scintigraphy was performed in all patients. 3 patients have family history of autoimmunity (1 Crohn's disease, 1 psoriasis, 1 ankylosing. 16 patients (72.7%) had comorbid autoimmune diseases (different types of JIA): 5 had monarthritis, 1 arthritis with uveitis, 1 psoriatic arthritis, 1 polyarthritis PF neg, 6 had enthesitis-related arthritis (3 had ankylosing spondyloarthritis) and 1 had Crohn's disease. Spine involvement was in 5/22 (22.7). Onset age was 8.5 (6.3; 10.5) years, the right diagnosis delay was 3.6 (1.7; 9.5) months. Results: Fever at onset, high painVAS and parental VAS scores highly correlated with risk of relapse disease course. Treatment: effectiveness of NSAID only 3/10 (30%), SSZ -1/5 (20%), corticosteroids - 0/3 (short-term effect only), MTX - 4/7 (57.1%), pamidronate (PAM) with partial response 2/12 (16.7%) and with complete response - 10/12 (83.3%). Biologics - adalimumab and etanercept were effective in 3/4 (75%) patients, who fail to NSAID, MTX, PAM and SSZ. During disease course treatment lead to decreasing sings of disease activity, such as: parental VAS (p = 0.015), pain VAS (p = 0.026), MDVAS (p = 0.026), CRP (0.0008), WBC (p = 0.006), ESR (p = 0.00024), PLT (0.014). The main effectiveness belonged to PAM (p = 0.003) and biologics (p = 0.07) in decreasing of pain VAS (-100% and -80%), parental VAS (-92% and -74%) and MD VAS (-93% and -70%, respectively). We calculated the cumulative probability of survival (event of interest: CNO flare) in the entire patient sample, depending the kind of treatment (PAM, MTX and NSAID) obtained by the Kaplan-Meier method. Significant difference was proved comparing 3 therapeutical branches (p = 0.028). MTX treatment was effective (p = 0.04), as well as PAM (p = 0.01) than NSAID. Only flu-like syndrome during PAM treatment was in 10/12 (83.3%). No any others side effects were reported. All patients who had flu-like syndrome on first infusion had complete response to PAM, vice verse patients, who had no such complication had only partial response to this treatment. Conclusion: CNO is a group of chronic inflammatory conditions associated with different rheumatic diseases. The most
Kostik, et al. (2013b), P03-006 pamidronate rapidly decreases CRP and TNFA in CNO. **Retrospective; Paediatric [Conference abstract]**

Introduction: Pediatric chronic nonbacterial osteomyelitis (CNO) is a sterile inflammatory bone disorder of presumed autoimmune or autoinflammatory etiology. Sometimes CNO associated with other rheumatologic conditions, such spondyloarthritides, sacroileitis, IBD, pyoderma gangrenosum and psoriasis as well as a part of distinct autoinflammatory disease (AID), such as DIRA syndrome. Case report: 14 year old girl was admitted to our department with pain, low and moderate grade fever, delay to thrive and history of osteomyelitis. Her family history was unremarkable. The onset of disease was in the age of 10 months with small bone lesion in distal epiphysis of femur and intensive irritability. After 1 month of immobilization she had an intensive bone overgrowth with peristomal reaction and deformity in distal epiphysis. The bone biopsy confirmed non-specific osteomyelitis, malignancy and infection was excluded. Antibiotic treatment was ineffective. Her disease had widespread course involving the whole femur from distal to proximal part. The main features included bone lesions, bone overgrowth, intensive periostal reaction and sclerosis. The disease had persistent course without remission episodes, accompanied with pain, irritability, fever and lead to elongation of femur (+8 cm). She had failure to thrive since the age of 6 years. Currently she looks like as 8 year old girl in her 14 years. Intellectual development is normal. No signs of any other diseases, particularly recurrent infections and involvement of other bones. A Tc99m bone scan revealed increased uptake only in the whole femur (+400%). Laboratorial features were specific for AID: persistent microcytic anemia (Hb-8.0 gr/dl), ESR>110 mm/h (n.v.<15), CRP >150 mg/l (n.v.<5), sideropenia. Immunological assessment was detected increased Ig A (5.2 gr/l), Ig G (26.2 gr/l) and decreased zymozaninduced chemoluminescence (11 Units, lower limit -160). Chronic granulomatose disease (CGD) was confirmed without any known foci of serious infection during her life. Also high levels of IL1beta, IL-6 and TNFAlpha were detected. NSAIDs appeared short temporary effect. In our clinic we started to treat her with pamidronate 1,5 mg/kg on 1 cycle, with monthly repeated courses. After first cycle the CRP was decreased from 150 to 19 mg/l, ESR from 58 to 12 mm/h, TNFalpha from 169 to 19 pg/ml. Hb increased up to 10.2 gr/dl. No pain, irritability and fever after initiating pamidronate therapy. Discussion: We describe a case of early presented chronic nonbacterial osteomyelitis affected of only one bone. Early onset (first year of life), permanent prodromal course, systemic features (fever, failure to thrive), typical laboratorial changes (microcytic anemia, very high ESR and CRP), increased levels of IL1beta, IL-6 and TNFalpha are characteristic for AID. The described case can be new form of an AID with clinical features resembling CRMO or DIRA diseases. Biologics can be considered to be a promising way of further treatment as it has been reported to be successful already for small number of cases.


**Retrospective; Age unclear**

We report on a young woman suffering from SAPHO syndrome with back pain and arthritis of the sternoclavicular joints. This inflammatory disorder of the osteoarticular system (synovitis, osteitis, and hyperostosis) is associated with severe acne or palmoplantar pustulosis. The patient was treated with pamidronate, NSAID and physiotherapy which improved the musculoskeletal symptoms completely. The acne was treated with isotretinoin.

