**ORTHOPEDICS (MUSCULOSKELETAL DISORDERS, FRACTURES, JOINT REPLACEMENT, SPORT INJURIES)**

Orthopedics, also known as orthopedic surgery, is a branch of medicine that focuses on the care of the skeletal system and its interconnecting parts. These parts include the following:

* bones
* muscles
* joints
* tendons
* ligaments
* nerves

There are generally two types of orthopedists: surgical and nonsurgical. The former are called orthopedic surgeons, while nonsurgical orthopedists include physiatrists and physical medicine and rehabilitation specialists.

An orthopedist often works as part of a larger orthopedic treatment team. This team may include:

* physician assistants
* nurse practitioners
* occupational and physical therapists
* athletic trainers

Once devoted to the care of children with spine and limb deformities, orthopedists now care for patients of all ages, from newborns with clubfeet to young athletes requiring arthroscopic surgery to older people with arthritis. And anybody can break a bone at any age.

**Who is an orthopedic surgeon?**

An orthopedic surgeon is also known as an orthopedist (sometimes it's spelled orthopedic surgeon or orthopedist). This specialist helps people get relief from pain and mobility problems due to musculoskeletal issues.

## **What Does an Orthopedic Surgeon Do?**

Orthopedic surgeons treat problems of the musculoskeletal system. This involves:

* Diagnosis of your injury or disorder
* Treatment with medication, injections, casting, bracing, surgery, or other options
* Rehabilitation by recommending exercises or physical therapy to restore movement, strength, and function
* Prevention with information and treatment plans to prevent injury or slow the progression of disease

The orthopedic surgeon is the leader of the orthopedic care team, which includes the following highly trained healthcare professionals:

* Other doctors, including primary care sports medicine specialists, pain management specialists, physical medicine and rehabilitation specialists (physiatrists), radiologists, and anesthesiologists
* Physician assistants
* Nurse practitioners
* Registered nurses
* Orthopedic technicians
* Physical therapists
* Trainees (fellows, residents, medical students)

During your appointment and throughout the course of your care, you will likely interact with multiple team members. While the team is led by your orthopedic surgeon, each team member plays a critical role in ensuring your safety and recovery.

### *Orthopedic Subspecialties*

While orthopedic surgeons are familiar with all aspects of the musculoskeletal system, many orthopedists specialize in certain areas, such as:

* Foot and ankle
* Hand and wrist
* Hip replacement and reconstruction
* Knee replacement and reconstruction
* Orthopedic oncology (bone tumors)
* Orthopedic trauma
* Pediatric orthopedic surgery
* Shoulder and elbow
* Spine
* Sports medicine

Some orthopedic surgeons may specialize in multiple areas, and several different types of specialists may treat the same conditions. For instance, sports medicine surgeons, shoulder and elbow surgeons, and hand and wrist surgeons all perform surgery on the elbow.

**A comprehensive list of diseases under orthopedics**

## Joint Conditions

* Osteoarthritis (OA)
* Rheumatoid arthritis (RA)
* Psoriatic arthritis
* Ankylosing spondylitis (Spondyloarthritis)
* Gout
* Bursitis
* Joint hypermobility syndrome
* Juvenile idiopathic arthritis
* Other inflammatory arthropathies (e.g., systemic lupus erythematosus with joint involvement)

## 2. Bone Conditions

* Osteoporosis
* Osteopenia
* OsteomaLacia
* Fragility fractures (e.g., hip, vertebral fractures)
* Traumatic fractures (e.g., long bone fractures, vertebral fractures)
* Bone tumors (benign and malignant)
* Paget’s disease of bone

## 3. Muscle and Tendon Disorders

* Muscular dystrophy (e.g., Duchenne muscular dystrophy)
* Sarcopenia (age-related muscle loss)
* Myasthenia gravis (neuromuscular disorder)
* Myositis (inflammatory muscle disease)
* Tendinitis / Tendinopathy
* Rotator cuff tear
* Muscle strains and sprains
* Myopathies (various muscle diseases)

## 4. Spine and Back Disorders

* Chronic low back pain
* Degenerative disc disease
* Herniated intervertebral disc
* Spinal stenosis
* Spondylolisthesis
* Vertebral compression fractures
* Ankylosing spondylitis (spinal involvement)

## 5. Soft Tissue Conditions

* Baker’s cyst (popliteal cyst)
* Fibromyalgia (widespread musculoskeletal pain)
* Ligament injuries (e.g., ACL tear)
* Tendon ruptures
* Capsulitis (e.g., frozen shoulder)

## 6. Congenital and Developmental Disorders

* Clubfoot (talipes equinovarus)
* Developmental dysplasia of the hip (DDH)
* Scoliosis
* Limb length discrepancy
* Osteogenesis imperfecta

## 7. Other Conditions

* Amputation (due to trauma or disease)
* Complex regional pain syndrome (CRPS)
* Vasculitis with musculoskeletal involvement
* Connective tissue diseases with musculoskeletal manifestations (e.g., systemic lupus erythematosus, scleroderma)
* Infectious arthritis and osteomyelitis
* Tendonitis and bursitis
* Overuse injuries (e.g., repetitive strain injuries, carpal tunnel syndrome)

## List of Orthopedic Diseases: Fractures and Sports Injuries

## Types of Bone Fractures

1. Transverse Fracture
2. Oblique Fracture
3. Spiral Fracture
4. Greenstick Fracture
5. Stress (Hairline) Fracture
6. Compression Fracture
7. Comminuted Fracture
8. Segmental Fracture
9. Impacted Fracture
10. Avulsion Fracture
11. Buckle (Torus) Fracture
12. Bowing Fracture
13. Open (Compound) Fracture
14. Closed (Simple) Fracture
15. Displaced Fracture
16. Non-displaced Fracture

## Common Named Fractures

* Colles Fracture (distal radius)
* Smith Fracture (distal radius, volar displacement)
* Scaphoid Fracture (wrist bone)
* Barton Fracture (intra-articular distal radius)
* Chauffeur Fracture (radial styloid)
* Metacarpal Fractures (hand bones)
* Femoral Neck Fracture
* Tibial Plateau Fracture
* Ankle Fractures (e.g., Weber classification)

## Common Sports Injuries (Orthopedic)

* Medial Collateral Ligament (MCL) Injury
* Meniscal Tears
* Rotator Cuff Tears
* Achilles Tendon Rupture
* Tennis Elbow (Lateral Epicondylitis)
* Golfer’s Elbow (Medial Epicondylitis)
* Patellar Tendinitis (Jumper’s Knee)
* Shin Splints (Medial Tibial Stress Syndrome)
* Stress Fractures (common in lower limbs)
* Muscle Strains and Sprains
* Dislocations (shoulder, patella, fingers)
* Bursitis (e.g., olecranon, prepatellar)
* Labral Tears (Hip and Shoulder)
* Avascular Necrosis (Osteonecrosis)
* Post-Traumatic Arthritis
* Congenital or Developmental Joint Disorders
* Inflammatory Arthritides Other Than Rheumatoid Arthritis
* Joint Deformities
* Failed Previous Joint Replacement (Revision Surgery).
* Bone Tumors Affecting Joints
* Severe Joint Infection (Septic Arthritis) Leading to Joint Destruction

**Clinical terminologies and codes for each disease**

**ICD-10 Codes;**

| **Disease** | **ICD-10-CM Code(s)** |
| --- | --- |
| Osteoarthritis (OA) | M15–M19 (e.g., M15 Poly arthrosis, M16 Coxarthrosis [hip], M17 Gon arthrosis [knee], M18 Arthrosis of first carpometacarpal joint) |
| Rheumatoid arthritis (RA) | M05–M06 |
| Psoriatic arthritis | M07 |
| Ankylosing spondylitis | M45 |
| Gout | M10 |
| Bursitis | M70 (e.g., M70.0 Olecranon bursitis) |
| Joint hypermobility syndrome | M35.7 |
| Juvenile idiopathic arthritis | M08 |
| Other inflammatory arthropathies (e.g., SLE with joint involvement) | M30–M36 (e.g., M32 Systemic lupus erythematosus) |

## **2. Bone Conditions**

| **Disease** | **ICD-10-CM Code(s)** |
| --- | --- |
| Osteoporosis | M80–M81 (M80 with fracture, M81 without fracture) |
| Osteopenia | M85.8 (Other specified disorders of bone density and structure) |
| Osteoma Lacia | M83 |
| Fragility fractures (hip, vertebral) | M80 (osteoporosis with current pathological fracture) |
| Traumatic fractures | S codes (e.g., S72.0 Femoral neck fracture), M84 (Disorder of continuity of bone) |
| Bone tumors (benign/malignant) | C40–C41 (malignant), D16 (benign) |
| Paget’s disease of bone | M88 |

## 3**. Muscle and Tendon Disorders**

| **Disease** | **ICD-10-CM Code(s)** |
| --- | --- |
| Muscular dystrophy (e.g., Duchenne) | G71 (muscular dystrophies) |
| Sarcopenia | M62.84 |
| Myasthenia gravis | G70.0 (neuromuscular junction disorders) |
| Myositis | M33 (dermatopolymyositis) |
| Tendinitis / Tendinopathy | M65 (synovitis and tenosynovitis) |
| Rotator cuff tear | M75.1 |
| Muscle strains and sprains | S codes (e.g., S66.0 Shoulder muscle strain) |
| Myopathies | G71 (other myopathies) |

## **4. Spine and Back Disorders**

| **Disease** | **ICD-10-CM Code(s)** |
| --- | --- |
| Chronic low back pain | M54.5 |
| Degenerative disc disease | M51 |
| Herniated intervertebral disc | M51.2 (lumbar), M50.2 (cervical) |
| Spinal stenosis | M48 |
| Spondylolisthesis | M43.1 |
| Vertebral compression fractures | M80.0 (osteoporotic), S22, S32 (traumatic) |
| Ankylosing spondylitis (spinal involvement) | M45 |

## **5. Soft Tissue Conditions**

| **Disease** | **ICD-10-CM Code(s)** |
| --- | --- |
| Baker’s cyst (popliteal cyst) | M71.2 |
| Fibromyalgia | M79.7 |
| Ligament injuries (e.g., ACL tear) | S83.5 (knee ligament), S83.4 (MCL) |
| Tendon ruptures | M66 (spontaneous rupture of synovium and tendon) |
| Capsulitis (frozen shoulder) | M75.0 |

## **6. Congenital and Developmental Disorders**

| **Disease** | **ICD-10-CM Code(s)** |
| --- | --- |
| Clubfoot (talipes equinovarus) | Q66.0 |
| Developmental dysplasia of hip (DDH) | Q65.0–Q65.9 |
| Scoliosis | M41 |
| Limb length discrepancy | Q74.3 |
| Osteogenesis imperfecta | Q78.0 |

## **7. Other Conditions**

| **Disease** | **ICD-10-CM Code(s)** |
| --- | --- |
| Amputation (trauma/disease) | Z89 (acquired absence of limb) |
| Complex regional pain syndrome (CRPS) | G90.5 |
| Vasculitis with musculoskeletal involvement | M30–M31 |
| Connective tissue diseases with musculoskeletal manifestations (e.g., SLE, scleroderma) | M30–M36 |
| Infectious arthritis and osteomyelitis | M00–M03 (infectious arthropathies), M86 (osteomyelitis) |
| Tendonitis and bursitis | M65–M70 |
| Overuse injuries (e.g., repetitive strain, carpal tunnel syndrome) | M70.2 (repetitive strain), G56.0 (carpal tunnel) |

## **Fractures and Sports Injuries (Selected ICD-10 Codes)**

| **Condition** | **ICD-10-CM Code(s)** |
| --- | --- |
| Transverse, oblique, spiral fractures | S codes by site (e.g., S42.2 humerus shaft fracture) |
| Greenstick fracture | S52.5 (radius greenstick fracture) |
| Stress fracture | M84.3 |
| Compression fracture | S22.0 (thoracic vertebra), S32.0 (lumbar vertebra) |
| Comminuted fracture | Included under fracture codes with displacement |
| Avulsion fracture | S codes with specific site and fracture type |
| Colles's fracture | S52.5 |
| Smith fracture | S52.5 (volar displacement) |
| Scaphoid fracture | S62.0 |
| Femoral neck fracture | S72.0 |
| ACL tear | S83.5 |
| MCL injury | S83.4 |
| Meniscal tear | S83.2 |
| Rotator cuff tear | M75.1 |
| Achilles tendon rupture | S86.0 |
| Tennis elbow (lateral epicondylitis) | M77.1 |
| Golfer’s elbow (medial epicondylitis) | M77.0 |
| Patellar tendinitis (jumper’s knee) | M76.5 |
| Shin splints (medial tibial stress syndrome) | M76.8 |
| Muscle strains and sprains | S codes by site (e.g., S76.0 thigh muscle strain) |
| Dislocations (shoulder, patella, fingers) | S43.0 (shoulder), S83.0 (patella) |

| **Condition** | **ICD-10 Code(s)** |
| --- | --- |
| Avascular Necrosis (Osteonecrosis) | M87.0–M87.9 |
| Post-Traumatic Arthritis (Osteoarthritis) | M19.1 (Post-traumatic osteoarthritis) |
| Congenital or Developmental Joint Disorders | Q65–Q79 (Congenital malformations of limbs/joints) |
| Inflammatory Arthritides Other Than Rheumatoid Arthritis | M07 (Psoriatic and enteropathic arthritis), M45 (Ankylosing spondylitis), M08 (Juvenile arthritis) |
| Joint Deformities | M20–M21 (Acquired deformities of fingers, toes, other joints) |
| Failed Previous Joint Replacement (Revision Surgery) | T84.0–T84.9 (Complications of internal orthopedic prosthetic devices) |
| Bone Tumors Affecting Joints (Benign and Malignant) | D16 (Benign neoplasm of bone and articular cartilage), C40–C41 (Malignant bone tumors) |
| Severe Joint Infection (Septic Arthritis) Leading to Joint Destruction | M00 (Pyogenic arthritis), T84.5 (Infection and inflammatory reaction due to prosthetic device) |

**CPT CODE**

| **Condition** | **Common CPT Codes (Examples)** | **Description** |
| --- | --- | --- |
| Osteoarthritis (OA) | 27447, 27130, 29877 | Total knee arthroplasty, hip replacement, knee arthroscopy with debridement |
| Rheumatoid arthritis (RA) | 20610, 20611, 20612 | Joint injections (large and small joints) |
| Psoriatic arthritis | Same as RA codes above | Joint injections, synovectomy |
| Ankylosing spondylitis | 22558, 22612 | Spinal fusion procedures |
| Gout | 20610 | Joint aspiration and injection |
| Bursitis | 20610 | Bursa injection |
| Joint hypermobility syndrome | 97110, 97112 | Physical therapy codes for strengthening |
| Juvenile idiopathic arthritis | 20610, 20611 | Joint injections |
| Other inflammatory arthropathies | 20610, 20611 | Joint injections |

## **2. Bone Conditions**

| **Condition** | **Common CPT Codes (Examples)** | **Description** |
| --- | --- | --- |
| Osteoporosis | 77080 | Bone density (DEXA) scan |
| Osteopenia | 77080 | Bone density scan |
| OsteomaLacia | 77080 | Bone density scan |
| Fragility fractures | 27236, 27244, 22325 | Hip fracture fixation, vertebral augmentation (kyphoplasty) |
| Traumatic fractures | 25515, 25600, 27758 | Open reduction internal fixation (ORIF) of humerus, radius, tibia |
| Bone tumors (benign/malignant) | 27300, 27310, 27320 | Tumor excision, biopsy |
| Paget’s disease of bone | 20610 | Injection therapy (e.g., bisphosphonates may be coded separately) |

## **3. Muscle and Tendon Disorders**

| Condition | **Common CPT Codes (Examples)** | **Description** |
| --- | --- | --- |
| Muscular dystrophy | 97110, 97112 | Physical therapy codes |
| Sarcopenia | 97110, 97112 | Physical therapy |
| Myasthenia gravis | 95860, 95861 | EMG studies |
| Myositis | 95860, 95861 | EMG studies |
| Tendinitis / Tendinopathy | 20550, 20551 | Trigger point injections, tendon sheath injections |
| Rotator cuff tear | 29827 | Arthroscopic rotator cuff repair |
| Muscle strains and sprains | 97110, 97112 | Therapeutic exercises |
| Myopathies | 95860, 95861 | EMG studies |

## **4. Spine and Back Disorders**

| **Condition** | **Common CPT Codes (Examples)** | **Description** |
| --- | --- | --- |
| Chronic low back pain | 99213, 99214 | Office visits (E/M codes) |
| Degenerative disc disease | 63030, 63047 | Discectomy, laminectomy |
| Herniated intervertebral disc | 63030 | Discectomy |
| Spinal stenosis | 63047 | Laminectomy |
| Spondylolisthesis | 22612 | Spinal fusion |
| Vertebral compression fractures | 22523, 22524 | Vertebroplasty, kyphoplasty |
| Ankylosing spondylitis | 22612 | Spinal fusion |

## **5. Soft Tissue Conditions**

| **Condition** | **Common CPT Codes (Examples)** | **Description** |
| --- | --- | --- |
| Baker’s cyst (popliteal cyst) | 20610 | Aspiration/injection |
| Fibromyalgia | 99213, 99214 | Office visits (E/M codes) |
| Ligament injuries (e.g., ACL tear) | 29888, 29889 | Arthroscopic ACL reconstruction |
| Tendon ruptures | 24342, 27650 | Tendon repair surgeries |
| Capsulitis (frozen shoulder) | 23700, 23705 | Manipulation under anesthesia, arthroscopic capsular release |

## **6. Congenital and Developmental Disorders**

| **Condition** | **Common CPT Codes (Examples)** | **Description** |
| --- | --- | --- |
| Clubfoot (talipes equinovarus) | 27650, 27652 | Surgical correction |
| Developmental dysplasia of hip (DDH) | 27125, 27130 | Open reduction, hip arthroplasty |
| Scoliosis | 22802, 22804 | Spinal fusion with instrumentation |
| Limb length discrepancy | 27758, 27759 | Limb lengthening procedures |
| Osteogenesis imperfecta | 27535 | Fracture fixation or corrective osteotomy |

## **7. Other Conditions**

| **Condition** | **Common CPT Codes (Examples)** | **Description** |
| --- | --- | --- |
| Amputation (trauma/disease) | 27590, 27880 | Lower extremity amputation |
| Complex regional pain syndrome (CRPS) | 64640, 64642 | Sympathetic nerve blocks |
| Vasculitis with musculoskeletal involvement | 96372, 96401 | Medication administration (e.g., immunosuppressants) |
| Connective tissue diseases (SLE, scleroderma) | 99213, 99214 | Office visits (E/M codes) |
| Infectious arthritis and osteomyelitis | 27096, 27097 | Joint aspiration, bone biopsy |
| Tendonitis and bursitis | 20550, 20610 | Trigger point injections, bursa injections |
| Overuse injuries (e.g., repetitive strain, carpal tunnel syndrome) | 64721, 29848 | Carpal tunnel release, arthroscopic decompression |

| condition | Common CPT Codes | Description/Notes |
| --- | --- | --- |
| Avascular Necrosis (Osteonecrosis) | 27130, 27132, 27134, 27137 | Total hip arthroplasty (THA) codes; 27130 = primary THA; 27134 = revision THA |
| Post-Traumatic Arthritis | 27447, 27486 | Total knee arthroplasty (TKA) primary (27447) and revision (27486) |
| Congenital or Developmental Joint Disorders | 27125, 27130, 27132 | Hip osteotomies (27125) and total hip arthroplasty codes |
| Inflammatory Arthritides Other Than Rheumatoid Arthritis | 23472, 23473 (shoulder arthroplasty); 27130 (hip); 27447 (knee) | Shoulder hemiarthroplasty (23472), total shoulder arthroplasty (23473) |
| Joint Deformities | 27702, 27703, 27704 | Ankle arthroplasty and reconstructive procedures |
| Failed Previous Joint Replacement (Revision Surgery) | 27134 (revision hip), 27486 (revision knee), 23474 (revision shoulder) | Revision arthroplasty codes for hip, knee, shoulder |
| Bone Tumors Affecting Joints | 27310, 27320, 27330 | Tumor excision and reconstruction codes for femur and knee |
| Severe Joint Infection (Septic Arthritis) Leading to Joint Destruction | 27090 (arthrotomy for infection), 27132 (hip resection arthroplasty), 27488 (knee arthrotomy) | Debridement, resection, or staged arthroplasty for infection |

## **Common Joint Replacement CPT Codes**

| Joint | CPT Code | Description |
| --- | --- | --- |
| Hip | 27130 | Primary total hip arthroplasty |
| Hip Revision | 27134 | Revision total hip arthroplasty |
| Knee | 27447 | Primary total knee arthroplasty |
| Knee Revision | 27486 | Revision total knee arthroplasty |
| Shoulder | 23472 | Shoulder hemiarthroplasty |
| Shoulder | 23473 | Total shoulder arthroplasty |
| Shoulder Revision | 23474 | Revision shoulder arthroplasty |
| Ankle | 27702 | Total ankle arthroplasty |

**DISEASES DESCRIPTION AND SYMPTOMS MAPPINGS**

**OSTEOARTHRITIS**

**DEFINITION AND DESCRIPTION**

Osteoarthritis is the most common form of arthritis, affecting millions of people worldwide. It happens when the protective cartilage that cushions the ends of the bones wears down over time.

Although osteoarthritis can damage any joint, the condition most commonly affects joints in the hands, knees, hips and spine.

Osteoarthritis symptoms can usually be managed, although the damage to joints can't be reversed. Staying active, maintaining a healthy weight and receiving certain treatments might slow progression of the disease and help improve pain and joint function.

## **Causes**

Osteoarthritis happens when the cartilage that cushions the ends of bones in the joints gradually wears away. Cartilage is a firm, slippery tissue that allows nearly frictionless joint motion.

Eventually, if the cartilage wears down completely, bone will rub on bone.

Osteoarthritis doesn't only affect the cartilage. It also affects the entire joint. It causes changes in the bone and weakens the strong bands of tissue that hold the joint together and attach muscle to bone. It also may cause swelling of the joint lining.

## **Risk factors**

Factors that can increase your risk of osteoarthritis include:

* **Older age.** The risk of osteoarthritis increases with age.
* **Sex assigned at birth.** People assigned female at birth are more likely to develop osteoarthritis, though it isn't clear why.
* **Obesity.** Carrying extra body weight contributes to osteoarthritis in several ways. The more you weigh, the greater your risk. Increased weight adds stress to weight-bearing joints, such as the hips and knees. Also, fat tissue produces proteins that can cause harmful swelling in and around your joints.
* **Joint injuries.** Injuries, such as those that happen when playing sports or from an accident, can increase the risk of osteoarthritis. Even injuries that occurred many years ago can increase the risk of osteoarthritis.
* **Repeated stress on the joint.** If a job or sport places repetitive stress on a joint, that joint might develop osteoarthritis someday.
* **Genetics.** Some people inherit a tendency to develop osteoarthritis.
* **Bone deformities.** Some people are born with malformed joints or defective cartilage.
* **Certain metabolic diseases.** These include diabetes and a condition in which your body has too much iron, called hemochromatosis.

## **Symptoms**

Osteoarthritis symptoms often develop slowly and worsen over time. Symptoms of osteoarthritis include:

* **Pain.** Affected joints might hurt during or after movement.
* **Stiffness.** Joint stiffness might be most noticeable upon awakening or after being inactive.
* **Tenderness.** Joints might feel tender when you apply light pressure to or near them.
* **Loss of flexibility.** You might not be able to move your joint through its full range of motion.
* **Grating sensation.** You might feel a grating sensation when you use the joint, and you might hear popping or crackling.
* **Bone spurs.** These extra bits of bone, which feel like hard lumps, can form around the affected joint.
* **Swelling.** This might be caused by soft tissue inflammation around the joint.

## **Diagnosis**

During the physical exam, your healthcare professional checks your affected joint for tenderness, swelling and flexibility.

### **Imaging tests**

To get pictures of the affected joint, your healthcare professional might recommend:

* **X-rays.** Cartilage doesn't show up on X-ray images, but cartilage loss is revealed by a narrowing of the space between the bones in your joint. An X-ray also can show bone spurs around a joint.
* **Magnetic resonance imaging (MRI).** An MRI uses radio waves and a strong magnetic field to produce detailed images of bone and soft tissues, including cartilage. An MRI isn't commonly needed to diagnose osteoarthritis but can help provide more information in complex cases.

### **Lab tests**

Analyzing blood or joint fluid can help confirm the diagnosis.

* **Blood tests.** Although there's no blood test for osteoarthritis, certain tests can help rule out other causes of joint pain, such as rheumatoid arthritis.
* **Joint fluid analysis.** A needle might be used to draw fluid from an affected joint. The fluid is then tested to determine whether your pain is caused by an inflammatory arthritis, such as rheumatoid arthritis or gout, or an infection rather than osteoarthritis.

## **Treatment**

Osteoarthritis can't be reversed, but treatments can reduce pain and help you move better.

### **Medicines**

Medicines that can help relieve osteoarthritis pain symptoms include:

* **Acetaminophen.** Acetaminophen (Tylenol, others) has been shown to help some people with osteoarthritis who have mild to moderate pain. Taking more than the recommended dose of acetaminophen can cause liver damage.
* **Nonsteroidal anti-inflammatory drugs (NSAIDs).** Common pain relievers, such as ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve), taken at the recommended doses, typically relieve osteoarthritis pain. Stronger NSAIDs are available by prescription.

NSAIDs can cause stomach upset, cardiovascular problems, bleeding problems, and liver and kidney damage. NSAIDs as gels, applied to the skin over the affected joint, have fewer side effects and may relieve pain just as well.

* **Duloxetine (Cymbalta).** Although typically used as an antidepressant, duloxetine also is approved to treat chronic pain, including osteoarthritis pain.

### **Therapy**

* **Physical therapy.** A physical therapist can show you exercises to strengthen the muscles around your joint, increase your flexibility and reduce pain. Regular gentle exercise that you do on your own, such as swimming or walking, can be equally effective.
* **Occupational therapy.** An occupational therapist can help you find ways to do everyday tasks without putting extra stress on an already painful joint. For instance, a toothbrush with a large grip could make brushing your teeth easier if you have osteoarthritis in your hands. A bench in your shower could help relieve the pain of standing if you have knee osteoarthritis.
* **Transcutaneous electrical nerve stimulation (TENS).** This uses a low-voltage electrical current to relieve pain. It provides short-term relief for some people with knee and hip osteoarthritis.

### **Surgical and other procedures**

If conservative treatments don't help, you might want to consider procedures such as:

* **Cortisone injections.** Injections of a corticosteroid into the joint might relieve pain for a few weeks. The number of cortisone injections you can receive each year is generally limited to three or four, because the medicine can worsen joint damage over time.
* **Lubrication injections.** Injections of hyaluronic acid might relieve pain by providing some cushioning in your knee, though some research suggests that these injections offer no more relief than a placebo. Hyaluronic acid is similar to a component typically found in joint fluid.
* **Realigning bones.** If osteoarthritis has damaged one side of your knee more than the other, an osteotomy might be helpful. In a knee osteotomy, a surgeon cuts across the bone either above or below the knee and removes or adds a wedge of bone. This shifts your body weight away from the worn-out part of your knee.
* **Joint replacement.** In joint replacement surgery, the surgeon removes the damaged joint surfaces and replaces them with plastic and metal parts. Surgical risks include infections and blood clots. Artificial joints can wear out or come loose and might need to be replaced.

**DRUG INFORMATION AND SIDE EFFECT**

### **Analgesics**

Analgesic medications block pain by interfering with the brain’s pain signals. There are three different types of analgesics for treating osteoarthritis: acetaminophen, topical analgesics, and opioid analgesics.

**Acetaminophen**

Acetaminophen is available over the counter (OTC) for treating mild to moderate osteoarthritis pain. Acetaminophen has no effect on inflammation, but it is a better choice if you have Aspirin or NSAID sensitivity, have a history of gastrointestinal tract disease, and or take anticoagulants (medications for preventing blood clots).

You should stop taking acetaminophen if you experience nausea, vomiting, stomach pain, lightheadedness, sweating, fainting, weakness, unusual bruising and bleeding, and yellowing of skin or eyes and call your doctor.

#### **Topical Analgesics**

Topical analgesics are used for osteoarthritis pain in joints located just below the skin, such as the knees and fingers. They are not effective for joints that are deeper, i.e. the hips.

Capsaicin, a commonly used topic analgesic, is the active material derived from hot chili pepper. It comes in a variety of OTC creams and works to reduce the pain in endings and lessens osteoarthritis pain in about 33 percent of people.

It could take at least two weeks before you see results with capsaicin. Side effects include burning, stinging, and redness.

#### **Opioid Analgesics**

Opioid analgesics are available by prescription only and should be used as your doctor prescribes. Your doctor will consider opioid analgesics when other treatments have not worked to control your OA pain or if you are unable to take NSAIDs.

No research has found them effective for long-term use in managing OA pain and restoring function, so they should only be used for short periods.

Opioid pain relievers pose side effects, including the risk for addiction. More common side effects are constipation, dizziness and drowsiness, feeling faint, nausea and vomiting.

### **Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

NSAIDs are the most effective treatments for OA pain and inflammation. Because they present an increased cardiovascular risk, NSAIDs are often prescribed at the lowest effective dosage.

Common over-the-counter NSAIDs are ibuprofen and naproxen. NSAIDs relieve pain and reduce inflammation, but their long-term side effects are far worse than acetaminophen.

Long-term use of NSAIDs may lead to stomach bleeding and kidney damage, in addition to increasing your risk for heart attack and stroke.

## **Self-care**

Learn all you can about your condition and how to manage it, especially about how lifestyle changes can affect your symptoms. Exercising and losing weight if you're overweight are important ways to lessen the joint pain and stiffness of osteoarthritis.

* **Exercise.** Low-impact exercise can increase your endurance and strengthen the muscles around your joint, making your joint more stable. Try walking, bicycling or water aerobics. If you feel new joint pain, stop.
* **Lose weight.** Carrying extra weight increases the stress on your weight-bearing joints, such as your knees and your hips. Even minor weight loss can relieve some pressure and reduce pain. Talk to a dietitian about healthy ways to lose weight.

Other things to try include:

* **Movement therapies.** Tai chi and yoga involve gentle exercises and stretches combined with deep breathing. Many people use these therapies to reduce stress in their lives. And research suggests that tai chi and yoga might reduce osteoarthritis pain and improve movement. Make sure the yoga you choose is a gentle form and that your instructor knows which of your joints are affected. Avoid moves that cause pain in your joints.
* **Heat and cold.** Both heat and cold can relieve pain and swelling in your joint. Heat, especially moist heat, can help muscles relax and ease pain. Cold can relieve muscle aches after exercise and decrease muscle spasms.
* **Capsaicin.** Capsaicin is a chili pepper extract. Applying capsaicin cream to your skin over a painful arthritic joint might help the pain. You might have to apply it 3 to 4 times a day for several weeks before you see a benefit. Capsaicin causes a burning or stinging feeling. Wash your hands well after applying capsaicin cream.
* **NSAID gels.** Topical nonsteroidal anti-inflammatory gel is available without a prescription. These gels may help relieve pain when applied to the skin over the affected joint.
* **Braces or shoe inserts.** Shoe inserts or other devices might help reduce pain when you stand or walk. These devices can support your joint to help take pressure off the joint.
* **Assistive devices.** Assistive devices can help relieve stress on your joints. A cane or walker take weight off your knee or hip as you walk. Hold the cane in the hand opposite the leg that hurts.

Tools for gripping and grabbing may make it easier to work in the kitchen if you have osteoarthritis in your fingers. Check catalogs or medical supply stores or ask your healthcare team about assistive devices.

## **Alternative medicine**

Complementary and alternative medicine treatments that have shown promise for osteoarthritis include:

* **Acupuncture.** Some studies indicate that acupuncture can relieve pain and improve function in people who have knee osteoarthritis. During acupuncture, hair-thin needles are inserted into your skin at precise spots on your body.
* **Glucosamine and chondroitin.** Studies have been mixed on these nutritional supplements. A few have found benefits for people with osteoarthritis, while most indicate that these supplements work no better than a placebo.
* **Omega-3 fatty acids.** Omega-3s, found in fatty fish and fish oil supplements, might help relieve pain and improve function.

Talk to your healthcare team about supplements you're considering.

## **Complications**

Osteoarthritis is a disease that worsens over time, often resulting in chronic pain. Joint pain and stiffness can become severe enough to make daily tasks difficult.

Depression and sleep disturbances can result from the pain, stiffness and mobility issues of osteoarthritis.

## **Outlook / Prognosis**

Most people with osteoarthritis need to manage their symptoms for the rest of their lives. Your healthcare provider will help you find the right combination of treatments to reduce your symptoms.

If you have osteoarthritis, it’s important to stay as active as possible. If joint pain and other symptoms make it too hard for you to move, you may face a greater risk for other serious health conditions like heart disease, diabetes and some types of cancer.

Talk to your healthcare provider if osteoarthritis makes it hard (or impossible) to stay active. They’ll help you find new treatments to manage your symptoms.

**Prevention**

The best way to prevent osteoarthritis is to maintain good overall health, including:

* Avoiding tobacco products.
* Doing low-impact exercise.
* Following a diet plan that’s healthy for you.
* Always wearing your seatbelt.
* Wearing proper protective equipment for any activity, sport or work you’re doing.
* Visiting a healthcare provider for regular checkups and as soon as you notice any changes in your joints.

**Living With**

You might need to tweak your routine to make living with osteoarthritis easier. Depending on when you’re experiencing symptoms (and how severe they are), you may need to avoid or modify your activities while you’re managing symptoms. You might work with an occupational therapist if you need help performing your daily tasks. Occupational therapists are healthcare providers who can help you manage physical challenges like arthritis. They may recommend:

* Adaptive equipment, such as grips for opening jars.
* Techniques for doing hobbies, sports or other activities safely.
* Tips for reducing joint pain during arthritic flare-ups.

### **When should I see my healthcare provider?**

Visit a healthcare provider as soon as you notice any symptoms of osteoarthritis. Even minor joint pain can be a sign that you need treatment — especially if it doesn’t get better in a few days.

You can’t repair any cartilage degeneration (breakdown) that’s already happened, but starting osteoarthritis treatment can slow down further damage inside your joints.

Talk to your provider if it feels like your symptoms are coming back more often or are more severe than they used to be. Ask your provider about other treatment options or changes you can make to your existing treatments if you feel like they’re not working as well as they usually do.

## **Diagnostic Considerations**

The initial diagnostic goal is to differentiate osteoarthritis from other arthritides, such as rheumatoid arthritis. The history and physical examination findings are usually sufficient to diagnose osteoarthritis. Radiographic findings confirm the initial impression (see Workup), and laboratory values are typically within the reference range.

## Rheumatoid arthritis

Rheumatoid arthritis predominantly affects the wrists, as well as the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. It rarely, if ever, involves the distal interphalangeal (DIP) joints or the lumbosacral spine.

Rheumatoid arthritis is associated with prominent, prolonged (>1 hour) morning stiffness and overtly swollen, warm joints. Radiographic findings include bone erosion (e.g., periarticular osteopenia or marginal erosions of bone) rather than formation. Laboratory findings that further differentiate rheumatoid arthritis from osteoarthritis include the following:

* Systemic inflammation (elevated erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP] level)
* Positive serologies (rheumatoid factor [RF] or anti–cyclic citrullinated peptide [anti-CCP] antibodies)
* Inflammatory joint fluid with a predominance of polymorphonuclear leukocytes (PMNs)
* Elevated white blood cell (WBC) count

## Other arthritides

Back pain may result from spondyloarthropathy or from osteoarthritis with sacroiliac and lumbosacral spine involvement. Clinical history and characteristic radiographic findings can be used to differentiate these disorders.

Secondary osteoarthritis must be considered in individuals with any of the following:

* Chondrocalcinosis
* History of joint trauma
* Metabolic bone disorders
* Hypermobility syndromes
* Neuropathic diseases

The following disorders should also be considered in the differential diagnosis:

* Crystalline arthropathies (i.e., gout and pseudogout)
* Inflammatory arthritis (e.g., rheumatoid arthritis)
* Seronegative spondyloarthropathies (e.g., psoriatic arthritis and reactive arthritis)
* Septic arthritis or post infectious arthropathy
* Fibromyalgia
* Tendonitis

In patients with knee pain, other disorders to consider in the differential diagnosis are patellofemoral syndrome and prepatellar bursitis.

## **Differential Diagnoses**

* Avascular Necrosis
* Fibromyalgia
* Gout and Pseudogout
* Ankylosing Spondylitis Imaging
* Imaging in Neuropathic Arthropathy (Charcot Joint)
* Lyme Disease
* Patellofemoral Arthritis
* Psoriatic Arthritis
* Rheumatoid Arthritis (RA)

## **Epidemiology**

### United States and international statistics

Osteoarthritis affects more than 32 million individuals in the United States, though statistical figures are influenced by how the condition is defined—that is, by self-report, by radiographic or symptomatic criteria, or by a combination of these.Based on the radiographic criteria for osteoarthritis, more than 50% of adults older than 65 years are affected by the disease.

Internationally, osteoarthritis is the most common articular disease. Estimates of its frequency vary across different populations but worldwide, more than 500 million people may be affected.An analysis of Global Burden of Disease data found that the age-standardized incidence rate of osteoarthritis increased by approximately 9% from 1990 to 2017; the crude incidence rate rose 102% over that 28-year period, with the increase driven by the aging of the global population.

### Age-related demographics

Primary osteoarthritis is a common disorder of the elderly, and patients may present asymptomatic. Approximately 80-90% of individuals older than 65 years have evidence of radiographic primary osteoarthritis.

Symptoms typically do not become noticeable until after the age of 50 years. The prevalence of the disease increases dramatically among persons older than 50 years, likely because of age-related alterations in collagen and proteoglycans that decrease the tensile strength of the joint cartilage and because of a diminished nutrient supply to the cartilage.

### Sex-related demographics

In individuals older than 55 years, the prevalence of osteoarthritis is higher among women than among men.Women are especially susceptible to osteoarthritis in the DIP joints of the fingers. Women also have osteoarthritis of the knee joints more frequently than men do, with a female-to-male incidence ratio of 1.7:1. Women are also more prone to erosive osteoarthritis, with a female-to-male ratio of about 12:1.

### Race-related demographics

Interethnic differences in the prevalence of osteoarthritis have been noted.The disorder is more prevalent in Native Americans than in the general population. Disease of the hip is seen less frequently in Chinese patients from Hong Kong than in age-matched white populations. However, symptomatic knee osteoarthritis is extremely common in China.

In persons older than 65 years, osteoarthritis is more common in Whites than in Blacks. Knee osteoarthritis appears to be more common in Black women than in other groups. Jordan et al found that in comparison with Whites, African American men and women had a slightly higher prevalence of radiographic and symptomatic knee osteoarthritis.

## **Management of Osteoarthritis (OA) — Key Recommendations**

## 1. Non-Pharmacologic Management

* Education and Self-Management Programs
  + Strongly recommended to improve patient self-efficacy, goal setting, and coping skills.
* Weight Loss
  + Strong recommendation for patients with hip and knee OA who are overweight or obese to reduce pain and improve function.
* Exercise
  + Aerobic, strengthening, neuromuscular, and aquatic exercises are strongly recommended.
  + Supervised exercise programs (e.g., with a physical therapist) may be more effective.
  + Tai chi is strongly recommended, especially for hip and knee OA.
  + Balance exercises are conditionally recommended.
* Assistive Devices
  + Use of canes (for hip and knee OA), orthotic devices, and wrist braces (for hand OA) is strongly recommended.
  + Tibiofemoral bracing for tibiofemoral knee OA is strongly recommended.
  + Patellofemoral bracing for patellofemoral knee OA is conditionally recommended.
* Other Mind-Body and Physical Approaches
  + Yoga, cognitive behavioral therapy, and acupuncture are conditionally recommended.
  + Thermal modalities (heat/cold) may provide slight symptom relief.

## 2. Pharmacologic Management

* Topical NSAIDs
  + Strongly recommended for knee and hand OA due to efficacy and safety profile.
* Oral NSAIDs
  + Strongly recommended for knee and hip OA for short-term pain relief.
  + Use with caution considering gastrointestinal, cardiovascular, and renal risks.
* Intra-articular Corticosteroid Injections
  + Strongly recommended for knee and hip OA for short-term symptom relief.
* Duloxetine
  + Conditionally recommended for knee OA, especially when other treatments are insufficient or contraindicated.
* Acetaminophen and Tramadol
  + Conditionally recommended for short-term pain control in select patients.
* Topical Capsaicin
  + Conditionally recommended for knee OA.
* Chondroitin Sulfate
  + Conditionally recommended for hand OA.

## 3. Treatments Not Recommended or Conditionally Recommended Against

* Hyaluronic Acid Injections
  + Strong recommendation against use in hip OA.
  + Conditional recommendation against use in knee and first carpometacarpal (CMC) OA.
* Transcutaneous Electrical Nerve Stimulation (TENS)
  + Strong recommendation against use for knee and hip OA.
* Manual Therapy with Exercise
  + Conditionally recommended for knee and hip OA.
* Non-Tramadol Opioids
  + Recommended against due to high risk of toxicity and dependency.
* Prolotherapy and Intra-articular Botulinum Toxin
  + Conditionally not recommended due to lack of evidence.
* Modified Shoes and Orthotics (lateral/medial wedges)
  + Conditionally recommended against for knee and hip OA.
* Supplements with Limited Evidence
  + Colchicine, fish oil, vitamin D have insufficient evidence for benefit.

## 4. Additional Considerations

* Treatment should be individualized based on patient preferences, comorbidities, and symptom severity.
* Shared decision-making between patient and clinician is emphasized.
* Management is multimodal and may require adjusting therapies over time as symptoms change.

## **Osteoarthritis (OA) Predefined Questions & Answers**

Q. What is osteoarthritis?  
A. Osteoarthritis is a common joint disease characterized by the breakdown of cartilage and changes in bone near the joints, leading to pain, stiffness, and decreased function

Q. What causes osteoarthritis?  
OA can result from aging, joint injury, repetitive stress, obesity, genetics, and joint malalignment. Previous joint injuries and repetitive strain increase risk

Q. What are the common symptoms of OA?  
A. Symptoms include joint pain worsened by activity, stiffness after inactivity (especially morning stiffness lasting less than 30 minutes), swelling, decreased range of motion, and sometimes joint deformity

Q. How is OA diagnosed?  
A. Diagnosis is based on clinical history, physical exam, and imaging (X-rays showing joint space narrowing, osteophytes). Blood tests may be used to exclude other types of arthritis

Q. How does OA progress?  
A. OA progression is characterized by worsening cartilage loss, joint space narrowing, osteophyte formation, and increasing pain and disability over time

Q. What treatments are available for OA?  
A. There is no cure, but treatments focus on symptom management:

* Exercise and physical therapy to improve strength and mobility
* Weight loss to reduce joint load
* Pain medications including acetaminophen, NSAIDs, topical agents
* Joint injections (corticosteroids) for flare-ups
* Assistive devices (canes, braces)
* Surgery (joint replacement) in severe cases

Q. What lifestyle changes help manage OA?  
A. Staying active, losing weight if overweight, avoiding activities that worsen symptoms, and using adaptive equipment can help maintain function and reduce pain

Q. Can exercise worsen OA?  
A. Exercise generally improves symptoms and function. However, high-impact or repetitive activities may exacerbate pain. Tailored exercise programs with professional guidance are recommended

Q. Are there any home remedies or over-the-counter options?  
A. Capsaicin cream may help relieve pain. Heat and cold therapy can also be beneficial. Glucosamine and chondroitin supplements have limited evidence

Q. When is surgery considered for OA?  
A. Surgery, such as joint replacement, is considered when conservative treatments fail and pain or disability significantly affect quality of life

Q. What complications can arise from OA?  
A. OA can lead to muscle weakness, reduced mobility, increased risk of falls, and associated comorbidities like cardiovascular disease due to inactivity

Q. How can patients stay informed and supported?  
A. Patient education, support groups, and resources from organizations like the Arthritis Foundation and American College of Rheumatology can empower patients to manage OA effectively

**Q. What is end stage osteoarthritis?**

A. Medical professionals may refer to osteoarthritis as “end stage” when it becomes severe. At this point, conservative treatments are unlikely to reduce pain or improve function. A person will often require surgery for end stage osteoarthritis.

**Procedures and Recovery Timeline**

## 1. Arthroscopy

* What it is:  
  Minimally invasive "keyhole" surgery where a small camera (arthroscope) is inserted into the joint. The surgeon smooths rough cartilage, removes loose fragments, or repairs minor damage.
* Best candidates:  
  Younger, active patients with mild to moderate OA or mechanical symptoms (e.g., loose bodies, meniscal tears).
* Recovery timeline:
  + Usually, outpatient or short hospital stay.
  + Return to normal activities in 4–6 weeks.
  + Less invasive, so quicker recovery than joint replacement.
* Limitations:  
  Not effective for severe OA with extensive cartilage loss.

## 2. Osteotomy

* What it is:  
  Bone is cut and reshaped (often near the knee or hip) to realign the joint and redistribute weight away from damaged cartilage.
* Best candidates:  
  Younger patients (<60 years) with localized joint damage who want to delay joint replacement.
* Recovery timeline:
  + Hospital stay typically 3–5 days.
  + Partial weight-bearing for 6–8 weeks.
  + Full recovery and return to activities may take 3–6 months.
* Pros and cons:  
  Preserves natural joint and delays replacement but requires longer rehab and is a technically demanding surgery.

## 3. Partial Joint Replacement (Uni compartmental Arthroplasty)

* What it is:  
  Replacement of only the damaged compartment of the joint (commonly knee), preserving healthy parts.
* Best candidates:  
  Patients with OA confined to one part of the joint.
* Recovery timeline:
  + Hospital stay 1–3 days.
  + Faster recovery than total replacement, often walking with assistance within days.
  + Return to normal activities in 6–12 weeks.
* Limitations:  
  May require total joint replacement later if OA progresses.

## 4. Total Joint Replacement (Arthroplasty)

* What it is:  
  Removal of damaged joint surfaces and replacement with artificial components (metal, plastic, ceramic).
* Common joints:  
  Hip, knee, shoulder, less commonly ankle, elbow.
* Recovery timeline:
  + Hospital stay: 1–4 days (some outpatient procedures possible).
  + Physical therapy starts immediately post-op.
  + Most patients walk with assistance within 1–2 days.
  + Return to most daily activities in 6–12 weeks.
  + Full recovery and maximal improvement can take 6 months to 1 year.
* Benefits:  
  Significant pain relief, improved function, and quality of life.

## 5. Joint Fusion (Arthrodesis)

* What it is:  
  Surgical fusion of joint bones to eliminate movement and pain, commonly used in smaller joints (spine, hand, foot).
* Recovery timeline:
  + Immobilization for 6–12 weeks.
  + Gradual return to activities over months.
  + Permanent loss of joint motion.
* Considerations:  
  Used when joint replacement is not feasible; may increase stress on adjacent joints.

## 6. Synovectomy

* What it is:  
  Removal of inflamed joint lining (synovium), usually via arthroscopy.
* Best candidates:  
  Patients with inflammatory arthritis or synovial overgrowth causing pain/swelling.
* Recovery timeline:
  + Short hospital stay or outpatient.
  + Recovery in weeks to months depending on extent.
* Note:  
  Provides temporary relief; synovium may regrow.

**DOCTOR- PATIENT CONVERSATION**

Doctor:  
I see you’ve been experiencing knee pain for some time now. Can you tell me more about it?

Patient:  
Yes, it’s been hurting especially when I walk or climb stairs. It feels stiff in the mornings but usually eases up after a bit.

Doctor:  
That sounds like symptoms typical of osteoarthritis, which is a common wear-and-tear condition affecting joints. Have you noticed any swelling or difficulty moving your knee?

Patient:  
Sometimes it swells a little, and bending it fully is harder than before.

Doctor:  
Thanks for sharing that. Based on your symptoms and the physical exam, I’d like to order an X-ray to look at the joint space and check for cartilage loss or bone changes.

Patient:  
Is osteoarthritis something that can be cured?

Doctor:  
Unfortunately, there’s no cure, but we have many ways to manage symptoms and improve your quality of life. This includes exercise, weight management, medications, and sometimes injections or surgery if needed.

Patient:  
I’m worried about medications. Are there side effects?

Doctor:  
That’s a valid concern. We usually start with topical treatments or acetaminophen, which have fewer side effects. If needed, we can consider NSAIDs but carefully monitor for any risks. We’ll tailor the treatment to what works best for you.

Patient:  
What kind of exercise should I do?

Doctor:  
Low-impact activities like walking, swimming, or tai chi are great. Physical therapy can help you strengthen muscles around the joint, which supports and stabilizes it.

Patient:  
Sometimes I feel overwhelmed with all the information. How can I make sure I understand what you’re saying?

Doctor:  
Please feel free to ask me to explain anything in simpler terms. You can also bring a family member or friend to appointments or record our discussions. It’s important that you feel confident managing your condition.

Patient:  
Thank you. That makes me feel better.

Doctor:  
You’re welcome. Remember, managing OA is a team effort. We’ll work together to find the best plan for you.

## **Osteoarthritis Genomic Data**

* Osteoarthritis (OA) is a complex, polygenic disease influenced by both genetic and environmental factors.
* A large genome-wide association study (GWAS) meta-analysis involving over 489,000 OA cases and 1.47 million controls identified 962 independent genetic associations, including 513 novel variants
* These variants map to 286 genomic loci, many involved in embryonic skeletal development and pathways such as TGFβ, FGF, WNT, BMP, retinoic acid signaling, and extracellular matrix organization
* Most variants have a minor allele frequency (MAF) ≥5% with modest effect sizes (odds ratios 1.016–1.186), while some low-frequency variants (MAF 1–5%) show higher effects
* The genetic influence on OA is estimated between 35% and 65% heritability, with polygenic inheritance involving multiple interacting genes rather than Mendelian patterns

## Key Genes and Pathways

* GDF5 (Growth Differentiation Factor 5): Promoter variants (e.g., rs143383) are strongly associated with hip and knee OA across populations
* SMAD3: Intronic variants linked to hip and knee OA, involved in TGFβ signaling
* COL9A1: Mutations associated with rare Mendelian disorders affecting cartilage and OA susceptibility
* Other implicated genes include those involved in circadian clock regulation, glial cell processes, and extracellular matrix maintenance[1](https://www.nature.com/articles/s41586-025-08771-z).

## Functional Genomics and Epigenetics

* OA-associated variants often correlate with epigenetic modifications, particularly DNA methylation changes in cartilage and subchondral bone tissues
* Transcriptomic studies reveal joint- and tissue-specific gene expression changes in OA progression, including differences between low-grade and high-grade cartilage degeneration
* Epigenetic alterations suggest dynamic regulation during OA development and progression, offering potential therapeutic targets

**REFERENCES**

[Osteoarthritis: Practice Essentials, Background, Anatomy](https://emedicine.medscape.com/article/330487-overview#a6)

<https://www.arthritis.org/health-wellness/treatment/joint-surgery/safety-and-risks/understand-your-joint-surgery-options>

[Osteoarthritis - Symptoms & causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/osteoarthritis/symptoms-causes/syc-20351925)

[Osteoarthritis: Symptoms, Causes & Treatment Options](https://my.clevelandclinic.org/health/diseases/5599-osteoarthritis#outlook-prognosis)

**RHEUMATOID ARTHRITIS**

**DEFINITION**

Rheumatoid arthritis is an ongoing, called chronic, condition that causes pain, swelling and irritation, called inflammation, in the joints. But it also can damage other parts of the body. These may include the skin, eyes, lungs, heart and blood vessels.

Rheumatoid arthritis happens when the immune system attacks its own body's tissues by mistake. This is called an autoimmune condition.

Rheumatoid arthritis differs from the more common osteoarthritis. Some people have both. Osteoarthritis causes damage to joint from overuse. Rheumatoid arthritis affects the lining of the joints and eats away at the bone under them. This causes a painful swelling that can cause joints to bend out of shape over time, called deformity.

The inflammation of rheumatoid arthritis also can damage other parts of the body. New medicines have improved treatment choices greatly. But rheumatoid arthritis still can cause long-term damage and increase the risk of heart disease.

**Causes**

Experts don't know the cause of rheumatoid arthritis. But it's a condition in which the immune system attacks healthy joint tissue by mistake, called autoimmune.

The cause is likely a mix of genetic changes and factors from outside the body, called environmental. Hormones may play a role. An infection with certain viruses may start rheumatoid arthritis in people whose genes make them more likely to get it.

**Risk factors**

Factors that may increase your risk of rheumatoid arthritis include:

* **Your sex.** People assigned female at birth are more likely than those assigned male at birth to get rheumatoid arthritis.
* **Age.** Rheumatoid arthritis can happen at any age. But most often it begins in middle age. Children and young teens may get a related condition called juvenile idiopathic arthritis.
* **Family history.** Having a family member with rheumatoid arthritis or other autoimmune conditions may raise the risk of the condition.
* **Smoking.** Cigarette smoking over time raises the risk of getting rheumatoid arthritis. Smoking also seems to make the condition worse in people who keep smoking.
* **Gum infection.** A serious gum infection, called periodontal disease, can damage the soft tissue around teeth and raise the risk of getting rheumatoid arthritis.
* **Excess weight.** People who are overweight seem to be at a somewhat higher risk of getting rheumatoid arthritis.

**Symptoms**

Symptoms of rheumatoid arthritis may include:

* Painful, warm, swollen joints.
* Joint stiffness that most often is worse in the mornings and after periods of rest. It can last for 45 minutes or longer.
* Tiredness, fever and not wanting to eat.

Rheumatoid arthritis may affect just a few joints at first. Most often, these are the small joints of the hands and the feet.

As the disease gets worse, symptoms may spread to more joints. These most often include the wrists, elbows, hips, knees and ankles. Most of the time, symptoms affect the same joints on both sides of the body.

Many people who have rheumatoid arthritis also have symptoms that affect more than the joints. Areas that may be affected include:

* Skin.
* Eyes.
* Lungs.
* Heart.
* Nerve tissue.
* Blood.

Rheumatoid arthritis symptoms may vary in how bad they are. They may come and go. Periods when the condition becomes more active, called flares, follow periods of less or no swelling and pain. This is called remission.

Over time, rheumatoid arthritis can cause joints to bend out of shape and shift out of place. The joints can be hard to use for daily activities at home or at work.

## **Diagnosis**

Rheumatoid arthritis can be hard to diagnose in its early stages. That's because the early symptoms can be like those of other common conditions.

During the physical exam, your healthcare professional checks your joints for swelling, redness and warmth. Your healthcare professional also may check your reflexes and muscle strength.

### **Blood tests**

People with rheumatoid arthritis often have an elevated erythrocyte sedimentation rate (ESR), also called sed rate, or C-reactive protein (CRP) level. This may show a higher level of inflammation in the body. Other blood tests look for rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies.

### **Imaging tests**

You may have X-rays to track rheumatoid arthritis in your joints over time. MRI scans and ultrasound tests may help with diagnosis. They can show how bad the condition is.

**Treatment**

There is no cure for rheumatoid arthritis. Joint damage can happen quickly without treatment. But clinical studies show that easing of symptoms, called remission, is more likely with early treatment with medicines called disease-modifying antirheumatic drugs (DMARDs).

Treatment of rheumatoid arthritis also involves regular follow-up with your healthcare team. This is to watch for joint damage, to see whether treatment is working and to look for possible side effects of treatment.

### **Medications**

Your healthcare professional will suggest medicines based on how bad your symptoms are and how long you've had rheumatoid arthritis. You and your healthcare professional will decide on treatment. Medicines might include:

* **NSAIDs.** Nonsteroidal anti-inflammatory drugs (NSAIDs) can relieve pain and ease swelling and irritation. NSAIDs you can get without a prescription include ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve).

There also are stronger prescription NSAIDs. Side effects for all NSAIDs may include stomach upset, heart problems and kidney damage.

* **Steroids.** Corticosteroid medicines, such as prednisone (Rayos), ease inflammation and pain and slow joint damage. There can be serious side effects. The risk of side effects rises when taken at high doses over a long time. Side effects may include thinning of bones, fractures, easy bruising from skin thinning, weight gain, diabetes, cataracts and glaucoma, among others.

Healthcare professionals often prescribe a corticosteroid for quick symptom relief. The goal is to taper off the medicine when the condition is under control.

* **Conventional DMARDs.** These drugs can slow the progression of rheumatoid arthritis and save the joints and other tissues from long-term damage. Common DMARDs include methotrexate (Trexall, Otrexup, others), leflunomide (Arava), hydroxychloroquine (Plaquenil, Sovuna) and sulfasalazine (Azulfidine). Side effects vary but may include liver damage and severe lung infections.
* **Biologic agents.** Also known as biologic response modifiers, this newer class of DMARDs includes abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sarilumab (Kevzara) and tocilizumab (Actemra).

Biologic DMARDs most often work best when used with a conventional DMARD, such as methotrexate. Biologic agents also raise the risk of rare infections such as tuberculosis, also called TB, or fungal infections. If you take biologic agents, you need to be watched closely.

* **Targeted synthetic DMARDs.** Healthcare professionals may prescribe these human-made medicines if conventional DMARDs and biologics haven't worked. They include baricitinib (Olumiant), tofacitinib (Xeljanz) and Upadacitinib (Rinvoq).

Higher doses of tofacitinib may raise the risk of blood clots in the lungs, serious heart-related events and cancer.

### **Therapy**

A physical or occupational therapist can teach you exercises to help keep your joints moving. The therapist also may suggest ways to do daily tasks that are easier on your joints. For instance, you may pick up an object using your forearms instead of your hands.

Assistive devices can make it easier to keep from stressing painful joints. For instance, a kitchen knife with a hand grip helps protect finger and wrist joints. Certain tools, such as buttonhooks, can make it easier to get dressed. Look for ideas in medical supply brochures and stores.

### **Surgery**

Better medicines to treat rheumatoid arthritis have lowered the need for surgery. But if medicines fail to prevent or slow joint damage, you and your healthcare professional may think about surgery for damaged joints.

Rheumatoid arthritis surgery may involve replacing or repairing a damaged joint. The type of surgery may depend on the joint involved. Surgery may help you use a joint again. It also can ease pain.

## **Rheumatoid Arthritis Medication List**

Medicines for treating rheumatoid arthritis include:

**Nonsteroidal anti-inflammatory agents (NSAIDs)**

These medicines that reduce minor aches, pain, and inflammation include:

* Celecoxib (Celebrex)
* Diclofenac (Voltaren)
* Diflunisal (Dolobid)
* Etodolac (Lodine)
* Fenoprofen (Nalfon)
* Flurbiprofen (Ansaid)
* Ibuprofen (Advil)
* Indomethacin (Indocin)
* Ketoprofen (Orudis)
* Ketorolac (Toradol)
* Mefenamic acid (Ponstel)
* Meloxicam (Mobic)
* Nabumetone (Relafen)
* Naproxen (Aleve)
* Oxaprozin (Coxanto)
* Piroxicam (Feldene)
* Sulindac (Clinoril)
* Tolmetin (Tolectin 600)

**Corticosteroids**

Corticosteroids reduce inflammation and manage symptoms such as pain, swelling, tenderness, and stiffness. These medicines include:

* Betamethasone (Alphatrex)
* Methylprednisolone (Depo-Medrol)
* Hydrocortisone (A-Hydrocort)
* Prednisone (Prednicot)
* Prednisolone (Bubbli-Pred)
* Triamcinolone (Aristocort)

**Disease-modifying antirheumatic drugs (DMARDs)**

Medications in this class help reduce inflammation symptoms such as swelling and tenderness, reduce or prevent joint damage, keep joints strong and working, and support everyday functioning. They include:

* Abatacept (Orencia)
* Adalimumab (Humira)
* Anakinra (Kineret)
* Certolizumab (Cimzia)
* Etanercept (Enbrel)
* Methotrexate (Trexall)
* Golimumab (Simponi)
* Hydroxychloroquine (Plaquenil)
* Infliximab (Remicade)
* Leflunomide (Arava)
* Rituximab (Rituxan)
* Sarilumab (Kevzara)
* Sulfasalazine (Azulfidine)
* Tocilizumab (Actemra)

Other rheumatoid arthritis medicines include:

* Non-NSAID pain relievers such as acetaminophen (Tylenol)
* Opioid medications such as codeine, oxycodone, hydrocodone, and tramadol

## **Rheumatoid Arthritis Medication: DMARDs**

If you've been diagnosed with rheumatoid arthritis, your doctor may recommend that you begin treatment with one of several types of DMARDs within a few months of diagnosis. DMARDs are one of the most important drugs for treating rheumatoid arthritis. They can often slow or stop RA from getting worse by interrupting the immune process that promotes inflammation. But they may take up to 6 months to be fully effective.

DMARDs have greatly improved the quality of life for many people with rheumatoid arthritis. These RA drugs are often used along with NSAIDs or glucocorticoids. But with this type of medication, you may not need other anti-inflammatories or analgesics.

Because DMARDs target the immune system, they also can weaken the immune system's ability to fight infections. This means you must be watchful for early signs of infection. In some cases, you may also need regular blood tests to make sure the drug is not hurting blood cells or certain organs such as your liver, lungs, or kidneys.

**Examples of DMARDs:**

| **Name** | **Brand Name(s)** | **Precautions** | **Potential Side Effects** |
| --- | --- | --- | --- |
| Hydroxychloroquine sulfate | Plaquenil | Tell your doctor if you have vision problems; vision may be damaged with high doses or long-term use. | • Blurry vision or increased light sensitivity • Headache • Belly cramps or pain • Loss of appetite, nausea, vomiting, or diarrhea • Itching or rashes |
| Leflunomide | Arava | Tell your doctor if you have: • Active infection • Liver or kidney disease • Cancer  Stop taking leflunomide before trying to conceive. | • Dizziness • Hair loss • Headache • Heartburn • High blood pressure • Gastrointestinal or liver problems • Low blood cell count • Neuropathy • Skin rash |
| Methotrexate | Rheumatrex, Trexall | Tell your doctor if you have: • Abnormal blood counts • Liver or lung disease • Alcoholism • Active infection or hepatitis • Active plans to conceive | • Belly pain • Chills or fever • Dizziness • Hair loss • Headache • Light sensitivity • Itching • Liver problems • Low blood counts  Rare, but serious: • Dry cough, fever, or trouble breathing, which may result from lung inflammation |
| Tofacitinib | Xeljanz | • Xeljanz adds to the risk of serious infections, cancers, lymphoma • May increase cholesterol levels and liver enzymes • May lower blood count | • Upper respiratory tract infection • Headache • Diarrhea • Inflammation of the nasal passage and the upper part of the throat • Blood clots and tears in the intestine |
| Baricitinib | Olumiant | • Olumiant increases the risk of serious infections and cancers such as lymphoma • May raise cholesterol levels and liver enzymes • May lower blood count | • Upper respiratory tract infection • Headache • Diarrhea • Inflammation of the nasal passage and the upper part of the throat • Blood clots and tears in the intestine |
| Upadacitinib | Rinvoq | • Rinvoq increases the risk of serious infections and cancers such as lymphoma and skin cancers | • Upper respiratory infections • Cough • Fever • Nausea • May cause blood clots • Tears in the stomach and intestines are possible |

Minocycline (Minocin) is an antibiotic that is not often prescribed. But it may help RA by stopping inflammation. It can take several months to start working and up to a year before the full effects are known. When taken for long periods, minocycline can discolor the skin.

**Are DMARDs Safe?**

Many people take DMARDs without ever having problems. But because they work throughout the body to fight RA, their powerful action typically does cause some side effects, commonly:

**Stomach upset.** DMARDs may cause nausea, sometimes with vomiting or diarrhea, which can be eased by taking other medicines. Often, these symptoms improve as you get used to the drug. However, if your symptoms are too uncomfortable, your rheumatologist will try a different medication.

**Liver problems.** These are less common than stomach upset. Your doctor will check blood tests on a regular basis to make sure your liver is not being harmed.

**Blood problems.** DMARDs can affect the immune system and raise the risk of infection. Infection-fighting white blood cells may also be decreased. Low red blood cells ([anemia](https://www.webmd.com/a-to-z-guides/understanding-anemia-basics)) can make you feel tired more easily. Regular blood tests by your doctor can help ensure your blood counts are high enough.

You should learn about the possible side effects of any medicine you are taking and discuss them with your doctor until you feel comfortable.

To lessen side effects, DMARDs are sometimes started one at a time and increased gradually. The goal is to lessen both rheumatoid arthritis disease activity and medication side effects. It often takes more than one DMARD to get control of active rheumatoid arthritis.

| **Name** | **Brand Name** | **Precautions** | **Potential Side Effects** |
| --- | --- | --- | --- |
| Abatacept | Orencia | • Tell your doctor if you have a serious infection, such as pneumonia or COPD. • Do not take live vaccines. • Get tested for TB and hepatitis before starting treatment. | • Cough • Dizziness • Headache • Serious infection • IV reaction • Serious infections, like TB, and infections from bacteria, viruses, or fungi |
| Adalimumab | Humira | • Tell your doctor if you have a serious infection, such as pneumonia. • Do not take live vaccines. • Get tested for TB and hepatitis before starting treatment. | • Redness, pain, itching, or bruising where you got the shot • Upper respiratory infection • Serious infections, like TB, and infections from bacteria, viruses, or fungi |
| Adalimumab-atto | Amjevita, a biosimilar to Humira | • Tell your doctor if you have congestive heart failure. • Your doctor should test you for tuberculosis and hepatitis. | • Reactions where you got the shot • Upper respiratory infections • Rash • Headaches • Serious infections, such as tuberculosis and sepsis, and infections from bacteria, viruses, or fungi • Higher risk for lymphoma and other cancers |
| Anakinra | Kineret | • Tell your doctor if you have a serious infection or a history of it. • Do not take live vaccines. | • Redness, swelling, pain, or bruising where you got the shot • Low white blood cell count • Upper respiratory infection • Serious infections, like TB, and infections from bacteria, viruses, or fungi |
| Etanercept | Enbrel | Do not take if you have congestive heart failure and tell your doctor if you have: • Diabetes, HIV, or a weakened immune system • Hepatitis B, or you have had it • Been exposed to TB • A serious nervous system disorder  Do not take live vaccines. | • Redness, pain, itching, swelling, or bruising at injection site • Headache • Rashes • Nausea • Fatigue • Belly pain  Rare complications: • Higher risk of malignancy • Neurological events • Increased risk of serious infections, like TB, and infections from bacteria, viruses, or fungi |
| Etanercept-szzs | Erelzi, a biosimilar version of Enbrel | Do not take if you have congestive heart failure and tell your doctor if you: • Have diabetes, HIV, or a weakened immune system • Have or have had hepatitis B • Have been exposed to TB • A serious nervous system disorder  Do not take live vaccines. | • Redness, pain, itching, swelling, or bruising at the injection site • Headache • Rashes • Nausea • Fatigue • Belly Pain  Rare complications: • Higher risk of malignancy • Neurological events • Increased risk of serious infections, such as TB, and infections from bacteria, viruses, or fungi |
| Infliximab | Remicade | • Tell your doctor if you have a serious infection or a history of it. • Tell your doctor if you are taking concomitant immunosuppressants such as corticosteroids or methotrexate. • Do not shake before administering. | • Headache • Rashes • Nausea • Fatigue • Belly pain • Fever • Itching  Rare complications include increased risks for: • Development of tuberculosis • Invasive fungal infections • Malignancies |
| Infliximab-abda | Renflexis | • Tell your doctor if you have a serious infection or a history of it. • Tell your doctor if you are taking concomitant immunosuppressants such as corticosteroids or methotrexate. • Do not shake before administering. | • Headache • Rashes • Nausea • Fatigue • Belly pain • Fever • Itching  Rare complications include: • Development of tuberculosis • Invasive fungal infections • Malignancies |
| Infliximab-dyyb | Inflectra | • Tell your doctor if you have a serious infection or a history of it. • Tell your doctor if you are taking concomitant immunosuppressants such as corticosteroids or methotrexate. • Do not shake before administering. | • Headache • Rashes • Nausea • Fatigue • Belly pain • Fever • Itching  Rare complications include increased risk for: • Development of tuberculosis • Invasive fungal infections • Malignancies |
| Rituximab | Rituxan | • Tell your doctor if you have a serious infection, or heart or lung disease. • Tell your doctor if you are taking immunosuppressants such as methotrexate or corticosteroids. | • Belly pain • Chills or fever • Headache • Infection • Itching  Serious side effects: • IV reactions • Tumor lysis syndrome • Severe skin reactions • Increased risk of serious infections, like TB, and infections from bacteria, viruses, or fungi |
| Rituximab-abbs | Truxima | • Tell your doctor if you have a serious infection, or heart or lung disease. • Do not take live vaccines. | • Belly pain • Chills or fever • Headache • Infection • Itching  Serious side effects: • IV reactions • Tumor lysis syndrome • Severe skin reactions • Increased risk of serious infections, like TB, and infections from bacteria, viruses, or fungi |
| Rituximab-pvvr | Ruxience | • Tell your doctor if you have a serious infection, or heart or lung disease. • Do not take live vaccines. | • Belly pain • Chills or fever • Headache • Infection • Itching  Serious side effects: • IV reactions • Tumor lysis syndrome • Severe skin reactions • Serious infections, like TB, and infections from bacteria, viruses, or fungi |
| Infliximab-dyyb | Inflectra, a biosimilar to Remicade | • Do not take this medicine if you have moderate to severe heart failure. • Tell your doctor if you have had tuberculosis or hepatitis. | • Diarrhea • Headache • Fatigue • Nausea • Rash at the IV site • Upper respiratory infections • Urinary tract infections • Tuberculosis • Sepsis • Fungal infections |
| Golimumab | Simponi  Simponi Aria | •Tell your doctor if you have any infections or health conditions, like heart disease, multiple sclerosis (MS), or diabetes • Get tested for TB before starting treatment. • Do not take live vaccines. • See your doctor right away if you have signs of an infection while taking this drug. | • Redness where you got the shot • Upper respiratory infections • Nausea • Abnormal liver tests  Rare complications: • Higher risk of serious infections, such as TB, as well as infections from bacteria, viruses, or fungi, and reactivation of a previous hepatitis B infection • Lupus • Multiple sclerosis |
| Certolizumab pegol | Cimzia | • Tell your doctor if you have or are being treated for an infection, or if you have diabetes, HIV, hepatitis B, cancer, or TB. | • Nerve problems such as MS • Allergic reactions • Autoimmune problems like lupus • Reactivation of hepatitis B • Serious infections, like TB, and infections from bacteria, viruses, or fungi |
| Tocilizumab | Actemra | • Tell your doctor if you have a serious infection, a history of gastrointestinal perforation, or if you are pregnant or plan on becoming pregnant. • Do not take live vaccines. | • Upper respiratory tract infection • Inflammation of the nose or throat • High blood pressure • Headache • Abnormal liver enzyme level • Increased risk of serious infections, such as TB, and infections from bacteria, viruses, or fungi |
| Sarilumab | Kevzara | Tell your doctor if you: • Have had TB, or if your immune system is weakened by conditions such as diabetes, hepatitis, or HIV • Are being treated for an infection. • Plan on becoming pregnant. | • Upper respiratory tract infection • Urinary tract infection • Nasal congestion • Sore throat • Runny nose • Redness where you got the shot |

## **Rheumatoid Arthritis Medication: Steroids for Rheumatoid Arthritis**

They are strong anti-inflammatory drugs that can also block other immune responses. Several man-made steroids called corticosteroids help relieve RA symptoms and may stop or slow joint damage. You receive these RA drugs by pill or as a shot.

