Joint aspiration and injection and synovial fluid analysis

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Keywords:
Intra-articular corticosteroid
Synovial fluid analysis
Monosodium urate crystals
Calcium pyrophosphate dihydrate crystals

Abstract

Joint aspiration/injection and synovial fluid (SF) analysis are both invaluable procedures for the diagnosis and treatment of joint disease. This chapter addresses (1) the indications, technical principles, expected benefits and risks of aspiration and injection of intra-articular corticosteroid and (2) practical aspects relating to SF analysis, especially in relation to crystal identification. Intra-articular injection of long-acting insoluble corticosteroids is a well-established procedure that produces rapid pain relief and resolution of inflammation in most injected joints. The knee is the most common site to require aspiration although any non-axial joint is accessible for obtaining SF. The technique involves only knowledge of basic anatomy and should not be unduly painful for the patient. Provided sterile equipment and a sensible, aseptic approach are used, it is very safe. Analysis of aspirated SF is helpful in the differential diagnosis of arthritis and is the definitive method for diagnosis of septic arthritis and crystal arthritis. The gross appearance of SF can provide useful diagnostic information in terms of the degree of joint inflammation and presence of haemarthrosis. Microbiological studies of SF are the key to the confirmation of infectious conditions. Increasing joint inflammation associates with increased SF volume, reduced viscosity, increasing turbidity and cell count and increasing ratio of polymorphonuclear:mononuclear cells, but such changes are non-specific and must be interpreted in the clinical setting. However,
detection of SF monosodium urate and calcium pyrophosphate dihydrate crystals, even from un-inflamed joints during intercritical periods, allows a precise diagnosis of gout and calcium pyrophosphate crystal-related arthritis.

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What are the indications for joint aspiration/injection?

Principal indications for joint aspiration and injection are listed in Table 1. It is particularly required for the diagnosis and management of the acute ‘hot red joint’, which is a medical emergency because of the morbidity and mortality related to septic arthritis. This largely relates to presentation with acute monoarthritis but is also relevant to the patient with pre-existing chronic polyarthritis such as rheumatoid arthritis who develops a ‘flare’ limited to one joint. It is only by aspirating synovial fluid (SF) that joint sepsis or crystal-associated synovitis (gout or pseudogout) can be accurately diagnosed.

Important clinical features that always require consideration of sepsis include:

- acute synovitis, especially in patients at increased risk of joint sepsis (rheumatoid arthritis (RA), diabetes and immunocompromised patients); sepsis most commonly, though not exclusively, occurs in joints with pre-existing damage;
- rapidly progressive symptoms in a single joint;
- additive joint involvement (e.g., first metatarsophalangeal joint (MTPJ), followed by ankle and then knee involvement on the same side);
- erythema overlying the joint (a sign of periarticular inflammation that particularly accompanies sepsis or crystals); and
- inflammatory pain in joints that are commonly asymptomatic if affected by other, non-septic, arthropathy (e.g., sternoclavicular joint).

Table 1
Indications for joint aspiration.

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>(a) acute synovitis</td>
<td>(a) common</td>
</tr>
<tr>
<td>• sepsis</td>
<td>• to reduce intra-articular pressure</td>
</tr>
<tr>
<td>• crystals:</td>
<td>• injection of corticosteroid</td>
</tr>
<tr>
<td>common: monosodium urate calcium pyrophosphate</td>
<td></td>
</tr>
<tr>
<td>rare: oxalate, cholesterol</td>
<td></td>
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<tr>
<td>(b) chronic arthropathy</td>
<td>(b) less common</td>
</tr>
<tr>
<td>• crystals (monosodium urate, calcium pyrophosphate)</td>
<td>• recurrent aspiration for sepsis</td>
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<td></td>
<td>saline lavage for resistant arthropathy</td>
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Frequent aspiration may be required as part of the management of septic arthritis. However, needle or arthroscopic lavage or surgical drainage should be undertaken if rapid reaccumulation or loculation resistant to simple aspiration occurs. A prosthetic joint should not be aspirated without prior consultation with an orthopaedic surgeon or rheumatologist. Crystal arthritis can be diagnosed by aspiration of currently inflamed joints and also from asymptomatic joints during intercritical periods, and even from knees and first MTPJs that have not suffered acute attacks [1].

Aspiration of SF from a tense swollen joint, due to synovitis or haemarthrosis, may quickly relieve severe pain by reducing intra-articular pressure. In the situation of inflammatory synovitis, reaccumulation of SF can be prevented (at least temporarily) by the intra-articular injection of long-acting corticosteroids. If sepsis is a possibility, steroid injection should only be done after exclusion of sepsis by joint-fluid culture. However, SF cultures are almost never positive in the absence of clinical suspicion of infection; hence, routine culture of aspirated SF is unnecessary [2]. A corticosteroid injection may avoid the requirement for additional systemic treatment or provide quick relief while slow disease-modifying drugs take effect. In the circumstance of inflammatory monoarthritis, intra-articular treatment is most appropriate. Intra-articular corticosteroid (IAC) injection can also provide rapid pain relief in clinically un-inflamed joints with osteoarthritis (OA).

**What are the general technical principles?**

**Setting**

An aseptic technique is mandatory with sterile equipment. Gloves should be worn to protect the operator, especially in high-risk situations such as human immunodeficiency virus (HIV) or hepatitis, but they need not be sterile if a no-touch technique is used. There is no need to gown up or go to theatre and it is perfectly acceptable to carry out the procedure in a general ward or outpatient clinic. However, considerable variation in practice occurs and audits have shown that between one-quarter and one-third of practitioners (rheumatologists, orthopaedic surgeons and primary-care physicians) routinely use sterile gloves [3,4] and some routinely use additional sterile precautions. Cawley and Morris demonstrated that simple swabbing with alcohol is as effective in killing skin flora as is chlorhexidine preparation [5]. The risk of infection is very small with simple swabbing, sterile equipment and a no-touch technique. A retrospective survey in France suggested an overall risk of sepsis of 13 per million injections with the incidence being much lower if pre-packaged steroid syringes were used [6]. In a retrospective 10-year survey of septic arthritis in Nottingham (population 600,000) only three cases of septic arthritis possibly related to corticosteroid injection were identified [7].