Lu, Kwiatzek and Limaye (2006). Intravenous pamidronate in the treatment of sternoclavicular hyperostosis. **Retrospective; Adult**

The SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) is a rare clinical entity in which osteosclerosis and osteolysis are consistent radiological findings. We present a patient with SAPHO syndrome manifesting as painful sternoclavicular hyperostosis treated successfully with pamidronate. For the first time, a reduction in isotope bone scan activity was documented in parallel to a favourable clinical response. Bisphosphonates have potent antosteoclastic and anti-inflammatory effects. By virtue of their dual effects on bone remodelling and inflammation, they seem an appropriate therapy in the management of SAPHO syndrome. This case demonstrates the efficacy of pamidronate, both clinically and radiologically, as first line therapy for patients with isolated hyperostosis. 2006 Asia Pacific League of Associations for Rheumatology.

Marshall, **Retrospective; Adult [Letter]**

Effective treatment modalities were PAM, biologics and MTX. PAM was safety and can reach the rapid response and maintain long sustained remission.
**Miettunen, Wei, Reslan and Kaura (2010).**

Long term outcome in pediatric patients with severe chronic non-bacterial osteitis following intravenous pamidronate therapy: Case series with 9 patients.

**Prospective; Paediatric [Conference abstract]**

Objectives: To describe long-term clinical outcome and bone resorption response in pediatric patients who were previously treated with intravenous pamidronate (IVP) for chronic non-bacterial osteitis (CNO). Methods: All patients who were treated with IVP for CNO between 2003-2006 at a single centre were prospectively followed until January 2010. Patients who developed recurrent pain for > 2 weeks were investigated with whole-body magnetic resonance imaging (WBMRI) to identify active CNO sites. Following confirmation of CNO, patients were offered either non-steroidal anti-inflammatory medications or retreatment with IVP (1 mg/kg/day, maximum 60 mg/day; given as 1-day cycles/month). Patients with a single CNO lesion received 1 IVP, and patients with 2 or more lesions received monthly IVP. WBMRI was repeated every 3 months. IVP was discontinued once WBMRI revealed resolution of CNO. Visual analog scale for pain (VAS) and bone resorption marker urine N-telopeptide/urine creatinine (uNTX/uCr) were measured at baseline, at CNO relapse, and at final follow-up. Results: Nine patients (5F, 4M) had received IVP for severe CNO at median age of 12.9 (range 4.5-16.3) years and had achieved complete clinical and MRI documented remission. Median follow-up was 52 (range 40-76) months. Five patients remained asymptomatic at median 47.5 (range 42-76) months. Four patients had WBMRI confirmed CNO flare at median 17 (range 7-25) months following completion of initial IVP treatment, with median 2 (range 1-13) active CNO sites. Three patients required IVP re-treatment, and one patient responded to naproxen. Mean VAS at CNO recurrence was 7/10, decreasing uniformly to 0/10 following 1st IVP re-infusion, although WBMRI resolution was slower. Median number of IVP monthly doses was 1 (range 1-5). Same 4 patients had 2nd WBMRM confirmed flare at median 22 (range 5-29) months following completion of 2nd IVP treatment, but only 2 patients required IVP. For patients with no flares, median uNTX/uCr prior to 1st ever IVP was 702 (range 430-945); and 104 (range 49-248) nmol/mmol/creatinine at final follow-up. For patients who flared, median uNTX/uCr prior to 1st ever IVP was 873 (range 165-1361); 344 (range 98-502) at first flare; and 145 (range 52-241) nmol/mmol/creatinine at final follow-up. Conclusions: 1. IVP resulted in prolonged symptom free intervals in patients with severe CNO. 2. No patient lost the efficacy to IVP with re-treatment(s). 3. UNTX/uCr gradually decreased in all patients.

**Miettunen, et al. (2009).** Dramatic pain relief and resolution of bone inflammation following pamidronate in 9 pediatric patients with persistent chronic recurrent multifocal osteomyelitis (CRMO).

**Prospective; Paediatric**

**BACKGROUND:** Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory, non-infectious osteopathy that affects predominantly patients <\= 18 years of age. There is no uniformly effective treatment. Our objective is to describe clinical, magnetic resonance imaging (MRI), and bone resorption response to intravenous pamidronate in pediatric CRMO. METHODS: We report our prospectively documented experience with all CRMO patients treated with pamidronate between 2003 and 2008 at a tertiary pediatric centre. Pamidronate was administered as intravenous cycles. The dose of pamidronate varied among subjects but was given as monthly to every 3 monthly cycles depending on the distance the patient lived from the infusion center. Maximum cumulative dose was <\= 11.5 mg/kg/year. Pamidronate treatment was continued until resolution of MRI documented bone inflammation. Visual analog scale for pain (VAS) and bone resorption marker urine N-telopeptide/urine creatinine (uNTX/uCr) were measured at baseline, preceding each subsequent pamidronate treatment, at final follow-up, and/or at time of MRI confirmed CRMO flare. MRI of the affected site(s) was obtained at baseline, preceding every 2nd treatment, and with suspected CRMO recurrence. RESULTS: Nine patients (5F: 4M) were treated, with a median (range) age at treatment of 12.9 (4.5-16.3) years, and median (range) duration of symptoms of 18 (6-36) months. VAS decreased from 10/10 to 0-3/10 by the end of first 3-day treatment for all patients. The mean (range) time to complete MRI resolution of bone inflammation was 6.0 (2-12) months. The mean (confidence interval (CI)) baseline uNTX/uCr was 738.83 (CI 464.25,
BACKGROUND/PURPOSE: Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory bone disease occurring primarily in children and adolescents. Delays in referral and diagnosis may lead to prolonged courses of antibiotics with in-patient treatment. The combination of synovitis, acne, pustulosis, hyperostosis and aseptic osteitis is known as SAPHO syndrome. Osteitis involves the anterior chest, particularly the sternoclavicular and upper costosternal junctions. Diagnosis is difficult when there are no typical skin and bone lesions and differential diagnosis includes bacterial osteomyelitis, malignancy and Paget's disease. We present a case of SAPHO syndrome with aseptic femoral osteitis and symmetrical involvement of the lower costosternal junctions. The main advantage of recognition and diagnosis of SAPHO syndrome is the avoidance of unnecessary prolonged antibiotic treatment and repeated invasive procedures. 2007 Elsevier Masson SAS. All rights reserved.