Because of the risk of side effects, it is generally recommended that you use these RA drugs only for brief periods — such as when your disease flares up or until DMARDs are fully effective. If your side effects are severe, don't stop taking the drug suddenly. Talk first with your doctor about what to do.

**Examples of corticosteroids:**

| **Name** | **Brand Name(s)** | **Precautions** | **Potential Side Effects** |
| --- | --- | --- | --- |
| Betamethasone injectable | Celes tone | Tell your doctor if you have: • Fungal infection • A history of TB • Underactive thyroid • Diabetes • Stomach ulcer • High blood pressure • Osteoporosis | • Bruising • Cataracts • Increased cholesterol • Atherosclerosis • High blood pressure • Increased appetite or indigestion • Mood swings or nervousness • Muscle weakness • Osteoporosis • Infections |
| Prednisone | Rayos | Tell your doctor if you have: • Fungal infection • A history of TB • Underactive thyroid • Diabetes • Stomach ulcer • High blood pressure • Osteoporosis | • Bruising • Cataracts • Increased cholesterol • Atherosclerosis • High blood pressure • Increased appetite or indigestion • Mood swings or nervousness • Muscle weakness • Osteoporosis • Infections |
| Methylprednisolone | Medrol | Tell your doctor if you have: • Skin rash • Swollen face, lower legs, or ankles • Trouble seeing • A cold or infection that lasts a long time • Weak muscles • Black poop | • Upset stomach • Stomach irritation • Vomiting • Headache • Trouble sleeping • Depression • Anxiety • Hair growth • Bruising • Skipped or irregular periods |

## **Rheumatoid Arthritis Medication: NSAIDs**

NSAIDs work by blocking an enzyme that promotes inflammation. By reducing inflammation, NSAIDs help reduce swelling and pain. But they are not effective in reducing joint damage. These drugs alone are not effective in treating the disease. They should be taken along with other rheumatoid arthritis medications.

As with glucocorticoids, you should use them for brief periods — they can cause severe digestive tract problems. Which type your doctor prescribes may depend on your medical history. If you have a history of stomach ulcers or liver, kidney, or heart problems, it's best to not take these drugs. Ask your doctor if any new NSAIDs with fewer side effects are available.

**Examples of NSAIDs:**

| **Name** | **Brand Name(s)** | **Precautions** | **Potential Side Effects** |
| --- | --- | --- | --- |
| Celecoxib | Celebrex | • Tell your doctor if you have had a heart attack, stroke, angina, blood clot, or high blood pressure or if you have sensitivity to NSAIDs or sulfa drugs. • Do not take with other NSAIDs. • Do not take late in pregnancy. | • Increased risk of heart attack and stroke • Indigestion, diarrhea, and stomach pain • Serious skin reactions |
| Diclofenac sodium | Voltaren | Tell your doctor if you: • Drink alcohol • Use blood thinners • Take ACE inhibitors, lithium, warfarin, or furosemide • Have sensitivity to aspirin; kidney, liver, or heart disease; asthma; high blood pressure; or ulcers  Do not take with other NSAIDs. | • Belly cramps, diarrhea • Dizziness or drowsiness • Heartburn, indigestion, nausea, vomiting, ulcer, or bleeding • Increased risk of blood clots, heart attacks, and stroke • Greater risk of complications for people with cardiovascular disease |
| Ibuprofen | Advil, Motrin | Tell your doctor if you: • Drink alcohol • Use blood thinners • Take ACE inhibitors, lithium, warfarin, or furosemide • Have sensitivity to aspirin; kidney, liver, or heart disease; asthma; high blood pressure; ulcers • Do not take with other NSAIDs. | • Higher risk of heart attack and stroke • Belly cramps, diarrhea • Dizziness or drowsiness • Heartburn, indigestion, nausea, vomiting, ulcer, or bleeding • Increased risk of blood clots, heart attacks, and stroke • Greater risk of complications for people with cardiovascular disease |

## **Rheumatoid Arthritis Medication: Analgesics**

Analgesics reduce pain, but they do not reduce swelling or joint damage.

There are a variety of over the counter and prescription analgesics. Narcotics are the most powerful type of analgesic. Use these carefully and be sure to let your doctor know if you have any history of alcoholism or drug abuse.

**Examples of analgesics:**

| **Name** | **Brand Name(s)** | **Precautions** | **Potential Side Effects** |
| --- | --- | --- | --- |
| Acetaminophen | Tylenol, Feverall | • Tell your doctor if you have three or more drinks of alcohol daily. • Avoid taking more than one product with acetaminophen. | Side effects uncommon if taken as directed. |
| Tramadol | Ultram | • Tell your doctor if you use central nervous system depressants, tranquilizers, sleeping medications, muscle relaxants, or narcotic pain medications or if you have a history of drug or alcohol abuse. • Do not stop suddenly or increase the dose on your own. • Do not drive or use heavy machinery until you know how your body reacts to the drug. | • Constipation • Diarrhea • Drowsiness • Increased sweating • Loss of appetite • Nausea |
| Oxycodone, hydrocodone, and other narcotics | OxyContin, Roxicodone | • Tell your doctor if you use central nervous system depressants, tranquilizers, sleeping medications, muscle relaxants, or narcotic pain medications or if you have a history of drug or alcohol abuse. • Never chew or cut tablets; a high dose can be fatal if released rapidly. | • Constipation • Dizziness • Drowsiness • Dry mouth • Headache • Increased sweating • Itchy skin • Nausea or vomiting • Shortness of breath |

## **New Rheumatoid Arthritis Medications**

Rheumatoid arthritis has no cure. Today's treatments, including NSAIDs, corticosteroids, and DMARDs, mostly reduce inflammation symptoms, prevent bone damage, and help the joints keep working for as long as possible. However, these treatments don’t work well for everyone — around 20%-40% of people with this condition don’t get any benefits — and they come with unpleasant side effects such as high blood pressure, stomach pain, and eye problems.

Researchers have been looking to develop newer and better treatment options. Some of these include:

* Cell-targeted therapies. These treatments target the immune cells involved in inflammation and cause symptoms to worsen. They reduce inflammation and slow the disease's progress.
* Cell-based treatments. This type of therapy involves using a cell type for medicine. They include mesenchymal stem cells, adoptive transfer of regulatory T cells (Treg), and chimeric antigen receptor (CAR) T cell therapy. Doctors may only consider this treatment option for people whose rheumatoid arthritis symptoms don’t improve with standard treatments such as DMARDs.
* Cannabinoid-based drugs. These are medicines made of substances found in the cannabis plant. These may help reduce symptoms such as pain and sleep problems in people with arthritis and reduce the processes causing the disease. These medicines are still being studied to see how safe they are and how well they work to treat rheumatoid arthritis.

Still, some people with rheumatoid arthritis don’t benefit much from these newer treatments. So, researchers are working to better understand how the disease happens in the body and how to personalize treatments, especially for those whose diseases are difficult to treat and don’t

**Lifestyle and home remedies**

Self-care measures, when used with your rheumatoid arthritis medicines, can help you manage your symptoms:

* **Exercise regularly.** Gentle exercise can help strengthen the muscles around your joints. And it can help you feel less tired. Check with your healthcare team before you start exercising. Walking is a good way to begin. Don't exercise tender, injured or inflamed joints.
* **Apply heat or cold.** Heat can help ease your pain and relax tense, painful muscles. Cold may dull pain. Cold also numbs and can ease swelling.
* **Relax.** Find ways to cope with pain by lowering your stress. Techniques such as guided imagery, deep breathing and muscle relaxation all can help control pain.
* **Don't smoke.** Smoking can make rheumatoid arthritis worse. If you smoke, ask your healthcare team to help you quit.

**Alternative medicine**

Some common complementary and alternative treatments that have shown promise for rheumatoid arthritis include:

* **Fish oil.** Some studies have found that fish oil supplements may ease rheumatoid arthritis pain and stiffness. Side effects can include nausea, belching and a fishy taste in the mouth. Fish oil can get in the way of medicines you take. So, check with your healthcare professional before trying it.
* **Tai chi.** This movement therapy involves gentle exercises and stretches and deep breathing. Many people use tai chi to relieve stress. Small studies have found that tai chi may improve mood and quality of life in people with rheumatoid arthritis. When led by a trained leader, tai chi is safe. But don't do any moves that cause pain or make it worse.

**Complications**

Rheumatoid arthritis increases the risk of getting:

* **Osteoporosis.** Rheumatoid arthritis itself, and some medicines used to treat it, can increase the risk of this condition. Osteoporosis weakens bones and makes them more likely to break.
* **Rheumatoid nodules.** These firm bumps of tissue most often form around pressure points, such as the elbows. But these nodules can form anywhere in the body, including the heart and lungs.
* **Dry eyes and mouth.** People who have rheumatoid arthritis are much more likely to get a condition that lowers the amount of moisture in the eyes and mouth. This is called secondary Sjogren's syndrome.
* **Infections.** Rheumatoid arthritis and many of the medicines used to treat it can harm the immune system. This can lead to more infections. Vaccinations can help prevent infections such as the flu, pneumonia, shingles and COVID-19.
* **Carpal tunnel syndrome.** If rheumatoid arthritis affects the wrists, the swelling can press on the nerve to the hand and fingers.
* **Heart problems.** Rheumatoid arthritis can raise the risk of hardened and blocked arteries. It also can raise the risk of swelling and irritation, called inflammation, of the sac around the heart.
* **Lung disease.** People with rheumatoid arthritis have a higher risk of swelling and irritation, called inflammation, of lung tissues. This can cause scarring and lead to shortness of breath that gets worse over time.
* **Lymphoma.** Rheumatoid arthritis raises the risk of a group of blood cancers that happen in the lymph system. This is called lymphoma. People with rheumatoid arthritis may have a higher risk of other cancers, as well.

## **Procedures for Rheumatoid Arthritis (RA)**

## 1. Joint Replacement (Arthroplasty)

* Description:  
  Removal of damaged joint surfaces and replacement with artificial components (metal, plastic, ceramic). Commonly performed on hips, knees, shoulders, wrists, fingers, ankles, toes.
* Purpose:  
  Relieves pain, restores function, and corrects deformity in severely damaged joints.
* Recovery Timeline:
  + Hospital stay: 1–4 days (sometimes outpatient).
  + Early mobilization: Walking with assistance within 1–2 days post-op.
  + Return to most daily activities: 6–12 weeks.
  + Full recovery and maximal improvement: 6 months to 1 year.
* Notes:  
  RA patients often have good hospital recovery outcomes, sometimes better than osteoarthritis patients.

## 2. Arthrodesis (Joint Fusion)

* Description:  
  Fusion of two bones forming a joint to eliminate movement and pain. Commonly used in ankles, wrists, fingers, thumbs, and spine.
* Purpose:  
  Increases joint stability and reduces pain but results in loss of joint motion.
* Recovery Timeline:
  + Immobilization: 6–12 weeks.
  + Gradual return to activities over several months.
* Notes:  
  Often used when joint replacement is not feasible or as a salvage procedure.

## 3. Synovectomy

* Description:  
  Surgical removal of inflamed synovial tissue that damages cartilage and bone. Can be done open or arthroscopically.
* Purpose:  
  Reduces pain, swelling, and joint damage, especially in early-stage RA with intact cartilage.
* Recovery Timeline:
  + Arthroscopic synovectomy: Shorter recovery, less pain, outpatient or short hospital stay.
  + Open synovectomy: Longer recovery due to muscle cutting, more discomfort.
  + Symptoms may recur over years as synovium can regrow.
* Notes:  
  Usually adjunct to medical therapy; may delay progression and reduce medication doses.

## 4. Tendon Surgery

* Description:  
  Repair or release of tendons damaged or ruptured due to chronic inflammation (e.g., rotator cuff, hand tendons).
* Purpose:  
  Restores tendon function, reduces pain, and corrects deformities.
* Recovery Timeline:
  + Varies by tendon and procedure; often weeks to months for healing and rehabilitation.

## 5. Osteotomy

* Description:  
  Bone-cutting surgery to realign bones and correct deformities, often around the knee.
* Purpose:  
  Redistributes joint load to healthier areas, delays joint replacement.
* Recovery Timeline:
  + Partial weight-bearing for 6–8 weeks.
  + Full recovery in 3–6 months.

## 6. Arthroscopy

* Description:  
  Minimally invasive surgery using a camera to inspect and sometimes treat joint damage (e.g., remove debris, repair cartilage).
* Purpose:  
  Diagnostic or therapeutic, usually in large joints like knees.
* Recovery Timeline:
  + Outpatient procedure.
  + Recovery in days to weeks depending on extent.

## 7. Carpal Tunnel Release

* Description:  
  Surgery to relieve pressure on the median nerve in the wrist, often caused by RA-related inflammation.
* Recovery Timeline:
  + Outpatient procedure.
  + Return to normal activities in weeks.

## **Outlook / Prognosis**

Although there isn’t currently a cure for rheumatoid arthritis, there are many effective methods for decreasing your pain and inflammation and slowing down the disease process. Early diagnosis and effective treatment are very important.

If you don’t see a provider for RA treatment, the disease can cause permanent damage to your cartilage and, eventually, your joints. RA can also harm organs like your lungs and heart.

**Living With**

It’s important to see your healthcare provider on a regular basis to monitor your symptoms. They’ll also want to know about any side effects you may experience from your medications. Your provider can adjust your dosage or change the types of medications you take. Continue to take your medications until you speak with your provider.

You can also take care of yourself by following a healthy eating plan and getting some physical activity every day. If you smoke, it’s important that you quit.

### **When to see a doctor**

Make an appointment with your healthcare professional if you have ongoing pain and swelling in your joints that is not getting better after several weeks.

## **Questions & Answers**

Q. What is rheumatoid arthritis?  
A. Rheumatoid arthritis is a chronic autoimmune disease that causes inflammation of the joints, leading to pain, swelling, stiffness, and potential joint damage.

Q. What causes rheumatoid arthritis?  
A. The exact cause is unknown, but it involves the immune system mistakenly attacking the synovium (joint lining). Genetic and environmental factors contribute.

Q. What are the common symptoms of RA?  
A. Symptoms include joint pain, swelling, morning stiffness lasting more than 30 minutes, fatigue, fever, and symmetrical joint involvement (often hands and feet).

Q. How is RA diagnosed?  
A. Diagnosis is based on clinical evaluation, blood tests (rheumatoid factor, anti-CCP antibodies, ESR, CRP), and imaging (X-rays, ultrasound, MRI) to assess joint inflammation and damage.

Q. How does RA differ from osteoarthritis?  
A. RA is an autoimmune inflammatory disease affecting joints symmetrically, often with systemic symptoms. Osteoarthritis is a degenerative joint disease caused by wear and tear, usually without systemic inflammation.

Q. What treatments are available for RA?  
A. Treatment includes disease-modifying antirheumatic drugs (DMARDs) like methotrexate, biologics, corticosteroids, NSAIDs, physical therapy, and sometimes surgery.

Q. Can RA be cured?  
A. There is no cure, but early and aggressive treatment can control symptoms, prevent joint damage, and improve quality of life.

Q. What lifestyle changes help manage RA?  
A. Regular exercise, balanced diet, quitting smoking, stress management, and adequate rest can help reduce symptoms and improve function.

Q. Are there complications associated with RA?  
A.Yes, including joint deformities, osteoporosis, cardiovascular disease, lung disease, and increased infection risk due to immune suppression.

Q. When is surgery considered in RA?  
A. Surgery may be needed for severe joint damage, deformities, or to relieve pain and improve function when medical treatment is insufficient.

Q. How often should patients with RA see their doctor?  
A. Regular follow-ups every 3–6 months or as recommended to monitor disease activity and adjust treatment.

Q. What support resources are available for people with RA?  
A. Patient education programs, support groups, counseling, and organizations such as the Arthritis Foundation provide valuable resources.

## **Doctor-Patient Conversation on Rheumatoid Arthritis (RA)**

Doctor:  
I understand you’ve been experiencing joint pain and stiffness. Can you tell me more about your symptoms?

Patient:  
Yes, my hands and wrists have been painful and swollen, especially in the mornings. The stiffness lasts for over an hour, and it’s been going on for several months.

Doctor:  
That’s important information. Morning stiffness lasting more than 30 minutes and symmetrical joint swelling are common signs of rheumatoid arthritis, an autoimmune condition where your immune system attacks the joints.

Patient:  
Is this serious? Can it get worse?

Doctor:  
RA can be serious if untreated because it can cause joint damage and affect your overall health. But with early diagnosis and treatment, we can control inflammation, relieve symptoms, and prevent joint damage.

Patient:  
How do you diagnose it?

Doctor:  
We’ll do a physical exam and order blood tests to check for markers like rheumatoid factor and anti-CCP antibodies. Imaging like X-rays or ultrasound can show joint inflammation or damage.

Patient:  
What treatments are available? Are there side effects?

Doctor:  
Treatment usually starts with medications called DMARDs, like methotrexate, which slow disease progression. We may also use NSAIDs or corticosteroids for symptom relief. Some medications have side effects, so we monitor you closely and adjust treatment as needed.

Patient:  
Will I need surgery?

Doctor:  
Most patients manage well with medications and lifestyle changes. Surgery is reserved for severe joint damage or deformities that don’t respond to treatment.

Patient:  
What can I do to help myself?

Doctor:  
Regular low-impact exercise, a balanced diet, quitting smoking, and managing stress all help. Physical therapy can improve joint function and reduce pain.

Patient:  
How often will I need to see you?

Doctor:  
Initially, every few months to monitor your response to treatment. Once stable, visits may be spaced out. Always contact us if symptoms worsen.

Patient:  
Thank you, doctor. I feel more hopeful knowing there are treatments.

Doctor:  
You’re welcome. We’ll work together to manage your RA and maintain your quality of life.

## **Genomic Data and Genetic Counseling for Rheumatoid Arthritis (RA)**

## 1. Genetic Basis of RA

* Heritability is estimated at about 60%, with genetic factors playing a major role alongside environmental triggers.
* The HLA-DRB1 gene, particularly certain alleles known as the "shared epitope" (SE) alleles such as HLA-DRB1\*01 and HLA-DRB1\*04, contribute substantially to susceptibility (11–37% of heritability). Other HLA alleles like HLA-DRB1\*13 and DRB1\*15 are also implicated.
* Non-HLA genes associated with RA include PTPN22, TRAF1, STAT4, CTLA4, IL23R, CCR6, PADI4, IRF5, FCGR, and others identified by genome-wide association studies (GWAS).
* Genetic variants may influence not only susceptibility but also disease severity, autoantibody status (e.g., anti-citrullinated protein antibody [ACPA] positivity), and response to therapy (pharmacogenomics).
* There is a notable gene-environment interaction, especially with smoking, which can trigger ACPA production and increase risk in genetically susceptible individuals.

## 2. Genomic Data Applications

* Risk Prediction: Genetic testing can identify individuals at higher risk, particularly those with family history or early symptoms.
* Disease Subtyping: Certain genetic profiles correlate with seropositive vs. seronegative RA, guiding prognosis and treatment.
* Pharmacogenomics: Genetic markers may predict response or adverse reactions to DMARDs and biologic therapies, enabling personalized medicine approaches.

## 4. Emerging Therapies and Research

* Gene Therapy:
  + Experimental approaches aim to deliver anti-inflammatory genes to affected joints to reduce inflammation and disease activity.
  + Clinical trials are ongoing, but gene therapy is not yet a standard treatment.

## **Epidemiology**

Worldwide, the annual incidence of RA is approximately 3 cases per 10,000 population, and the prevalence rate is approximately 1%, increasing with age and peaking between the ages of 35 and 50 years. RA affects all populations, though it is much more prevalent in some groups (e.g., 5-6% in some Native American groups) and much less prevalent in others (e.g., Black persons from the Caribbean region).

First-degree relatives of individuals with RA are at 2- to 3-fold higher risk for the disease. Disease concordance in monozygotic twins is approximately 15-20%, suggesting that non genetic factors play an important role. Because the worldwide frequency of RA is relatively constant, a ubiquitous infectious agent has been postulated to play an etiologic role.

Women are affected by RA approximately 3 times more often than men are.For example, a nationwide study from Norway reported that the point prevalence of RAl was 1.10% in women and 0.46% in men.However, sex differences in RA diminish in older age groups.In investigating whether the higher rate of RA among women could be linked to certain reproductive risk factors, a study from Denmark found that the rate of RA was higher in women who had given birth to just 1 child than in women who had delivered 2 or 3 offspring.However, the rate was not increased in women who were nulliparous or who had a history of lost pregnancies.

Time elapsed since pregnancy is also significant. In the 1- to 5-year postpartum period, a decreased risk for RA has been recognized, even in those with higher-risk HLA markers.

The Danish study also found a higher risk of RA among women with a history of preeclampsia, hyperemesis during pregnancy, or gestational hypertension.In the authors’ view, this portion of the data suggested that a reduced immune adaptability to pregnancy may exist in women who are predisposed to the development of RA or that there may be a link between fetal microchimerism (in which fetal cells are present in the maternal circulation) and RA.

## **Diagnostic Considerations**

Differentiation of rheumatoid arthritis (RA) from other diseases of connective tissue can be difficult; however, certain clinical features are helpful.

Rheumatic fever is characterized by the migratory nature of the arthritis, an elevated anti-streptolysin O titer, and a more dramatic and prompt response to aspirin. Carditis and erythema marginatus may occur in adults, but chorea and subcutaneous nodules virtually never do.

Systemic lupus erythematosus (SLE) is suggested by the presence of the following:

* Butterfly rash
* Discoid lupus erythematosus
* Photosensitivity
* Alopecia
* High anti-DNA titer
* Renal disease
* Central nervous system (CNS) abnormalities

Degenerative joint disease (DJD) is not associated with constitutional manifestations; in contrast to the morning stiffness of RA, the joint pain from DJD is characteristically relieved by rest. Signs of articular inflammation prominent in RA are usually minimal in DJD, and in contrast to RA, osteoarthritis spares the wrist and the MCP joints.

During the early years of disease, gouty arthritis is almost always intermittent and monoarticular; in later years, it can become a chronic polyarticular process that mimics RA. Gouty tophi can at times resemble rheumatoid nodules. The early history of intermittent monoarthritis and the presence of synovial urate crystals are distinctive features of gout.

Septic arthritis can be distinguished by chills and fever, demonstration of the causative organism in joint fluid, and the frequent presence of a primary focus elsewhere (e.g., gonococcal arthritis). Chronic Lyme disease typically involves only 1 joint, most commonly the knee, and is associated with positive serologic tests. Human parvovirus B19 infection in adults can occasionally mimic RA.

Polymyalgia rheumatica, which is relatively common in persons older than 50 years, occasionally causes polyarthritis. However, these patients have chiefly proximal muscle pain and stiffness and remain negative for rheumatoid factor (RF).

A variety of cancers produce paraneoplastic syndromes, including polyarthritis. One form is hypertrophic pulmonary osteoarthropathy, which is most often produced by lung and gastrointestinal carcinomas. Hypertrophic pulmonary osteoarthropathy is characterized by a rheumatoid like arthritis associated with clubbing, periosteal new bone formation, and a negative RF test. Diffuse swelling of the hands with palmar fasciitis has also been reported with a variety of cancers, especially ovarian carcinoma.

## **Differential Diagnoses**

* Fibromyalgia
* Lyme Disease
* Myelodysplastic Syndrome (MDS)
* Osteoarthritis
* Paraneoplastic Syndromes
* Relapsing Polychondritis
* Polymyalgia Rheumatica (PMR)
* Psoriatic Arthritis
* Sarcoidosis
* Sjogren Syndrome
* Systemic Lupus Erythematosus (SLE)

#### **Recommendations for DMARD Initiation**

| **Strong Recommendations** |
| --- |
| • For DMARD-naive patients with moderate to high disease activity, methotrexate (MTX) is recommended over [hydroxychloroquine](https://www.rheumatologyadvisor.com/home/topics/systemic-lupus-erythematosus/arthritis-lupus-hydroxychloroquine-retinal-toxicity/) (HCQ) or sulfasalazine, b/tsDMARDs, and MTX plus b/tsDMARD combination therapy. • Initiation of csDMARDs without longer-term (≥3 mo) GCs is recommended over initiation with longer-term GCs. |
| **Conditional Recommendations** |
| • For DMARD-naive patients with moderate to high disease activity, MTX is recommended over leflunomide, csDMARDs, and MTX plus tumor necrosis factor inhibitor (TNFi) combination therapy. • For DMARD-naive patients with low disease activity, HCQ is recommended over other csDMARDs; sulfasalazine over MTX; MTX over leflunomide. • For csDMARD-treated but MTX-naive patients, MTX monotherapy is recommended over MTX plus b/tsDMARD combination therapy • Initiation of csDMARDs without short-term (<3 mo) GCs is recommended over initiation with short-term GCs. |

#### **Recommendations for MTX Administration**

| **Conditional Recommendations** |
| --- |
| • For patients initiating MTX, oral MTX is recommended over subcutaneous MTX. • Initiation/titration of MTX to a weekly dose of at least 15 mg within 4 to 6 weeks is recommended over initiation/titration of MTX to less than 15 mg/week. • For patients with intolerance to oral weekly MTX, a split dose of oral or subcutaneous injections of MTX over a 24-hour period and/or an increased dose of folic/folinic acid is recommended over switching to alternative DMARDs. • For patients receiving oral MTX and not at target, switching to subcutaneous MTX is recommended over addition of or switching to alternative DMARDs. |

#### **Recommendations for Treatment Modifications**

| **Strong Recommendations** |
| --- |
| • For patients not previously treated with b/tsDMARDs, a treat-to-target (TTT) approach is recommended over standard care. |
| **Conditional Recommendations** |
| • For patients with an inadequate response to b/tsDMARDs, a TTT approach is recommended over standard care. • A minimal initial treatment goal of low disease activity is recommended over a goal of remission. • For patients receiving maximally tolerated doses of MTX and not at target, addition of a b/tsDMARD is recommended over triple therapy. • For patients receiving b/tsDMARDs and not at target, switching to a b/ts DMARD of a different class is recommended over switching to the same class. • For patients receiving GCs to remain at target, addition of or switching to DMARDs is recommended over continuation of GCs. • For patients receiving DMARDs and not at target, addition of or switching to DMARDs with or without intra-articular (IA) GCs is recommended over use of IA GCs alone. |

#### **Recommendations for Tapering DMARDs**

| **Conditional Recommendations** |
| --- |
| • Continuation of a DMARD at the current dose is recommended over dose reduction; dose reduction is recommended over gradual discontinuation; gradual discontinuation is recommended over abrupt discontinuation of a [DMARD](https://www.rheumatologyadvisor.com/home/conference-highlights/eular-2021/tofacitinib-baricitinib-treatment-rheumatoid-arthritis-clinical-practice-eular-2021/). • For patients receiving triple therapy who intend to discontinue a DMARD, gradual discontinuation of sulfasalazine is recommended over that of HCQ. • For patients receiving MTX plus a b/tsDMARD who intend to discontinue the DMARD, gradual discontinuation of MTX is recommended over discontinuation of the b/tsDMARD. |

#### **Recommendations for Specific Patient Populations**

| **Conditional Recommendations** |
| --- |
| Subcutaneous Nodules • For patients with moderate to high disease activity, MTX is recommended over alternative DMARDs. • For patients with progressive disease receiving MTX, switching to a non-MTX DMARD is recommended over continuation of MTX. |
| Pulmonary Disease • For patients with mild or stable airway or parenchymal lung disease with moderate to high disease activity, MTX is recommended over alternative DMARDs for inflammatory arthritis treatment. |
| Heart Failure • For patients with New York Heart Association (NYHA) class 3 or 4 heart failure with an inadequate response to csDMARDs, the addition of a non-tumor necrosis factor inhibitor (TNFi) b/tsDMARD is recommended over the addition of a TNFi. • For patients receiving a TNFi who develop heart failure, switching to a non-TNFi b/tsDMARD is recommended over continuation of a TNFi. |
| Lymphoproliferative Disorder • For patients with a previous lymphoproliferative disorder with moderate to high disease activity, rituximab is recommended over other DMARDs. |
| Nonalcoholic Fatty Liver Disease (NAFLD) • For DMARD-naive patients with NAFLD, normal liver enzymes and liver function tests, and no advanced liver fibrosis, with moderate to high disease activity, MTX is recommended over alternative DMARDs. |
| Persistent Hypogammaglobulinemia Without Infection • For patients at target, continuation of rituximab is recommended over switching to a different b/tsDMARD. |
| Previous Serious Infection • For patients with a serious infection in the previous 12 months with moderate to high disease activity despite csDMARD monotherapy, the addition of csDMARDs is recommended over the addition of a b/tsDMARD. • For these patients, addition of or switching to DMARDs is recommended over the initiation/dose escalation of GCs. |
| Nontuberculous Mycobacterial Lung Disease • Lowest dose or discontinuation of GCs is recommended over continuation of GCs. • For patients with moderate to high disease activity despite csDMARD monotherapy, addition of csDMARDs is recommended over the addition of a b/tsDMARD. However, abatacept is recommended over other b/tsDMARDs. |
| Hepatitis B Infection – Strong Recommendations • For patients who test positive for the hepatitis B core antibody (regardless of hepatitis B surface antigen status) and initiating rituximab, prophylactic antiviral therapy is recommended over frequent monitoring alone. • For patients who test positive for both the hepatitis B core antibody and the surface antigen and initiating b/ts DMARDs, prophylactic antiviral therapy is recommended over frequent monitoring alone.  Hepatitis B Infection – Conditional Recommendation • For patients who test positive for the hepatitis B core antibody and negative for the hepatitis B surface antigen and initiating a bDMARD other than rituximab or a tsDMARD, frequent monitoring alone is recommended over prophylactic antiviral therapy. |

**DOCTOR-PATIENT CONVERSATION**

## Patient:

Hello, doctor. I’ve been having pain and stiffness in my hands and wrists for several weeks now. It’s worse in the mornings and lasts for over an hour.

## Doctor:

I see. Morning stiffness lasting more than 30 minutes is often a sign of inflammatory arthritis. Have you noticed swelling or redness in your joints?

## Patient:

Yes, my knuckles and wrists are swollen and sometimes feel warm. I also feel tired and sometimes have a low-grade fever.

## Doctor:

Those symptoms are consistent with rheumatoid arthritis, an autoimmune condition that causes joint inflammation. Do you have any family history of arthritis or autoimmune diseases?

## Patient:

My mother had arthritis, but I’m not sure if it was rheumatoid arthritis.

## Doctor:

Thank you for sharing. RA often affects small joints symmetrically, especially in the hands and feet. Have you experienced any difficulty with daily tasks like buttoning clothes or opening jars?

## Patient:

Yes, it’s been harder to grip things and do fine movements.

## Doctor:

That’s important to note. I’d like to order some blood tests, including rheumatoid factor (RF), anti-CCP antibodies, ESR, and CRP, to check for inflammation and autoimmune markers. We’ll also do X-rays of your hands and wrists.

## Patient:

Will these tests confirm if I have RA?

## Doctor:

They help us make the diagnosis but are not definitive alone. We consider your symptoms, physical exam, lab tests, and imaging together. Early diagnosis and treatment are crucial to prevent joint damage.

## Patient:

What treatments are available if I have RA?

## Doctor:

Treatment includes disease-modifying antirheumatic drugs (DMARDs) like methotrexate, which slow disease progression. We may also use NSAIDs or corticosteroids for symptom relief. Physical therapy and lifestyle changes are important too.

## Patient:

Are there side effects to these medications?

## Doctor:

Yes, DMARDs can affect your liver and immune system, so regular monitoring is needed. NSAIDs can cause stomach upset, and steroids have their own risks if used long-term. We’ll discuss these in detail if treatment starts.

## Patient:

How long will I need treatment?

## Doctor:

RA is a chronic condition requiring long-term management. The goal is to achieve remission or low disease activity to maintain your quality of life.

## Patient:

Thank you, doctor. What should I do next?

## Doctor:

I’ll arrange the tests and schedule a follow-up in a few weeks to discuss results and start treatment if needed. Meanwhile, try to keep active within your limits and avoid joint strain.

## Patient:

Okay, I appreciate your help.

## Doctor:

You’re welcome. We’ll work together to manage your symptoms and keep you functioning well.

**REFERENCES**

https://emedicine.medscape.com/article/331715-guidelines

<https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Rheumatoid-Arthritis>

<https://www.arthritis-health.com/types/rheumatoid/surgery-rheumatoid-arthritis-ra>

<https://www.nhs.uk/conditions/rheumatoid-arthritis/treatment/>

<https://www.hss.edu/health-library/conditions-and-treatments/surgery-for-people-with-rheumatoid-arthritis-inflammatory-arthritis>

[Rheumatoid arthritis - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/diagnosis-treatment/drc-20353653)

[Rheumatoid Arthritis (RA): Symptoms, Stages & Treatment](https://my.clevelandclinic.org/health/diseases/4924-rheumatoid-arthritis#outlook-prognosis)

[American College of Rheumatology Releases Updated Guidelines for the Treatment of Rheumatoid Arthritis - Rheumatology Advisor](https://www.rheumatologyadvisor.com/features/2021-acr-guidelines-recommendations-management-treatment-of-rheumatoid-arthritis/)

**PSORIATIC ARTHRITIS**

**DEFINITION AND DESCRIPTION**

Psoriatic arthritis is a form of arthritis that affects some people who have psoriasis — a disease that causes red patches of skin topped with silvery scales. Most people develop psoriasis years before being diagnosed with psoriatic arthritis. But for some, the joint problems begin before skin patches appear or at the same time.

Joint pain, stiffness and swelling are the main signs and symptoms of psoriatic arthritis. They can affect any part of the body, including your fingertips and spine, and can range from relatively mild to severe. In both psoriasis and psoriatic arthritis, disease flares can alternate with periods of remission.

There's no cure for psoriatic arthritis. Treatment is aimed at controlling symptoms and preventing joint damage. Without treatment, psoriatic arthritis can be disabling.

## **Causes**

Psoriatic arthritis occurs when your body's immune system attacks healthy cells and tissue. The immune response causes inflammation in your joints as well as overproduction of skin cells.

It seems likely that both genetic and environmental factors play a role in this immune system response. Many people with psoriatic arthritis have a family history of either psoriasis or psoriatic arthritis. Researchers have discovered certain genetic markers that appear to be associated with psoriatic arthritis.

Physical trauma or something in the environment — such as a viral or bacterial infection — might trigger psoriatic arthritis in people with an inherited tendency.

## **Risk factors**

Several factors can increase your risk of psoriatic arthritis, including:

* **Psoriasis.** Having psoriasis is the single greatest risk factor for developing psoriatic arthritis.
* **Family history.** Many people with psoriatic arthritis have a parent or a sibling with the disease.
* **Age.** Although anyone can develop psoriatic arthritis, it occurs most often in adults between the ages of 30 and 55.

## **Symptoms**

Both psoriatic arthritis and psoriasis are chronic diseases that worsen over time. However, you might have periods when your symptoms improve or go away temporarily.

Psoriatic arthritis can affect joints on one or both sides of your body. The signs and symptoms of psoriatic arthritis often resemble those of rheumatoid arthritis. Both diseases cause joints to become painful, swollen and warm to the touch.

However, psoriatic arthritis is more likely to also cause:

* **Swollen fingers and toes.** Psoriatic arthritis can cause a painful, sausage-like swelling of your fingers and toes.
* **Foot pain.** Psoriatic arthritis can also cause pain at the points where tendons and ligaments attach to your bones — especially at the back of your heel (Achilles tendinitis) or in the sole of your foot (plantar fasciitis).
* **Lower back pain.** Some people develop a condition called spondylitis as a result of psoriatic arthritis. Spondylitis mainly causes inflammation of the joints between the vertebrae of your spine and in the joints between your spine and pelvis (sacroiliitis).
* **Nail changes.** Nails can form tiny dents (pits), crumble or separate from the nail beds.
* **Eye inflammation.** Uveitis can cause eye pain, redness and blurry vision. If untreated, uveitis can lead to vision loss.

## **DIAGNOSIS**

Psoriatic arthritis is easier to confirm if you already have psoriasis. If you don’t have the skin symptoms, diagnosis is more difficult. The process starts with a health history and a physical exam. Your healthcare provider will ask about your symptoms. You may have blood tests to check the following:

**Erythrocyte sedimentation rate (ESR or sed rate).**  This test looks at how quickly red blood cells fall to the bottom of a test tube. When swelling and inflammation are present, the blood’s proteins clump together and become heavier than normal. They fall and settle faster at the bottom of the test tube. The faster the blood cells fall, the more severe the inflammation.

**Uric acid.**  High blood uric acid levels can be seen in psoriatic arthritis but are not used for diagnosis or monitoring.

**Imaging tests.** X-rays, CT scans, ultrasound, MRI, and skin biopsies may all be used to help diagnose psoriatic arthritis.

**TREATMENT**

Treatment will depend on your symptoms, age, and general health. It will also depend on the severity of your condition.

Both the skin condition and the joint inflammation are treated. Early diagnosis and treatment help prevent joint damage. Some medicines used to treat psoriatic arthritis include:

Nonsteroidal anti-inflammatory medicines (NSAIDs) to ease symptoms

Corticosteroids for inflammation

Immunosuppressive medicines, such as disease modifying antirheumatic medicines, to decrease inflammation.

Vitamins and minerals, such as calcium and vitamin D, to support bone health.

Other treatment may include:

Exercise

Heat and cold

Occupational therapy to help you do your daily activities

Physical therapy to help your muscle and joint function

Management of psoriasis skin rash

Splints

Surgery to fix or replace a damaged joint. This is often not needed until years after diagnosis.

Ultraviolet light treatment

* Clinical Stages / Disease Progression (Informal):
  + Pre-PsA: Psoriasis without arthritis, but risk of developing PsA.
  + Early PsA: Initial joint symptoms such as swelling, pain, dactylitis (sausage digits), often involving fingers, toes, and sometimes larger joints.
  + Established/Progressive PsA: Persistent joint inflammation, possible joint damage, reduced mobility, and systemic symptoms like fatigue.
  + Late/Severe PsA: Significant joint damage, deformities, and disability.

## **Differential Diagnosis of Psoriatic Arthritis (PsA)**

## 1. Rheumatoid Arthritis (RA)

* Typically presents with symmetric polyarthritis, especially involving the metacarpophalangeal (MCP) joints and proximal interphalangeal joints.
* PsA often shows asymmetric oligoarthritis and involvement of the distal interphalangeal (DIP) joints.
* RA is usually rheumatoid factor (RF) and anti-CCP antibody positive, whereas PsA is mostly seronegative.
* Imaging: RA shows marginal erosions without new bone formation, while PsA shows both erosions and new bone formation (periostitis, "pencil-in-cup" deformity).
* PsA may have enthesitis, dactylitis, nail dystrophy, and axial involvement (sacroiliitis), which are less common in RA.

## 2. Osteoarthritis (OA)

* OA is a non-inflammatory degenerative joint disease.
* OA pain worsens with activity and improves with rest; PsA and RA often have morning stiffness lasting >30 minutes.
* OA commonly affects DIP joints but lacks the inflammatory signs of PsA.
* Imaging: OA shows joint space narrowing, osteophytes, and subchondral sclerosis; PsA shows erosions plus new bone formation.
* Nail changes and skin psoriasis help distinguish PsA.

## 3. Gout and Pseudogout

* Both present with acute monoarticular arthritis, often with severe pain and swelling.
* Gout involves deposition of monosodium urate crystals, pseudogout of calcium pyrophosphate crystals.
* Joint aspiration and crystal analysis differentiate these from PsA.
* PsA tends to have more chronic, polyarticular involvement.

## 4. Reactive Arthritis

* Occurs after certain infections (e.g., gastrointestinal or genitourinary).
* May present with arthritis, urethritis, and conjunctivitis.
* Like PsA, can have enthesitis and dactylitis.
* History of recent infection and presence of HLA-B27 may aid differentiation.

## 5. Septic Arthritis

* Acute joint infection with severe pain, swelling, and systemic symptoms.
* Requires urgent diagnosis and treatment.
* Joint aspiration with culture distinguishes it from PsA.

## 6. Other Spondyloarthropathies

* Includes ankylosing spondylitis and enteropathy arthritis.
* May have overlapping features with PsA, especially axial involvement.
* Clinical history and imaging help differentiate.

**Treating Psoriatic Arthritis**  
The over the counter (OTC) and prescription medicines for psoriatic arthritis include:   
  
**NSAIDs.** Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually taken by mouth, although some can be applied to the skin. Popular over the counter (OTC) versions, such as ibuprofen and naproxen sodium, help to ease pain. Many prescription NSAIDs can help reduce inflammation, too.   
  
**Corticosteroids.**These powerful anti-inflammatory medicines can be taken by mouth (orally) or injected into a joint at a doctor’s office. In the case of oral corticosteroids, doctors try to use these drugs at the lowest dose for the shortest time possible because of side effects, which can include facial swelling, easy bruising, weight gain and weak bones.   
  
**DMARDs.** Disease-modifying antirheumatic drugs (DMARDs) are powerful medications that reduce inflammation and can stop PsA from getting worse. They are available as pills, can be self-injected or given as an infusion. There are three types of DMARDs:

* **Traditional DMARDs** have been used the longest and have a broad immune-suppressing effect. The most commonly-used drug is methotrexate. These medicines are usually taken by mouth and can take up to three months to become fully effective.
* **Biologics** interrupt certain chemicals or steps in the inflammatory process and they generally work more quickly than traditional DMARDs. They are self-injected or given by infusion in a doctor’s office.
* **Targeted DMARDs**, like biologics and Janus kinase (JAK) inhibitors, also block certain steps in the inflammatory process, but these drugs are taken by mouth.

While DMARDs can be very effective, in many cases they suppress the immune system and raise the risk of infection.   
  
Every person with PsA is different. Doctors recommend certain medications depending on:

* How many and which parts of the body are affected.
* How severe the disease is.
* How many joints are affected.
* Drug allergies and other health conditions.
* Current medication use.

## **Procedures and Recovery Timeline**

## 1. Non-Surgical Management

* Medications:
  + NSAIDs and corticosteroids for inflammation and pain relief.
  + Disease-modifying antirheumatic drugs (DMARDs), including biologics, to control immune activity and prevent joint damage.
  + Treatment is personalized based on disease severity and skin involvement.
* Physical Therapy:
  + Helps maintain joint mobility, strengthen muscles, and improve function.
  + Typically started after inflammation is controlled to avoid tendon injury.
* Lifestyle:
  + Weight loss (especially if overweight) improves medication response and reduces joint stress.
  + Skin treatments (topicals, phototherapy) for psoriasis managed alongside joint symptoms.

## 2. Steroid Joint Injections

* Purpose:
  + Reduce inflammation and pain in specific affected joints.
* Recovery:
  + Usually outpatient; relief begins within days.
  + Temporary effect; may be repeated as needed.

## 3. Surgical Procedures

* Joint Replacement Surgery (Arthroplasty):
  + Indicated for joints severely damaged by PsA (commonly hip, knee).
  + Artificial joints made of metal and plastic replace damaged joint surfaces.
* Arthroscopic Synovectomy:
  + Minimally invasive removal of inflamed synovial tissue to reduce pain and swelling.
* Other Surgeries:
  + Corrective surgeries for deformities or tendon repairs may be performed.

## **4. Recovery Timelines**

| Procedure | Hospital Stay | Initial Recovery | Full Recovery | Notes |
| --- | --- | --- | --- | --- |
| Steroid Joint Injection | Outpatient | Days to weeks | Temporary relief | Repeat injections possible |
| Arthroscopic Synovectomy | Outpatient or 1–2 days | 2–4 weeks | Several weeks to months | Less invasive, shorter recovery |
| Joint Replacement Surgery | 1–4 days | 6–12 weeks | 6 months to 1 year | Significant pain relief, improved function |
| Physical Therapy | N/A | Ongoing | Ongoing | Essential adjunct to medical/surgical treatment |

## **Complications**

A small percentage of people with psoriatic arthritis develop arthritis mutilans — a severe, painful and disabling form of psoriatic arthritis. Over time, arthritis mutilans destroys the small bones in the hands, especially the fingers, leading to permanent deformity and disability.

Psoriatic arthritis also puts some people at higher risk of developing hypertension, metabolic syndrome, diabetes and cardiovascular disease

## **When to see a doctor**

If you have psoriasis, tell your doctor if you develop joint pain. Psoriatic arthritis can severely damage your joints if left untreated.

**Outlook / Prognosis**

You should expect to manage your symptoms for a long time (maybe the rest of your life). Some people experience long periods of time between flares, but there’s no cure for psoriatic arthritis.

It can be frustrating when a flare happens suddenly. Eventually, you might learn to recognize the warning signs of a flare and start managing symptoms before they become more severe. Talk to a healthcare provider if you feel like your symptoms are getting worse or your current treatments aren’t managing them well enough.

**Prevention**

Because experts don’t know what causes psoriatic arthritis, you can’t prevent it. You can lower your chances of developing all types of arthritis by:

* Avoiding tobacco products.
* Following a diet and exercise plan that’s healthy for you.
* Doing low-impact, non-weight-bearing exercise.
* Always wearing proper protective equipment for any activity that could damage your joints.

## **Questions & Answers**

Q. What is psoriatic arthritis?  
A. Psoriatic arthritis is a chronic inflammatory arthritis associated with psoriasis, causing joint pain, swelling, and stiffness.

Q. Who gets psoriatic arthritis?  
A. PsA can affect adults of any age but commonly occurs between ages 30 and 50. It affects men and women equally and often develops in people with psoriasis.

Q. What causes psoriatic arthritis?  
A. The exact cause is unknown but involves genetic, immune, and environmental factors leading to inflammation in joints and skin.

Q. What are the symptoms of psoriatic arthritis?  
A. Symptoms include joint pain, swelling, morning stiffness, dactylitis (sausage-like swelling of fingers or toes), nail changes (pitting, onycholysis), and skin psoriasis.

Q. How is psoriatic arthritis diagnosed?  
A. Diagnosis is based on clinical evaluation, family and personal history of psoriasis, blood tests (usually negative for rheumatoid factor), and imaging showing joint inflammation and damage.

Q. How does psoriatic arthritis differ from rheumatoid arthritis?  
A. PsA often affects distal joints (fingers and toes), may be asymmetric, and is associated with psoriasis and nail changes. RA usually affects joints symmetrically and is rheumatoid factor positive.

Q. What treatments are available for psoriatic arthritis?  
A. Treatment includes NSAIDs, DMARDs (like methotrexate), biologic agents targeting immune pathways, corticosteroids, physical therapy, and sometimes surgery.

Q. Can psoriatic arthritis be cured?  
A. There is no cure, but treatments can control symptoms, reduce inflammation, and prevent joint damage.

Q. What lifestyle changes help manage psoriatic arthritis?  
A. Maintaining a healthy weight, regular low-impact exercise, avoiding smoking, and managing stress can improve outcomes.

Q. Can psoriatic arthritis affect other parts of the body?  
A. Yes, PsA can affect the spine (axial disease), entheses (tendon insertions), eyes (uveitis), and cardiovascular system.

Q. When should I see a doctor about joint symptoms?  
A. If you have persistent joint pain, swelling, or stiffness, especially with psoriasis or nail changes, seek medical evaluation promptly.

Q. Are there support resources for people with psoriatic arthritis?  
A. Yes, organizations like the National Psoriasis Foundation and Arthritis Foundation offer education, support groups, and resources.

## **Doctor-Patient Conversation on Psoriatic Arthritis (PsA)**

Doctor:  
I understand you’ve been having joint pain and some skin issues. Can you tell me more about how you’ve been feeling?

Patient:  
Yes, I’ve had swelling and stiffness in my fingers and toes, and my skin has these red, scaly patches. The joint pain is worse in the mornings and sometimes I feel very tired, even after resting.

Doctor:  
That sounds consistent with psoriatic arthritis, which often affects the joints and skin. Fatigue is a common but sometimes overlooked symptom. How has fatigue been impacting your daily life?

Patient:  
It’s been tough. Some days I feel too exhausted to do simple things or meet friends. It’s frustrating because I look fine on the outside, but inside I’m really struggling.

Doctor:  
I understand. Fatigue in PsA can be challenging, but there are ways to manage it. Planning your activities, ensuring good sleep, and gentle physical activity can help. Have you noticed if any activities make your symptoms better or worse?

Patient:  
Exercise helps sometimes, but on bad days, even moving hurts. I’m not sure how to balance it.

Doctor:  
We’ll work together to find the right balance. Also, treating the inflammation with medications can reduce both joint pain and fatigue. We’ll review your treatment options soon.

Patient:  
How do you confirm it’s psoriatic arthritis?

Doctor:  
We’ll do some blood tests and imaging. Blood tests help rule out other conditions like rheumatoid arthritis, and imaging shows joint inflammation and damage. We also look for nail changes and skin psoriasis.

Patient:  
Will this get worse over time?

Doctor:  
PsA can be progressive, but with early diagnosis and treatment, we can control symptoms and prevent joint damage. Regular monitoring is important.

Patient:  
What else can I do to help myself?

Doctor:  
Maintaining a healthy lifestyle, managing stress, quitting smoking if you smoke, and staying active within your limits are all helpful. Also, it’s important to communicate openly about your symptoms and concerns.

Patient:  
Sometimes I find it hard to explain how I feel, especially about fatigue.

Doctor:  
That’s common. You might find it helpful to keep a symptom diary or use apps to track how fatigue and pain affect your daily activities. This helps us tailor your treatment.

Patient:  
Thank you. I feel better knowing you understand.

Doctor:  
You’re welcome. We’re a team, and I’m here to support you in managing PsA.

## 1. **Genomic Data in Psoriatic Arthritis**

* Key genetic markers include HLA alleles:
  + HLA-Cw\*0602 is strongly associated with early-onset psoriasis but less frequent in PsA.
  + In PsA, HLA-B27, HLA-Cw2, HLA-DRw52 are linked to axial disease; HLA-B38 and B39 with polyarthritis.
  + Certain combinations of alleles (e.g., HLA-B27 homozygosity) correlate with more severe disease, while others (e.g., HLA-B44:02) may be protective.
* Non-HLA genes also contribute, including polymorphisms in IL13, IL4, PTPN22, and others related to immune regulation.
* Over 20 genetic variants have been identified as potentially linked to PsA susceptibility and severity.
  + Genetic counseling should accompany testing to interpret results and guide management.

REFERENCES

<https://www.psoriasis.org/psoriatic-arthritis>

[Psoriatic Arthritis: Symptoms and Treatments](https://my.clevelandclinic.org/health/diseases/13286-psoriatic-arthritis#outlook-prognosis)

[Psoriatic Arthritis | Johns Hopkins Medicine](https://www.hopkinsmedicine.org/health/conditions-and-diseases/arthritis/psoriatic-arthritis)

[Psoriatic arthritis - Symptoms & causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/psoriatic-arthritis/symptoms-causes/syc-20354076)

**SPONDYLOARTHRITIS**

**DEFINITION AND DESCRIPTION**

Spondyloarthritis (SpA) means arthritis of the spine (*spondyl-*). Arthritis is pain and stiffness in your joints. Spondyloarthritis affects the joints connected to your spine — the facet joints between your vertebrae and the sacroiliac joints that connect your spine to your pelvis. Lower back pain is the most common symptom. But spondyloarthritis can also affect other joints and cause other symptoms.

Spondyloarthritis isn’t one condition but a group of conditions with common features. They begin with arthritis of the spine, but they don’t end there. Healthcare providers also describe these conditions as spondyloarthropathy, which means disease (*-pathy*) in the joints (*arthro-*) of the spine. These conditions are distinct from osteoarthritis and rheumatoid arthritis, which can also affect the joints in your spine.

Some key features of spondyloarthritis (spondyloarthropathy) are:

* **It’s rheumatic.** Spondyloarthritis is a rheumatic disease, which means it’s an inflammatory type of arthritis. Chronic inflammation causes the symptoms of pain and swelling in your joints. Unlike osteoarthritis, which is a product of wear and tear on your joints, inflammatory arthritis is usually a type of autoimmune disease. That means your immune system causes the constant inflammation in your joints — and often causes it in other places in your body, too.
* **It’s not RA**. Despite being a type of rheumatic arthritis, it’s not the most famous type, which is rheumatoid arthritis (RA). We know this because people with spondyloarthritis don’t test positive for rheumatoid factor, the antibody that’s typical of RA. This is why healthcare providers sometimes refer to spondyloarthritis as “seronegative spondyloarthropathy.” “Seronegative” means the blood test for RA is negative. There’s no known SpA antibody.
* **Enthesitis**. Inflammation in your entheses (enthesitis) is a hallmark of spondyloarthritis that healthcare providers will look for during diagnosis. Entheses are fibrous connective tissues that act as the “joints” where your tendons and ligaments insert into your bones. Spondylarthritis can cause enthesitis in different places in your body. Heels and knees are common sites.
* **A gene called *HLA-B27***. Between 80% and 95% of people with spondyloarthritis who are of northern European descent have a gene called *HLA-B27*. It isn’t as common in people of other ethnicities who have spondyloarthritis. And the gene alone doesn’t cause the disease. But it’s common enough that your healthcare provider might test for it to help make your diagnosis.

Although it’s not as well known, spondyloarthritis is actually more common than rheumatoid arthritis. An estimated 0.5% to 2% of the population worldwide has some form of spondyloarthropathy.

### **Types of spondyloarthritis**

Several distinct diseases fall under the general heading of spondyloarthritis. Healthcare providers separate them into two main categories: axial spondyloarthritis and peripheral spondyloarthritis.

#### **Axial spondyloarthritis**

Axial spondyloarthritis is spondyloarthritis that mainly affects the joints in your axial skeleton: your neck, chest and spine. As it progresses, it may involve other joints and even organs.

**Ankylosing spondylitis** is a severe form of axial spondyloarthritis that causes visible changes to the bones in your spine, called ankylosis. It’s the most common type of spondyloarthritis overall.

**Peripheral spondyloarthritis**

Peripheral spondyloarthritis affects your peripheral joints and entheses first — the ones on the outside of your axial skeleton (like your limbs). As it progresses, it may or may not go on to affect your spine.

Peripheral spondyloarthritis also typically involves inflammation in other organs. Different types tend to affect different organs — like your eyes, skin or bowels — but symptoms can overlap. Types include:

* **Psoriatic arthritis**. Psoriatic arthritis is arthritis that occurs together with psoriasis, an autoimmune skin condition that causes an inflammatory skin rash. It most often affects the small joints in your hands and feet, causing painful swelling in your fingers and toes.
* **Enteropathic arthritis**. Enteropathic arthritis is arthritis that occurs together with inflammatory bowel disease (IBD). Enteropathic means that it’s related to your intestines.
* **Reactive arthritis**. Reactive arthritis is an autoimmune reaction to an infection in your intestines or urinary tract. It may affect your eyes, skin, bladder, genitals or bowels. It’s typically temporary, but it can last up to 12 months, and some people develop chronic arthritis.

#### **Undifferentiated spondyloarthritis**

Undifferentiated spondyloarthritis is the diagnosis when your symptoms fit the profile of spondyloarthritis in general, but they don’t quite fit the profile of any specific subtype.

#### **Juvenile spondyloarthritis**

Juvenile spondyloarthritis is spondyloarthritis that develops during childhood — usually before age 16. Children may develop a specific type of spondyloarthritis or symptoms from many types.

## **Symptoms and Causes**

Symptoms of different types of spondyloarthritis often overlap. While some symptoms are more characteristic of certain types of spondyloarthritis than others, all symptoms can occur with any type.

Symptoms may include:

* Lower back pain that may spread to your butt (sacroiliitis).
* Stiffness that’s worse in the morning and gets better with movement.
* Mid- and upper back pain, musculoskeletal chest pain or neck pain.
* Gradual curvature of the spine.
* Pain and stiffness in the joints of your limbs — hips, shoulders, knees, elbows, wrists or ankles.
* Severely swollen fingers or toes (“sausage fingers” or dactylitis).
* Gastrointestinal symptoms, like abdominal pain and diarrhea.
* Pain and inflammation in your urinary tract.
* An itchy, flakey skin rash (psoriasis).
* Nail pitting (nail psoriasis).
* Fatigue.
* Loss of appetite.
* Eye inflammation (uveitis).
* Mouth sores.
* Heel pain (due to enthesitis).
* Bone spurs.

Symptoms of spondyloarthritis tend to appear earlier than other types of arthritis — usually before the age of 45. They begin slowly and may pile on gradually. In most cases, symptoms continue indefinitely.

### **Causes of spondyloarthritis**

Chronic inflammation in your joints and other tissues causes the symptoms of spondyloarthritis. Your immune system generates chronic inflammation automatically. This is called autoimmune disease.

Researchers don’t entirely understand why autoimmune diseases occur, but there seem to be several factors involved. Many autoimmune conditions, including spondyloarthritis, seem to be partly genetic.

Genes in the HLA (human leukocyte antigen) family are often involved in inflammatory arthritis. These genes encode a protein that your immune system uses to distinguish your own cells from harmful ones.

Certain variations in these genes may not work as well as others. When your immune system can’t properly distinguish between your cells and foreign ones, it may mistakenly attack your cells.

**What triggers spondyloarthritis?**

Genetics may play a part in spondyloarthritis, but they don’t cause it alone. While many people with spondyloarthritis carry the *HLA-B27* gene, most people who carry it don’t get spondyloarthritis.

Something else must trigger the process. Researchers have many theories about what those triggers might be. Some of these include severe infections, environmental toxins, smoking and alcohol use.

One theory is that spondyloarthritis might be linked to dysbiosis in your gut microbiome. People with SpA tend to have less diversity in their gut, which makes it easier for harmful microbes to take over.

Gut dysbiosis can weaken your immune system by making you more susceptible to infections and triggering chronic inflammation in your gut. Your mix of gut microbiota is partly inherited at birth.

## **Diagnosis and Tests**

Spondyloarthritis can be tricky to diagnose, especially if you don’t have a recognizable combination of symptoms. Some people only have joint pain and stiffness, which has many other possible causes.

A healthcare provider will start by asking you about your symptoms and check for any related symptoms you might not have mentioned. They’ll also ask about your health history and family health history.

They’ll physically examine your back or other joints and test your range of motion. They’ll take X-rays to look for evidence of arthritis or enthesitis, but evidence won’t always be visible in images.

They might order a blood test to check for signs of inflammation or autoimmune disease. They might also test you for the *HLA-B27* gene. These tests can help to distinguish SpA from other diseases.

## **Management and Treatment**

Treatment depends on your specific symptoms. Healthcare providers take a stepwise approach to treatment, starting with exercise and over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs).

If these don’t do enough to manage your pain and inflammation, your provider might suggest:

* Periodic cortisone shots for more localized pain relief.
* Traditional or biologic DMARDs (disease-modifying anti-rheumatic drugs).

Some specific types of spondyloarthritis, like psoriatic arthritis and enteropathic arthritis, have other treatments that specifically relate to the underlying condition (psoriasis or inflammatory bowel disease).

### **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

NSAIDs are the most commonly used class of medication for the treatment of pain and stiffness associated with spondyloarthritis. Ibuprofen, for instance, is a generic NSAID and is found in over-the-counter pain relievers such as Advil and Motrin.

Sometimes, high doses of NSAIDs are needed to maintain relief from the symptoms of ankylosing spondylitis and related diseases. This can pose a problem because NSAIDs can cause significant side effects, especially in the gastrointestinal tract (stomach, intestines, etc.). NSAIDs can cause reduced amounts of protective mucus in the stomach, which can result in stomach irritation. Over time, this can lead to heartburn, gastritis, and possibly ulcers and even bleeding. People can take other medications (such as antacids) to neutralize or prevent the production of excess stomach acid, help coat and protect the stomach (such as Carafate), or restore the lost mucus (such as Cytotec).

There may also be an increased risk of heart attack or stroke associated with NSAIDs, especially in people with a history of heart diseases.

A different class of NSAIDs known as COX-2 inhibitors (or COXIBs) seem to reduce the risk of gastrointestinal complications associated with traditional NSAID therapy. Celebrex (Celecoxib) is still being used to treat spondyloarthritis. Others, such as Vioxx, were pulled from the market in 2004 because of the high rate of heart attacks caused by the drug.

### **When NSAIDs Are Not Enough**

Although NSAIDs are commonly the first line of medications used to treat ankylosing spondylitis and related diseases, sometimes they aren’t enough to control the symptoms. It is important to note, however, that it may take several weeks for some NSAIDs to show positive results. If you are considering changing medications, remember to ask your doctor about the potential benefits and side effects before you and your doctor decide whether a change in treatment is right for you.

In severe cases of ankylosing spondylitis or related disease, NSAIDs may only be partially effective or the side effects too severe to continue their use. In this case, a doctor may prescribe one of the following medications.

### **Sulfasalazine**

Sulfasalazine is one medication that can be helpful to some people with severe disease. It is known to effectively control not only pain and joint swelling from arthritis of the small joints, but also the intestinal lesions in inflammatory bowel disease. It comes in tablet form and is taken orally. Sulfasalazine is generally not utilized for spinal arthritis.

Side effects are relatively infrequent, but can include headaches, abdominal bloating, nausea, and oral ulcers. Rarely, someone being prescribed this medication can develop bone marrow suppression, which is why it is important for your doctor to regularly monitor your blood count.

### **Methotrexate**

Originally developed to treat cancer, this chemotherapy drug is widely used and often very effective for the treatment of rheumatoid arthritis. When prescribed for treating symptoms of spondyloarthritis, it is given in smaller doses and is generally not utilized for spinal arthritis. Methotrexate can either be taken via a self-injectable shot or orally in tablet form. When taking methotrexate, it is also necessary to take the vitamin folic acid in order to help suppress some of the possible side effects, including oral ulcers and nausea. Because of other potential serious side effects, frequent monitoring of blood counts and liver function are required. Methotrexate is strongly contraindicated in pregnant women, as it has caused birth defects and death in unborn babies.

### **Apremilast**

Apremilast (Otezla) is a medication used primarily to treat adults with moderate to severe plaque psoriasis who are candidates for phototherapy or medications. Additionally, it is approved for the treatment of adults with active psoriatic arthritis and oral ulcers associated with Behçet’s Disease. Apremilast works by inhibiting an enzyme involved in the inflammatory process. Unlike some other treatments, it does not require laboratory monitoring and is administered orally.

### **Azathioprine**

Azathioprine is a medication primarily used as an immunosuppressant in organ transplantation. It is also used to treat autoimmune diseases, including rheumatoid arthritis, Crohn’s disease, and ulcerative colitis. Due to its impact on the immune system, azathioprine carries significant warnings; it can increase the risk of infection and has been associated with a higher risk of developing certain types of cancer. Patients on azathioprine require regular monitoring of blood counts and liver function to manage these risks effectively.

### **Corticosteroids**

While corticosteroids such as prednisone can be effective in relieving inflammation, the side effects of long-term use of *systemic* corticosteroids (which impact the entire body) can be very severe. As such, experts strongly recommend against using oral or injectable systemic corticosteroids. In contrast, local injections into inflamed joints (which do not impact the entire body) are acceptable, and can provide temporary relief of the pain caused by arthritis or bursitis.

### **The Biologics**

Biologic medications are made from living organisms. The material they are made from can come from many sources, including humans, animals, and microorganisms such as bacteria or yeast.

### **TNF Inhibitors**

The tumor necrosis factor alpha (TNF-α) inhibitors were the first biologic medications to have shown great promise in treating spondyloarthritis, with the first TNF inhibitor – Enbrel – being approved in 2003. These medications have been shown to be highly effective in treating not only the arthritis of the joints, but also the inflammation in the gut and eyes, as well as the spinal arthritis associated with ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), and related diseases.

A serious and well-known complication of the TNF inhibitors is an increased frequency of infections, along with a reduced ability to fight infections, including tuberculosis. Thus, a TB test is required before starting any of the TNF therapies. There is also a slightly increased risk of certain cancers associated with TNF inhibitors, such as lymphoma (most notably in children and teens) and skin cancers.

It should be noted that each TNF inhibitor/biologic medication works in a slightly different manner. Thus, if one does not have a positive effect, another one might.

The following TNF inhibitors are currently approved for forms of spondyloarthritis: Enbrel, Humira, Remicade, Simponi, and Cimzia.

### **IL-17 Inhibitors**

IL-17 inhibitors are another class of biologic medications approved for spondyloarthritis. There are currently three IL-17 inhibitors approved by the FDA for forms of spondyloarthritis – specifically for ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), and psoriatic arthritis (PsA). Cosentyx (secukinumab) was approved for AS and PsA in January of 2016, and Taltz (ixekizumab) was approved for PsA in December of 2017, and for AS in August of 2019. Both were approved for nr-axSpA in June of 2020. In September of 2024, Bimzelx (bimekizumab-bkzx) was approved for active PSA, active nr-axSpA with objective signs of inflammation, and active AS.

Both IL-17 and TNF-α are inflammatory cytokines (cell signaling molecules) that, as the name implies, signal to activate inflammation throughout the body, modulating or altering the immune system response. Inflammatory cytokines play an important role; however, when there is an overabundance of these, as has been described in inflammatory disease, they can cause harm to the body if left unchecked.

IL-17 and TNF-α cytokines signal to specific immune cells directing them to activate inflammation, with each cytokine being responsible for signaling to a different set of cells. IL-17 and TNF inhibitor *medications* work by targeting their respective cytokines, obstructing their signaling pathways, and by this mechanism seek to reduce inflammation. Since IL-17 inhibitors target different cytokines than the TNF inhibitors, the hope is that this newer class of biologic medications will help those who haven’t responded well to the TNF inhibitors, or are not able to tolerate them.

Bimzelx is currently the first and only inhibitor of both IL-17A & IL-17F approved to treat chronic immune-mediated inflammatory diseases, providing another variation of biologic that may help those who haven’t responded well to others.

IL-17 inhibitors carry similar risks of infections, and reduced ability to fight infections as the TNF inhibitors. They have also shown in clinical trials to exacerbate inflammatory bowel disease in patients who have it, as well as bring on new cases of inflammatory bowel disease.

### **IL 12/23 Inhibitor**

Ustekinumab (Stelara) works similarly to the IL-17 inhibitor, but targets different cytokines: IL-12 and IL-23. Stelara was approved in 2013 for psoriatic arthritis. Stelara also carries increased risks of infections, and reduced ability to fight infections, as well as a slightly increased risk of certain cancers.