**Preparation of the patient**

The patient should be positioned on a couch with the injection area supported sufficiently so that the muscles can comfortably relax. The surface anatomy and joint landmarks should be identified. The overlying skin should be cleaned with an alcohol swab. A no-touch technique is essential after cleaning; hence, any mark to identify the point of entry should be made earlier. The point of entry can be marked by a cross with the centre removed by the antiseptic swab. An alternative method is to make a small indentation of the skin. Local anaesthetic, either as a anaesthetic gel/cream or as a cooling refrigerant spray, is not usually applied to the skin for adults but is necessary for children.

**Technical considerations**

Large joints such as the knee and shoulder are aspirated using a 21-gauge (green) needle although a larger needle may be required to readily aspirate very purulent fluid. A 23- or 25-gauge (blue or orange) needle is appropriate for smaller joints. Smaller syringes are easier to operate when aspirating joints and it is often easier to disengage, empty and re-use a 20-ml syringe than to employ a larger barrel size.

If injection is also required the corticosteroid should be drawn up in a 2-ml syringe and kept close to hand capped with a sheathed needle. A ‘reciprocating’ syringe that has two barrels connected to a single exit is reported to improve operator control of the needle, reduce likelihood of displacement and...
reduce procedure time [8]. Initial aspiration of SF was shown to improve the outcome in RA patients treated with intra-articular steroid [9]. This study of 191 knee injections showed that the proportion of relapses over a 6-month follow-up period was significantly reduced if aspiration was performed prior to injection. However, if concomitant steroid injection is required it is best not to aspirate to complete dryness as leaving a little fluid may reduce the risk of needle displacement. Furthermore, although aspiration to near dryness should be attempted for tense, acute effusions, the quadriceps may adapt its proprioceptive acuity to chronic, large, knee effusions and complete emptying may cause destabilization of proprioception and ‘giving way’. Jones et al. have shown the uncertainty of correct injection placement in the absence of SF aspiration [10]. In this study a large proportion of injections were shown to be extra-articular by the concomitant injection of contrast medium. In another study Bliddal showed that 9% of knee-joint injections were extra-articular [11]. A more recent study of subacromial injections showed an accuracy of 70% [12] but, unlike the Jones et al. study [10], clinical improvement did not correlate with accuracy. At the end of aspiration the needle should be held firmly with one hand as the syringe barrel is disengaged. The predrawn steroid syringe is then attached taking care not to displace the needle. If there is resistance to injection the needle should be withdrawn slightly, the landmarks redefined and the needle then reinserted in the correct direction.

The commonly used preparations for intra-articular injection are the longer-acting hydrophobic steroids such as methylprednisolone acetate (MPA) and triamcinolone hexacetonide. Hydrocortisone acetate is shorter acting and less effective but has a role in some soft-tissue injections such as carpal tunnel syndrome [13]. Corticosteroid preparations such as MPA should not be mixed with local anaesthetic as this results in precipitation. At the end of aspiration or injection the puncture site should be pressed with a cotton-wool ball until local skin bleeding has stopped.

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**Practice points**

- Aseptic no-touch technique is mandatory.
- There is no requirement to ‘gown up’ or go to theatre.
- Gloves should be worn.
- The patient should be positioned with the joint relaxed.
- Avoid surface blood vessels or cellulitis at point of entry.
- Aspirate tense, acute effusions to near dryness, but do not aspirate to complete dryness if an injection is to be given or if it is a large, chronic, knee effusion.
- Steroid should not be injected against resistance.
- Hydrophobic corticosteroids (triamcinolone acetonide and hexacetonide) are more effective than hydrocortisone.
- MPA should not be mixed with local anaesthetic.

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**What equipment is required?**

The equipment required is listed in Table 2.

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**Table 2**

<table>
<thead>
<tr>
<th>Equipment for Intra-articular corticosteroid injection.</th>
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<tbody>
<tr>
<td>Patient couch</td>
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<tr>
<td>Gloves</td>
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<tr>
<td>Sterile swabs</td>
</tr>
<tr>
<td>Prepacked sterile needles (19, 21 and 23 gauge) and syringes (2, 5, 10 and 20 ml)</td>
</tr>
<tr>
<td>Single-dose sealed ampoules of injectable corticosteroid</td>
</tr>
<tr>
<td>Single-dose sealed ampoules of local anaesthetic (lignocaine 1% or 2%)</td>
</tr>
<tr>
<td>Synovial fluid collection bottles</td>
</tr>
<tr>
<td>Elastoplast or cotton-wool</td>
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</table>
What information should I give to the patient?

Explain the rationale and nature of the procedure to the patient. Include a clear discussion of the expected level of discomfort and the symptom relief that may follow. The more relaxed and informed the patient is, the better. Although aspiration involves a needle prick and some discomfort, in experienced hands it should not be much more uncomfortable than venepuncture. This is especially true for large joints such as the knee, ankle or glenohumeral joint and joints with significant effusions. The procedure is relatively quick and any discomfort should be short-lived.

If the joint is to be injected the risks and possible side effects should be discussed. The toxicity of steroid injection is low but patients should be warned regarding facial flushing (12%), post-injection flare (15%) and sepsis (<1:78,000 risk). Although the risk of infection is very small indeed, individual cases continue to be reported, and the patient should be warned [6,7]. Subcutaneous atrophy is more of a concern with peri-articular injections but has been described with intra-articular injections, especially small-joint or complex injections [14]. A small area of depigmentation may occur at the site of steroid injection. It is generally proposed that the frequency of injections should be no more than 3-monthly although there is no conclusive evidence of any detrimental effect on cartilage or bone from steroid injection into an arthritic joint. A large case series of long-term follow-up of children with juvenile idiopathic arthritis, who had received multiple injections, failed to demonstrate any adverse effect on the joint [15]. Raynauld et al. showed that there were no deleterious effects from 3-monthly steroid injections for knee OA over 2 years [16].

There is some evidence of significant systemic corticosteroid absorption following intra-articular injection in an animal model [17], but this is unlikely to be clinically important in the majority of cases. Laaksonen et al. described alterations in plasma cortisol levels which persisted for at least 4 weeks, following IAC injection in children [18]. The authors suggested that this transient suppression of endogenous cortisol may not be clinically important. Another concern is the possible systematic absorption of corticosteroid to osteoporosis but Emkey et al. reassuringly concluded that IAC has no net effects on bone resorption in patients with RA [19]. Although systemic absorption raises some other potential concerns, such as temporary worsening of diabetic control [20], it can give symptomatic benefit to other joints. Improvement to the un-injected knee was demonstrated by McDonald et al. following IAC of the knee using microwave thermography [21]. Therefore the patient may be informed that a small amount of the injection is absorbed into the system but that this is unlikely to have any significant effects.

