# Procedures in Family Practice

# Examination of the Synovial Fluid

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Synovial fluid examination is an easily performed, economical, and safe diagnostic procedure for use in the evaluation of inflammatory joint disease. It can be diagnostic for joint space infection or hemorrhage and crystal induced arthritis as well as being helpful in the diagnosis and management of many other conditions.

Examination of the synovial fluid is frequently helpful and on occasion is vital to the correct diagnosis and proper management of inflammatory joint disease. Conversely, in most forms of chronic arthritis it is of limited value. Thus the physician needs to have a clear picture of what information can be acquired by these studies. The most helpful data are obtained with appropriate patient selection, correct aspiration technique, and thoughtful choice of indicated tests. In this setting, arthrocentesis with joint fluid examination is safe, relatively painless, cost effective, and will positively identify joint infections, crystal induced arthritis, and joint hemorrhage.

The joint cavity should be considered as an extravascular tissue space because the synovial lining is not a true membrane. The synovial fluid is essentially a dialysate of plasma to which hyaluronate synthesized by the synovial cells is added. In a normal joint, synovial fluid is present in only small amounts and has the function of nourishment of the avascular articular cartilage and lubrication of the joint surfaces. Normal synovial fluid is clear, relatively acellular, with less than 200 cells/cu mm, and has high viscosity because of the hyaluronic acid content. It does not clot in noninflamed joints because fibrinogen, clotting factors, and other large proteins do not enter the joint freely from the vascular space.

As a dialysate of plasma, synovial fluid may reflect general disorders as well as specific localized articular processes. Thus in a patient with generalized edema of any etiology, it would be expected to find joint effusions with the characteristics of a transudate. These swollen joints would be cool to the touch and typically not tender. On the other hand, a recently traumatized joint might be very painful because of rapid accumulation of fluid or blood. An inflamed joint from whatever cause will tend to be warm and painful. As with other tissue spaces, inflammation of the cells and vessels of the synovial lining tends to potentiate the inflow and egress of plasma, inflammatory mediators, white blood cells, and antibiotics.

While a joint effusion may reflect a solely intra-articular problem such as local trauma or a disease such as pigmented villonodular synovitis, it usually reflects a localized soft tissue or bony inflammatory process or a systemic condition such as rheumatoid arthritis. The setting of the patient usually gives important clues to the diagnosis, so that after obtaining a thoughtful history and careful physical examination, judicious study of the synovial fluid is confirmatory with only a few appropriately chosen tests.

Increased volume on occasion may be found in joints when the synovial fluid itself is normal by all

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**Table 1. Synovial Fluid Classification**

| | Color | Clarity | WBC*/ cu mm | PMN** (%) | Culture | Volume | Protein (gm/100 ml) |
|---|---|---|---|---|---|---|---|
| Normal | Colorless | Clear | <200 | <25 | Negative | Normal | <2 |
| Noninflammatory | Straw | Transparent | <2,000 | <25 | Negative | Often increased | <3.5 |
| Inflammatory | Yellow | Translucent | 2,000 to 80,000 | Variable | Negative | Usually increased | >3.5 |
| Septic | Variable | Opaque | 2,000 to >100,000 | Usually >75 | Usually positive | Usually increased | >3.5 |

*White blood cells
**Polymorphonuclear leukocyte

measured parameters. This is often the case with myxedema, congestive heart failure, renal failure, or any condition leading to significant tissue edema.

## Arthrocentesis

### *Indications*

Joint aspiration is simple and safe and may be accomplished in the office, clinic, or emergency room. Frequently it may not be done even when indicated because of general lack of knowledge about technique and also because of fear of introducing infection. With proper attention to sterile procedure and careful observation of anatomical landmarks, arthrocentesis can be as safe and painless as venipuncture. Clear indications for arthrocentesis are suspicion of septic arthritis, hemarthrosis, or crystal induced arthritis, because in these cases the procedure is diagnostic. Even with proven inflammatory joint disease such a rheumatoid arthritis, septic arthritis is not rare, and thus joint aspiration should be considered in any situation in which the cause of increased joint inflammation is not clear. In addition, joint fluid examination may be helpful in characterizing Reiter's syndrome, rheumatoid arthritis, systemic lupus erythematosus, and other conditions.

### *Contraindications*

Arthrocentesis may be hazardous in anticoagulated patients or those with bleeding problems. In addition, in patients with total joint protheses the possibility of introducing an infection must be considered, and the procedure should be done with as many precautions as possible.

