

# EULAR recommendations for calcium pyrophosphate deposition. Part II: Management

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## ABSTRACT

**Objectives** To develop evidence-based recommendations for management of calcium pyrophosphate deposition (CPPD).

**Methods** A multidisciplinary guideline development group of 15 experts, representing 10 European countries, generated key propositions for management of CPPD using a Delphi consensus approach. For each recommendation research evidence was searched systematically. Whenever possible, the effect size and number needed to treat for efficacy and RR or OR for side effects were calculated for individual treatment modalities. Strength of recommendation was assessed by the European League Against Rheumatism visual analogue scale.

**Results** Nine key recommendations were generated, including topics for general management, treatment of acute attacks, prophylaxis against recurrent acute attacks and management of chronic symptoms. It was recommended that optimal treatment requires both non-pharmacological and pharmacological treatments. For acute CPP crystal arthritis, cool packs, temporary rest and joint aspiration combined with steroid injection are often sufficient. For prophylaxis or chronic inflammatory arthritis with CPPD, oral non-steroidal anti-inflammatory drugs with gastroprotective treatment and/or low-dose colchicine 0.5–1.0 mg daily may be used. Other recommendations included parenteral or oral corticosteroid for acute CPP arthritis in those unresponsive or unsuited to other measures, and low-dose corticosteroid, methotrexate or hydroxychloroquine for chronic inflammatory arthritis with CPPD.

Asymptomatic CPPD requires no treatment. Strength of recommendations varies from 79% to 95%.

**Conclusion** Nine key recommendations for management of CPP crystal associated arthritis were developed using both research evidence and expert consensus. Strength of recommendations was provided to assist the application of these recommendations.

## INTRODUCTION

As discussed in Part I: Terminology and Diagnosis,<sup>1</sup> calcium pyrophosphate deposition (CPPD) may present different clinical phenotypes, from asymptomatic chondrocalcinosis (CC) to acute calcium pyrophosphate (CPP) crystal arthritis and osteoarthritis (OA) with CPPD, which may be associated with chronic symptoms and functional impairment of varying severity. Because of this diversity the management of CPP-associated arthritis is challenging. Unlike gout, currently there is no specific treatment to eliminate CPP crystals.

Management therefore focuses on symptomatic control for both the acute attacks and the chronic symptoms associated with CPPD. Treatment modalities used to control acute attacks in gout<sup>2</sup> and to relieve pain and symptoms in OA<sup>3</sup> are often used for symptomatic CPPD. However, evidence to support these treatments for CPPD has yet to be systematically evaluated.

Following the agreement of terminology and recommendations for diagnosis of CPPD, the European League Against Rheumatism (EULAR) CPPD Task Force developed nine key recommendations for management of CPPD using a combined systematic literature review and expert consensus approach.<sup>4</sup>

## METHODS

A Delphi exercise was used to reach consensus and a systematic literature review of research evidence was used to support the recommendations.<sup>1</sup> Evidence was categorised according to Shekelle's level of evidence<sup>5</sup> (table 1). Wherever possible, effect size (ES),<sup>6</sup> number needed to treat (NNT) was estimated for efficacy,<sup>7</sup> and RR or OR were calculated for side effects.<sup>8</sup> Strength of recommendation was graded using the EULAR 0–100 mm visual analogue scale (VAS).<sup>9–10</sup> All measures were reported with 95% CI unless otherwise specified.

## Future research agenda

After the propositions for management had been searched, reviewed and discussed, each participant submitted independently 10 propositions for future research. Consensus was again obtained using the Delphi technique.

## RESULTS

Of 78 initial propositions suggested by the task force members, nine were agreed after three anonymous Delphi rounds. Recommendations covered the following four domains: general, treatment for acute attacks, prophylaxis treatment and management of chronic CPPD with or without OA and other comorbidities (table 2).

The systematic literature search yielded only 20 studies relevant for management of CPPD, including four randomised controlled trial (RCTs).<sup>11–13</sup> After reading the abstracts, 13 met the inclusion criteria, including six studies for acute attacks,<sup>14–19</sup> two for prophylactic treatment to prevent recurrent acute attacks<sup>20–21</sup> and five for management of chronic CPPD<sup>11–13 22–23</sup>.

**Optimal treatment of CPPD**

The full recommendation is shown in table 2.