If a local anaesthetic is given with the steroid, the patient should be warned that this component of the injection may wear off after 2–4 h resulting in a temporary return of pain. Some advocate bed rest or reduced activity for 12–24 h following injection into a large weight-bearing joint to improve therapeutic benefit as injected material is cleared from the joint more rapidly with use of the joint [22]. Chakravarty et al. have demonstrated a greater degree of clinical and serological improvement with 24 h of hospital bed rest following knee injection [23]. However, two subsequent randomised controlled found no advantage from resting after injection [24,25]. The constraints on bed capacity in most rheumatology services result in the pragmatic advice for patients to rest as much as possible for the first 24 h following the injection. Some rheumatologists provide written information for the patient but often this will not be read and understood until after the injection; hence, the discussion with the patient remains very important.

Practice points on what to tell the patient

- Discomfort should be minor and short-lived.
- Joint infection is extremely rare (comparable to sepsis after venepuncture).
- Subcutaneous atrophy is a rare complication.
- Flushing and post-injection pain may occur but settle spontaneously.
- Minor systemic corticosteroid absorption occurs but is unlikely to be clinically significant.
- The joint should be (relatively) rested for 24 h if possible after the injection.
- Benefit is expected within 24 h, which may persist for 2 months or longer.
- There is no evidence of damage to the joint from corticosteroid injection.
How do I know the needle is in the correct position?

The patient may experience some discomfort as the needle pierces the skin and joint capsule. Marked discomfort usually reflects inaccurate placement, for example direct contact with periosteum. A slight ‘give’ is usually felt as the needle enters the joint cavity but difficulty advancing the needle suggests that it is in the wrong position. If there is marked resistance or discomfort, the syringe and needle should be withdrawn slightly and gently advanced again after reassessment of the anatomical landmarks. When the needle is correctly placed, the syringe should be pulled taking care not to dislodge the needle. Aspiration of SF confirms correct placement. Correct placement is also suggested by low resistance to injection. If the flow of SF becomes intermittent or stops, this may be due to:

- temporary obstruction by synovial fronds,
- blockage by fibrin and debris,
- loculation of SF or
- displacement of the needle outside the joint cavity.

If this happens, a small amount of fluid should be injected back in from the barrel of the syringe. This often clears the needle of debris or overlying fronds permitting the aspiration to continue. Increasing use of ultrasound, especially for technically challenging joints such as the hip, may aid accuracy of injections.

What benefit can be expected?

The aspiration of SF from a tensely swollen joint may quickly relieve pain by reducing intra-articular hypertension. In the absence of sepsis, the injection of a long-acting steroid into the joint may prevent reaccumulation of fluid and reduce synovial inflammation. The duration of benefit from steroid injection often starts within 24 h and usually persists for more than 2 months [19–23]. The clinical benefit associated with IAC therapy has been shown by many uncontrolled studies [26–32] following the first use of such therapy in 1951 [26], although the extent of benefit differs considerably between studies. Blyth et al. reported the results of 300 adults with RA who were evaluated weekly for 12 weeks following IAC into the knee [29]. The authors showed that < 40% of patients were pain free at 1 week with a steady decline in the percentage of patients who were pain free at 12 weeks. Padeh and Passwell reported the results of IAC injection in 71 patients with juvenile idiopathic arthritis in whom 82% of injections resulted in remissions of >6 months duration [30]. The investigation of factors that may predict a good response to intra-articular injection has been unhelpful [28,31]. None of the following correlated with the efficacy of IAC: disease duration, radiological scores, inflammatory markers and signs of inflammation. Patients with inflammatory polyarthritis and more than two joints requiring injection may benefit more from a change in systemic disease-modifying therapy than multiple injections. A study of polyarticular IAC injection demonstrated better efficacy and less adverse effects than intramuscular corticosteroids [33]; however, in practice multiple injections may not be well tolerated by some patients. Intra-articular injections in large and small joints have shown efficacy in early RA as part of a treat-to-target strategy [34].

Other intra-articular injectables

Osmic acid, yttrium and hyaluronic acid (HA) can also be given by intra-articular injection. Osmic acid synovectomy has been used as an alternative to surgery for chronic synovitis that is unresponsive
to IAC [35], although much of the efficacy data for osmic acid comes from open studies and retrospective series [36–41]. Initial remission with osmic acid is achieved in approximately half of the cases, with long-term remission in approximately 20% [40].

Yttrium synovectomy may also be considered when IAC treatment of chronic monoarticular synovitis fails [42–45]. Short-term efficacy is good but there are conflicting reports on long-term efficacy of yttrium [46–49].

HA is a high-molecular-weight polysaccharide that is a major component of SF and cartilage [50–52]. Despite an unclear mechanism of action, some randomised controlled trials report pain relief in knee OA from various HA products, which is evident 2–5 weeks after starting treatment and which may persist for several months [53–59]. However, because of cost, inconvenience and doubts concerning its efficacy due to some negative trials, the clinical indications for HA are limited. Anti-tumour necrosis factor (anti-TNF) alpha drugs have been administered by the intra-articular route with similar efficacy to corticosteroid injection [60], but their much greater cost will limit use.

What are the contraindications to joint injection?