**Mylona, et al. (2008). Femoral and lower costosternal junctions’ osteitis in an adult with SAPHO syndrome: An unusual presentation.**


**Ramanan, et al. (2014).**

**Retrospective; Adult**

**Retrospective; Paediatric**

**Retrospective; Paediatric [Conference abstract]**
the Bristol Criteria for the Diagnosis of Chronic Non-bacterial Osteitis From a Cohort of 41 Patients.


Retrospective; Paediatric

Chronic recurrent multifocal osteomyelitis is an inflammatory and aseptic disorder, which can affect any bone and be associated with dermatologic lesions. Thanks to better knowledge, this condition is now more often diagnosed. We present two cases, with and without dermatologic lesions. The whole-body bone scintigraphy allows early detection of lesions and bone biopsy is of great help for diagnosis because it rules out tumor or infection. Disease course can be chronic and recurrent. The treatment of choice is non-steroidal anti-inflammatory drugs which can be combined or alternated with osteotropic hormones. 2007 Elsevier Masson SAS. All rights reserved.

Razzouk, et al. (2007). [Chronic recurrent multifocal osteomyelitis CRMO, whose disease is refractory to more conventional treatment. Whole body MRI is routinely used to diagnose CRMO in children and monitor response to therapy. It is sensitive to the inflammatory bone lesions caused by CRMO and can detect lesions that are asymptomatic. Treatment decisions are based on not only symptoms, but also asymptomatic lesions. Objective. To assess changes in bone lesions due to CRMO on whole body MRI, in children who are being treated with a bisphosphonate agent. Methods and materials. A retrospective study of 50 children with clinical diagnosis of CRMO was conducted. Whole body scans. Around 20%-30% patients having pamidronate therapy will continue to have troublesome symptoms.

Conclusions: We suggest that using the Bristol diagnostic criteria (table) with an experienced clinician may obviate the need for biopsy in some patients. Pamidronate was found to be a useful second-line agent with objective MRI evidence of benefit. Copyright 2014 by the American College of Rheumatology.

Retrospective; Adult

Still's disease and chronic recurrent multifocal osteomyelitis (CRMO) are febrile rheumatic diseases of unknown etiology, which predominantly affect children but can also have their initial manifestation in adults. Both can present as intermittent, relapsing episodes and are considered potential candidates within the expanding spectrum of autoinflammatory disorders, although no genetic abnormalities have been described for either of them. Here, we describe a man with an initial manifestation of abacterial multifocal osteitis at the age of 41. During a relapsing-remitting course of his illness, he increasingly developed symptoms of adult-onset Still's disease (AOSD), and the diagnosis was established according to the Yamaguchi criteria. When treated with anakinra, not only the acute symptoms disappeared promptly, but also the osteitis went into complete remission. This is to our knowledge the first description of a simultaneous occurrence of these two manifestations of autoinflammation in adulthood. Springer-Verlag 2011.

Richard, et al. (2014). Follow up MRI of Chronic Recurrent Multifocal Osteomyelitis (CRMO) in Children after Bisphosphonate care. Substantial radiation exposure from multiple plain radiographs or bone scans and bone biopsies which may be repeated. METHODS: Children (aged less than 18 years) diagnosed with CRMO between January 2005 and December 2012, who were reviewed at Bristol Royal Hospital for Children were included; their clinical notes were reviewed, laboratory, histopathology and radiology data were extracted. We retrospectively applied the Bristol criteria for diagnosis (table). [Table: see text]

RESULTS: Forty-one patients (Female: Male ratio 31:10) were diagnosed as CRMO and assessed at the Bristol centre over the 8-year period. The onset of symptoms occurred at a median of 9 years with a delay in diagnosis with a median of 15 months (range 0-92). Initial plain radiograph was abnormal in 28 out of 36 patients; whole body MRI (WB-MRI) detected lesions in seven of the patients with normal plain radiograph. 162 lesions were identified by imaging, of which, 47 were asymptomatic and detected only by MRI. After imaging, only ten patients (24%) had a solitary lesion (six of which were clavicle alone). From the data, diagnostic criteria were developed. Using the proposed criteria retrospectively, thirty-four children could have potentially been diagnosed by criterion 1, with 6 children requiring a biopsy (criterion 2) for diagnosis, either for a solitary lesion not clavicle or atypical features such as age. Bone biopsies in our cohort had been repeated in a third of patients prior to referral. Thirteen children completed at least one year of pamidronate treatment with MRI available both before and after treatment on eleven of these. After a year of pamidronate therapy, 71% of lesions improved and 29% remained stable on MRI scans. Around 20%-30% patients having pamidronate therapy will continue to have troublesome symptoms. CONCLUSION: We suggest that using the Bristol diagnostic criteria (table) with an experienced clinician may obviate the need for biopsy in some patients. Pamidronate was found to be a useful second-line agent with objective MRI evidence of benefit. Copyright 2014 by the American College of Rheumatology.
(Pamidronate) Therapy.