### **Biosimilars**

Biosimilars are highly similar to FDA-approved biologics (also known as reference products) with no meaningful differences in safety, effectiveness, or dosage. Like biologics, they are made from living cells or microorganisms and provide the same benefits as their reference products.

To gain FDA approval, biosimilars must undergo rigorous testing to prove they are just as safe and effective as the original biologic. Even after approval, the FDA continuously monitors their quality, safety, and patient-reported outcomes.

Biosimilars are often more affordable than biologics, making them a potential option if insurance coverage changes. Their lower cost does not compromise safety or effectiveness, and they expand treatment options.

Some biosimilars are interchangeable, meaning they can be substituted at the pharmacy without consulting a doctor, depending on state laws. Regardless of interchangeability, all biosimilars meet strict FDA standards for safety and effectiveness.

## **Signs a person might need surgery**

A doctor may recommend surgical treatment for AS if a person experiences one or more of the following symptoms:

* **Severe pain:** The person experiences pain that does not respond to over-the-counter (OTC) or prescription pain relief.
* **Reduced mobility:** The person experiences severe mobility impairment that reduces their quality of life.
* **Spinal fracture**: The person has sustained a spinal fracture or is at increased risk of developing a spinal fracture.
* **Spinal fusion:** The condition has caused two or more cervical vertebrae to fuse, limiting motion in the neck or back.
* **Severe kyphosis:** The condition has caused severe kyphosis, a severe curvature of the spine in the upper back.

A doctor may also recommend surgery if a person cannot carry out day-to-day functions, such as working or driving.

**Types of surgery**

### **Laminectomy**

A laminectomy, or decompression surgery is a procedure that involves removing part or all of a vertebra to alleviate pressure on the spinal cord and nerves. This can help reduce pain and improve mobility.

A surgeon can perform a laminectomy as an open surgery or as a minimally invasive procedure. The latter involves using specialized equipment to access the spine through small surgical incisions.

**Spinal osteotomy**

A spinal osteotomy is a surgical procedure that involves cutting and reshaping bones to straighten the spine. This procedure may be suitable for people who have a severe spine curvature that causes pain and reduces mobility.

The procedure may differ according to the location of the spinal curve and the bones that the surgeon needs to operate on.

### **Spinal fusion**

Spinal fusion surgery involves fusing two or more vertebrae. This procedure can help to alleviate pain caused by mechanical pressure between the vertebrae or between the vertebrae and the spinal cord. It can also help to stabilize the spine.

A surgeon will fuse the vertebrae using a bone graft from the person’s own body or a donor. The surgeon will then use rods, wires, and screws to hold the vertebrae in place while they fuse.

Following surgery, a person will need to wear a back or neck brace to ensure the bones heal in the correct position.

### **Hip joint replacement**

Hip joint replacement surgery involves removing the hip joint and replacing it with an artificial joint. This procedure aims to improve mobility in people who have sustained severe damage to the hip joint.

A surgeon may perform the procedure as an open surgery or as a minimally invasive procedure.

## **Benefits of surgery**

A person who receives surgery for AS may experience the following benefits:

* **Pain relief:** Surgery may help to alleviate severe pain caused by spinal compression, joint damage, or bone fractures.
* **Increased mobility:** Surgery can help to improve the range of motion in the joints.
* **Improved posture:** Following surgery, a person may find that they can sit or stand with a straight back or maneuver themselves into positions they previously found too difficult.
* **Spinal stability:** Some surgeries may help to stabilize the spine.

## **Risks and complications**

Some potential risks and complications associated with spinal surgery include:

* infection at the incision site
* damage to blood vessels
* blood clots
* allergic reactions
* spinal fractures
* nerve damage
* scarring

## **Outlook / Prognosis**

When inflammatory arthritis is severe and lasts a long time, it can cause some serious complications. But they’re usually the type of complications that affect your quality of life rather than your life expectancy.

For example, you may lose mobility in your joints and may become more prone to bone fractures. But not everyone develops severe symptoms, and treatment can affect how the disease progresses.

How spondyloarthritis progresses is different from person to person. For some, it’s slow and easy to control with treatment. Others can develop ankylosing spondylitis with spinal fusion in just a few years.

How severe your inflammation is affects how quickly spondyloarthritis progresses. Being consistent with your treatment can help manage the inflammation and may prevent complications from developing.

## **Living With**

Regular exercise is crucial for anyone living with arthritis to maintain your mobility as much as possible. Many healthcare providers will tell you it’s more important and more effective than any medication.

If you aren’t sure what type of exercise would be best for you, ask your healthcare provider. Many providers also recommend formal [physical therapy](https://my.clevelandclinic.org/health/treatments/physical-therapy) to address specific joints or problem areas.

## **Epidemiology of Spondyloarthritis (SpA)**

## Global Prevalence

* The global prevalence of SpA varies widely by region, ranging approximately from 0.2% to 2% of the population.
* Prevalence estimates are influenced by genetic factors (notably HLA-B27 prevalence), environmental exposures, and diagnostic criteria used.
* Northern Arctic communities show the highest prevalence of SpA (~1.6%) and ankylosing spondylitis (AS) (~0.35%), while South-East Asia and Sub-Saharan Africa report the lowest prevalence (~0.2% or less)
* Psoriatic arthritis (PsA), a subtype of SpA, has a global prevalence ranging from 0.01% to 0.19%, with higher rates in Europe

## Incidence Rates

* Incidence of SpA varies from 0.48 to 63 per 100,000 person-years, depending on the population and criteria used
* Ankylosing spondylitis incidence ranges from 0.44 to 7.3 per 100,000 person-years
* Psoriatic arthritis incidence ranges from 3.6 to 23.1 per 100,000 person-years
* Reactive arthritis incidence is estimated between 0.6 and 28 per 100,000 person-years

## Geographic and Genetic Influences

* The prevalence of SpA correlates strongly with the frequency of HLA-B27 in populations:
  + High HLA-B27 prevalence in Western countries (~90% of AS patients).
  + Moderate prevalence in Arab countries (~50%).
  + Very low in Sub-Saharan Africa (<1%), corresponding with low SpA prevalence
* Variability in prevalence may also reflect differences in healthcare access, diagnostic awareness, and study methodologies

## Demographic Characteristics

* SpA typically affects young adults, with onset usually between 20 and 40 years of age
* There is a male predominance in ankylosing spondylitis but less pronounced in other SpA subtypes
* The disease burden includes chronic pain, stiffness, reduced quality of life, and work disability

## **Differential Diagnoses of Spondyloarthritis**

1. Mechanical and Degenerative Conditions

* Mechanical Back Pain (MBP)
* Degenerative Disk Disease
* Herniated Nucleus Pulposus
* Spondylolysis and Spondylolisthesis
* Diffuse Idiopathic Skeletal Hyperostosis (DISH)
* Osteitis Condensans Ilii
* Scheuermann Disease
* Spinal Calcium Pyrophosphate Deposition Disease (CPPD)
* Idiopathic Hypoparathyroidism (with syndesmophytes)
* Ochronosis

2. Inflammatory and Autoimmune Diseases

* Rheumatoid Arthritis (RA)
* Psoriatic Arthritis (PsA)
* Reactive Arthritis
* Inflammatory Bowel Disease (IBD)-associated Arthritis (Enteropathic Arthritis)
* Behçet Disease
* Sarcoidosis
* Familial Mediterranean Fever

3. Infectious Causes

* Infectious Sacroiliitis
* Septic Arthritis
* Osteomyelitis

4. Other Conditions Mimicking SpA

* Fibromyalgia
* Whipple Disease
* Astrocytomas (spinal cord tumors causing back pain)

## **Key Genetic Findings**

* HLA-B27:
  + The most significant genetic association with SpA, particularly ankylosing spondylitis.
  + Present in over 85% of AS patients but varies by ethnicity.
  + Accounts for about 20–25% of the heritability of SpA.
  + Plays a role in antigen presentation and immune response.
* Other HLA Class I Alleles:
  + HLA-B40, HLA-B38, and HLA-B39 also contribute to susceptibility.
  + Different alleles may influence disease phenotype and severity.
* Non-MHC Genes:
  + Genome-wide association studies (GWAS) have identified multiple non-MHC loci involved in immune regulation and inflammation.
  + Notable genes include ERAP1 (endoplasmic reticulum aminopeptidase 1), which interacts with HLA-B27 in antigen processing.
  + Genes in the IL-23/IL-17 cytokine pathway (e.g., IL23R, STAT3) are implicated, highlighting the role of Th17 cells in pathogenesis.
  + Other genes: RUNX3, KIR, EOMES, IL7R, ZMIZ1, involved in immune cell differentiation and function.

## **Doctor-Patient Conversation**

## Patient:

Hi, doctor. I’ve been having lower back pain for several months. It’s worse in the morning and improves with activity, but it wakes me up at night sometimes.

## Doctor:

Thanks for sharing. Morning stiffness and back pain that improves with movement can be signs of inflammatory back pain, often seen in spondyloarthritis. Do you have any joint swelling or pain elsewhere?

## Patient:

Yes, sometimes my heels hurt, and I’ve noticed some swelling in my fingers. Also, my right eye was red and painful a few weeks ago.

## Doctor:

Heel pain can be due to enthesitis, inflammation where tendons attach to bone, common in SpA. The eye symptoms sound like uveitis, which is associated with this condition. Do you have any family history of arthritis or related diseases?

## Patient:

My father has psoriasis, but no arthritis that I know of.

## Doctor:

Psoriasis in a family member increases the likelihood of psoriatic arthritis, a type of spondyloarthritis. Have you noticed any skin changes or nail problems yourself?

## Patient:

I have some patches of dry, scaly skin on my elbows and some pitting on my fingernails.

## Doctor:

That supports the possibility of psoriatic arthritis. I’d like to do some blood tests, including HLA-B27, inflammatory markers like ESR and CRP, and imaging of your sacroiliac joints and affected areas.

## Patient:

What does HLA-B27 mean?

## Doctor:

HLA-B27 is a genetic marker often found in people with spondyloarthritis, but not everyone with the gene develops the disease. It helps support the diagnosis.

## Patient:

What treatments are available if I have spondyloarthritis?

## Doctor:

Treatment includes NSAIDs for pain and inflammation, physical therapy to maintain mobility, and disease-modifying drugs like biologics if needed to control inflammation and prevent joint damage.

## Patient:

Are these treatments safe long-term?

## Doctor:

They are generally safe but require monitoring. Biologics suppress the immune system, so we watch for infections and other side effects.

## Patient:

How will this affect my daily life?

## Doctor:

With proper treatment and lifestyle adjustments, many people manage symptoms well and maintain an active life. Early diagnosis and treatment are key.

## Patient:

Thank you. What should I do next?

## Doctor:

I’ll arrange the tests and imaging, and we’ll review the results together soon to plan your treatment.

## Patient:

Sounds good. Thanks for your help.

## Doctor:

You’re welcome. We’ll work together to keep you moving and comfortable.

REFERENCES

<https://www.frontiersin.org/articles/10.3389/fgene.2021.671976/full>

<https://emedicine.medscape.com/article/332945-differential?form=fpf>

[Ankylosing spondylitis and surgery: Types, recovery, cost, and more](https://www.medicalnewstoday.com/articles/ankylosing-spondylitis-surgery#benefits)

[Medications Used to Treat Ankylosing Spondylitis | SPONDYLITIS.ORG](https://spondylitis.org/about-spondylitis/treatment-information/medications/#id-1)

[Spondyloarthritis (Spondyloarthropathy): Types & Treatments](https://my.clevelandclinic.org/health/diseases/spondyloarthritis-spondyloarthropathy)

**GOUT**

**DEFINITION AND DESCRIPTION**

Gout is a form of inflammatory arthritis that causes pain and swelling in your joints. Gout happens when there’s a buildup of uric acid in your body.

Gout most commonly affects your big toe joint. But it can affect other joints, including your:

* Knees.
* Ankles.
* Feet.
* Hands and wrists.
* Elbows.

Gout symptoms come and go (recur) in episodes called flares or gout attacks. A healthcare provider will suggest medications and changes to your diet that will lower your uric acid levels and minimize how often you experience gout attacks in the future.

**Symptoms and Causes**

Gout attacks are very painful and can happen suddenly, often overnight. During a gout attack, symptoms in your affected joints may include:

* Intense pain.
* Discoloration or redness.
* Stiffness.
* Swelling.
* Tenderness, even to a light touch (like a bed sheet covering your affected joint).
* Warmth, or a feeling like the joint is “on fire.”

Gout attacks usually last a week or two. You might have some flares that last longer than others, and some might cause more severe symptoms. Between attacks, you might not experience any gout symptoms.

### **Causes of gout**

A buildup of excess uric acid in your body causes gout. Your body naturally makes uric acid when it breaks down chemicals called purines found in certain foods and drinks. Your kidneys usually filter uric acid out of your blood, and then it leaves your body when you pee.

Sometimes your body makes too much uric acid, or your kidneys don’t remove it from your blood fast enough. When your body has high levels of uric acid (hyperuricemia), uric acid crystals can build up and settle into your joints. The sharp crystals clump together and cause sudden episodes of pain, swelling and other symptoms.

Having temporarily high uric acid levels doesn’t mean you’ll definitely develop gout. Many people with hyperuricemia never get gout.

**Gout risk factors**

Gout can affect anyone. Men are three times more likely to develop gout. Women usually don’t experience gout until after menopause. People with certain health conditions are more likely to develop gout, including:

* Overweight or obesity.
* Congestive heart failure.
* Diabetes.
* Hypertension (high blood pressure).
* Kidney disease.
* Blood cancer.

You’re more likely to experience gout if you:

* Have a biological parent or grandparent who has gout.
* Eat a lot of animal proteins — especially animal flesh, shellfish and foods that contain organ meat.
* Drink alcohol regularly.
* Take diuretic medication (water pills).
* Take immunosuppressants.

#### **Which foods cause gout?**

Eating or drinking foods high in purines are more likely to lead to high uric acid levels in your body that cause gout, including:

* **Sugary drinks and sweets:** Standard table sugar is half fructose (fruit sugar), which breaks down into uric acid. Any food or drink with high sugar content can trigger gout.
* **High fructose corn syrup**: This is a concentrated form of fructose. Packaged food products and processed snacks can contain lots of high fructose corn syrup.
* **Alcohol**: Even though not all alcoholic drinks are high in purines, alcohol prevents your kidneys from eliminating uric acid, pulling it back into your body, where it continues to accumulate.
* **Organ meats:** These include liver, tripe, sweetbreads, brains and kidneys.
* **Game meats**: Specialties such as goose, veal and venison all contain high levels of purines.
* **Certain seafood:** Herring, scallops, mussels, codfish, tuna, trout and haddock.
* **Red meat:** Beef, lamb, pork and bacon.
* **Turkey**: Especially processed deli turkey.
* **Gravy and meat sauces.**

## **Diagnosis and Tests**

A healthcare provider will diagnose gout with a physical exam. They’ll ask you about your symptoms and examine your affected joints. Tell your provider when you first noticed symptoms like pain and swelling in your joint and how often the symptoms come and go.

#### **What tests will be done to diagnose gout?**

Your healthcare provider might use a few imaging tests to take pictures of your affected joints. These tests can also show if gout has caused any changes in your joints. You might need:

* X-rays.
* Ultrasound.
* Magnetic resonance imaging (MRI).
* A CT (computed tomography) scan — specifically a dual-energy CT scan.

Other common tests to diagnose gout include:

* Blood tests to measure the uric acid in your blood.
* Joint aspiration — using a needle to remove a sample of fluid from inside a joint.

## **Management and Treatment**

Treating gout is usually a combination of managing your symptoms during a flare and reducing how often you consume high-purine foods and drinks.

#### **Gout medication**

Your healthcare provider might suggest medications to help manage your symptoms, including:

* **NSAIDs:** Over-the-counter (OTC) NSAIDs, like ibuprofen and naproxen, can reduce pain and swelling during a gout attack. Some people with kidney disease, stomach ulcers and other health problems shouldn’t take NSAIDs. Talk to your provider before taking NSAIDs.
* **Colchicine**: Colchicine is a prescription medication that can reduce inflammation and pain if you take it within 24 hours of a gout attack.
* **Corticosteroids:** Corticosteroids are prescription medications that reduce inflammation. Your provider might prescribe oral (by mouth) pills. They may also inject corticosteroids into your affected joints or into a muscle near your joint (intramuscularly).

Your provider might prescribe medications to help lower your uric acid levels. The most common medications that lower uric acid include:

* Allopurinol.
* Febuxostat.
* Pegloticase.
* Probenecid.

#### **Low purine diet for gout**

Your healthcare provider may suggest you follow a low-purine diet. A low-purine diet encourages you to consume fewer foods and drinks with high purine content. This will help reduce uric acid in your body. It also encourages you to eat some select foods that may reduce your uric acid levels.

### **Can gout be cured?**

There’s no cure for gout. You’ll experience fewer attacks once you work with a healthcare provider to find treatments that manage your symptoms and lower your uric acid levels.

### **allopurinol**

Allopurinol is commonly used to treat [gout](https://www.webmd.com/arthritis/arthritis-gout), which is a form of arthritis caused by too much uric acid in your blood and joints.

Allopurinol may also be used to lower your uric acid levels if you are receiving chemotherapy for cancer, or if you have certain types of kidney stones.

Allopurinol may also be used for other conditions as determined by your healthcare provider.

### **How does allopurinol work (mechanism of action)?**

Allopurinol works by reducing the production of uric acid in your body. If uric acid levels get too high, crystals can form in your joints and cause inflammation and pain (gout flares) or stones can form in your kidneys. By reducing the formation of uric acid, allopurinol helps prevent gout flares and kidney stones.

### **How is allopurinol supplied (dosage forms)?**

Allopurinol is available as Lopurin, Zyloprim, and generic allopurinol in the following dosage forms that are taken by mouth.

* 100 mg oral tablets
* 200 mg oral tablets
* 300 mg oral tablets

### **How should I store allopurinol?**

Allopurinol should be stored at room [temperature](https://www.webmd.com/first-aid/normal-body-temperature), between 68 F to 77 F (20 C to 25 C). It can be exposed to temperatures between 59 F to 86 F (15 C to 30 C), for shorter periods of time, such as when transporting it. Store in a cool, dry place. Keep tightly closed.

**Side Effects**

The most common side effects of allopurinol are listed below. Tell your healthcare provider if you have any of these side effects that bother you.

* Skin rash (see below)
* Diarrhea
* Nausea

There may be other side effects of allopurinol that are not listed here. Contact your healthcare provider if you think you are having a side effect of a medicine.

### **Side effects of allopurinol**

While less common, the most serious side effects of allopurinol are described below, along with what to do if they happen.

**Gout Flares.** Allopurinol may increase your gout flares before making your symptoms better. It may take several months to reduce uric acid levels enough to control your gout flares. It is very important to follow your healthcare provider’s recommendations, which may include taking medicine for pain and inflammation while taking allopurinol, and drinking enough fluids.

**Kidney Damage.**[Kidney damage](https://www.webmd.com/a-to-z-guides/what-is-acute-kidney-failure) can happen when taking allopurinol. Call your healthcare provider right away if you have any of the following symptoms of kidney damage.

* Reduced need to pee
* Swelling in your feet, ankles, or legs
* Weakness or unusual tiredness
* Difficulty catching your breath or chest pain/pressure
* Confusion
* Nausea
* [Seizures](https://www.webmd.com/epilepsy/understanding-seizures-basics)

**Liver Damage.** Liver damage, also called [hepatotoxicity](https://www.webmd.com/hepatitis/toxic-liver-disease), can happen when taking allopurinol. Call your healthcare provider right away if you have any of the following symptoms of liver damage.

* Nausea or vomiting
* Stomach or belly pain
* Fever
* Weakness or unusual tiredness
* Itching
* Loss of appetite
* Light-colored poop
* Dark-colored urine
* Your skin or the whites of your eyes turning yellowish in color (also called [jaundice](https://www.webmd.com/hepatitis/jaundice-why-happens-adults))

**Blood Disorders.** Allopurinol can cause blood disorders, such as agranulocytosis, aplastic anemia, hemolytic anemia, low platelet levels (thrombocytopenia), and low white blood cell levels (leukopenia). Stop using allopurinol and get help right away if you have any of the following symptoms of blood disorders.

* Fever
* Shortness of breath
* Pale or yellowish skin
* Easy bruising or bleeding
* Frequent infection
* Unusual weakness or tiredness
* Dizziness, lightheadedness, or feeling like you are about to pass out
* Headache
* Fast or abnormal heartbeat

**Dizziness and Sleepiness.** Allopurinol can make you dizzy or sleepy. Do not drive or do other activities that require alertness or coordination until you know how allopurinol affects you.

**Severe Skin Reactions.** Allopurinol can cause severe skin reactions called [Stevens-Johnson Syndrome (SJS)](https://www.webmd.com/skin-problems-and-treatments/stevens-johnson-syndrome) and [Toxic Epidermal Necrolysis (TEN)](https://www.webmd.com/skin-problems-and-treatments/what-is-toxic-epidermal-necrolysis) that can lead to death if not treated. If you develop a rash, stop allopurinol and call your healthcare provider right away. Get emergency help right away if you have any of the following symptoms of SJS or TEN.

* Painful red or purple skin that looks burned and peels off
* Flat red rash or blisters on your skin, mouth, nose, and genitals
* Red, painful, watery eyes

**Severe Allergic Reactions.** Allopurinol may cause [allergic reactions](https://www.webmd.com/allergies/allergic-reaction-causes), including a specific type of allergic reaction called DRESS. DRESS stands for Drug Reaction with Eosinophilia and Systemic Symptoms. It is also sometimes called multiorgan hypersensitivity. This is a reaction that can affect multiple parts of the body, including your liver, kidneys, and heart. Stop taking allopurinol and get help right away if you have any of the following symptoms of a serious allergic reaction.

* Breathing problems or wheezing
* Racing heart
* Fever or general ill feeling
* Swollen [lymph nodes](https://www.webmd.com/a-to-z-guides/what-are-lymph-nodes)
* Swelling of the face, lips, mouth, tongue, or throat
* Trouble swallowing or throat tightness
* Itching, skin rash, or pale red bumps on the skin called [hives](https://www.webmd.com/skin-problems-and-treatments/hives-urticaria-angioedema)
* Nausea or vomiting
* Dizziness, feeling lightheaded, or fainting
* Stomach cramps
* Joint pain
* Dark-colored pee
* Your skin or the whites of your eyes turning yellowish in color (also called jaundice)

**Warnings & Precautions**

**Allergies to Ingredients.** People who are allergic to any of the following should not use allopurinol.

* Allopurinol
* Lopurin
* Zyloprim
* Any of the ingredients in the specific product dispensed

Your pharmacist can tell you all of the ingredients in the specific allopurinol products they stock.

### **What should I know about allopurinol before using it?**

Do not take allopurinol unless it has been prescribed to you by a healthcare provider. Take it as prescribed.

Do not share allopurinol with other people, even if they have the same condition as you. It may harm them.

Keep allopurinol out of the reach of children.

If you are being treated for gout, your symptoms may get worse before getting better while taking allopurinol. Talk to your healthcare provider about managing gout flares while taking allopurinol.

Take allopurinol after a meal to limit stomach upset.

Stay well hydrated to prevent kidney stones.

### **What should I tell my healthcare provider before using allopurinol?**

Tell your healthcare provider about all of your health conditions and any prescription or over-the-counter (OTC) medicines, vitamins/minerals, herbal products, and other supplements you are using. This will help them determine if allopurinol is right for you.

**Current and Past Health Conditions.** Tell your healthcare provider if you have any of the following.

* Kidney problems
* Liver problems
* Blood disorders
* Cancer

**African, Asian, Native Hawaiian/Pacific Islander Ancestry.** Tell your healthcare provider if you are of African, Asian, Native Hawaiian or Pacific Islander Ancestry. If you are of one of these ancestries, your healthcare provider may wish to perform genetic testing to determine your risk of a specific allergic reaction to allopurinol.

**Other Medicines and Supplements.** Allopurinol may interact with other medicines and supplements. Before taking allopurinol, tell your healthcare provider about any prescription or over-the-counter (OTC) medicines, vitamins/minerals, herbal products, and other supplements you are using. See the *Interactions* section for more details.

**Pregnancy.** It is not known if or how allopurinol could affect pregnancy or harm an unborn baby. Tell your healthcare provider if you are or plan to become pregnant. Your healthcare provider will advise you if you should take allopurinol while you are pregnant or trying to get pregnant.

**Breastfeeding.** Do not take allopurinol while you are breastfeeding and for one week after your last dose. Allopurinol passes into breast milk. Tell your healthcare provider if you are breastfeeding or plan to breastfeed.

**Interactions**

### **Does allopurinol interact with foods or drinks?**

There are no known interactions between allopurinol and foods or drinks.

It is unknown if drinking alcohol will affect allopurinol. The risk of dizziness and drowsiness may be increased if you drink alcohol while taking allopurinol.

### **Does allopurinol interact with other medicines (drug interactions)?**

Always tell your healthcare provider about any prescription or over-the-counter (OTC) medicines, vitamins/minerals, herbal products, and other supplements you are using.

In particular, make sure that you discuss if you are using any of the following before taking allopurinol.

* Any thiazide diuretic, including hydrochlorothiazide and chlorthalidone, which are commonly used to reduce fluid buildup (edema) or lower blood pressure
* Ampicillin or amoxicillin, which are antibiotics used to treat infections
* Cyclosporine (Gengraf, Neoral, Sandimmune, and others), which is a medicine to suppress your immune system
* Any medicine used to treat cancer
* Mercaptopurine or azathioprine, which are used to suppress your immune system in treating certain diseases
* Theophylline, which is used to treat certain breathing conditions
* Pegloticase (Krystexxa) or probenecid, which are other medicines used to treat gout
* Warfarin (Jantoven), which is a blood thinner

This may not be a complete list of medicines that can interact with allopurinol. Always check with your healthcare provider.

**STAGING**

**Stage 1. Asymptomatic Gout**  
  
The characteristic collection of uric acid crystals in the joint begins with the accumulation of uric acid in the blood. Uric acid is a natural waste product that is formed when the body breaks down purines. Purine is a compound that occurs naturally in our tissue and in high levels in some foods, including alcoholic beverages, shellfish, and some meats, including bacon, turkey, venison and organ meats.   
  
Normally, uric acid dissolves in the blood, is filtered by the kidneys and excreted through urine. However, if the body produces too much uric acid or the kidneys are not efficient at eliminating it, uric acid can reach high levels in the blood, a condition called hyperuricemia. For some people, hyperuricemia never causes symptoms. For others, it is the first stage of gout.   
  
**Stage 2. Acute Gout**  
  
When uric acid levels in the blood become too high, it can seep out and form crystals in the spaces around the joints, causing intense pain and swelling. The pain often comes on suddenly and unexpectedly (thus the term, “attack”) and can last from a few days to a few weeks.   
  
Your first attack will likely be the first time you realize or suspect you have gout. Your doctor can make the diagnosis by drawing some fluid from the affected joints and examining it for uric acid crystals. The presence of crystals is the only way to confirm you have gout rather than another form of arthritis that would require completely different treatment. One of these is calcium pyrophosphate deposition disease (CPPD), a condition commonly known as “pseudogout” because of its resemblance to gout. Similar to gout, pseudogout comes on suddenly and painfully due to crystals that form in the joints. The difference is that the crystals are composed of calcium pyrophosphate dihydrate. It is unknown why these crystals form in the joint.   
  
Treatment during the acute stage of gout is targeted at relieving the pain and inflammation of the attacks as well as managing uric acid levels to lessen or prevent further attacks. This often involves a diet low in purines along with the use of medications that either decrease the body’s production of uric acid or increase uric acid excretion.   
  
**Stage 3. Inter critical or Interval Gout**  
  
After your first gout attack(s) you’ll probably experience a time without symptoms until another attack occurs, which could be months or even years. The stage during which attacks come at intervals — short or long — is known as “intercritical” or “interval” gout.  
  
Even when attacks are not occurring, uric acid can continue to build in the blood and joints at this stage, so your doctor may continue to prescribe uric acid-lowering medications to reduce the chance or severity of future attacks.  
  
If you are overweight, losing weight helps in the management of gout. It is also important during this stage to drink plenty of water and consume a diet low in purines.   
  
**Stage 4. Chronic Tophaceous Gout**  
  
If uric acid levels are not well controlled during the interval stage, gout may progress to its final and most problematic stage — chronic tophaceous gout.  
  
Chronic gout is characterized by accumulations of urate crystals called tophi that can appear as bumps or nodules under the skin. A tophus can form in a joint, in the bursa that cushions and protects the joint, in the bones or cartilage and under the skin.   
  
Tophi that form in the small joints of the fingers can cause physical changes and restrict movement. Tophi in the cartilage and bone can eventually lead to joint damage and deformity, and tophi under the skin can be unsightly and become infected and sometimes painful.   
  
Other problems that can occur during this chronic stage include painful joints, aching and kidney stones.

**Lifestyle and home remedies**

Medications are often the most effective way to treat gout attacks and prevent recurrent symptom flares. However, lifestyle choices also are important, and you may want to:

* **Choose healthier beverages.** Limit alcoholic beverages and drinks sweetened with fruit sugar (fructose). Instead, drink plenty of nonalcoholic beverages, especially water.
* **Avoid foods high in purines.** Red meat and organ meats, such as liver, are especially high in purines. Purine-rich seafood includes anchovies, sardines, mussels, scallops, trout and tuna. Low-fat dairy products may be a better source of protein for people prone to gout.
* **Exercise regularly and lose weight.** Keeping your body at a healthy weight reduces your risk of gout. Choose low-impact activities such as walking, bicycling and swimming — which are easier on your joints.

## **Complications**

People with gout can develop more-severe conditions, such as:

* **Recurrent gout.** Some people may never experience gout signs and symptoms again. Others may experience gout several times each year. Medications may help prevent gout attacks in people with recurrent gout. If left untreated, gout can cause erosion and destruction of a joint.
* **Advanced gout.** Untreated gout may cause deposits of urate crystals to form under the skin in nodules called tophi (TOE-fie). Tophi can develop in several areas, such as your fingers, hands, feet, elbows or Achilles tendons along the backs of your ankles. Tophi usually aren't painful, but they can become swollen and tender during gout attacks.
* **Kidney stones.** Urate crystals may collect in the urinary tracts of people with gout, causing kidney stones. Medications can help reduce the risk of kidney stones.

**Outlook / Prognosis**

If you have gout, you should expect to have flares of symptoms that come and go. Flares can happen more frequently if you don’t get gout diagnosed and treated by a healthcare provider.

Some people with gout experience more severe or more frequent attacks right after starting treatment as the uric acid in their body adjusts to new medications or changes in their diet.

Most people with gout eventually find a combination of treatments and lifestyle tweaks to manage their symptoms and reduce how often they experience gout attacks. Gout is treatable, People who have a blood uric level lower than 6 mg/dL are much less likely to experience gout attacks.

Untreated gout can lead to permanent joint damage. The buildup of uric acid in your joints and soft tissue is called tophus. Some people with gout can also develop other health problems, including:

* Severe arthritis and changes to the shape of your joint (joint deformity).
* Tophi (the plural form of tophus — a buildup of uric acid in the joints and soft tissue).
* Kidney stones.
* Heart disease.

**Prevention**

The best way to prevent gout is to limit how often you consume high-purine foods and drinks. Make sure you drink plenty of water to help your kidneys function better and avoid dehydration.

Getting regular exercise can help reduce stress on your joints and reduce your risk for obesity and other health conditions that make you more likely to develop gout.

## **Living With**

When you have a gout attack, you can manage your symptoms by:

* Avoiding alcohol and sweet drinks.
* Drinking plenty of water.
* Elevating your affected joints above the level of your heart as often as you can.
* Icing your joints. Wrap an ice pack in a thin towel or put a cold compress on your joint for 15-20 minutes at a time a few times a day.
* Limiting stress on your joints by avoiding intense exercise or physical activities.

#### **When should I see my healthcare provider?**

Visit a healthcare provider if you experience sudden intense pain in any of your joints, especially if your joint is also swollen and your skin is red or discolored. Gout shares many symptoms with infections that need to be treated right away.

Talk to your provider if you’re having more frequent gout attacks or if your symptoms are more severe than they used to be.

## **Epidemiology of Gout**

## Global Prevalence and Incidence

* The global prevalence of gout is estimated at 1% to 4% of the population worldwide, with variation by region and demographic factors
* The incidence rate ranges from 0.1% to 0.3% annually globally
* The total number of people living with gout is projected to reach approximately 95.8 million by 2050, driven largely by population growth and aging
* Gout prevalence and incidence have been increasing over the past decades in many regions

## Regional Variations

* High-income regions such as Australasia and North America show some of the highest prevalence rates, with Australasia reaching over 1,400 cases per 100,000 population and North America over 1,700 per 100,000
* Regions like East Asia, Western Europe, and South Asia have moderate prevalence rates ranging from approximately 400 to 800 per 100,000
* Lower prevalence is reported in some Sub-Saharan African regions, but data may be limited

## Demographic Patterns

* Gout is more common in men than women, with male-to-female ratios reported between 3:1 and 10:16
* The disease typically affects adults, with increasing incidence and prevalence with age.
* Recent studies highlight an increasing burden of gout among adolescents and young adults (ages 10–24), particularly linked to rising obesity rates

## Risk Factors and Burden

* High body mass index (BMI) is a leading modifiable risk factor contributing to gout incidence and years lived with disability (YLD)
* Other risk factors include diet, alcohol consumption, comorbidities (e.g., hypertension, kidney disease), and genetic predisposition.
* Gout is associated with significant morbidity, including recurrent acute arthritis episodes and chronic joint damage if untreated.

## **Differential Diagnoses of Gout**

1. Septic Arthritis
   1. Most important differential diagnosis; requires urgent exclusion.
   2. Presents with acute joint pain, swelling, redness, fever.
   3. Joint fluid culture and Gram stain essential for diagnosis.
2. Pseudogout (Calcium Pyrophosphate Deposition Disease, CPPD)
   1. Mimics gout clinically with acute arthritis.
   2. Joint fluid shows rhomboid-shaped calcium pyrophosphate crystals with positive birefringence.
3. Rheumatoid Arthritis (RA)
   1. Usually symmetric polyarthritis.
   2. Positive rheumatoid factor and anti-CCP antibodies.
   3. Chronic course with joint erosions.
4. Psoriatic Arthritis
   1. Associated with psoriasis and nail changes.
   2. Can present with dactylitis and asymmetric joint involvement.
5. Reactive Arthritis
   1. Occurs after infections; may have conjunctivitis, urethritis.
   2. Can mimic acute gouty arthritis.
6. Trauma
   1. Joint swelling and pain following injury.
   2. May precipitate gout flare.
7. Cellulitis
   1. Infection of skin and subcutaneous tissue may mimic joint swelling.
8. Tophaceous Gout vs. Neoplasms
   1. Large tophi can be mistaken for tumors like basal cell carcinoma.
9. Amyloidosis
   1. Can cause joint swelling and mimic arthritis.
10. Bursitis and Calcific Periarthritis
    1. Localized inflammation around joints mimicking gout.
11. Other Crystal Arthropathies
    1. Such as chondrocalcinosis.

## **Key Genetic Findings**

* + A landmark GWAS involving 2.6 million people (including 120,295 gout cases) identified 377 loci and 410 independent genetic signals associated with gout and serum urate levels, including 149 previously unreported loci
  + These loci implicate genes involved in urate transport, inflammation, epigenetic regulation, cell osmolarity, and inflammasome (NLRP3) activity.
* Major Genes Associated with Gout and Hyperuricemia:
  + SLC2A9 (GLUT9): Urate transporter influencing serum uric acid (SUA) levels and gout risk.
  + ABCG2: A urate efflux transporter; variants reduce urate excretion, strongly increasing gout risk.
  + SLC22A12, SLC17A1, SLC22A11: Other urate transporters linked to gout susceptibility.
  + GCKR, LRRC16A, PDZK1: Genes involved in metabolism and urate regulation.
  + Novel loci recently identified include CD160, UBE2Q2, DAP3, OVOL1, among others
* Rare Variants:
  + Whole-genome sequencing studies identified rare variants associated with gout susceptibility in specific populations (e.g., Taiwanese males), such as variants near NPHS2 and NFIA-SLC2A9 gene interactions
* Inflammatory Pathways:
  + Genes regulating the NLRP3 inflammasome and innate immune responses contribute to gout’s inflammatory pathogenesis
* Heritability:
  + SNP-based heritability estimates for gout are modest but significant, reflecting complex polygenic inheritance

## **Gout: Predefined Questions and Answers Set**

## 1. What is gout?

Gout is a form of inflammatory arthritis caused by the deposition of monosodium urate crystals in joints and tissues due to elevated blood uric acid levels (hyperuricemia).

## 2. What causes gout?

Gout results from high levels of uric acid in the blood, which can be due to increased production, decreased excretion by the kidneys, or both. Risk factors include genetics, diet (high purine intake), obesity, certain medications, and medical conditions like kidney disease.

## 3. What are the symptoms of gout?

Symptoms include sudden, severe attacks of joint pain, swelling, redness, and warmth, often affecting the big toe (podagra), but can involve other joints such as ankles, knees, wrists, and fingers.

## 4. How is gout diagnosed?

Diagnosis is primarily clinical but confirmed by identifying monosodium urate crystals in joint fluid under polarized light microscopy. Blood tests showing elevated serum uric acid support the diagnosis but are not definitive alone.

## 5. What triggers a gout attack?

Common triggers include alcohol consumption, high-purine foods (red meat, seafood), dehydration, trauma, surgery, and certain medications like diuretics.

## 6. How is an acute gout attack treated?

Treatment focuses on reducing inflammation and pain using nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroids.

## 7. How is gout prevented?

Long-term management includes lifestyle modifications (diet, weight loss, limiting alcohol), and urate-lowering therapy (e.g., allopurinol, febuxostat) to maintain serum uric acid below target levels.

## 8. Can gout cause joint damage?

Yes, chronic untreated gout can lead to joint damage, tophi formation (urate crystal deposits), and decreased joint function.

## 9. Are there complications associated with gout?

Complications include recurrent attacks, chronic arthritis, kidney stones, and urate nephropathy.

## 10. When should I see a doctor for gout?

Seek medical advice if you experience sudden, severe joint pain, swelling, or redness, especially if it’s your first attack or if symptoms worsen or recur frequently.

## **Doctor-Patient Conversation**

## Patient:

Hi, doctor. I woke up with severe pain and swelling in my big toe. It’s red, hot, and very tender. I can barely walk.

## Doctor:

That sounds quite painful. How long has this been going on?

## Patient:

It started last night and got worse quickly.

## Doctor:

Have you had similar episodes before, or is this the first time?

## Patient:

This is the first time I’ve had something like this.

## Doctor:

Do you have any history of kidney problems, high blood pressure, or take medications regularly?

## Patient:

I have high blood pressure and take medication for it.

## Doctor:

Certain medications and conditions can increase uric acid levels, which may cause gout. Have you noticed any other joint pains or swelling?

## Patient:

No, just this toe so far.

## Doctor:

Gout is caused by the buildup of uric acid crystals in joints, leading to sudden, intense inflammation. The big toe is a common site. I’d like to do some blood tests to check your uric acid level and possibly joint fluid analysis if needed.

## Patient:

What causes uric acid to build up?

## Doctor:

Uric acid comes from the breakdown of substances called purines found in some foods and your body. When uric acid levels get too high, crystals can form in joints causing gout attacks.

## Patient:

How is gout treated?

## Doctor:

For the acute attack, we use anti-inflammatory medications like NSAIDs, colchicine, or corticosteroids to reduce pain and swelling. Long-term treatment may include medications to lower uric acid levels to prevent future attacks.

## Patient:

Are there lifestyle changes I can make?

## Doctor:

Yes, limiting foods high in purines like red meat, shellfish, and alcohol, especially beer, helps. Staying hydrated and maintaining a healthy weight are also important.

## Patient:

Will I need to take medication forever?

## Doctor:

Not necessarily. Some people need long-term urate-lowering therapy, especially if they have frequent attacks or joint damage. We’ll monitor your condition and decide what’s best.

## Patient:

What should I do now?

## Doctor:

I’ll prescribe medication to relieve your current symptoms and arrange blood tests. Avoid putting pressure on the joint and keep it elevated. We’ll follow up soon to discuss results and further management.

## Patient:

Thank you, doctor.

## Doctor:

You’re welcome. Let me know if the pain worsens or you develop a fever.

REFERENCES

[4 Phases Stages of Gout | Arthritis Foundation](https://www.arthritis.org/diseases/more-about/stages-of-gout)

[Allopurinol: Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD](https://www.webmd.com/drugs/2/drug-8610/allopurinol-oral/details)

[Gout: Symptoms, Treatment & Prevention](https://my.clevelandclinic.org/health/diseases/4755-gout)

[Gout - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/gout/diagnosis-treatment/drc-20372903)

<https://emedicine.medscape.com/article/329958-differential?form=fpf>

**BURSITIS**

**DEFINITION AND DESCRIPTION**

Bursitis (bur-SY-tis) is a painful condition that affects the small, fluid-filled sacs — called bursae (bur-SEE) — that cushion the bones, tendons and muscles near your joints. Bursitis occurs when bursae become inflamed.

The most common locations for bursitis are in the shoulder, elbow and hip. But you can also have bursitis by your knee, heel and the base of your big toe. Bursitis often occurs near joints that perform frequent repetitive motion.

Treatment typically involves resting the affected joint and protecting it from further trauma. In most cases, bursitis pain goes away within a few weeks with proper treatment, but recurrent flare-ups of bursitis are common.

#### **Types of bursitis**

There are more than 150 bursae in your body. Bursitis can affect any of them. You’re most likely to develop bursitis in joints you use for repetitive motions or in places you put a lot of pressure, including your:

* Shoulders (subacromial bursitis).
* Elbows (olecranon bursitis — sometimes called miner’s elbow or barfly’s elbow).
* Knees (prepatellar bursitis — housemaid’s knee).
* Feet (especially near your [heel](https://my.clevelandclinic.org/health/diseases/21706-heel-bursitis), big toe or the ball of your foot).
* Hips (iliopectineal or trochanteric bursitis).
* Butt (ischial bursitis or weaver’s bottom).

Healthcare providers might refer to different types of bursitis with a specific name, but they’re all the same issue — swelling in and around a bursa.

## **Causes**

The most common causes of bursitis are repetitive motions or positions that put pressure on the bursae around a joint. Examples include:

* Throwing a baseball or lifting something over your head repeatedly
* Leaning on your elbows for long periods
* Extensive kneeling for tasks such as laying carpet or scrubbing floors

Other causes include injury or trauma to the affected area, inflammatory arthritis such as rheumatoid arthritis, gout and infection.

**Risk factors**

Anyone can develop bursitis, but certain factors can increase your risk:

* **Age.** Bursitis becomes more common with aging.
* **Occupations or hobbies.** If your work or hobby requires repetitive motion or pressure on a particular bursae, your risk of developing bursitis increases. Examples include carpet laying, tile setting, gardening, painting and playing a musical instrument.
* **Other medical conditions.** Certain systemic diseases and conditions — such as rheumatoid arthritis, gout and diabetes — increase your risk of developing bursitis. Being overweight can increase your risk of developing hip and knee bursitis.

### **Bursitis symptoms**

The most common symptoms of bursitis are:

* Pain, especially when you’re moving the affected part of your body.
* A limited range of motion (how far you can move a body part).
* Swelling.

If you have an infection that’s causing bursitis, you might have other symptoms, including:

* Discoloration or redness on your skin.
* A feeling of warmth or heat.
* Fever.
* Chills.

## **Diagnosis**

Doctors can often diagnose bursitis based on a medical history and physical exam. Testing, if needed, might include:

* **Imaging tests.** X-ray images can't positively establish the diagnosis of bursitis, but they can help to exclude other causes of your discomfort. Ultrasound or MRI might be used if your bursitis can't easily be diagnosed by a physical exam alone.
* **Lab tests.** Your doctor might order blood tests or an analysis of fluid from the inflamed bursa to pinpoint the cause of your joint inflammation and pain.

**TREATMENT**

Bursitis generally gets better on its own. Conservative measures, such as rest, ice and taking a pain reliever, can relieve discomfort. If conservative measures don't work, you might require:

* **Medication.** If the inflammation in your bursa is caused by an infection, your doctor might prescribe an antibiotic.
* **Therapy.** Physical therapy or exercises can strengthen the muscles in the affected area to ease pain and prevent recurrence.
* **Injections.** A corticosteroid drug injected into the bursa can relieve pain and inflammation in your shoulder or hip. This treatment generally works quickly and, in many cases, one injection is all you need.
* **Assistive device.** Temporary use of a walking cane or other device will help relieve pressure on the affected area.
* **Surgery.** Sometimes an inflamed bursa must be surgically drained, but only rarely is surgical removal of the affected bursa necessary.

## **Drugs Used for Bursitis and Their Side Effects**

| Drug Name | Drug Class | Common Side Effects | Notes |
| --- | --- | --- | --- |
| Ibuprofen (Advil, Motrin) | NSAID | Nausea, stomach pain, gastrointestinal bleeding, kidney impairment, allergic reactions | OTC and prescription; used for mild to moderate pain and inflammation |
| Naproxen (Aleve, Naprosyn) | NSAID | Nausea, stomach upset, ulcers, bleeding, dizziness | OTC and prescription; longer-acting NSAID |
| Indomethacin (Indocin) | NSAID | Headache, dizziness, GI upset, ulcers, kidney issues | Prescription only; potent NSAID |
| Diclofenac (Voltaren) | NSAID | GI upset, liver enzyme elevation, headache | Available as tablets, gels, injections |
| Ketoprofen (Profenid) | NSAID | GI upset, dizziness, rash | Available orally and topically |
| Celecoxib (Celebrex) | COX-2 selective NSAID | Abdominal pain, diarrhea, hypertension, cardiovascular risk | Prescription; fewer GI side effects than non-selective NSAIDs |
| Acetaminophen (Tylenol) | Analgesic | Liver toxicity (in overdose), nausea | Used for pain relief; no anti-inflammatory effect |
| Prednisone | Oral corticosteroid | Weight gain, mood changes, hypertension, hyperglycemia, osteoporosis | Used for systemic inflammation control |
| Corticosteroid injections (e.g., Triamcinolone, Kenalog, Methylprednisolone) | Corticosteroids (injectable) | Injection site pain, infection risk, tendon weakening or rupture with repeated use | Direct injection into bursa for rapid relief |
| Trolamine salicylate | Topical analgesic | Skin irritation, rash | OTC topical option for localized pain |
| Antibiotics (e.g., Cephalexin, Clindamycin) | Antibiotics (for septic bursitis) | Diarrhea, nausea, allergic reactions | Only if bursitis is infected |

* NSAIDs are the first-line treatment for pain and inflammation in bursitis but should be used cautiously in patients with GI, renal, or cardiovascular risks.
* Corticosteroid injections provide quick symptom relief but should be limited to avoid tendon damage and infection.
* Antibiotics are reserved for septic bursitis and chosen based on culture results.
* Topical agents offer localized relief with fewer systemic side effects.
* Acetaminophen is useful for pain but lacks anti-inflammatory properties.

**Procedures and Recovery Timeline**

## 1. Initial Conservative Treatment (Weeks 0–2+)

* Rest and Activity Modification:
  + Avoid activities that put pressure on the affected bursa to allow healing.
  + Duration depends on severity but generally at least 1–2 weeks of rest are recommended.
* Ice Application:
  + Apply ice packs several times daily to reduce pain and swelling.
* Medications:
  + NSAIDs (e.g., ibuprofen, naproxen) for pain and inflammation.
  + Over-the-counter analgesics like acetaminophen may be used.
* Assistive Devices:
  + Use of canes, braces, or padding to offload pressure on the bursa.

## 2. Physical Therapy and Gradual Activity Resumption (Weeks 2–6)

* Physical Therapy:
  + Strengthening and flexibility exercises to support the joint and prevent recurrence.
  + Guided by a physical therapist to avoid overuse.
* Activity Modification:
  + Gradual return to normal activities as symptoms improve.
  + Avoid repetitive motions or positions that caused bursitis.

## 3. Interventional Procedures (If Conservative Treatment Fails, Weeks 2–8+)

* Aspiration (Bursal Fluid Drainage):
  + Performed if there is significant fluid buildup causing pain or to rule out infection.
  + Fluid is withdrawn with a sterile needle; may be repeated if fluid reaccumulates.
  + Provides symptomatic relief but not always a permanent solution.
* Corticosteroid Injection:
  + Injected directly into the bursa to reduce inflammation and pain.
  + Typically considered if symptoms persist after 10 days of conservative treatment.
  + Usually one injection is sufficient; repeated injections are used cautiously due to risk of tendon weakening or infection.

## 4. Surgical Intervention (Rare, for Chronic or Septic Bursitis)

* Indications:
  + Persistent bursitis not responding to medical treatment.
  + Septic bursitis with abscess formation or failure of needle drainage.
  + Chronic bursitis with recurrent symptoms affecting quality of life.
* Procedures:
  + Incision and drainage of infected bursa.
  + Surgical removal (bursectomy) of the bursa in refractory cases.
* Recovery:
  + Usually outpatient surgery with local or regional anesthesia.
  + Immobilization of the affected area for 1–2 weeks.
  + Stitches removed after 7–12 days.
  + Full recovery can take several weeks; physical therapy may be needed post-op.

## **Prevention**

While not all types of bursitis can be prevented, you can reduce your risk and the severity of flare-ups by changing the way you do certain tasks. Examples include:

* **Using kneeling pads.** Use some type of padding to reduce the pressure on your knees if your job or hobby requires a lot of kneeling.
* **Lifting properly.** Bend your knees when you lift. Failing to do so puts extra stress on the bursae in your hips.
* **Wheeling heavy loads.** Carrying heavy loads puts stress on the bursae in your shoulders. Use a dolly or a wheeled cart instead.
* **Taking frequent breaks.** Alternate repetitive tasks with rest or other activities.
* **Maintaining a healthy weight.** Being overweight places more stress on your joints.
* **Exercising.** Strengthening your muscles can help protect your affected joints.
* **Warming up and stretching** before strenuous activities to protect your joints from injury.

**EPIDEMIOLOGY**

In general, bursitis is encountered equally in the male and female populations. However, some types of bursitis have documented female predilection, specifically pes anserine and trochanteric bursitis. Furthermore, these forms of bursitis are more common in individuals who are obese. Men are more often affected by olecranon bursitis due to the increased rate of men who perform manual labor for a living (plumbers, gardeners, mechanics, and construction workers, among others). Since certain occupational stressors increase one's risk of developing bursitis, many colloquial terms for specific types of bursitis have been coined to reflect these epidemiologic connections. For example, prepatellar bursitis is also known as "housemaid's knee," while olecranon bursitis is sometimes referred to as "student's elbow."

Likewise, infrapatellar bursitis is often called "clergyman's knee," while ischial bursitis is called "weaver's bottom." Bursitis of the subcutaneous calcaneal bursa can be provoked by footwear that is too tight or ill-fitting, and this is frequently encountered in dancers and figure skaters. In each of these cases, the cause of the bursitis is usually prolonged pressure over the affected bursa. While bursitis affects people of all ages, the elderly may be at greater risk, given that many older people are afflicted by osteoarthritis and other chronic diseases, which can increase the risk of bursitis. For septic bursitis, immunocompromised patients, such as people with diabetes, those with certain rheumatologic disorders, people who suffer from alcoholism, or those with HIV, are at increased risk.

## **Differential Diagnosis of Bursitis**

* Tendonitis
  + Inflammation of tendons rather than bursae.
  + Pain localized along the tendon rather than over the bursa.
* Cellulitis
  + Infection of skin and subcutaneous tissue causing redness, warmth, swelling, and systemic signs like fever.
  + Usually no localized fluid collection as in bursitis.
* Septic Bursitis vs. Septic Arthritis
  + Infection within the bursa (septic bursitis) or joint (septic arthritis) requires urgent differentiation.
  + Septic bursitis often has purulent fluid on aspiration; systemic signs may be present.
* Gout and Pseudogout (Crystal-Induced Arthropathies)
  + Acute joint inflammation due to urate or calcium pyrophosphate crystals.
  + Can cause swelling near bursae and mimic bursitis.
  + Diagnosis confirmed by crystal identification in aspirated fluid.
* Rheumatoid Arthritis (RA)
  + Chronic, symmetric polyarthritis with joint swelling and tenderness.
  + May have associated bursitis but usually distinguished by serology and joint pattern.
* Osteoarthritis (OA)
  + Degenerative joint disease causing joint pain and stiffness, less acute inflammation.
  + May coexist with bursitis but usually distinguished by imaging.
* Ligamentous Injuries and Soft Tissue Trauma
  + Sprains or tears of ligaments (e.g., ACL, MCL) or muscle injuries can cause localized pain and swelling.
  + History of trauma and imaging help differentiate.
* Fractures
  + Bone injury causing pain and swelling near joints.
  + Confirmed by radiographs.
* Morel-Lavallée Lesion
  + Closed degloving injury causing fluid collection between skin and fascia, mimicking bursitis.

## **Doctor-Patient Conversation: Bursitis**

Doctor:  
Hello! I understand you’ve been experiencing pain and swelling in your right shoulder. Can you tell me more about when this started and what activities you were doing?

Patient:  
Yes, doctor. It started about a week ago. I usually play cricket on weekends, and I think the repeated swinging of the bat and throwing might have caused this pain. The shoulder feels swollen and hurts especially when I move it.

Doctor:  
That sounds like it could be bursitis, which is inflammation of the small fluid-filled sacs called bursae that cushion your joints. The repetitive motion from cricket can irritate these bursae. Did you notice any redness or warmth over the shoulder?

Patient:  
Yes, it’s a bit red and warm to touch. The pain is worse when I try to lift my arm or reach behind my back.

Doctor:  
Those are common symptoms. I will examine your shoulder now to check for tenderness and range of motion. Sometimes, bursitis can cause decreased movement because of pain.

Patient:  
Is this serious? How is it treated?

Doctor:  
Most cases of bursitis improve with rest and avoiding activities that aggravate it. Applying ice packs several times a day can help reduce swelling. I’ll also recommend some anti-inflammatory medications to ease the pain and inflammation.

Patient:  
Will I need any injections or surgery?

Doctor:  
Usually, injections are only needed if symptoms persist despite rest and medication. Surgery is rare and reserved for chronic or complicated cases. If the bursa is swollen with fluid, sometimes we may aspirate it to relieve pressure or check for infection.

Patient:  
How long will it take to get better?

Doctor:  
Most people recover within a few weeks with proper rest and treatment. It’s important not to return to the activities that caused the bursitis too soon, or it might come back.

Patient:  
Are there any exercises I should do?

Doctor:  
Once the pain decreases, gentle stretching and strengthening exercises guided by a physiotherapist can help restore shoulder function and prevent recurrence.

Patient:  
Thank you, doctor. I’ll follow your advice.

Doctor:  
You’re welcome. If the pain worsens or you develop fever or increased redness, please come back immediately as that might indicate infection.

## **Bursitis Genomic Data**

* Hip Pain and Associated Genetic Loci:  
  A genome-wide association study (GWAS) on hip pain (which can include bursitis as a cause) identified seven genetic loci associated with hip pain in the UK Biobank cohort, including variants in genes such as EXD3 and sex-specific loci like CUL1 in males and others on chromosomes 7, 9, and 13 in females
* Frozen Shoulder and Adhesive Capsulitis (Related Soft Tissue Inflammatory Conditions):  
  GWAS analyses identified multiple genetic loci associated with frozen shoulder and adhesive capsulitis, conditions involving inflammation and fibrosis of joint capsules and periarticular tissues, which share some pathophysiological features with bursitis. Key genes implicated include WNT7B, TSPAN2/NGF, SATB2, MMP14, and FGF13
  + Notably, there is a strong genetic overlap between adhesive capsulitis and Dupuytren disease, suggesting shared fibrotic pathways.
* Inflammation and Fibrosis Pathways:  
  The genes identified in these studies are involved in pathways regulating fibrosis, extracellular matrix remodeling, and inflammatory responses, which are relevant to the pathogenesis of bursitis.
* Diabetes as a Genetic Risk Factor:  
  Mendelian randomization studies indicate that type 1 diabetes is a causal risk factor for frozen shoulder, implying metabolic and genetic links that may also influence bursitis susceptibility

**REFERENCES**

[Bursitis - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK513340/#article-18728.s9)

<https://emedicine.medscape.com/article/2145588-treatment>

[Bursitis - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/bursitis/diagnosis-treatment/drc-20353247)

[Bursitis: Types, Treatment & Prevention](https://my.clevelandclinic.org/health/diseases/10918-bursitis#overview)

### **Joint hypermobility syndrome**

**DEFINITION AND DESCRIPTION**

Joint hypermobility syndrome is a connective tissue disorder. Thick bands of tissue (ligaments) hold your joints together and keep them from moving too much or too far out of range. In people with joint hypermobility syndrome, those ligaments are loose or weak. If you have joints that are more flexible than normal and it causes you pain, you may have joint hypermobility syndrome.

**Joint hypermobility and joint hypermobility syndrome**

Joint hypermobility is very common. Hypermobility means your joints can move beyond the normal range of motion. You may also hear the term double-jointed. This means your joints are very flexible. The most affected joints are your elbows, wrists, fingers and knees.

In most people, hypermobility doesn’t cause any pain or medical issues. However, for some people, hypermobility causes joint pain, joint and ligament injuries, tiredness (fatigue), bowel issues and other symptoms. Joint hypermobility syndrome is most common in children and young people. It affects females and people of Asian and Afro-Caribbean descent more often. It usually gets better with age.

### **Is joint hypermobility syndrome the same as Ehlers-Danlos syndrome?**

Joint hypermobility syndrome can be a sign of a more serious underlying genetic condition. These conditions are called Heritable Disorders of Connective Tissue (HDCT). Rare medical conditions associated with joint hypermobility syndrome include:

* **Ehlers-Danlos syndrome**: A group of conditions that affect your cartilage, bone, fat and blood. A defect in collagen — the protein that adds flexibility and strength to your connective tissue — causes this syndrome.
* **Marfan syndrome**: A condition that affects your connective tissue. A defect in the gene responsible for building fibrillin and elastic fibers — a major part of your connective tissue — causes this syndrome.
* **Down syndrome**: A genetic disorder that affects the way your brain and body develop. People with Down syndrome are born with an extra chromosome.

**Symptoms and Causes**

The most common symptom of joint hypermobility syndrome is pain in your joints and muscles. Other symptoms may include:

* Frequent joint and ligament injuries, including dislocations and sprains.
* Joint and muscle stiffness.
* Tiredness (fatigue).
* Clumsiness/poor balance.
* Bladder and bowel issues.
* Dizziness and fainting.
* Thin, stretchy skin.

### **Causes of joint hypermobility syndrome**

The exact cause of joint hypermobility syndrome isn’t known. However, the disorder tends to run in families. The genes that are involved in the creation of collagen are believed to play a role. Collagen is the protein that adds flexibility and strength to your joints, ligaments and tendons. People with joint hypermobility syndrome have loose joints because they have weak ligaments. They have weak ligaments because of the defect in their collagen.

## **Diagnosis and Tests**

The difference between a person with a neutral stance and with joint hypermobility syndrome.

Your healthcare provider may perform a physical exam to see the range of motion in your joints. They may also order blood tests to check for possible genetic conditions.

Your healthcare provider may use a test or questionnaire to measure the flexibility of your joints. The Beighton score measures your joint flexibility on a nine-point scale. You receive one point for each of the following:

* Being able to bend forward and place your hands flat on the floor without bending your knees.
* Being able to bend your elbows backward (one point each).
* Being able to bend your knees backward (one point each).
* Being able to bend your thumbs backward to touch your forearms (one point each).
* Being able to bend your little fingers backward beyond 90 degrees (one point each).

If you scored four or more points and have had pain in four or more joints for at least three months, you may have joint hypermobility syndrome.

Your healthcare provider may also ask you the five-point hypermobility questionnaire. The five questions asked are:

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself double-jointed?

If you answered “yes” to two or more questions, you may have joint hypermobility syndrome.

## **Management and Treatment**

There’s no cure presently for joint hypermobility syndrome. Treatment involves protecting your joints and managing your pain. You can protect your joints by strengthening your muscles through exercise. Other recommendations include:

* Maintain good posture.
* Stand with your knees slightly bent and avoid extreme ranges of motion.
* Wear shoes with good arch support.
* Use orthotics to help correct flat feet.
* See a physical therapist to help reduce pain, increase muscle strength and improve your posture and balance.

For mild pain, your healthcare provider may recommend an over-the-counter pain reliever such as acetaminophen (Tylenol®), ibuprofen (Advil®, Motrin®) or naproxen (Aleve®). For more severe pain, your healthcare provider may prescribe stronger pain medication or provide additional resources to help manage your pain.

## **Common Medications Used**

* Paracetamol (Acetaminophen): Often used to relieve mild to moderate joint pain and reduce fever. It is generally well tolerated but can cause side effects such as nausea or loss of appetite in some cases
* Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Examples include ibuprofen and diclofenac. These help reduce joint pain and inflammation. They are available in tablets, gels, and sprays. Side effects can include gastrointestinal upset, nausea, and in some cases, increased risk of cardiovascular issues or kidney problems with long-term use
* Stronger Painkillers: For severe pain, GPs may prescribe stronger analgesics, which might include opioids. However, opioids are generally avoided due to risks of dependence and side effects
* Gabapentin: Sometimes prescribed if there is nerve-related pain or comorbid fibromyalgia. Side effects can include dizziness, fatigue, and coordination problems
* Antispasticity Agents: Such as baclofen or tizanidine may be used for muscle spasms, but patients with exercise intolerance or orthostatic symptoms may not tolerate these well
* Antidepressants: Low-dose tricyclic antidepressants (TCAs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) may be used to manage chronic pain. Side effects vary but can include drowsiness, dry mouth, and dizziness

**Types of Exercises Commonly Used in Hypermobility Physical Therapy**

1. **Strengthening Exercises**  
   Exercises aimed at strengthening the muscles around hypermobile joints are central to physical therapy. These exercises may include:
2. **Isometric contractions** (holding a position without movement to build stability).

**Resistance training** (using weights, resistance bands, or body weight to build muscle strength).

**Core exercises** (targeting the abdominals, obliques, and back muscles).

1. **Stabilization Exercises**  
   These exercises aim to teach the body to better control joint movements. These could include:

**Bracing exercises** (such as holding specific positions to promote stability).

**Balance exercises** (like standing on one leg or using a balance board).

1. **Stretching**  
   Stretching exercises are often done under the guidance of a physical therapist to ensure that they are done correctly, with an emphasis on avoiding overstretching and protecting joint stability. Examples include:

**Gentle yoga poses** (to stretch without overextending).

**Dynamic stretching** (involving movement through a range of motion).

1. **Proprioception and Balance Drills**  
   These exercises aim to improve body awareness, reduce the likelihood of injury, and enhance coordination. Common examples include:

**Standing on unstable surfaces** (e.g., balance pads or stability balls).

**Tai Chi or other mind-body exercises** (which can help improve coordination and awareness).

**Physical Therapy for Hypermobility**

It’s important to note that a tailored approach to physical therapy is essential for individuals with hypermobility. Each person’s condition may vary, and a physical therapist will customize the treatment plan to suit the individual’s specific symptoms, needs, and fitness level.

The first step in physical therapy typically involves an assessment, where the therapist evaluates the range of motion, strength, and stability of the joints. Based on this assessment, the therapist will create a program that focuses on strengthening weak muscles, improving joint stability, and reducing pain or discomfort.

As physical therapy progresses, the therapist will monitor improvements and make adjustments to the treatment plan as needed. It’s essential for individuals with hypermobility to communicate openly with their therapist about any discomfort or concerns to ensure that the therapy remains effective and safe.

## **Procedure and Timelines**

## Diagnostic Procedure

1. Initial Assessment by GP or Specialist:
   1. Evaluation of symptoms such as joint pain, stiffness, frequent sprains, dislocations, fatigue, and balance issues.
   2. Use of the Beighton score to measure joint hypermobility on a 9-point scale; a score of 4 or more along with pain in 4 or more joints for at least 3 months suggests JHS.
   3. Administration of the five-point hypermobility questionnaire; answering "yes" to two or more questions supports diagnosis.
   4. Additional tests like blood tests or X-rays may be done to rule out other conditions such as arthritis

## Treatment and Management Procedure

1. Referral and Multidisciplinary Approach:
   1. Referral to physiotherapy, occupational therapy, and podiatry for specialist management.
   2. Physiotherapy focuses on strengthening muscles, improving posture, balance, and joint stability.
   3. Occupational therapy advises on assistive devices, splints, and activity modifications.
   4. Podiatry assesses foot mechanics and may provide insoles to prevent injury
2. Physical Therapy Timeline:
   1. A progressive, individualized exercise program is initiated to strengthen muscles supporting hypermobile joints.
   2. Patients are encouraged to gradually increase activity levels to improve fitness and reduce fatigue.
   3. Therapy sessions typically occur multiple times per week initially, with ongoing home exercises.
   4. Improvement in symptoms such as pain reduction and increased joint stability may be observed within 6 to 8 weeks, though long-term management is often required
3. Pain Management:
   1. Use of over-the-counter painkillers like paracetamol or NSAIDs for mild to moderate pain.
   2. Stronger pain medications or referral to pain clinics may be considered for severe pain.
   3. Adjunct measures such as warm baths, heat rubs, and lifestyle modifications to reduce joint stress are recommended.
4. Emerging Treatments:
   1. Prolotherapy, a regenerative injection therapy aimed at strengthening ligaments and tendons, is gaining attention as a potential first-line treatment.
   2. This involves a series of minimally invasive injections over weeks to months to promote healing and improve joint stability5

## **Outlook / Prognosis**

Joint hypermobility syndrome is most commonly found in children and adolescents. As you get older, symptoms tend to decrease. For some people, symptoms are mild. For others, pain can be severe. It’s important to work with your healthcare provider on ways to protect your joints and manage your pain.

## **Prevention**

Joint hypermobility syndrome is a genetic disorder that usually runs in families. Therefore, it can’t be prevented.

## **Living With**

Researchers have found there may be a link between hypermobility and gastrointestinal issues such as irritable bowel syndrome (IBS). The symptoms of IBS are commonly found in joint hypermobility syndrome. Therefore, your healthcare provider may recommend an exclusion diet to test for an intolerance to certain food products. If whatever’s causing the intolerance is removed, your symptoms may resolve.

The three most common exclusion diets are:

* **Gluten-free diet**: Gluten is removed from your diet to see if you have a gluten allergy.
* **Lactose-free diet**: Lactose is removed from your diet to see if you’re intolerant to dairy products.
* **Low-FODMAP diet:** A group of five sugars found in certain foods is removed from your diet. These sugars are lactose, fructose, fructans, galactans and polyols. FODMAP stands for fermentable, oligosaccharides, disaccharides, monosaccharides and polyols.

### **How do I take care of myself?**

If you have joint hypermobility syndrome, it’s important to maintain a healthy lifestyle and protect your joints. You can improve joint and muscle strength by:

* Getting regular exercise.
* Taking regular breaks while exercising.
* Eating a healthy diet.
* Wearing supportive shoes.
* Easing joint pain and stiffness with warm baths.
* Not overextending your joints on purpose.

**EPIDEMIOLOGY**

* Prevalence in General Population:  
  The prevalence of joint hypermobility ranges widely from about 5% to 40% in children and 10% to 20% in adults, reflecting differences in assessment methods and population characteristics. Another review reports GJH prevalence between 2% and 57% depending on the population studied
* Age and Sex Differences:  
  Hypermobility is most common in infants and children, with prevalence decreasing through adolescence and adulthood. Females generally exhibit a higher prevalence than males, although some studies report no gender difference. For example, some studies show prevalence rates of 36.7% in females versus 13.7% in males
* Ethnic and Geographic Variation:  
  Prevalence varies by ethnicity, with higher rates reported in African, Asian, and Arabian populations compared to Caucasians. For instance, a Nigerian study found a high prevalence (up to 64.7% using a Beighton score cutoff of ≥5), attributed partly to ethnicity and age range. Australian studies also show higher prevalence in non-Caucasian groups
* Sport and Activity Influence:  
  Certain athletic populations, such as ballet dancers and gymnasts, show very high prevalence rates (up to 97%), reflecting selection for hypermobility traits in these disciplines
* Joint Hypermobility Syndrome (JHS) Specific Prevalence:  
  The prevalence of JHS, which includes symptomatic hypermobility, is estimated at about 3% in the UK adult population

## **Differential Diagnosis**

1. Heritable Connective Tissue Disorders (HDCTs):  
   These are the primary differential diagnoses and include:
   1. Ehlers-Danlos Syndrome (EDS), especially the hypermobile type (hEDS):  
      Classical, Vascular, and Kyphoscoliotic types of EDS:  
      Marfan Syndrome:  
      Loeys-Dietz Syndrome:
2. Osteogenesis Imperfecta:  
   Arterial Tortuosity Syndrome and Lateral Meningocele Syndrome:  
   Inherited Myopathies with Joint Hypermobility:  
   1. Collagen VI-related dystrophies
   2. FKBP14-related kyphoscoliotic EDS
3. RYR1- and SEPN1-related myopathies  
   Benign Joint Hypermobility Syndrome (BJHS):  
   Sometimes used synonymously with JHS, characterized mainly by joint hypermobility and musculoskeletal pain without systemic involvement.
4. Inflammatory Joint Conditions:  
   Conditions such as juvenile idiopathic arthritis or other inflammatory arthropathies may present with joint symptoms but typically have different clinical and laboratory features.
5. Other Considerations:
   1. Fibromyalgia: May share symptoms like widespread pain and fatigue but lacks joint hypermobility.
   2. Marfan-like habitus or other syndromic features: Presence of skin signs, eye abnormalities, or vascular symptoms suggests alternative diagnoses.