There are very few contraindications to joint aspiration. Injecting through cellulitic or broken skin should be avoided. Joints of patients who are anticoagulated may be aspirated and injected but more prolonged pressure should be applied over the aspiration site and the procedure should be as atraumatic as possible. The level of anticoagulation should ideally be within the therapeutic range. In patients with suspected sepsis, it is imperative to aspirate the joint to make the diagnosis but corticosteroid should not be injected if infection is suspected. Caution should be exercised if there is evidence of a localised staphylococcal infection such as a furuncle or suspicion of systemic infection. Corticosteroids should not be injected into a prosthetic joint without consulting an orthopaedic surgeon. It is important to make a diagnosis before injection as some conditions such as avascular necrosis may be exacerbated by IAC injection. Active tuberculosis, ocular herpes and acute psychosis have also previously been considered as contraindications to steroid injection but cautious use may be considered in specific circumstances.
Site-specific technique

Knee injection

The knee is the largest synovial joint and the easiest to aspirate. All major arthropathies may target the knee and it is the most common site for septic arthritis and pseudogout. The knee is therefore the commonest site to require aspiration and injection. A knee effusion is first evident as a loss of the medial and lateral dimples around the patella. A large effusion represents a horseshoe swelling of the suprapatellar pouch above and to either side of the patella. There are several approaches to knee injection:

Medial approach

This is the preferred approach when there is relatively little fluid in the knee and for aspiration of asymptomatic knees for diagnosis of gout or calcium pyrophosphate dihydrate (CPPD) crystal-associated arthritis (see below). The patient should rest on a couch with their whole leg supported and relaxed. For smaller fluid collections that do not fully open up the suprapatellar reflection, a medial approach may be preferred. The site of entry is just below the mid-point of the patella and the needle is aimed directly under the patella (Fig. 1). SF may be aspirated after as little as 1 cm of penetration and
deep introduction of the needle can be avoided. Pressure can be applied with the other hand to encourage fluid to the medial side. The injection is performed using a 19-gauge needle and 40 mg of triamcinolone or equivalent.

**Superolateral approach**

A superolateral approach is commonly used for large effusions that distend the suprapatellar pouch. With a large tense effusion, the knee is most comfortable in mild flexion and may require a soft support under the mildly flexed knee. The needle is introduced above and to the lateral side of the patella at the maximum convexity of the distended pouch, aiming downward and medially as if to go under the posterolateral aspect of the patella (Fig. 2). The distended pouch is superficial and the needle may not need to be introduced far before SF is aspirated. The other hand should be used to tip the patella laterally and encourage fluid to accumulate at the site of aspiration.

Popliteal cysts may be directly aspirated and injected by a posterior approach with ultrasound guidance and there is some preliminary evidence of reduced size and reduced symptoms from the cyst when compared to response of the cyst to conventional intra-articular injection [61].

**Shoulder injection**

**Glenohumeral joint**

Limitation of external rotation is typical with glenohumeral problems. The glenohumeral joint can be injected by an anterior or a posterior approach.

**Anterior approach**

The patient should place their forearm across the abdomen to partially internally rotate the shoulder. The point of entry is just inferolateral to the coracoid process (Fig. 3). SF may be aspirated in the setting of inflammatory arthritis but with other shoulder lesions, especially adhesive capsulitis the finding of fluid is unusual. The ease of injection should determine that the needle is in the right place if no SF is obtained. The joint is injected using a 19-gauge needle and 40 mg of triamcinolone or equivalent.

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**Fig. 2.** Superolateral aspiration of the knee. The examiner’s left hand is putting pressure on the medial suprapatellar pouch.
Posterior approach

Identify the coracoid process anteriorly and the joint line posteriorly. The joint line can be identified if the patient is relaxed on the couch and the arm is rotated. Having marked the joint line, the injection is pointing the needle towards the outer side of the coracoid process (Fig. 4).

Acromioclavicular joint

The acromioclavicular joint is a plane joint and can therefore be injected centrally from the front. The joint line is identified by palpation. The joint cavity is small and only accepts 0.5 ml of fluid. A fine needle (23 gauge) is recommended with injection of 10 mg MPA or equivalent from a 2-ml syringe.
Elbow joint

Anterolateral approach

The elbow joint may be involved in RA and other types of inflammatory arthritis. Fluid usually accumulates earliest and most prominently anteriorly around the radial head. With the patient’s elbow resting on a firm, comfortable surface and held flexed at 90°, palpate the radial head while passively supinating and pronating the forearm. The joint line should be readily identified. Pass the 21-gauge needle towards the joint line from a superolateral angle (Fig. 5), aiming to place the tip just within the capsule, rather than deep between the two bones. The injection is performed with 20 mg of triamcinolone or equivalent.

Wrist joint

The wrist is commonly involved in RA and other types of inflammatory arthritis including pseudogout. Swelling of wrist synovitis should not be confused with swelling of the extensor tendon sheath. The radiocarpal joint space should be identified by palpation, feeling for the triangular space between the scaphoid and lunate in the centre of the distal radius (Fig. 6), and the injection is carried out whilst holding the wrist partially flexed. For the distal radioulnar joint, the injection is performed using a superior approach just medial to the distal ulnar prominence with 20 mg of triamcinolone or equivalent via a 21-gauge needle. If the needle is in the correct position, it can be pushed easily to the required depth and the injection can be made with little resistance.

First carpometacarpal joint

The pain of OA is the most common indication for local injection of this joint although the evidence of efficacy is largely anecdotal [62]. The joint may also be involved in psoriatic arthritis and other inflammatory arthritides. The joint line should be identified by palpation and the injection performed from the lateral aspect near the abductor tendon using 10 mg of MPA or equivalent via a 23-gauge needle (Fig. 7). It is useful to distract the thumb with the other hand while making the injection to stretch the joint capsule.

Metacarpal and interphalangeal joints

These small-joint injections are most commonly performed for the management of RA or other inflammatory arthritis. If multiple small-joint injections seem to be required, then an

Fig. 5. Aspiration of elbow.
increase in systemic disease-modifying therapy is generally advised in preference to multiple injections.

The metacarpal joint line should be identified by gently flexing and extending the joint. The joint line is about 1 cm distal to the crest of the metacarpal head (Fig. 8). The injection is performed by a superolateral approach using a 23-gauge needle to ensure that the neurovascular bundle is avoided. The patient should feel the joint being expanded by the injection and a maximum of 10 mg of MPA or equivalent should be used.

Similarly the proximal (Fig. 9) or distal interphalangeal joint line should again be identified by gently flexing and extending the joint. The superolateral approach avoids the neurovascular bundle, and a low volume only should be injected (2 mg MPA).

**Ankle joint**

With the foot in moderate plantar flexion, insert the 19-gauge needle in the space between the tibia and the talus bounded medially by the tibialis anterior tendon and laterally by the extensor hallucis longus tendon (Fig. 10). It is important to direct the needle tangentially to the curve of the talus; the most common mistake is to direct the needle too much towards the heel. Injection of the ankle is more liable to be complicated by infection than other sites because of the tendency to oedema; hence, a careful aseptic technique is particularly important.