MRIs of children at baseline were evaluated by two pediatric MSK radiologist and one pediatric radiology fellow. Patients had a follow up MRI, as clinically indicated, after IV Pamidronate to assess radiological response. The primary outcome measure was binary (Better or Worse) based on the lesion size. Secondary outcomes were signal intensity and number of lesions in the baseline and follow up MRIs. Preliminary results. Up to three index (largest) lesions were assessed for size and signal intensity in each patient. Of these the majority (85%) demonstrated improvement in size after pamidronate. Twenty-six percent showed improvement in signal intensity, 5% showed more intense signal than the baseline study. Of the total number of lesions, 17% resolved. Several patients had new bone lesions. Preliminary Conclusion. Whole body MRI is helpful in assessing disease activity of CRMO, after bisphosphonate treatment.


Retrospective; Paediatric [Conference abstract]

Background: There is increasing evidence supporting the use of bisphosphonates, particularly pamidronate, for patients with chronic recurrent multifocal osteomyelitis (CRMO) who have breakthrough pain on NSAIDs. Pamidronate is known to inhibit osteoclasts and may reduce CRMO lesion expansion by this action; however, it also has anti-cytokine properties and this may also be what makes it an effective treatment for CRMO. Objective: To establish the safety and efficacy of pamidronate in the reduction of clinical symptoms and radiological features of CRMO in a cohort of 18 patients at Bristol Childrens Hospital. Methods: Case-notes of 38 patients undergoing treatment for CRMO from 2003 to 2012 at Bristol Childrens Hospital were analysed. The children undergoing pamidronate treatment were identified and their radiology and clinical findings examined in relation to their treatment. Symptoms were assessed using a questionnaire regarding functionality and bone pain. MRI scans were performed in all patients following therapy. Results: Thirty-three of 38 patients (87%) had been treated with NSAIDs and 16 of 33 (42%) were suffering from persistent symptoms. A total of 18 patients were treated with i.v. pamidronate (1 mg/kg/day, 3-day regimen, 3-month intervals for up to 1 year) and received an average of four doses. If symptoms persisted, they received a further infusion (providing MRI results were favourable). Of the 18 children treated with pamidronate, at the time of this review, 11 had completed the dosage regime. Of these 11 completing treatment, 7 (64%) had a reduction in high signal on MRI and became clinically asymptomatic. In the remaining four (36%) bone pain persisted and MRI was unchanged. Seven patients were still undergoing pamidronate therapy at the time of this review and had no post-treatment MRI results. Conclusion: In children with CRMO resistant to NSAIDs, pamidronate may induce remission in a significant number of patients as demonstrated by both clinical symptoms and radiological assessment. However, as CRMO is a relapsing remitting condition a randomized controlled trial would provide the best evidence but the rarity of the condition makes this very difficult.

Rogers, Stockley, Finn and Ramanan (2011). Chronic recurrent multifocal osteomyelitis: Diagnosis and treatment in 15 paediatric cases.

Retrospective; Paediatric [Conference abstract]

BACKGROUND: Chronic recurrent multi-focal osteomyelitis (CRMO) is a noninfectious inflammatory ostesitis predominantly affecting children and adolescents. Diagnosis is often difficult as initial symptoms and clinical course can vary widely. CRMO can result in significant morbidity. Treatment regimes are varied but bisphosphonate therapy with Pamidronate is proving effective at reducing pain and improving bone remodelling in some patients. OBJECTIVES: To determine the route to diagnosis, the clinical course and the effectiveness of treatment in patients with CRMO. METHOD: The clinical, radiological and laboratory data of 15 patients identified with CRMO between 2000 and 2009 were reviewed. RESULTS: Median age at diagnosis: 9.6 years (range 3-15); 6 were male, 9 female. Median follow-up: 2 years. Sites of bony involvement: clavicle(8), proximal tibia(4), distal femur(2), vertebrae(2), ankle(2) and rib(1). 2 patients had skin changes. All had x-ray and MRI studies. 11 underwent diagnostic bone biopsy. All had extensive microbiological investigations with no organism identified. The clinical course varied - 4 patients had a single episode of osteitis, 5 experienced one recurrence and 6 had more than two relapses. 8 patients suffered chronic persistent inflammation and pain lasting over one year. All patients were initially treated with intravenous antibiotics (IVAB) for presumed infectious osteomyelitis; 9 had more than one course of IVAB before diagnosis. Non-steroidal anti-inflammatory drugs (NSAIDs) were used in 7 patients; 2
received NSAIDs alone. 2 patients received oral prednisolone; 1 IV methyl prednisolone, 4 sulphasalazine and 4 methotrexate. 5 received bisphosphonates (Pamidronate) and have shown significant improvement in function and reduction of pain. CONCLUSIONS: CRMO is a diagnosis of exclusion often resulting in delay of appropriate treatment. We highlight the importance of an early biopsy in confirming the disease. Pamidronate was potentially effective in the management of 5 patients.