## **Questions and Answers**

## Q. What is Joint Hypermobility Syndrome (JHS)?

A. JHS is a condition characterized by joints that move beyond the normal range, often accompanied by symptoms such as joint pain, instability, and sometimes dislocations

## Q. How is joint hypermobility assessed clinically?

A. The most common clinical tool is the Beighton Scoring System, which evaluates hypermobility on a 9-point scale by testing specific joints: little fingers, thumbs, elbows, knees, and spine. A positive score is ≥5/9 in adults, ≥6/9 in children before puberty, and ≥4/9 in adults over 50

## Q. What is the Beighton Score test?

A. It involves assessing:

* Ability to bend the little finger back beyond 90°
* Ability to bend the thumb to the forearm
* Hyperextension of elbows and knees beyond 10°
* Ability to place hands flat on the floor without bending knees  
  Each positive test scores one point, with a maximum of 9 points

## Q. Is there a questionnaire for assessing joint hypermobility?

A. Yes, the 5-Point Questionnaire (5PQ) developed by Hakim and Grahame is a self-assessment tool that screens for historical and present joint hypermobility. It includes questions such as:

* Can you place your hands flat on the floor without bending your knees?
* Can you bend your thumb to touch your forearm?
* As a child, could you do the splits or contort your body?  
  Answering "yes" to two or more questions suggests hypermobility

## Q .How is hypermobile Ehlers-Danlos Syndrome (hEDS) diagnosed?

1. Diagnosis requires meeting all three criteria:

* Criterion 1: Generalized joint hypermobility (age- and sex-specific Beighton score thresholds or a combination of Beighton score and 5PQ)
* Criterion 2: Presence of systemic connective tissue features, family history, or musculoskeletal complications
* Criterion 3: Exclusion of other connective tissue disorders

## Q. What are the age- and sex-specific Beighton score cut-offs?

* Pre-pubertal children and adolescents: ≥6/9
* Pubertal men and women up to age 50: ≥5/9
* Adults over 50: ≥4/9[1](https://www.ehlers-danlos.com/assessing-joint-hypermobility/)[5](https://dralisongrimaldi.com/blog/identifying-joint-hypermobility-syndromes/)[6](https://www.ehlers-danlos.com/wp-content/uploads/2017/05/hEDS-Dx-Criteria-checklist-1.pdf)[7](https://mobile.fpnotebook.com/Rheum/Exam/GnrlzdJntHyprmbltyDgns.htm).

## Q. Why use the 5-Point Questionnaire?

A. It is a practical, reliable, and validated screening tool for generalized joint hypermobility, especially useful when physical examination is not feasible or to assess historical hypermobility

## Q. What other scoring systems exist for JHS?

A. Besides Beighton and 5PQ, the Brighton criteria and Hospital del Mar criteria are used, incorporating joint and extra-articular features to improve diagnostic accuracy

## **Genetic Basis and Heritability**

## Candidate Genes and Genetic Findings

* COL3A1: A pathogenic variant in the *COL3A1* gene was identified in a family with hEDS-like features, though this variant is rare and not widely reported in hEDS cases. *COL3A1* encodes type III collagen, important for connective tissue integrity.
* TNXB: Mutations in *TNXB* cause classical-like EDS (clEDS), an autosomal recessive disorder with joint hypermobility, highlighting the role of extracellular matrix glycoproteins in hypermobility
* Genome-wide association studies (GWAS) on hypermobility spectrum disorders and hEDS are ongoing, aiming to identify novel loci, but the genetic heterogeneity makes pinpointing causative variants challenging
* No single gene or mutation has been definitively linked to the majority of JHS/hEDS cases, underscoring its complex and heterogeneous genetic architecture.

## Related Genetic Syndromes

* JHS can be part of a spectrum including Marfan syndrome (FBN1 mutations), Osteogenesis imperfecta (COL1A1/2 mutations), and other connective tissue disorders with joint hypermobility features
* These syndromes have known genetic causes, but JHS/hEDS remains largely a clinical diagnosis due to lack of definitive genetic markers.

## Recent GWAS and Loci of Interest

* Recent GWAS on related musculoskeletal traits such as hip pain and connective tissue disorders have identified multiple loci (e.g., *EXD3*, *CUL1*, *SDK1*, *ASTN2*), some showing sex-specific associations, which may provide insights into pain and hypermobility phenotypes
* Studies also suggest involvement of genes regulating extracellular matrix, collagen formation, and connective tissue remodeling.

## **Doctor-Patient Conversation**

## Doctor:

Hello! What brings you in today?

## Patient:

Hi, doctor. I’ve always been very flexible — I can bend my fingers back and do splits easily. But lately, I’ve been having joint pain and sometimes my joints feel unstable or “give way.”

## Doctor:

Thanks for sharing. Being very flexible can be a sign of joint hypermobility. When did you start noticing the pain and instability?

## Patient:

It’s been going on for a few years but has gotten worse recently, especially after exercise or long periods of activity.

## Doctor:

Do you have any history of joint dislocations or injuries?

## Patient:

Yes, I’ve had a couple of ankle sprains and my shoulder has popped out once.

## Doctor:

Do you experience other symptoms like fatigue, muscle aches, or digestive issues?

## Patient:

Yes, I often feel tired and sometimes have stomach discomfort.

## Doctor:

Joint Hypermobility Syndrome (JHS) is a condition where joints move beyond the normal range and can cause pain, instability, and other symptoms. It’s related to connective tissue differences. Have you had any family members with similar symptoms?

## Patient:

My mother is also very flexible, but I don’t know if she has pain.

## Doctor:

That’s helpful to know. I’d like to perform a physical exam including the Beighton score to assess your joint hypermobility. We may also consider other tests to rule out related conditions.

## Patient:

Is there a treatment for this?

## Doctor:

Treatment focuses on managing symptoms. Physical therapy to strengthen muscles around joints and improve stability is key. Pain management, activity modification, and sometimes braces or supports can help.

## Patient:

Will this get worse over time?

## Doctor:

Symptoms can fluctuate. Some people improve with proper management, while others may have ongoing issues. Early intervention helps prevent injuries and improve quality of life.

## Patient:

Are there any complications I should watch for?

## Doctor:

Watch for frequent joint dislocations, severe pain, or signs of other connective tissue disorders. Let me know if you notice new symptoms.

## Patient:

Thank you, doctor. What’s the next step?

## Doctor:

I’ll do the physical exam today and refer you to a physiotherapist experienced with hypermobility. We’ll also monitor your symptoms over time.

## Patient:

Sounds good. I appreciate your help.

## Doctor:

You’re welcome. We’ll work together to keep your joints strong and pain-free.

**REFERENCES**

[Joint Hypermobility Syndrome: Symptoms, Causes, Diagnosis & Treatments](https://my.clevelandclinic.org/health/diseases/21763-joint-hypermobility-syndrome)

<https://www.nhs.uk/conditions/joint-hypermobility-syndrome/>

<https://www.alleviatepainclinic.com/blog/unraveling-joint-hypermobility-syndrome-understanding-diagnosis-prolotherapy-as-a-first-line-treatment/>

**JUVENILE IDIOPATHIC ARTHRITIS**

**DEFINITION**

Juvenile idiopathic arthritis, formerly known as **juvenile rheumatoid arthritis,** is the most common type of arthritis in children under the age of 16.

Juvenile idiopathic arthritis can cause persistent joint pain, swelling and stiffness. Some children may experience symptoms for only a few months, while others have symptoms for many years.

Some types of juvenile idiopathic arthritis can cause serious complications, such as growth problems, joint damage and eye inflammation. Treatment focuses on controlling pain and inflammation, improving function, and preventing damage.

**Causes**

Juvenile idiopathic arthritis occurs when the body's immune system attacks its own cells and tissues. It's not known why this happens, but both heredity and environment seem to play a role.

**Risk factors**

Some forms of juvenile idiopathic arthritis are more common in girls.

## **Symptoms**

The most common signs and symptoms of juvenile idiopathic arthritis are:

* **Pain.** While your child might not complain of joint pain, you may notice that he or she limps — especially first thing in the morning or after a nap.
* **Swelling.** Joint swelling is common but is often first noticed in larger joints such as the knee.
* **Stiffness.** You might notice that your child appears clumsier than usual, particularly in the morning or after naps.
* **Fever, swollen lymph nodes and rash.** In some cases, high fever, swollen lymph nodes or a rash on the trunk may occur — which is usually worse in the evenings.

Juvenile idiopathic arthritis can affect one joint or many. There are several different subtypes of juvenile idiopathic arthritis, but the main ones are systemic, oligoarticular and polyarticular. Which type your child has depends on symptoms, the number of joints affected, and if a fever and rashes are prominent features.

Like other forms of arthritis, juvenile idiopathic arthritis is characterized by times when symptoms flare up and times when symptoms may be minimal.

## **Diagnosis**

Diagnosis of juvenile idiopathic arthritis can be difficult because joint pain can be caused by many different types of problems. No single test can confirm a diagnosis, but tests can help rule out some other conditions that produce similar signs and symptoms.

### **Blood tests**

Some of the most common blood tests for suspected cases include:

* **Erythrocyte sedimentation rate (ESR).** The sedimentation rate is the speed at which your red blood cells settle to the bottom of a tube of blood. An elevated rate can indicate inflammation. Measuring the ESR is primarily used to determine the degree of inflammation.
* **C-reactive protein.** This blood test also measures levels of general inflammation in the body but on a different scale than the ESR.
* **Antinuclear antibody.** Antinuclear antibodies are proteins commonly produced by the immune systems of people with certain autoimmune diseases, including arthritis. They are a marker for an increased chance of eye inflammation.
* **Rheumatoid factor.** This antibody is occasionally found in the blood of children who have juvenile idiopathic arthritis and may mean there's a higher risk of damage from arthritis.
* **Cyclic citrullinated peptide (CCP).** Like the rheumatoid factor, the CCP is another antibody that may be found in the blood of children with juvenile idiopathic arthritis and may indicate a higher risk of damage.

In many children with juvenile idiopathic arthritis, no significant abnormality will be found in these blood tests.

### **Imaging scans**

X-rays or magnetic resonance imaging may be taken to exclude other conditions, such as fractures, tumors, infection or congenital defects.

Imaging may also be used from time to time after the diagnosis to monitor bone development and to detect joint damage.

**Treatment**

Treatment for juvenile idiopathic arthritis focuses on helping your child maintain a normal level of physical and social activity. To accomplish this, doctors may use a combination of strategies to relieve pain and swelling, maintain full movement and strength, and prevent complications.

### **Medications**

The medications used to help children with juvenile idiopathic arthritis are chosen to decrease pain, improve function and minimize potential joint damage.

Typical medications include:

* **Nonsteroidal anti-inflammatory drugs (NSAIDs).** These medications, such as ibuprofen (Advil, Motrin, others) and naproxen sodium (Aleve), reduce pain and swelling. Side effects include stomach upset and, much less often, kidney and liver problems.
* **Disease-modifying antirheumatic drugs (DMARDs).** Doctors use these medications when NSAIDs alone fail to relieve symptoms of joint pain and swelling or if there is a high risk of damage in the future.

DMARDs may be taken in combination with NSAIDs and are used to slow the progress of juvenile idiopathic arthritis. The most commonly used DMARD for children is methotrexate (Trexall, Xatmep, others). Side effects of methotrexate may include nausea, low blood counts, liver problems and a mild increased risk of infection.

* **Biologic agents.** Also known as biologic response modifiers, this newer class of drugs includes tumor necrosis factor (TNF) blockers, such as etanercept (Enbrel, Erelzi, Eticovo), adalimumab (Humira), golimumab (Simponi) and infliximab (Remicade, Inflectra, others). These medications can help reduce systemic inflammation and prevent joint damage. They may be used with DMARDs and other medications.

Other biologic agents work to suppress the immune system in slightly different ways, including abatacept (Orencia), rituximab (Rituxan, Truxima, Ruxience), anakinra (Kineret) and tocilizumab (Actemra). All biologics can increase the risk of infection.

* **Corticosteroids.** Medications such as prednisone may be used to control symptoms until another medication takes effect. They are also used to treat inflammation when it is not in the joints, such as inflammation of the sac around the heart.

These drugs can interfere with normal growth and increase susceptibility to infection, so they generally should be used for the shortest possible duration.

### **Therapies**

Your doctor may recommend that your child work with a physical therapist to help keep joints flexible and maintain range of motion and muscle tone.

A physical therapist or an occupational therapist may make additional recommendations regarding the best exercise and protective equipment for your child.

A physical or occupational therapist may also recommend that your child make use of joint supports or splints to help protect joints and keep them in a good functional position.

### **Surgery**

In very severe cases, surgery may be needed to improve joint function.

#### **MEDICATIONS**

| aminolevulinic acid oral, candesartan  captopril  carbenoxolone  carvedilol  celecoxib  celiprolol  chlorothiazide  chlorthalidone  cholestyramine  choline magnesium trisalicylate  cinnamon  ciprofloxacin  citalopram | agrimony  albuterol  alfalfa  alfuzosin  aliskiren  alteplase  American ginseng  amiloride  antithrombin alfa  antithrombin III  arformoterol  argatroban  Asenapine, salsalate  saw palmetto  sertraline  Siberian ginseng  silodosin  sodium picosulfate/magnesium oxide/anhydrous citric acid  sodium sulfate/?magnesium sulfate/potassium chloride  sodium sulfate/potassium chloride/magnesium sulfate/polyethylene glycol  sodium sulfate/potassium sulfate/magnesium sulfate  sotalol  sparsentan  spironolactone | aspirin  aspirin rectal  aspirin/citric acid/sodium bicarbonate  atenolol  azficel-T  azilsartan  bemiparin  benazepril  bendroflumethiazide  betaxolol  betrixaban  bimatoprost  bisoprolol  bivalirudin  budesonide  bumetanide |
| --- | --- | --- |
| aminolevulinic acid topical, clomipramine  clopidogrel  cordyceps  cortisone  cyclopenthiazide  cyclosporine  dabigatran  dalteparin  deferasirox  defibrotide  deflazacort  dexamethasone  diclofenac | Aceclofenac, diflunisal  digoxin  dobutamine  dong quai  dopexamine  doxazosin  drospirenone  duloxetine  edoxaban  efavirenz  eltrombopag | Acemetacin, latanoprostene bunod ophthalmic  levalbuterol  levofloxacin  levomilnacipran  lisinopril  lithium  lornoxicam  losartan  meclofenamate  mefenamic acid  mesalamine  metaproterenol  methyclothiazide  methylprednisolone  metolazone  metoprolol  milnacipran  mipomersen |
| Apixaban, mistletoe  moexipril  moxifloxacin  moxisylyte  mycophenolate  nabumetone  nadolol  naproxen  nebivolol  nefazodone  nettle  nevirapine  norepinephrine | Trandolapril, vortioxetine  warfarin  xanomeline/trospium  zanubrutinib  zotepine  aceclofenac  acemetacin  acyclovir  alendronate  amikacin  aminohippurate sodium  amiodarone  amobarbital | Acebutolol, ofloxacin  oxaprozin  parecoxib  paromomycin  pentobarbital  phenobarbital  piroxicam  primidone  rifampin  rifapentine  rose hips  salicylates (non-asa)  salsalate |
| Benazepril, pindolol  pirbuterol  piroxicam  potassium acid phosphate  potassium chloride  potassium citrate  potassium iodide  pralatrexate  prasugrel  prazosin  prednisolone  prednisone | Ramipril, meclofenamate  mefenamic acid  mesalamine  methyclothiazide  metolazone  metronidazole  miconazole vaginal  nabumetone  naproxen  nateglinide  neomycin PO  nilotinib  noni juice | tacrolimus |
| Captopril, probenecid  propranolol  protamine  quinapril  ramipril  reishi  reteplase  rivaroxaban  rivastigmine  sacubitril/valsartan  salicylates (non-asa)  salmeterol | Perindopril, olmesartan  oxaprozin  panax ginseng  parecoxib  paroxetine  pau d'arco  pegaspargase  perindopril  phenindione  phenoxybenzamine  phentolamine  phytoestrogens | Quinapril, streptomycin  sulfamethoxazole  sulfasalazine  sulindac  tobramycin  tolfenamic acid  tolmetin  triamterene  valganciclovir  valproic acid  vancomycin  voriconazole  willow bark |
| Enalapril, succinylcholine  sulfasalazine  sulindac  tafluprost  telmisartan  temocillin  tenecteplase  tenofovir DF  terazosin  terbutaline  ticagrelor  timolol  tolfenamic acid | Methotrexate, tolmetin  tolvaptan  torsemide  trandolapril  travoprost ophthalmic  trazodone  triamcinolone acetonide injectable suspension  triamterene  valsartan  venlafaxine  vitamin K1 (phytonadione)  voclosporin  vorapaxar | Pemetrexed, hydrochlorothiazide  ibuprofen  ibuprofen IV  imidapril  indapamide  indomethacin  ketoconazole  ketoprofen  ketorolac  ketorolac intranasal  leflunomide  levoketoconazole  lornoxicam |
| Fosinopril, anamu  aspirin  aspirin rectal  aspirin/citric acid/sodium bicarbonate  balsalazide  bendroflumethiazide  bosentan  butabarbital  butalbital  carbamazepine  cefadroxil  cefamandole  cefixime | Lisinopril, cefpirome  ceftibuten  celecoxib  cephalexin  chlorothiazide  chlorthalidone  choline magnesium trisalicylate  colestipol  creatine  cyclopenthiazide  danshen  devil's claw  diclofenac | Moexipril, diclofenac topical  diflunisal  disulfiram  eplerenone  etodolac  etravirine  felbamate  fenoprofen  feverfew  fluconazole  flurbiprofen  furosemide  ganciclovir  gentamicin |
| Ketorolac, elvitegravir/cobicistat/emtricitabine/tenofovir DF  emtricitabine  enalapril  enoxaparin  ephedrine  epinephrine  epinephrine racemic  epoprostenol  eprosartan  escitalopram  esmolol  ethacrynic acid  etodolac  fennel  fenoprofen  feverfew  zafirlukast | ketorolac intranasal  fish oil triglycerides  fludrocortisone  fluoxetine  flurbiprofen  fluvoxamine  fondaparinux  formoterol  forskolin  fosinopril  furosemide  garlic  gemifloxacin  gentamicin  ginger  ginkgo biloba  glimepiride  glipizide  glyburide  green tea | methyl aminolevulinate  heparin  horse chestnut seed  hydralazine  hydrochlorothiazide  hydrocortisone  ibrutinib  ibuprofen  ibuprofen IV  icosapent  imatinib  indapamide  indomethacin  irbesartan  isoproterenol  ketoprofen  ketorolac  ketorolac intranasal  labetalol  latanoprost |

## Adverse Effects

### 1-10%

Indigestion (3.8-9.5%)

Upper respiratory infection (≤8.3%)

Headache (2.4-8.3%)

Diarrhea (1.9-7.8%)

Constipation (0.8-7.6%)

Nausea (2.4-7.2%)

Abdominal pain (1.9-4.7%)

Edema (0.6-4.5%)

Anemia (≤4.1%)

Dizziness (1.1-3.8%)

Angina (<2%)

Congestive heart failure (<2%)

Decreased platelet aggregation, purpuric disorder (<2%)

Gastrointestinal (GI) hemorrhage (<2%)

GI perforation, GI ulcer (<2%)

Hepatitis (<2%)

Hypertension (<2%)

Inflammatory disorder of digestive tract (<2%)

Myocardial infarction (<2%)

Vomiting (<3%)

#### IV

* Constipation (7.6%)
* GGT increased (2.8%)
* Anemia (2.4%)

### <1%

Anaphylactoid reaction

Angioedema

Fever

Asthma, bronchospasm

Cerebrovascular accident

Erythema multiforme, erythroderma

Immune hypersensitivity reaction

Interstitial nephritis, renal failure

Jaundice, liver failure

Stevens-Johnson syndrome

Tinnitus, hearing loss

Toxic epidermal necrolysis

Skin and appendages: Exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and fixed drug eruption (FDE)

#### Cardiovascular risk

* Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase risk of serious cardiovascular thrombotic events, myocardial infarction (MI), and stroke, which can be fatal
* Risk may increase with duration of use
* Patients with existing cardiovascular disease or risk factors for such disease may be at greater risk
* NSAIDs are contraindicated for perioperative pain in setting of coronary artery bypass graft (CABG) surgery

#### **Gastrointestinal risk**

* NSAIDs increase risk of serious GI adverse events, including bleeding, ulceration, and gastric or intestinal perforation, which can be fatal
* GI adverse events may occur at any time during use and without warning symptoms
* Elderly patients are at greater risk for serious GI events

### Contraindications

Known hypersensitivity (eg, anaphylactic or serious skin reactions)

History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs

Perioperative pain management in the setting of coronary artery bypass graft (CABG) surgery

### Cautions

#### **Cardiovascular thrombotic events**

* Increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal
* Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs
* The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease; however, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events
* Increased CV thrombotic risk has been observed most consistently at higher doses

##### Minimize potential risk by using lowest effective dose for the shortest duration possibleCABG

* + 2 large, controlled clinical trials of a COX-2 selective NSAID for pain in the first 10-14 days following CABG surgery found an increased incidence of MI and stroke
  + NSAIDs are contraindicated in the setting of CABG

##### Post-MI

* + Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs post-MI were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment
  + Avoid in patients with recent MI unless benefits outweigh risk of recurrent CV thrombotic events; if used, monitor for cardiac ischemia

#### GI effects

* NSAIDs can cause serious GI adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal
* Patients with a prior history of PUD and/or GI bleeding who used NSAIDs have >10-fold increased risk for developing a GI bleed compared with patients without these risk factors
* Other risk factors include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or SSRIs; smoking; use of alcohol; advanced liver disease and /or coagulopathy; older age; and poor general health status

#### Heart failure and edema

* The Coxib and traditional NSAID Trialists’ Collaboration meta-analysis of randomized controlled trials demonstrated an ~2-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared with placebo-treated patients
* Fluid retention and edema observed in some patients treated with NSAIDs
* Meloxicam may blunt the CV effects of several therapeutic agents used to treat these medical conditions (eg, diuretics, ACE inhibitors, ARBs)

#### Renal toxicity and hyperkalemia

* Long-term administration of NSAIDs has resulted in renal papillary necrosis, renal insufficiency, acute renal failure, and other renal injury
* NSAIDs are not recommended with moderate to severe renal insufficiency and are contraindicated in patients with moderate to severe renal insufficiency at risk for renal failure due to volume depletion
* Increased serum potassium concentration, including hyperkalemia, reported with NSAIDs, even in some patients without renal impairment

#### Asthma exacerbation

* A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs
* Contraindicated in aspirin-sensitive asthma owing to cross-reactivity
* Caution in patients with asthma without known aspirin sensitivity

#### Serious Skin Reactions

* NSAIDs, including this drug, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal
* NSAIDs can cause fixed drug eruption (FDE); FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening; these serious events may occur without warning
* Inform patients about signs and symptoms of serious skin reactions, and to discontinue therapy at first appearance of skin rash or any other sign of hypersensitivity; this drug is contraindicated in patients with previous serious skin reactions to NSAIDs

#### Drug reaction with eosinophilia and systemic symptoms (DRESS)

* Drug Reaction reported in patients taking NSAIDs; some of these events have been fatal or life-threatening; DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling
* Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis; sometimes symptoms of DRESS may resemble an acute viral infection
* Eosinophilia is often present; because this disorder is variable in its presentation, other organ systems not noted here may be involved
* Early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident; if such signs or symptoms are present, discontinue therapy and evaluate the patient immediately

#### Additional cautions

* Hepatotoxicity: May increase ALT or AST
* Hypertension: Can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events
* Anaphylactic reactions reported in patients with and without known hypersensitivity to meloxicam and in patients with aspirin-sensitive asthma
* Serious skin reactions reported, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, which can be fatal
* Premature closure of fetal ductus arteriosus: Avoid NSAIDs in pregnant women starting at 30 weeks of gestation (third trimester)
* Hematologic toxicity: Anemia reported; causes vary including blood loss, fluid retention, or effect on erythropoiesis
* Masking of inflammation and fever: Reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections
* Monitoring: Consider monitoring patients on long-term PO NSAID treatment with a CBC and a chemistry profile periodically to detect GI bleeding, hepatotoxicity, or renal injury

#### Drug interaction overview

##### CYP2C9 inhibitors

* + Meloxicam is a CYP2C9 substrate
  + Coadministration with CYP2C9 inhibitors (eg, amiodarone, fluconazole) may increase meloxicam plasma levels owing to reduced metabolic clearance
  + Consider meloxicam dose reduction

##### Drugs that interfere with hemostasis

* + Monitor if coadministered with anticoagulants (eg, warfarin), antiplatelet agents (eg, aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding
  + Coadministration with analgesic doses of aspirin is not recommended owing to increased risk of bleeding
  + If coadministration with low-dose aspirin for cardiac prophylaxis, monitor closely for evidence of GI bleeding

##### ACE inhibitors, ARBs, or beta blockers

* + NSAIDs may diminish antihypertensive effect of ACE inhibitors, angiotensin receptor blockers (ARBs), or beta blockers
  + In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, coadministration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible
  + If coadministered, patients should be well hydrated; monitor for signs of worsening renal function

##### Diuretics

* + NSAIDs may reduce the natriuretic effect of loop and thiazide diuretics
  + This effect is attributed to the NSAID inhibition of renal prostaglandin synthesis
  + However, studies with furosemide and meloxicam have not demonstrated a reduced natriuretic effect

##### Lithium

* + NSAIDs elevate plasma lithium levels and reduce renal lithium clearance
  + Mean minimum lithium concentration increased 15%; renal clearance decreased by ~20%
  + Effect attributed to NSAID inhibition of renal prostaglandin synthesis
  + Monitor for lithium toxicity

##### Methotrexate

* + Coadministration of NSAIDs and methotrexate may increase risk for methotrexate toxicity (eg, neutropenia, thrombocytopenia, renal dysfunction)

##### Cyclosporine

* + Coadministration may increase nephrotoxicity
  + If coadministered, monitor for worsening renal function

##### NSAIDs or salicylates

* + Coadministration with other NSAIDs or salicylates increases risk of GI toxicity, with little or no increase in efficacy
  + Concomitant use no recommended

##### Pemetrexed

* + Coadministration may increase risk of pemetrexed-associated myelosuppression, renal, and GI toxicity
  + CrCl 45-79 mL/min: Interrupt meloxicam dosing for at least 5 days before, the day of, and 2 days after pemetrexed administration
  + CrCl <45 mL/min: Concomitant administration of meloxicam with pemetrexed is not recommended

## Pregnancy & Lactation

### Pregnancy

Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive

#### Fetal toxicity

* Avoid use of NSAIDs in pregnant women at about 30 weeks gestation and later; NSAIDs increase risk of premature closure of fetal ductus arteriosus at approximately this gestational age
* Use of NSAIDs at about 20 weeks gestation or later in pregnancy may also cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment
* These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hr. after NSAID initiation
* Oligohydramnios is often, but not always, reversible with treatment discontinuation; complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation
* In some post marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required
* If NSAID treatment is necessary between about 20 weeks and 30 weeks' gestation, limit use to the lowest effective dose and shortest duration possible
* Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hr; discontinue drug if oligohydramnios occurs and follow up according to clinical practice

#### Animal studies

* Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization
* In animal studies, administration of prostaglandin synthesis inhibitors, such as meloxicam, resulted in increased pre- and post-implantation loss

#### Clinical considerations

* Human data are not available on the effects during labor or deliveryIn animal studies, NSAIDs inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth

#### Infertility

##### Females

* + Based on the mechanism of action, prostaglandin-mediated NSAIDs may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women

##### Males

* + May compromise fertility in males of reproductive potential
  + Oral administration of meloxicam to male rats for 35 days resulted in decreased sperm count and motility and histopathological evidence of testicular degeneration at 0.3-times the MRHD based on BSA comparison
  + Clinical relevance of these findings is unknown

### Lactation

Human data are not available regarding presence in human milk, effects on breastfed infants, or on milk production

#### Animal data

* Present in milk of lactating rats at concentrations higher than those in plasma

### Pregnancy Categories

A: Generally acceptable. Controlled studies in pregnant women show no evidence of fetal risk.

B: May be acceptable. Either animal studies show no risk but human studies not available or animal studies showed minor risks and human studies done and showed no risk.

C: Use with caution if benefits outweigh risks. Animal studies show risk and human studies are not available or neither animal nor human studies done.

D: Use in LIFE-THREATENING emergencies when no safer drug available. Positive evidence of human fetal risk.

X: Do not use it in pregnancy. Risks involved outweigh potential benefits. Safer alternatives exist.

NA: Information not available.

## Pharmacology

### Mechanism of Action

Member of oxicam class; inhibits synthesis of prostaglandins in body tissues by inhibiting at least 2 cyclo-oxygenase (COX) isoenzymes, COX-1 and COX-2; COX-2 may be inhibited to a greater extent than COX-1 is

### Absorption

Bioavailability: 89% (tablet)

Peak plasma concentration: 1221.9 ng/mL (tablet); 8.1-8.7 mcg/mL (IV)

AUC: 53,988.8 ng⋅hr/mL (tablet); 112-118 mcg⋅hr/mL (IV)

#### Peak plasma time

* Tablet: 6.57 hr
* Capsule: 2 hr (fasting); 5 hr (fed)
* IV: 0.045-0.049 hr

### Distribution

Protein bound: 99.4%; primarily to albumin

Vd: ~10 L

### Metabolism

Metabolized in liver by CYP2C9 (major) and CYP3A4 (minor)

Metabolites (inactive): 5'-Carboxy meloxicam, 5'-hydroxymethyl meloxicam

Enzymes inhibited: COX-1, COX-2

### Elimination

Half-life: 15-20 hr (PO); 20-21 hr (IV)

Plasma clearance: 7-9 mL/min

Dialyzable: No

Excretion: Equally excreted in urine and feces, mostly as metabolites

### Pharmacogenomics

#### Poor CYP2C9 metabolizers

* Consider dose meloxicam reduction
* Abnormally high plasma levels owing to reduced metabolic clearance may occur

## Administration

### Oral Administration

Tablet, capsule, or oral suspension: May take with or without meals

Oral suspension: Shake well before using

### IV Preparation

Visually inspect parenteral drug products for particulate matter and discoloration before administration; should appear as a clear, greenish-yellow solution

Discard vial if contents appear discolored or contain particulate matter

### IV Administration

For IV administration only

Give as IV bolus injection over 15 seconds

Ensure patients is well hydrated before administration to reduce risk of renal toxicity

#### Monitor analgesic response

* Median time to meaningful pain relief was 2-3 hr after IV administration in 2 clinical studies
* A non-NSAID analgesic with a rapid onset of effect may be needed upon anesthetic emergence or resolution of local or regional anesthetic blocks
* Some patients may not experience adequate analgesia for the entire 24-hour dosing interval and may require administration of short-acting, non-NSAID, immediate-release analgesics

### Storage

#### Capsule or tablet

* Store at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF)
* Store in original container and keep the bottle tightly closed to protect from moisture
* Dispense in a tight container if package is subdivided

#### **IV solution**

* Store at 20-25ºC (68-77ºF), with excursions permitted to 15-30ºC (59-86ºF)
* Do not freeze
* Protect from light
* Discard unused portion

## **Disease-Modifying Antirheumatic Drugs**

Disease-modifying antirheumatic drugs (DMARDs) can retard or prevent disease progression and, thus, joint destruction and subsequent loss of function. Successful DMARD therapy may eliminate the need for other anti-inflammatory or analgesic medications; however, until the full action of DMARDs takes effect, anti-inflammatory or analgesic medications may be required as bridging therapy to reduce pain and swelling.

## [**Sulfasalazine (Azulfidine, EN-tabs)**](https://reference.medscape.com/drug/azulfidine-sulfasalazine-343280#1)

Sulfasalazine decreases the inflammatory response and systemically inhibits prostaglandin synthesis. The pediatric dosage has not been established for patients younger than 6 years; for patients 6 years or older, the typical dose range is 30-50 mg/kg/d; to lessen GI irritation, start at one half to one third of maintenance dose, increasing the dose weekly, not to exceed 2 g/d.

### Dosage Forms & Strengths

#### tablet

* 500mg

#### tablet, enteric coated (delayed release)

* 500 mg

### Ulcerative Colitis

Mild to moderate cases, adjunctive therapy in severe cases, and prolongation of remission

<6 years old: Safety and efficacy not established

#### 6 years or older

* Initial: 40-60 mg/kg/day PO divided q4-8hr after meals
* Maintenance: 30 mg/kg/day PO divided q6hr after meals

### Juvenile Rheumatoid Arthritis

Polyarticular course with inadequate response to salicylates or other NSAIDs

<6 years old: Safety and efficacy not established

6 years or older: Gradually titrate at weekly intervals up to 30-50 mg/kg/day PO divided BID after meals; not to exceed 2 g/day

## Serious (20) Monitor Closely (218)

| axicabtagene ciloleucel  brexucabtagene autoleucel  ciltacabtagene autoleucel  deferiprone  enasidenib  idecabtagene vicleucel  ketorolac  ketorolac intranasal  lasmiditan  leniolisib  lisocabtagene maraleucel  measles, mumps, rubella and varicella vaccine, live  methotrexate  pemetrexed  pexidartinib  pretomanid  ropeginterferon alfa 2b  tisagenlecleucel  varicella virus vaccine live  zavegepant intranasal | metaproterenol  methazolamide  methyclothiazide  methylprednisolone  metolazone  metoprolol  milnacipran  mistletoe  moexipril  momelotinib  moxisylyte  mycophenolate  nabumetone  pau d'arco  pegaspargase  perindopril  phenindione  phenoxybenzamine  phentolamine  phytoestrogens  pindolol  pirbuterol  piroxicam  ponatinib  potassium acid phosphate  potassium chloride | sulindac  tafamidis  tafamidis meglumine  telmisartan  temocillin  terazosin  terbutaline  timolol  tobramycin inhaled  tolfenamic acid  tolmetin  tolvaptan  Torsemide  trazodone  triamcinolone acetonide injectable suspension  triamterene  vadadustat  valoctocogene roxaparvovec  valsartan  vanzacaftor/tezacaftor/deutivacaftor  venlafaxine  vitamin K1 (phytonadione)  voclosporin  warfarin  zotepine |
| --- | --- | --- |
| **Minor (111)** aceclofenac  acemetacin  acyclovir  alendronate  aluminum hydroxide  amikacin  aminohippurate sodium  anamu  aspirin  aspirin rectal  aspirin/citric acid/sodium bicarbonate  balsalazide  bendroflumethiazide  budesonide  bumetanide  calcium carbonate  cefaclor  cefadroxil  cefamandole  cefazolin  cefotaxime  cefpirome  cefprozil  ceftazidime  ceftibuten  celecoxib  cephalexin  chlorothiazide  chlorthalidone  choline magnesium trisalicylate | potassium citrate  prazosin  prednisolone  prednisone  pretomanid  probenecid  propranolol  protamine  quinapril  ramipril  regorafenib  reishi  sacubitril/valsartan |  |
| cortisone  creatine  cyanocobalamin  cyclopenthiazide  danshen  deflazacort  devil's claw  dexamethasone  diclofenac  diflunisal  eplerenone  ethanol  etodolac | safinamide  salicylates (non-asa)  salmeterol  salsalate  sertraline  Siberian ginseng  silodosin  sodium picosulfate/magnesium oxide/anhydrous citric acid  sofosbuvir/velpatasvir  sotalol  spironolactone  stiripentol  succinylcholine | nadolol  nafcillin  naproxen  nebivolol  nefazodone  nettle  norepinephrine  olmesartan  oteseconazole  oxaprozin  panax ginseng  parecoxib  paroxetine |
| fenoprofen  feverfew  fludrocortisone  flurbiprofen  folic acid  furosemide  ganciclovir  gentamicin  glimepiride  glipizide  glyburide  hydrochlorothiazide  hydrocortisone  ibuprofen  imidapril | dalteparin  danicopan  darolutamide  deflazacort  dexamethasone  diclofenac  dicloxacillin  diflunisal  digoxin  dobutamine  dong quai  dopexamine  doxazosin | ketorolac intranasal  L-methylfolate  labetalol  levalbuterol  levomilnacipran  lisinopril  lithium  lornoxicam  losartan  meclofenamate  mefenamic acid  meloxicam  mesalamine |
| ibuprofen  imidapril  indapamide  indomethacin  insulin aspart  insulin detemir  insulin glargine  insulin glulisine  insulin lispro  insulin NPH  insulin regular human  ketoprofen  ketorolac  ketorolac intranasal  L-methylfolate | carvedilol  celecoxib  celiprolol  chlorothiazide  chlorthalidone  choline magnesium trisalicylate  cinnamon  clomipramine  clopidogrel  cordyceps  cortisone  cyclopenthiazide | heparin  horse chestnut seed  hydralazine  hydrochlorothiazide  hydrocortisone  ibuprofen  ibuprofen IV  indapamide  indomethacin  irbesartan  isoproterenol  ketoprofen  ketorolac |
| lornoxicam  meclofenamate  mefenamic acid  meloxicam  mesalamine  methyclothiazide  methylprednisolone  metolazone  nabumetone  naproxen  neomycin PO  noni juice  ofloxacin  oxaprozin  parecoxib | bemiparin  benazepril  bendroflumethiazide  betaxolol  bisoprolol  bivalirudin  brinzolamide  budesonide  bumetanide  bupivacaine implant  candesartan  captopril  carbenoxolone | fosinopril  fostamatinib  fostemsavir  furosemide  garlic  gentamicin  ginger  ginkgo biloba  glecaprevir/pibrentasvir  glimepiride  glipizide  glyburide  griseofulvin |
| paromomycin  piroxicam  prednisolone  prednisone  rose hips  salicylates (non-asa)  salsalate  sodium bicarbonate  sodium citrate/citric acid  streptomycin  sulfadiazine  sulfamethoxazole  sulfisoxazole | amoxicillin  ampicillin  antithrombin alfa  antithrombin III  apalutamide  arformoterol  argatroban  asenapine  aspirin  aspirin rectal  aspirin/citric acid/sodium bicarbonate  atenolol  azilsartan | esmolol  ethacrynic acid  etodolac  fennel  fenoprofen  feverfew  fludrocortisone  fluoxetine  flurbiprofen  fluvoxamine  fondaparinux  formoterol  forskolin |
| sulindac  teniposide  tobramycin  tolfenamic acid  tolmetin  trandolapril  triamcinolone acetonide injectable suspension  triamterene  valganciclovir  vancomycin  verapamil  willow bark | acalabrutinib  acebutolol  aceclofenac  acemetacin  acetazolamide  agrimony  albuterol  alfalfa  alfuzosin  American ginseng  amiloride | drospirenone  duloxetine  eltrombopag  eluxadoline  enalapril  encorafenib  enoxaparin  ephedrine  epinephrine  epinephrine racemic  epoprostenol  eprosartan  escitalopram |

## Adverse Effects

### >10%

Anorexia (~33%)

Headache (~33%)

Nausea (~33%)

Vomiting (~33%)

Gastric distress (~33%)

Apparently reversible oligospermia (~33%)

### <1%

Skin rash

Pruritus

Urticaria

Fever

Heinz body anemia

Hemolytic anemia

Cyanosis

Blood dyscrasias: Pseudomononucleosis

Cardiac disorders: Myocarditis

Hepatobiliary disorders: reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, hepatitis cholestatic, cholestasis and possible hepatocellular damage including liver necrosis and liver failure; some of these cases were fatal; 1 case of Kawasaki-like syndrome

Immune system disorders: Anaphylaxis

Metabolism and nutrition system disorders: Folate deficiency

Renal and urinary disorders: Nephrolithiasis

Respiratory, thoracic and mediastinal disorders: Oropharyngeal pain

Skin and subcutaneous tissue disorders: Angioedema, purpura

Vascular disorders: Pallor

Hypersensitivity reactions: Erythema multiforme, epidermal necrolysis (SJS/TEN) with corneal damage, exfoliative dermatitis, DRESS, serum sickness syndrome, interstitial lung disease, pneumonitis with or without eosinophilia, vasculitis, fibrosing alveolitis, pleurisy/pleuritis, pericarditis with or without tamponade, allergic myocarditis, polyarteritis nodosa, lupus erythematosus-like syndrome, hepatic necrosis with or without immune complexes, fulminant hepatitis, sometimes leading to liver transplantation, parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), rhabdomyolysis, photosensitization, arthralgia, periorbital edema, conjunctival and scleral injection, and alopecia

## Warnings

### Contraindications

Hypersensitivity to sulfasalazine or its metabolites, to sulfonamides, or to salicylates

Intestinal or urinary tract obstruction

Porphyria

### Cautions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and toxic epidermal necrolysis; discontinue at first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity

Severe hypersensitivity reported; may include internal organ involvement, such as hepatitis, nephritis, myocarditis, mononucleosis-like syndrome (ie, pseudomononucleosis), hematological abnormalities (including hematophagic histiocytosis), and/or pneumonitis including eosinophilic infiltration; if signs or symptoms are present, the patient should be evaluated immediately; Sulfasalazine drug should be discontinued if an alternative etiology for signs or symptoms cannot be established

Administer tablets with caution to patients with severe allergy or bronchial asthma; adequate fluid intake must be maintained in order to prevent crystalluria and stone formation; patients with glucose-6 phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia; reaction is frequently dose-related; if toxic or hypersensitivity reactions occur, the drug should be discontinued immediately

Oligospermia and infertility reported; however, withdrawal of drug appears to reverse these effects

#### Hepatic, renal, and hematologic toxicity

* Only after critical appraisal should therapy be administered to patients with hepatic or renal damage or blood dyscrasias; deaths associated with administration of sulfasalazine reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and central nervous system changes, and fibrosing alveolitis
* The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice may be indications of serious blood disorders or hepatotoxicity; complete blood counts, as well as urinalysis with careful microscopic examination, should be done frequently in patients receiving therapy; discontinue treatment with sulfasalazine while awaiting results of blood tests
* Discontinue therapy if renal function deteriorates

#### Infections

* Blood dyscrasias; serious infections reported, including fatal sepsis and pneumonia
* Some infections were associated with agranulocytosis, neutropenia, or myelosuppression; discontinue therapy if patient develops a serious infection
* Closely monitor patients for the development of signs and symptoms of infection during and after treatment
* Frequently perform complete blood counts, as well as urinalysis with careful microscopic examination; discontinue treatment while awaiting results of blood tests;

## Pregnancy & Lactation

Pregnancy category: B; D if used for prolonged periods or near term; increased potential for kernicterus in the newborn

Oral sulfasalazine inhibits the absorption and metabolism of folic acid which may interfere with folic acid supplementation and protection from neural tube defects

Lactation: Excreted into human breast milk; caution with breastfeeding, some reports of bloody stools or diarrhea in human milk fed infants of mothers taking sulfasalazine

### Pregnancy Categories

A: Generally acceptable. Controlled studies in pregnant women show no evidence of fetal risk.

B: May be acceptable. Either animal studies show no risk but human studies not available or animal studies showed minor risks and human studies done and showed no risk.

C: Use with caution if benefits outweigh risks. Animal studies show risk and human studies are not available or neither animal nor human studies done.

D: Use in LIFE-THREATENING emergencies when no safer drug is available. Positive evidence of human fetal risk.

X: Do not use it in pregnancy. Risks involved outweigh potential benefits. Safer alternatives exist.

NA: Information not available.

## Pharmacology

### Mechanism of Action

Sulfasalazine is a prodrug that is metabolized to its active components, sulfapyridine and 5-aminosalicylic acid (5-ASA; mesalamine); beneficial effects are predominantly from the anti-inflammatory properties of 5-ASA, which inhibits leukotriene synthesis and lipoxygenase

### Absorption

Bioavailability: <15% of parent drug; 60% (sulfapyridine); 10-30% (5-ASA)

Peak plasma time: 6 hr; 10 hr (sulfapyridine and 5-ASA)

Peak plasma concentration: 6 mcg/mL

### Distribution

Protein bound: >99% to albumin; 70% (sulfapyridine)

Vd: 7.5 L

### Metabolism

Approximately 90% of sulfasalazine is converted by colon bacteria into its active components, sulfapyridine and mesalamine

### Elimination

Half-life: 10.4-14.8 hr (sulfapyridine)

Renal clearance: 37%

Excretion: Urine (systematically absorbed sulfapyridine and 5-ASA); feces (majority of 5-ASA)

## [Methotrexate (Rheumatrex, Trexall)](https://reference.medscape.com/drug/trexall-otrexup-methotrexate-343201#1)

Methotrexate has an unknown mechanism of action in the treatment of inflammatory reactions; it may affect immune function. It ameliorates symptoms of inflammation (eg, pain, swelling, stiffness). Adjust the dose gradually to attain a satisfactory response. Consider the SC route for patients who do not respond to PO methotrexate or who have GI intolerance to PO dosing.

The pediatric dosage is 10-25 mg/m2/wk PO/IM/SC as a single dose or divided into 2 doses weekly; many pediatric rheumatologists increase the dose (not to exceed 30 mg/m2, approximately equivalent to 1 mg/kg); administer with folic acid 1-2 mg PO qd or folinic acid 2.5-5 mg PO qwk

### Dosage Forms & Strengths

#### injectable solution

* 25 mg/mL

#### powder for injection

* 1g/vial (25mg/mL when reconstituted)

#### SC autoinjector (Otrexup)

* 10 mg/0.4mL
* 12.5mg/0.4mL
* 15mg/0.4mL
* 17.5mg/0.4mL
* 20mg/0.4mL
* 22.5mg/0.4mL
* 25 mg/0.4mL

#### SC autoinjector (Rasuvo)

* 2.5mg/0.05mL (delivers doses between 7.5 mg and 30 mg in 2.5 mg increments)

#### SC prefilled syringe (RediTrex)

* 7.5mg/0.3mL
* 10 mg/0.4mL
* 12.5mg/0.5mL
* 15mg/0.6mL
* 17.5mg/0.7mL
* 20 mg/0.8mL
* 22.5mg/0.9mL
* 25mg/mL

#### tablet

* 2.5mg
* 5mg
* 7.5mg
* 10mg
* 15mg

#### oral solution

* 2.5mg/mL (Xatmep)
* 2mg/mL (Jylamvo)

### Polyarticular Juvenile Idiopathic Arthritis (pJIA)

Management of active pJIA in children who have had an insufficient response or intolerance to an adequate trial of first-line therapy including full dose NSAIDs

Initial: 10 mg/m2 PO/IM/SC once weekly

If switching from PO to SC (Otrexup, Rasuvo, RediTrex), consider higher bioavailability with SC compared with PO (see Pharmacology Absorption section)

#### Dosing Considerations (PJIA)

* Data with doses up to 30 mg/m²/wk in children exist, although there are too few published studies to assess how doses >20 mg/m²/wk might affect the risk of serious toxicity in children, especially bone marrow suppression
* Experience does suggest, however, that children receiving 20-30 mg/m2/week (0.65-1 mg/kg/week) may have better absorption and fewer GI side effects if methotrexate is administered either IM or SC
* Jylamvo: Indicated for pJIA; titrate dosage to achieve optimal response; most responses occur after 3-6 weeks of treatment
* Administer folic acid or folinic acid to reduce the risk of methotrexate adverse reactions

## **Corticosteroids**

Corticosteroids are potent anti-inflammatory drugs used in patients with JIA to bridge the time until DMARDs are effective. Adverse events associated with long-term steroid use make dose reductions and cessation important in due course.

## [Methylprednisolone (Solu-Medrol, Medrol, A-Methapred)](https://reference.medscape.com/drug/medrol-medrol-dosepak-methylprednisolone-342746#1)

Methylprednisolone decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability. It is used temporarily for JIA until longer-term treatment provides effective relief. The pediatric dosage is 15-30 mg/kg IV qd administered over 30-60 min for 2-3 d.

## [Prednisone](https://reference.medscape.com/drug/prednisone-intensol-342747#1)

Prednisone is an immunosuppressant for treatment of JIA. It may decrease inflammation by reversing increased capillary permeability and suppressing polymorphonuclear neutrophil (PMN) activity, and it stabilizes lysosomal membranes and also suppresses lymphocytes and antibody production. The pediatric dosage is 4-5 mg/m2/d PO; alternatively, the dosage is 0.05-2 mg/kg PO divided bid/qid; taper over 2 wk as symptoms resolve and other antirheumatic drugs take effect.

## [Triamcinolone (Aristospan, Kenalog)](https://reference.medscape.com/drug/Kenalog-10-kenalog-40-triamcinolone-acetonide-injectable-suspension-342748#1)

Triamcinolone decreases inflammation by suppressing the migration of polymorphonuclear leukocytes and reversing capillary permeability.

## **Immunomodulators**

The recognition of tumor necrosis factor-alpha (TNF-alpha) and interleukin (IL)–1 as central proinflammatory cytokines has led to the development of agents that block these cytokines or their effects. In addition to improving signs and symptoms and quality of life, all biologic agents significantly retard radiographic progression of joint erosions. The TNF blockers, which bind TNF and thus prevent its interaction with its receptors, include etanercept, infliximab, and adalimumab. Consensus statements do not recommend their use until at least one xenobiotic DMARD, usually methotrexate (MTX), has been administered without sufficient success, although one study reported better results with etanercept in patients with less disability and when used before methotrexate.

Adverse effects associated with the biologic agents include the generation of antibodies against these compounds, emergence of antinuclear antibodies, occasional drug-induced lupuslike syndromes, and infections. Rarely, demyelinating disorders and bone marrow suppression occur. Acute and chronic infections, demyelinating disorders, class 3 or 4 heart failure, and recent malignancies are contraindications for TNF blockers. Thoroughly searching for latent tuberculosis using chest radiography and/or purified protein derivative (PPD) testing is recommended before these agents are started.

## Adalimumab (Amjevita, Cyltezo, Humira, Hadlima, Hyrimoz, Adalimumab-atto, Adalimumab-adbm, Adalimumab-bwwd, Adalimumab-adaz)

Adalimumab is a recombinant human IgG1 monoclonal antibody that is specific for human TNF.

### Dosage Forms & Strengths

#### injection, prefilled glass syringe

* 10mg/0.1mL (Humira, Hyrimoz)
* 10mg/0.2mL (Abrilada, Amjevita, Cyltezo)
* 20mg/0.2mL (Abrilada, Amjevita, Humira, Hyrimoz, Simlandi, Yuflyma)
* 20mg/0.4mL (Amjevita, Cyltezo)
* 40mg/0.4mL (Humira, Amjevita, Cyltezo, Hadlima, Hyrimoz, Simlandi, Yuflyma)
* 40mg/0.8mL (Abrilada, Amjevita, Cyltezo, Hadlima, Hyrimoz, Idacio, Yusimry)
* 80mg/0.8mL (Amjevita, Simlandi, Yuflyma)

#### injection, prefilled syringe/pen

* 20mg/0.4mL (Hulio)
* 40mg/0.4mL (Humira, Cyltezo, Hyrimoz)
* 40mg/0.8mL (Abrilada, Amjevita, Cyltezo, Hulio, Idacio, Yusimry)
* 80mg/0.8mL (Humira, Hyrimoz)

#### injection, prefilled autoinjector

* 40mg/0.4mL (Amjevita, Cyltezo, Hadlima, Simlandi, Yuflyma)
* 40mg/0.8 mL (Amjevita, Hadlima)
* 80mg/0.8mL (Amjevita, Simlandi, Yuflyma)

#### injection, vial

* 40mg/0.8mL (Abrilada, Hadlima, Idacio)

#### Biosimilars to Humira

* Abrilada (adalimumab-afzb)
* Amjevita (adalimumab-atto)
* Cyltezo (adalimumab-adbm)
* Hadlima (adalimumab-bwwd)
* Hulio (adalimumab-fkjp)
* Hyrimoz (adalimumab-adaz)
* Idacio (adalimumab-aacf)
* Simlandi (adalimumab-ryvk)
* Yuflyma (adalimumab-aaty)
* Yusimry (adalimumab-aqvh)

### Juvenile Idiopathic Arthritis

Indicated for reduction of signs and symptoms of moderately-to-severely active polyarticular juvenile idiopathic arthritis

May be administered with methotrexate, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics

#### Hulio, Simlandi, and Yuflyma

* <2 years or <15 kg: Safety and efficacy not established

##### ≥2 years

* + 15 kg to <30 kg: 20 mg SC q2wk
  + ≥30 kg: 40 mg SC q2wk

#### Humira, Hadlima, Hyrimoz, Abrilada, Amjevita, Cyltezo, or Idacio

<2 years or <10 kg: Safety and efficacy not established

##### ≥2 years

* + 10 to <15 kg: 10 mg SC q2wk
  + 15 to <30 kg: 20 mg SC q2wk
  + ≥30 kg: 40 mg SC q2wk
  + For Hadlima and Idacio, only dosage form that allows weight-based dosing for pediatric patients <30 kg is the single-dose glass vial for institutional use

#### Yusimry

* ≥2 years and ≥30 kg: 40 mg SC q2wk

### **When to see a doctor**

Take your child to the doctor if he or she has joint pain, swelling or stiffness for more than a week — especially if he or she also has a fever.

## **Epidemiology**

### United States statistics

Approximately 300,000 children in the United States are estimated to have some type of arthritis. The incidence rate estimates for JIA range from 4-14 cases per 100,000 children annually; for JRA, the prevalence has ranged from 1.6 to 86.1 cases per 100,000.These wide-ranging numbers are attributable to differing definitions and criteria for childhood arthritis; population differences, including environmental exposure and immunogenetic susceptibility; and difficulty in case ascertainment and lack of population based data.

### International statistics

Worldwide, JIA appears to occur more frequently in certain populations (eg, indigenous peoples) from such disparate areas as British Columbia and Norway. In Europe, the average prevalence is 70 cases per 100,000 population.

A study in Sweden found the prevalence of JIA there to be similar to that in Minnesota, approximately 85 cases per 100,000 population, with an incidence of 11 cases per 100,000 population. A study from Germany found a prevalence rate of 20 cases per 100,000 population, with an incidence rate of 3.5 cases per 100,000 population.

Estimates from Norway include a prevalence rate of 148 cases per 100,000 population with an incidence rate of 22 cases per 100,000 population. The incidence of JIA in Japan has been reported to be low.

## **Differential Diagnoses**

1. Septic Arthritis
2. Trauma
   1. Joint swelling or effusion following injury.
   2. History of trauma is often present.
   3. Usually resolves with conservative management
3. Hematologic Diseases
   1. Conditions like hemophilia can cause joint bleeding and swelling.
   2. May present with recurrent joint effusions without inflammation
4. Systemic Lupus Erythematosus (SLE)
   1. Can present with arthritis resembling polyarticular JIA, especially in preadolescent/adolescent girls.
   2. Accompanied by other systemic features such as rash, renal involvement, and positive autoantibodies
5. Infectious Diseases
   1. Viral arthritis (e.g., Epstein-Barr Virus, Parvovirus B19) can mimic JIA.
   2. Lyme disease arthritis should be considered in endemic areas
6. Other Connective Tissue Diseases
   1. Behçet syndrome, Kawasaki disease, and other vasculitides may present with arthritis and systemic symptoms
7. Malignancies
   1. Leukemia and other malignancies can present with joint pain and swelling.
   2. Systemic symptoms like weight loss, night sweats, and abnormal blood counts may be clues
8. Psoriatic Juvenile Idiopathic Arthritis
   1. Arthritis with psoriasis or psoriatic features such as nail changes or family history of psoriasis
9. Juvenile Spondyloarthritis
   1. Involves spine, hips, entheses, and may have associated eye inflammation.
   2. More common in males over 7 years old
10. Systemic JIA (Still’s Disease)
    1. Characterized by arthritis plus systemic features: high spiking fever, rash, lymphadenopathy, hepatosplenomegaly.
    2. Fever pattern and rash help distinguish from infections

## **Procedure and Timeline**

## Diagnostic Timeline

* Symptom Duration: Arthritis must begin before age 16 and persist for at least 3 months to meet diagnostic criteria
* Initial Evaluation: When a child has joint pain, stiffness, or swelling lasting 6 weeks or more, they should be evaluated by a healthcare provider
* Laboratory and Imaging Tests: Used to rule out other causes (e.g., infection, malignancy) and support diagnosis. There are no definitive blood tests for JIA, so diagnosis is clinical

## Treatment Procedure and Timeline

1. Initial Treatment Phase (0–1 month):
   1. Start with NSAIDs to reduce pain and inflammation, especially in patients with low disease activity
   2. Physical and occupational therapy begin early to maintain joint function and muscle strength
   3. Joint injections with corticosteroids may be used for rapid symptom relief in affected joints
2. Assessment of Response (1–2 months):
   1. For patients with moderate disease activity but without poor prognostic features (e.g., hip/cervical spine involvement, positive rheumatoid factor), NSAIDs are continued and response evaluated
   2. If inadequate response or poor prognostic features present, initiate Disease-Modifying Anti-Rheumatic Drugs (DMARDs) such as methotrexate
3. Advanced Treatment Phase (2+ months):
   1. If DMARDs are insufficient, or in more severe cases, biologic agents (e.g., TNF inhibitors, IL-1 or IL-6 blockers) are introduced to better control inflammation and prevent joint damage
   2. Corticosteroids may be used short-term for systemic symptoms or severe flares but tapered quickly due to side effects
4. Ongoing Management:
   1. Regular monitoring including blood tests approximately every 3 months to assess medication safety and disease activity
   2. Continued physical therapy and occupational therapy to preserve joint mobility and function
   3. Psychosocial support and school accommodations as needed
   4. Surgical interventions (e.g., synovectomy, osteotomy, joint replacement) are rare and reserved for severe, refractory cases

## Remission and Long-Term Outlook

* Remission Criteria (American College of Rheumatology):  
  No joint inflammation, pain, stiffness, fatigue, or progression of damage; normal inflammatory markers
* Many children achieve remission with early and aggressive treatment, though some may have persistent symptoms into adulthood
* Treatment is often gradually reduced once remission is sustained

**Lifestyle and home remedies**

Caregivers can help children learn self-care techniques that help limit the effects of juvenile idiopathic arthritis. Techniques include:

* **Getting regular exercise.** Exercise is important because it promotes both muscle strength and joint flexibility. Swimming is an excellent choice because it places minimal stress on joints.
* **Applying cold or heat.** Stiffness affects many children with juvenile idiopathic arthritis, particularly in the morning. Some children respond well to cold packs, particularly after activity. However, most children prefer warmth, such as a hot pack or a hot bath or shower, especially in the morning.
* **Eating well.** Some children with arthritis have poor appetites. Others may gain excess weight due to medications or physical inactivity. A healthy diet can help maintain an appropriate body weight.

Adequate calcium in the diet is important because children with juvenile idiopathic arthritis are at risk of developing weak bones due to the disease, the use of corticosteroids, and decreased physical activity and weight bearing.

## **Outlook / Prognosis**

JIA affects each child differently. For some, it affects one or two joints, and the disease is easy to manage. For others, JIA may involve many joints and cause more severe or longer-lasting symptoms.

With early detection and treatment, it’s possible to manage the arthritis, prevent joint damage, and allow normal or near-normal function for most children with JIA.

JIA can last for months or years. Some children go into full remission, while others still have active symptoms into adulthood. Providers call this “aging out” of JIA and into adult arthritis. There’s really no way to predict whether this will happen. But your healthcare provider can help manage your child’s condition, find effective treatments and set them up for success in the future.

## **Prevention**

Because healthcare providers don’t currently know what causes JIA, there’s no method to prevent it from developing. Experts continue to research the cause and prevention of JIA.

## **Questions and Answers**

## 1. What is Juvenile Idiopathic Arthritis (JIA)?

JIA is the most common chronic rheumatologic disease in children under 16, characterized by persistent arthritis lasting at least 6 weeks with unknown cause. It causes joint pain, swelling, stiffness, and can affect multiple joints

## 2. What are the common symptoms of JIA?

Symptoms include swollen, stiff, and painful joints, often affecting knees, hands, feet, ankles, shoulders, and elbows. Morning stiffness and fatigue are common. Some children may also have systemic symptoms like fever or rash depending on the subtype

## 3. How is JIA diagnosed?

Diagnosis is clinical, based on arthritis lasting 6 weeks or more in children under 16, after excluding other causes such as infection or malignancy. There are no definitive blood tests; however, tests may be done to rule out other diseases

## 4. What treatments are available for JIA?

Treatment aims to reduce pain and inflammation and maintain joint function. It includes:

* NSAIDs for pain and inflammation
* Disease-modifying antirheumatic drugs (DMARDs) like methotrexate
* Biologic agents if DMARDs are insufficient
* Corticosteroids for severe inflammation
* Physical and occupational therapy to maintain mobility and function

## 5. What are the side effects of medications used in JIA?

* NSAIDs: stomach upset, nausea, kidney issues
* Methotrexate: nausea, liver toxicity, low blood counts
* Biologics: increased infection risk, injection site reactions
* Corticosteroids: weight gain, mood changes, growth suppression if used long-term

## 6. How important is physical therapy in JIA?

Physical and occupational therapy are crucial to maintain joint flexibility, muscle strength, and function. Therapists may recommend exercises, splints, or joint supports to protect joints and improve daily activities

## 7. Can children with JIA live a normal life?

Yes, with early diagnosis and proper management, many children achieve remission or good disease control, allowing them to attend school, participate in sports, and lead active lives

## 8. What support resources are available for families?

Organizations like the Arthritis Foundation and the American Juvenile Arthritis Organization provide education, support, and resources for patients and families managing JIA

## **Genetic Architecture**

* JIA is a complex autoimmune inflammatory joint disease with a strong genetic component involving multiple loci.
* Recent large genome-wide association studies (GWAS) have identified 59 JIA-risk loci regulating the expression of 210 target genes across diverse tissues and immune cell types
* Most risk loci lie in non-coding regions but regulate gene expression through spatial (3D genome) interactions, affecting distant target genes

## Key Genetic Findings

* HLA Locus: The majority of causal genes (about 85%) are located within the highly polymorphic HLA region on chromosome 6p21.3–6p22.1, a critical immune-regulatory region
* Novel Risk Loci: Five novel significant loci were identified in a meta-analysis of over 3,000 JIA cases and controls, with fine-mapping nominating causal SNPs and key transcription factors such as RELA and EBF1 contributing to disease risk
* Target Genes: Identified genes are involved in immune pathways including antigen processing and presentation (e.g., *ERAP2*, HLA class I and II genes), cytokine signaling (e.g., *LTBR*, *TYK2*), immune cell proliferation/differentiation (e.g., *AURKA* in Th17 cells), and joint inflammation mechanisms (e.g., *LRG1*)
* Potential Drug Targets: *IL6ST* was highlighted as a potential therapeutic target based on genetic evidence

## Tissue and Cell Type Specificity

* JIA risk loci act as expression quantitative trait loci (eQTLs) in multiple tissues beyond classical immune sites, including blood, spleen, lung, and small intestine, indicating systemic immune involvement
* Immune cell types such as neutrophils and Th17 cells show altered gene regulation linked to JIA risk loci

## Causal Gene Identification and Functional Insights

* Integrative analyses combining GWAS, eQTL, and Mendelian randomization identified 52 genes with putative causal roles in JIA, mostly within the HLA locus
* Many of these genes have not been previously linked to JIA, expanding understanding of disease biology and suggesting new biomarkers and therapeutic targets.
* JIA shares genetic and biological pathways with other autoimmune and inflammatory diseases, including rheumatoid arthritis and multiple sclerosis

REFERENCES

<https://cassieandfriends.ca/faqs/>

[Juvenile Idiopathic Arthritis (JIA) Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/10370-juvenile-idiopathic-arthritis#outlook-prognosis)

[Juvenile idiopathic arthritis - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/juvenile-idiopathic-arthritis/diagnosis-treatment/drc-20374088)

<https://reference.medscape.com/drug/qamzova-xifyrm-meloxicam-343299#11>

### **LUPUS(SYSTEMIC LUPUS ERYTHEMATOSUS)**

**DEFINITION AND DESCRIPTION**

Lupus is a condition that causes inflammation throughout your body. It’s an autoimmune disease, which means your immune system damages your body instead of protecting it. You may experience symptoms throughout your body depending on where your autoimmune system damages tissue, including in your:

* Skin.
* Blood.
* Joints.
* Kidneys.
* Brain.
* Heart.
* Lungs.

Visit a healthcare provider if you notice new pain, rashes or changes to your skin, hair or eyes.

#### **Types of lupus**

Healthcare providers sometimes call lupus systemic lupus erythematosus (SLE). It’s the most common type of lupus, and means you have lupus throughout your body. Other types include:

* **Cutaneous lupus erythematosus:** Lupus that only affects your skin.
* **Drug-induced lupus:** Some medications trigger lupus symptoms as a side effect. It’s usually temporary and might go away after you stop taking the medication that caused it.
* **Neonatal lupus:** Babies are sometimes born with lupus. Babies born to biological parents with lupus aren’t certain to have lupus, but they might have an increased risk.

## **Symptoms and Causes**

Lupus causes symptoms throughout your body, depending on which organs or systems it affects. Everyone experiences a different combination and severity of symptoms.

Lupus symptoms usually come and go in waves called flare-ups. During a flare-up, the symptoms can be severe enough to affect your daily routine. You might also have periods of remission when you have mild or no symptoms.

Symptoms usually develop slowly. You might notice one or two signs of lupus at first, and then more or different symptoms later on. The most common symptoms include:

* Joint pain, muscle pain or chest pain (especially when you’re taking a deep breath).
* Headaches.
* Rashes (it’s common to have a rash across your face that providers sometimes call a butterfly rash).
* Fever.
* Hair loss.
* Mouth sores.
* Fatigue (feeling tired all the time).
* Shortness of breath (dyspnea).
* Swollen glands.
* Swelling in your arms, legs or on your face.
* Confusion.
* Blood clots.

Lupus can sometimes cause other health conditions or issues, including:

* Photosensitivity (sensitivity to sunlight).
* Dry eyes.
* Depression (or other mental health conditions).
* Seizures.
* Anemia.
* Raynaud’s syndrome.
* Osteoporosis.
* Heart disease.
* Kidney disease.

### **What causes lupus?**

Experts don’t know for certain what causes lupus. Studies have found that certain factors about your health or where you live may trigger lupus:

* **Genetic factors:** Having certain genetic mutations may make you more likely to have lupus.
* **Hormones:** Reactions to certain hormones in your body (especially estrogen) may make you more likely to develop lupus.
* **Environmental factors:** Aspects about where you live and how much pollution or sunlight you’re exposed to might affect your lupus risk.
* **Your health history:** Smoking, your stress level and having certain other health conditions (like other autoimmune diseases) might trigger lupus.

#### **Risk factors**

Anyone can develop lupus, but some groups of people have a higher risk:

* Women, especially women between the ages of 15 and 44.
* Black people.
* Hispanic people.
* Asian people.
* Native Americans, Alaska Natives and First Nations people.
* Pacific Islanders.
* People with a biological parent who has lupus.

## **Diagnosis and Tests**

A healthcare provider will diagnose lupus with a physical exam and some tests. They’ll examine your symptoms and talk to you about what you’re experiencing. Tell your provider when you first noticed symptoms or changes in your body. Your provider will ask about your medical history, including conditions you may have now and how you’re treating or managing them.

Lupus can be tricky to diagnose because it can affect so many parts of your body and cause lots of different symptoms. Even small changes or issues that seem unusual for you can be a key. Don’t be afraid to tell your provider about anything you’ve felt or sensed — you know your body better than anyone.

#### **Which tests do providers use to diagnose lupus?**

There’s not one test that can confirm a lupus diagnosis. Diagnosing it is usually part of a differential diagnosis. This means your provider will probably use a few tests to determine what’s causing your symptoms before ruling out other conditions and diagnosing you with lupus. They might use:

* Blood tests to see how well your immune system is working and to check for infections or other issues like anemia or low blood cell counts.
* Urinalysis to check your pee for signs of infections or other health conditions.
* An antinuclear antibody (ANA) test looks for antibodies (protein markers that show a history of your body fighting off infections). People who have lupus usually have certain antibodies that show their immune system has been overly active.
* A biopsy of your skin or kidney tissue can show if your immune system has damaged them.