**Subtalar joint**

The subtalar joint is frequently involved in RA but often communicates with the ankle joint. The joint can be injected using a lateral approach with the patient lying prone. The landmarks are a horizontal line drawn 2.5 cm above the distal end of the lateral malleolus and a vertical line 1.0 cm from the posterior border of the shaft of the fibula. The point where these lines cross marks the site of entry with the needle pointed towards the proximal head of the first metatarsal. The injection should be given without resistance using 20 mg triamcinolone or equivalent via a 21-gauge needle.
First MTP joint

This joint is classically associated with podagra but may be involved in RA, psoriatic arthritis or reactive arthritis. Examination of SF aspirated from this joint, even between attacks, may confirm the diagnosis of gout and IAC injection is an effective treatment for podagra. The joint line is identified by palpation, aided by slight flexion and distal distraction of the proximal phalanx, and the joint is entered superolaterally from the medial side, aiming under the extensor tendon, using a 23-gauge needle (Fig. 11). If aspirating an asymptomatic joint to confirm gout and an apparently dry tap is obtained, it is still worth emptying the syringe onto a slide – often a few drops of SF, sufficient for crystal identification, are contained within the barrel of the needle. For IAC injection, use 4 mg MPA or equivalent.

MTP joints

MTP joints are commonly involved in RA and some cases of seronegative arthritis. Injection of these joints can be helpful particularly in early disease. The joint line is identified by gentle palpation and the 23-gauge needle introduced obliquely under the extensor tendon. The injection should be performed without resistance using 10 mg MPA or equivalent.
Hip joint

The major indication for hip arthrocentesis is suspected infection. However, IAC injection has been advocated for the treatment of OA and inflammatory arthritis of the hip [63,64]. One double-blind randomised trial [64] and some open studies [65,66] have suggested short-term benefit from IAC injection for hip OA, but the benefit was not sustained beyond 1–2 months. The use of imaging control is recommended for aspiration or injection of the hip as arthrocentesis of the hip joint is technically difficult. Unless fluid is aspirated the needle cannot be confirmed in the joint space without the use of imaging. Leopold et al. studied 15 human cadavers with 30 hip injections (15 anterior and 15 lateral approach) of methylene blue dye without fluoroscopic guidance [67]. Anatomic dissections were done on all specimens to determine the rate of success and the proximity of the needle to neurovascular structures with each approach. Neither the anterior nor the lateral injection approach was sufficiently reliable to recommend for clinical use without radiographic guidance.

Technique for hip arthrocentesis

The patient is positioned supine with the hip slightly flexed and internally rotated. The femoral artery and the inguinal ligament are identified by palpation. The skin and tissues down to the joint are infiltrated with local anaesthetic at the point of entry, which is lateral to the femoral artery and
2 cm inferior to the inguinal ligament. The aspirating needle or trochar and cannula are inserted under full aseptic precautions. If bone is encountered, the needle is withdrawn and inserted further laterally towards the femoral neck as judged by the position of the greater trochanter. An alternative method is to pierce the skin more laterally at the level of the lower edge of the greater trochanter and point the needle inwards medially and upwards along the line of the femoral neck. The needle path is adjusted (usually to a more shallow angle) until it passes through the capsule and the synovial membrane.

With fluoroscopic control, the injection of a small amount of contrast material identifies the position of the needle tip. With ultrasonography, the hip joint is identified and marked in the longitudinal and transverse planes. The needle is inserted where the two lines cross, and the position of the needle tip can be confirmed on scanning.

Sacroiliac joint

The sacroiliac (SI) joint is relatively inaccessible and requires imaging when aspiration or injection is attempted. This is best done under computed tomography (CT) fluoroscopy or magnetic resonance imaging (MRI) usually by an experienced radiologist or orthopaedic surgeon [68,69]. The major indication for arthrocentesis of the SI joint is suspected sepsis (unilateral presentation with fever, systemic upset and elevated C-reactive protein (CRP)). There are conflicting reports regarding the efficacy of SI-
Joint injection with long-acting corticosteroids in the management of inflammatory sacroiliitis [68,70]. There may be some merit in considering IAC injection of the SI joint if maximal oral and physical therapy have failed to provide adequate relief of symptoms.

**Apophyseal joints**

Interapophyseal (facet) joint injections were first reported by Mooney and Robertson with a success rate of 52% [71]. However, controlled studies using corticosteroid and local anaesthetic injection showed no benefit over saline [72,73]. Dolan et al. showed that single-photon emission computed tomography (SPECT) scanning can identify back pain sufferers likely to obtain short-term benefit from facet joint injections [74]. This study showed that clinical examination alone may be unreliable as facet joints are innervated from branches to the posterior primary ramus at the corresponding level and from the nerve root above. The technique should only be performed under imaging control by an experienced radiologist or anaesthetist.

![Fig. 10. (A) Palpation of the space between the tibialis anterior and extensor hallucis longus. (B) Approach to the ankle joint.](image)

**Practice points on sites of injection**

- The hip, SI and interapophyseal joints should be approached under imaging control.
- The preferred approach to the joint may depend upon individual patient circumstances.

**Research agenda**

- Appropriately powered prospective studies may identify the factors predicting a better response to IAC injection at specific joints with specific diagnoses.
- The merits of intra-articular hip, SI and apophyseal joint injections should be determined by appropriately powered, randomised, placebo-controlled trials.
Summary

Joint aspiration/injection is an invaluable and safe procedure for the diagnosis and treatment of joint disease. Joint aspiration provides important diagnostic information on septic arthritis and crystal arthritis. Intra-articular injection of long-acting insoluble corticosteroids produces rapid resolution of inflammation in most injected joints. Making a correct diagnosis before undertaking an intra-articular injection and explaining the technique to the patient are crucial. Provided simple aseptic precautions are taken, joint injection is a safe and well-tolerated procedure. Most peripheral joints are readily accessible to an experienced clinician but other joints (hip, SI and interapophyseal joints) require imaging assistance. More information regarding the efficacy of corticosteroid injection at these and other individual sites such as the first carpometacarpal joint would be welcome. In conclusion, IAC injection is an important adjunct to the management of inflammatory arthritis and OA, providing worthwhile and often dramatic benefit for localised symptoms.

Synovial fluid analysis

The joint cavity is delineated by the two articulating surfaces of hyaline cartilage and by the peripherally located synovium. The synovial membrane has no basal layer or epithelial cells [75] but contains a
rich vascular net. The more superficial capillaries close to the lining cells are fenestrated, facilitating rapid changes in water and solutes and supporting an active physiological role for the membrane.