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<th>Reference</th>
<th>Study Type</th>
<th>Population</th>
<th>Description</th>
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<tr>
<td>Salles, et al. (2011). The SAPHO syndrome: a clinical and imaging study.</td>
<td>Retrospective; Adult</td>
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<td>The purpose of this study is to describe the clinical and radiological manifestations of patients with the synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. Retrospective study (1984-2007) was performed in a single center. All patients with the SAPHO syndrome were included. Fifty-two patients were included: 26 male, mean age at diagnosis is 42±12 years. Ostearticular involvement was present before cutaneous involvement in 59.6% of patients and concomitantly in 23.5%. Anterior chest pain was the commonest clinical manifestation, it was present in 38 patients (73%), followed by peripheral arthritis in 17 patients (32%), and sacroiliac pain in 14 patients (26.9%). Cutaneous involvement was present in 33 patients (63.5%). HLA B27 antigen was present in eight patients (17.7%). Bone scintigraphy showed an increased uptake in 42 patients (93.3%). The location of the uptake was mainly in sternoclavicular and manubriosternal joints. CT scan was performed in all &quot;hot joints&quot; showing sclerosis, erosions, hyperostosis, and soft tissue involvement. Refractory patients were treated mainly with pamidronate. Although SAPHO syndrome is an entity that share features that fit into a variety of established disease categories, the present study has a homogenous clinical and radiological pattern that gives support to believe that the SAPHO syndrome is an isolated clinical entity.</td>
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<td>Schuller, Franova and Macku (2013). PReS-FINAL-2229: Pamidronate in CRMO-a small case series.</td>
<td>Retrospective; Paediatric [Conference abstract].</td>
<td>Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare autoinflammatory disorder which affects predominantly girls with peak onset between ages of 7 to 12 years. There is a frequent association of CRMO with inflammatory skin or gut disorders. Patients with isolated CRMO are usually treated with nonsteroidal anti-inflammatory drugs (NSAIDs) prior to escalation to corticoids and disease-modifying antirheumatic drugs such as methotrexate (MTX), sulfasalazine, azathioprine. Recently, TNF inhibitors and bisphosphonates have been recommended for treatment of most severe cases. Objectives: To evaluate pamidronate treatment in patients with isolated CRMO relapsing despite NSAID, corticosteroid and methotrexate therapy in a retrospective study of a case series. Methods: Since 2011, 4 patients (3 girls and 1 boy) with CRMO have been treated with pamidronate in Paediatric Department of University Hospital Brno, Czech Republic. All these patients had chronic relapsing multifocal osteomyelitis without any associated inflammatory condition. The diagnosis of CRMO was set in the mean age of 12 years based on radiographic findings (x-ray, CT, MRI) and histological findings of a nonbacterial inflammatory bone lesion. Previous treatment with NSAIDs, corticosteroids, and MTX (MTX used only in 3 of 4 cases) was insufficient. Results: Intravenous pamidronate administered every 3 to 6 months was added to MTX in 3 patients, in the fourth case it was started in a MTX naive patient. Corticosteroids were used to control acute symptoms. All the patients with pamidronate significantly improved. In 3 patients including 1 patient without MTX no corticosteroids were needed after 1 month of pamidronate therapy and there are no clinical signs of the disease activity now. In 1 patient treated with pamidronate and MTX the dose of corticosteroids has significantly decreased. No adverse event was observed. Conclusion: In accordance with previous observations of other authors the results of our small case series indicate good efficacy of pamidronate treatment in patients with CRMO. In contrast, MTX alone had no benefit in our patients. We recommend considering pamidronate a second line therapy in more severe cases of isolated CRMO.</td>
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<td>Siau and Laversuch (2010a). SAPHO syndrome in an adult with</td>
<td>Retrospective; Adult</td>
<td>Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome is a rare group of sterile, inflammatory osteoarticular disorders classically associated with skin lesions. It is occasionally associated with enteropathic disease such as ulcerative colitis. We present a 39-year-old patient with chronic ulcerative colitis who developed</td>
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**Simm, Allen and Zacharin (2008). Bisphosphonate treatment in chronic recurrent multifocal osteomyelitis.**

**Retrospective; Paediatric**

OBJECTIVE: To test the safety and efficacy of bisphosphonates in chronic recurrent multifocal osteomyelitis (CRMO). STUDY DESIGN: Five patients with CRMO, all of whom had ongoing pain and loss of function despite conventional treatment with non-steroidal anti-inflammatory agents, were treated with pamidronate (1 mg/kg/dose with a dosing frequency of 2 to 4 monthly for a total treatment duration of 12 to 42 months). RESULTS: Pain decreased after the first infusion for 4 of 5 patients, with symptomatic improvement maintained with time. Significant improvement was seen in radiological lesions for these 4 patients. CONCLUSION: Bisphosphonates appear to be a useful and safe adjunctive treatment in CRMO when simple therapies such as anti-inflammatory agents fail to control symptoms or cases in which lesion expansion continues.

**Sirisha, et al. (2012). Hip subluxation complicating chronic recurrent multifocal osteomyelitis-A case report.**

**Retrospective; Paediatric [Conference abstract]**

Aim:Introduction/Background: Chronic recurrent multifocal osteomyelitis (CRMO) complicated by hip subluxation has not been reported in literature. Results: 11 year old male child presented with recurrent inflammatory bilateral knee arthritis, inflammatory left buttock pain, recurrent, intermittent fever (up to 103°F) over the past one and a half year. He was bedridden at admission. A diagnosis of systemic onset JIA was considered. MRI pelvis showed altered signal intensities at left neck of femur, left pubic bone, left ischium, right medial femoral condyle and superior and inferior pubic ramus. Skeletal scintigraphy revealed arthritis at left sacroiliac, hip and ankle joints. During hospital stay he had right eye uveitis. In view of the young age, recurrent arthritis, inflammation at multiple bony sites and raised inflammatory markers a diagnosis of chronic recurrent multifocal osteomyelitis was made. He was treated with NSAIDs, short course of steroids and monthly pamidronate. He improved symptomatically and repeat MRI pelvis showed improved signal intensities. He was readmitted after 4 months for ongoing severe arthritis with disability. Evaluation revealed left hip subluxation. Hip joint repositioning was done. Repeat MRI revealed Bilateral sacroiliitis, left hip synovitis with synovial hypertrophy, marrow edema at left ileum, sacral ala, ischium, edema of surrounding muscles and soft tissue. Synovial biopsy revealed synovium thrown into papillary folds with lymphoplasmacytic infiltrate. He was restarted on steroids. Methotrexate was added. He improved symptomatically. Conclusions: The present case is being reported in view of a rare and unreported complication associated with CRMO.