## **Management and Treatment**

Your healthcare provider will suggest treatments for lupus that manage your symptoms. The goal is minimizing damage to your organs and how much lupus affects your day-to-day life. Most people with lupus need a combination of medications to help them prevent flare-ups and lessen their symptom severity during one. You might need:

* **Hydroxychloroquine:** Hydroxychloroquine is a disease-modifying antirheumatic drug (DMARD) that can relieve lupus symptoms and slow down how they progress (change or get worse).
* **Nonsteroidal anti-inflammatory drugs (NSAIDs):** Over-the-counter (OTC) NSAIDs relieve pain and reduce inflammation. Your provider will tell you which type of NSAID will work best for you, and how often you should take it. Don’t take NSAIDs for more than 10 days in a row without talking to your provider.
* **Corticosteroids:** Corticosteroids are prescription medications that reduce inflammation. Prednisone is a common corticosteroid providers use to manage lupus. Your provider might prescribe you pills you take by mouth or inject a corticosteroid directly into one of your joints.
* **Immunosuppressants:** Immunosuppressants are medications that hold back your immune system and stop it from being as active. They can help prevent tissue damage and inflammation.

You might need other medications or treatments to manage specific lupus symptoms you have or other health conditions it’s causing. For example, you may need treatment for anemia, high blood pressure (hypertension) or osteoporosis if lupus causes those issues.

### Systemic Lupus Erythematosus

Indicated for treatment of chronic discoid lupus erythematosus and systemic lupus erythematosus

200-400 mg/day (155-310 mg base/day) PO as a single daily dose or in two divided doses

Doses >400 mg/day are not recommended

Incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded

## **Common Drugs Used in Systemic Lupus Erythematosus (SLE) and Their Side Effects**

| Drug/Class | Common Drugs (Examples) | Common Side Effects |
| --- | --- | --- |
| Antimalarials | Hydroxychloroquine (Plaquenil) | Retinopathy (rare but serious), GI upset, skin rash, headache |
| Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) | Ibuprofen, Naproxen | GI irritation/bleeding, kidney impairment, cardiovascular risks |
| Corticosteroids | Prednisone, Dexamethasone, Triamcinolone | Weight gain, hypertension, hyperglycemia, osteoporosis, infection risk |
| Immunosuppressants | Azathioprine (Imuran, Azasan), Mycophenolate mofetil (Cellcept), Methotrexate (Rheumatrex), Cyclophosphamide, Leflunomide | Bone marrow suppression, liver toxicity, increased infection risk, nausea |
| Calcineurin Inhibitors | Cyclosporine (Neoral, Sandimmune), Tacrolimus | Nephrotoxicity, hypertension, tremor, increased infection risk |
| Biologics | Belimumab (Benlysta), Anifrolumab (Saphnelo), Rituximab (Rituxan) | Infusion reactions, increased risk of infections, nausea, diarrhea |
| Other Agents | Aspirin, Dapsone, Cyclophosphamide | Bleeding risk (aspirin), hemolysis (dapsone), bone marrow suppression (cyclophosphamide) |

## **Treatment Procedures and Timelines**

| Phase/Procedure | Description | Typical Timeline/Duration |
| --- | --- | --- |
| Initial Therapy for Severe Flares | Pulse intravenous methylprednisolone (high-dose steroids) for rapid inflammation control | 1–3 days of IV pulses followed by oral steroids |
| Oral Corticosteroids | Prednisone or equivalent to maintain control after IV pulses | Dosing adjusted based on symptoms; tapered over weeks to months to minimize side effects |
| Immunosuppressive Induction Therapy | Cyclophosphamide or mycophenolate mofetil for lupus nephritis or severe organ involvement | Several months (3–6 months) for induction phase |
| Maintenance Therapy | Lower doses of immunosuppressants (azathioprine, mycophenolate) and hydroxychloroquine for long-term disease control | Ongoing, often lifelong |
| Hydroxychloroquine (HCQ) | Baseline therapy for all SLE patients to reduce flares and improve survival | Lifelong treatment with regular ophthalmologic monitoring |
| Biologic Therapies | Belimumab, anifrolumab, rituximab for refractory or moderate-to-severe disease | Administered as scheduled infusions; ongoing therapy |
| Symptomatic Treatment | NSAIDs for pain and inflammation, topical treatments for skin involvement | As needed |
| Regular Monitoring and Follow-up | Routine clinical visits and lab tests to track disease activity and medication side effects | Every 1–3 months initially, then adjusted per stability |

## **Response and Remission Timelines**

* Improvement in severe disease often occurs within 4 to 12 weeks of induction therapy.
* Mean duration of clinical response ranges from approximately 20 to 32 weeks, with variability based on disease severity and treatment regimen.
* Corticosteroids are typically tapered within 6 months to reduce adverse effects.
* Long-term disease control requires ongoing therapy and monitoring.

## **Multidisciplinary Care**

* Patients often require care from rheumatologists, nephrologists, dermatologists, and other specialists depending on organ involvement.
* Regular assessments aim to prevent flares, organ damage, and manage treatment side effects

## **Epidemiology**

### United States Statistics

*Incidence*

Estimates from the five national lupus registries funded by the Centers for Disease Control and Prevention (CDC) place the incidence of SLE at roughly 5.1 per 100,000 person-years (95% CI 4.6 to 5.6), higher in women than in men (8.7 vs 1.2 per 100,000 person-years), and highest among Black women (15.9 per 100,000 person-years). The American Indian/Alaska Native population had the second highest race-specific SLE estimates for women (10.4 per 100,000) and highest for men (3.8 per 100,000). Incidence in Hispanic women with SLE was 6.7 per 100,000. Based on those data and extrapolating age- and race-specific rates to the 2018 US Census data, it is estimated that 14,263 persons (95% CI 11,563 to 17,735) were newly diagnosed with SLE in the US.

*Prevalence*

Older national prevalence estimates vary widely due to differences in case definitions, and study methods. The Lupus Foundation of America currently estimates prevalence to be at least 1.5 million cases, which likely reflects inclusion of milder forms of the disease.

The pooled prevalence of SLE from the five national CDC-funded lupus registries was 72.8 cases per 100,000 people. In 2018, an estimated 204,295 individuals (95% confidence interval [CI] 160,902–261,725) in the US fulfilled the American College of Rheumatology (ACR) classification criteria for SLE.

## **Outlook / Prognosis**

Lupus is a lifelong (chronic) condition. You should expect to manage lupus symptoms for the rest of your life.

Lupus can be unpredictable, and the way it impacts you can change over time. You’ll need to regularly visit your healthcare provider so they can track changes in your symptoms.

You’ll probably work with a team of providers as you learn to live with lupus. Your primary care provider will suggest specialists who can help with specific issues or symptoms. You’ll probably need to visit a rheumatologist — a healthcare provider who specializes in diagnosing and treating autoimmune diseases. Which specialists you need to visit depends on which symptoms you have and how they affect your body.

**Is there a cure for lupus?**

There’s currently no cure for lupus. Your healthcare provider will help you find a combination of treatments to manage your symptoms and hopefully put lupus into remission (long periods of time with no symptoms or flare-ups).

## **Prevention**

You can’t prevent lupus because experts aren’t sure what causes it. Talk to a healthcare provider about your risk if one of your biological parents has lupus.

### **How can I prevent lupus flare-ups?**

You might be able to prevent and reduce lupus flare-ups by avoiding activities that trigger your symptoms, including:

* **Avoiding sun exposure:** Spending too much time in the sun can trigger lupus symptoms in some people. Try to avoid going outside when the sun is brightest (usually between 10 a.m. and 4 p.m.). Wear long sleeves, a hat or sun-protective clothing. Use a sunscreen that’s at least SPF 50.
* **Staying active:** Joint pain can make it hard or painful to move. But moving and gently using your joints can be the best way to relieve symptoms like pain and stiffness. Walking, biking, swimming, yoga and tai chi are all great ways to move your body without putting too much stress on your joints. Ask your healthcare provider which types of activities are safest for you.
* **Getting enough sleep and protecting your mental health:** Living with lupus can be frustrating. Getting the right amount of sleep (seven to nine hours for adults) and reducing your stress can help prevent flare-ups for some people. A psychologist or other mental health professional can help you develop healthy coping mechanisms.

### **When should I see my healthcare provider?**

Visit a healthcare provider as soon as you notice any new or changing symptoms. Even small shifts in what you’re feeling and experiencing can be important.

Talk to your provider if it feels like your treatments aren’t managing lupus symptoms as well as they used to. Tell your provider if you’re having flare-ups more often — or if the flare-ups cause more severe symptoms. They’ll help you adjust your treatments as needed.

Go to the emergency room or call 911 (or your local emergency services number) if you’re experiencing any of the following symptoms:

* You can’t breathe.
* You’re in severe pain.
* You think you’re experiencing heart attack symptoms.

## **Differential Diagnosis of SLE**

1. Other Autoimmune and Connective Tissue Diseases
   1. Rheumatoid Arthritis (RA): Especially when joint symptoms predominate; presence of anti-CCP antibodies favors RA.
   2. Mixed Connective Tissue Disease (MCTD): Features of SLE plus systemic sclerosis, myositis, or rheumatoid-like arthritis.
   3. Systemic Sclerosis (Scleroderma): Skin thickening and Raynaud’s phenomenon predominate.
   4. Sjogren’s Syndrome: Dry eyes and mouth, positive anti-Ro/SSA and anti-La/SSB antibodies.
   5. Dermatomyositis/Polymyositis: Muscle weakness and characteristic skin findings.
   6. Antiphospholipid Syndrome: Can occur with or without SLE; characterized by thrombosis and pregnancy morbidity.
2. Infectious Diseases
   1. Bacterial Endocarditis: Can cause fever, cytopenias, and positive autoantibodies.
   2. Viral Infections: EBV, parvovirus B19, HIV can mimic lupus symptoms.
   3. Histoplasmosis and Other Fungal Infections: May cause systemic symptoms and organ involvement.
3. Malignancies and Paraneoplastic Syndromes
   1. Hematologic malignancies (leukemia, lymphoma) can cause cytopenias and systemic symptoms.
   2. Paraneoplastic syndromes may mimic autoimmune features.
4. Other Inflammatory and Rheumatic Disorders
   1. Sarcoidosis: Multisystem granulomatous disease with lymphadenopathy and skin lesions.
   2. Fibromyalgia: Chronic widespread pain without inflammation; may coexist with SLE.
   3. Vasculitis: Primary systemic vasculitides can mimic lupus vasculitis.
5. Drug-Induced Lupus Erythematosus
   1. Caused by certain medications (e.g., hydralazine, procainamide) with lupus-like symptoms but usually milder and reversible on drug withdrawal.
6. Hematologic Disorders
   1. Autoimmune hemolytic anemia and thrombocytopenia may have other causes such as idiopathic or secondary to malignancy.

**GENOMIC DATA**

* Important genes and loci include:
  + IRF5 (Interferon Regulatory Factor 5): Strongly associated with SLE in multiple populations; specific variants (e.g., rs2004640) show ethnic differences in association
  + PTPN22, STAT4: Genes also implicated in other autoimmune diseases like rheumatoid arthritis and diabetes
  + TNFAIP3, BLK, BANK1: Additional loci involved in immune regulation
  + MHC Class II region: Variants in super-enhancers regulating MHC class II gene expression are critical in SLE pathogenesis
* Both common genetic variants and rare non-synonymous mutations contribute to disease risk, sometimes synergistically

## Population and Ethnic Variations

* Genetic susceptibility loci are largely shared across ethnicities but some variants show population-specific effects.
* Studies in diverse populations, including Europeans, Asians, Latin Americans, and admixed Egyptians, have expanded the catalog of risk loci and highlighted novel associations
* For example, a novel susceptibility locus near IRS1/miR-5702 was identified in an Egyptian cohort

## **Question and Answer Set**

## 1. What is Systemic Lupus Erythematosus (SLE)?

SLE is a chronic autoimmune disease where the immune system attacks the body’s own tissues, causing inflammation and damage to multiple organs including skin, joints, kidneys, and the nervous system.

## 2. What causes SLE?

The exact cause is unknown, but it involves a combination of genetic predisposition, environmental triggers (such as UV light, infections), hormonal factors, and immune system abnormalities.

## 3. What are the common symptoms of SLE?

Symptoms vary widely but often include fatigue, joint pain and swelling, skin rashes (especially a butterfly-shaped rash on the face), photosensitivity, fever, mouth ulcers, and organ-specific symptoms like kidney problems.

## 4. How is SLE diagnosed?

Diagnosis is based on clinical features and laboratory tests including positive antinuclear antibody (ANA), anti-dsDNA, anti-Smith antibodies, low complement levels, and evidence of organ involvement.

## 5. What treatments are available for SLE?

Treatment includes hydroxychloroquine for all patients, corticosteroids for inflammation control, immunosuppressants (like azathioprine, mycophenolate), and biologics (such as belimumab) for more severe or refractory cases.

## 6. Can SLE be cured?

There is currently no cure for SLE, but with appropriate treatment, many patients can achieve remission or low disease activity and lead normal lives.

## 7. What lifestyle changes can help manage SLE?

Avoid sun exposure, use sunscreen, maintain a healthy diet, exercise regularly, avoid smoking, and manage stress.

## 8. What are the potential complications of SLE?

Complications include kidney failure, cardiovascular disease, infections, neuropsychiatric symptoms, and increased risk of blood clots.

## 9. How often should patients with SLE see their doctor?

Regular follow-up every 3 to 6 months is typical, but frequency depends on disease activity and organ involvement.

## 10. Is pregnancy possible with SLE?

Yes, but pregnancies require careful planning and monitoring due to increased risks for both mother and baby.

## **Doctor-Patient Conversation on Systemic Lupus Erythematosus (SLE)**

## Patient:

Doctor. I’ve been feeling really unwell lately. I have joint pain and swelling in my hands and knees, extreme fatigue, and I’ve been getting a weird rash on my face after being in the sun.

## Doctor:

I see. Can you describe the rash on your face? Where exactly is it?

## Patient:

It’s mostly across my nose and cheeks, kind of like a butterfly shape, and it gets worse when I’m outside.

## Doctor:

That’s significant. Have you noticed any other symptoms, like hair loss, mouth sores, or chest pain when you breathe deeply?

## Patient:

Yes, my hair has been thinning, and I’ve had a few mouth sores that don’t seem to heal. Sometimes my chest hurts, especially when I take a deep breath.

## Doctor:

Those symptoms, especially the fatigue, joint pain, and the butterfly rash, are very concerning for Systemic Lupus Erythematosus, often just called lupus. It's an autoimmune disease where your immune system mistakenly attacks your own tissues. Is there any history of autoimmune conditions in your family?

## Patient:

My aunt has rheumatoid arthritis, but I don't know about lupus specifically.

## Doctor:

Family history of autoimmune diseases can increase the risk. To investigate this further, I’d like to order some blood tests. We’ll check for general inflammation markers like ESR and CRP, specific antibodies such as ANA (Antinuclear Antibody) and anti-dsDNA, and kidney function. We may also do a urine test to check for kidney involvement.

## Patient:

Will these tests confirm if I have lupus?

## Doctor:

The ANA test is very sensitive, meaning most people with lupus will have a positive ANA. However, a positive ANA doesn't automatically mean lupus, as it can be positive in other conditions or even in healthy individuals. The anti-dsDNA and other specific antibody tests, combined with your symptoms, will help us make a diagnosis. Lupus is diagnosed based on a combination of clinical symptoms and lab test results.

## Patient:

What kind of treatments are there for lupus?

## Doctor:

Treatment for lupus varies widely depending on which organs are affected and how severe your symptoms are. It usually involves medications to reduce inflammation and suppress the immune system. Common medications include antimalarials like hydroxychloroquine, corticosteroids for flares, and sometimes immunosuppressants for more severe organ involvement.

## Patient:

Are there a lot of side effects with those medications?

## Doctor:

Yes, most medications for lupus can have side effects. For example, hydroxychloroquine rarely can affect the eyes, so regular eye exams are needed. Corticosteroids have many side effects with long-term use, and immunosuppressants can increase your risk of infections. We'll discuss the specific risks and benefits of any medication we prescribe in detail.

## Patient:

How long will I need to be on medication? Is this a lifelong condition?

## Doctor:

Lupus is a chronic, lifelong condition. The goal of treatment is to control inflammation, reduce symptoms, prevent organ damage, and improve your quality of life. Treatment plans are often adjusted over time based on disease activity.

## Patient:

What can I do to help myself?

## Doctor:

Protecting your skin from the sun is very important, as UV light can trigger flares. Managing stress, getting enough rest, and maintaining a healthy lifestyle are also crucial. We'll discuss these in more detail.

## Patient:

Thank you, doctor. What's the next step?

## Doctor:

I'll order those tests right away. We'll schedule a follow-up appointment to discuss your results and formulate a treatment plan. It's important to start treatment early if a diagnosis is confirmed.

## Patient:

Okay, I appreciate your help.

## Doctor:

You're welcome. We'll work together closely. Please don't hesitate to call if your symptoms worsen or you have any new concerns before your next appointment.

**REFERENCES**

<https://emedicine.medscape.com/article/332244-differential>

<https://www.ncbi.nlm.nih.gov/books/NBK535405/>

<https://my.clevelandclinic.org/health/diseases/4875-lupus>

<https://www.mayoclinic.org/diseases-conditions/lupus/diagnosis-treatment/drc-20365790>

<https://www.lupus.org/news/american-college-of-rheumatology-new-systemic-lupus-erythematosus-guideline>

**FRAGILITY FRACTURE**

**DEFINITION AND DESCRIPTION**

Bone fractures are partial or complete breaks in a bone, which may spontaneously occur (due to diseases such as osteoporosis and associated chronic conditions) or result from a fall or a trauma (due to road traffic accidents, sports, etc.). Fractures are a global public health concern and are associated with significant morbidity, mortality and healthcare costs.

Due to worldwide population growth and ageing, the number of people sustaining a fracture each year has been increasing. Currently, there are no global estimates on fragility fractures, and available data include all fractures combined. The absolute incidence, prevalence and years lived with disability for fractures have significantly increased from 1990 to 2019, with highest age-specific incidence rates in the oldest age groups in which most fractures are due to bone fragility (fragility fractures). These substantial increases have been associated with increased healthcare costs globally.

In the largest five countries of the European Union plus Sweden, the annual costs of fragility fractures are expected to increase by 27% by 2030. The same trend is reported in other parts of the world. Therefore, preventing fragility fractures through early assessment of risk factors and treatment of osteoporosis is essential for good health and well-being for all adults, and particularly so for older people.

## **Types of fragility fractures**

Fragility fractures result from low-energy trauma (a mechanical force that would not ordinarily cause a fracture), such as a fall from standing height or less. These fractures are the main clinical consequence of osteoporosis, although they may occur in postmenopausal women even in the absence of osteoporosis.

The most common sites of fragility fractures are the:

* spine
* hip
* distal forearm (wrist)
* proximal humerus (upper arm).

Other fragility fracture sites include the pelvis, ribs, and proximal tibia. Hip and vertebral (spine) fractures are considered the most serious fragility fractures.

## **Risk factors**

Risk factors are lifestyle, genetic, social or environmental factors that increase an individual’s risk or propensity of developing a disease or sustaining a health-related problem and are generally categorized into modifiable and non-modifiable factors. Modifiable risk factors can be changed by modifying one’s lifestyle or environment, so that the probability of occurrence of a disease or a health condition may be reduced.

Modifiable risk factors for fragility fractures include:

* smoking
* alcohol consumption
* sedentary behavior/physical inactivity
* low body weight
* nutrient-poor diet
* vitamin D and calcium deficiency
* eating disorders (for example anorexia nervosa and bulimia)
* malabsorption
* medications (including glucocorticoids, antidepressants, anticonvulsants, androgen deprivation therapy, etc.)
* falls.

Non-modifiable risk factors include:

* older age
* sex (women have a higher risk)
* ethnicity (Caucasian people have a higher risk)
* history of prior fractures
* history of parental fractures
* menopause.

Although non-modifiable risk factors cannot be altered by lifestyle or environmental changes, knowledge of these factors is fundamental for health workers and patients for optimal prevention strategies. In fact, as with many age-related conditions, fragility fractures can result from multiple causes and risk factors.

### **Osteoporosis and low bone mineral density**

Osteoporosis is a disease characterized by low bone density and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. Aside from the factors listed above, osteoporosis itself is a risk factor for fracture the same way hypertension is for stroke, for example.

## **Can an individual’s risk of fragility fracture be predicted?**

Many tools have been developed to predict the probability of a fracture, most of which use combinations of clinical risk factors (for example, age, sex, history of previous fractures), with or without bone mineral density (BMD) measurement. These tools are used to calculate the individuals’ risk of fracture over a certain number of years (for example, five or ten years), which supports the clinical decision-making process. However, there is no global consensus on which fracture risk assessment tools have the best prediction performance.

WHO is currently assessing all available fracture risk prediction tools to determine which tools would be recommended for use globally.

## **Strategies for primary prevention**

Primary prevention refers to actions, strategies or interventions for preventing or avoiding the initial occurrence of diseases or health conditions. These include actions to identify risk factors in individuals or populations, and actions to mitigate or eliminate these risk factors.

Primary prevention strategies for fragility fractures mainly aim at promoting or maintaining bone density and strength. These include:

* improvement of diet and nutrition
* regular exercise and physical activity
* smoking cessation
* limitation of alcohol consumption
* treatment of osteoporosis
* prevention of falls.

Whereas there is some consensus on basic principles for primary prevention of fragility fractures (for example, nutrition/healthy diet, physical activity), controversies still exist over the effectiveness of some specific interventions, as well as treatment duration.

## **Treatment and management**

Early detection of fragility fractures and treatment (secondary prevention) is fundamental, as delayed treatment may lead to complications and compromise optimal treatment outcomes. In fact, although they are common in postmenopausal women and older men, most vertebral fractures are undiagnosed.

Management of clinical fragility fractures and of complications secondary to fractures is also key. Treatment of fragility fractures can be surgical or non-surgical, with orthopedic surgeons playing a central role.

Prevention of refracture (usually called secondary fracture prevention) is also essential, and counts as tertiary prevention strategies, which include effective rehabilitation and improvement of quality of life.

Timely rehabilitation provided by a skilled rehabilitation workforce following treatment is crucial to support people to recover from the fracture and related functioning loss. Ensuring access to assistive products (e.g. walking aids, orthoses) and providing associated training is a crucial component of rehabilitation.

### **Hip fracture**

A hip fracture is the medical name for breaking the upper part of your thigh bone (femur) near your hip joint.

Your femur is the longest and strongest bone in your body, so it usually takes a serious fall, car accident or other trauma to break it. You’ll almost always need surgery to repair a hip fracture.

People sometimes joke about broken hips as shorthand for a friend getting older. This is usually just playful teasing, but it’s important to remember that broken hips are serious, potentially life-changing injuries.

#### **Types of hip fractures**

Your hip is a ball-and-socket joint. The ball-shaped top (the head) of your femur fits into a socket (the acetabulum) in your pelvis. A broken hip is a broad category that means any type of bone fracture that affects the upper part of your femur.

Healthcare providers classify broken hips based on where the femur breaks:

* **Femoral head fractures:** The femoral head is the rounded cap at the top (proximal) end of your femur. It’s very rare to break your femoral head.
* **Femoral neck fractures (subcapital or intracapsular fractures):** The femoral neck is the bridge between your femur’s rounded head and the long shaft that runs down through your thigh. It’s the most common place for hips to break.
* **Intertrochanteric fractures:** The greater and lesser trochanters are bumps of bone that stick out just around the femoral neck. Muscles and tendons attach to the trochanters. Intertrochanteric fractures happen when a hip fracture breaks the space between these bony bumps.

Providers may also give a hip fracture a name based on the fracture’s pattern (its shape or direction), including:

* Transverse fractures.
* Oblique fractures.
* Spiral fractures.
* Comminuted fractures.

## **Symptoms and Causes**

The most common hip fracture symptoms include:

* Severe hip pain.
* Not being able to move your hip or leg (limited mobility).
* A bump you can feel or see.
* Swelling.
* Bruising.
* Your hip looking noticeably different (deformity).

### **What causes hip fractures?**

It usually takes severe trauma to break your hip. The most common causes of hip fractures include:

* Falls.
* Car accidents.
* Sports injuries.

#### **Risk factors**

Anyone can experience sudden trauma and break a hip, but some people are more likely to, including:

* Adults older than 65.
* People with health conditions that weaken their bones (like osteoporosis or osteopenia).
* Females.
* Athletes who play contact sports.

It usually takes a fall from a big height (like off a ladder or roof) to fracture your hip. But adults older than 65 or people with health conditions that weaken their bones are much more likely to break a hip after minor slips and falls at home or in their daily routines.

Any health condition that affects your balance, stability or ability to walk and move (your gait) can increase your risk of breaking a hip. Some conditions that can reduce your stability include:

* Parkinson’s disease.
* Vertigo.
* Gait abnormalities.
* Epilepsy and other conditions that cause seizures.

## **Diagnosis and Tests**

A healthcare provider will diagnose a broken hip with a physical exam and imaging tests. Providers in the emergency room might diagnose the fracture in the ER if you experience a severe fall or other trauma.

Your provider will use at least one of the following types of imaging test to take pictures of your hip and the area around it:

* Hip X-ray.
* MRI (magnetic resonance imaging).
* CT scan (computed tomography scan).

### **Hip fracture treatments**

Almost everyone with a hip fracture needs surgery. Which type of surgery you’ll need depends on the fracture’s severity and type, and if you have any other injuries or health conditions. The two most common surgeries for hip fractures include:

* **Hip replacement (hip arthroplasty):** Adults older than 65 who experience a hip fracture usually need a hip replacement. You may need a total or partial replacement.
* **Open reduction and internal fixation (ORIF):** Your surgeon will insert screws, pins or plates, or a metal rod into your femur to secure the pieces of your bone in place while they heal. Some people live with these fasteners in their bodies forever. Others need them removed once their hips heal.

#### **Hip fracture surgery complications**

Hip fracture surgery complications can include:

* **Avascular necrosis:** Avascular necrosis is bone death that happens when blood flow is cut off to a bone for too long.
* **Nonunion:** Your bone may not grow back together completely or at all.
* **Malunion:** This happens when a broken bone doesn’t line up correctly while it heals.
* **Bone infection (osteomyelitis):** If you have an open fracture (the bone breaks through your skin) you have an increased risk of bacterial infection.

## **Antibiotics**

Antibiotic therapy must be comprehensive and cover all likely pathogens in the context of the clinical setting.

## **Cefazolin (Ancef, Kefzol, Zolicef)**

First-generation semisynthetic cephalosporin that arrests bacterial cell wall synthesis, inhibiting bacterial growth. Primarily active against skin flora, including *Staphylococcus aureus*. Typically used alone for skin and skin-structure coverage. IV and IM dosing regimens are similar.

### Dosage Forms & Strengths

#### **injection, powder for reconstitution**

* 500mg
* 1g
* 2g
* 3g
* 10g
* 100g
* 300g

#### **injection, premixed solution**

* 1g/50mL
* 2g/100mL

### Moderate-to-Severe Infections

0.5-1 g IV q6-8hr

### Mild Infections With Gram-Positive Cocci

250-500 mg IV q8hr

### Mild-to-Moderate Cholecystitis

1-2 g IV q8hr for 4-7 days

### Acute Uncomplicated Urinary Tract Infection

1 g IV q12hr

### Pneumococcal Pneumonia

500 mg IV q12hr

### Severe, Life-threatening Infection

1-1.5 g IV q6hr

### Perioperative Prophylaxis

Preoperatively: 1-2 g IV/IM 30-60 minutes before procedure

During surgery for lengthy procedures (ie, >2 hr): 0.5-1 g IV

Postoperatively: 0.5-1 g IV q6-8hr for 24 hr

#### Surgical infection

* Cardiac procedures, hysterectomy, oral or pharyngeal procedures, craniotomy, joint replacement, thoracic procedures, arterial procedures, amputation, traumatic wounds; high-risk esophageal, gastroduodenal, or biliary tract procedures: 1-2 g IV
* Colorectal procedures: 1-2 g IV plus metronidazole 0.5 g IV
* High-risk cesarean section, 2nd trimester abortion: 1 g IV
* Ophthalmic procedures: 100 mg subconjunctivally

### Endocarditis

1 g IV/IM 30-60 minutes before procedure

Endocarditis prophylaxis recommended only for high-risk patients

### Bacterial Keratitis (Off-label)

1 drop instilled into affected eye(s) q1-2hr; typically alternated every other hour with antibiotic providing gram-negative coverage (eg, tobramycin)

#### **Extemporaneous compounded fortified cefazolin 50 mg/mL**

* Dilute 500 mg parenteral cefazolin powder in sterile water to form 10 mL solution
* Store refrigerated; preparation expires in 7 days

### Dosing Modifications

#### Renal impairment

* CrCl 35-54 mL/min: Give recommended dose at intervals ≥8hr
* CrCl 11-34 mL/min: Give half of recommended dose q12hr
* CrCl ≤10 mL/min: Give half of recommended dose q18-24hr

#### Hepatic impairment

* Not studied

### Dosing Considerations

#### Susceptible organisms

* Streptococcus pneumoniae, Klebsiella, Haemophilus influenzae, Staphylococcus aureus, group A beta-hemolytic streptococcus, Escherichia coli, Proteus mirabilis, Enterobacter (some strains)

#### **Serious (12)**

| antithrombin alfa  antithrombin III  argatroban  BCG vaccine live  bivalirudin  cholera vaccine  dalteparin  enoxaparin  fondaparinux  heparin  microbiota oral  typhoid vaccine live | **Monitor Closely (32)** amikacin  atezolizumab  avelumab  balstilimab  bazedoxifene/conjugated estrogens  camrelizumab  cemiplimab  cosibelimab  dienogest/estradiol valerate  dostarlimab  durvalumab  estradiol  ethinylestradiol | **Minor (9)** aspirin/citric acid/sodium bicarbonate  biotin  chloramphenicol  furosemide  ketorolac intranasal  pyridoxine (Antidote)  rose hips  sulfasalazine  willow bark Adverse Effects |
| --- | --- | --- |
|  | gentamicin  kanamycin  levonorgestrel oral/ethinylestradiol/ferrous bisglycinate  neomycin PO  nivolumab  pembrolizumab  penpulimab  plazomicin  probenecid  retifanlimab  sintilimab | Frequency Not Defined Anorexia  Diarrhea  Eosinophilia  Fever  Increased transaminases  Leukopenia  Nausea and vomiting  Neutropenia  Oral candidiasis  Pain at injection site  Phlebitis  Pseudomembranous colitis  Seizure  Stevens-Johnson syndrome |
|  | sodium picosulfate/magnesium oxide/anhydrous citric acid  streptomycin  tislelizumab  tobramycin  toripalimab  voclosporin  warfarin  xanomeline/trospium | Thrombocytopenia  Thrombocytosis  Transient elevation of hepatic enzymes  Vaginitis |

Immune system disorders: Serum sickness-like reaction

Renal and urinary disorders: Acute tubulointerstitial nephritis

Skin and subcutaneous tissue disorders: Acute generalized exanthematous pustulosis (AGEP)

### Cautions

Endocarditis prophylaxis recommended only for high-risk patients, per AHA guidelines

Prolonged treatment, hepatic or renal disease, or nutritional deficiency may be associated with increased international normalized ratio (INR)

Use with caution in patients with seizure disorder (high levels are associated with increased risk of seizures); seizures may occur, particularly in patients with renal impairment when dosage is not reduced appropriately; dose must be adjusted in severe renal insufficiency (high doses may cause CNS toxicity); discontinue if seizures occur or make appropriate dosage adjustments in patients with renal impairment; continue anticonvulsant therapy in patients with known seizure disorders

Prescribing cefazolin injection in absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases risk of development of drug-resistant bacteria

As with other antimicrobials, prolonged use of cefazolin injection may result in overgrowth of nonsusceptible microorganisms; repeated evaluation of the patient's condition is essential; should superinfection occur during therapy, appropriate measures should be taken

Therapy may result in a false-positive reaction with glucose in urine when using glucose tests based on Benedict’s copper reduction reaction that determine amount of reducing substances like glucose in urine; it is recommended that glucose tests based on enzymatic glucose oxidase be used

Hypersensitivity reactions, including anaphylaxis, reported with administration of dextrose-containing products; these reactions have been reported in patients receiving high concentrations of dextrose (i.e. 50% dextrose); reactions have been reported when corn-derived dextrose solutions were administered to patients with or without a history of hypersensitivity to corn products

As with other dextrose-containing solutions, cefazolin injection should be prescribed with caution in patients with overt or known subclinical diabetes mellitus or carbohydrate intolerance for any reason

Cefazolin injection may be associated with a fall in prothrombin activity; those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy; prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated

#### **Antibiotic associated diarrhea**

* Clostridioides difficile-associated diarrhea (CDAD) reported with use; may range in severity from mild diarrhea to fatal colitis; treatment with antibacterial agents alters normal flora of colon leading to overgrowth of C. difficile
* C. difficile produces toxins A and B, which contribute to development of CDAD; hyper toxin-producing isolates of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy
* CDAD must be considered in all patients who present with diarrhea following antibacterial drug use; careful medical history is necessary since CDAD has been reported to occur over two months after administration of antibacterial agents
* If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against C. difficile may need to be discontinued; appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of C. difficile, and surgical evaluation instituted as clinically indicated

## Pregnancy & Lactation

### Pregnancy

cephalosporin use, including cefazolin, in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes; drug crosses the placenta

#### Animal data

* Animal reproduction studies with rats, mice and rabbits administered cefazolin during organogenesis at doses 1 to 3 times maximum recommended human dose (MRHD) did not demonstrate adverse developmental outcomes; in rats subcutaneously administered cefazolin prior to delivery and throughout lactation, there were no adverse effects on offspring at a dose approximately 2 times the MRHD

### Lactation

cefazolin is present in human milk, but not expected to accumulate in a breastfed infant; there are no data on effects of drug on breastfed child or on milk production

Developmental and health benefits of breastfeeding should be considered along with mother’s clinical need for therapy and any potential adverse effects on breastfed child from drug or from the mother’s underlying condition

### Pregnancy Categories

A: Generally acceptable. Controlled studies in pregnant women show no evidence of fetal risk.

B: May be acceptable. Either animal studies show no risk but human studies not available or animal studies showed minor risks and human studies done and showed no risk.

C: Use with caution if benefits outweigh risks. Animal studies show risk and human studies not available or neither animal nor human studies done.

D: Use in LIFE-THREATENING emergencies when no safer drug is available. Positive evidence of human fetal risk.

X: Do not use it in pregnancy. Risks involved outweigh potential benefits. Safer alternatives exist.

NA: Information not available.

## Pharmacology

### Mechanism of Action

First-generation semisynthetic cephalosporin that binds to 1 or more penicillin-binding proteins, thereby arresting bacterial cell-wall synthesis and inhibiting bacterial replication; has poor capacity to cross blood-brain barrier; primarily active against skin flora, including S aureus

### Absorption

Peak plasma time: 0.5-2 hr (IM); 5 min (IV)

### Distribution

Crosses placenta; penetrates CSF poorly

Protein bound: 74-86%

### Metabolism

Minimally metabolized in liver

### Elimination

Half-life: 90-150 min

Excretion: Urine (80-100% as unchanged drug)

## Administration

### IV Incompatibilities

Additive: Amikacin, gentamicin

Syringe: Cimetidine, lidocaine

Y-site: Amiodarone(?), amphotericin B

Not specified: Erythromycin, norepinephrine, pentobarbital, tetracycline

### IV Compatibilities

Additive: Cimetidine, verapamil

Y-site: Aminophylline, amiodarone(?), calcium gluconate, lidocaine, vitamins B and C

Not specified: Ampicillin, diazepam, hydrocortisone, potassium chloride

### IV Preparation

#### Powder for reconstitution

* Reconstituted solutions may range in color from pale yellow to yellow

##### 2 g vial

* + Reconstitute with 15 mL 0.9% NaCl or D5W to yield ~136 mg/mL
  + Further dilution: 50 mL or 100 mL to achieve final concentrations of ~40 mg/mL or 20 mg/mL respectively

##### 3 g vial

* + Reconstitute with 15 mL 0.9% NaCl or D5W to yield ~196 mg/mL
  + Further dilution: 100 mL to achieve final concentrations of ~30 mg/mL

#### **Premixed solution**

* Thaw frozen container at room temperature 20-25ºC (68-77ºF) or under refrigeration 2-8ºC (36-46ºF)
* Do not thawed by immersion in water baths or by microwave irradiation; do not force thaw
* No further dilution is necessary
* Check for minute leaks by squeezing container firmly; if leaks detected, discard solution as sterility may be impaired
* Do not add supplementary medication
* Visually inspect container; if outlet port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired
* Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation; potency is not affected
* Agitate after solution has reached room temperature
* Discard if after visual inspection the solution remains cloudy or if an insoluble precipitate is noted or if any seals are not intact

### IM Preparation

Reconstitute vials 500 mg or 1 g with 2 mL or 2.5 mL sterile water for injection, respectively, to provide solutions containing ~225 or 330 mg/mL

### IV Administration

IV infusion: Infuse over 30 minutes

IV push: Administer directly into vein over 3-5 minutes or slowly into tubing of compatible IV infusion solution

IM Administration

Inject deep into large muscle mass

### Storage

#### **Unopened vials**

* Store at 20-25ºC (68-77ºF)
* Protect from light

#### **Reconstituted and diluted solutions**

* 24 hours at room temperature, or7 days refrigerated at 2-8ºC (36-46ºF)

#### P**remixed solution**

* Store in freezer capable of maintaining temperature ≤ -20ºC (-4ºF)
* Thawed solution stable for 30 days under refrigeration (5ºC/41ºF) or 48 hr at 2ºC/77ºF
* Do not refreeze thawed antibacterial drugs

## [**Tobramycin (Nebcin)**](https://reference.medscape.com/drug/nebcin-injection-tobramycin-342521)

Used in skin, bone, and skin-structure infections caused by *S aureus*, *Pseudomonas aeruginosa*, *Proteus* species, *Escherichia coli*, *Klebsiella* species, and *Enterobacter* species. Indicated in the treatment of staphylococcal infections when penicillin or potentially less toxic drugs are contraindicated and when bacterial susceptibility and clinical judgment justifies its use.

### Dosage Forms & Strengths

#### injectable solution

* 10mg/mL
* 40mg/mL

#### Solution reconstituted

* 1.2g

### B**acterial Infections**

3-6 mg/kg/day IV/IM divided q8hr OR

4-7 mg/kg/dose IV/IM qDay

### **Renal Impairment**

Clcr >60 mL/min: q8hr

Clcr 40-60 mL/min: q12hr

Clcr 20-40 mL/min: q24hr

Clcr 10-20 mL/min: q48hr

Clcr <10 mL/min: q72hr

Following dialysis in ESRD

### Monitor

Peak and trough concentrations, renal and auditory function

Life-threatening infection: 8-10 mcg/mL

Serious infection: 6-8 mcg/mL

UTIs: 4-6 mcg/mL

Synergy for infections caused by gram-positive organisms: 3-5 mcg/mL

### **Other Indications & Uses**

May have increase activity against resistant Gram negatives

Citrobacter spp., E. coli, P. aeruginosa, Proteus spp. (indole-positive and negative), Providencia spp. (including Klebsiella-Enterobacter-Serratia), S. aureus (coagulase-positive and negative)

## Interactions

#### Serious (21)

| amphotericin B deoxycholate  atracurium  bacitracin  BCG vaccine live  bumetanide  cholera vaccine  cidofovir  cisatracurium  ethacrynic acid  furosemide  mannitol  microbiota oral  neomycin PO  pancuronium | Monitor Closely (94) abobotulinumtoxinA  acyclovir  amikacin  amiodarone  bazedoxifene/conjugated estrogens  capreomycin  carboplatin  cefaclor  cefadroxil  cefazolin  cefdinir  cefditoren  cefepime  cefepime/enmetazobactam | Minor (70) aceclofenac  acemetacin  adefovir  aspirin  aspirin rectal  aspirin/citric acid/sodium bicarbonate  aztreonam  balsalazide  biotin  calcium acetate  calcium carbonate  calcium chloride  calcium citrate |
| --- | --- | --- |
| quinidine  rapacuronium  rocuronium  succinylcholine  torsemide  typhoid vaccine live  vecuronium | cefiderocol  cefixime  cefotaxime  cefotetan  cefoxitin  cefpirome  cefpodoxime  cefprozil  ceftaroline  ceftazidime  ceftazidime/avibactam  ceftibuten  ceftizoxime  ceftobiprole medocaril sodium | calcium gluconate  celecoxib  choline magnesium trisalicylate  clotrimazole  cordyceps  cyanocobalamin  diclofenac  diflunisal  entecavir  etodolac  fenoprofen  fluconazole  flurbiprofen  foscarnet  ibuprofen |
|  | ceftolozane/tazobactam  ceftriaxone  cefuroxime  cephalexin  cephaloridine  cisplatin  clarithromycin  clotrimazole  colistin  conjugated estrogens  contrast media (iodinated)  cyclosporine  daptomycin  daxibotulinumtoxinA | ibuprofen IV  indomethacin  ketoconazole  ketoprofen  ketorolac  ketorolac intranasal  levoketoconazole  lornoxicam  magnesium chloride  magnesium citrate  magnesium hydroxide  magnesium oxide  magnesium sulfate  meclizine  meclofenamate |
|  | deferasirox  dichlorphenamide  digoxin  dronedarone  elvitegravir/cobicistat/emtricitabine/tenofovir DF  erythromycin base  erythromycin ethylsuccinate  erythromycin lactobionate  erythromycin stearate  estradiol  estrogens conjugated synthetic  estropipate  felodipine | mefenamic acid  meloxicam  methoxyflurane  miconazole vaginal  nabumetone  naproxen  oxaprozin  pantothenic acid  parecoxib  paromomycin  pentamidine  piperacillin  piroxicam  posaconazole  pyridoxine |
|  | fosphenytoin  gentamicin  incobotulinumtoxinA  ioversol  ketoconazole  letibotulinumtoxinA  levoketoconazole  loratadine  magnesium supplement  mestranol  nefazodone  nicardipine  nifedipine  nilotinib  onabotulinumtoxinA | pyridoxine (Antidote)  salicylates (non-asa)  salsalate  streptomycin  sulfasalazine  sulindac  thiamine  tolfenamic acid  tolmetin  vancomycin  voriconazole  zoledronic acid |
|  | oxaliplatin  peramivir  phenobarbital  phenytoin  polymyxin B  prabotulinumtoxinA  quercetin  rifampin  rimabotulinumtoxinB  ritonavir  sirolimus |  |
|  | sodium picosulfate/magnesium oxide/anhydrous citric acid  sodium sulfate/?magnesium sulfate/potassium chloride  sodium sulfate/potassium sulfate/magnesium sulfate  St John's Wort  streptozocin  tacrolimus  teicoplanin  tenofovir DF  tolvaptan  trazodone  trimagnesium citrate anhydrous  verapamil  voclosporin |  |

## Adverse Effects

### 1-10%

Ototoxicity

Nephrotoxicity

Neurotoxicity (neuromuscular blockade)

### <1%

Hypotension

Drug fever

Drowsiness

Headache

Paresthesia

Tremor

Rash

Nausea

Vomiting

Anemia

Eosinophilia

Arthralgia

Weakness

Eyelid edema

Itching eyes

Keratitis

Lacrimation

Dyspnea

## **Ampicillin and sulbactam (Unasyn)**

Drug combination of beta-lactamase inhibitor with ampicillin. Covers skin, enteric flora, and anaerobes. Not ideal for nosocomial pathogens.

### Dosage Forms & Strengths

#### **powder for solution**

* 1.5g (ampicillin 1g/sulbactam 0.5g)
* 3g (ampicillin 2g/sulbactam 1g)
* 15g (ampicillin 10g/sulbactam 5g)

### Gynecologic Infections

1.5 g (1 g ampicillin + 0.5 g sulbactam) to 3 g (2 g ampicillin + 1 g sulbactam) IV/IM q6hr; not to exceed 12 g/day

### Intra-Abdominal Infections

1.5 g (1 g ampicillin + 0.5 g sulbactam) to 3 g (2 g ampicillin + 1 g sulbactam) IV/IM q6hr; not to exceed 12 g/day

### Skin & Skin Structure Infections

1.5 g (1 g ampicillin + 0.5 g sulbactam) to 3 g (2 g ampicillin + 1 g sulbactam) IV/IM q6hr; not to exceed 12 g/day

### Orbital Cellulitis

3 g (2 g ampicillin + 1 g sulbactam) IV q6hr

### Pelvic Inflammatory Disease

3 g (2 g ampicillin + 1 g sulbactam) IV q6hr

### Pneumonia

Aspiration or community acquired: 1.5 g (1 g ampicillin + 0.5 g sulbactam) to 3 g (2 g ampicillin + 1 g sulbactam) IV q6hr for 5 or more days

Hospital acquired: 3 g IV q6hr for 5 or more days

### Urinary Tract Infections

Pyelonephritis: 3 g (2 g ampicillin + 1 g sulbactam) IV q6hr for 14 days

### Acute Bacterial Rhinosinusitis (Off-label)

Severe infection requiring hospitalization

1.5 g (1 g ampicillin + 0.5 g sulbactam) to 3 g (2 g ampicillin + 1 g sulbactam) IV q6hr for 5-7 days

### Endocarditis (Off-label)

Enterococcus infection resistant to penicillin/susceptible to aminoglycosides: 3 g (2 g ampicillin + 1 g sulbactam) IV q6hr for 6 weeks if not aminoglycoside resistant; >6 weeks if aminoglycoside resistant

HACEK infection: 3 g (2 g ampicillin + 1 g sulbactam) IV q6hr for 4 weeks

### Dosing Modifications

#### Renal impairment

* CrCl 5-14 mL/min/1.73 m²: 1.5 g (1 g ampicillin + 0.5 g sulbactam) to 3 g (2 g ampicillin + 1 g sulbactam) IV q24hr
* CrCl 15-29 mL/min/1.73 m²: 3 g (2 g ampicillin + 1 g sulbactam) IV q12hr
* CrCl ≥ 30 mL/min/1.73 m²: No dose adjustment necessary

## Adverse Effects

### >10%

IM injection site pain (16%)

### 1-10%

Diarrhea (3%)

IV injection site pain (3%)

Thrombophlebitis (3%)

Rash ( < 2%)

### <1%

Abdominal distention

Black, "hairy" tongue

Candidiasis

Chest pain

Chills

Dysuria

Edema

Epistaxis

Erythema

Fatigue

Flatulence

Glossitis

Headache

Itching

Malaise

Mucosal bleeding

Nausea

Pseudomembranous colitis

Seizure

Tightness in throat

Thrombocytopenia

Urine retention

Vomiting

Infections and infestations: Clostridioides difficile-associated diarrhea

Blood and lymphatic system disorders: Hemolytic anemia, thrombocytopenic purpura, agranulocytosis, positive direct Coombs Tests

Gastrointestinal disorders: Abdominal pain, cholestatic hepatitis, cholestasis, hyperbilirubinemia, jaundice, abnormal hepatic function, melena, gastritis, stomatitis, dyspepsia, black “hairy” tongue

General disorders and administration site conditions: Injection site reaction

Immune system disorders: Serious and fatal hypersensitivity (anaphylactic) reactions, acute myocardial ischemia with or without myocardial infarction occurring as part of allergic reaction

Nervous system disorders: Convulsion, dizziness

Renal and urinary disorders: Tubulointerstitial nephritis

Musculoskeletal and connective tissue disorders: Arthralgia

Respiratory, thoracic, and mediastinal disorders: Dyspnea

Skin and subcutaneous tissue disorders: TEN, SJS, DRESS, angioedema, acute generalized exanthematous pustulosis (AGEP), erythema multiforme, exfoliative dermatitis, urticaria, linear IgA bullous dermatosis

## [**Gentamicin (Gentacidin, Garamycin)**](https://reference.medscape.com/drug/gentak-garamycin-gentamicin-342517)

Aminoglycoside antibiotic for gram-negative coverage. Used in combination with both an agent against gram-positive organisms and one that covers anaerobes.

## **Differential Diagnoses**

* Femoral Head Avascular Necrosis
* Femoral Neck Fracture
* Femoral Neck Stress Fracture
* Femur Injuries and Fractures
* Hip Pointer
* Hip Tendonitis and Bursitis
* Iliopsoas Tendinitis
* Slipped Capital Femoral Epiphysis

## **Epidemiology of Hip Fracture**

* Global Incidence and Projections:  
  In 1990, approximately 1.26 million hip fractures occurred worldwide (338,000 men and 917,000 women). Assuming no change in age- and sex-specific incidence rates, the number of hip fractures is projected to nearly double to about 2.6 million by 2025 and reach approximately 4.5 million by 2050. Some projections suggest the number could rise even higher, between 7.3 and 21.3 million by 2050 depending on secular trends
* Sex Differences:  
  Hip fractures are more common in women than men. The increase in hip fractures over time is expected to be proportionally greater in men (310%) than in women (240%) by 2050
* Age Distribution:  
  Hip fractures predominantly affect older adults, especially those aged 65 and above. Incidence rates increase sharply with age due to factors like osteoporosis and fall risk.
* Geographic and Demographic Trends:  
  The majority of hip fractures currently occur in Europe and North America, but demographic shifts predict a significant increase in Asia’s share—from 26% of all hip fractures in 1990 to 37% in 2025 and 45% by 2050. This reflects population aging and growth in developing countries
* Regional Data Examples:
  + In South Korea, hip fracture incidence is increasing annually by about 4.3%, with a faster rise in women. The aging population is contributing to a growing socioeconomic burden
  + In Zimbabwe, incidence rates are rising, especially in adults over 40, with projections indicating a doubling of hip fractures by 2052
  + In centenarians in Spain, hip fracture admissions increased significantly from 2004 to 2020, reflecting aging populations and increased multimorbidity
* Incidence Rates:  
  Age- and sex-standardized incidence rates vary globally, ranging from approximately 95 per 100,000 population (e.g., Brazil) to over 300 per 100,000 (e.g., Denmark)
* Public Health Impact:  
  Hip fractures contribute substantially to morbidity, mortality, loss of independence, and healthcare costs worldwide. Despite some declines in incidence rates in developed countries, the absolute number of fractures is rising due to population aging, underscoring the urgent need for prevention strategies

## **Surgical Procedures for Hip Fracture**

1. Internal Fixation (Hip Pinning or Nailing):
   1. Used for fractures of the femoral neck or intertrochanteric region.
   2. Involves inserting screws, nails, or plates to stabilize the fracture.
   3. Surgery duration: Typically 1 to 4 hours depending on complexity.
   4. Goal: To hold bone fragments in place to allow healing while preserving the natural hip joint.
2. Partial Hip Replacement (Hemiarthroplasty):
   1. Replaces only the femoral head (ball) of the hip joint.
   2. Used when the fracture is displaced or healing potential is poor.
   3. Surgery duration: Around 2 to 3 hours.
   4. Often chosen for older patients or those with pre-existing joint disease.
3. Total Hip Replacement (Arthroplasty):
   1. Replaces both the femoral head and the acetabulum (socket).
   2. Recommended for some displaced fractures or patients with arthritis.
   3. Surgery duration: Approximately 2 to 3 hours.
   4. Provides better long-term outcomes in healthy, independent adults.

## **Recovery Timeline**

| Timeframe | Key Recovery Milestones and Procedures |
| --- | --- |
| Days 1–3 (Hospital Stay) | Pain management; early physiotherapy begins within 24 hours; simple bed exercises progressing to sitting and standing; monitoring for complications such as infection or blood clots. |
| Days 4–14 (Early Recovery) | Most patients discharged; focus on walking with aids (walker, crutches); increasing walking distances; learning safe daily activities with hip precautions; wound care and monitoring. |
| Weeks 3–6 | Continued physical therapy to improve strength, mobility, and balance; gradual reduction in use of walking aids as tolerated. |
| Weeks 6–12 | Most fractures heal by 10–12 weeks; increasing independence in daily activities; ongoing rehabilitation to restore muscle strength and joint function. |
| 3–6 Months | Near-full recovery expected for many patients; ability to walk normally improves; balance and strength continue to improve. |
| Up to 1 Year | Full recovery including return to pre-injury activity levels may take up to a year, especially in older adults or those with severe fractures. |

## **Outlook / Prognosis**

### **Recovery time for a fractured hip**

It usually takes at least a few months to recover from a broken hip. You may feel and notice improvements gradually over a year after treatment. How long it takes you to recover will depend on a few factors, including:

* Which type of surgery you needed.
* Which other injuries you may have.
* Your age.
* Your overall health.
* What caused the fracture.

Your surgeon will tell you what to expect and give you a recovery timeline that matches your unique needs.

You’ll start physical therapy (PT) soon after surgery. You may need PT for several months to help you regain your ability to move and walk. A physical therapist will give you exercises and stretches to strengthen the muscles around your hip.

You may need a walker, cane or crutches while you recover from surgery. Some people need them for longer. Ask your surgeon or physical therapist how long you should use mobility aids.

### **Why is a hip fracture so dangerous?**

Hip fractures are emergencies. In addition to the damage to your femur and hip joint, hip fractures often happen alongside other major injuries. That’s especially true if you experience a severe fall or car accident.

Any injury severe enough to break your femur may also damage your femoral artery. This can cause a fatal amount of blood loss if a healthcare provider doesn’t treat it immediately. A broken hip can also increase your risk of blood clots.

The kinds of trauma that cause hip fractures can be especially dangerous for adults older than 65. The older you are, the longer it takes your body to heal any injury, and that’s especially true when you have a major one like a hip fracture. The surgery to treat a hip fracture (and the recovery from it) can be harder for an older adult, too.

Studies have found that adults older than 65 who’ve experienced a hip fracture are more likely to reduce or stop physical activity like walking and to cut back on social activities and hobbies, even after they recover. This isolation can impact your overall health. Talk to your provider about how to stay active after you’ve had a hip fracture. They can suggest safe ways to stay engaged with your loved ones and favorite activities.

## **Prevention**

You may not always be able to prevent hip fractures, especially because sudden falls or other trauma you can’t plan for cause them. Follow these general safety tips to reduce your risk of falls and injuries:

* Make sure your home and workspace are free of clutter that could trip you or others.
* Talk to your provider about a bone density test if you’re older than 65 or if members of your biological family have osteoporosis.
* Follow an eating and physical activity plan that’ll help you maintain good bone health.
* Always use the proper tools or equipment at home to reach things. Never stand on chairs, tables or countertops.
* Always wear your seatbelt.
* Wear the right protective equipment for all activities and sports.

## **Living With**

All hip fractures are medical emergencies. Call 911 (or your local emergency services number) if you think you have a broken hip. Call emergency services if you experience a fall, car accident or another trauma and experience any of the following symptoms:

* You can’t move your hip or leg.
* You’re in intense pain.
* Your hip or leg is noticeably different-looking or out of its usual place.
* You can see bone through your skin.
* Your hip is very swollen.
* You notice severe bruising that develops at the same time as any of these other symptoms.

## **Questions and Answers**

## 1. Can I be as active as I was before my hip fracture?

After a hip fracture, you may not immediately regain your previous level of activity. However, with proper treatment, rehabilitation, and a positive attitude, many people can return to many activities they enjoyed before the injury

## 2. When will the pain in my hip stop?

Hip pain after surgery is common and can last for several weeks. Pain is managed with medications and usually decreases over time with proper exercise and healing

## 3. Why do I need to begin doing exercises right after surgery?

Early exercises help promote correct healing, prevent complications such as blood clots, and build strength needed to get out of bed and move safely

## 4. What types of surgery are used to treat hip fractures?

Common surgical options include:

* Partial hip replacement (replacing the femoral head)
* Total hip replacement (replacing both femoral head and socket)
* Internal fixation with screws, plates, or rods to stabilize the fracture  
  The choice depends on fracture type, severity, and patient factors.

## 5. Who will be involved in my care?

Your care team may include ambulance paramedics, emergency department staff, orthopedic surgeons, anesthetists, geriatricians, nurses, physiotherapists, occupational therapists, pharmacists, dietitians, and social workers

## 6. How is pain managed after a hip fracture?

Pain is managed with medications such as paracetamol and stronger painkillers if needed. A nerve block injection may be given in the emergency department to provide significant pain relief

## 7. What happens if I become confused or have memory problems in hospital?

Delirium can occur due to pain, medications, dehydration, or infection. It is common in older patients and should be promptly reported to hospital staff for management

## 8. How soon will I start walking again?

Early mobilization usually begins within 24 to 48 hours after surgery, with assistance from physiotherapists. Walking aids are used initially and gradually reduced as strength and balance improve.

## 9. What are the risks of complications after hip fracture surgery?

Risks include infection, blood clots, delirium, and delayed healing. Close monitoring and early rehabilitation help reduce these risks

## 10. How long will recovery take?

Recovery varies but generally takes several months. Most patients regain significant function by 3 to 6 months, with full recovery potentially taking up to a year

**GUIDELINES**

### **Timing of surgery**

Perform surgery on the day of, or the day after, admission.

Identify and treat correctable comorbidities immediately so that surgery is not delayed by:

* anemia
* anticoagulation
* volume depletion
* electrolyte imbalance
* uncontrolled diabetes
* uncontrolled heart failure
* correctable cardiac arrhythmia or ischaemia
* acute chest infection
* exacerbation of chronic chest conditions.

### **Analgesia**

Assess the person's pain:

* immediately upon presentation at hospital **and**
* within 30 minutes of administering initial analgesia **and**
* hourly until settled on the ward **and**
* regularly as part of routine nursing observations throughout admission.

Offer immediate analgesia to people presenting at hospital with suspected hip fracture, including people with cognitive impairment.

Ensure analgesia is sufficient to allow movements necessary for investigations (as indicated by the ability to tolerate passive external rotation of the leg), and for nursing care and rehabilitation

Offer paracetamol every 6 hours preoperatively unless contraindicated.

Offer additional opioids if paracetamol alone does not provide sufficient preoperative pain relief.

Consider adding nerve blocks if paracetamol and opioids do not provide sufficient preoperative pain relief, or to limit opioid dosage. Nerve blocks should be administered by trained personnel. Do not use nerve blocks as a substitute for early surgery.

Offer paracetamol every 6 hours postoperatively unless contraindicated.

#### Offer additional opioids if paracetamol alone does not provide sufficient postoperative pain relief.

Non-steroidal anti-inflammatory drugs (NSAIDs) are not recommended.

### **Anaesthesia**

Offer people a choice of spinal or general anaesthesia after discussing the risks and benefits.

Consider intraoperative nerve blocks for all people undergoing surgery.

### **Planning the theatre team**

Schedule hip fracture surgery on a planned trauma list.

Consultants or senior staff should supervise trainee and junior members of the anaesthesia, surgical and theatre teams when they carry out hip fracture procedures.

### **Surgical procedures**

Operate on people with the aim to allow them to fully weight bear (without restriction) in the immediate postoperative period.

Offer replacement arthroplasty (total hip replacement or hemiarthroplasty) to people with a displaced intracapsular hip fracture.

Consider total hip replacement rather than hemiarthroplasty for people with a displaced intracapsular hip fracture who:

* were able to walk independently out of doors with no more than the use of a stick **and**
* do not have a condition or comorbidity that makes the procedure unsuitable for them **and**
* are expected to be able to carry out activities of daily living independently beyond 2 years.

## **Doctor-Patient Conversation on Hip Fracture (De-Identified)**

## Doctor:

Hello, I understand you had a fall recently. Can you tell me what happened?

## Patient:

Yes, doctor. I slipped and fell while walking at home. Since then, I’ve had severe pain in my right hip and I can’t put weight on that leg.

## Doctor:

I’m sorry to hear that. Is the pain constant, and does it get worse with movement?

## Patient:

Yes, it’s constant and sharp. Moving the leg or trying to stand makes it much worse.

## Doctor:

Have you noticed any swelling, bruising, or deformity around your hip or thigh?

## Patient:

There’s some swelling and the leg looks a bit shorter and turned outward compared to the other side.

## Doctor:

Those are common signs of a hip fracture. Have you had any previous fractures or bone problems?

## Patient:

I had a wrist fracture a couple of years ago after a minor fall, but no other bone issues.

## Doctor:

Do you have any history of osteoporosis or other conditions affecting your bones?

## Patient:

I was told I have low bone density but haven’t been on any treatment.

## Doctor:

Okay. We’ll need to get an X-ray of your hip to confirm the fracture and see the exact location and type. Hip fractures usually require surgery to repair, especially if you can’t bear weight.

## Patient:

What kind of surgery would I need?

## Doctor:

It depends on the fracture type. Options include fixation with screws or plates or partial or total hip replacement. The goal is to stabilize the bone so you can start moving and reduce complications.

## Patient:

How long will I be in the hospital?

## Doctor:

Typically, patients stay about a week, but it depends on your recovery and any other health issues. Early mobilization with physiotherapy is important.

## Patient:

What are the risks of surgery?

## Doctor:

Risks include infection, blood clots, bleeding, and complications related to anesthesia. We take many precautions to minimize these risks.

## Patient:

Will I be able to walk again?

## Doctor:

Most patients regain mobility with surgery and rehabilitation. Some may need walking aids initially, and physical therapy will help you regain strength and balance.

## Patient:

Is there anything I can do to prevent future fractures?

## Doctor:

Yes, treating osteoporosis with medications, ensuring adequate calcium and vitamin D intake, regular weight-bearing exercise, and fall prevention strategies at home are important.

## Patient:

Thank you, doctor. What’s the next step?

## Doctor:

I’ll arrange the X-ray now and consult the orthopedic surgery team. We’ll discuss the surgical plan once we have the imaging.

## Patient:

Okay, I appreciate your help.

## Doctor:

You’re welcome. We’ll take good care of you.

REFERENCES

[Recommendations | Hip fracture: management | Guidance | NICE](https://www.nice.org.uk/guidance/cg124/chapter/Recommendations#timing-of-surgery)

<https://spireknee.com.sg/recovery-timeline-after-hip-fracture-surgery/>

[Hip Fracture (Broken Hip): Symptoms, Risks & Recovery](https://my.clevelandclinic.org/health/diseases/17101-hip-fracture)

[Fragility fractures](https://www.who.int/news-room/fact-sheets/detail/fragility-fractures)

[Unasyn, (ampicillin-sulbactam) dosing, indications, interactions, adverse effects, and more](https://reference.medscape.com/drug/unasyn-ampicillin-sulbactam-342476#4)

### **VERTEBRAL FRACTURE**

### **Fractured spine**

A fractured spine is a medical term for breaking any of your vertebrae, the 33 bones that make up your spinal column. A single bone in your spine is a vertebra — vertebrae is the plural form.

People sometimes refer to a spinal fracture as a broken back. Fractured vertebrae are usually caused by osteoporosis and traumas like falls, sports injuries or car accidents.

Most spinal fractures won’t need surgery, but you might need to wear a brace for a few months. However, severe spinal fractures will need to be surgically repaired.

### **Types of spinal fractures**

A healthcare provider will classify the fracture in your spine based on where it is in your back and how your vertebrae are broken. They’ll also classify the fracture as stable or unstable, depending on whether your vertebrae are out of their usual alignment.

#### **Segments of the spine**

Your spine is divided into three main sections, all of which can experience a spinal fracture:

* **Cervical spine fracture:** Broken vertebrae in your neck.
* **Thoracic spine fracture:** Broken vertebrae in your upper back that runs from the bottom of your neck to the bottom of your ribs.
* **Lumbar spine fracture:** Broken vertebrae in your lower back.

#### **Fracture types**

The most common types of spinal fractures include:

* **Compression fractures**: Compression fractures are small breaks or cracks in your vertebrae that are caused by traumas or develop over time as a result of osteoporosis. Osteoporosis is a disease that weakens your bones, making them more susceptible to sudden and unexpected fractures. An undiagnosed spinal compression caused by osteoporosis can make you lose several inches from your height or develop a hunched forward posture (kyphosis).
* **Burst fractures:** Burst fractures happen when your spine is suddenly compressed with a strong force. They can cause your vertebrae to break into many pieces.
* **Chance (flexion/distraction) factures:** Chance fractures happen when your vertebrae are suddenly pulled away from each other. They’re almost like the opposite of a burst fracture.

#### **Chance fractures vs burst fractures**

Chance fractures and burst fractures are both types of spinal fractures. The difference is what causes them.

A strong force that suddenly presses your spine together causes burst fractures. This extreme compression on your vertebrae can break them in many places at the same time. Falling from a great height and landing upright on your feet is a common cause of burst fractures.

Chance fractures are caused by a strong force pulling your vertebrae away from each other. Instead of your spine getting compressed, Chance fractures happen when something pulls it apart. Many people with Chance fractures get them during car accidents after their seatbelt catches their lower body and their upper body is jerked forward. Always wear your seatbelt with the shoulder harness around the upper half of your body.

#### **Stable vs unstable spine fractures**

A stable versus an unstable fracture is another way a provider will classify your spinal fracture.

If you have a stable fracture, the injury that broke your vertebrae didn’t push or pull them out of their usual place in your spine. You still need treatment, but you’re less likely to need surgery.

Unstable spinal fractures happen when the injury moved your vertebrae out of their usual alignment. They’re more serious injuries than stable fractures. There’s a much higher chance you’ll need surgery to repair your broken vertebrae, and you’ll have a higher risk for dangerous complications that can affect your spinal cord.

### **Who gets spinal fractures?**

Spinal fractures — like any bone fracture — can affect anyone. This is especially true for fractures caused by traumas like falls and car accidents.

Females and adults older than 50 are more likely to experience spinal fractures.

You’re much more likely to experience a spinal fracture (especially a compression fracture) if you have osteoporosis. Once you’ve had a compression fracture, you’re five times more likely to develop another compared to someone who’s never experienced one.

In addition to osteoporosis, people with some health conditions or who take certain medications are more likely to experience a spinal fracture, including:

* [Cancer](https://my.clevelandclinic.org/health/diseases/12194-cancer) (especially if you’re receiving chemotherapy or radiation therapy).
* People who use corticosteroids for a long time.
* Hyperthyroidism.
* Bone infections (osteomyelitis).
* Kidney disease.
* Anorexia nervosa.
* Vitamin D deficiency.

You’re also more likely to experience a spinal fracture if you:

* Smoke.
* Drink too much alcohol.

In the U.S. each year:

* Osteoporosis causes more than 1.5 million compression fractures.
* More than 150,000 spinal fractures are caused by traumas.

### **How does a spinal fracture affect my body?**

A spinal fracture might make it painful, difficult or impossible to move the way you usually can.

You’ll probably need to wear a brace that holds your back in place while the fracture heals (especially if you need surgery). While you’re wearing the brace it’ll be hard to move as freely as you’re used to. It might be uncomfortable, but it’s important to give your vertebrae the time they need to heal.

Severe fractures — especially unstable fractures — can damage your spinal cord and affect your ability to stand or walk. This damage might be permanent and irreversible.

#### **Can you walk with a broken back?**

Depending on what caused your spinal fracture — and which type of fracture you have — you’ll still be able to walk with a broken back. It might be painful (or make your pain worse), but if your fracture wasn’t caused by sudden trauma, it’s likely you’ll still be able to move. You won’t be able to walk if the fracture damages your spinal cord enough to make you paralyzed.

Even if you have minor symptoms, visit your provider if you’re experiencing back pain that’s getting worse or doesn’t go away in a few days — especially if it’s accompanied by swelling or affects your posture. Go to the emergency room if you’ve experienced trauma.

### **Symptoms of a spinal fracture**

Many people never notice they have a compression fracture. This is especially true if your broken vertebrae happen over time from osteoporosis and not after trauma. You might experience no pain and only find out you’ve had a compression fracture during imaging tests to identify or diagnose other conditions in the future.

Traumas usually cause burst fractures and Chance fractures. If you experience trauma like a fall or car accident, your broken back will be diagnosed as your injuries are treated. You might not notice specific symptoms from the fracture itself, especially if you’re treated in the emergency room.

If you do experience symptoms, they will include the following:

* **Back pain:** A sharp, intense pain in your back. Pain might also get increasingly worse over time, especially when you’re walking or moving.
* **Swelling or tenderness:** The area around the broken vertebrae may be swollen and painful to touch.
* **Changes to your posture:** A new slump or stoop in your spine that causes you to lean forward in ways you didn’t before.
* **Tingling or numbness:** A tingling or numb feeling in your back that might run down your arms or legs.
* **Height loss:** You might get noticeably shorter over time (sometimes up to 6 inches).
* **Incontinence:** A new loss of your ability to control your bladder or bowels.

### **What causes spinal fractures?**

Fractured spine causes include:

* **Osteoporosis:** Osteoporosis makes your bones lose density and strength over time. This increased fragility increases your risk for many types of fractures.
* **Trauma:** Traumas put a lot of stress on your bones. Your spine is usually very flexible and moves with you. But, a sudden intense force like a car accident or a sports injury can exert more force than your spine can tolerate, which causes spinal fractures.
* **Spinal tumors**: Most spinal tumors result from cancer metastasis — cancer that has spread from another area of your body to your spine.