All diarthrodial joints contain minute amounts of SF in their cavity. Paracelso (1493–1541) named this fluid 'synovial' because of its similarity to egg white in being clear yellow, transparent and viscous [76]. SF originates from the plasma that is filtered by the capillary net and diffuses into the joint cavity, with the addition of locally synthesised HA, which gives SF its characteristic viscosity [77]. The synovial membrane also lines the inner aspect of tendon sheaths and synovial bursae. The function of the synovial membrane and SF includes the transport of nutrients to the avascular joint cartilage, assistance in joint lubrication and joint 'cleaning' and defence. Approximately 0.5 ml of SF can be obtained by aspiration of a normal knee (Fig. 12), with only a drop or two coming from a clinically normal first MTPJ [1], but in joint disease the volume of SF generally increases, making aspiration technically easier.

**Joint inflammation and SF**

Essentially two types of conditions affect joints: inflammatory and non-inflammatory (most commonly OA). Although inflammation targets the synovial membrane, some cellular elements of inflammation cross into the joint cavity and can be detected in SF. In some non-inflammatory conditions, the increased SF volume appears to originate from dilated capillaries adjacent to altered joint structures, suggesting a primary role for mechanical factors [78]. In most instances, the macroscopic appearance of aspirated SF permits distinction between inflamed and uninflamed joints and may also provide additional diagnostic information.

**Macroscopic appearance**

The appearance of aspirated SF is evident at the bedside, providing immediate information [79,80]. In general, the more a joint is inflamed the greater the SF volume, the higher the cell count and subsequent turbidity, and the lower the viscosity (Fig. 13). 'Non-inflammatory' SF has very few cells and

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**Fig. 12.** Synovial fluid aspirated from a normal knee - small volume of clear, slightly yellow, highly viscous fluid.
looks transparent. Plastic syringes are not always totally clear and it may be helpful to transfer the SF to a clear glass or plastic tube to distinguish transparent from slightly turbid SF. Sometimes small fragments of synovial membrane, cartilage or fibrous tissue may be seen as faint floating debris within such transparent SF. SF from markedly inflamed joints (e.g., pyogenic infection, active RA and acute crystal synovitis) have the highest cell counts and turbidity and may even appear as frank yellow–green pus (Fig. 13). Although such ‘pyo-arthritis’ should always lead to consideration of sepsis, it is not specific for this diagnosis. Slight turbidity can result from red as well as white cells and microscopic examination of the SF may be needed to determine the cell type. Large numbers of red cells give the appearance of haemarthrosis (Fig. 14), which can be caused by a generalised bleeding diathesis (e.g., overcoagulation and haemophilia), joint trauma or synovial tumours (e.g., pigmented villonodular synovitis) but more commonly by aggressive synovitis (e.g., sepsis, RA and crystal synovitis) or internal derangement. The combination of haemarthrosis topped by a layer of glistening pale yellow fat is diagnostic of a subchondral fracture (the lighter fat deriving from subchondral bone).

Occasionally particles other than cells contribute to the turbidity and colour of SF. For example, a milky-white SF can result from the presence of a high concentration of

- monosodium urate (MSU) crystals,
- CPPD crystals; and
- basic calcium phosphates, mainly carbonate-substituted hydroxyapatite.

Cholesterol crystals may also give a yellow-to-creamy appearance. Metal wear particles from joint prostheses may give a greyish hue [81] and fragments of ochronotic cartilage [82] can give a ‘salt and pepper’ appearance. In RA and other inflammatory arthropathies, fibrin shreds may contribute to SF turbidity and mislead the observer with respect to the degree of joint inflammation [83]. It is wise to routinely check SF samples under the microscope to determine the precise cause of SF turbidity.

**Differential cell counts and cytology**

In general the percentage of polymorphonuclear (PMN) leucocytes in SF broadly equates to the degree of inflammation, but due to considerable variation between patients its diagnostic value is limited. Effusions containing only mononuclear cells have been described in some viral arthritides and in early RA. A predominance of eosinophils may be seen in parasitic arthritides, hypereosinophilic

![Fig. 13. Range of naked eye appearances of synovial fluids: non-inflammatory SF (A); inflammatory SF (B); and pyarthrosis(C).](image-url)
syndrome and other hypereosinophilic conditions [84]. Malignant cells have been identified in tumoural or metastatic joint disease and leukaemia cells may be seen in SF. Bone marrow cells may be identified following intra-articular fracture. Lupus erythematosus (LE) cells and haematoxophilic bodies can be seen rarely in lupus arthropathy. Reiter cells can be identified in some inflammatory SF [85] but have little diagnostic specificity.

SF and infection

When an infection is suspected, appropriate stains and cultures should be carried out depending on the growth requirements of the different possible organisms. SF taken into blood-culture bottles rather than just sterile universal containers increases the detection rate, especially for Gram-negative organisms. Where clinical suspicion of infection is high, antibiotic treatment should be commenced once samples are obtained and not delayed to wait for results. High levels of lactic acid and low levels of glucose in an SF sample are suggestive but not specific for septic arthritis but these tests are rarely undertaken in practice [86–88].

Analysis of crystals

Identification of MSU crystals in SF or in an aspirate of a tophus is considered the gold standard for definitive diagnosis of gout [89]. Similarly the finding of CPPD crystals in SF is diagnostic of CPPD-associated arthropathy [90]. MSU and CPPD crystals can be identified in SF aspirated from joints during acute attacks of gout or pseudogout and also from more chronically inflamed joints. They may also be identified in SF aspirated from an intercritical, asymptomatic and clinically un-inflamed joint, and even from an asymptomatic knee or first MTPJ that has not previously been affected by an acute

Fig. 14. (A) Haemarthrosis and (B) blood tinged synovial fluid, reflecting trauma at the time of needle insertion.
attack [91–94]. Although it is common practice to diagnose typical presentations of both conditions primarily on clinical grounds alone, it is best to confirm the diagnosis by SF crystal identification, especially in atypical cases. Imaging with ultrasonography can give helpful diagnostic information (‘double contour sign’) [95] but the definitive diagnosis still relies on crystal identification. Examination of SF for crystals is advised also for any undiagnosed inflammatory arthritis in an adult and crystals may be found in patients with an alternative prior diagnosis [96]. For untreated gout, aspiration of the first MTPJ with a 29-gauge needle permits definite MSU identification in over 90% of cases [1,97]. Since its introduction by McCarty and Hollander, the standard instrument for routine identification of MSU and CPPD crystals in SF has been the polarised light microscope equipped with a first-order red compensator. Apatite crystals are too small to be seen by light microscopy although the use of calcium stains (mainly for research purposes) permits visualisation of aggregates of apatite in SF. Crystals other than MSU or CPPD are rarely identified.