**Smith, et al. (2005). Ocular presentation of the SAPHO syndrome.**

**Retrospective; Adult [Letter]**

SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) is a seronegative spondylarthropathy. The term, introduced in 1987, describes a syndrome with various previous pseudonyms: multifocal recurrent osteomyelitis; arthritis with acne; and osteitis with pustulosis palmaris and plantaritis.1 Skeletal changes are commonest in the chest wall and skull involvement is uncommon.2,3 We present an unusual case of orbital SAPHO syndrome.

**Spacey, et al. (2014). A case of cervical SAPHO.**

**Retrospective; Adult [Conference abstract]**

A Case of Cervical SAPHO: A 49 year old Caucasian female smoker presented to the emergency department with acute severe chest pain, raised CRP at 225, ESR 48 and raised D-Dimer of 4000. She had a prominent family history of psoriasis, and at this time was exhibiting plantar lesions. Three years previously she described experiencing palmar lesions. She complained of symptoms suggestive of inflammatory back, shoulder and knee pains for the preceding 3 years and an
episode of plantar fasciitis. Coincidentally she was awaiting review by a Spinal Surgeon referred from Orthopaedics with posterior neck pain and a sclerotic lesion within the C5 vertebral body. To exclude pulmonary embolism she underwent a CTPA. Although negative, the CTPA revealed a further lesion within the right 4th rib. Isotope bone scan revealed multiple further lesions within the 3rd and 8th ribs, and hypertrophy of the facet joint of T1. Her case was discussed within the multidisciplinary team meeting, and felt that this was typical of psoriatic arthro-osteitis presenting with the SAPHO type pathology, and therefore did not proceed with biopsy. Treatment was commenced with weekly methotrexate and two infusions of Pamidronate. Her psoriatic lesions resolved within 2 months and the pain around her ribs and neck vastly improved. A further Pamidronate infusion was given and methotrexate titrated when she showed features of relapse. Palmar Plantar Pustulosis (PPP) is more commonly associated with the osseous features, of SAPHO than other Psoriatic dermatoses, particularly of the anterior chest wall [1]. SAPHO affecting the thoraco-lumbar vertebrae is also recognised, although unusually, as in this case only a few reports of cervical lesions have been described [2].


Susanto and Nanayakkara (2003). The skin is the clue.


had antibiotic therapies for infection at different times. At admission, she had diffuse mandibular swelling bilaterally, arthritis in ankle, knees, elbows and wrists bilaterally. There was sclerotic bone lesions at tibia and diffuse osteoporosis at extremity graphies. There was diffuse activity of mandibula and focal activity at right femur at total body bone scintigraphy. Erythrocyte sedimentation rate (ESR) was 120 mm/hour. Antinuclear antibody tests were negative. She had osteoporosis at bone densitometry. Temporomandibular joint MR and extremity MR findings were related to the findings seen in CRMO. Oral corticosteroid 20mg/day and colchicine treatment with intravenous pamidronate infusion were started. After 3 months of therapy she had begun to walk with support. At that time as she had osteoporosis, corticosteroid dose was reduced to 10 mg/day and azathiopurine was started. After therapy during 6 months, she had begun to walk without any support. With immunosuppressive therapy she had pamidronate infusions 5 times in every 3 months. After 1 year of therapy she is in clinical and laboratory remission. Methods CASE 2: Nine years old brother had myalgia at lower extremities during four years. His physical examination was normal. ESR was 120 mm/hour. He had osteopetrosis and sclerotic bone lesions of femur at lower extremity graphies. The findings of lower extremity MR was related to the findings seen in CRMO. Nonsteroidal antiinflammatory (NSAID) treatment and later corticosteroid 20mg/day and pamidronate therapy were started. After 1.5 months of therapy, he had no complaint and ESR was normal. As he had cushingoid appearance, corticosteroid dose was decreased to 10mg/day and cyclophosphamide was started. With immunosuppressive treatment he had pamidronate infusion 5 times in every 3 months. After 3 months of therapy, he is in clinical and laboratory remission. Results CASE 3: 13 years old brother had pain in lower extremity during 6 months. His physical examination was normal. ESR was 90 mm/hour. There was sclerotic bone lesions on X ray of foot. The findings on lower extremity MR were related to the findings in CRMO. NSAID and later corticosteroid therapy (20mg/day) were started. He had cushingoid appearance, so corticosteroid was stopped and azathiopurine was started. After 1 month of therapy he had clinical and laboratory remission. LPIN 2 mutation was negative in three siblings. Conclusions CRMO should be thought when chronic and sclerotic bone lesions were confirmed. The family members should be assessed for symptoms. As an initial therapy, pamidronate and corticosteroid were effective and as maintenance therapy low dose corticosteroid and azathiopurine were effective.


**Retrospective; Mixed [Letter]**

No abstract

### Van Doornum, Barraclough, McColl and Wicks (2000). SAPHO: rare or just not recognized?

**Retrospective; Adult**

OBJECTIVE: The SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome describes an association between musculoskeletal disorders, in particular hyperostosis involving the bones and joints of the anterior chest wall, and various dermatologic conditions. It has been reported in Europe and Japan, but no Australian series have been published. We describe the clinical, laboratory, and radiographic features of a group of patients with the SAPHO syndrome and compare this with the literature.