## **Diagnosis and Tests**

### Your healthcare provider will diagnose a spinal fracture with a physical exam and imaging tests. They’ll look at your back, feel for any spots that are tender or painful and identify any changes to the shape of your spine and posture. Make sure to tell them exactly where you’re hurting and when you noticed any new pain or discomfort.

If you experience trauma, the fracture might be diagnosed by providers in the emergency room. They’ll diagnose your fracture and any other injuries after you’re stabilized.

### **What tests are done to diagnose a compression fracture?**

After a physical exam, you’ll likely need at least one of a few imaging tests to take pictures of your spine:

* **X-rays:** A spine X-ray will confirm a fractured spine, and show how out of place your bones are.
* **Magnetic Resonance Imaging (MRI):** Your provider might use an MRI to get a complete picture of your back and any damage inside it. This will show them tissue around your spine as well as your vertebrae. This is especially important to determine if your spinal cord is at risk of being damaged by your fracture.
* **CT scan:** If you need surgery, your provider or surgeon needs to know exactly how damaged your bones are. A CT scan will give them a more detailed picture of your bones and the surrounding tissue than an X-ray.

You’ll probably also need a bone density test (sometimes called a DEXA or DXA scan). This will show if you have osteoporosis, and how much it has weakened your bones.

## **Management and Treatment**

How your fractured spine is treated depends on a few factors, including:

* What caused the fracture
* Which type of fracture it is.
* Where in your back the broken vertebrae are.

Most spinal fractures don’t require surgery. The most common treatments include:

* **Bracing**: You might need to wear a back brace to hold your spine in alignment and help your broken vertebrae heal properly. Most people need to wear a brace for a few months. Your provider will talk to you about which type of brace you’ll need and how long you’ll need to wear it.
* **Physical therapy:** Strengthening the muscles in your back can improve your overall strength, help reduce bone loss and reduce the risk of future spinal fractures. You might need to work with a physical therapist in person or do at-home exercises.
* **Treating osteoporosis:** If you have osteoporosis, your provider might prescribe medicine or over-the-counter (OTC) supplements to help strengthen your bones to prevent future fractures.

If you experience trauma, providers in the emergency room will treat your injuries in the order of severity, especially if some of them are life-threatening.

#### **Spinal fracture surgery**

If the spinal fracture is in danger of damaging your spinal cord, or if your pain doesn’t improve a few months after non-surgical treatments, you might need surgery. The most common surgeries to repair fractures are vertebroplasty and kyphoplasty.

* **Vertebroplasty:** Your surgeon injects liquid cement into your fractured vertebrae to strengthen it.
* **Kyphoplasty:** Kyphoplasty is similar to vertebroplasty, but before your surgeon injects the liquid cement into your vertebrae, they insert a tiny balloon into them. When they inflate the balloon, it pushes your bones back into their correct place and re-creates the space that was originally there before your fracture.

These are both usually outpatient procedures, so you should be able to go home the same day. You’ll need to rest in bed for up to 24 hours before returning to your normal routine. Avoid heavy lifting or intense exercise for up to six weeks after your surgery.

Your provider or surgeon will explain which surgery you need and why. If your spinal fracture was caused by a tumor — either cancerous or benign — you might need different or additional procedures to remove the mass before your spine can be repaired.

### **What medications are used to treat spinal fractures?**

Usually, over-the-counter NSAIDs are all you’ll need to reduce the symptoms of a spinal fracture. Talk to your provider or surgeon before taking NSAIDs for more than 10 days in a row.

#### **Osteoporosis medications**

Your provider might prescribe medications to strengthen your bones if osteoporosis caused your spinal fracture, including:

* **Calcitonin salmon**: Calcitonin salmon is a synthetic hormone you take as a nasal spray. It can reduce pain and your risk of future spinal fractures.
* **Calcium supplements**: You might need to start a calcium supplement to support your overall bone health and reduce your risk for more fractures in the future.

Your provider may refer you to a bone specialist for additional treatments and to monitor your bone health in the future.

#### **Complications/side effects of the treatment**

Side effects of NSAIDs include:

* Bleeding.
* Ulcers.
* Stomach pain.
* Bowel complications.

Calcitonin salmon can have serious side effects, including:

* Nosebleeds.
* Sinus pain.
* Difficulty breathing.
* Difficulty swallowing.
* Swelling in the tongue or throat.

Spinal fracture surgery complications include:

* Failure to repair the fracture fully.
* Spinal cord damage.
* Bleeding.
* Infection at the injection site.
* Increased stress on vertebrae around the repaired bones.
* Developing a humpback (kyphosis).

### **How soon after treatment will I feel better?**

Most people feel better a few weeks after starting treatment.

How long it takes your vertebrae to heal depends on which type of fracture you have, which of your vertebrae were broken and any other injuries you experienced.

**Outlook / Prognosis**

If the spinal fracture didn’t damage your spinal cord, nerves or other tissue around your spine, you shouldn’t have any long-term effects after a spinal fracture. If you were diagnosed with osteoporosis after your fracture, you’ll need regular bone density screenings to monitor how it’s affecting your bones.

If the fracture or other injuries damaged your spinal cord, your ability to move or walk might be permanently affected. These kinds of complications are more common after traumatic injuries, like unstable burst fractures or Chance fractures.

#### **How long does it take a fractured spine to heal?**

Most spinal fractures heal in around three months if you don’t need surgery.

People who need surgery will need longer to recover. It might take as long as six weeks to recover from the surgery, then an additional few months for your spine to heal. Your surgeon or provider will give you a customized recovery timeline after your procedure.

**When can I go back to work/school**

If you’re receiving non-surgical treatment for a fractured spine, you might not need to miss any time away from work or school if your job or coursework doesn’t involve heavy lifting.

You should be able to return to work or school within a week after spinal fracture surgery, but talk to your surgeon or provider before resuming any intense physical activities.

## **Prevention**

Follow these general safety tips to reduce your risk of an injury:

* Always wear your seatbelt — including the shoulder harness around the upper half of your body.
* Wear the right protective equipment for all activities and sports.
* Make sure your home and workspace are free from clutter that could trip you or others.
* Always use the proper tools or equipment at home to reach things. Never stand on chairs, tables or countertops.
* Follow a diet and exercise plan that will help you maintain good bone health.
* Talk to your provider about a bone density test if you’re older than 50 or if you have a family history of osteoporosis.
* Use your cane or walker if you have difficulty walking or have an increased risk for falls.

You can prevent osteoporosis by eating a healthy diet and getting regular exercise. A diet rich in calcium and vitamins C and D encourages bone growth and strength. Exercises that make your muscles work against gravity like walking, jogging, aerobics and lifting weights strengthen your bones.

## **Living With**

Talk to your provider about a diet and exercise plan that will help you maintain good bone health.

1 in 4 females with a compression fracture caused by osteoporosis never get it diagnosed, even if they’re experiencing mild symptoms. Talk to your provider if you’re having any new pain or discomfort in your back. They can help you figure out what’s causing it, and potentially catch osteoporosis or other health conditions before they cause severe symptoms or fractures.

### **When should I see my healthcare provider?**

Get any new symptoms or changes in your back examined by a healthcare provider as soon as possible including:

* Pain.
* Swelling.
* Discoloration.
* Tenderness.
* A noticeable change to your height or posture.

Go to the emergency room right away if you’ve experienced trauma

## **Common Procedures for Vertebral Fractures**

1. Conservative (Non-Surgical) Treatment:
   1. Most vertebral fractures, especially stable compression fractures, are treated without surgery initially.
   2. Includes pain management, bracing, physical therapy, and activity modification.
   3. Healing and symptom improvement typically occur over weeks to months.
2. Vertebroplasty:
   1. Minimally invasive procedure where bone cement is injected directly into the fractured vertebra under X-ray guidance to stabilize the bone and relieve pain.
   2. Usually performed under sedation or general anesthesia with the patient prone.
   3. Cement hardens within minutes, providing immediate stability.
   4. Recovery is rapid, often allowing return to normal activities within days.
   5. Mainly used for painful osteoporotic or tumor-related compression fractures not responding to conservative treatment.
3. Kyphoplasty:
   1. Similar to vertebroplasty but involves inserting and inflating a small balloon inside the vertebra to restore vertebral height and reduce deformity before cement injection.
   2. Balloon is then deflated and removed, and the cavity is filled with bone cement.
   3. Also minimally invasive with rapid recovery.
   4. Helps correct spinal alignment and reduce kyphotic deformity.
4. Lumbar (Spinal) Fusion Surgery:
   1. Used for unstable fractures, fractures causing neurological compromise, or severe deformity.
   2. Involves joining adjacent vertebrae with bone grafts and metal instrumentation (screws, rods) to stabilize the spine permanently.
   3. Can be done via minimally invasive techniques or open surgery.
   4. Recovery is longer, often requiring months for bone fusion and rehabilitation.

## Timeline Overview

| Timeframe | Procedure/Stage | Details |
| --- | --- | --- |
| Initial Diagnosis | Physical exam and imaging (X-ray, MRI, CT) | Immediate after injury or onset of symptoms |
| Conservative Treatment | Weeks to months | Pain control, bracing, physical therapy; monitor healing |
| Vertebroplasty/Kyphoplasty | Procedure time: ~1 hour; Recovery: days to weeks | Rapid pain relief, early mobilization; outpatient or short hospital stay |
| Lumbar Fusion Surgery | Surgery duration: 2–4 hours; Recovery: months | Hospital stay several days; bone fusion takes 6–9 months; physical therapy essential |

**QUESTION AND ANSWERS SET**

Q. What is a spinal fracture?

A. A spinal fracture is a break to one of the bones (vertebrae) in your spine. The force from the break also bruises the muscles, ligaments and nerves that surround the spinal bone. Injured muscles and ligaments can cause ‘spasm’ pains that shoot in all directions.

There are three natural curves in a normal spine:

a) the cervical spine (the neck) containing seven vertebrae (bones)

b) the thoracic spine (middle spine) containing twelve vertebrae

c) the lumbar spine (lower spine) containing five vertebrae The portion of the spine you have fractured, and the number of spinal fractures you have, will affect where you feel pain and how you are treated.

Q. How is my fractured spinal bone treated?

A. Your consultant will discuss the type of fracture you have and the options for treating it.

There are three main treatment options:

a) conservative management (a medical treatment that is non-invasive and aims to preserve the function of the spine)

b) a spinal brace or collar

c) surgery

a) Conservative treatment Most spinal fractures are treated conservatively. This means allowing the bone to heal naturally without a brace or the need for surgery. This does not mean recovery is simple and easy; spinal fractures are painful. Standing, sitting and some movement puts weight across the fractured bone, which can be painful. There is pain from the spinal fracture during the healing period. This healing process can take up to four months, but most of the pain settles between six to eight weeks.

People often find sitting or standing for long periods difficult, so changing position and regular light activity such as walking is encouraged. These actions can spread the weight across your spinal fracture, helping to ease the pain slightly.

Your symptoms will guide your degree of movement and the pain your body can take. Usually, the pain is noticeably improved four weeks after the fracture. Regular pain medication can help to ease the pain, such as paracetamol and ibuprofen (if you can take them).

Codeine or tramadol can be added if additional pain is felt. Please discuss pain management options with your consultant, GP or pharmacist.

b) Spinal brace or collar Some fractures may be helped by a supportive brace. These include: cervical thoracic orthosis (CTO), thoracic lumbar sacral orthosis (TLSO) and lumbar sacral orthosis (LSO). In cervical (neck) fractures, a hard collar may be used (such as an orthotic called a ‘Miami-J’). This may be an orthotist, physiotherapist or spinal nurse.

Q. How long do I wear the brace or collar?

A. Your consultant will inform you how long to wear your brace for and if it can be removed at certain times during the day or night. There may be times when they will ask you to keep the brace on throughout the day and night. On average, a brace is worn for 12 weeks.

Most people are advised to wear the brace when moving but do not need to wear it at night or when sitting comfortably. You may prefer to wear the brace when sitting upright as it can help with pain. Managing issues with your brace or collar Spinal braces or collars can cause pressure ulcers.

Wearing the brace or collar increases your temperature and may cause excessive sweating in and around the area. Constant moisture can cause skin breakdown. A spinal brace also applies some pressure to your skin, which increases the risk of skin problems.

We recommend wearing a cotton t-shirt or vest underneath the brace to help protect the skin. In most cases, braces do not cause any problems, but it is important to check your skin daily for possible skin pressure effects such as pressure sores.

Early symptoms of pressure sores include skin discolouration and/or pain. These symptoms can develop into a blister or open wound. If skin discolouration continues despite padding, or you think you may have a pressure sore, please seek medical advice from your GP.

c) Surgery

Occasionally an operation or an interventional procedure, such as an injection, is recommended to treat your spinal fracture. If surgery is necessary, your consultant will discuss the operation with you.

Q. How long will it take my fracture to heal?

A.Most spinal fractures heal naturally without any intervention such as surgery. Fractures usually take up to 12 weeks to heal.

Q.How do I cope with the pain?

A.If you are in pain, contact your consultant, GP or pharmacist for pain management. This usually means taking pain medication.

Q. Do I need to change the way I do daily activities while my spine is healing? A. Avoid lifting anything heavier than the weight of a filled kettle (1.69kg/3.75lbs), during the first 6 weeks following injury. Be careful with your movement for the first twelve weeks after a spinal fracture.

Follow the advice below for lifting, twisting and bending:

• Twisting: If you need to reach an object that is behind you, make sure you turn your feet. Do not twist from your spine.

• Bending: When brushing your teeth at the sink keep a good posture, do not stoop. When getting dressed and putting your shoes on, bring your knees towards your chest rather than bending down to the floor.

Q. When can I return to work?

A. There is no set time to be off work. Time off work will depend on the work you do, the demands of your job and the symptoms you have. People with office-based work are usually off for four to six weeks. Those with manual jobs may be off for up to three months. You should discuss return to work options with your consultant, GP and employer, and speak to your local occupational health department for further guidance. If you are self-employed please contact your GP. Your GP is responsible for reviewing and offering you a sick note until you fully recover from your injury.

Q. Do I need physiotherapy and occupational therapy?

A. Most people do not need routine physiotherapy after a spinal fracture. Once the fracture heals, you will be able to return to normal activity and your pain may improve. However, 50 per cent of patients with spinal fractures have pain that lasts more than six months. With time, the muscular soreness or pain will also fully improve. If problems continue, the team will usually choose to see you again before considering a referral to physiotherapy. If you were admitted to hospital following the spinal fracture and have any difficulties with your mobility and daily activities, a referral will be made to the physiotherapist and occupational therapist for assessment before you go home.

Q. Do I need to see my consultant again to check progress?

A. Most people with stable fractures (a bone that is broken with little damage) do not need a follow up hospital appointment with the consultant. Your GP or local district hospital can provide a follow-up appointment.

Q. What happens if my fracture does not heal?

A. Most spinal fractures heal within four months. If your pain continues or gets worse after this time, you should talk to your GP.

## **Epidemiology of Vertebral Fractures**

* Prevalence:  
  Approximately 12% of adults have vertebral fractures, with prevalence increasing with age. In a recent study, prevalence rose from about 10.8% in people aged 50–59 to 19% in those aged 70 and older. Men showed a slightly higher prevalence (14.8%) compared to women (10.6%)
* Incidence:  
  The annual incidence of new vertebral fractures is about 1% per year in the general adult population. Other studies report incidence rates varying with age and sex; for example, in women aged up to 85 years, incidence can reach nearly 30 per 1,000 person-years
* Fracture Location:  
  The most affected vertebrae are T12 and L1, with over one-third of fractures occurring at L1. Wedge-type fractures constitute the majority (around 89.3%)
* Sex and Age Distribution:  
  Vertebral fractures predominantly affect older adults, especially those over 70 years. Women represent a higher proportion of cases in many populations, though some data show men have slightly higher prevalence. For example, in Germany, 63.7% of vertebral fractures occurred in women, and nearly 69% of patients were aged 70 or older
* Global Burden:  
  Globally, vertebral fractures are among the most common fragility fractures, causing significant morbidity comparable to hip fractures. In Germany, the incidence of vertebral fractures increased by 45.6% from 2009 to 2019, reaching approximately 150.7 per 100,000 inhabitants in 2019
* Underdiagnosis:  
  Many vertebral fractures are clinically silent and only detected by imaging, with only about 25–33% recognized at the time of occurrence. This underdiagnosis complicates accurate epidemiological assessment.
* Associated Risk Factors:  
  Osteoporosis is a major risk factor, with vertebral fractures often serving as a sentinel event for skeletal fragility. Other risk factors include advancing age, female sex, low bone mineral density, and prior fracture history.

## **Differential Diagnosis of Vertebral Fractures**

1. Osteoporotic Vertebral Compression Fractures (OVF):
   1. Most common cause, especially in elderly patients with osteoporosis.
   2. Typically low-energy or spontaneous fractures.
   3. Radiographically show wedge-shaped vertebral body collapse.
   4. Usually stable fractures without neurological compromise.
2. Malignant Vertebral Fractures (MVF):
   1. Due to primary bone tumors or metastatic disease (e.g., breast, lung, prostate cancer).
   2. May present with pathological fractures from weakened bone.
   3. Often associated with systemic symptoms such as weight loss, night pain.
   4. MRI is essential to distinguish malignant from benign fractures; malignant fractures often show marrow replacement and soft tissue masses.
3. Traumatic Fractures:
   1. Result from high-energy trauma (e.g., falls, motor vehicle accidents).
   2. May involve vertebral body, posterior elements, or cause instability.
   3. Require urgent assessment for spinal cord injury.
4. Infectious Causes:
   1. Vertebral osteomyelitis or discitis can weaken vertebrae leading to fractures.
   2. May present with fever, back pain, elevated inflammatory markers.
   3. MRI and laboratory tests (blood cultures, inflammatory markers) aid diagnosis.
5. Other Conditions:
   1. Multiple Myeloma: Can cause lytic lesions and pathological fractures.
   2. Hemangioma of Vertebral Body: Usually incidental but can rarely cause fractures.
   3. Pott Disease (Spinal Tuberculosis): Chronic infection leading to vertebral destruction and collapse.
   4. Renal Failure: Associated with bone fragility and fractures.

Emerging research points to roles of long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) as biomarkers and regulators in osteoporosis and vertebral fracture susceptibility

Genetic Risk Scores:  
Genetic risk scores (GRS) based on multiple variants have been developed to predict vertebral fracture risk, as demonstrated in Japanese cohorts with osteoporosis

## **Doctor-Patient Conversation**

## Doctor:

Good morning. I understand you’ve been experiencing back pain recently. Can you tell me more about it?

## Patient:

Yes, doctor. I’ve had persistent pain in my mid-back for a few weeks now. It started after I bent down to pick something up, and it’s been getting worse. It’s quite sharp and sometimes feels like it’s deep in my spine.

## Doctor:

I see. Do you remember any specific injury or trauma, like a fall or accident?

## Patient:

No, nothing major. Just the bending motion I mentioned.

## Doctor:

Have you noticed any changes in your height or posture? Sometimes vertebral fractures can cause a loss of height or a stooped posture.

## Patient:

Now that you mention it, I think I seem a bit shorter, and my clothes don’t fit the same around my waist.

## Doctor:

That can happen with compression fractures in the spine. Do you have any history of osteoporosis or other bone problems?

## Patient:

I was told I have low bone density a few years ago but haven’t been on any treatment.

## Doctor:

Low bone density increases the risk of vertebral fractures, especially with minor stresses. We’ll need to get an X-ray or MRI of your spine to confirm if there’s a fracture.

## Patient:

What happens if it is a fracture?

## Doctor:

Treatment depends on the severity. Many vertebral fractures heal with pain management, rest, and physical therapy. In some cases, procedures like vertebroplasty or kyphoplasty may be considered to stabilize the fracture and reduce pain.

## Patient:

Will I be able to walk and do my usual activities?

## Doctor:

Most patients recover mobility with appropriate treatment, though some may need to modify activities during healing. Physical therapy helps strengthen your back and improve function.

## Patient:

Is there a risk of more fractures?

## Doctor:

Yes, having one vertebral fracture increases your risk of future fractures. That’s why treating underlying osteoporosis and preventing falls are very important.

## Patient:

What can I do to prevent more fractures?

## Doctor:

We’ll discuss medications to strengthen your bones, ensure adequate calcium and vitamin D intake, encourage safe exercise, and address any fall risks at home.

## Patient:

Thank you, doctor. What’s the next step?

## Doctor:

I’ll arrange imaging tests and blood work to evaluate your bone health. We’ll review the results and make a treatment plan together.

## Patient:

Okay, I appreciate your help.

## Doctor:

You’re welcome. Please let me know if your pain worsens or if you develop any new symptoms like numbness or weakness.

REFERENCES

[Vertebral Fracture - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK547673/#article-31121.s9)

[3346-Spinal-fracture-format-V8\_FINAL.pdf](https://www.kch.nhs.uk/wp-content/uploads/2023/05/3346-Spinal-fracture-format-V8_FINAL.pdf)

[Fractured Spine (Vertebrae): Types, Long-Term Effects & Treatment](https://my.clevelandclinic.org/health/diseases/17498-spinal-fractures)

<https://emedicine.medscape.com/article/309615-differential>

### **TRAUMATIC FRACTURE**

**DEFINITION AND DESCRIPTION**

A bone fracture is the medical definition for a broken bone.

Fractures are usually caused by traumas like falls, car accidents or sports injuries. But some medical conditions and repetitive forces (like running) can increase your risk for experiencing certain types of fractures.

If you break a bone, you might need surgery to repair it. Some people only need a splint, cast, brace or sling for their bone to heal. How long it takes to recover fully depends on which of your bones are fractured, where the fracture is and what caused it.

Bone fractures and broken bones are the same injury and mean the same thing. You might see them used interchangeably. A fracture is the medical term for a broken bone, so your healthcare provider will probably refer to your broken bone as a certain type of fracture after they diagnose it.

Bone fractures and bone bruises are both painful injuries caused by a strong force hitting your body — usually a fall, car accident or sports injury. The difference is how damaged your bone is.

Your bones are living tissue that can get bruised in lots of the same ways your skin can. It takes much more force to bruise a bone than it does your skin, but the injury is very similar. If something hits your bones with enough force, they can bleed without being broken. Blood trapped under the surface of your bone after an injury is a bone bruise.

A bone fracture happens when something hits your bone with enough force not only to damage it, but to break it in at least one place. Fractures are more serious injuries and can take much longer to heal than bone bruises.

If you’ve experienced a trauma and have pain on or near a bone, go to the emergency room or visit your provider as soon as possible. No matter which injury you have, it’s important to get your bone examined right away.

Bone fractures and sprains are common sports injuries.

If you experience a bone fracture, you’ve broken one or more of your bones. You can’t sprain a bone. A sprain happens when one of your ligaments is stretched or torn.

It’s possible to experience a bone fracture and a ligament sprain during the same injury, especially if you damage a joint like your knee or elbow.

### **Types of bone fractures**

There are many different types of fractures. Your provider will diagnose a specific fracture type depending on a few criteria, including its:

* **Pattern:** A fracture pattern is the medical term for the shape of a break or what it looks like.
* **Cause:** Some fractures are classified by how they happen.
* **Body part:** Where in your body your broke a bone.

#### **Fractures diagnosed by pattern or shape**

Some fractures are classified by their pattern. This can either be the direction a break goes (if it’s a straight light across your bone) or its shape (if it’s more than a single line break).

Fractures that have a single straight-line break include:

* Oblique fractures.
* Transverse fractures.
* Longitudinal fractures (breaks that happen along the length of the bone).

Fracture patterns that don’t break your bone in a single straight line include:

* Greenstick fractures.
* Comminuted fractures.
* Segmental fractures.
* Spiral fractures.

**Fractures diagnosed by cause**

A few types of fractures are named or classified by what causes them. These include:

* Stress fractures (sometimes referred to as hairline fractures).
* Avulsion fractures.
* Buckle fractures (sometimes referred to as torus or impacted fractures).

#### **Fractures diagnosed by location**

Lots of fractures are specific to where they happen in your body. In some cases, it’s possible to experience a location-based fracture that’s also one of the other types listed above. For example, someone who experiences a severe fall might have a comminuted tibia (shin bone) fracture.

Fractures that affect people’s chest, arms and upper body include:

* Clavicle fractures (broken collarbones).
* Shoulder fractures.
* Humerus (upper arm bone) fractures.
* Elbow fractures.
* Rib fractures.
* Compression fractures.
* Facial fractures.

Some fractures that can affect your hands or wrists include:

* Barton fractures.
* Chauffeur fractures.
* Colles fractures.
* Smith fractures.
* Scaphoid fractures.
* Metacarpal fractures (breaking any of the bones in your hand that connect your wrist to your fingers).

Fractures that damage the bones in your lower body and legs include:

* Pelvic fractures.
* Acetabular fractures.
* Hip fractures.
* Femur fractures.
* Patella fractures.
* Growth plate fractures.
* Tibia (your shin bone) and fibula (your calf bone) fractures.

Fractures that affect your feet and ankles are more likely to have complications like nonunion. They include:

* Calcaneal stress fractures.
* Fifth metatarsal fractures.
* Jones fractures.
* Lisfranc fractures.
* Talus fractures.
* Trimalleolar fractures.
* Pilon fractures.

#### **Open vs. closed fractures**

Your provider will classify your fracture as either open or closed. If you have an open fracture, your bone breaks through your skin. Open fractures are sometimes referred to as compound fractures. Open fractures usually take longer to heal and have an increased risk of infections and other complications. Closed fractures are still serious, but your bone doesn’t push through your skin.

#### **Displaced vs. nondisplaced fractures**

Displaced or nondisplaced are more words your provider will use to describe your fracture. A displaced fracture means the pieces of your bone moved so much that a gap formed around the fracture when your bone broke. Non-displaced fractures are still broken bones, but the pieces weren’t moved far enough during the break to be out of alignment. Displaced fractures are much more likely to require surgery to repair.

Bone fractures can affect anyone. Because they’re usually caused by traumas like falls, car accidents or sports injuries, it’s hard to know when someone will break a bone.

You’re more likely to experience a fracture if your bones are weakened by osteoporosis.

#### **Osteoporosis**

Osteoporosis weakens bones, making them more susceptible to sudden and unexpected fractures. Many people don’t know they have osteoporosis until after it causes them to break a bone. There usually aren’t obvious symptoms.

Females and adults older than 50 have an increased risk for developing osteoporosis. Talk to your provider about a bone density screening that can catch osteoporosis before it causes a fracture.

Bone fractures are a common injury. Millions of people break a bone every year.

### **Symptoms of a bone fracture**

Symptoms of bone fractures include:

* Pain.
* Swelling.
* Tenderness.
* Inability to move a part of your body like you usually can.
* Bruising or discoloration.
* A deformity or bump that’s not usually on your body.

### **What causes bone fractures?**

Bone fractures are almost always caused by traumas. Anything that hits one of your bones with enough force can break it. Some of the most common causes include:

* Car accidents.
* Falls.
* Sports injuries.

Sometimes you can fracture a bone without experiencing a trauma. Repetitive forces — like running or practicing a sport — can cause stress fractures. Similarly, repeating one movement or motion constantly over a long period of time can lead to overuse syndrome in your hands and arms. If you play an instrument or use your hands in the same way every day at work you’re more likely to develop a stress fracture.

Your risk of experiencing a fracture is greatly increased if you have osteoporosis. Osteoporosis causes more than one million fractures each year.

## **Diagnosis and Tests**

Your provider will diagnose a bone fracture with a physical exam and imaging tests. In some cases, this may be done in the emergency room if you’re admitted after a trauma.

If you’re taken to the ER, a team of providers stabilize you and treat your injuries in the order of severity, especially if some are life-threatening. After you’re stabilized, you will need imaging tests to confirm any fractures.

### **What tests are done to diagnose bone fractures?**

You’ll need at least one of a few imaging tests to take pictures of your fracture:

* **X-rays:** An X-ray will confirm any fractures, and show how damaged your bones are.
* **Magnetic Resonance Imaging (MRI):** Your provider might use an MRI to get a complete picture of the damage to your bones and the area around them. An MRI will show tissue like cartilage and ligaments around your bones too.
* **CT scan:** A CT scan will give your provider or surgeon a more detailed picture of your bones and the surrounding tissue than an X-ray.
* **Bone scan:** Healthcare providers use a bone scan to find fractures that don’t show up on an X-ray. This scan takes longer — usually two visits four hours apart — but it can help find some fractures.

## **Management and Treatment**

How your fracture is treated depends on which type it is, what caused it and how damaged your bones are.

#### **Immobilization**

If your fracture is mild and your bones did not move far out of place (if it’s non-displaced), you might only need a splint or cast. Splinting usually lasts for three to five weeks. If you need a cast, it will likely be for longer, typically six to eight weeks. In both cases you’ll likely need follow up X-rays to make sure your bones are healing correctly.

#### **Closed reduction**

More severe breaks require a closed reduction to set (realign) your bones. During this non-surgical procedure, your provider will physically push and pull your body on the outside to line up your broken bones inside you. To prevent you from feeling pain during the procedure you’ll receive one of the following:

* Local anesthetic to numb the area around your fracture.
* Sedatives to relax your whole body.
* General anesthesia to make you sleep through the procedure.

After the closed reduction, your provider will put you in a splint or cast.

#### **Bone fracture surgery**

Some bone fractures require surgery. Depending on which type of fracture you have — and how badly your bones are damaged — there are few techniques your surgeon might use.

##### **Internal fixation**

Your surgeon will realign (set) your bones to their correct position and then secure them in place so they can heal and grow back together. They usually perform what’s called an internal fixation, which means your surgeon inserts pieces of metal into your bone to hold it in place while it heals. You’ll need to limit how much you use that part of your body to make sure your bone can fully heal.

Internal fixation techniques include:

* **Rods:** A rod inserted through the center of your bone that runs from top-to-bottom.
* **Plates and screws:** Metal plates screwed into your bone to hold the pieces together in place.
* **Pins and wires:** Pins and wires hold pieces of bone in place that are too small for other fasteners. They’re typically used at the same time as either rods or plates.

Some people live with these pieces inserted in them forever. You might need follow-up surgeries to remove them.

##### **External fixation**

You might need an external fixation. Your surgeon will put screws in your bone on either side of the fracture inside your body then connect them to a brace or bracket around the bone outside your body. This is usually a temporary way to stabilize your fracture and give it time to begin healing before you have an internal fixation.

##### **Arthroplasty**

If you fracture a joint (like your shoulder, elbow or knee) you might need an arthroplasty (joint replacement). Your surgeon will remove the damaged joint and replace it with an artificial joint. The artificial joint (prosthesis) can be metal, ceramic or heavy-duty plastic. The new joint will look like your natural joint and move in a similar way.

##### **Bone grafting**

You might need bone grafting if your fracture is severely displaced or if your bone isn’t healing back together as well as it should. Your surgeon will insert additional bone tissue to rejoin your fractured bone. After that, they’ll usually perform an internal fixation to hold the pieces together while your bone regrows. Bone grafts can come from a few sources:

* Internally from somewhere else in your body — usually the top of your hip bone.
* An external donor.
* An artificial replacement piece.

After your surgery, your bone will be immobilized. You’ll need some combination of a splint, cast, brace or sling before you can start using it like you did before your fracture.

##### **Complications of bone fracture treatment**

Fracture surgery complications include:

* **Acute compartment syndrome** (ACS): A build-up of pressure in your muscles may stop blood from getting to tissue, which can cause permanent muscle and nerve damage.
* **Malunion**: This happens when your broken bones don’t line up correctly while they heal.
* **Nonunion**: Your bones may not grow back together fully or at all.
* **Bone infection** (osteomyelitis): If you have an open fracture (the bone breaks through your skin) you have an increased risk of bacterial infection.
* **Other internal damage**: Fractures can damage the area around the injury including your muscles, nerves, blood vessels, tendons and ligaments.

### **What medications are used to treat bone fractures?**

Over-the-counter NSAIDs like aspirin or ibuprofen can lead to bleeding and other complications after a surgery. Your surgeon will talk to you about the medications you can take to reduce pain after your surgery.

#### **NSAID side effects**

Side effects of NSAIDs include:

* Bleeding.
* Ulcers.
* Stomach pain.
* Bowel complications.

### **How long does it take bone fractures to heal?**

How long it takes a bone fracture to heal depends on a few factors, including:

* What caused it.
* Which bone is broken.
* Which type of fracture it is.
* Which treatment(s) you need.
* Any other injuries you experienced.

Depending on which type of immobilization or surgery you needed to repair your fracture, you should be able to start moving again in a few weeks. More severe fractures can take a year or more to heal.

Talk to your provider or surgeon about what to expect while you’re recovering.

Contact your provider right away if you experience intense pain that doesn’t get better.

## **Outlook / Prognosis**

Most people who break a bone make a full recovery and can resume their typical routine after their bone heals. Some fractures can have a long-term impact on your life, especially if you experienced other injuries. Talk to your surgeon or provider before resuming any physical activities or playing sports while you’re recovering.

## **Prevention**

Follow these general safety tips to reduce your risk of an injury:

* Always wear your seatbelt.
* Wear the right protective equipment for all activities and sports.
* Make sure your home and workspace are free from clutter that could trip you or others.
* Always use the proper tools or equipment at home to reach things. Never stand on chairs, tables or countertops.
* Follow a diet and exercise plan that will help you maintain good bone health.
* Talk to your provider about a bone density test if you’re older than 50 or if you have a family history of osteoporosis.
* Use your cane or walker if you have difficulty walking or have an increased risk for falls.

## **Epidemiology of Bone Fractures**

* Global Incidence:  
  In 2019, there were approximately 178 million new bone fractures worldwide, representing a 33.4% increase in the absolute number of fractures since 1990. This rise is largely driven by global population growth and aging
* Prevalence and Burden:  
  The number of people living with acute or long-term symptoms from fractures was about 455 million in 2019, a 70.1% increase since 1990. Fractures accounted for 25.8 million years lived with disability (YLDs) globally, increasing by 65.3% over the same period
* Age Distribution:  
  Fracture incidence rates increase sharply with age, especially in older adults. For example, incidence rates reach over 15,000 per 100,000 population in those aged 95 years and older. Older women are particularly affected due to higher rates of osteoporosis and fragility fractures
* Common Fracture Sites:  
  Lower leg fractures (patella, tibia, fibula, ankle) are the most common and burdensome fractures globally, with an incidence rate of about 420 per 100,000 population in 2019
* Sex Differences:  
  Males generally have higher incidence rates of fractures overall, especially in younger age groups, but females experience a greater increase in fracture cases with aging, largely due to osteoporosis
* Trends Over Time:  
  Although the age-standardized incidence rate of fractures has decreased by about 9.6% since 1990, the absolute number of fractures continues to rise due to demographic changes. For example, femoral fractures increased by over 35% in absolute numbers from 1990 to 2021, despite a slight decline in incidence rate
* Regional Variations:  
  Fracture incidence and burden vary by region, influenced by factors such as socioeconomic status, healthcare access, and population aging. High-income countries report higher documented fracture rates, partly due to better detection and reporting

## **Bone Fracture Recovery Process**

### Phase One – A Few Hours after the Injury

The bone repair process starts with the formation of swelling around the break. This inflammation is caused by a blood clot forming at the injury site, as your immune system sends cells to clean the area. These cells can remove minute bone shards and destroy any germs that may have entered the wound.

Soon, blood vessels will start growing into the area to help with the healing process.

### Phase Two – 2-3 Weeks after the Injury

During the next 21 days after the fracture, you may need to go to hospital for checkup. This is an important phase in the healing process and the doctors need to check that it is progressing as it should.

At this point, a soft callus made of collagen is forming around the fractured area. As this callus will eventually solidify, it is essential to check that the bone is properly aligned and will heal normally.

The callus can break, so you must continue wearing the cast to keep the bone perfectly motionless. If our doctors notice on the X-ray that the bone is not healing in the correct position, they may remove the cast and correct the problem with surgery.

### Phase Three – Up to 6-12 Weeks after the Injury

The soft callus starts solidifying little by little. Specialized cells called osteoblasts will add minerals, turning the callus into a sort of spongy bone. The broken bone pieces are completely bridged and the bone is preparing to heal completely.

### Phase Four – an Ongoing Process

The last phase in bone fracture recovery may continue for years after you are pronounced fully healed. During this phase, osteoclast cells will perform fine-tuning on the injured site by removing excess bone growth.

## **Factors Influencing the Duration of Bone Fracture Recovery**

The timeline presented above is not a one-size-fits-all for all patients. Specialists have identified various factors which may slow it down or make it more difficult, such as:

* Old age
* Obesity
* Endocrine conditions, such as diabetes mellitus
* Poor nutrition
* Smoking
* Steroid administration

## **Differential Diagnoses**

1. Traumatic Fracture:
   1. Caused by a sudden force exceeding bone strength (falls, accidents, direct blows).
   2. Presents with acute pain, swelling, deformity, and loss of function.
2. Stress Fracture:
   1. Result of repetitive microtrauma or overuse, common in athletes and military recruits.
   2. Presents with gradual onset localized pain worsened by activity.
   3. Often subtle or not visible on initial X-rays; MRI or bone scan may be needed.
3. Pathological Fracture:
   1. Occurs when bone weakened by underlying disease fractures with minimal or no trauma.
   2. Causes include:
      1. Osteoporosis: Most common cause of fragility fractures in the elderly.
      2. Bone tumors: Primary (benign or malignant) or metastatic cancers weaken bone integrity.
      3. Infections: Osteomyelitis can cause bone destruction leading to fractures.
      4. Metabolic bone diseases: Osteomalacia, Paget’s disease.
   3. History may reveal systemic symptoms or known malignancy.
4. Bone Contusion or Bruise:
   1. Trauma causing bone marrow edema without cortical disruption.
   2. Pain and swelling present but no fracture line on imaging.
5. Soft Tissue Injuries:
   1. Muscle strains, ligament sprains, or hematomas can cause localized pain mimicking fracture.
6. Other Causes of Bone Pain:
   1. Inflammatory arthritis, referred pain from adjacent joints, or nerve root irritation.

## **Living With**

Go to the emergency room right away if you’ve experienced a trauma.

If you think you have a bone fracture, you need to see a healthcare provider as soon as possible. Go to the emergency room if you experience any of the following:

* Intense pain.
* You can’t move a part of your body like you usually can.
* A part of your body is noticeably different looking or out of its usual place.
* You can see your bone through your skin.
* Swelling.
* New bruising that appears at the same time as any of these other symptoms.

#### **Can bone fractures cause fevers?**

Bone fractures themselves don’t cause fevers. However, if you have a fever, or the area around your broken bone feels warm or hot go to the emergency room. This can be a sign of a serious infection that needs to be examined by a provider right away.

## **Questions and Answers Sets**

## 1. What is a bone fracture?

A bone fracture is a break or crack in a bone, usually caused by trauma such as falls, car accidents, or sports injuries. Fractures can range from mild cracks to complete breaks

## 2. How are bone fractures classified?

Fractures are classified by type (e.g., transverse, greenstick, comminuted), displacement (displaced or non-displaced), and whether the skin is broken (open or closed fracture)

## 3. What are the common symptoms of a bone fracture?

Symptoms include pain, swelling, bruising, deformity, inability to move the affected limb, and sometimes a visible bone protrusion if the fracture is open

## 4. How are bone fractures treated?

Treatment depends on the fracture type and severity:

* Non-surgical: Splinting (3–5 weeks) or casting (6–8 weeks) for stable fractures.
* Closed reduction: Non-surgical realignment of displaced bones followed by casting or splinting.
* Surgical: Internal fixation using metal plates, screws, or rods to stabilize severe or unstable fractures

## 5. What is the healing timeline for bone fractures?

Bone healing involves phases: inflammatory (1 week), soft callus formation (2–3 weeks), hard callus formation (3–6 weeks), and remodeling (months to years). Most fractures heal sufficiently for normal use within 6–12 weeks.

## 6. What are possible complications of bone fractures?

Complications include delayed healing, non-union, infection (especially in open fractures), nerve or blood vessel damage, and compartment syndrome

## 7. How can I reduce my risk of fractures?

Maintain bone health by ensuring adequate calcium and vitamin D intake, engaging in weight-bearing exercise, avoiding smoking, and managing osteoporosis if present

## 8. What should I expect during recovery?

Pain typically decreases over weeks; physical therapy may be needed to restore strength and mobility. Follow-up imaging is important to monitor healing

## 9. When should I seek emergency care for a fracture?

Seek immediate medical attention if there is severe deformity, open wounds with bone exposure, uncontrolled bleeding, or signs of nerve or vascular injury

## 10. How do healthcare providers decide between surgical and non-surgical treatment?

The decision depends on fracture type, displacement, stability, patient health, and functional needs. Surgery is often required for unstable or displaced fractures to ensure proper healing

## **Doctor-Patient Conversation**

## Doctor:

Hello, I understand you had an injury recently. Can you tell me what happened?

## Patient:

Yes, doctor. I fell off my bike yesterday and landed hard on my left arm. Since then, it’s been very painful and swollen.

## Doctor:

I’m sorry to hear that. Can you describe the pain? Is it constant, and does it get worse with movement?

## Patient:

It’s a sharp pain, constant, and moving my arm makes it much worse. I can’t lift anything with that arm.

## Doctor:

Do you notice any deformity, bruising, or numbness in your arm or hand?

## Patient:

Yes, the arm looks a bit crooked near the elbow, and I have some numbness in my fingers.

## Doctor:

That suggests a possible fracture and nerve involvement. We’ll need to get an X-ray to confirm the fracture type and location.

## Patient:

What happens if it is a fracture?

## Doctor:

Treatment depends on the fracture. Some fractures can be treated with a cast or splint, while others may require surgery to realign and stabilize the bone.

## Patient:

Will I need surgery?

## Doctor:

We’ll decide after reviewing the X-rays. Surgery is more likely if the bone is displaced or if there’s nerve or blood vessel injury.

## Patient:

How long will it take to heal?

## Doctor:

Most fractures take 6 to 8 weeks to heal, but it varies depending on the bone and severity. Physical therapy will help regain strength and motion after healing.

## Patient:

Are there any complications I should watch for?

## Doctor:

Yes, watch for increasing pain, swelling, numbness, or changes in skin color, which could indicate complications like compartment syndrome or nerve damage.

## Patient:

What can I do to help the healing process?

## Doctor:

Keep the arm immobilized as advised, elevate it to reduce swelling, follow pain management instructions, and avoid putting weight on it until cleared.

## Patient:

Thank you, doctor. What’s the next step?

## Doctor:

I’ll arrange the X-ray now and we’ll discuss the results and treatment plan once they’re available.

## Patient:

Okay, I appreciate your help.

## Doctor:

You’re welcome. We’ll take good care of you.

**References**

<https://www.hopkinsmedicine.org/health/conditions-and-diseases/fractures>

<https://emedicine.medscape.com/article/90779-differential>

<https://my.clevelandclinic.org/health/diseases/15241-bone-fractures>

##### **Bone Tumors**

**DEFINITION AND DESCRIPTION**

A bone tumor is a growth of abnormal cells within a bone. Tumors can occur in any bone in the body but are most commonly found in the long bones of the arms and legs. These growths are classified into two main categories:

* Benign bone tumors: Non-cancerous growths that generally do not spread to other parts of the body. They can still cause complications like fractures or deformities if left untreated.
* Malignant bone tumors: Cancerous growths that can spread beyond the bone to other areas in the body, requiring more aggressive treatment.

Whether benign or malignant, understanding the specific type of bone tumor is critical to determining appropriate management and care.

##### Types of Bone Tumors

Bone tumors come in various forms, each with unique characteristics. Here's an overview of the primary types:

##### Benign Bone Tumors

Osteochondroma

* The most common type of benign bone tumor.
* Typically found in adolescents and young adults.
* Often painless but can cause discomfort if they press on surrounding tissues.

Osteoid Osteoma

* Small benign tumors that typically appear in long bones such as the femur or tibia.
* Known for causing localized pain, especially at night.
* Pain is usually relieved with over-the-counter medications like aspirin or ibuprofen.

Giant Cell Tumor

* Usually develops near the ends of long bones, like the knee.
* More common in adults aged 20 to 40 years.
* While benign, they can behave aggressively, leading to bone destruction.

Enchondroma

* Tumors that form inside the bone cartilage.
* Commonly found in hands and feet.
* Often discovered incidentally during imaging tests performed for other reasons.

##### Malignant Bone Tumors

Osteosarcoma

The most prevalent type of primary bone cancer.

* Common in teenagers and young adults.
* Often affects the long bones around the knee and shoulder.

Ewing Sarcoma

* A rare and aggressive form of cancer that typically occurs in children and young adults.
* Found in long bones, pelvis, or chest wall.

Chondrosarcoma

* A cancer that develops in cartilage cells.
* More frequently diagnosed in adults over 40 years old.
* Grows slower than other malignant bone cancers.

Metastatic Bone Cancer

* Cancer that spreads (metastasizes) to the bone from another part of the body, such as the breast, lung, or prostate.
* Considered secondary bone cancer since the origin is a different organ.

##### Causes and Risk Factors

The exact causes of bone tumors remain unclear, but researchers have identified several factors that may increase the likelihood of developing a tumor:

* Genetic Disorders: Conditions like Li-Fraumeni syndrome, hereditary multiple exostoses, or retinoblastoma are associated with increased cancer risk.
* Radiation Exposure: Prolonged exposure to radiation, either from medical treatments or the environment, can contribute to tumor growth.
* Bone Injuries: While rare, some studies suggest that bone injuries or repeated stress to the bone may create an environment where tumors are more likely to form.
* Paget’s Disease of Bone: Individuals with this chronic bone condition are at a heightened risk for malignant bone tumors, particularly osteosarcoma.

Even without a known risk factor, anyone can develop a bone tumor. Regular check-ups and awareness of early warning signs are crucial.

##### **Recognizing the Symptoms of Bone Tumors**

##### Malignant Bone Tumors

The symptoms of a bone tumor can vary depending on its size, type, and location. However, some common signs to watch for include:

* Persistent bone pain, which may worsen at night or during activity.
* Swelling or a palpable lump near the affected bone area.
* Unexplained fractures caused by weakened bones.
* Reduced mobility in nearby joints.
* Generalized symptoms like fatigue, weight loss, or fever (mainly for malignant tumors).

If you experience any of these symptoms, consult a healthcare professional promptly for evaluation.

##### **Diagnosis of Bone Tumors**

Diagnosing a bone tumor involves a combination of clinical assessments and imaging studies. Key diagnostic tools include:

* X-rays: Often the first imaging test used to evaluate the affected bone.
* MRI and CT Scans: Provide more detailed images of the tumor and surrounding tissues.
* Biopsy: A sample of tissue is taken to determine whether the tumor is benign or malignant.
* Blood Tests: May assist in identifying specific markers associated with cancers.

A thorough diagnosis is essential to determine the best course of action for treatment.

##### **Treatment Options for Bone Tumors**

Treatment strategies depend on the tumor type, size, location, and whether it is benign or malignant. Imaging studies may be used to make the diagnosis, but a biopsy is frequently necessary. Options for treatment vary from straightforward observation to tumour removal surgery. Modern medicine provides a variety of effective treatment options:

##### Benign Tumor Treatments

* Observation: Some benign tumors may not require intervention and are monitored regularly with periodic imaging tests.
* Surgery: If the tumor causes pain or structural issues, surgical removal is an option. Surgeons focus on preserving as much bone function as possible.

##### Malignant Tumor Treatments

Surgery

* Surgical removal of the tumor is often necessary for malignant tumors. Limb-sparing techniques minimize the need for amputation wherever possible.

Chemotherapy

* Frequently used before or after surgery to kill cancer cells or shrink tumors.
* Commonly applied in cases of osteosarcoma or Ewing sarcoma.

Radiation Therapy

* Used to target and destroy cancer cells in cases where surgery isn't feasible or to reduce tumor size before an operation.

Targeted Therapy and Immunotherapy

* These innovative treatments focus on using the body’s immune system or specific drugs that target cancer cells, leaving healthy cells mostly unaffected.

Multidisciplinary care teams work together to create personalized treatment plans, ensuring patients receive holistic and effective care.

##### Secondary Bone cancer:

When cancer cells from a primary tumour in another area of the body travel to the bone, it is referred to as secondary bone cancer, bone metastases, or metastatic bone cancer. Compared to primary bone cancer, which occurs when the disease begins in the bone, secondary bone cancer is more frequent. The main cancer determines the kind of treatment required.

## **Bone Cancer**

Bone cancer is when cells in your bones grow out of control. Usually, when you have bone cancer, it comes from another cancer that has spread to your bones or metastatic bone cancer. But sometimes, the cancer cells start in your bones. In that case, it's called primary bone cancer. Primary bone cancer is very rare; only about 1% of all cancers are primary bone cancers.

There are four types of primary bone cancer which vary in the people they tend to affect and treatments. The types include:

1. Osteosarcoma. This type generally affects children and teens more than adults. It may be fast growing and more likely to spread.
2. Chondrosarcoma. This type generally affects adults older than 40 years. It tends to grow slowly and is less likely to spread.
3. Chordoma. This type generally affects adults older than 50 years. It may spread easily to your brain and spinal cord, so it can be challenging to treat.
4. Ewing's sarcoma. This type generally affects children and teens. It tends to grow fast and is more likely to spread.

The earliest symptom of bone cancer is unusual pain or swelling in or around the affected area of your bone. Your doctor will refer you for imaging tests, such as X-rays to diagnose you. The mainstay of treatment is surgery to remove the tumor, but you may also take chemotherapy and targeted therapies.

Keep reading to learn more about the types of bone cancer, some of the treatment options, and living as a bone cancer survivor.

## **Bone Cancer Types**

A couple types of cancer can grow in your bones. Primary bone cancer is cancer that starts in the cells of your bones. This type is rare; only about 1% of all cancers are primary bone cancer.

More often, cancer in your bones starts in other cells of your body and spreads to your bones. This is known as secondary or metastatic bone cancer.

Primary bone cancers are broadly known as sarcomas. Sarcomas are cancers that start in your bone, cartilage, fat, muscles, blood vessels, fibrous tissues, or other connective or supportive tissues. These sarcomas are further classified by the cells where they start.

There are four types of primary bone cancer, including:

**Osteosarcoma**

Osteosarcoma starts in the cells that build your bones called osteoblasts. It can happen in any of your bones, especially if you're an older adult. But in children, teens, and younger adults, it often starts in your upper arm bone close to your shoulder or your leg bone close to your knee. It tends to grow fast and spread to other parts of your body, such as your lungs.

It's most common in kids and teens aged between 10 and 19 years. And it affects boys and people assigned male at birth more often than girls and people assigned female at birth. It's more common in Black children and other racial or ethnic groups than in White children. But in adults, it's more common in White people.

You may have a raised risk of osteosarcoma if you have Paget's disease of bone or if you have had radiation exposure to your bones.

**Chondrosarcoma**

Chondrosarcoma generally starts in your cartilage cells. Cartilage is a connective tissue that protects the ends of your bones and lines your joints. Chondrosarcoma often starts in the cartilage in your pelvis, upper leg, and shoulder. It tends to grow slowly, although sometimes it may grow fast and spread to other parts of your body. A rare type of chondrosarcoma called extraskeletal chondrosarcoma doesn't start in your cartilage. Instead, it starts in the muscle, fat, fibrous tissue, or blood vessels in the upper part of your arms or legs.

Chondrosarcoma mostly affects people who are older than 40 years, and your risk of it raises as you get older.

**Ewing's sarcoma**

Ewing's sarcoma usually starts in your bones, but it can sometimes start in your muscle, fat, fibrous tissue, blood vessels, or other supporting tissues. It can affect any bone, but it usually affects your pelvis, legs, or ribs. It tends to grow fast and spread, often to your lungs.

Ewing's sarcoma generally affects kids and teens younger than 19 years. It's more common in boys and people assigned male at birth than in girls and people assigned female at birth. It's also more common in White people than people in other racial or ethnic groups, specifically Black children and children of Asian ancestry.

**Chordoma**

This is a very rare bone cancer that starts in your spine or the base of your skull. About 1%-4% of primary bone tumors are chordomas. A little over a third of cases start in the base of your spine (sacrum) or the base of your skull. Slightly less than a third of cases start in your mobile spine, which includes the bones in your neck, mid back, and lower back.

These cancers are most likely to affect people aged 50-80 years, but about 5% of cases are in children. They're also more likely in men and people assigned male at birth than in women and people assigned female at birth.

Chordomas are typically slow growing cancers, but they can easily grow into your spinal cord and brain, which makes them challenging to treat. And in about 30%-40% of cases, they will also spread to your lungs, lymph nodes, liver, skin, or other bones.

**Secondary or metastatic bone cancer**

Secondary or metastatic bone cancer is much more common than primary bone cancer. Metastatic bone cancer is cancer that started elsewhere in your body and then spread to your bones.

Most cancers can spread to your bones, but certain cancers are particularly likely to metastasize to your bones, including:

* Breast cancer
* Prostate cancer
* Lung cancer

**Benign bone tumors**

Tumors are abnormal groups of cells that multiply and grow faster than usual or don't die off when they should. Tumors can be benign or malignant. Benign tumors may cause symptoms and grow bigger, but they usually don't spread to nearby tissues or other parts of your body. Because they don't spread, they aren't considered cancer. However, some types of benign bone tumors have a low chance of becoming malignant over time.

Benign bone tumors are more common in people younger than 30 years. Most are seen in kids and teens because their skeleton is still growing and developing. Generally, once their bones stop growing in length, these benign tumors will stop growing too. In girls and people assigned female at birth, this is usually between 14 and 16 years. In boys and people assigned male at birth, it's usually between 16 and 19 years.

Benign bone tumors are relatively rare, but a few of the more common types include:

**Osteochondroma**

This is the most commonly diagnosed benign bone tumor. It's caused by overgrowth of the cartilage at the end of your bones called the growth plate. Your growth plates are where new bone is formed, and they're generally at the end of your long bones, such as your upper arm (humerus) and leg (femur) bones. Osteochondroma most often affects people aged between 10 and 30 years.

**Enchondroma**

Enchondroma is a tumor in the cartilage in the center of your bones. It's the most common tumor that affects the hand; it's usually found in the bigger bones in your hands or feet. But it can also develop in your upper arm bone (humerus), upper thigh bone (femur), and shin bone (tibia). Enchondromas usually don't cause any symptoms, and you may not know you have it until you get an X-ray for another reason. It usually affects people aged between 10 and 40 years.

**Non-ossifying fibroma**

This is the most common benign bone tumor in children. Experts estimate that about 20%-40% of healthy kids have one of these. It generally starts at the end of your thigh bone (femur) or shin bone (tibia) at your knee, although it sometimes affects your other long bones.

Non-ossifying fibromas are kind of like scar tissue on the bone, but they don't usually cause symptoms. Most people never know they have or had it. It will grow while your bones are growing, and then go away on its own once they stop.

**Chondroblastoma**

This tumor may also be called a calcifying giant cell tumor or Codman tumor. This is a rare type of benign bone tumor that usually starts at the growth plates toward the end of your thigh (femur), upper arm (humerus), or shin (tibia). It usually affects teens and young adults aged between 11 and 25 years. However, about 25% of cases are diagnosed in kids younger than 10 years. It's more common in boys and people assigned male at birth than in girls and people assigned female at birth.

Chondroblastoma can cause joint pain, swelling around your joints, discomfort in your bones, and muscle weakness near the tumor. Because it can cause bone and muscle damage, it's almost always removed during surgery. Damage to your bones can be repaired using a bone graft from another area of your body.

**Osteoid osteoma**

About 10% of benign bone tumors are osteoid osteomas. These tumors are generally smaller than one inch across and affect your shin bone (tibia) and thigh bone (femur). But it can also form in the bones of your arms, hands, feet, ankles, and spine. It's most common in people aged 5-25 years, and it's about three times more common in boys and people assigned male at birth than in girls and people assigned female a birth.

The main symptom of an osteoid osteoma is dull, achy pain that gets worse at night. And resting generally doesn't help with the pain. You may also have swelling and stiffness in the joint closest to the tumor and bone deformities, such as one leg that's shorter than the other or a side-to-side curve in your spine (scoliosis).

Osteoid osteomas often go away on their own after you stop growing. Your doctor may suggest you take a nonsteroidal anti-inflammatory drug (NSAID), such as ibuprofen or naproxen, to help ease your pain. NSAIDs may also help shrink the tumor. If this doesn't help, your doctor may suggest you have surgery to remove it.

**Osteoblastoma**

This is a rare tumor related to osteoid osteoma. The difference is that osteoblastoma tumors tend to be larger than osteoma, and they may continue to grow, whereas osteomas don't.

Osteoblastoma breaks down healthy bone tissue and replaces it with a tissue called osteoid, which is weaker than bone and more prone to break. Osteoblastomas can grow on any bone, but they are more likely in your spine, hands, and legs. Anyone can develop it, but It's most common in people aged 10-30 years. Boys and people assigned male at birth are about twice as likely to get it as girls and people assigned female at birth.

As with osteoid osteoma, the main symptom is pain that gets worse at night. Treatment is usually surgery to remove the tumor.

**Giant cell tumor**

This is a rare benign tumor that tends to grow fast. It usually starts at the end of bones near your joints, for instance, in your knee or elbow. It sometimes also grows in your breastbone (sternum) or pelvis. It mostly affects people aged 20-40 years. And it's slightly more common in women and people assigned female at birth than in men and people assigned male at birth.

Symptoms vary from person to person but generally include a visible lump and swelling, pain, and limited movement of the joint closest to the tumor. Treatment is usually with surgery to remove the tumor or radiation therapy if you aren't fit enough to have surgery.

## **Bone Cancer Causes**

No matter where it starts in your body, cancer is caused by changes (or mutations) in certain genes that cause some of your cells to grow and multiply out of control. Usually, your body has ways of shutting down cells that have these kinds of changes. But when you get cancer, it's because you've developed mutations in those genes that help control that shutdown process.

It generally takes a long time for you to develop enough mutations for that shutdown process to stop working, which is why your risk of cancer goes up as you get older. Experts don't know exactly why people develop these mutations. But it's probably due to a combination of risk factors, such as:

* Environmental exposures you've had over your lifetime. For instance, radiation exposure can raise your risk of bone cancer.
* Mutations you may have inherited from your parents. For instance, certain inherited condition, like Li-Fraumeni syndrome, raise your risk of bone cancer.
* Medical conditions that may affect how fast your cells grow and multiply. For instance, Paget's disease of bone causes abnormal development of new bone cells and can raise your risk of some types of bone cancer.

## **Bone Cancer Risk Factors**

Some factors that may make you more likely to get bone cancer include:

**Older age**

As you get older, your risk of cancers that may spread to your bones goes up. And your risk of certain primary bone cancers, such as chondrosarcoma and chordoma, goes up as you get older.

**Having radiation therapy, chemotherapy, or a stem cell transplant for cancer treatment**

Osteosarcoma in particular seems to be more common in people who have had treatment with high-dose external radiation therapy or chemotherapy with an alkylating agent, especially as children. Alkylating agents are common chemotherapy medicines that help keep cancer cells from multiplying. They're used to treat different cancers, such as lung, breast, and ovarian cancers, as well as leukemias, lymphomas, and sarcomas. Examples include:

* Carboplatin
* Chlorambucil
* Cisplatin
* Cyclophosphamide
* Mechlorethamine
* Melphalan
* Oxaliplatin

About 5% of children who have had a myeloablative hematopoietic stem cell transplant as cancer treatment may develop osteosarcoma, as well.

**Inherited conditions**

Some conditions that run in your family may raise your risk of primary bone cancer, including:

* Hereditary retinoblastoma, which causes cancer in the eye but also raises your risk of osteosarcoma
* Li-Fraumeni syndrome, which raises your risk of a number of cancers, including osteosarcoma and chondrosarcoma
* Tuberous sclerosis complex, which can cause benign tumors in your kidneys, brain, eyes, heart, lungs, and skin and raise your risk of chordoma
* Paget's disease of bone, which is a long-term condition that causes your body to break down and regrow bone faster than is typical; it can raise your risk of osteosarcoma

**Being especially tall**

Kids who are taller than average or very tall may have a raised risk of osteosarcoma. Experts think this may be because when you're tall, cells in the growth plate of your long bones multiply more than is typical. This extra growth may raise the risk that you develop mutations in those cells.

## **Bone Cancer Symptoms**

You may or may not have symptoms of bone cancer. Sometimes, your doctor only finds it when you have an X-ray for another problem, such as a sprain. If you do have symptoms, it's usually persistent or unusual pain or swelling in or around the affected area of your bone. In the case of Ewing sarcoma or chondrosarcoma, your pain may be worse at night.

Other symptoms vary depending on which type of bone cancer you have, but they include:

* A lump on a bone in your arms, legs, chest, or pelvis that may feel soft and warm
* Discoloration of your skin that shows you have inflammation near the tumor
* If you have a tumor in an arm bone, pain in that arm when you lift something
* If you have a tumor in a leg bone, limping
* If the tumor is near a joint, stiffness or limited movement in that joint
* Unexplained fevers that may not go away
* Unexplained broken bones, especially if they happen without an injury
* If the tumor has spread outside of your bone, fatigue and unexpected weight loss

If you have a chordoma, you may get nervous system symptoms as the tumor puts pressure on parts of your spinal cord or brain. Nervous system symptoms include:

* Double vision
* Blurry vision
* Headaches
* Numbness or pain in your face
* Trouble holding your pee or poop (urinary and fecal incontinence) or other issues with your urinary system or bowels
* Low back or tailbone pain

**Symptoms of bone cancer in legs**

If you have symptoms of bone cancer in your leg, it's usually pain or tenderness; a soft, warm lump; discoloration of your skin; stiffness in your knee or ankle; limping; or an unexplained broken bone in your leg.

**What does bone cancer feel like?**

You may or may not be able to feel it if you have bone cancer. If you do, you'll usually feel pain around the tumor in your bone. The pain may come and go at first and become more constant over time. Or your pain may get worse when you use that bone. For instance, if you have a tumor in an arm bone, your arm may hurt when you lift something. If you have Ewing sarcoma or chondrosarcoma, your pain may be worse at night. If the tumor weakens your bone, you may have intense pain if the bone breaks. In this case, you may have sudden, severe pain in a bone that had been tender for a while before that.

## **Bone Cancer Diagnosis**

Your doctor will usually start by asking about your personal and family medical history. They will ask about your symptoms and do a physical exam. They will usually have you do some laboratory and imaging tests to help them with their diagnosis. Tests may include:

**X-rays**

These are usually the first imaging test your doctor will recommend. It can show where a tumor is, how big it is, and what it's shaped like. If your X-ray shows you may have a tumor on your bone, they will likely have you do specialized imaging tests to help them find out more about it.

These specialized imaging tests may include:

**Bone scan (also called bone scintigraphy).** This can show if you have damage or abnormal spots in your bone. During this test, a small amount of radioactive material is injected into your vein. It travels through your blood to collect in your bones. The technician can then use a special camera to form a picture of your bones.

**CT scan.** This test uses a computer hooked up to an X-ray machine to make a series of detailed pictures of your bone.

**MRI scan.** This test uses a computer hooked up to a powerful magnet to make detailed pictures of your bone without using X-rays.

**PET scan.** This can show your doctor if you have cancer cells in your body and where they are. In this test, a technician injects radioactive glucose (sugar) into your vein. Your cells use glucose to help them grow and divide. Cancer cells use more glucose than healthy cells because they grow faster than healthy cells. So a special camera can help them find areas of your body using a lot more glucose than other areas.

**Angiogram.** In this test, your doctor gets an X-ray or computer image of your blood vessels. Tumors generally have a lot more blood vessels going to them than other tissues.

Aside from imaging, other tests your doctor may suggest include:

**Biopsy.** This test can confirm the diagnosis. Your doctor will likely refer you to a specialist experienced in treating bone tumors called an orthopedic oncologist for this test. This is because where and how the biopsy is performed can affect your later options for surgery. Your oncologist will take a sample of your tumor with a needle or through a cut in your skin. A pathologist will then look at the tissue or cells under a microscope. They can tell from this if your tumor is benign or if it's a primary or secondary cancer. They may also get an idea of how fast the tumor is growing.

**Blood tests.** Your doctor can look at the levels of two enzymes in your blood: alkaline phosphatase (ALP) and lactate dehydrogenase (LDH). Lots of things can cause high levels of ALP and LDH, so your doctor can't use this to diagnose you. But it can be a clue because your ALP and LDH levels may be very high if you have osteosarcoma or Ewing sarcoma.

## **Bone Cancer Staging**

Staging is the process your doctor will use to figure out if your cancer has spread, and if it has spread, how far. This helps your doctor advise you on the most effective treatment strategies based on your specific situation. They will use the results from all your tests to do this.

There are a couple of different staging systems your doctor can use: the Musculoskeletal Tumor Society (MSTS) staging system and the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) system. You may be familiar with the AJCC TNM system because that is the system most commonly used to stage other cancers. But the system that many surgeons find most helpful is the MSTS system. Surgery is the foundation of treatment for most bone cancers, so we'll explore that system here.

The MSTS system is based on these three pieces of information:

1. Whether the tumor has metastasized. This can be to lymph nodes near the tumor or other organs, such as your lungs or liver. If your tumor hasn't spread, you will see M0 on a pathology report. If your tumor has spread, you will see M1 on a pathology report. If your tumor has metastasized, your cancer will be classified as stage III under the MSTS system.
2. Cancer grade. Under the MSTS system, cancer grade is the second most important piece of information. It's based on what your tumor cells look like under the microscope and tells your doctor how likely your cancer is to grow and spread. It will be either low grade (G1 on a pathology report) or high grade (G2 on a pathology report). Low-grade cancers look more like healthy cells under the microscope and are less likely to grow and spread. High-grade cancers look less like healthy cells and are more likely to grow and spread.
3. Extent of your primary tumor. Bone cancers will be classified as either intracompartmental (T1 on a pathology report) or extracompartmental (T2 on a pathology report). Intracompartmental tumors are those that haven't grown outside your bone. For this reason, your doctor may also call it a "localized" tumor. Extracompartmental tumors have grown outside the bone into other tissues that are close to the tumor.

These three pieces of information are combined to classify your cancer into a stage. Under the MSTS system, there are three stages:

**Stage I bone cancer**

All low-grade bone tumors are classified as stage I under the MSTS system. If it hasn't grown outside your bone into nearby tissues, it'll be classified as stage IA. If it has grown outside your bone, it'll be classified as stage IB.

**Stage II bone cancer**

All high-grade bone tumors are classified as stage II under the MSTS system. If it hasn't grown outside your bone into nearby tissues, it'll be classified as stage IIA. If it has grown outside your bone, it'll be classified as stage IIB.

**Stage III or metastatic bone cancer**

No matter the grade or extent of your tumor, if your doctor finds metastases, it'll be classified as stage III.

## **Bone Cancer Treatment**

Your treatment options will depend on several things, including:

* What type of bone cancer you have
* Which bone it started in
* Your cancer stage
* Your overall health and life stage
* Your preferences

You will usually need a combination of different treatments, including:

**Surgery for bone cancer**

Surgery to remove the tumor is the most important treatment option for most types of bone cancer. If possible, the biopsy to confirm your diagnosis and the surgery to remove your tumor should be planned together. This is because where and how your biopsy is done can affect your surgical options during your treatment.

Preferably, both the biopsy and the surgery will be done by an orthopedic surgeon. These specialists have the best knowledge base to help minimize the chance you'll need a more extensive surgery to remove your tumor.

The goal of surgery is to remove all the cancer. Your surgeon will do this by removing the tumor plus some of the normal tissue that surrounds it. So, the type of surgery you have will depend on the size of your tumor and where it is in your body.

If you have a bone tumor in your arms or legs, your surgeon will generally recommend one of the following:

**Curettage (intralesional excision)**

This is an option for some types of bone tumors that are unlikely to spread or come back after treatment. During this procedure, your surgeon will scrape as much of the tumor as they can out of your bone with an instrument called a curette. After that, they may treat your nearby bone with medicines or extreme cold to kill any remaining cancer cells. They can fill the hole left after curettage with a bone cement.

**Limb salvage (or limb-sparing) surgery**

Most people with bone cancer in their arms and legs can have limb salvage surgery, but it depends on where the tumor is, how big it is, and if it has grown into any nearby tissues. During this procedure, your surgeon will remove the part of your bone with the tumor. Their goal will be to keep as much of your limb's function and appearance as possible. They will replace the section of bone that they removed with a bone graft, an internal prosthesis (such as a metal rod), or a combination of bone graft and prosthesis.

If your bone tumor is large or has grown into other tissues nearby, it may not be possible for your surgeon to completely remove the tumor and keep enough of your limb's function. In this case, they may recommend removing all or part of that limb with an amputation.

**Amputation**

Your surgeon will plan your amputation based on imaging tests you've had before surgery and guidance from a pathologist at the time of your surgery. They will attempt to leave enough muscle, bone, and skin so that you can be fitted with an external prosthesis after you've healed. If the tumor is too large to allow for that, they may fit an internal prosthesis into your remaining bone, which can then connect to an external prosthesis.

In most cases, you will also need reconstructive surgery, which will help you regain some function in a lost limb and get you ready for your prosthesis.