Most studies report low inter-observer reliability for detection of MSU and CPPD in SF, particularly for CPPD crystals [98,99]. In two such studies, SF samples were divided and sent to laboratories that routinely report on SF crystals [100,101]; in a third, cytocentrifuge slides were distributed [98,102]; and in a fourth the search was carried out using Gram-stained slides [103]. Artificial MSU and CPPD crystals have also been used in reliability studies [104]. However, none of these studies reflect microscopy undertaken in the optimal setting: that is, analysis of fresh SF by properly trained, expert observers who are blind to clinical details. Lumbreras et al. have shown that observer training results in very acceptable consistency in the identification of both MSU and CPPD crystals, although CPPD remain the most difficult to identify [105]. It therefore appears that any problems in SF crystal identification relate more to training than to the technique itself. The search for crystals is best done in fresh SF where cell integrity is well preserved. This is particularly important for CPPD crystals, which are often intracellular. Nevertheless, both CPPD and MSU crystals can still be readily identified after 24 h in refrigerated or even frozen SF samples [106].

One problem with CPPD crystal identification is overdependence on birefringence as the means of identification. All MSU crystals are strongly birefringent and are clearly distinguished by means of compensated polarised light microscopy (CPLM). However, CPPD crystals are only weakly birefringent. In one study, in which CPPD crystals in SF were first identified using ordinary light and then examined using polarised filters, only 20% of CPPD crystals showed sufficient birefringence to be identified as birefringent [107]. Thus, using CPLM alone, only one in five CPPD crystals will be identified as weakly birefringent crystals compared to the much higher detection rate for brightly birefringent MSU. In the first seminal description of SF CPPD crystals, McCarty et al. noted this weak birefringence and used phase-contrast microscopy in addition to CPLM to increase the sensitivity for detection [108]; this combination remains the standard for searching for crystals (Figs. 15 and 16) [109]. This weak and occasionally absent birefringence of CPPD has been noted by others [110,111]. Importantly, however, both MSU and CPPD crystals can be distinguished by their morphological characteristics alone using ordinary light microscopy [112]. To avoid missing crystals, especially CPPD, a two-step procedure for SF crystal analysis is recommended, at least during the training phase [105]:

1. Crystal detection: to determine whether crystals are present; and
2. Crystal identification: in which any identified crystals are correctly assigned as MSU, CPPD or some other crystal.

The initial crystal-detection step is carried out first under ordinary light, to identify crystals by their geometric, sharp line morphology (this shows CPPD crystals well), then under plain polarised light (no compensator) to identify crystals by birefringence (this readily detects MSU crystals) (Figs. 17 and 18). In general, ×400 magnification is adequate. However, especially during training, observation under ordinary light at ×1000 using an oil immersion lens helps familiarise the observer to polymorphic (rhomboidal, parallelepipedic and needle-shaped) CPPD crystals (Fig. 19). Many CPPD crystals are intracellular, even in SF from un-inflamed joints [96,113]. The intracellular position of crystals in fresh SF helps to confirm that they were aspirated from the joint and are not artefacts. CPPD crystals are often very small and within cells may appear as small squares or needles or even as inclusions but with a
Such inconclusive findings should prompt a further search until larger, more typical-looking crystals are found. Under uncompensated polarised light, all MSU crystals show strong birefringence and appear as bright, shining white objects against the dark background. Most, but not all MSU crystals are needle-shaped. When crystals are strongly suspected but not seen in an SF sample, the detection rate may be increased by centrifugation and a repeat search instituted in the pellet where crystals concentrate along with cells and fibrin debris. In apparently crystal-negative SF from OA joints, submicroscopic CPPD crystals may be identified by analytical electron microscopy [114].

In the crystal-identification step, CPLM essentially permits distinction between MSU and CPPD crystals. MSU crystals show strong negative birefringence and are bright yellow when parallel to the axis of the compensator and bright blue when perpendicular to it (Fig. 20). By contrast, CPPD crystals show only weak positive birefringence, appearing pale yellow when their long axis is perpendicular to the compensator and pale blue when parallel (Fig. 21). The large number of CPPD crystals that show no birefringence under plain polarised light may show very faint or no colour under CPLM. Keeping a reference slide with MSU crystals...
(easily obtained from a tophus) is useful for confirming the axis of the compensator. CPLM is particularly useful when SF contains both CPPD and MSU crystals and when other potentially confusing crystals are present, such as needle-shaped cholesterol or corticosteroid crystals.

In patients with tophi, material with crystals can be obtained by puncture with a syringe fitted with a simple intramuscular needle; the white thick material usually stays inside the needle. CPLM will show that the sample is composed almost exclusively of tightly arranged masses of MSU crystals, often with tissue or cellular debris (Fig. 22).

**Some tips for the beginner**

**Buying the microscope**

Manufacturers and retailers may encourage you to buy multifunctional polarised microscopes used by geologists. Although excellent, these can be expensive and unnecessarily sophisticated. For routine
clinical use, a simple light microscope (with \(\times 100\), \(\times 400\) and \(\times 1000\) oil immersion) fitted with polarised filters and a first-order red compensator should suffice. These are produced by many manufacturers and are much cheaper.

**Acquiring familiarity with the crystals**

To the experienced observer, CPPD and MSU crystals look very different and are easily distinguished by shape alone. It is important to become familiar with MSU and CPPD crystals and also with artefacts. To do so it helps to spend time looking under both ordinary and polarised light at SF samples obtained from diagnosed patients.

**Fig. 19.** (a) Calcium pyrophosphate dihydrate (CPPD) crystals. Note the small rhomboidal and large needle-shaped crystals (ordinary light, magnification 1000). (b) Same field as shown in (a) but here seen using polarised filters, without a first order red compensator. Note that the large needle-shaped crystal does not show birefringence and could have passed unnoticed if the search had been conducted with polarised light only (magnification 1000).