Although direct research evidence to support this recommendation is lacking, it is apparent that the management strategy will vary according to the clinical presentation. Asymptomatic CC does not require any treatment and is usually an age-related feature in the normal population.<sup>24 25</sup> Acute CPP crystal arthritis, however, is extremely painful so a key management objective will be rapid relief of severe symptoms. In contrast, assessment of a patient during an intercritical period or when there is accompanying OA and chronic symptoms should lead to the development of an individualised long-term management plan to reduce symptoms and disability, to correct any modifiable adverse risk factor and to reduce structural progression.

As with gout and OA, treatment should be individualised according to patient characteristics, risk factors and comorbidities. Because CPPD predominates in the older patient, care must be taken when advising drug treatments. For example, the use of non-steroidal anti-inflammatory drugs (NSAIDs) should be carefully considered according to the benefit and relative risk.<sup>3 26</sup>

To optimise management, education is essential as this allows patient involvement in decision-making. This is a core aspect of patient-centred care, where both care provider and receiver understand the disease characteristics, available treatment options and the pros and cons of these treatments.

**Treatment for acute CPP crystal arthritis**

There is no RCT evidence for the non-drug treatment modalities recommended in this proposition. Nevertheless, the use of ice or cool packs and temporary rest was strongly supported by

expert opinion and in part is extrapolated from some evidence for these treatments for other causes of acute synovitis, including gout.<sup>2 27–29</sup> Similarly, although joint aspiration and/or intra-articular injection of long-acting glucocorticosteroids (GCS) is very commonly used to treat monoarticular or oligoarticular attacks of acute CPP crystal arthritis, there are no controlled trials, either of efficacy or dose requirement, in acute CPP crystal arthritis and the evidence to support the use of this treatment is predominantly based on clinical expertise and evidence in gout.<sup>2</sup> Standard/usual precautions should be applied relating to GCS injection.<sup>30</sup>

**NSAID and colchicine**

The evidence to support the use of either oral NSAIDs or oral colchicine for acute CPP crystal arthritis is mainly extrapolated from evidence relating to treatment of acute attacks of gout.<sup>2</sup> Evidence for gout suggests that colchicine is effective at relieving symptoms of acute crystal synovitis. However, using traditional regimens (1 mg loading dose followed by 0.5 mg every 2 h until development of side effects) the incidence of marked side effects is 100%,<sup>31</sup> therefore a lower-dose regimen (0.5 mg up to three to four times daily with or without loading dose of 1 mg) is recommended, predominantly based on expert opinion.<sup>2</sup> The length of treatment depends on the symptom relief and side effects. Although one uncontrolled hospital case series has showed the efficacy of intravenous colchicine in seven patients with acute CPP crystal arthritis,<sup>16</sup> this route of delivery is no longer used in most countries owing to the high risk of serious toxicity (and even fatality).

In contrast to the sparse evidence for efficacy, there is abundant evidence about side effects from the use of NSAIDs (eg, gastrointestinal bleeding, cardiovascular events, renal impairment)<sup>26</sup> and colchicine (eg, diarrhoea).<sup>2</sup> These side effects greatly restrict the use of these agents, especially in older people who often have chronic renal impairment and other comorbidity that increases the likelihood of toxicity or drug interaction.

**Steroids**

The management of acute CPP crystal arthritis can be difficult in the older person, and in those with comorbidity and contraindications to NSAIDs or colchicine. Intra-articular

**Table 1** Level of evidence<sup>5</sup>

Ia – Meta-analysis of randomised controlled trials
Ib – Randomised controlled trial
IIa – Controlled study without randomisation
IIb – Quasi-experimental study
III – Non-experimental descriptive studies, such as comparative, correlation and case-control studies
IV – Expert committee reports or opinion or clinical experience of respected authorities, or all