METHODS: We performed a retrospective review of patients seen in our department between 1990 and 1998 who met the proposed diagnostic criteria for SAPHO. Information regarding age, sex, disease duration, skeletal site(s) of disease, presence of skin disease, previous treatment, and response to treatment was collected. Laboratory tests were reviewed, as was all available radiology and bone scintigraphy.

RESULTS: Six women with a mean age of 40 years fulfilled the criteria for SAPHO. The skeletal manifestations were similar to those reported in the literature, with hyperostosis of the anterior chest wall being the central feature. Cervical spine and pubic bone were other sites of involvement, whereas sacroiliitis and peripheral joint synovitis were not seen. Skin disease was less frequent in our population than has been reported in other series. Nonsteroidal anti-inflammatory drugs were frequently prescribed as first-line treatment but had limited efficacy. Intravenous pamidronate was administered to two patients, resulting in complete resolution of pain in one patient and 50% reduction in pain in the other.

CONCLUSIONS: The SAPHO syndrome may be underrecognized as the skin manifestations in our patients were mild or absent. Although optimal treatment for
these patients remains unclear, it is important to make the diagnosis of SAPHO to avoid unnecessary investigations and treatment.

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<th>Author(s)</th>
<th>Study Type</th>
<th>Abstract</th>
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<tr>
<td>Watts, et al. (1993). Arthro-osteitis - A clinical spectrum.</td>
<td>Retrospective; Adult</td>
<td>Arthro-osteitis is an uncommon condition which can be associated with palmoplantar pustulosis. It forms part of a group of conditions which include the synovitis, acne, pustulosis, hyperostosis, osteitis syndrome (SAPHO) and sternocostoclavicular hyperostosis. We report four cases illustrating the clinical spectrum of this condition which occurred in the absence of concomitant skin lesions. One patient had extensive aortic calcification a feature not previously reported in this condition, which may represent a low grade inflammatory aortitis.</td>
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<td>Witt, et al. (2014). Disease burden, disease manifestations and current treatment regimen of the SAPHO syndrome in Germany: Results from a nationwide patient survey.</td>
<td>Cross-sectional; Adult</td>
<td>Background: Due to diagnostic and therapeutic advances, quality of life of patients with spondyloarthritides (SpA) has improved substantially in recent years. However, little is known about how patients with the SAPHO syndrome, a heterogeneous disease counted among the SpAs, profit from these advances. Objective: To investigate current aspects of patient care in a nationwide SAPHO cohort. Methods: Patients were recruited in a university centre and via a nationwide SAPHO patient support group. Medical records were reviewed and patients were asked to complete a questionnaire on the course of diagnosis, disease burden and treatment regimen. Results: A total of 64 patients were included in the analysis. The mean time from disease onset to diagnosis was 3.8 + 5.3 years. The patients’ overall satisfaction with the course of diagnosis was 23.0 + 28.9 on a visual analogue scale (VAS) from 0 to 100. Musculoskeletal symptoms had the highest impact on the patients’ wellbeing. The mean overall disease burden on a VAS for pain was 45.4 + 25.9. Limitations in the quality of life were reported mainly in the general health, bodily pain and vitality dimensions of the SF-36 questionnaire. Current treatments consisted of NSAIDs (77%), DMARDs (27%), glucocorticoids (23%), TNF-inhibitors (16%) and bisphosphonates (11%). Conclusions: The SAPHO syndrome has a high impact on the patients’ general health and quality of life. Establishing the diagnosis still takes years and expends multiple medical resources. Effective treatments such as TNF-inhibitors are rarely prescribed and current disease burden is not acceptable. 2014 Elsevier Inc.</td>
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<td>Wollina, et al. (2008). Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new</td>
<td>Retrospective; Adult</td>
<td>Tumor necrosis factor-alpha (TNFalpha) inhibition is effective in the treatment of moderate-to-severe psoriasis. We report on 120 patients from the literature including six new patients (three women and three men) who developed pustular lesions during treatment with TNFalpha inhibitors. We identified 72 women and 36 men (several papers did not specify the gender of patients) with an age range of 13-78 years (mean 42.3 years). The primary diagnoses were rheumatoid arthritis (n = 61), ankylosing spondylitis (n = 21), psoriasis (n = 10), Crohn disease (n = 8), SAPHO (synovitis acne pustulosis hyperostosis osteitis) syndrome (n = 3), psoriatic arthritis (n = 2), and other diagnoses (n = 15). Psoriasis (except palmoplantar pustular type) was the most common adverse effect during anti-TNFalpha treatment (n = 73), followed by palmoplantar pustular psoriasis (n = 37) and psoriasis of the nail (n = 6), sometimes combined in the same patient. Palmoplantar pustulosis and psoriasiform</td>
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We report a juvenile case of diffuse sclerosing osteomyelitis of the mandible that started in 2008. The clinical features and treatment results in 31 Japanese patients with SAPHO syndrome were retrospectively reported from 2003 to 2011. HLA typing was performed in 30 patients, and their allele frequencies were compared with those in healthy Japanese controls. On the other hand, the frequency of HLA B51 was significantly higher in Japanese patients with SAPHO syndrome compared to healthy controls. In six patients, switching from one TNFalpha inhibitor to another immediately after cutaneous adverse effects occurred resulted in an improvement in five patients. In nine patients, a second TNFalpha inhibitor was initiated after a break in TNFalpha inhibition. The response to a second or third drug in these patients was mixed. The underlying pathomechanisms of induction of psoriasis or psoriasisiform exanthemata by TNFalpha inhibitors remain elusive but there is reason to assume that induction of such adverse events has more than one pathophysiology.