If your bone cancer has spread, you may also need surgery to remove this tissue. Bone cancer most often metastasizes to your lungs, but it can spread to many organs, including your liver, kidneys, and brain. Whether or not you have surgery to remove these depends on many factors, including your general health.

If you have a bone tumor in your pelvis, lower jaw, spine, skull, or a joint, surgery may not be an option or you may need other treatments before you have surgery. This will usually be with chemotherapy, radiation therapy, or targeted therapy.

**Chemotherapy for bone cancer**

Chemotherapy medicines help to kill cancer cells in your body. Some types of bone tumors, such as chondrosarcoma and chordoma, don't respond well to chemotherapy. But it can be an important part of treatment for osteosarcoma and Ewing sarcoma. In some cases where your tumor is big or in a hard-to-reach place, you may get chemotherapy to shrink the tumor before you get surgery.

Most of the time, you will get two or more chemotherapy medicines together. Some of the most common chemo medicines used for bone cancer include:

* Cisplatin
* Cyclophosphamide
* Doxorubicin
* Etoposide
* Ifosfamide
* Methotrexate
* Vincristine

**Radiation therapy**

Radiation therapy isn't used that often for bone cancers because bone cells are resistant to radiation. It's used most often to treat Ewing sarcoma. It uses high-energy radiation beams or particles to kill cancer cells and shrink tumors. You may get radiation therapy using:

* External beam radiation therapy
* Intensity-modulated therapy
* Stereotactic radiosurgery
* Proton beam radiation therapy

You may get radiation therapy after surgery to kill any cancer cells left after surgery or in place of surgery if you can't have surgery or your doctor doesn't think the tumor can be removed completely with surgery.

**Other bone cancer treatments**

**Rehabilitation**

Whether you've had limb salvage surgery or an amputation, you will need to have rehabilitation therapy afterward. This is often the most challenging part of treatment. If possible, try to meet with your rehabilitation specialist before you have surgery so you understand what the process is going to be like.

Oddly enough, people who've had a limb amputation often have a less intense time in rehabilitation than people who've had limb salvage surgery. For instance, on average, it takes about three to six months to relearn how to walk after a leg amputation. In contrast, it takes about a year for people to relearn to walk after limb salvage surgery to their leg.

Even if you've had limb salvage surgery, it's very important you follow your specialist's recommendations. If you don't attend your rehab sessions and do the exercises they recommend, you may wind up with a nonfunctional limb that may need to be amputated anyway.

**Targeted therapy**

Targeted therapies are medicines that target some of the genetic, protein, or other changes in or around cancer cells to help stop or slow their growth. They're most important for bone cancers that don't respond well to chemotherapy, such as chordoma.

The most commonly used targeted therapies for bone cancer are kinase inhibitors. You may get a kinase inhibitor if you have a chordoma that has spread or come back after previous treatment or an advanced chondrosarcoma. Examples of kinase inhibitors include:

* Dasatinib (Sprycel)
* Erlotinib (Tarceva)
* Imatinib (Gleevec)
* Lapatinib (Tykerb)
* Pazopanib (Votrient)
* Regorafenib (Strivarga)
* Sorafenib (Nexavar)
* Sunitinib (Sutent)

## **Living With Bone Cancer**

It can be challenging living with a cancer diagnosis, but there are ways you can help keep yourself healthy as you go through treatment and afterward. Consider the following:

* Keep up with your follow-up appointments and tests. You will usually need to have tests done every three to six months for the first few years after your treatment. After that, the risk that your cancer may come back goes down. So your doctor will probably recommend testing less often.
* Learn as much about your cancer as you can so you can feel confident making decisions about your care.
* Ask your doctor about a survivorship care plan. This plan can include the schedule for your follow-up exams and appointments, a list of possible side effects from your treatment, and diet and exercise recommendations.
* Keep copies of all your medical records in case you need to move or change doctors. You can order records from any former doctors, but they probably won't have as many details as you have. Try to keep good records while you're going through treatment.
* Take good care of your general health by eating a healthy diet, getting to and staying at a healthy weight, staying physically active, avoiding smoking, and limiting the amount of alcohol you drink.
* Reach out to your support network when you need help. Your family and friends can help provide practical support, like helping you get to all your appointments. But they can also help emotionally support you. And consider joining a support group or going to see a therapist for more emotional support.

## **Bone Cancer Outlook**

**Is bone cancer curable?**

Yes, if you catch bone cancer before it has a chance to spread to your other organs, it can be cured. This is why it's important to follow-up with your doctor when you have any symptoms that worry you. The earlier you catch it, the easier your treatment process will be and the more likely you are to be cured when you go through treatment.

**Bone cancer survival rates**

Survival rates depend on many factors, such as your age, your overall health, the type of bone cancer you have, and the stage of your cancer. Doctors sometimes use a relative survival rate to give you an idea of your outcome. But these are estimates based on large numbers of people who had a specific cancer at a specific stage. This won't tell you what your specific chances of survival are. This is why it's important to talk to your cancer care team about what to expect in your situation.

In general, the outlook for primary bone cancer is good. For instance, the five-year relative survival rate for all primary bone cancers diagnosed at any stage is about 67%. This means that 67% of people who have treatment for primary bone cancer, regardless of the kind of cancer and the stage, will be alive five years after they're diagnosed. Of course, people who are diagnosed before the cancer has spread tend to do better. But new treatments are developed all the time, so people who are diagnosed today may have even better outcomes than these numbers suggest.

## **Epidemiology**

## Incidence and Mortality

* In 2025, about 3,770 new cases of primary bone and joint cancers are expected to be diagnosed in the United States (2,150 males and 1,620 females), with approximately 2,190 deaths (1,240 males and 950 females)
* Primary bone cancers are rare, accounting for less than 1% of all cancers.
* Globally, in 2021, the incidence of malignant neoplasms of bone and articular cartilage (MNBAC) was approximately 91,375 cases, with about 66,114 deaths

## Age and Sex Distribution

* Bone cancers show a bimodal age distribution:
  + A peak incidence in adolescents and young adults (especially osteosarcoma and Ewing sarcoma).
  + A second peak in the elderly (often secondary or different histologies)
* Osteosarcoma incidence in persons ≤24 years ranges from 3–5 per million worldwide, with a male-to-female ratio of about 1.28:1 in younger patients and near equal in older adults
* Bone and joint cancers are most frequently diagnosed in people under 20 years old (about 23.3% of new cases)
* The median age at diagnosis for bone and joint cancers is 47 years[4](https://seer.cancer.gov/statfacts/html/bones.html).
* Males generally have a slightly higher incidence than females, with male-to-female ratios varying by region and tumor type

## Geographic and Ethnic Variations

* Incidence rates vary globally:
  + Highest bone cancer incidence among males reported in Chinese males in Hawaii (6.4 per 100,000), and among females in Paraguay (1.6 per 100,000)
  + In Africa, Mali (males) and Algeria (females) have higher standardized rates (~1.4 and 1.2 per 100,000, respectively)
  + Europe shows moderate incidence, with Poland having some of the highest rates and Italy among the lowest
  + Australia and Oceania show variable rates, with Maori males having higher incidence compared to other groups.
* Mortality trends differ by continent, with increases noted in Africa and Asia, while Europe and Oceania have seen declines

## Common Bone Cancer Types and Their Epidemiology

* Osteosarcoma:
  + Most common primary malignant bone tumor, accounting for about 36% of bone cancers
  + Peaks in adolescence and elderly; more common in males.
* Chondrosarcoma:
  + Second most common (~20.8% of malignant bone tumors)
  + Typically affects adults in middle to older age.
* Ewing Sarcoma:
  + Accounts for about 16.7% of malignant bone tumors
  + Most common in children and young adults.

## Trends and Patterns

* Some regions report increasing incidence and mortality rates, particularly in Africa and parts of Asia
* Developed countries generally report stable or declining mortality rates due to improved diagnosis and treatment
* Incidence rates of primary bone tumors may be declining in some areas (e.g., urban China), but increasing in others (e.g., Iran)
* Males have consistently higher incidence rates than females in most regions, though exceptions exist depending on ethnicity and geography

## **Differential Diagnosis of Bone Cancer**

## Malignant Bone Tumors

* Osteosarcoma
* Ewing sarcoma
* Chondrosarcoma
* Fibrosarcoma of bone
* Malignant fibrous histiocytoma (undifferentiated pleomorphic sarcoma)
* Adamantinoma
* Primary bone lymphoma
* Plasmacytoma / Multiple myeloma

## Benign Bone Tumors

* Osteochondroma
* Enchondroma
* Osteoid osteoma
* Osteoblastoma
* Giant cell tumor of bone
* Fibrous dysplasia
* Non-ossifying fibroma
* Aneurysmal bone cyst
* Simple (unicameral) bone cyst

## Tumor-like and Reactive Lesions

* Osteomyelitis (infection)
* Eosinophilic granuloma (Langerhans cell histiocytosis)
* Bone infarct
* Bone cysts (e.g., intraosseous ganglion)
* Stress fracture

## Secondary Bone Lesions

* Metastatic bone disease (from breast, prostate, lung, kidney, thyroid cancers)
* Multiple myeloma

**Genomic data**

* + 911 protein-coding genes and 81 microRNAs linked to OS based on literature mining
  + Another integrated database (HOsDb) identified 7,191 OS tumor-related genes, 763 metastasis-related genes, and 1,589 drug-related genes, along with thousands of gene-transcription factor and gene-miRNA interactions
* Somatic Mutations and Structural Variations:
  + Whole genome and exome sequencing reveal a high burden of somatic mutations (~1,483 mutations per sample on average) and structural variations (~317 per sample)
  + Key mutated genes include TP53, RB1, BRCA2, BAP1, PTEN, RECQL4, and others involved in DNA repair, cell cycle regulation, and tumor suppression
  + TP53 is the most significantly mutated gene across OS samples[5](https://www.nature.com/articles/s41467-022-34689-5).
* Genomic Instability:
  + OS exhibits complex numerical and structural chromosomal alterations, leading to deregulation of multiple oncogenic pathways.
  + Copy number variations and chromosomal rearrangements affect many cancer-related genes
* Molecular Subtypes:
  + Multi-omics analyses classify OS into distinct molecular subtypes with differing immune profiles and DNA repair deficiencies, such as:
    - Immune activated
    - Immune suppressed
    - Homologous recombination deficiency dominant (HRD)
    - Other subtypes with distinct clinical outcomes
* Genetic Risk Variants:
  + Genome-wide association studies (GWAS) have identified variants in genes such as CTLA-4, ERCC3, IL-8, RECQL5, TNF-α, and others associated with OS susceptibility

## **Doctor-Patient Conversation on Bone Cancer (De-Identified)**

## Doctor:

The tests indicate that the lesion in your femur is malignant, meaning it is a type of bone cancer.

## Patient:

Bone cancer? What does that mean exactly?

## Doctor:

Bone cancer means that abnormal cells are growing uncontrollably in your bone. This can be a primary bone cancer, which starts in the bone, or secondary, meaning it spread from another area. Your tests suggest it is a primary bone tumor.

## Patient:

What kind of bone cancer is it?

## Doctor:

Based on the biopsy, it appears to be an osteosarcoma, which is one of the more common types of primary bone cancer, especially in younger adults.

## Patient:

What are the treatment options?

## Doctor:

Treatment usually involves a combination of surgery to remove the tumor and chemotherapy to target cancer cells. Radiation therapy may be used in some cases.

## Patient:

Will I need to have my leg amputated?

## Doctor:

In many cases, limb-sparing surgery is possible, where we remove the tumor and some surrounding tissue but preserve the limb. Amputation is considered only if the tumor is very extensive or involves critical structures.

## Patient:

What is the prognosis?

## Doctor:

Prognosis depends on factors like tumor size, location, response to chemotherapy, and whether cancer has spread. Early diagnosis and treatment improve outcomes.

## Patient:

What side effects should I expect from treatment?

## Doctor:

Chemotherapy can cause nausea, fatigue, hair loss, and increased infection risk. Surgery may involve pain and rehabilitation. We’ll provide supportive care to manage side effects.

## Patient:

What can I do to prepare?

## Doctor:

It’s important to maintain good nutrition, stay as active as possible, and have a support system. We’ll coordinate with oncology, surgery, and rehabilitation teams to provide comprehensive care.

## Patient:

Thank you for explaining everything.

## Doctor:

You’re welcome. We’ll take this step by step, and I’m here to support you through the process.

REFERENCES

### **https://www.ncbi.nlm.nih.gov/books/NBK560830/**

### **https://www.mayoclinic.org/diseases-conditions/bone-cancer/diagnosis-treatment/drc-20350221**

### [**https://pmc.ncbi.nlm.nih.gov/articles/PMC3048853/**](https://pmc.ncbi.nlm.nih.gov/articles/PMC3048853/)

<https://www.cancer.org/cancer/types/bone-cancer/about/key-statistics.html>

### **Benign bone tumors**

**DEFINITION AND DESCRIPTION**

Most tumors that start in your bones are benign (not cancer). This means that benign tumors will not spread from their original site to a new location.

Tumors can form in any of the bones of your skeletal system and in any part of the bone. In general, the most common bones involved are also some of the largest: the femur, tibia, humerus, pelvis, spine and ribs.

Some types of tumors are most common in specific locations, such as the spine or near the growth plates in your hip, knee or shoulder.

Benign bone tumors are most common in people who are under 30 years old. A large portion of benign bone tumors are found in children while their skeletons are still growing.

Many benign tumors actually stop growing once a child reaches skeletal maturity, which is the term used to describe the time at which bones stop growing in length. Skeletal maturity usually happens between the ages of 14 to 16 in girls and between the ages of 16 to 19 in boys.

### **Types of benign bone tumors**

The most common types of benign bone tumors include:

* **Enchondroma:** This type of tumor starts in the cartilage. These tumors are found inside the bone, in the marrow space.
* **Osteochondroma:** This type of tumor is made up of cartilage and bone and can get bigger while the skeleton is growing. These tumors grow outside the bone.
* **Non-ossifying fibroma:** This bone tumor is the most common bone tumor found in children. They often go away on their own and are most commonly discovered incidentally on X-rays after an injury.
* **Chondroblastoma:** This type of tumor is usually removed because its growth affects nearby joints. It’s found in children and can cause significant pain.
* **Osteoid osteoma:** This type of tumor usually affects the long bones of the body and is more common in males. It can cause significant pain at nighttime due to hormone interaction and can be relieved with nonsteroidal anti-inflammatory medications (NSAIDs).
* **Osteoblastoma:** This type of tumor is also more common in males. Treatment is almost always surgery.
* **Periosteal chondroma:** These tumors are made up of cartilage and are located on the surface of a bone. Treatment is almost always surgery.
* **Giant cell tumor:** These tumors, though rare, grow aggressively. Females are slightly more likely to develop giant cell tumors. Treatment is almost always surgery.
* **Chondromyxoid fibroma:** This very rare type of tumor begins in the bone marrow. Treatment is almost always surgery.
* **Aneurysmal bone cyst (ABC):** These tumors can grow very large. Treatment with repeated injections of a sclerotherapy medication or with surgery is commonly needed. The sclerotherapy medication helps the space fill in.
* **Unicameral [simple] bone cysts (UBC):** These tumors are generally found near growth plates and are often found when they weaken the bone enough to cause a fracture. Treatment is usually surgery to do a bone graft or add a sclerotherapy medication.
* **Fibrous dysplasia:** This is a common bone tumor that shows up as a single bone tumor or multiple bone tumors. Generally, it doesn’t need surgery unless the bone becomes weakened by the size of the tumor.

## **Symptoms and Causes**

Bone tumors form when bone cells divide and grow out of control, forming a lump or a mass of cells. We don’t know why this happens in most cases.

### **What are the symptoms of benign bone tumors?**

Symptoms of benign bone tumors include:

* An obvious swelling or lump.
* Pain, possibly severe, increases in intensity. It may hurt even when you’re resting.
* Breaks or fractures due to bones made weaker by a growing bone tumor.

In most cases, these tumors have no symptoms and are incidentally discovered on an X-ray obtained for an injury.

## **Diagnosis and Tests**

If you’re concerned about a lump or swelling on a bone, first make an appointment with your healthcare provider. They will start with a complete physical examination and are likely to order tests, such as:

* Imaging tests, including X-rays, computed tomography (CT) scans and magnetic resonance imaging (MRI) scans.
* Bone scan.

It’s rare that your provider will order blood or urine tests to diagnose a benign blood tumor. A bone tumor specialist will likely order a bone scan, CT scan, MRI scan or biopsy. The appropriate first step is an initial evaluation and X-rays. Your pediatrician or primary care provider can order these first tests.

## **Management and Treatment**

There is no single treatment for benign bone tumors. Treating a benign bone tumor depends on things like the specific type of tumor, its size, its location and the effect has on bone strength.

In many cases, your provider may suggest just watching and waiting (observation). In other cases, your provider may suggest medication, specialized imaging, a biopsy, or removing the tumor surgically.

Most benign tumors respond well to surgical removal. In many cases, the likelihood that the tumor will come back is low — usually less than 5%. Some benign bone tumors, like giant cell tumors of bone, have a higher rate of return, but there are good methods to treat these tumors if they do come back.

### **procedures treat benign bone tumors?**

Treating benign bone tumors using surgery calls for removing the tumor as well as promoting the growth of new healthy bone at the site of the tumor. The surgeon caring for these tumors should try to remove the tumor with the least amount of trauma to surrounding normal bone tissue.

Surgeons should also have experience with proper stabilization of the bone with orthopedic hardware and bone grafting — as necessary. The combination of these techniques allows people with benign bone tumors, especially young people, to be able to return to full and unlimited activities after treatment.

Other treatments can be used for certain types of bone tumors. One treatment for osteoid osteoma may include radiofrequency ablation or thermal necrosis. These procedures require anesthesia, are often done as a combined approach and involve orthopedic surgeons and radiologists. Aneurysmal bone cysts (ABCs) can be treated with serial (repeated) injections of a medication called doxycycline and have a good chance of resolving without an open surgery.

### **What are the risks of surgery for treating benign bone tumors?**

It’s unusual to have major problems with these surgeries because they are mostly straightforward. However, rare (but possible) risks include nerve injury, infection, bleeding, stiffness and an inability to return to a high level of sport.

## **Bone Tumors (Benign) Treatment, Drug Information, and Side Effects**

## Treatment Approaches

* Observation ("Watch and Wait"):  
  Many benign bone tumors do not cause symptoms or problems and can be safely monitored with periodic imaging to check for growth or changes. No immediate treatment is necessary in these cases
* Surgical Removal:  
  Surgery is the mainstay treatment for symptomatic or aggressive benign bone tumors. The goal is to remove the tumor while preserving as much normal bone and joint function as possible. Techniques include:
  + Curettage: Scraping out the tumor from the bone.
  + Use of Adjuvants: Chemical (phenol, hydrogen peroxide), thermal (cryosurgery with liquid nitrogen, radiofrequency ablation), or bone cement (polymethylmethacrylate - PMMA) to reduce recurrence risk.
  + Bone Grafting and Stabilization: Bone grafts and orthopedic hardware may be used to fill defects and stabilize the bone post-removal
* Minimally Invasive Treatments:
  + Radiofrequency Ablation (RFA): Heating and destroying tumor tissue, often used for osteoid osteoma.
  + Cryosurgery: Freezing the tumor with liquid nitrogen.
  + Percutaneous Injections: Serial injections of doxycycline for aneurysmal bone cysts, corticosteroids, or sclerosing agents to reduce tumor size without open surgery
* Drug Therapy:
  + Denosumab: A monoclonal antibody that inhibits RANKL, used for benign giant cell tumors of bone that are not amenable to complete surgical removal or in cases with pulmonary metastases. It helps reduce tumor size and bone destruction
  + Bisphosphonates: Occasionally used to ossify lesions in fibrous dysplasia or reduce recurrence risk, though less common

## **Side Effects and Considerations**

* Surgical Risks:  
  Include infection, bleeding, damage to surrounding tissues, and potential need for further surgery if the tumor recurs.
* Adjuvant Treatments:  
  Chemical agents like phenol and hydrogen peroxide can cause local tissue irritation or damage if not carefully applied. Cryosurgery and RFA carry risks of thermal injury to adjacent structures.
* Denosumab Side Effects:  
  May include hypocalcemia, osteonecrosis of the jaw, and atypical fractures with long-term use; requires monitoring of calcium levels and dental health.
* Percutaneous Injection Side Effects:  
  Usually well tolerated; doxycycline injections may cause local inflammation or pain temporarily.

## **Bone Tumors (Benign) Procedures and Timeline**

## Diagnostic Procedures

* Initial Evaluation:  
  Includes physical examination, medical history, and imaging studies such as X-rays, CT, or MRI to characterize the tumor’s size, location, and aggressiveness.
* Biopsy:  
  Often performed to confirm diagnosis and rule out malignancy before definitive treatment.

## Treatment Procedures

1. Observation (Watchful Waiting):
   1. Many benign bone tumors are asymptomatic and stable, requiring no immediate treatment.
   2. Regular follow-up with imaging is done to monitor for growth or symptom development.
   3. This approach can continue for months to years depending on tumor behavior.
2. Surgical Removal:
   1. Curettage: Scraping out the tumor from the bone, often the primary surgical method for benign tumors.
   2. Adjuvant Treatments: Use of local chemical agents (phenol, hydrogen peroxide), thermal methods (cryosurgery with liquid nitrogen, argon beam), or bone cement (methyl methacrylate) to reduce recurrence risk.
   3. Bone Grafting and Stabilization: Filling the defect with bone grafts and stabilizing with orthopedic hardware (plates, screws, nails) as needed.
   4. Hospitalization typically lasts 1 to 3 days for benign tumors.
   5. Recovery focuses on bone healing and restoring function, with many patients returning to full activity after healing.
3. Minimally Invasive Techniques:
   1. Radiofrequency Ablation (RFA): Used especially for osteoid osteoma; involves thermal destruction of tumor tissue under imaging guidance.
   2. Percutaneous Injections: Serial injections of doxycycline for aneurysmal bone cysts can resolve lesions without open surgery.
4. Drug Therapy:
   1. Denosumab: A RANKL inhibitor used for giant cell tumors not amenable to complete surgical resection or with pulmonary metastases.
   2. May be used preoperatively to reduce tumor size or postoperatively for residual disease.

## **Timeline Overview**

| Stage | Timeline | Description |
| --- | --- | --- |
| Diagnosis and Biopsy | Days to weeks | Imaging and biopsy to confirm diagnosis |
| Observation Phase | Months to years (if stable) | Periodic imaging and clinical monitoring |
| Surgical Treatment | Hospital stay: 1–3 days | Curettage with adjuvants, bone grafting, stabilization |
| Postoperative Recovery | Weeks to months | Bone healing, physical therapy, gradual return to activities |
| Minimally Invasive Therapy | Outpatient or short stay | RFA or injections with rapid recovery |
| Drug Therapy (Denosumab) | Weeks to months | Administered as needed, often combined with surgery |

## **Epidemiology of Benign Bone Tumors**

* Prevalence and Incidence:  
  Benign bone tumors are more common than malignant bone tumors, though their true incidence is likely underestimated because many benign lesions are asymptomatic and not clinically detected. Hospital-based studies report that benign tumors account for approximately 41% to 79% of all primary bone tumor cases in various populations. For example, a Nigerian systematic review found benign tumors comprised 41.2% to 79% of cases, while a Chinese hospital-based study reported benign tumors represented 58.7% of all bone tumors.
* Age Distribution:  
  The peak incidence of benign bone tumors occurs in the second and third decades of life (ages 11–30 years). Over 60% of patients with benign bone tumors are younger than 30 years old, reflecting their predominance in children and young adults.
* Sex Distribution:  
  There is a male predominance in benign bone tumors, with studies showing around 52–63% of cases occurring in males.
* Common Types of Benign Bone Tumors:
  + Osteochondroma: The most common benign bone tumor, accounting for 20–50% of benign tumors and 10–15% of all bone tumors.
  + Enchondroma: Represents about 29% of benign tumors in some series.
  + Giant Cell Tumor (GCT): Accounts for approximately 30% of benign bone tumors in some populations, with peak incidence in the third and fourth decades.
  + Osteoblastoma: Rare, but occurs mostly in the first four decades of life.
* Anatomic Distribution:  
  The most common sites for benign bone tumors are the femur, tibia, and humerus, which together account for over 50% of cases. Osteochondromas and giant cell tumors frequently involve these long bones.
* Geographic Variations:  
  Epidemiological patterns vary by region and ethnicity. For example, data from Nigeria, China, and the United States show similar trends in age and sex distribution but differ in incidence rates and tumor subtype frequencies.
* Data Limitations:  
  Most epidemiological data come from hospital-based registries rather than population-based studies, which may underestimate the true incidence of benign bone tumors due to asymptomatic cases not presenting for medical care.

## **Outlook / Prognosis**

The outlook for people with benign bone tumors is excellent. Treatment is possible and provides pain relief. The condition is almost never fatal. Benign bone tumors rarely become cancerous (far less than a 1% chance).

## **Prevention**

As far as researchers know, there’s no way to prevent benign bone tumors from forming

### **When should I contact my healthcare provider regarding benign bone tumors?**

You should always feel that you’re able to contact your healthcare provider with any concerns. If you notice a lump or swelling near your bone, or if you have pain that gets worse and not better, call your provider.

## **Differential Diagnosis**

## Benign Bone Tumors

* 1. Osteochondroma
  2. Enchondroma
  3. Giant Cell Tumor (GCT)
  4. Osteoid Osteoma
  5. Osteoblastoma
  6. Chondroblastoma
  7. Non-Ossifying Fibroma (NOF)
  8. Fibrous Dysplasia
  9. Aneurysmal Bone Cyst (ABC)
  10. Simple (Unicameral) Bone Cyst
  11. Osteoma / Enostosis (Bone Island)
  12. Osteopoikilosis

1. Malignant Bone Tumors (to exclude)
   1. Osteosarcoma
   2. Ewing Sarcoma
   3. Chondrosarcoma
   4. Primary Bone Lymphoma
   5. Metastatic Bone Disease
   6. Multiple Myeloma
2. Tumor-like Lesions and Reactive Processes
   1. Osteomyelitis (Infection)
   2. Eosinophilic Granuloma (Langerhans Cell Histiocytosis)
   3. Bone Infarct
   4. Intraosseous Ganglion / Synovial Cyst
   5. Stress Fracture
   6. Brown Tumor (Hyperparathyroidism)
   7. Tug Lesion
3. Other Conditions Mimicking Bone Tumors
   1. Bone Contusion / Bruise
   2. Bone Marrow Edema
   3. Bone Infarcts
   4. Paget Disease
   5. Adamantinoma
   6. Osteofibrous Dysplasia

## **Questions and Answers**

## 1. What is a benign bone tumor?

A benign bone tumor is a non-cancerous growth in the bone that does not spread to other parts of the body and usually grows slowly.

## 2. What are common types of benign bone tumors?

Common types include osteochondroma, enchondroma, osteoid osteoma, giant cell tumor, fibrous dysplasia, and aneurysmal bone cyst.

## 3. How do benign bone tumors usually present?

Many benign bone tumors are asymptomatic and found incidentally. When symptomatic, they may cause localized pain, swelling, or a palpable lump.

## 4. How are benign bone tumors diagnosed?

Diagnosis involves clinical examination, imaging studies such as X-rays, CT scans, MRI, and sometimes biopsy to confirm the nature of the lesion.

## 5. Do benign bone tumors require treatment?

Not all benign bone tumors require treatment. Some are monitored with regular imaging, while others causing symptoms or risk of fracture may need surgical removal.

## 6. Can benign bone tumors become cancerous?

Most benign bone tumors do not become malignant. However, some, like osteochondromas, have a small risk of transforming into chondrosarcoma.

## 7. What is the typical treatment for osteoid osteoma?

Osteoid osteoma is often treated with minimally invasive techniques like radiofrequency ablation or surgical excision if symptomatic.

## 8. How often should benign bone tumors be monitored?

Monitoring frequency depends on the tumor type and symptoms but generally involves periodic imaging every 6 to 12 months.

## 9. What complications can benign bone tumors cause?

Complications include bone weakening leading to fractures, nerve compression, and rarely malignant transformation.

## 10. Is recovery from benign bone tumor surgery usually complete?

Yes, most patients recover well after surgery with low recurrence rates, but follow-up is important to detect any regrowth.

## **Genomic Data**

## 1. Giant Cell Tumor of Bone (GCTB)

* Represents 15–20% of benign bone tumors; locally aggressive with potential for pulmonary metastases.
* Genetic Features:
  + Nearly all GCTBs harbor somatic mutations in the H3F3A gene (encoding histone H3.3), specifically the p.Gly34Trp (G34W) substitution.
  + This mutation leads to epigenetic dysregulation and abnormal histone function.
  + Other alterations include 20q11.1 amplification, RANKL overexpression (promoting osteoclast recruitment and osteolysis), and sometimes p53 overexpression linked to recurrence and metastasis.
  + Histone modification mutations are found in over 90% of GCTBs, making H3F3A mutation a reliable diagnostic marker.
  + These molecular features enable targeted therapy, e.g., with denosumab (RANKL inhibitor).

## 2. Osteoblastoma

* A benign bone-forming tumor that can be difficult to distinguish from osteosarcoma.
* Genetic Marker:
  + Mutations in the FOS and FOSB transcription factor genes are specific to osteoblastoma and not found in osteosarcoma or other tumors.
  + This mutation can serve as a diagnostic marker to differentiate benign osteoblastoma from aggressive osteosarcoma.

## 3. Chondroblastoma

* Rare benign tumor with chondrogenic differentiation, usually occurring in young adults.
* Genetics:
  + Part of simple genetics category; often harbors mutations in H3F3B (a histone 3 variant gene), similar to but distinct from GCTB’s H3F3A mutations.

## 4. Other Genetic Findings in Benign Bone Tumors

* Somatic mutations are generally rare in benign bone tumors compared to malignant ones.
* Some benign tumors show chromosomal aberrations such as 1p13-p22 region alterations.
* Gene amplifications (e.g., 20q11) and telomerase activity changes have been reported in subsets of benign tumors.
* Mutations in genes related to bone remodeling and osteoclast activation (e.g., RANKL pathway) are common in giant cell-rich lesions.

## 5. Diagnostic and Research Implications

* Molecular testing for H3F3A mutations (G34W) is now widely used to confirm diagnosis of GCTB.
* Identification of FOS/FOSB mutations aids in distinguishing osteoblastoma from osteosarcoma, guiding treatment decisions.
* Next-generation sequencing (NGS) panels improve diagnosis by detecting gene fusions and mutations in ambiguous cases.
* Understanding these genomic alterations supports targeted therapies and personalized management.

REFERENCES

[Benign Bone Tumors: Common Types, Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/16775-benign-bone-tumors)

<https://pmc.ncbi.nlm.nih.gov/articles/PMC9213736/>

<http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S1681-150X2022000300012>

### **Osteopenia**

**DEFINITION AND DESCRIPTION**

Osteopenia is a loss of bone density. Having reduced bone density means your bones don’t have as much mineral content as they should. This can make them weaker and increase your risk of bone fractures (broken bones).

If you have osteopenia, your bone density is lower than average. It can progress to osteoporosis.

Most people need their bone density checked every few years after they turn 50 or enter postmenopause, but you might need yours monitored more often. Visit a healthcare provider for regular checkups. They’ll tell you when you’ll need your bone density tested.

#### **Osteopenia vs. osteoporosis**

Osteopenia is an early sign of osteoporosis. Their names sound so similar because they’re closely related.

Osteopenia is the medical definition for having reduced bone density. Osteopenia is the warning sign that means you have an increased osteoporosis and fracture risk.

If it’s not treated, osteopenia can become osteoporosis. Osteoporosis silently weakens your bones. People with osteoporosis are much more likely to break a bone, especially from falls. If you have osteoporosis, even a minor slip that might not normally cause injuries can lead to fractures.

Experts estimate that more than 40 million Americans have osteopenia. They think around one-third of adults older than 50 have some degree of bone density loss.

### **Osteopenia symptoms**

Osteopenia doesn’t usually cause any symptoms you can feel or notice. That’s why healthcare providers sometimes call osteopenia and osteoporosis silent disease.

### **What causes osteopenia?**

Osteopenia usually happens naturally as you age. Your bones are living tissue like any other part of your body. It might not seem like it, but they’re constantly growing, changing and reshaping themselves throughout your life.

Most people lose some bone density as they get older. Your bones are densest around age 25 and start breaking down faster than your body can rebuild them after that. This natural decline doesn’t cause issues in most people. However, if you lose too much bone density, you can develop osteopenia, which may mean you’re more likely to have osteoporosis later in your life.

#### **Risk factors**

Anyone can develop osteopenia, but some groups of people are more likely to have it, including:

* Adults older than 50
* Sex: Females are four times more likely to have osteopenia
* Women after menopause
* People who [smoke](https://my.clevelandclinic.org/health/articles/17488-smoking) or use tobacco products
* People who regularly drink alcohol (more than two drinks per day)

Some health conditions can lower your bone density or worsen osteopenia, including:

* Hyperthyroidism
* Diabetes
* Chronic kidney disease (CKD)
* Malnutrition
* A calcium or vitamin D deficiency
* Hormonal imbalances (like Cushing syndrome)
* Anorexia and other eating disorders
* Autoimmune diseases that affect your bones (like rheumatoid arthritis or collagen defects)

Medications that can increase your osteopenia risk include:

* Diuretics
* Corticosteroids
* Medications used to treat seizures
* Hormone therapy for cancer (including to treat breast cancer or prostate cancer)
* Anticoagulants
* Proton pump inhibitors (PPIs, like those that treat acid reflux, which can affect your calcium absorption)

### **Osteopenia complications**

Increasing your bone fracture and osteoporosis risk are osteopenia’s main complications. Osteopenia on its own won’t cause symptoms. But having reduced bone density makes you much more likely to break a bone, even after small injuries or falls.

## **Diagnosis and Tests**

A healthcare provider will diagnose osteopenia with a bone density test. A bone density test is an imaging test that measures the strength of your bones. It uses X-rays to measure how much calcium and other minerals are in your bones.

Checking for changes in your bone density is the best way to catch osteopenia before it becomes osteoporosis. Your provider might suggest you get regular bone density tests if you have a family history of osteoporosis. Females usually need bone density screenings regularly after they turn 50. Males typically need them after age 70.

If you have osteopenia, you’ll probably need a bone density test every few years to see how your bones have changed.

## **Management and Treatment**

Your provider will suggest osteopenia treatments that slow down your bone loss and strengthen your existing bone tissue. The most important part of treating osteopenia is preventing bone fractures and osteoporosis.

The most common osteopenia treatments include:

* **Physical activity and exercise:** Staying active can strengthen your bones (and all the tissue connected to them, like your muscles, tendons and ligaments). Your provider might suggest weight-bearing exercises to strengthen your muscles and train your balance. Physical activities that make your body work against gravity like walking, yoga, Pilates and tai chi can improve your strength and balance without putting too much stress on your bones. You might need to work with a physical therapist to find exercises and movements that are right for you.
* **Vitamin and mineral supplements:** You might need over-the-counter (OTC) or prescription calcium or vitamin D supplements. Your provider will tell you which type you need, how often you should take them and which dosage you’ll need. Most people don’t need prescription medication to treat osteopenia. Your provider may suggest prescription medication to treat osteoporosis if you develop it later.
* **Following an eating plan that’s healthy for you:** Eating enough, and getting the right kinds of vitamins and minerals, can strengthen your bones (and improve your overall health). Your provider or a registered dietitian can help you create an eating plan that fits your unique needs.

## **Osteopenia Medications**

### Bisphosphonates

Bisphosphonates are medications that work by slowing the rate of bone loss, thereby improving bone density. Most of these reduce the risk of spine fractures, but not all have been shown to reduce the risk of hip fractures. Some bisphosphonates are taken orally while others are given by injection.

Available biphosphonates include:

**Fosamax (alendronate):** Taken orally, Fosomax appears to reduce both hip and spine fractures.

**Actonel (risedronate):** Taken orally, Actonel may reduce the risk of both hip and spine fractures.

**Ibandronate:** Available orally or by injection, reduces the risk of spine fractures but not hip fractures.

**Zometa** or **Reclast (zoledronic acid):** Given by injection, Zometa reduces the risk of both hip and spine fractures.

Side effects of bisphosphonates vary based on whether they are used orally or by injection. With oral bisphosphonates, the medication should be taken with a full glass of water and you should remain upright for 30 to 60 minutes.

Possible side effects of bisphosphonates include:

Heartburn

Esophageal irritation

Flu-like symptoms (injections only)

Muscle and joint pain at the injection site

An uncommon but severe side effect is osteonecrosis (bone cell death) of the jaw. People who have gum disease or poor dental hygiene, have a dental device, or require procedures such as a tooth extraction are at greatest risk. Other uncommon side effects include atrial fibrillation and atypical femur fractures.

### Selective Estrogen Recept Modulators

Selective estrogen receptor modulators (SERMS) are medications that can have both estrogen-like and anti-estrogen effects, depending on the part of the body they act on.

Evista (raloxifene) and Soltamox (tamoxifen) are hormone therapies approved for the prevention of osteoporosis in postmenopausal women. These drugs are also thought to reduce the risk of breast cancer.

Like estrogen (as in hormone replacement therapy) their action on bone increases bone mineral density and reduces the risk of vertebral (spinal) fractures. They may also reduce the risk of hip fractures, but more research is needed.

Possible side effects of SERMS include:

Hot flashes

Leg cramps

Joint aches

Serious but rare side effects include deep vein thrombosis and pulmonary emboli.

### Hormone Replacement Therapy

While hormone replacement therapy (HRT) was once referred to as nearly a miracle drug to prevent osteoporosis in women, it is no longer approved for this indication. In addition, studies finding an increased risk of breast cancer, heart disease, and strokes in women taking HRT have resulted in these medications being used much less frequently.

Certainly, there are still people who use HRT for menopausal symptoms, and it can work well for these symptoms. One significant cause of bone loss in menopausal women is the reduction in the amount of estrogen produced by the body. It makes sense then that hormone replacement therapy (HRT) would help reduce bone loss.

As with any medication, you must weigh the risks and benefits of any medication you use. For young women who have had surgical menopause and are suffering from life-limiting hot flashes, HRT may be a good option. Yet, even in this setting, the goal of treatment with HRT should not be a reduction in osteoporosis risk.

### Denosumab

Prolia (denosumab) is a monoclonal antibody that prevents the formation of osteoclasts, cells which cause the breakdown of bone.

Denosumab can reduce the risk of osteoporosis and fractures in women who are on aromatase inhibitors (drugs for postmenopausal breast cancer), or men who are on androgen deprivation therapy for prostate cancer. Denosumab is also used for people with any type of cancer that has spread to their bones to reduce the risk of fractures.

Possible side effects of denosumab include:

Bone, joint, or muscle pain

Rash

High cholesterol

Bladder infection

Cold-like symptoms, such as runny nose and sore throat

Serious but rare side effects include low calcium levels, osteonecrosis, and serious infections.

### Calcitonin

Calcitonin is a man-made version of a hormone that regulates bone metabolism and helps change the rate at which the body reabsorbs bone.

Calcitonin is available both as a nasal spray and by injection and can reduce the risk of spine fractures. Calcitonin nasal spray, in particular, may be an option for postmenopausal women who can't tolerate the side effects of other medications.

Possible side effects of the nasal spray include:

Nasal symptoms, such as runny nose, dryness, and nasal bleeding

Back and/or joint pain

Headache

### Parathyroid Hormone and Derivatives

Forteo (teriparatide) is a man-made version of the body's natural parathyroid hormone administered by injection. This drug is usually used only for people with severe osteoporosis who are at a high risk of fractures.

Forteo is the only medication that can actually stimulate the body to grow new bone. Use is currently restricted to only 2 years. Tymlos (abaloparatide) is similar and is a synthetic version of a portion of parathyroid hormone.

Possible side effects of Forteo include:

Dizziness

Swelling, itchiness, or redness at the injection site

Achey joints

Nausea

Although rare, Forteo can cause increased levels of calcium in the blood.

## **Osteopenia Medication Prescribed**

Treatment for osteopenia can be beneficial for people with low bone density who have had a fragility fracture or who are particularly at risk for them. But, the decision to medicate is somewhat controversial for people with osteopenia who have not had a fragility fracture or do not have other risk factors.

Not every person with osteopenia has experienced a fragility fracture. According to one study, approximately 72% of people with osteopenia in their 60s have had a spinal fragility fracture, compared to 68% of people with normal bone density, and 86% of people with osteoporosis.

FDA-approved medications for the prevention of osteoporosis can be prescribed to people with osteopenia. While these medications are effective, some have serious side effects. For this reason, many healthcare providers hesitate to prescribe osteoporosis medications unless they are absolutely necessary.

The decision to treat osteopenia with medications is highly individual and will depend on several factors, including:

**Age and sex:** The risk of osteopenia, osteoporosis, and fragility fractures is highest in women over the age of 65, women who are postmenopausal, and men over the age of 70. Osteopenia treatment is recommended for individuals who fall within these groups.

**Overall health:** People who have autoimmune conditions like rheumatoid arthritis, should be treated for osteopenia. People who have been treated for cancer should also be prescribed medication for osteopenia, since radiation and chemotherapy cause bones to weaken.

**Bone density:** Bone mineral density is measured with a noninvasive test called dual-energy x-ray absorptiometry (DXA)*.* The result comes in what's known as a T-score. Your provider may prescribe medication if your T-score is nearing -2.5, which indicates osteoporosis.

**Fracture risk:** Your provider may prescribe medication if you have a history of one or more fragility fractures, an increased risk of falling due to conditions like dementia or epilepsy, poor posture, or an elevated 10-year fracture risk.

## **Managing Osteopenia With Lifestyle Changes**

Whether or not you choose to use medications for osteopenia, there are things you can do to reduce your risk of fractures:

Declutter your home, keep objects off your stairs, and place slip-proof mats in your shower, bathroom, and other wet spaces to prevent falls.

Pack your diet with nutritious foods. Get adequate calcium and vitamin D to boost bone health. Ask your healthcare provider if a supplement is right for you.

Exercise regularly to improve strength, balance, and coordination. Make sure you do plenty of cardio, strength, and balance exercises.

Don't smoke or use tobacco products. Nicotine in tobacco decreases the absorption of calcium in your diet and slows the production of osteoblast cells so that they make less bone.

Limit your alcohol intake. Don't have more than two alcoholic drinks per day if you are a female, or more than three drinks per day if you are a male.

## **Osteopenia Procedures and Timelines**

## 1. Diagnosis and Monitoring Procedures

* DXA Bone Densitometry:
  + Gold standard for diagnosing osteopenia (T-score between –1.0 and –2.4).
  + Surveillance frequency depends on T-score:
    - T-score –1.0 to –1.5: Repeat every 5 years
    - T-score –1.5 to –2.0: Repeat every 3–5 years
    - T-score below –2.0: Repeat every 1–2 years
    - Patients on long-term high-dose prednisone: DXA every 1–2 years
* FRAX Score Assessment:
  + Performed with each DXA test to estimate 10-year fracture risk and guide treatment decisions.
* Laboratory Tests:
  + Serum calcium, phosphate, alkaline phosphatase, 25-OH vitamin D, PTH (if calcium abnormal), renal function tests, CBC.

## 2. Prevention and Lifestyle Interventions

* Vitamin D Supplementation:
  + Aim to maintain serum 25-OH vitamin D >30 ng/mL (75 nmol/L).
* Calcium Intake:
  + Usually from diet; supplementation only if dietary intake is low.
* Lifestyle Modifications:
  + Smoking cessation, alcohol moderation, strength training, weight-bearing exercises.
  + Balance exercises (e.g., tai chi) to prevent falls.
  + Home safety measures: reduce tripping hazards, adequate lighting, use of walking aids if needed.

## 3. Pharmacologic Treatment

* Generally not required for osteopenia alone unless:
  + Patient is on long-term high-dose glucocorticoids.
  + History of fragility fractures.
  + FRAX 10-year fracture risk >20% or hip fracture risk >3%.
* First-line medications:
  + Bisphosphonates (alendronate, risedronate, zoledronic acid).
  + Alternatives include denosumab, especially if bisphosphonates are contraindicated or not tolerated.
* Anabolic agents (e.g., romosozumab, teriparatide):
  + Reserved for patients at very high fracture risk, often followed by antiresorptive therapy.

## 4. Treatment Timelines and Follow-up

* Initial Evaluation:
  + Baseline DXA, labs, and FRAX assessment at diagnosis.
* Monitoring:
  + Repeat DXA as per risk stratification (1–5 years depending on severity and risk factors).
  + Clinical follow-up every 6–12 months to assess adherence, side effects, and fracture occurrence.
* Pharmacologic Therapy Duration:
  + Bisphosphonates typically prescribed for 3–5 years; reassessment needed to decide continuation or drug holiday.
  + Denosumab requires continuous administration every 6 months; stopping without follow-up therapy may cause rebound fractures.
* Lifestyle and Supplementation:
  + Lifelong adherence recommended.

## **Osteopenia Staging Based on T-Scores**

Osteopenia is classified primarily by bone mineral density (BMD) measurements obtained through dual-energy X-ray absorptiometry (DXA) scans. The key metric used is the T-score, which compares a person’s BMD to that of a healthy young adult (around age 30).

## T-Score Ranges and Corresponding Bone Health Status

| T-Score Range | Interpretation | Description |
| --- | --- | --- |
| Above –1.0 | Normal bone density | Bone density is within normal limits. |
| Between –1.0 and –2.5 | Osteopenia (Low bone mass) | Bone density is below normal but not low enough to be osteoporosis. Indicates increased fracture risk. |
| –2.5 or below | Osteoporosis | Significant bone loss with high fracture risk. |

* Osteopenia is a radiographic diagnosis based on T-score and does not specify cause.
* The World Health Organization (WHO) defines osteopenia as a T-score between –1 and –2.5, applicable mainly to postmenopausal women and men over 50.
* For premenopausal women, younger men, and children, Z-scores (age-matched comparisons) are preferred over T-scores.
* Some conditions (e.g., arthritis) may falsely elevate T-scores; clinical correlation is essential.

## Clinical Implications of Osteopenia Staging

* Osteopenia indicates increased fracture risk, which rises progressively as T-score decreases.
* A T-score closer to –2.5 suggests higher risk and closer monitoring or intervention.
* Osteopenia staging guides frequency of monitoring and treatment decisions.

## **Outlook / Prognosis**

You should expect to monitor your bone density for the rest of your life if you have osteopenia. Most people with osteopenia need their bone density checked every few years. Your provider will tell you how often you’ll need bone density tests.

#### **Can I reverse my osteopenia?**

Osteopenia is a natural progression of bone loss. But you can slow it down to prevent osteoporosis. The sooner you know you have osteopenia, the better. Once you start treatment, you may slow down your bone loss so much that you never develop osteoporosis. Some people can reverse osteopenia and regain a typical amount of bone density.

## **Prevention**

You usually can’t prevent osteopenia. Everyone naturally loses some bone density as they age, and you can’t stop that from happening. Some of the best ways to strengthen your bones and slow bone loss are the same as the treatments for osteopenia. Talk to your provider about ways to improve your bone health if you’re worried about osteopenia or osteoporosis.

## **Living With**

Some of the best ways to take care of your bones are great ways to support your overall health:

* Stay physically active as often as you can.
* Get plenty of vitamin D and calcium in your diet.
* Limit how much alcohol you drink.
* Avoid smoking and other tobacco products.

### **When should I see my healthcare provider?**

Visit a healthcare provider if you notice any changes in your body that make you worried about your bone health. Tell your provider about any other symptoms you’re experiencing, especially if you have bone pain or trouble moving.

Ask your provider how often you should have your bone density checked, especially if someone in your biological family has osteopenia or osteoporosis.

## **Osteopenia Epidemiology**

## Global Prevalence

* Osteopenia affects a large proportion of adults worldwide, especially those aged 50 years and older.
* Among adults aged 50+, the prevalence of osteopenia is approximately 43–47% globally, with higher rates in women than men.
* In some regions, vertebral osteopenia prevalence in women over 50 ranges from 45.5% to 49.7%; femoral neck osteopenia ranges from 46% to 57.2%.
* Osteopenia prevalence generally increases with age, reaching over 50% in older populations.

## Regional and Country-Specific Data

* Australia: About 42% of men and 51% of women have osteopenia; in 2012, 66% of Australians aged 50+ had osteopenia or osteoporosis.
* India: High prevalence reported, with about 52% overall osteopenia in some populations; vitamin D deficiency and nutritional factors contribute.
* China: Osteopenia prevalence among adults 50+ is around 43.1%, with higher rates in older adults (65+).
* Middle East and Africa: Higher prevalence of low bone mass, partly due to hypovitaminosis D despite ample sunlight.
* Japan: Osteopenia prevalence estimated at about 35% in women aged 50–79 years at the spine.
* Nigeria: Among persons aged 60+, osteopenia prevalence is about 27.8%, with higher rates in males.
* Postmenopausal Women in Punjab, India: Osteopenia prevalence reported at 44.2%.
* Type 2 Diabetes Patients (Saudi Arabia): Lower osteopenia prevalence (~2.8%) reported in a specific hospital cohort.

## Sex and Age Differences

* Osteopenia is more common in women than men, especially postmenopausal women due to hormonal changes.
* Prevalence rises sharply with advancing age, particularly after 50 years.

## Trends and Projections

* The global burden of osteopenia and osteoporosis is increasing due to aging populations.
* In China, annual osteoporosis-related fractures are projected to rise to nearly 6 million by 2050, with osteopenia contributing significantly to fracture risk.
* Increasing prevalence of comorbidities such as diabetes and cardiovascular diseases may compound osteopenia risk.

**DIFFERENTIAL DIAGNOSIS**

* Homocystinuria
* Hyperparathyroidism
* Imaging in osteomalacia
* Mastocytosis
* Multiple myeloma
* Paget disease
* Scurvy
* Sickle cell anaemia

## **Predefined Questions and Answers Set for Osteopenia**

## 1. What is osteopenia?

Osteopenia is a condition characterized by lower-than-normal bone mineral density (BMD), meaning your bones have less mineral content than they should, making them weaker and more prone to fractures. It is less severe than osteoporosis but can progress to it if untreated

## 2. What causes osteopenia?

Osteopenia can be caused by aging, hormonal changes (especially after menopause), nutritional deficiencies (calcium and vitamin D), certain medications (steroids, anti-seizure drugs), smoking, excessive alcohol use, and medical conditions like lupus, rheumatoid arthritis, and celiac disease

## 3. What are the symptoms of osteopenia?

Osteopenia typically does not cause symptoms. It is usually detected through bone density testing before any fractures occur

## 4. How is osteopenia diagnosed?

Osteopenia is diagnosed using a bone density test called dual-energy X-ray absorptiometry (DEXA or DXA) scan. A T-score between –1.0 and –2.5 indicates osteopenia. Additional blood tests may be done to check calcium, vitamin D, thyroid, and other related levels

## 5. Who should get tested for osteopenia?

Women over 50 and men over 70 are commonly recommended to have regular bone density screenings. People with risk factors such as family history, previous fractures, or certain medical conditions may need earlier or more frequent testing

## 6. How is osteopenia treated?

Treatment focuses on preventing further bone loss and fractures through lifestyle changes:

* Regular weight-bearing and strength-training exercises
* Adequate calcium and vitamin D intake through diet and supplements
* Avoiding smoking and excessive alcohol
* Fall prevention strategies  
  Medications are typically reserved for people at high fracture risk or those progressing toward osteoporosis

## 7. Can osteopenia be reversed?

With appropriate lifestyle changes and, if necessary, medication, bone loss can be slowed or partially reversed, reducing the risk of fractures and progression to osteoporosis

## 8. What lifestyle changes help manage osteopenia?

Engaging in weight-bearing exercises (walking, jogging, dancing), ensuring sufficient calcium and vitamin D intake, quitting smoking, limiting alcohol, and preventing falls at home are key strategies

## 9. What are the risks if osteopenia is left untreated?

Untreated osteopenia increases the risk of fractures, especially in the hip, spine, and wrist. Fractures can lead to pain, disability, and increased mortality, particularly in older adults

## 10. Are there medications for osteopenia?

Medications like bisphosphonates or denosumab are usually prescribed if fracture risk is high or if osteopenia progresses. Some bone-building drugs (romosozumab, teriparatide) are reserved for severe cases. Some medications carry risks and require careful monitoring

## **Genomic Data for Osteopenia**

## Genetic Influence on Osteopenia and Bone Mineral Density (BMD)

* Osteopenia, characterized by low bone mineral density (BMD), has a strong genetic component, as bone density is highly heritable. Studies estimate that 25% to 85% of BMD variation is due to genetic factors[5](https://www.healthline.com/health/is-osteoporosis-genetic)[7](https://www.medicalnewstoday.com/articles/osteoporosis-genetics).
* Family history of osteopenia or osteoporosis significantly increases risk, indicating inherited susceptibility

## Key Genes and Genetic Variants Associated with Bone Density and Osteopenia

* Vitamin D Receptor (VDR) gene: Variants affect calcium absorption and bone metabolism.
* Estrogen Receptor genes (ESR1 and ESR2): Influence bone remodeling, especially relevant in postmenopausal bone loss.
* COL1A1 gene: Encodes type I collagen, a major bone matrix protein; mutations or polymorphisms can reduce bone strength and increase fracture risk.
* BMP2 (Bone Morphogenetic Protein 2): Located on chromosome 20; important for bone and cartilage formation, implicated as a risk locus in osteoporosis and related low bone mass conditions
* STAT1: Involved in bone metabolism regulation.
* DAAM2: Recently associated with decreased bone strength in large population studies

## Polygenic and Multifactorial Nature

* Osteopenia and osteoporosis are polygenic disorders, influenced by multiple genes each contributing modestly to bone mass and fracture risk
* Genetic variants interact with environmental factors like nutrition, physical activity, and hormonal status to determine overall bone health

## **Doctor-Patient Conversation on Osteopenia (De-Identified)**

## Doctor:

Hello! I have your bone density scan results. Would you like to go over them?

## Patient:

Yes, please. I’m a bit worried about my bones.

## Doctor:

Your scan shows that you have osteopenia, which means your bone density is lower than normal but not low enough to be classified as osteoporosis.

## Patient:

Is osteopenia serious? What does it mean for me?

## Doctor:

Osteopenia indicates that your bones are weaker than average, which increases your risk of fractures compared to people with normal bone density. It’s a warning sign that we should take steps to protect your bones.

## Patient:

What causes osteopenia?

## Doctor:

It can be caused by aging, hormonal changes (especially after menopause), insufficient calcium or vitamin D, lack of exercise, smoking, excessive alcohol, and certain medications or medical conditions.

## Patient:

What can I do to prevent it from getting worse?

## Doctor:

Lifestyle changes are very important. This includes a balanced diet rich in calcium and vitamin D, regular weight-bearing and muscle-strengthening exercise, avoiding smoking and limiting alcohol, and fall prevention strategies.

## Patient:

Do I need medication?

## Doctor:

Not necessarily at this stage. We usually reserve medication for osteoporosis or if you have other risk factors for fractures. However, if your bone density worsens or you have fractures, we may consider treatment.

## Patient:

How often should I have bone density scans?

## Doctor:

Typically, we repeat the scan every 1 to 2 years to monitor your bone density and adjust management if needed.

## Patient:

Are there symptoms I should watch for?

## Doctor:

Osteopenia itself usually doesn’t cause symptoms. But if you experience sudden back pain, height loss, or fractures, please seek medical attention promptly.

## Patient:

Thank you, doctor. What’s the next step?

## Doctor:

I’ll provide you with guidance on diet and exercise, and we’ll schedule follow-up scans. If you have any questions or concerns, don’t hesitate to contact me.

## Patient:

I appreciate your help.

## Doctor:

You’re welcome. Together, we’ll work to keep your bones healthy.

REFERENCES

https://www.webmd.com/osteoporosis/osteopenia-early-signs-of-bone-loss

[Osteopenia Medications and Treatment](https://www.verywellhealth.com/osteopenia-medications-and-treatment-2223517)

<https://my.clevelandclinic.org/health/diseases/21855-osteopenia>

<https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/bone-densitometry>

<https://www.niams.nih.gov/health-topics/bone-mineral-density-tests-what-numbers-mean>

**AVASCULAR NECROSIS (OSTEONECIOSIS)**

**DEFINITION AND DESCRIPTION**

Avascular necrosis is the death of bone tissue due to a lack of blood supply. Also called osteonecrosis, it can lead to tiny breaks in the bone and cause the bone to collapse. The process usually takes months to years.

A broken bone or dislocated joint can stop the blood flow to a section of bone. Avascular necrosis is also associated with long-term use of high-dose steroid medications and too much alcohol.

Anyone can be affected. But the condition is most common in people between the ages of 30 and 50.

## **Causes**

Avascular necrosis occurs when blood flow to a bone is interrupted or reduced. Reduced blood supply can be caused by:

* **Joint or bone trauma.** An injury, such as a dislocated joint, might damage nearby blood vessels. Cancer treatments involving radiation also can weaken bone and harm blood vessels.
* **Fatty deposits in blood vessels.** The fat (lipids) can block small blood vessels. This can reduce blood flow to bones.
* **Certain diseases.** Medical conditions, such as sickle cell anemia and Gaucher's disease, also can lessen blood flow to bone.

Sometimes the cause of avascular necrosis not brought on by trauma isn't fully understood. Genetics combined with overuse of alcohol, certain medications and other diseases likely play a role.

## **Risk factors**

Risk factors for developing avascular necrosis include:

* **Trauma.** Injuries, such as hip dislocation or fracture, can damage nearby blood vessels and reduce blood flow to bones.
* **Steroid use.** Use of high-dose corticosteroids, such as prednisone, is a common cause of avascular necrosis. The reason is unknown, but some experts believe that corticosteroids can increase lipid levels in the blood, reducing blood flow.
* **Drinking too much alcohol.** Having several alcoholic drinks a day for several years also can cause fatty deposits to form in blood vessels.
* **Bisphosphonate use.** Long-term use of medications to increase bone density might contribute to developing osteonecrosis of the jaw. This rare complication has occurred in some people treated with high doses of these medications for cancers, such as multiple myeloma and metastatic breast cancer.
* **Certain medical treatments.** Radiation therapy for cancer can weaken bone. Organ transplants, especially kidney transplants, also are associated with avascular necrosis.

Medical conditions associated with avascular necrosis include:

* Pancreatitis
* Gaucher's disease
* HIV/AIDS
* Systemic lupus erythematosus
* Sickle cell anemia
* Decompression sickness, also known as divers' disease or the bends
* Certain types of cancer, such as leukemia

## **Symptoms**

Some people have no symptoms in the early stages of avascular necrosis. As the condition worsens, affected joints might hurt only when putting weight on them. Eventually, you might feel the pain even when you're lying down.

Pain can be mild or severe. It usually develops gradually. Pain associated with avascular necrosis of the hip might center on the groin, thigh or buttock. Besides the hip, the shoulder, knee, hand and foot can be affected.

Some people develop avascular necrosis on both sides, such as in both hips or in both knees.

## **Diagnosis**

During a physical exam, a health care provider will press around your joints, checking for tenderness. They might also move the joints through different positions to see if the range of motion is lessened.

### **Imaging tests**

Many conditions can cause joint pain. Imaging tests can help pinpoint the source of pain. Tests may include:

* **X-rays.** They can reveal bone changes that occur in the later stages of avascular necrosis. In the condition's early stages, X-rays usually don't show any problems.
* **MRI and CT scan.** These tests produce detailed images that can show early changes in bone that might indicate avascular necrosis.
* **Bone scan.** A small amount of radioactive material is injected into a vein. This tracer travels to the parts of bones that are injured or healing. It shows up as bright spots on the imaging plate.

## **Treatment**

The goal is to prevent further bone loss.

### **Medications**

In the early stages of avascular necrosis, certain medications may help ease symptoms:

* **Nonsteroidal anti-inflammatory drugs (NSAIDs).** Over-the-counter medications like ibuprofen (Advil, Motrin IB, others) or naproxen sodium (Aleve) might help relieve pain associated with avascular necrosis. Stronger nonsteroidal anti-inflammatory drugs (NSAIDs) are available by prescription.
* **Osteoporosis drugs.** These types of medications might slow the progression of avascular necrosis, but the evidence is mixed.
* **Cholesterol-lowering drugs.** Reducing the amount of cholesterol and fat in the blood might help prevent the vessel blockages that can cause avascular necrosis.
* **Medications that open blood vessels.** Iloprost (Ventavis) might increase blood flow to the affected bone. More study is needed.
* **Blood thinners.** For clotting disorders, blood thinners, such as warfarin (Jantoven), might prevent clots in the vessels feeding the bones.

### **Therapy**

Your health care provider might recommend:

* **Rest.** Restricting physical activity or using crutches for several months to keep weight off the joint might help slow the bone damage.
* **Exercises.** A physical therapist can teach exercises to help maintain or improve the range of motion in the joint.
* **Electrical stimulation.** Electrical currents might encourage the body to grow new bone to replace the damaged bone. Electrical stimulation can be used during surgery and applied directly to the damaged area. Or it can be administered through electrodes attached to the skin.

### **Surgical and other procedures**

Because most people don't develop symptoms until avascular necrosis is advanced, your health care provider might recommend surgery. The options include:

* **Core decompression.** A surgeon removes part of the inner layer of bone. Besides reducing pain, the extra space inside the bone triggers the production of healthy bone tissue and new blood vessels.
* **Bone transplant (graft).** This procedure can help strengthen the area of bone affected by avascular necrosis. The graft is a section of healthy bone taken from another part of the body.
* **Bone reshaping (osteotomy).** A wedge of bone is removed above or below a weight-bearing joint, to help shift weight off the damaged bone. Bone reshaping might help postpone joint replacement.
* **Joint replacement.** If the affected bone has collapsed or other treatments aren't helping, surgery can replace the damaged parts of the joint with plastic or metal parts.
* **Regenerative medicine treatment.** Bone marrow aspirate and concentration is a newer procedure that might help avascular necrosis of the hip in early stages. During surgery, the surgeon removes a sample of dead hip bone and inserts stem cells taken from bone marrow in its place. This might allow new bones to grow. More study is needed.

## **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

Examples: Ibuprofen (Advil, Motrin), Naproxen (Aleve), Diclofenac  
Use: Pain relief and inflammation reduction in early stages.  
Side Effects:

* Gastrointestinal irritation, ulcers, bleeding
* Kidney dysfunction with long-term use
* Increased cardiovascular risk (rare)
* Allergic reactions

## 2. Bisphosphonates

Examples: Alendronate (Fosamax), Risedronate  
Use: Experimental/Off-label use to slow bone loss by inhibiting osteoclast activity, potentially preventing subchondral collapse.  
Side Effects:

* Gastrointestinal upset (esophagitis, gastritis)
* Osteonecrosis of the jaw (rare)
* Atypical femoral fractures (rare)
* Hypocalcemia

## 3. Cholesterol-Lowering Drugs (Statins)

Examples: Atorvastatin, Simvastatin  
Use: May help prevent vessel blockages causing AVN by lowering cholesterol and improving endothelial function.  
Side Effects:

* Muscle pain or weakness (myopathy)
* Liver enzyme elevation
* Increased risk of diabetes (rare)
* Gastrointestinal symptoms

## 4. Blood Thinners (Anticoagulants)

Examples: Warfarin (Jantoven), Enoxaparin (Lovenox)  
Use: Used when AVN is caused by clotting disorders to prevent further thrombosis in vessels supplying bone.  
Side Effects:

* Increased bleeding risk
* Bruising
* Warfarin-specific: Requires frequent INR monitoring, dietary restrictions
* Heparin-induced thrombocytopenia (rare)

## 5. Vasodilators

Example: Iloprost (Ventavis)  
Use: Experimental use to increase blood flow to affected bone areas and promote healing.  
Side Effects:

* Headache
* Flushing
* Hypotension
* Nausea

## 6. Aspirin (Acetylsalicylic Acid)

Use: Sometimes used for its antiplatelet effects to improve blood flow.  
Side Effects:

* Gastrointestinal irritation and bleeding
* Allergic reactions
* Increased bleeding risk

## 7. Other Pain Relievers

* Acetaminophen (Tylenol) may be used for mild pain but does not affect disease progression.
* Opioids may be prescribed for severe pain but carry risk of dependence and side effects like sedation, constipation.

## **Complications**

Untreated, avascular necrosis worsens. Eventually, the bone can collapse. Avascular necrosis also causes bone to lose its smooth shape, possibly leading to severe arthritis.

## **Prevention**

To reduce the risk of avascular necrosis and improve general health:

* **Limit alcohol.** Heavy drinking is one of the top risk factors for developing avascular necrosis.
* **Keep cholesterol levels low.** Tiny bits of fat are the most common substance blocking blood supply to bones.
* **Monitor steroid use.** Make sure your health care provider knows about your past or present use of high-dose steroids. Steroid-related bone damage appears to worsen with repeated courses of high-dose steroids.
* **Don't smoke.** Smoking narrows blood vessels, which can reduce blood flow.

## **Outlook / Prognosis**

Treatment can slow the progress of avascular necrosis, but there is no cure. Most people who have avascular necrosis eventually have surgery, including joint replacement. People who have avascular necrosis can also develop severe osteoarthritis.

### **When should I call my healthcare provider?**

Avascular necrosis is a progressive condition that gets worse over time. If you have avascular necrosis, you should monitor your symptoms, such as pain and mobility.

You should call your healthcare provider if you have:

* Pain that doesn't improve with rest or pain relievers.
* Pain that makes walking or movement difficult.
* Unexplained limping.

**PROCEDURES AND TIMELINES**

## Non-Surgical Management (Early Stage)

* Rest and Activity Modification:
  + Restrict weight-bearing on affected joint using crutches or braces.
  + Timeline: Several months (3–6 months) to slow progression.
* Medications:
  + NSAIDs for pain relief.
  + Bisphosphonates or vasodilators (experimental).
* Physical Therapy:
  + Maintain joint mobility and strengthen surrounding muscles.
* Electrical Stimulation:
  + May promote bone growth; used adjunctively.
* Regenerative Medicine:
  + Bone marrow aspirate concentrate (BMAC) or stem cell therapy to promote bone repair, especially in early stages.
  + Timeline: Single or repeated injections; ongoing evaluation over months.

## 2. Core Decompression Surgery

* Description:
  + Most common surgical procedure for early-stage AVN (pre-collapse).
  + Drilling one or more channels into necrotic bone to reduce intraosseous pressure, improve blood flow, and stimulate healing.
  + Often combined with bone grafting or stem cell implantation.
* Timeline:
  + Performed once diagnosis is confirmed in the early stage.
  + Recovery involves partial weight-bearing for 6–12 weeks; full recovery may take 3–6 months.
* Effectiveness:
  + Best outcomes when lesions are small and before bone collapse.

## 3. Bone Grafting

* Non-Vascularized Grafts:
  + Bone grafts (autograft, allograft, or synthetic) placed into decompression channels to support bone regeneration.
* Vascularized Bone Grafts:
  + Transplantation of living bone with its blood supply to replace necrotic bone, used in advanced cases.
* Timeline:
  + Surgery followed by several months of rehabilitation.
  + Used in conjunction with core decompression or osteotomy.

## 4. Osteotomy

* Description:
  + Surgical realignment of bone to shift weight-bearing from damaged to healthy bone.
  + Used in cases with limited necrosis and no joint collapse.
* Timeline:
  + Recovery and rehabilitation may take 3–6 months.
  + Aims to delay joint replacement.

## 5. Total Joint Replacement (Arthroplasty)

* Indication:
  + Advanced AVN with femoral head collapse or secondary arthritis.
* Procedure:
  + Removal of damaged bone and replacement with prosthetic joint components.
* Timeline:
  + Surgery followed by an inpatient stay of a few days.
  + Rehabilitation and return to normal activities typically within 3–6 months.
* Considerations:
  + Most definitive treatment but may require revision surgery over time.

## 6. Emerging and Adjunctive Therapies

* Stem Cell Therapy:
  + Injection of mesenchymal stem cells into the necrotic area to promote bone regeneration.
* Bone Marrow Aspirate Concentrate (BMAC):
  + Concentrated stem cells and growth factors injected after core decompression.
* Electrical Stimulation:
  + Used preoperatively or non-invasively to encourage bone healing.

## **Differential Diagnoses**

## 1. Inflammatory Synovitis

* Inflammation of the synovial membrane causing joint pain and swelling.
* Can mimic early AVN symptoms but typically presents with more joint effusion and systemic inflammatory signs.

## 2. Complex Regional Pain Syndrome (CRPS)

* A chronic pain condition often following trauma or surgery.
* Characterized by severe pain, swelling, and changes in skin color and temperature, which can resemble AVN pain.

## 3. Osteoarthritis (OA)

* Degenerative joint disease causing joint space narrowing, pain, and stiffness.
* OA typically affects older patients and shows characteristic radiographic changes distinct from AVN.

## 4. Soft Tissue Trauma

* Injuries such as labral tears (especially in the hip) can cause localized pain similar to AVN.
* History of trauma and MRI findings help differentiate.