**Fig. 20.** Monosodium urate (MSU) crystals seen using a polarised microscope fitted with a first order red compensator. The crystal parallel to the axis of the compensator shows bright yellow while the one perpendicular to the axis is bright blue (magnification 400).
Artefacts and non-crystalline material

Artefacts such as dust, hairs, glass fragments and talc powder are common causes of confusion for beginners. Letting a glass slide stand overnight on the bench and examining it using the polarised microscope will often reveal large amounts of birefringent particulate contaminants. With practice, most artefacts soon became evident, being suggested by one or more of the following: lack of geometric shape, very large or very small size or mixed birefringence. Small ‘beach-balls’ or Maltese crosses raise consideration of calcium oxalate crystals (see below) but are more commonly caused by dust or talc (Fig. 23). Cartilage fragments are commonly observed in SF, even from normal joints, and appear as irregular-shaped translucent particles of varying size (Fig. 24).

Fig. 21. Calcium pyrophosphate dihydrate (CPPD) crystal seen using a polarised microscope fitted with a first order red compensator. The axis of the compensator is parallel to the longer axis of the crystal, which shows a blue colour (magnification 1000).

Fig. 22. Aspirate from a tophus viewed under low power (x100) CPLM, showing a mass of brightly birefringent needle-shaped crystals and tissue debris.
Apatite crystals

Apatite and other basic calcium phosphate crystals [115] have been noted in SF in rapidly destructive forms of OA [116,117], acute monoarthritis [118,119], systemic sclerosis and dermatomyositis [120], advanced OA [121,122] and RA [123,124]. In general they appear more abundant in joints with advanced damage [124], suggesting that their origin may be from subchondral bone (apatite and basic calcium phosphates are the normal mineral components of bone). Thus, SF apatite is a non-specific finding that can occur in a wide range of arthropathies [124,125]. Apatite crystals are too small to be seen by light microscopy and appreciation of individual crystals requires electron microscopy. Electron-probe analysis allows determination of the relative amounts of the crystal components whereas the X-ray diffraction pattern allows definitive identification. Alizarin Red S stain, a non-
specific stain for calcium salts, has been proposed as a means of detecting apatite-crystal aggregates (Fig. 25) [126]. However, it is only positive in SF with high concentrations of crystals, and other calcium-containing crystals, including CPPD, may also give positive Alizarin Red staining [124]. The specificity for apatite is increased if the stain is used at acidic pH. Oxytetracycline staining may prove to be a useful adjunct to available methods [127] but at present, largely because of its lack of disease specificity and

Fig. 25. Apatite aggregates stained with alizarin red at acidic pH under ordinary light x400.

Fig. 26. Large cholesterol crystals (CPLM x400) showing flat envelope appearance, deleted corners and bright mixed birefringence.
technical difficulties related to its detection, investigation for apatite and other basic calcium phosphates in SF has little clinical utility and is largely reserved for research.

**Calcium oxalate crystals**

Calcium oxalate crystals have been identified in SF from joints of patients undergoing periodic haemodialysis and also in those with hyperoxalaemia and oxalosis. Although the irregular shape of many of the crystals does not allow morphological identification, a few have a characteristic bipyramidal or ‘Maltese cross’ shape [128]. Being a calcium salt, oxalate crystals also stain with Alizarin Red. Oxalate arthropathy was largely eliminated by modifying filter systems during haemodialysis and except in this setting the investigation of these crystals has little clinical relevance.

**Cholesterol crystals**

These are occasionally found in SF from chronic, largely inflammatory effusions [129–133]. Their pathogenic potential appears to be small, although in some animal models cholesterol crystals produce granulomata, synovial cell hyperplasia and fibrosis [123]. Cholesterol crystals appear as extremely large rhomboidal plates, often with a broken or folded-over corner and showing bright, mixed birefringence (Fig. 26) [17,115].

**Corticosteroid crystals**

A post-injection flare following IAC injection may simulate an infection and lead to a diagnostic joint aspiration [134]. Often in this setting, birefringent crystalline particles of steroid can be seen in SF for some time following their injection (Fig. 27). Different preparations have different microscopic appearances [135], but none should cause confusion with MSU or CPPD.

**Other crystals**

Much of the information on other crystals is anecdotal. SF lipid crystals, round inclusions that show a birefringent Maltese cross under CPLM, have been described in acute arthritis [136] and can be seen in the arthropathy associated with pancreatic disease [137] and in joints with intra-articular fracture [138]. Charcot–Leyden crystals have been noted in eosinophilic synovitis [84].

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*[Fig. 27. Corticosteroid crystals (CPLM x400) showing rounded contour with no sharp angles.]*

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**Practice points**

Macroscopic appearance and cell count:

- The macroscopic appearance of SF often provides immediate information about the degree of inflammation present in a joint and may also provide other diagnostic information.
- The total number and percentage of PMN leucocytes tends to be higher in more inflammatory processes, but this is non-specific.

SF from joints with infections:

- Appropriate microbiological cultures are the essential diagnostic tool in the identification of infection.

Crystal detection and identification:

- Only about one in five CPPD crystals show birefringence when observed using a polarised microscope: their initial detection is better carried out with an ordinary microscope.
- By contrast, almost all MSU crystals are strongly birefringent under uncompensated polarised light and are easily identified using this method.
- MSU and CPPD crystals are regularly found in asymptomatic joints of patients with gout and CPPD-related arthropathy, permitting confirmation of the diagnosis of crystal deposition during the intercritical period.
- Crystal deposition and sepsis may co-exist; hence, despite the presence of crystals SF should be cultured if sepsis is suspected clinically.
- CPPD and MSU crystals should be searched for in all undiagnosed joint effusions.

**Research agenda**

- In general, data on the more basic procedures of SF analysis, such as the gross appearance, the usefulness of cellularity and the percentage of PMN leucocytes, are based on opinion and anecdotal information. Formal critical evaluation would be useful.
- CPPD crystals are more difficult to identify in SF than MSU crystals. Study of the comparative ability to detect CPPD crystals in SF by means of a light microscope, a polarised microscope and a phase microscope would be welcomed.
- Gout and CPPD-related arthropathy are often diagnosed on clinical grounds alone. An evaluation and analysis of the crystal yield in undiagnosed ‘less typical’ arthropathies would be very useful.

**References**