### *Complications*

Complications of arthrocentesis are rare, with the major concern being the introduction of an intra-articular infection. With proper technique, procedure induced infection is extremely unlikely. Hemorrhage into the joint may occur in anticoagulated patients, in those with bleeding diatheses, or with trauma to a blood vessel. Allergies to local anesthetics are also reported.

### *Technique*

Detailed instructions for aspirating specific joints exceed the scope of this paper, and knowledge about proper approaches is essential for success. The following general suggestions and principles should be helpful. The avoidance of introducing an external infection into a joint space is of prime importance. Thus, appropriate sterile technique, such as antiseptic preparation of the overlying skin, sterile drapes, gloves, and mask, should be employed as necessary. In addition, a needle should not be introduced into a joint by passing through overlying tissues that may be infected. Generally, if a bulging effusion is present, this area is the optimal entry site. When possible, the joint is best approached from the extensor side, where the synovial space is more superficial and fewer nerves and vessels are likely to be encountered.

Frequently, it is helpful to anesthetize the entry site with ethyl chloride spray or local anesthetic,

**Table 2. Synovial Fluid Study Priorities**

| | Suspected Sepsis | Suspected "Crystal" Arthritis | Suspected Hemorrhage | Suspected Systemic Disease |
|---|---|---|---|---|
| Gross inspection (color, clarity, volume) | 1 | 1 | 1 | 1 |
| Gram stained culture, counter immunoelectrophoresis | 1 | 1 | 1 | 1 |
| White blood cell count and differential | 1 | 1 | 1 | 1 |
| Polarized microscopy | 2 | 1 | 2 | 2 |
| Hematocrit | 3 | 3 | 1 | 2 |
| Chemistry | | | | |
| Glucose | 2 | 3 | 3 | 3 |
| Enzymes | 3 | 3 | 3 | 3 |
| Protein | 2 | 3 | 3 | 2 |
| Serology | | | | |
| Complement | 3 | 3 | 3 | 2 |
| Other | 3 | 3 | 3 | 2 |

1—necessary study
2—may be helpful
3—doubtful benefit

particularly if introduction of the needle into the intra-articular space may be difficult. For a diagnostic arthrocentesis on larger joints, an 18-gauge needle or larger is appropriate; crystals or thick pus often will not be easily aspirated through a smaller bore needle. If used with care, the larger needle need not be much more painful or traumatic than a small one. For small joints, a higher gauge needle will be necessary and is usually adequate.

## Examination of Synovial Fluid

The examination of the synovial fluid must be done either by the physician or in a laboratory that is prepared to deal with these studies appropriately. Typical synovial fluid parameters are found in Table 1. Specific tests should be done with particular purposes in mind. In addition, priorities need to be established because on occasion only a small amount of fluid may be obtained, and all desirable studies may not be possible. Ranked priorities for several parameters are found in Table 2 for a group of common problems. In virtually all acutely inflamed joints or chronic monarticular arthritis, the question of infection should be raised, and thus culture and Gram stain should always be done. Conversely, crystal examination in the fluid from a young female with sepsis may be superfluous, and complement determination probably does not add much to the care of the elderly man with gout.

### *Classification*

Convention has usually divided pathological synovial fluids into those that are inflammatory and those that are noninflammatory (Table 1). More than 75 percent of the white cells in noninflammatory effusions are mononuclear and total white cells are less than 2,000/cu mm. The fluids are transudate in nature, are transparent, and typically have high viscosity. Inflammatory synovial

fluids have more than 2,000 white cells/cu mm, with a higher percentage of polymorphonuclear leukocytes. Other cells may be present, and the protein content is higher together with the possible presence of bacteria, crystals, and cellular debris, depending on the etiology of the condition. The fluid is often turbid or opaque.

A hemorrhagic fluid may narrow the diagnostic possibilities, but trauma induced by the tap may itself lead to blood in fluid present for other reasons. Etiologies of hemarthrosis include anticoagulant therapy, bleeding disorders, hemangioma, idiopathic disease, pigmented villonodular synovitis, severe destructive joint disease, synovioma and other tumors, trauma, and vascular abnormalities.[6] If the synovial fluid is blood streaked or clears during aspiration, a traumatic aspiration is assured. A bloody effusion should always be evaluated by a synovial fluid hematocrit to determine if it is blood alone or blood mixed with synovial fluid. Frequently, it is difficult to make this decision on gross examination alone when the hematocrit is above 7 to 10 percent. A bloody effusion usually will not clot. Bone marrow elements in the synovial fluid are diagnostic of a joint surface fracture, but fat globules have been reported in a number of conditions.