**Table 2** LOE and SOR: order according to topic (general, acute attacks, prophylaxis and chronic CPPD management)

No	Proposition	LOE	SOR(95% CI)
1	Optimal treatment of CPPD requires both non-pharmacological and pharmacological modalities and should be tailored according to: Clinical features (isolated CC, acute, chronic CPP crystal inflammatory arthritis, OA with CPPD) General risk factors (age, comorbidities) The presence of a predisposing metabolic disorder	IV	93 (85 to 100)
2	For acute CPP crystal arthritis, optimal and safe treatment comprises application of ice or cool packs, temporary rest, joint aspiration and intra-articular injection of long-acting GCS. For many patients these approaches alone may be sufficient	IIa–IV	95 (92 to 98)
3	Both oral NSAID (with gastroprotective treatment if indicated) and low-dose oral colchicine (eg, 0.5 mg up to 3–4 times a day with or without an initial dose of 1 mg) are effective systemic treatments for acute CPP crystal arthritis, although their use is often limited by toxicity and comorbidity, especially in the older patient	Ib–IIb	79 (66 to 91)
4	A short tapering course of oral GCS, or parenteral GCS or ACTH, may be effective for acute CPP crystal arthritis that is not amenable to intra-articular GCS injection and are alternatives to colchicine and/or NSAID	IIb–III	87 (76 to 97)
5	Prophylaxis against frequent recurrent acute CPP crystal arthritis can be achieved with low-dose oral colchicine (eg, 0.5–1 mg daily) or low-dose oral NSAID (with gastroprotective treatment if indicated)	IIb–IV	81 (70 to 92)
6	The management objectives and treatment options for patients with OA and CPPD are the same as those for OA without CPPD	Ia	84 (74 to 94)
7	For chronic CPP crystal inflammatory arthritis, pharmacological options in order of preference are oral NSAID (plus gastroprotective treatment if indicated) and/or colchicine (0.5–1.0 mg daily), low-dose corticosteroid, methotrexate and hydroxychloroquine	Ib–IV	79 (67 to 91)
8	If detected, associated conditions such as hyperparathyroidism, haemochromatosis or hypomagnesaemia should be treated	Ib	89 (81 to 98)
9	Currently, no treatment modifies CPP crystal formation or dissolution and no treatment is required for asymptomatic CC	IV	90 (83 to 97)

ACTH, adrenocorticotropic hormone; CC, chondrocalcinosis; CPP, calcium pyrophosphate; CPPD, calcium pyrophosphate deposition; GCS, glucocorticosteroids; LOE, level of evidence (see table 1 for further details); NSAID, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; SOR, strength of recommendation on visual analogue scale (0–100 mm, 0=not recommended at all, 100=fully recommended).

GCS are particularly useful and safe for the treatment of acute monoarticular or oligoarticular microcrystalline synovitis. Oral GCS, parenteral GCS and corticotrophin (adrenocorticotrophic hormone (ACTH)) are useful alternative treatment modalities for patients with polyarticular attacks.

One small non-RCT was undertaken in patients with acute crystal-induced arthritis (n=27) to compare the efficacy of a single intramuscular injection of 7 mg betamethasone (n=10), a single intravenous injection of 125 mg methylprednisolone (n=7) and diclofenac 150 mg a day for 3 days then 75 mg a day for 3 days (n=10).<sup>18</sup> Patients in the GCS groups were either contraindicated or intolerant of NSAIDs. The number needed to treat (NNT) to obtain at least 50% improvement for the GCS injection groups compared with the diclofenac group was significant on day 1 (NNT=3, 95% CI 2 to 16), but not on days 3, 6 and 15, suggesting that the GCS may be more effective at gaining quick control of severe pain. No significant difference was found between intravenous and intramuscular injections. However, this was a non-randomised trial and patients in the GCS groups differed from patients in the diclofenac group in response to NSAIDs, so these results need to be confirmed. GCS treatment was well tolerated apart from one patient with profuse sweating and another with hot flushes within a few hours of injection. This is supported by an uncontrolled trial in which all patients (n=14), including 12 who were contraindicated to NSAIDs, had at least 50% clinical improvement on a VAS after one or two intramuscular injections of triamcinolone acetonide 60 mg within 14 days without any significant side effect.<sup>19</sup>

A retrospective cohort study was undertaken in 38 patients with acute gout (n=33) or CPP crystal arthritis (n=5) who were treated with parenteral ACTH. Parenteral ACTH 40 or 80 units was given intravenously, intramuscularly or subcutaneously three times. A total of 43 acute attacks were treated, all resolved in an average of 4.2 days. Although mild hypokalaemia, hyperglycaemia, fluid retention and rebound arthritis occurred as adverse effects, none was severe and all were easily controlled. The study suggests that ACTH may be a safe and effective treatment for acute gout and acute CPP crystal arthritis.

### Prophylaxis

In contrast to gout it is less evident whether prophylactic treatment with NSAIDs or low-dose colchicine is effective.<sup>2</sup> One uncontrolled trial was undertaken to determine the prophylactic efficacy of low-dose colchicine.<sup>20</sup> Ten patients with recurrent acute attacks of CPP crystal arthritis were followed up for 1 year after receiving oral colchicine 0.6 mg twice daily. Thirty-two episodes of acute arthritis were recorded in the year (3.2% per year) before the start of the drug and only 10 after taking the drug (1% per year) ( $p<0.001$ ). Ninety per cent of the patients benefited from the drug. The study suggests that oral colchicine may be efficacious as a prophylactic agent in recurrent acute attacks of CPP crystal arthritis. Whether NSAIDs have similar clinical effect remains to be investigated. If NSAIDs or colchicine are used for this purpose their potential side effects need to be carefully considered.<sup>2 26</sup>

### Treatment for concurrent OA

It was agreed that the treatment of OA with CPPD should follow the same treatment objectives as for OA:

- ▶ Educating patients about the nature of the disorder and its management;
- ▶ Reducing joint pain and stiffness;

- ▶ Maintaining and improving joint mobility;
- ▶ Reducing physical disability and handicap;
- ▶ Improving health-related quality of life;
- ▶ Limiting the progression of joint damage.