**Retrospective; Mixed**
Background/Purpose: SAPHO syndrome is a disorder characterized by pustular skin lesions and osteoarticular lesions, which was proposed by Chamot et al. in 1987. Clinical studies based on the diagnostic criteria of SAPHO syndrome are mainly reported from Europe, and still limited in East-Asia. Methods: We investigated the clinical features and treatment results in 31 Japanese patients with SAPHO syndrome (male 10, female 21) diagnosed and treated between 2003 and 2011. HLA-A and -B typing was performed in 30 patients, and their allele frequencies were compared with those in the healthy Japanese controls, using Fisher’s exact test. Results: The average age at onset was ranged between 16 and 68 years old (average: 48.3), and the age at diagnosis from 16 to 74 y.o. (average: 53.8). The average follow-up period was 42 months. Sternocostoclavicular hyperostosis was the main manifestation and recognized in 29 cases (94%). Pustular dermatitis including palmoplantar pustulosis was seen in 26 cases (84%). As other manifestations, recurrent oral ulceration was seen in 6 cases (19%), and inflammatory bowel disease in 2 cases. Most patients had intermittent attacks of pain, therefore oral NSAIDs were needed in all cases and oral prednisolone (PSL) in 14 cases (45%). The oral NSAIDs and/or PSL were effective for temporary pain relief. DMARDs (SSZ and/or MTX) were used in 14 cases (45%) with recurrent chronic pain. Pain relief more than 50% was seen in only 4 cases (29%) out of DMARDs users. In two refractory cases with severe spondylitis, adalimumab (ADA) was tried. Both cases showed immediate pain-relief and ADA was effective during at least one year. HLA tests revealed that the allele frequencies of HLA-B27 and HLA-B51 were respectively 0% and 12%, which were similar with those in healthy Japanese controls. On the other hand, the frequency of HLA-B61 was 27% and significantly higher than that (12%) in healthy controls. Conclusion: Mucosal lesions seem to be a rather frequent complication of SAPHO syndrome in our study. The efficacy of DMARDs (SSZ and/or MTX) was observed in a small number of patients. ADA was effective in two refractory cases with severe spondylitis. This study revealed that HLA-B61 was significantly increased in Japanese patients with SAPHO syndrome.

**Yamazaki, et al. (2007). Remarkable**

**Retrospective; Paediatric**

We report a juvenile case of diffuse sclerosing osteomyelitis of the mandible that showed a favorable response to pamidronate, a bisphosphonate derivative. Although...
response of juvenile diffuse sclerosing osteomyelitis of mandible to pamidronate. Conventional treatments had been ineffective for 5 years, pamidronate administration brought about conspicuous improvement both clinically and radiographically. Severe adverse reaction was not found except for low-grade fever and lassitude on the day following administration. During the course of the treatment, however, non-suppurative osteomyelitis of the right humerus also occurred, leading to the established diagnosis of chronic recurrent multifocal osteomyelitis. Pamidronate therapy was again performed successfully with near disappearance of clinical symptoms. Both bone-specific alkaline phosphatase (bone formation marker) and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (bone resorption marker) showed a marked decrease with pamidronate therapy, suggesting that pamidronate is useful for the treatment of chronic recurrent multifocal osteomyelitis with inhibitory effect on bone turnover.

Zhang, Zhao and Liu (2012). Successful treatment of SAPHO syndrome with severe spinal disorder using entercept: A case study. Retrospective; Adult

SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) is a rare disease. Presently, there is no treatment guideline for this illness. Several studies suggested entercept, a novel biological agent against tumor necrosis factor-Alpha, is effective in treating SAPHO syndrome. We report a case in which the clinical conditions of a middle-aged female patient diagnosed with SAPHO syndrome, with noted spinal disorder, improved significantly after receiving entercept treatment. The patient remained stable after 3-month follow-up. Springer-Verlag 2011.

Ziobrowska-Bech, et al. (2013). Ten-year review of Danish children with chronic non-bacterial osteitis. Retrospective; Paediatric

OBJECTIVES: To compare clinical characteristics of children with chronic non-infectious osteomyelitis (CNO) with either mono- or multifocal bone lesions, and to report potential advantages of using whole-body MRI. METHODS: A retrospective evaluation of 31 children (19 girls, 12 boys) diagnosed with CNO between 2001 and 2011. CNO was diagnosed as mono-, or multifocal inflammatory bone lesions (osteomyelitis, osteitis, osteosclerosis), duration of complaints more than 6 weeks and exclusion of infection and malignancy. Clinical and radiological data were registered. The definition of mono- or multifocality was based on the description of imaging results. RESULTS: Mean age at disease onset was 10.3 + 2.6 years. Mean duration of active disease was 44.4 + 25.6 months. Twenty-two (71.0%) had two or more bone lesions and 9 (29.0%) had one lesion. Of those with multifocal lesions six were initially detected as monofocal. The most frequent location of the bone lesions was in the metaphysis of the lower extremities. MRI/CT discovered most lesions compared to x-ray and scintigraphy. MRI was performed in 93.5% of which 25.8% had a whole-body-MRI. Whole-body MRI revealed disclosure of several silent lesions. Extra-osseous involvement occurred in 64.5%. In the multifocal group 22.7% had psoriasis and 13.6% had pustulosis palmar-planar but neither was seen in the monofocal group. All were treated with NSAIDs; 54.8% corticosteroids, 29.1% methotrexate, 9.7% pamidronate and 3.2% infliximab. CONCLUSIONS: Monofocal CNO had comparable clinical and radiological characteristics to multifocal disease. We conclude that whole-body MRI is a relevant screening instrument for the diagnosis of CNO.