## *Microbiology Studies*

After the synovial fluid is aspirated into a sterile syringe, a small amount should be placed in a sterile and empty container for Gram staining and culture. Sufficient material for aerobic, anaerobic, mycobacterial, and fungal cultures should be reserved, but these studies may be obtained with only several drops if necessary. This fluid should be taken to the laboratory immediately unless gonococcal arthritis is suspected; in this case, the fluid must be plated at the bedside on chocolate agar media and then taken directly to the incubator. Thayer-Martin should not be used because it contains antibacterial properties that, while helpful in removing nonpathologic genital flora, may suppress the gonococcal organisms.

## *Cell Characteristics*

The synovial fluid should be placed in a heparinized tube to evaluate the cell content in a qualitative and quantitative fashion. Because normal synovial fluid lacks fibrinogen, prothrombin, and several clotting factors, it does not clot. Pathological fluids will clot because the inflamed synovium leads to increased passage of plasma proteins, including clotting factors, into the joint. Thus, the rapidity and extent of clotting correlate somewhat with the degree of inflammation found in the joint.

Acetic acid, which is found in Turk's solution and standard blood count diluents, will precipitate the hyaluronic acid protein in synovial fluid and thus trap cells in the clot. Therefore, when required, saline should be used to dilute the synovia to avoid this precipitation and resultant falsely lowered counts. The actual counting is done in a similar fashion to that of blood. If the diluting saline is hypotonic (0.2 to 0.4 percent), the erythrocytes in the fluid will be lysed and not influence the counts obtained. Smears for white blood cell differential counts can be prepared on cover slips or glass slides and read in the same fashion as peripheral blood smears, remembering that thin films are technically superior.

A number of interesting white blood cell findings in synovial fluid have been reported.[1] While a detailed description of such cells as "ragocytes" or "RA cells," "LE cells," "tart cells," and "Reiter cells" is beyond the scope of this paper, they have been described and may be seen. In general, they usually do not provide precise diagnostic precision but may give helpful information. Large cells such as lymphoblasts and monocytes are not rare in synovial fluids, and phagocytosis of polymorphonuclear neutrophils, crystals, and debris by other leukocytes commonly occurs in inflammatory synovial fluids.

The finding of large numbers of eosinophils in joint fluid is very uncommon but recently has been reported in a number of settings. Moderate levels of eosinophilia in synovial fluids have been reported with large cell lung carcinoma metastatic to the knee synovium, guinea worm joint infestations, and after arthrography. In addition, patients with rheumatoid arthritis who have peripheral blood eosinophilia have also had eosinophils in the synovia to a similar degree. The most impressive synovial fluid eosinophilia however, was reported[2] in a patient without known systemic disease who had a self-limited arthritis and effusion of the elbow. This patient had a white blood cell count of 10,000/cu mm, with 83 percent eosinophils in the

joint fluid but only 2 percent eosinophils in the peripheral blood.

In addition, intracellular lipid inclusions have been reported in synovial fluid leukocytes that were only identified under polarizing microscopy in a self-limited monarthritis.[3] While lipid droplets in the synovia of rheumatoid arthritis and other processes have been reported, their significance remains elusive. Recently, "synovial fluid pseudoleukocytosis" was reported.[4] Fat globules were read by the automated Coulter counter technique as white blood cells in the synovial fluid of a patient with a posttraumatic monarthritis. Synovial fluid leukocytosis is unusual with trauma alone, and reliance on automated cell counts for synovial fluids that may contain fat globules is inappropriate.

The diagnosis of sickle cell anemia has been made by finding sickled erythrocytes in the synovial fluid.[5] This has been supported by hemoglobin electrophoresis, but it must be recalled that sickle shaped red cells can occur after prolonged storage of synovial fluid and that erythrocytes occasionally are elongated in fluids with very high viscosity.

Recent work has characterized the various lymphocyte subpopulations in synovial fluid.[6] Whereas these findings might provide insights with respect to the etiology and pathogenesis of various inflammatory joint diseases, as yet they have no practical clinical significance.