Over 50 treatment modalities are currently available for management of OA including non-pharmacological, pharmacological and surgical treatments. Evidence for clinical effectiveness and cost effectiveness has been systematically reviewed.<sup>26 32</sup> The management of OA with CPPD should follow evidence-based recommendations that have been developed by EULAR<sup>9 33 34</sup> and other organisations<sup>3 35</sup> according to the patient need, availability of the treatment, clinical effectiveness and cost effectiveness of the treatment and affordability by the individual or healthcare system. Concurrence of CPPD with OA might be associated with an increased inflammatory component and a different prognosis with respect to rate of clinical and radiographic progression<sup>36 37</sup> but the repertoire of treatments remains basically the same as that for OA. Special caution should be taken when using intra-articular high molecular weight hyaluronan since it might induce acute attacks.<sup>32 38</sup>

### Treatment for chronic CPP crystal inflammatory arthritis

There is no specific RCT evidence for NSAIDs in chronic CPP crystal inflammatory arthritis. The recommendation for NSAIDs is largely based upon research evidence obtained for management of gout<sup>2</sup> and OA.<sup>26</sup> As NSAIDs cause gastrointestinal bleeding<sup>26</sup> they are recommended in combination with gastro-protective agents such as proton pump inhibitors, especially in patients with a high risk of side effects (eg, older patients) or for those who need long-term use of these agents.<sup>3 35</sup>

One double-blind, placebo-controlled RCT has been undertaken for low-dose colchicine (0.5 mg twice daily for 8 weeks then as required until 20 weeks) in knee OA with persistent inflammation caused by CPPD (n=39).<sup>13</sup> The NNT of the clinical response (>30% pain reduction on VAS) over placebo was 2 (95% CI 1 to 4) at 4 months and 4 (-13 to 2) at 5 months. Side effects (eg, dyspepsia) were minor and not statistically significant (RR=2.11, 95% CI 0.76 to 5.86) and no marked diarrhoea was documented.<sup>13</sup>

One uncontrolled trial examined the treatment effect of low-dose methotrexate (MTX, 5–10 mg/week) in five patients with chronic symptoms and recurrent acute CPP crystal arthritis who were resistant to common treatments. The mean follow-up time with MTX was 50.4 months (range 6–81 months). All patients reported an excellent clinical response, with marked improvement within a mean period of 7.4 weeks. A significant decrease in pain intensity ( $p<0.0001$ ), swollen and tender joint counts ( $p<0.0001$ ) and frequency of attacks was observed. No significant side effects were reported. This study suggests that MTX may be a valuable treatment for severe CPPD that is refractory to conventional treatment, and a larger trial of MTX treatment is now underway.

A 6-month double-blind, placebo-controlled RCT investigated the treatment effect of hydroxychloroquine in 36 patients with chronic inflammatory arthritis with CPPD. The NNT for clinical response was 2 (95% CI 1 to 7). Clinical response rate was defined as the percentage of patients with more than 30% reduction of joint count for swelling and tenderness. No significant side effects were observed.<sup>12</sup> Animal studies suggest that blockade of the NLRP3 (cryopyrin) inflammasome interleukin 1 $\beta$  pathway may offer a new treatment strategy for crystal-associated arthritis.<sup>39</sup> This has been piloted in a non-randomised, crossover RCT in 10 patients with gout and a significant reduction of pain and

clinical improvement was observed.<sup>40</sup> Further large-scale RCTs in gout and other crystal-associated arthritis are needed.

No data for low-dose GCS was found, and the recommendation is supported by expert opinion alone.

Although not recommended, intra-articular injection of radiocolloid (yttrium-90) has been studied in patients with symptomatic knee OA plus CPPD in one small double-blind, placebo-controlled RCT.<sup>11</sup> Significant improvement was observed for pain (NNT=2, 95% CI 1 to 3, defined as number of knees with pain reduction  $\geq 1$  grade on a 1–3 scale), global response (NNT=2, 95% CI 1 to 7, defined as knees with  $\geq 3$  grade response on a 0–5 scale) and stiffness (ES=0.79, 95% CI 0.04 to 1.53, stiffness in minutes). As this is the only study of radiosynovectomy for OA plus CPPD the usefulness of such treatment is unclear. Recurrent haemarthrosis is an occasional clinical problem, especially in older patients with OA plus CPPD affecting the shoulder, and radiosynovectomy is sometimes used in this situation, though in the absence of any supporting trials.

### Treatment for other comorbidities

Patients with CPPD are three times more likely to have primary hyperparathyroidism than patients without CPPD (OR=3.03, 95% CI 1.15 to 8.02) and haemochromatosis and hypomagnesaemia also predispose to CPPD.<sup>1</sup> Conversely, patients with primary hyperparathyroidism may have an increased risk of acute attacks of CPP arthritis.<sup>41 42</sup> In patients with such predisposing conditions, treatment of their comorbidity is obviously required, though whether treatment of such comorbidity affects the outcome of CPPD-associated arthritis is unclear. Corresponding treatment guidelines have been published for some of these comorbidities.<sup>2 43 44</sup> The management of comorbidities for CPPD should follow the treatment guidelines for these conditions.

### Treatment for asymptomatic CPPD

Unlike the situation with urate crystals in gout, at present there is no definitive treatment to prevent formation or enhance dissolution of CPP crystals in affected joints or tissues. In vitro studies, however, have shown that magnesium can solubilise CPP crystals and has inhibitory effects on nucleation and growth of these crystals.<sup>45</sup> The possibility that magnesium supplementation might influence CPP crystals in vivo is suggested by the precipitation of acute CPP crystal arthritis following lavage of joints with magnesium sulphate<sup>46</sup> and by the reported benefit of magnesium replacement treatment in a patient with hypomagnesaemia and CC.<sup>47</sup> One small double-blind, placebo-controlled RCT has been undertaken in 38 patients with symptomatic knee OA plus CPPD.<sup>23</sup> However, despite possible clinical benefits (eg, pain reduction) there was no reduction in radiographic CC in those receiving magnesium compared with those given placebo.

High inorganic pyrophosphate levels appear central to CPP crystal formation and there is considerable interest, but no relevant data, on the possibility of using other pharmacological agents (such as probenecid,<sup>48</sup> polyphosphates,<sup>49</sup> phosphocitrate<sup>50</sup>) to modulate pyrophosphate levels and influence CPP crystal formation and dissolution, either by local intra-articular or systemic administration. At present, however, this remains only a theoretical possibility.

### Future research agenda

After four rounds of the Delphi exercise, three topics were highlighted for future research in the management of CPPD:

1. Basic studies are required to better elucidate the mechanism of CPPD and the effects of CPP crystals on joint tissues.
2. The value of biological agents, in particular interleukin 1 inhibitors, in the treatment both of acute and chronic CPP crystal inflammatory arthritis merits investigation.
3. The value of MTX in the treatment of chronic CPP crystal inflammatory arthritis needs to be evaluated.

### DISCUSSION

CPP crystal-associated arthritis is one of the most common forms of inflammatory arthritis.<sup>51</sup> Currently, no evidence-based treatment guidelines are available. This is the first attempt to develop evidence-based recommendations for the management of CPPD. Only four published RCTs have been identified. The majority of the recommendations are supported mainly by expert opinion together with research evidence extrapolated from studies relating to the management of gout, based on the control of similar clinical symptoms and the use of the same analgesics in these two conditions.<sup>2</sup> However, unlike the situation with urate crystals, much of the pathogenesis of CPPD remains unclear and there are no pharmacological options to influence CPP crystal formation and dissolution, so treatment of CPPD is restricted to symptomatic control.

In addition to the lack of research evidence, there are number of other limitations to these recommendations. First, they were proposed before the tailored literature search was undertaken, therefore only the perceived key issues of management are covered. Second, there is no treatment algorithm for the recommended treatments, and users should apply the recommendations according to individual patient characteristics. Furthermore, CPPD may be associated with a number of metabolic conditions and these require management in their own right according to existing guidelines or recommendations which are not reviewed here.

In summary, the EULAR CPPD Task Force has developed recommendations for the management of CPPD based on expert consensus and the systematic literature review of current available research evidence. The objectives of management are to relieve symptoms and to prevent acute attacks. Disease-modifying treatments have yet to be developed. Research evidence to support the recommendations is sparse and further clinical trials in CPPD are needed.

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