### *Fluid Appearance*

Completely normal synovial fluid is colorless. A yellow or xanthochromic color found in many inflammatory fluids usually results from the local breakdown of red cell hemoglobin in the joint space to bilirubin. The presence of leukocytes gives a white or creamy color depending on the concentration present, and certain bacteria give off chromogens or pigments into the fluid. The fluid usually is clear unless there are large numbers of leukocytes or crystals present. In this case, the opacity correlates with the quantity of cells or crystals in the synovial fluid.

The hyaluronate of normal synovial fluid is degraded in many inflammatory conditions, and the viscosity of these abnormal fluids is thus decreased. The viscosity may be estimated clinically by the "string test" and more precisely with a viscometer, but rarely does this parameter add significant data to diagnostic and therapeutic decisions. Likewise, the mucin clot test has important historical interest as an evaluation of synovial hyaluronic acid content but presently has limited clinical utility.

### *Crystal Examination*

The proper examination of synovial fluid for crystals is vital because when properly done, it can be diagnostic for the crystal induced arthropathies. Special attention to technique is essential to properly identify crystals since improper or incomplete study of the aspirated effusion may lead to faulty diagnosis and inappropriate management of the patient. A wet smear is obtained by placing a drop of synovial fluid on a clean glass slide and then covering it with a clean cover slip. Dust and lint may be optically birefringent and thus confusing. If possible, the preparation should be examined immediately to avoid the nonsignificant crystalization that occurs with evaporation. Evaporation may be retarded in an important specimen by sealing the edges of the mounted coverslip with clear fingernail polish or petroleum jelly.

Many crystals, particularly when abundant, may be seen even with standard light microscopy. Frequently, however, there are only a few crystals, or they may be very small, and thus are not found unless compensated polarized microscopy is employed. Therefore, examination of synovial fluid with a microscope equipped with polarizing lens and a first-order red compensator is necessary.[7] A high-quality instrument expressly designed for this effort is ideal, but an ordinary microscope may be adapted with polarizing lens and red compensator if necessary. Clinically important crystals have distinctive morphology (Table 3 and Figure 1).

### *Serologic Tests*

In normal synovial fluid, smaller proteins such as albumin are found in greater abundance than the larger proteins such as fibrinogen or globulins, and the total protein concentration is less than 2.0 gm/100 ml. With inflammation, blood flow to the synovial tissues increases, and it is common to see the synovial fluid concentration of various proteins approach their concentration in the patient's plasma.

On occasion, measurement of complement levels in synovial fluid may be helpful diagnosti-

**Table 3. Synovial Fluid Crystal Morphology**

| Crystal | Birefringence | Shape | Size (microns) | Other |
|---|---|---|---|---|
| Monosodium urate (MSU) | Negative | Needle | 1-20 | |
| Calcium pyrophosphate dihydrate (CPPD) | Positive (weak) | Rod | 5-100 | |
| Dicalcium phosphate dihydrate (DCPD) | Positive (strong) | Variable | Variable | Highly soluble |
| Hydroxy apatite | — | Needle | 0.1-1.0 | Seen only with electron microscopy |
| Cholesterol | Negative | Flat, rhomboid plates with notched corners, or needle | >100 | Ether soluble; never phagocytosed |
| Calcium oxalate | Positive | Cuboidal | 2-10 | From oxalated tube collection; may be phagocytosed |
| Corticosteroid | Positive and negative | Variable | 1-20 | Strongly phagocytosed |
| Others (cartilage fragments, metal fragments (joint prothesis) amyloid fragments) | Usually | Variable | Variable | |

cally and prognostically.[8] In normal fluids the hemolytic complement ($CH_{50}$) level, which estimates the functional level of all the components of complement, is low, usually one-third to one-half of that found in the patient's serum. In inflammatory synovial fluids the $CH_{50}$ levels are proportional to the total protein levels in the same fluid and also to the serum $CH_{50}$ concentration unless complement is being locally consumed. Thus, synovial complement levels are often high in Reiter's syndrome and low in systemic lupus erythematosus as a reflection of serum levels. While complement levels are usually normal or increased in rheumatoid arthritis (RA), they may be low as a result of local consumption in severe RA and also can be depressed with sepsis and crystal induced inflammation. Usually, synovial fluid complement levels add little to diagnosis and management.

Cryoprecipitable proteins are found in inflammatory fluids of diverse etiologies. In RA they are common and usually are composed of mixed immunoglobulins and rheumatoid factor. Most non-

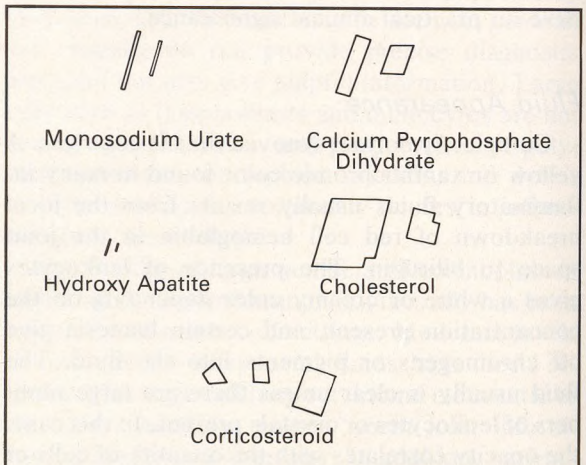


Figure 1. Synovial fluid crystal morphology

RA cryoproteins are predominantly fibrinogen and do not fix complement.

Rheumatoid factors have been found in fluids from patients with RA and other inflammatory conditions. While the titers usually reflect those found in serum, on occasion rheumatoid factor has

been found in the synovia when absent in the serum, with the converse being true as well.

Systemic lupus erythematosus has been diagnosed by observing the LE cell phenomenon in synovial fluid initially. Antinuclear antibodies, anti-DNA antibodies, and free DNA have been found in synovial fluids as well. In general, serological evaluation of synovial fluid has not been shown to be particularly helpful with respect to either diagnosis or prognosis.

### *Chemical Studies*

On occasion, synovial fluid glucose determinations may be helpful. It has been reported that concentrations of glucose more than 40 mg/100 ml lower than corresponding serum levels are seen only in bacterial or tuberculous infections.[9] The value of these observations must be tempered by other reports that indicate glucose levels may overlap in septic and noninfectious synovial fluids. Further, the patient must be fasting to ensure appropriate equilibrium between serum and joint fluid.

The routine measurement of enzymes in the synovial fluid has thus far not had significant clinical utility. Several enzymes have been studied in effusions of various etiologies and can be done routinely by most clinical chemistry laboratories. They include acid phosphatase, alkaline phosphates, 5′-nucleotidase, muramidase or lysozyme, lactic dehydrogenase (LDH), SGOT, and others.

The LDH is normal in the serum of almost all patients with arthritis and in the synovial fluid of degenerative joint disease and other noninflammatory arthropathies. Synovial fluid LDH levels have been reported to be increased in rheumatoid arthritis, gout, and infectious arthritis. Isoenzyme determinations show the highest concentration of $LDH_5$, indicating that the enzyme is probably derived from the neutrophils of the inflammatory fluid. In these same patients, the SGOT levels were consistently normal.

Alkaline phosphatase is present in synovial fluid but reflects the serum levels and has not been reported to be elevated in any situation with normal blood concentrations. Acid phosphatase levels are frequently increased in inflammatory fluids and correlate best with the neutrophil concentrations in the synovia. Generally, increased enzyme levels are found in inflammatory fluids but add little, if any, to the information gathered in other ways for the diagnosis and management of synovial inflammation.

Potentially helpful is the lysozyme-lactoferrin ratio in determining cartilage degeneration and the degree of inflammation in the joint. Lysozyme in the synovial fluid is derived from both cartilage and white blood cell lysosomes and increases with increased inflammation. Lactoferrin is produced in only leukocyte lysosomes, so that by measuring both simultaneously, it is possible to assess the probability of cartilage destruction.

Several years ago, collagen fibers were reported in synovial fluid sediment. Recently, it has been possible to identify collagen subtypes, and there is preliminary evidence that type II collagen levels correlate with joint space narrowing and lowered pH in some osteoarthritis patients.[10] This observation is of interest because type II collagen is uniquely characteristic of articular hyaline cartilage and thus may be a parameter reflecting cartilage damage and destruction.

In summary, the synovial fluid is easily and safely obtained from the patient with arthritis and a joint effusion. It often adds helpful and occasionally vital information to the careful history, physical examination, and standard laboratory profile in the differential evaluation of the swollen joint. Identification of hemorrhage, infection, or crystals usually provides a specific diagnosis and other parameters may be useful adjuncts to the basic data gathered by the physician.

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