## 5. Bone Marrow Edema Syndrome (Transient Osteopenia)

* Self-limiting condition causing bone pain and marrow edema on MRI.
* Unlike AVN, it usually resolves spontaneously without bone collapse.

## 6. Neoplastic Bone Conditions

* Primary bone tumors or metastases can cause bone pain and radiographic changes.
* Biopsy and imaging help distinguish from AVN.

## 7. Osteomyelitis

* Infection of bone presenting with pain, fever, and sometimes swelling.
* Laboratory markers of infection and imaging assist in differentiation.

## 8. Osteoporosis

* Generalized bone loss causing fractures and pain, but without localized bone death characteristic of AVN.

## 9. Femoral Neck Fracture and Stress Fracture

* Can present with hip pain and limited mobility; history and imaging differentiate these from AVN.

## 10. Other Specific Conditions

* Legg–Calvé–Perthes disease: Pediatric AVN of the femoral head.
* Osteopetrosis: Bone sclerosis that can mimic AVN radiographically.
* Sickle Cell Disease: Causes bone infarcts that may resemble AVN.
* Hip Dislocation or Tendonitis: Cause hip pain but have distinct clinical and imaging features.

## **Epidemiology**

### Frequency

United States

The frequency of AVN depends on the site involved. The most common site is the hip; other locations include the carpals, talus, femur, metatarsal, mandible, and humerus. In the United States, approximately 15,000 new cases of AVN are reported each year. AVN accounts for more than 10% of total hip replacement surgeries performed in the United States. Osteonecrosis of the jaw associated with bisphosphonate has also been well studied and reported.Most patients with osteonecrosis of the jaw also had an ongoing malignancy and/or had undergone a recent dental procedure.

International

In most countries, the incidence and prevalence of AVN are not well reported. A Japanese survey estimated that 2500-3300 cases of AVN of the hip occur each year; of these, 34.7% were due to corticosteroid use, 21.8% to alcohol abuse, and 37.1% to idiopathic mechanisms.

### Race-, sex-, and age-related demographics

AVN has no racial predilection except for cases associated with sickle cell disease and hemoglobin S and SC disease, which predominantly occur in people of African and Mediterranean descent.

With the exception of AVN associated with systemic lupus erythematosus, AVN is more common in men, with an overall male-to-female ratio of 8:1.

AVN is a disease of middle age that most often occurs during the fourth or fifth decade of life and is bilateral in more than half of cases.

| Stage | Clinical and Laboratory Findings |
| --- | --- |
| Stage 0 | Patient is asymptomatic.  Radiography findings are normal.  Histology findings demonstrate osteonecrosis. |
| Stage I | Patients may or may not be symptomatic.  Radiography and CT scan findings are unremarkable.  AVN is considered likely based on MRI and bone scan results (may be subclassified by extent of involvement [see below]).  Histology findings are abnormal. |
| Stage II | Patient is symptomatic.  Plain radiography findings are abnormal and include osteopenia, osteosclerosis, or cysts.  Subchondral radiolucency is absent.  MRI findings are diagnostic. |
| Stage III | Patient is symptomatic.  Radiographic findings include subchondral lucency (crescent sign) and subchondral collapse. |

## **Genomic Data**

## 1. COL2A1 Gene Mutations

* The COL2A1 gene, encoding type II collagen, is strongly implicated in inherited AVN, particularly avascular necrosis of the femoral head (ANFH).
* Mutations such as c.3508G>A (p.G1170S) and other missense mutations disrupt the Gly-X-Y triple-helix structure of collagen, impairing cartilage integrity and predisposing to bone necrosis.
* These mutations are inherited in an autosomal dominant manner and have been identified in multiple families with familial AVN and related collagenopathies like Legg-Calvé-Perthes disease.
* Pathological findings include abnormal collagen fibrils in the epiphyseal cartilage, affecting bone strength and repair.

## 2. Genes Involved in Angiogenesis and Vascular Function

* VEGF (Vascular Endothelial Growth Factor): Critical regulator of angiogenesis and bone repair; altered expression correlates with AVN progression.
* Experimental therapies involving VEGF gene transfection improve angiogenesis and bone healing in animal models.
* eNOS (endothelial Nitric Oxide Synthase) gene polymorphism (T-786C): Leads to reduced nitric oxide production causing vasoconstriction, platelet aggregation, and impaired angiogenesis, contributing to AVN pathogenesis.

## 3. Coagulation and Thrombophilia-Related Genes

* Mutations linked to hypercoagulability increase AVN risk by promoting microvascular thrombosis and ischemia.
* Notable genes:
  + Factor V Leiden (F5 gene mutation)
  + Prothrombin 20210A mutation
  + Genes involved in alcohol metabolism such as ADH2, ADH3, ALDH2, and CYP450E1 may contribute via toxic metabolite accumulation.
* These mutations are associated with idiopathic and secondary AVN, especially in patients with clotting disorders or alcohol abuse.

## 4. Polymorphisms Associated with AVN in Sickle Cell Disease (SCD)

* Polymorphisms in BMP6 (Bone Morphogenetic Protein 6), Klotho (KL), and Annexin A2 (ANXA2) genes have been linked to increased AVN risk in SCD patients.
* These genes relate to bone growth, vascular function, and coagulation, influencing susceptibility to bone infarcts.
* Polymorphisms in MTHFR and other thrombophilia-related genes show inconsistent associations.

## 5. Other Genetic Factors

* Genetic variants affecting lipid metabolism, oxidative stress, and endothelial function may modulate AVN risk, though data are less definitive.
* Environmental factors like alcohol, corticosteroids, and trauma interact with genetic predisposition.

## **Predefined Question and Answer**

## 1. What is avascular necrosis?

Avascular necrosis (AVN), also called osteonecrosis, is the death of bone tissue due to a lack of blood supply. It commonly affects the ends of long bones, especially the femoral head, and can lead to bone collapse and joint dysfunction

## 2. What causes avascular necrosis?

AVN is caused by interrupted or reduced blood flow to the bone. Common causes include bone or joint trauma (fractures, dislocations), long-term use of high-dose corticosteroids, excessive alcohol consumption, fatty deposits blocking blood vessels, certain diseases (sickle cell anemia, lupus, pancreatitis), radiation therapy, and clotting disorders

## 3. What are the symptoms of avascular necrosis?

Symptoms often develop gradually and include joint pain that worsens with activity and limited range of motion. Early stages may be asymptomatic, with symptoms appearing as the bone deteriorates

## 4. How is avascular necrosis diagnosed?

Diagnosis involves clinical evaluation and imaging. X-rays may be normal early on; MRI is the most sensitive test to detect early bone changes. Other imaging such as CT or bone scans may be used. Laboratory tests help rule out other causes

## 5. What treatments are available for avascular necrosis?

* Medications: NSAIDs for pain, cholesterol-lowering drugs, blood thinners for clotting disorders, and vasodilators like iloprost may be used in early stages
* Therapies: Rest, physical therapy, and electrical stimulation can help maintain joint function
* Surgery: Core decompression, bone grafting, osteotomy, or total joint replacement may be necessary depending on disease stage

## 6. Can avascular necrosis be prevented?

Prevention includes limiting alcohol intake, avoiding smoking, monitoring and minimizing corticosteroid use, controlling cholesterol levels, and managing underlying diseases that increase risk

## 7. What is the prognosis of avascular necrosis?

AVN is progressive and may lead to joint collapse and arthritis if untreated. Early diagnosis and treatment can slow progression, but many patients eventually require surgery

## 8. Who is most at risk for avascular necrosis?

People aged 30–50 years, those with a history of trauma, long-term steroid use, heavy alcohol consumption, clotting disorders, or certain systemic diseases are at higher risk

## 9. How long does it take for avascular necrosis to progress?

The process usually takes months to years, with symptoms and bone damage worsening over time

## 10. When should I see a doctor about joint pain?

If you experience persistent joint pain, especially with limited motion or after injury, seek medical evaluation to rule out AVN or other serious conditions

REFERENCES

https://my.clevelandclinic.org/health/diseases/14205-avascular-necrosis-osteonecrosis#outlook-prognosis <https://emedicine.medscape.com/article/333364-treatment>

[Avascular necrosis (osteonecrosis) - Diagnosis & treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/avascular-necrosis/diagnosis-treatment/drc-20369863)

# **Developmental dysplasia of the hip**

# **DEFINITION AND DESCRIPTION**

Developmental dysplasia of the hip (DDH) is a condition where the "ball and socket" joint of the hip does not properly form in babies and young children.

It's sometimes called congenital dislocation of the hip, or hip dysplasia.

The hip joint attaches the thigh bone (femur) to the pelvis. The top of the femur (femoral head) is rounded, like a ball, and sits inside the cup-shaped hip socket.

In DDH, the socket of the hip is too shallow, and the femoral head is not held tightly in place, so the hip joint is loose. In severe cases, the femur can come out of the socket (dislocate).

DDH may affect 1 or both hips, but it's more common in the left hip. It's also more common in:

* girls
* firstborn children
* families where there have been childhood hip problems (parents, brothers or sisters)
* babies born in the breech position (feet or bottom downwards) after 28 weeks of pregnancy

Without early treatment, DDH may lead to:

* problems moving around, for example a limp
* pain
* osteoarthritis of the hip and back

With early diagnosis and treatment, children are less likely to need surgery, and more likely to develop normally.

## **causes of DDH**

A combination of things may lead to DDH. It may be partly genetic. DDH tends to run in families. It may also be partly environmental, such as:

* The baby’s response to the mother’s hormones during pregnancy
* A tight uterus that makes it hard for the fetus to move around
* A breech delivery, when the baby is born bottom-first instead of headfirst

## **Risk factors for DDH**

First-born babies are at higher risk because the uterus is small and there is limited room for the baby to move. That may affect how the hip develops. Other risk factors are:

* Family history of DDH, or very flexible ligaments
* Position of the baby in the uterus, especially the breech position
* Other orthopedic problems, such as clubfoot
* Female sex. DDH is more common in girls than boys.

## **symptoms of DDH in a child**

The following are the most common symptoms of DDH. Symptoms can occur a bit differently in each baby. They can include:

* The leg may appear shorter on the side of the dislocated hip
* The leg on the side of the dislocated hip may turn outward
* The folds in the skin of the thigh or buttocks may appear uneven
* The space between the legs may look wider than normal

The symptoms of DDH may seem like other health problems of the hip. Make sure your baby sees his or her healthcare provider for a diagnosis.

## **Diagnosing DDH**

Your baby's hips will be checked as part of the newborn physical screening examination within 72 hours of being born, and again at 6 to 8 weeks of age.

The examination involves gently moving your baby's hip joints to check if there are any problems. It should not cause them any discomfort.

If a doctor, midwife or nurse thinks your baby's hip feels unstable, they should have an ultrasound scan of their hip between 4 and 6 weeks old.

Babies should also have an ultrasound scan of their hip between 4 and 6 weeks old if:

* there have been childhood hip problems in your family
* your baby was born in the breech position (feet or bottom downwards) after 28 weeks of pregnancy

If you have had twins or multiples and 1 of the babies was in the breech position, each baby should have an ultrasound scan of their hips by the time they're 4 to 6 weeks old.

Sometimes a baby's hip stabilises on its own before the scan is due, but they should still be checked to make sure.

## **Treating DDH**

### **Pavlik harness**

Babies diagnosed with DDH early in life are usually treated with a fabric splint called a Pavlik harness.

This secures both of your baby's hips in a stable position and allows them to develop normally.

The harness needs to be worn constantly for 6 to 12 weeks and should not be removed by anyone except a health professional.

The harness may be adjusted during follow-up appointments. Your clinician will discuss your baby's progress with you.

Your hospital will provide detailed instructions on how to look after your baby while they're wearing a Pavlik harness.

This will include information on:

* how to change your baby's clothes without removing the harness – nappies can be worn normally
* cleaning the harness if it's soiled – it still should not be removed, but can be cleaned with detergent and an old toothbrush or nail brush
* positioning your baby while they sleep – they should be placed on their back and not on their side
* how to avoid skin irritation around the straps of the harness – you may be advised to wrap some soft, hygienic material around the bands

Eventually, you may be given advice on removing and replacing the harness for short periods of time until it can be permanently removed.

You'll be encouraged to allow your baby to move freely when the harness is off. Swimming is often recommended.

### **Surgery**

Surgery may be needed if your baby is diagnosed with DDH after they're 6 months old, or if the Pavlik harness has not helped.

The most common surgery is called reduction. This involves placing the femoral head back into the hip socket.

Reduction surgery is done under general anaesthetic and may be done as either:

* closed reduction – the femoral head is placed in the hip socket without making any large cuts
* open reduction – a cut is made in the groin to allow the surgeon to place the femoral head into the hip socket

Your child may need to wear a cast for at least 12 weeks after the operation.

Their hip will be checked under general anaesthetic again after 6 weeks, to make sure it's stable and healing well.

After this investigation, your child will probably wear a cast for at least another 6 weeks to allow their hip to fully stabilise.

Some children may also require bone surgery (osteotomy) during an open reduction, or at a later date, to correct any bone deformities.

## **Late-stage signs of DDH**

The newborn physical screening examination, and the infant screening examination at 6 to 8 weeks, aim to diagnose DDH early.

But sometimes hip problems can develop or show up after these checks.

It's important to contact a GP as soon as possible if you notice your child has developed any of the following symptoms:

* 1 leg cannot be moved out sideways as far as the other when you change their nappy
* 1 leg seems to be longer than the other
* 1 leg drags when they crawl
* a limp or "waddling" walk

Your child will be referred to an orthopaedic specialist in hospital for an ultrasound scan if your doctor thinks there's a problem with their hip.

## **Hip-healthy swaddling**

A baby's hips are naturally more flexible for a short period after birth. But if your baby spends a lot of time tightly wrapped (swaddled) with their legs straight and pressed together, there's a risk this may affect their hip development.

Using hip-healthy swaddling techniques can reduce this risk. Make sure your baby is able to move their hips and knees freely to kick.

**Drug Information and Side Effects**

## 1. Medications Used in DDH Management

## a) Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

* Examples: Ibuprofen (Motrin, Advil), Naproxen (Aleve)
* Purpose:
  + Relieve pain and reduce inflammation associated with hip dysplasia, especially in older children or adults.
  + Improve joint function and comfort during physical therapy or conservative management.
* Common Side Effects:
  + Gastrointestinal irritation, ulcers, or bleeding
  + Kidney function impairment with long-term use
  + Increased cardiovascular risk (rare)
  + Allergic reactions

## b) Intra-articular Corticosteroid Injections (occasionally used in older patients)

* Purpose:
  + Reduce joint inflammation and pain when conservative treatments fail.
  + Provide temporary relief to improve mobility and delay surgery.
* Common Side Effects:
  + Local pain or swelling at injection site
  + Infection risk (rare)
  + Potential cartilage damage with repeated injections
  + Elevated blood sugar levels temporarily

## 2. Non-Pharmacologic Mainstays of DDH Treatment

* Pavlik Harness: Soft brace used in infants up to ~4–6 months to hold hips in correct position.
* Casting (Spica Cast): Used in older infants or after surgical reduction to maintain hip position.
* Surgical Procedures: Open or closed reduction, osteotomies (e.g., periacetabular osteotomy) to correct bone alignment.

## **Procedures and Timelines**

## Birth to 3 Months

* Pavlik Harness:
  + First-line treatment for unstable but reducible hips.
  + Positions hips in flexion and abduction to promote normal joint development.
  + Worn full-time (23 hours/day) for about 10–12 weeks.
  + Follow-up with ultrasound every 2 weeks to monitor hip stability and harness adjustment.
  + If the harness fails or hips are irreducible, proceed to surgical intervention.
* Frejka Pillow:
  + Alternative abduction device, less commonly used.
* Observation:
  + Stable or mildly dysplastic hips may be observed with close follow-up.

## 3 to 6 Months

* Continued Use of Abduction Devices:
  + Pavlik harness or other braces (Von Rosen splint, Ilfeld orthosis) may be used.
* Closed Reduction and Spica Casting:
  + Indicated if the harness fails or hips remain dislocated.
  + Closed reduction performed under general anesthesia.
  + Followed by application of a spica cast for 1 month per month of age, up to a maximum of 6 months.
  + Cast changes every 6 weeks due to child growth.
* Pre-reduction Traction:
  + Used by some surgeons for 2–4 weeks before reduction to relax soft tissues.

## 6 Months to 1–2 Years

* Closed Reduction and Spica Casting:
  + Still possible but less successful than in younger infants.
* Open Reduction Surgery:
  + Performed if closed reduction fails or hips are irreducible.
  + Approaches: anterior-lateral (most common) or medial.
  + May be combined with soft tissue release and ligament repair.
* Spica Casting:
  + Postoperative immobilization for about 3 months.

## 1.5 to 6 Years

* Open Reduction with Osteotomies:
  + Required for older children with persistent dysplasia or dislocation.
  + Pelvic osteotomy (to reshape acetabulum) and femoral osteotomy (to realign femur) often performed.
  + Ligament tightening may also be done.
* Postoperative Casting:
  + Typically 6–8 weeks in a body cast.
* Longer Recovery:
  + Rehabilitation and monitoring for hip development continue.

## Over 6 Years

* Treatment becomes more complex and may involve reconstructive surgeries or joint replacement in severe cases.

### **Hip dysplasia complications**

Adults and babies with hip dysplasia are more likely to experience hip dislocation. Usually, hip dislocations only happen during serious traumas like car accidents or severe falls. But if you have hip dysplasia, your hip joint is naturally weaker than it should be, which can increase the risk of dislocation. Having hip dysplasia can also cause looser than usual muscles and ligaments around your hip.

A healthcare provider will suggest ways to prevent injuries and reduce the risk you experience a dislocation.

Other hip dysplasia complications can include:

* **Hip labral tears**: Damage to the cartilage inside your hip joint.
* **Osteoarthritis**: Wear and tear arthritis that develops when your joint cartilage is worn away over time.
* **Unstable hip joints**: Chronic (recurring) pain from your hip joint not fitting together correctly.

## **Outlook / Prognosis**

Most babies with hip dysplasia have no long-term effects if it’s treated early. They usually need to wear a brace for a few months to help their hips develop correctly, but after that should have no issues or complications.

Adults with hip dysplasia can usually return to all their activities once their healthcare provider says it’s safe.

**Prevention**

You can’t prevent your child from being born with hip dysplasia. You also can’t prevent it in yourself. It happens on its own when your hips are shaped differently than usual.

Talk to your healthcare provider about protecting your child’s hips while they’re developing. They can give you tips to prevent putting too much stress on your baby’s joints.

### **When should I see my healthcare provider?**

Visit a healthcare provider if you’re having hip pain that doesn’t get better after a few days of rest or if your child has any symptoms of hip dysplasia.

## **Epidemiology**

## Prevalence and Incidence

* The pooled prevalence of DDH in infants is approximately 1.4% (14 per 1000 infants) globally, based on a meta-analysis of 65 studies including over 3.4 million infants
* The incidence rate varies by region and study, ranging from about 1 to 11.6 per 1000 live births:
  + A study reported an incidence of 11.58 per 1000 live births in a cohort of 8031 infants
  + Other reports indicate incidence rates around 4.6 to 5 per 1000 live births in South America, and about 1.05 per 1000 live births in Oman
  + Incidence rates of approximately 1.19% (11.9 per 1000) were found in a Chinese population screened by ultrasound
* Some studies report a slight upward trend in overall DDH prevalence over the past three decades, though the prevalence of hip dysplasia (a subset of DDH) has decreased

## Gender Differences

* DDH is more common in females than males, with female-to-male ratios ranging from about 2:1 to 4.5:1 across studies
* The pooled prevalence in girls is approximately 1.46%, compared to 0.66% in boys

## Laterality and Bilaterality

* DDH may affect one or both hips:
  + Bilateral involvement occurs in about 45% of cases in some studies[4](https://journals.lww.com/md-journal/fulltext/2024/02090/incidence_and_characteristics_of_developmental.44.aspx).
  + Left hip involvement is more common than right

## Age at Diagnosis

* Diagnosis often occurs in infancy but can be delayed:
  + Mean age at diagnosis in some cohorts was around 22.8 months, with earlier diagnosis associated with unilateral cases and presence of risk factors

## **Differential Diagnoses**

* + Transient hip synovitis
  + Septic arthritis
  + Legg-Calvé-Perthes disease
  + Neuromuscular hip subluxation
  + Congenital femoral deficiency
  + Hip fractures or trauma

## **Question and Answer Set**

## 1. What is developmental dysplasia of the hip (DDH)?

DDH is a condition where the hip joint does not form properly in infants and young children. The ball of the thigh bone (femoral head) may be loose in the socket or completely out of it, leading to instability or dislocation of the hip joint

## 2. What causes DDH?

DDH is mostly due to loose ligaments around the hip joint developing around birth. It is not caused by anything during pregnancy or delivery. Genetic factors and in utero positioning also play a role. Risk factors include female sex, breech presentation, firstborn status, family history, and associated deformities like torticollis or clubfoot

## 3. Can DDH be diagnosed before birth?

No, DDH cannot be diagnosed prenatally. It is not detectable on prenatal ultrasounds and usually develops or is recognized after birth

## 4. What are the signs of DDH in infants?

Signs vary by age but may include uneven buttock creases, extra skin folds on the upper thigh, limited hip abduction (difficulty spreading the legs), leg length differences, and in older children, a waddling or uneven gait. However, even complete dislocation is usually painless before adolescence

## 5. How is DDH screened and diagnosed?

Screening involves physical examination using the Ortolani and Barlow maneuvers in infants up to 3 months old. Limited hip abduction after 8 weeks is a sensitive sign. Ultrasound is used for infants under 6 months, and X-rays for older infants. Referral to an orthopedist is recommended for dislocatable or dislocated hips or persistent equivocal findings

## 6. What is the treatment for DDH?

Treatment depends on age and severity. For infants under 6 months, the Pavlik harness is commonly used to hold the hips in place. Older infants or those who fail harness treatment may require closed or open reduction and casting. Surgery with osteotomies may be needed for older children or complex cases

## 7. What happens if DDH is untreated?

Untreated DDH can lead to problems with walking, pain, limb length discrepancy, early hip osteoarthritis, and chronic disability

## 8. Can children with DDH lead normal lives?

Yes, with early diagnosis and appropriate treatment, most children with DDH develop normally and can participate fully in physical activities and sports

## 9. Is DDH more common in boys or girls?

DDH is more common in girls, with female-to-male ratios ranging from about 2:1 to 4.5

## 10. Can DDH affect one or both hips?

DDH can affect one or both hips. Bilateral involvement occurs in roughly 45% of cases. The left hip is more commonly affected than the right

## **Doctor-Patient Conversation**

## Doctor:

Hello! I understand you’re here to discuss your child’s hip screening results?

## Parent:

Yes, doctor. I’m worried because the nurse mentioned something about my baby’s hip not being quite right.

## Doctor:

I see. Developmental Dysplasia of the Hip, or DDH, means that the hip joint hasn’t developed normally. It can range from mild looseness to complete dislocation of the hip.

## Parent:

What causes DDH?

## Doctor:

Several factors can contribute, including family history, breech position during pregnancy, firstborn status, and being female. Sometimes it happens without a clear cause.

## Parent:

How do you diagnose DDH?

## Doctor:

In infants, we use physical exams like the Barlow and Ortolani tests. Ultrasound imaging is the best way to assess the hip joint in babies under 6 months. For older children, X-rays are used.

## Parent:

What treatment does my baby need?

## Doctor:

Treatment depends on the baby’s age and severity. For newborns and infants, a harness called a Pavlik harness is often used to keep the hip in the correct position and encourage normal development. Older infants or children may need casting or surgery.

## Parent:

Is the Pavlik harness safe? Will it hurt my baby?

## Doctor:

The harness is generally safe and well-tolerated. It keeps the hips stable while allowing movement. We monitor closely to avoid complications like pressure sores or nerve issues.

## Parent:

What happens if DDH is not treated?

## Doctor:

Untreated DDH can lead to hip pain, limping, and early arthritis later in life. Early treatment usually results in excellent outcomes.

## Parent:

How long will the treatment last?

## Doctor:

The harness is usually worn full-time for 6 to 12 weeks, with regular follow-ups to check progress. Treatment duration varies based on response.

## Parent:

What should I watch for during treatment?

## Doctor:

Look for skin irritation, redness, or swelling. Also, ensure the harness fits properly and follow all care instructions. We’ll guide you through this.

## Parent:

Thank you, doctor. What’s the next step?

## Doctor:

We’ll start treatment promptly and schedule regular appointments to monitor your baby’s hips. Please contact us if you have any concerns.

## Parent:

I appreciate your help.

## Doctor:

You’re welcome. We’re here to support you and your baby every step of the way.

REFERENCES

https://emedicine.medscape.com/article/86930-overview?form=fpf <https://my.clevelandclinic.org/health/diseases/17903-hip-dysplasia>

<https://www.aafp.org/pubs/afp/issues/2014/1215/p843.html>

### **Arthrogryposis (arthrogryposis multiplex congenita)**

**DEFINITION AND DESCRIPTION**

Arthrogryposis (arthrogryposis multiplex congenita, AMC) is a characteristic of over 300 disorders, including muscular dystrophy and trisomy 18 (Edwards syndrome). It refers to the occurrence of more than one contracture at birth. A contracture is a congenital anomaly that causes permanent tightening of your baby’s muscles, skin and tendons that make their joints short and stiff. Arthrogryposis means crooking (bending) of the joint. “Artho” means joint, and “gryposis” means crooking.

People with arthrogryposis are born with joints that are difficult to move — the joints might be fixed, curved or straight joints frozen in place. Your joints are where two or more bones connect. Examples of joints in your body include your:

* Wrists.
* Hips.
* Knees.
* Neck.

Babies with arthrogryposis are born with several distinctive features, including:

* Sloped shoulders rotated toward the center of their body.
* Extended elbows.
* Curled wrists and fingers.
* Dislocated hips.
* Extended knees.
* Feet pointed downward and inward.
* Their spine curved sideways.

### **Types of arthrogryposis**

There are a couple of types of arthrogryposis, including:

* **Amyoplasia** is when contractures happen in your limbs.
* **Distal arthrogryposis** is when the contractures happen in your hands and feet but not your larger joints.

Arthrogryposis is uncommon. It occurs in 1 in 3,000 live births.

### **Is arthrogryposis (arthrogryposis multiplex congenita) genetic or hereditary?**

Arthrogryposis is congenital, meaning the symptoms begin before birth. The cause of arthrogryposis is often unknown. But genetic diseases might cause it. Experts have identified more than 400 altered (mutated) genes that affect arthrogryposis, and arthrogryposis is linked to over 35 genetic disorders.

### **Arthrogryposis and an isolated congenital contracture**

Isolated congenital contractures happen only in one area of your body instead of two or more areas. One example of an isolated congenital contracture is clubfoot.

### **What causes arthrogryposis (AMC)?**

In most cases, the exact underlying cause of arthrogryposis is unclear. However, the most common possible causes of arthrogryposis include:

* **Limitation of fetal movement during development** caused by insufficient amniotic fluid, another fetus in the uterus or an unusually shaped uterus. If the fetus can’t move its joints, then excess tissues form around those joints.
* **A disorder in the pregnant woman** like multiple sclerosis. Your risk of multiple sclerosis increases if someone in your family has it.
* **A genetic disorder** like muscular dystrophy.
* **Diseases of your central nervous system,** including Moebius syndrome and spina bifida (meningomyelocele).
* **Diseases of your neuromuscular system,** including myasthenia gravis.
* **Diseases of your connective tissues,** including dysplasia and metatropic dwarfism.

In some cases, the cause of arthrogryposis is likely a combination of genetic and environmental issues.

### **Symptoms of arthrogryposis**

The signs and symptoms of arthrogryposis can vary from person to person. One person’s symptoms might be different or more severe than another’s, even within the same family.

Universal symptoms that everyone with arthrogryposis experiences include:

* A limited ability to move small and large joints.
* An inability to move small and large joints.
* Underdeveloped muscles (hypoplastic muscles).
* Soft, tube-shaped limbs.
* Soft tissue webbing over your joints that keep your joints from moving.

Additional symptoms a majority of people with arthrogryposis experience include:

* Extra slender and fragile long bones in your arms and legs.
* Undescended testes (cryptorchidism).

Symptoms that a smaller percentage of people with arthrogryposis have include:

* Dislocated hips, elbows or knees.
* Problems with the structure of the central nervous system (your brain and spine).
* Problems with the functions of the central nervous system (the way it works).

People with amyoplasia usually don’t have issues with their internal organs or cognitive function. But 10% have issues with their abdomen. Abdominal problems include:

* **Gastroschisis** is a hole in your abdomen.
* **Intestinal atresia** is a blocked intestine.

Leg joints are affected more than any other joint, with arms next in line. Other commonly affected joints include your:

* Shoulders.
* Knees.
* Elbows.
* Ankles.
* Fingers.
* Wrists.
* Toes.
* Hips.
* Jaw.

### **How long does arthrogryposis (AMC) last?**

Arthrogryposis doesn’t go away, but there are some treatments that can improve your quality of life. Physical therapy helps with everyday tasks like getting dressed and drinking water.

**Diagnosis and Tests**

Sometimes, a fetus is diagnosed with arthrogryposis before birth. Routine ultrasounds can reveal atypical limbs that might mean the fetus has arthrogryposis. Usually, your healthcare provider discovers the contractures during the second trimester of pregnancy. Your healthcare provider might recommend genetic counseling.

Your genetic counselor should give you information about the genetic conditions that might affect the fetus. They’ll interview you about your family health history and recommend genetic tests, including:

* Chorionic villus samplings.
* Amniocentesis.

Healthcare providers can also diagnose arthrogryposis after your baby’s born by observing their symptoms and performing tests like:

* **Nerve conduction** measures how quickly nerves transport electrical impulses.
* **Electromyography** records electrical activity in their muscles.
* **Muscle biopsy** is where a small amount of muscle is removed and studied.
* **Genome sequencing** identifies the altered genes.
* **Blood tests** look for gene and chromosome abnormalities.
* **A comparative genomic hybridization (CGH) array** detects chromosome changes.
* **A microarray** analyzes thousands of genes at once.
* **Exome studies** identify gene variations.

Healthcare providers sometimes also rely on imaging tests, including:

* Ultrasound.
* Electromyography (EMG).

Your healthcare provider will create a treatment plan once they identify a possible underlying cause of the arthrogryposis. You can help develop that plan.

## **Management and Treatment**

Although there isn’t a cure for arthrogryposis, treatments can improve your child’s quality of life.

The treatments are different for each person because the probable causes of arthrogryposis are different for everyone.

The most common types of treatment for arthrogryposis include:

* **Casts** that move stiff joints.
* **Physical therapy** that improves joint motion and prevents muscle atrophy (when the muscles waste away).
* **Joint manipulation**, a type of therapy where joints get gently moved.
* **Stretching exercises** increase flexibility and range of motion.
* **Surgery** on ankles, hips, knees, wrists or elbows can also increase the range of motion. The goal is to improve your child’s function by detaching bones from tissues that stop them from moving and forcing the muscles to flex and move. Surgery is rare.

Experts recommend a multidisciplinary approach. Your child might need more than one type of treatment.

### **Do I need to see a specialist?**

You’ll need to see specialists who help with your child’s arthrogryposis. A pediatrician, orthopaedist, neurologist, medical geneticist, rehabilitation physician and physical therapist might all be involved in the care of your child.

**Are there any at-home treatments for arthrogryposis?**

Most people with arthrogryposis need to do physical therapy well into their teenage years. There are some exercises that physical therapists can teach you to do at home.

## **Treatment Drug Information and Side Effects**

## 1. Pharmacologic Treatments in AMC

* Pain Management:
  + NSAIDs (e.g., ibuprofen, naproxen): Used to relieve joint pain and inflammation associated with stiffness or post-surgical recovery.
  + Side Effects: Gastrointestinal irritation, kidney function impairment, cardiovascular risks with long-term use.
* Muscle Relaxants:
  + Occasionally used if muscle spasticity or stiffness contributes to limited mobility.
  + Examples include baclofen or diazepam.
  + Side Effects: Drowsiness, dizziness, weakness, dependence with long-term use.
* Other Medications:
  + No disease-modifying drugs currently exist for AMC.
  + Genetic counseling and supportive care are important.

## 2. Non-Pharmacologic Treatments (Primary Management)

* Physical Therapy:
  + Gentle joint manipulation, stretching exercises, kinesitherapy to improve range of motion and prevent muscle atrophy.
  + Often lifelong therapy starting from infancy.
* Splinting and Casting:
  + Removable splints and serial casting to gradually increase joint mobility and correct deformities.
* Surgical Interventions:
  + Tendon releases, transfers, osteotomies to improve joint positioning and function.
  + Surgery is individualized based on severity and joints involved.
* Assistive Devices:
  + Braces, walkers, wheelchairs to support mobility.

## 3. Side Effects and Considerations

* NSAIDs and Muscle Relaxants:
  + Monitor for gastrointestinal, renal, and central nervous system side effects.
  + Use the lowest effective dose for the shortest duration.
* Physical Therapy and Orthopedic Interventions:
  + Risk of discomfort, skin irritation from splints or casts.
  + Surgical risks include infection, bleeding, nerve injury.
* Long-Term Outlook:
  + AMC is non-progressive but underlying causes may vary.
  + Early and multidisciplinary treatment improves functional outcomes.

## **PROCEDURES AND TIMELINES**

## Early Infancy (Birth to 6 Months)

* Physical Therapy and Joint Manipulation:
  + Begin immediately after diagnosis.
  + Passive stretching and gentle joint mobilization to improve range of motion and prevent muscle atrophy.
  + Daily home exercises taught to caregivers.
  + Duration: Continuous, often lifelong.
* Serial Casting and Splinting:
  + Used to gradually increase joint mobility and correct deformities, especially in ankles, knees, and elbows.
  + Typically applied in weekly or biweekly intervals over several weeks to months.
  + Allows for controlled correction while permitting some movement.
* Orthotic Devices:
  + Removable splints for knees, feet, and wrists to maintain alignment and support muscle function.
  + Worn daily, often for months to years depending on severity.

## 2. Infancy to Toddler Age (6 Months to 2 Years)

* Surgical Interventions:
  + Indicated if conservative management fails to improve joint position or function.
  + Common procedures include:
    - Tendon releases or lengthening to reduce contractures.
    - Tendon transfers to improve muscle function.
    - Osteotomies to correct bone alignment.
  + Surgery is often staged and individualized based on joints involved.
  + Postoperative immobilization with casting or splinting for 4–8 weeks.
  + Followed by intensive rehabilitation.
* Continued Physical Therapy:
  + Focus on strengthening, motor skill development, and functional mobility.
  + Therapy intensity remains high to maximize gains.

## 3. Childhood to Adolescence

* Additional Surgeries:
  + May be required for residual deformities or to improve ambulation.
  + Spinal surgeries (e.g., for scoliosis) may be performed in older children.
  + Non-fusion spinal instrumentation with expandable implants may be used up to ~5 years due to spine stiffness.
* Ongoing Rehabilitation:
  + Lifelong physical and occupational therapy to maintain function and independence.
  + Assistive devices (walkers, braces) as needed.

## 4. Long-Term Outlook

* Most children with AMC become ambulatory with varying levels of independence.
* Early aggressive management improves joint mobility and walking ability.
* Prognosis for ambulation can often be predicted by 2.5 years of age.
* Multidisciplinary care including pediatricians, orthopedists, neurologists, geneticists, and therapists is essential.

## Procedures

See the list below:

* Skin biopsy - This is rarely performed, being carried out if the patient has a history of intellectual disability with no known diagnosis.
* Muscle biopsy
  + Muscle biopsy is probably the most important diagnostic procedure. It should be included in all autopsies and at time of surgery.
  + Distinguish myopathic from neuropathic conditions by obtaining muscle specimens from normal and affected areas.
  + Special histopathologic and electron micrographic studies are used to evaluate fatty and connective tissue replacement of muscle fibers and variations in fiber size, such as decreased fiber diameter. All are nonspecific signs of muscle atrophy.
* Electromyography (EMG) of normal and affected areas is useful in differentiating neurogenic and myopathic causes.
* Nerve conduction tests measure conduction velocities in motor and sensory nerves; these should be performed when a peripheral neuropathy is suspected.
* An autopsy should be performed to discover more about the following:
  + CNS (ie, brain neuropathology)
  + Spinal cord (number and size of anterior horn cells, presence or absence of tracts at various levels)
  + Ganglia and peripheral nerves
  + Eye (ie, neuropathology)
  + Muscle tissue from different muscle groups (ie, electron microscopy and special stains)
  + Fibrous bands replacing muscle
  + Tendon attachments
  + Other visceral anomalies, malformations, deformations, and disruptions

## **Outlook / Prognosis**

The long-term outlook for people with AMC depends on a few circumstances, including:

* The severity of the arthrogryposis.
* The underlying cause of arthrogryposis.
* How your or your child’s body responds to therapy.

The majority of people with arthrogryposis grow up to be independent adults. Treatment helps them improve their mobility to the point that they can lead lives similar to people who don’t have arthrogryposis.

### **Does arthrogryposis get worse?**

Arthrogryposis isn’t progressive. Although arthrogryposis doesn’t get worse, the underlying condition that causes it might. You might want to educate yourself about the possible cause of your child’s arthrogryposis when your healthcare providers confirm it.

## **Prevention**

### **How can I prevent arthrogryposis** Preventing arthrogryposis is out of your hands. There’s nothing you could’ve done to reduce your child’s risk of arthrogryposis.

## **Epidemiology**

### Frequency

*United States*

The frequency is about 1 in 3000 live births.

*International*

Arthrogryposis multiplex congenita is more common in isolated populations such as Finland and the Bedouin community in Israel.

### Mortality/Morbidity

The life span of affected individuals depends on the disease severity and associated malformations but is usually normal. About 50% of patients with limb involvement and central nervous system (CNS) dysfunction die in the first year of life.

Scoliosis may compromise respiratory function. A retrospective study by Li et al found that arthrogryposis patients with concomitant scoliosis have worse pulmonary function than do individuals with adolescent idiopathic scoliosis. In study patients with arthrogryposis/secondary scoliosis, mean values for forced vital capacity (%FVC), forced expiratory volume in 1 second (%FEV1), and the ratio of FEV1 to FVC (%FEV1/FVC) were 48.8, 45.3, and 92.1, respectively, compared with 70.3, 69.7, and 96.9, respectively, for subjects with adolescent idiopathic scoliosis.

A literature review by Cirillo et al indicated that in patients with arthrogryposis, adults have a greater tendency to experience pain than do children, with self reports of pain being more common in individuals in whom multiple corrective procedures have been performed.

### Race

No racial predilection has been described.

### Sex

Males are primarily affected in X-linked recessive disorders; otherwise, males and females are equally affected.

## **Differential Diagnoses of AMC**

1. Amyoplasia (Classic Arthrogryposis)
   1. Most common form of AMC.
   2. Characterized by symmetric limb contractures and muscle hypoplasia without neurological deficits.
2. Distal Arthrogryposis
   1. Group of disorders primarily affecting distal joints (hands and feet).
   2. Often inherited in an autosomal dominant pattern.
   3. Includes Freeman-Sheldon syndrome (whistling face syndrome) and Sheldon-Hall syndrome.
3. Multiple Pterygium Syndrome
   1. Characterized by webbing (pterygia) across joints, causing contractures.
   2. Can be lethal or non-lethal forms.
4. Neuropathic and Myopathic Disorders
   1. Congenital muscular dystrophies and myopathies causing decreased fetal movement.
   2. Includes congenital myasthenic syndromes, mitochondrial myopathies.
5. Central Nervous System Disorders
   1. Conditions causing fetal akinesia due to brain or spinal cord abnormalities.
   2. Examples: cerebral malformations, spinal muscular atrophy.
6. Connective Tissue Disorders
   1. Contractural arachnodactyly (Beals syndrome)
   2. Larsen syndrome (multiple joint dislocations and characteristic facial features)
   3. Congenital contractural arachnodactyly
7. Bony Fusion Disorders
   1. Symphalangism (fusion of phalanges)
   2. Coalition and synostosis of bones causing joint immobility.
8. Chromosomal and Genetic Syndromes
   1. Trisomy 18 (Edwards syndrome)
   2. DiGeorge syndrome (22q11 deletion)
   3. Other syndromic causes with multiple anomalies.
9. Fetal Akinesia Deformation Sequence (FADS)
   1. Severe reduction or absence of fetal movement leading to contractures and other deformities.
10. More than 400 genes have been linked to AMC, reflecting its broad genetic heterogeneity

## **Key Genes and Molecular Mechanisms**

* TPM2 (Tropomyosin 2): Mutations cause distal arthrogryposis type 1A (DA1A) via gain-of-function mutations increasing muscle contractility
* ERGIC1: Identified homozygous mutations affect protein trafficking between the endoplasmic reticulum and Golgi, expanding the spectrum of hereditary AMC
* ZC4H2: Mutations cause a neurodevelopmental disorder with AMC features, including point mutations and deletions
* Other genes involve pathways related to skeletal muscle development (40% of cases), brain development (22%), connective tissue, and neuromuscular function
* Genetic causes include mutations affecting neuromuscular junctions, anterior horn cells, muscle fibers, connective tissue, and fetal movement

## **Question and Answer Set**

## 1. What is Arthrogryposis Multiplex Congenita (AMC)?

AMC is a group of congenital conditions characterized by multiple joint contractures present at birth, causing stiffness and limited movement in two or more body areas. It is non-progressive but results in physical disability.

## 2. What causes AMC?

AMC has diverse causes including genetic mutations, environmental factors, and problems during fetal development that reduce fetal movement. About 30% of cases have a genetic origin, while others may be due to neurological, muscular, or connective tissue abnormalities.

## 3. How is AMC diagnosed?

Diagnosis is based on clinical evaluation of multiple joint contractures, patient history, and specialized tests such as nerve conduction studies, electromyography, muscle biopsy, imaging of the central nervous system, and genetic testing including whole genome sequencing.

## 4. Is there a cure for AMC?

No, there is no cure for AMC. Treatment focuses on improving joint mobility, muscle strength, and function through physical therapy, splinting, casting, and sometimes surgery.

## 5. What treatments are available for AMC?

* Physical therapy: Gentle joint manipulation, stretching, and exercises to improve motion and prevent muscle atrophy.
* Splinting and serial casting: To mobilize stiff joints and correct deformities.
* Surgery: Tendon releases, tendon transfers, osteotomies to improve joint positioning and function.
* Multidisciplinary care: Involving pediatricians, neurologists, orthopedists, rehabilitation specialists, therapists, and geneticists.

## 6. What is the prognosis for people with AMC?

Most people with AMC grow up to be independent adults with improved mobility through treatment. AMC is non-progressive, but the underlying cause may vary. Early and ongoing therapy improves outcomes.

## 7. Can AMC affect cognitive abilities?

Generally, AMC does not affect intelligence or cognitive development. Most children have normal cognitive function.

## 8. How important is early intervention in AMC?

Early treatment is crucial to prevent complications, improve joint function, and enhance independence. Therapy often starts in infancy and continues into adolescence or longer.

## 9. Are genetic tests useful in AMC?

Yes, genetic testing including whole genome sequencing can identify causative mutations, guide prognosis, and assist in family counseling.

## 10. How can families support a child with AMC?

Families play a vital role by participating in therapy routines, encouraging activity, and providing emotional support. Connecting with support groups can also be beneficial.

**references**

<https://emedicine.medscape.com/article/941917-overview#a6>

[Arthrogryposis Multiplex Congenita (AMC): Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/23190-arthrogryposis)

**CLUB FOOT**

**DEFINITION AND DESCRIPTION**

Clubfoot describes a condition present at birth in which a baby's foot is pointed in and down. The tissues connecting the muscles to the bone are called tendons. In clubfoot, the tendons are shorter than usual, pulling the foot out of position.

Also called congenital talipes equinovarus (TAL-ih-peez e-kwie-no-VAY-rus), clubfoot is a common foot condition. It can occur in up to 1 in 1,000 babies. Most newborns with clubfoot do not have other medical conditions.

Clubfoot can be mild to severe. About half of children with clubfoot have it in both feet. If a child has clubfoot that is not treated, the child may walk on the side or top of the foot. This can cause a limp, skin sores or calluses, and problems wearing shoes.

Clubfoot will not get better without treatment. But it can be successfully treated using a specific casting technique. Usually, babies also need a minor procedure to lengthen the heel tendon. Treatment results are best with casting that begins within several weeks after birth.

**Causes**

The cause of clubfoot is not known, but it may be due to genetics and environmental factors.

**Risk factors**

Boys are about twice as likely as girls to have clubfoot.

Risk factors include:

* **Family history.** If a child has a parent, brother or sister with clubfoot, that child is more likely to have it too.
* **Part of other conditions.** Sometimes clubfoot may happen with other skeletal conditions that are present at birth. One example is spina bifida, a condition that happens when the spine and spinal cord don't develop or close properly before birth. Certain conditions related to changes in chromosomes also may raise the risk of clubfoot.
* **Environment.** Smoking during pregnancy can raise the baby's risk of clubfoot.
* **Not enough amniotic fluid during pregnancy.** Amniotic fluid is the liquid that surrounds the baby in the womb. Not having enough amniotic fluid may raise the risk of clubfoot.

## **Symptoms**

If your child has clubfoot, here's what it might look like:

* The top of the foot is usually pointed in and down. This raises the arch and turns the heel inward.
* The foot may be turned so severely that it looks like it is upside down.
* The foot or big toe may be slightly shorter than the other foot.
* The calf muscles in the leg with clubfoot are usually smaller.

At birth, clubfoot doesn't cause any discomfort or pain.

## **Diagnosis**

Many times, a healthcare professional diagnoses clubfoot soon after birth just from looking at the shape and position of the newborn's foot. Sometimes X-rays are taken to fully understand how severe the clubfoot is. But usually X-rays are not needed.

Often clubfoot can be seen before birth during a routine ultrasound exam in week 20 of pregnancy. While the condition can't be treated before birth, knowing about the condition may give you time to learn more about clubfoot. You'll have time to talk with health experts, such as a pediatric orthopedic surgeon, to plan treatment. If needed, a medical genetics counselor can talk with you about genetic test results and your risk of having a baby with clubfoot in future pregnancies.

**Treatment**

Because a newborn's bones, joints and tendons are very flexible, treatment for clubfoot usually begins in the first week or two after birth. The goals of treatment are to move the child's foot into a corrected position with the bottom of the foot facing the ground. Treatment with casting allows for the best movement of the foot and best long-term results. Treatment is most effective if done in the first few months of age.

Treatment options include:

* Stretching and casting, called the Ponseti method.
* Stretching, splinting and taping, called the French method.
* Surgery.

### **Casting: Ponseti method**

Casting is the main treatment for clubfoot. The healthcare professional typically:

* Moves your baby's foot into an improved position and then places it in a cast to hold it there.
* Repositions and recasts your baby's foot once a week for several months.
* Performs a minor procedure to lengthen the heel tendon, called the Achilles tendon, toward the end of this process.

After the shape of your baby's foot is improved, the foot needs to stay in position. To help your child keep the foot in position:

* Put your child in special shoes and braces.
* Make sure your child wears the shoes and braces as long as needed. This is usually all day and all night for 3 to 6 months, and then at night and during naps until your child is 3 to 4 years of age.

For this method to be successful, the braces need to be worn exactly as instructed so that the foot doesn't go back to its original turned position. When the Ponseti casting approach doesn't work, the main reason is because the braces aren't worn as instructed. If your child can't wear the braces or outgrows the braces, talk with your healthcare professional right away.

Even with treatment, clubfoot may not be totally correctable. For some children, the foot may begin to turn in again. If this happens before age 2, it can require more casting to return the foot to the correct position. But most of the time, babies who are treated early grow up to wear regular shoes without braces, participate in sports, and lead full, active lives.

### **Stretching, splinting and taping: French method**

The French method was developed in France and is most often used only in France. It is a type of stretching treatment that is best for mild clubfoot. The foot is stretched into position, then taped and splinted every day. The method involves frequent physical therapy appointments and daily treatments done by parents until the child is 2 to 3 years old. A minor procedure to lengthen the heel tendon, called the Achilles tendon, is usually needed.

### **Surgery**

If a baby's clubfoot doesn't improve with the casting method or if a child doesn't have complete correction later in life, surgery may be needed. Even with a successful result in infancy, surgery is sometimes needed around 3 to 5 years of age if the child's foot is still turning in. During surgery, an orthopedic surgeon repositions tendons to help keep the foot in a better position. This surgery is called a tibialis anterior tendon transfer and has very good results.

Rarely for severe clubfoot or for clubfoot that is part of a syndrome or other underlying medical conditions, more extensive surgery may be needed in infancy. This surgery is called a posterior release or posteromedial release. This surgery loosens the ligaments in the back and side of the ankle and can result in larger correction of the foot. Even though the foot is in a better position, the foot can become stiff and pain in the foot is more likely later in life.

After surgery, the child is in a cast for up to two months. Then the child wears a brace for several years or so to keep clubfoot from coming back.

## **Medications Used in Clubfoot Management**

* Pain Relief Medications (Post-Surgery or Discomfort):
  + Acetaminophen (Paracetamol): Used for mild to moderate pain relief.
    - Side effects: Rare but may include liver toxicity in overdose.
  + Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (e.g., ibuprofen): Used to reduce pain and inflammation after surgery or casting.
    - Side effects: Gastrointestinal irritation, kidney effects, allergic reactions.
  + Local Anesthetics: Occasionally used during minor procedures like Achilles tenotomy.
* Sedatives or Anesthetics:
  + Used during surgical procedures or tendon release.
  + Side effects depend on agents used (e.g., respiratory depression, allergic reactions).

## **Clubfoot (Talipes Equinovarus) — Procedures and Timelines**

## 1. Correction Phase (6 to 8 Weeks)

* Weekly Manipulation and Casting:
  + Gentle stretching and positioning of the foot followed by application of a plaster cast from toes to upper thigh.
  + Casts are changed weekly to progressively correct foot deformity.
  + Typically requires 5 to 7 casts over 6 to 8 weeks.
* Achilles Tendon Tenotomy:
  + Performed in about 80–90% of cases near the end of casting phase to lengthen the tight Achilles tendon.
  + Minor outpatient procedure under local anesthesia.
  + Followed by a final cast for 3 weeks to allow tendon healing and elongation.

## 2. Maintenance Phase (Up to 5 Years)

* Foot Abduction Brace (Orthotic Device):
  + After cast removal, the child wears a brace consisting of shoes attached to a bar holding feet in corrected position.
  + Worn 23 hours per day for 3 months initially.
  + Then worn during naps and nighttime until about 4 to 5 years of age to prevent relapse.
* Compliance is critical; improper use of the brace is the main cause of recurrence.

## 3. Additional Notes

* Treatment usually completes well before the child starts crawling or walking.
* Some children may require additional casting or surgery if relapse occurs.
* The French Functional Method (stretching, taping, splinting) is an alternative but less commonly used.
* Surgery beyond Achilles tenotomy is rare with early and proper Ponseti treatment.

**Complications**

Clubfoot usually doesn't cause any problems until a child starts to stand and walk. Treatment can bring the foot into the proper position and help a child walk well. But a child may still have some problems with:

* **Movement.** The foot may be a little stiff and not bend easily.
* **Leg length.** The leg with clubfoot may be slightly shorter, but this usually doesn't stop a child from learning to walk.
* **Shoe size.** The foot may be up to 1 1/2 shoe sizes smaller than the other foot.
* **Calf size.** The muscles of the calf on the side with clubfoot may always be smaller than those on the other side.
* **Foot shape.** It's common for the foot to have a bean shape and a small inward point, even after treatment.

If clubfoot is not treated, more-serious problems can happen. These can include:

* **Problems walking.** When clubfoot is not treated, children with the condition can walk but may put their weight on the side of the foot or the top of the foot. This can cause sores or calluses, problems finding shoes, and a limp.
* **Problems with late treatment.** Delayed treatment of clubfoot can result in needing more casts and even surgery to correct the foot. Results are better with early treatment before the bones of the foot become misshapen from the poor foot position.
* **Arthritis.** There may be swelling and tenderness in one or more joints.
* **Poor self-image.** The unusual look of the foot may make body image a concern during the teen years.

## **Outlook / Prognosis**

Clubfoot doesn’t go away on its own. Early treatment is essential for a positive outcome. Babies who start treatment early have good results. They can wear regular shoes, walk, run and play without pain. They can even play sports.

If only one foot was affected, you may notice that:

* The affected foot is a smaller size and less mobile than the unaffected foot.
* The calf muscles in the leg with the clubfoot may be smaller.
* Your child may get tired or complain about sore legs sooner than children without clubfoot.
* The affected leg may be slightly shorter. But this usually doesn’t cause major problems.

If your child has another condition along with clubfoot, the outlook may depend on treatment for the other condition.

#### **Can clubfoot return?**

Clubfoot can come back. It’s more likely to happen if the treatment schedule wasn’t followed correctly. If the foot returns to the clubfoot position, see your child’s healthcare provider. They can advise you on the next steps. You may need to repeat some stages of the treatment plan.

## **Prevention**

Because healthcare professionals don't know what causes clubfoot, there's no sure way to prevent it. But if you're pregnant, you can do things to have a healthy pregnancy and lower your baby's risk of problems that affect the baby's development:

* Don't smoke or spend time in places with secondhand smoke.
* Don't drink alcohol.
* Don't use legal or illegal drugs that may be sold on the streets or take medicines that aren't approved by your healthcare professional.

### **When to see a doctor**

Your healthcare professional is likely to notice clubfoot during an exam soon after your child is born. You may be referred to a doctor who specializes in bone and muscle conditions in children called a pediatric orthopedic surgeon.

## **Epidemiology**

The incidence of clubfoot is approximately 1 case per 1000 live births in the United States. An analysis using data from the EUROCAT network reported that the total prevalence of congenital clubfoot in Europe was 1.13 per 1000 births.

The incidence differs among ethnicities. For example, it is close to 75 cases per 1000 live births in the Polynesian islands, particularly in Tonga.

The male-to-female ratio has been reported to be 2:1. Bilateral involvement is found in 30-50% of cases. A 2017 study by Zionts et al found that severity did not differ significantly by either sex or bilaterality, though patients with bilateral clubfoot had a wider range of severity.

There is a 10% chance of a subsequent child being affected if the parents already have a child with a clubfoot.

Parker et al pooled data from several birth defects surveillance programs (6139 cases of clubfoot) to better estimate the prevalence of clubfoot and investigate its risk factors.The overall prevalence of clubfoot was 1.29 per 1000 live births, with figures of 1.38 among non-Hispanic whites, 1.30 among Hispanics, and 1.14 among non-Hispanic blacks or African Americans. Maternal age, parity, education, and marital status were significantly associated with clubfoot, along with maternal smoking and diabetes.

## **Clubfoot (Talipes Equinovarus) — Genomic Data**

* Genome-Wide Association Studies (GWAS):
  + Identified a significant association with a single nucleotide polymorphism (SNP) rs7969148 linked to isolated clubfoot
* Rare Variants and Candidate Genes:
  + Rare variants enriched in clubfoot cases include genes such as PITX1, HOXD12, COL12A1, COL9A3, and LMX1B
  + Variants in posterior HOX genes (HOX9–13) are implicated in about 8.4% of cases
* FLNB Gene:
  + Missense mutations in FLNB are associated with isolated clubfoot and syndromic forms like Larsen syndrome
* Other Genetic Pathways:
  + Genes involved in TGF-β signaling, extracellular matrix components, peroxisomal function, and proteoglycan synthesis have been linked to clubfoot
* Homeobox (HOX) Genes:
  + Variants near HOX homeobox genes and genes like IGFBP3 and caspase genes have been associated with susceptibility
* Animal Models:
  + Mouse models (e.g., PMA mouse) have identified candidate genes like Limk1 affecting neuronal growth and muscle development, contributing to clubfoot phenotype

## Genetic Inheritance and Risk

* Clubfoot inheritance follows a polygenic threshold model with multiple common variants each conferring small risk
* Both common variants (SNPs) and rare variants contribute to disease susceptibility.
* Genetic heterogeneity explains variable penetrance and phenotype severity.

## Associated Syndromes and Aneuploidies

* Clubfoot can be part of syndromic presentations associated with chromosomal abnormalities such as trisomy 21, trisomy 13, and triploidy
* Syndromic clubfoot genes overlap with isolated clubfoot genes, suggesting shared pathways

## **Question and Answer Set**

## 1. What is clubfoot?

Clubfoot, or talipes equinovarus, is a congenital deformity where one or both feet are twisted inward and downward. The foot appears rotated internally at the ankle, making walking difficult without treatment.

## 2. What causes clubfoot?

The exact cause is unknown but involves a combination of genetic and environmental factors. It may be associated with abnormal muscle or nerve development, and sometimes occurs as part of genetic syndromes or chromosomal abnormalities.

## 3. How common is clubfoot?

Clubfoot occurs in about 1 in every 1,000 live births worldwide. It is more common in males than females, with a ratio of approximately 2:1.

## 4. How is clubfoot diagnosed?

Diagnosis is usually made at birth by physical examination. Prenatal ultrasound can sometimes detect clubfoot before birth. The foot’s position, stiffness, and range of motion are assessed.

## 5. What are the treatment options for clubfoot?

* The Ponseti method (serial casting and manipulation) is the gold standard.
* Achilles tendon tenotomy is often performed to release tight tendons.
* Bracing is used after casting to maintain correction.
* Surgery is reserved for resistant or relapsed cases.

## 6. How long does treatment take?

Initial correction with casting usually takes 6 to 8 weeks. After casting, bracing continues for several years (up to 4–5 years) to prevent relapse.

## 7. Can clubfoot be cured?

Yes, with early and proper treatment, most children achieve normal or near-normal foot function and appearance.

## 8. Are there any complications of clubfoot?

Without treatment, clubfoot can cause pain, difficulty walking, and disability. Even with treatment, relapse can occur if bracing protocols are not followed.

## 9. Is clubfoot hereditary?

There is a genetic component, and having a family member with clubfoot increases risk. However, it is a multifactorial condition involving multiple genes and environmental influences.

## 10. Can clubfoot be detected before birth?

Yes, prenatal ultrasound can detect clubfoot in the second trimester, although some cases may not be identified until after birth.

## **Doctor-Patient Conversation on Clubfoot (De-Identified)**

## Doctor:

Hello! I understand you’re here to discuss your baby’s foot.

## Parent:

Yes, doctor. At birth, we noticed my baby’s foot is twisted inward and downward. We’re worried about what this means.

## Doctor:

Thank you for sharing. What you’re describing sounds like clubfoot, a common congenital condition where the foot is turned inward and downward.

## Parent:

What causes clubfoot?

## Doctor:

The exact cause isn’t always clear. It can be due to genetic factors, positioning in the womb, or sometimes associated with other conditions. Most cases occur in otherwise healthy babies.

## Parent:

Is clubfoot painful for my baby?

## Doctor:

Clubfoot itself isn’t painful at birth, but if untreated, it can lead to walking difficulties and discomfort later on.

## Parent:

How is clubfoot treated?

## Doctor:

The most effective treatment is the Ponseti method, which involves gentle manipulation and casting of the foot over several weeks to gradually correct the position. Sometimes a minor procedure called a tenotomy is needed to release tight tendons.

## Parent:

Will my baby need surgery?

## Doctor:

Most babies respond well to the Ponseti method without major surgery. Surgery is reserved for rare cases where the foot doesn’t correct fully.

## Parent:

How long does treatment take?

## Doctor:

The casting phase usually lasts about 6 to 8 weeks, followed by wearing a brace for several years to maintain correction and prevent relapse.

## Parent:

Can my baby walk normally after treatment?

## Doctor:

Yes, with timely and proper treatment, most children with clubfoot walk, run, and play normally.

## Parent:

Are there any complications?

## Doctor:

Complications are rare if treatment is started early and followed carefully. Relapse can occur but is manageable with further treatment.

## Parent:

What should we do next?

## Doctor:

We’ll start the Ponseti casting as soon as possible and schedule regular follow-ups to monitor progress.

## Parent:

Thank you, doctor. I feel more hopeful now.

## Doctor:

You’re welcome. We’ll support you and your baby throughout the treatment.

**REFERENCES**

<https://emedicine.medscape.com/article/1237077-overview#a7>

<https://my.clevelandclinic.org/health/diseases/16889-clubfoot>

<https://www.mayoclinic.org/diseases-conditions/clubfoot/diagnosis-treatment/drc-20350866>

## **multiple epiphyseal dysplasia**

**DEFINITION AND DESCRIPTION**

Multiple epiphyseal dysplasia is a condition that affects the ends of the long bones, otherwise known as epiphysis. The condition results from a problem in the cartilage oligomeric matrix protein, which accumulates in the cartilage and causes premature destruction, and can lead to early arthritis. Multiple epiphyseal dysplasia is usually inherited dominantly, meaning through one parent, but it may also be recessive.

Patients with multiple epiphyseal dysplasia have minimal short stature, averaging 57 to 67 inches tall, and are usually diagnosed later in life after suffering from joint pain in the lower extremities. They may also have ankles that roll inward (valgus) and suffer from a disruption of blood flow to the joints (avascular necrosis).

## **Causes Multiple Epiphyseal Dysplasia**

Multiple Epiphyseal Dysplasia (MED) is caused by genetic mutations that impact cartilage and bone development. It can be inherited in two ways: **autosomal dominant**, where one parent passes on a mutated gene, or **autosomal recessive**, where both parents must pass on the gene. Common genes involved include **COMP, MATN3, and COL9A1**. Identifying these genetic factors is key for diagnosis and counseling.

## **What are the symptoms of multiple epiphyseal dysplasia?**

Hip problems due to misalignment, subluxation or Perthes disease

Knee problems due to misalignment

Ankle problems due to misalignment

Double-layer kneecap (patella)

Premature arthritis, which can occur when the patient is in their 20s or 30s in the hips, knees and shoulders

## **Symptoms of Multiple Epiphyseal Dysplasia**

The symptoms of Multiple Epiphyseal Dysplasia can vary significantly among individuals, even within the same family. However, some common clinical features often observed include:

### **Early-Onset Joint Pain and Stiffness**

One of the earliest indicators of MED is joint pain and stiffness, particularly in the hips, knees, and ankles. This discomfort is usually exacerbated by physical activity and can lead to a reluctance to participate in sports or other physical activities.

### **Delayed Growth and Short Stature**

Children with MED may exhibit delayed growth and ultimately achieve a shorter stature compared to their peers. This growth delay is due to the impaired development of the long bones, which are crucial for height.

### **Abnormal Skeletal Development**

MED can lead to skeletal abnormalities, such as irregularly shaped epiphyses, broadening of the metaphyses, and early-onset osteoarthritis. These skeletal changes can be identified through radiographic imaging and are critical for differentiating MED from other skeletal dysplasias.

### **Other Associated Features**

In addition to the primary symptoms, some individuals with MED may experience other complications, such as scoliosis, brachydactyly (short fingers or toes), and a waddling gait. It is important to monitor for these associated features to provide comprehensive care.

## **Multiple Epiphyseal Dysplasia Diagnosis**

A doctor makes the diagnosis of multiple epiphyseal dysplasia with a complete medical history, physical examination and X-rays of the pelvis, lower extremities and shoulders if pain is present.

Accurate diagnosis of Multiple Epiphyseal Dysplasia involves a combination of clinical evaluation, radiographic imaging, and genetic testing.

### **Clinical Evaluation**

A thorough clinical evaluation by a healthcare professional specializing in genetic disorders is the first step in diagnosing MED. The clinician will review the patient's medical history, assess symptoms, and conduct a physical examination to identify any characteristic signs of the condition.

### **Radiographic Imaging**

Radiographic imaging, particularly X-rays, plays a pivotal role in diagnosing MED. The imaging will reveal characteristic features such as irregular epiphyses, widened metaphyses, and possible early-onset osteoarthritis. These findings are instrumental in distinguishing MED from other similar skeletal conditions.

### **Genetic Testing**

Genetic testing can confirm the diagnosis of MED by identifying mutations in the associated genes. This testing is especially valuable for families with a history of the disorder or when the clinical presentation is ambiguous. Genetic counseling is recommended to discuss the implications of test results for the patient and their family.

## **Multiple Epiphyseal Dysplasia Treatment**

Treatment for multiple epiphyseal dysplasia varies depending on the associated orthopaedic conditions that present in the patient and may include:

Realignment surgery of the hips

Guided growth of the lower extremities (hemiepiphysiodesis) to help correct deformities

Osteotomies for severe deformities of the lower extremities as the patient matures

Excision of patella if there is a double layer and it is causing pain

Total joint replacements of the hips, knees and shoulders

While there is currently no cure for Multiple Epiphyseal Dysplasia, various treatment strategies aim to manage symptoms and improve the quality of life for affected individuals.

### **Pain Management**

Effective pain management is crucial for individuals with MED. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed to alleviate joint pain and reduce inflammation. In some cases, physical therapy may be recommended to strengthen muscles and improve joint flexibility.

### **Surgical Interventions**

In severe cases, surgical interventions may be necessary to address joint deformities or replace damaged joints. Procedures such as osteotomies, epiphyseal stapling, or joint replacement can help alleviate pain and improve mobility. However, surgery is typically considered only after conservative treatments have been exhausted.

### **Growth Hormone Therapy**

For children with significantly delayed growth, growth hormone therapy may be considered. This treatment can help improve growth velocity and achieve a height closer to the expected range for age and sex. It is important to discuss the potential benefits and risks of growth hormone therapy with a healthcare professional.

## **Drug Treatments for MED**

* Pain Management:
  + Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or naproxen are commonly used to relieve joint pain and inflammation.
  + Side Effects:
    - Gastrointestinal irritation, ulcers, or bleeding
    - Kidney function impairment with long-term use
    - Allergic reactions or rash
  + NSAIDs are typically taken as needed, especially after physical activity or during flare-ups.
* Other Pain Medications:
  + In some cases, stronger analgesics or pain management specialists may be involved, especially if pain is severe or chronic.
  + Side effects depend on the specific medications used.
* Physical Therapy Adjuncts:
  + While not drugs, therapies such as warm baths (hydrotherapy) can help reduce stiffness and pain.

## 2. Non-Drug Treatments

* Physical Therapy:
  + Exercises to improve joint mobility, muscle strength, and reduce stiffness.
  + Water therapy is especially beneficial.
* Weight Management:
  + Maintaining a healthy weight reduces stress on affected joints.
* Assistive Devices:
  + Braces or orthotics may support joints and improve function.
* Surgical Treatments:
  + Indicated for significant joint deformities or severe osteoarthritis.
  + Procedures include osteotomies (bone realignment), joint replacement (hip, knee, shoulder), and excision of painful bone structures.
  + Surgery aims to improve joint mechanics and reduce pain.

## **Procedures and Timelines**

## 1. Early Childhood (Symptoms Usually Begin Between 2 and 10 Years)

* Initial Assessment and Monitoring:
  + Diagnosis often occurs when children present with joint pain, waddling gait, or stiffness.
  + Regular clinical and radiographic monitoring to assess joint development and deformities.
* Physical Therapy:
  + Started early to improve joint mobility, muscle strength, and reduce pain.
  + Includes exercises and hydrotherapy (water therapy).
  + Ongoing as needed.
* Pain Management:
  + NSAIDs (ibuprofen, naproxen) used as needed for joint pain relief.
  + Weight management advised to reduce joint stress.

## 2. Adolescence and Maturity

* Orthopedic Surgical Interventions:  
  Surgery is considered when joint deformities cause significant pain or functional limitations.
  + Realignment Surgery (Osteotomy):
    - Corrects bone deformities to improve joint mechanics and slow arthritis progression.
    - Timing depends on severity and growth; often performed during adolescence or early adulthood.
  + Guided Growth (Hemiepiphysiodesis):
    - Used in growing children to correct angular deformities of lower limbs (e.g., knock-knees or bowlegs).
    - Typically performed during childhood/adolescence.
  + Patellar Excision:
    - Removal of a double-layered patella if it causes pain.
  + Joint Replacement Surgery:
    - Total hip, knee, or shoulder replacements may be necessary in adulthood due to severe joint degeneration.
    - Usually performed after skeletal maturity.

## 3. Long-Term Management

* Regular Follow-Up:
  + Lifelong monitoring by orthopedic specialists to manage symptoms and prevent complications.
  + Adjustments in therapy and surgical planning as needed.
* Supportive Care:
  + Use of braces or orthotics to support joints and improve function.
  + Counseling and support for coping with chronic pain and physical limitations.

## **Managing Multiple Epiphyseal Dysplasia**

Managing Multiple Epiphyseal Dysplasia involves a multidisciplinary approach that includes regular monitoring, lifestyle modifications, and supportive care.

### **Regular Monitoring**

Regular follow-up appointments with healthcare providers specializing in skeletal dysplasias are essential for monitoring disease progression and addressing any emerging complications. These appointments may include radiographic assessments, physical evaluations, and discussions about symptom management.

### **Lifestyle Modifications**

Individuals with MED are encouraged to adopt lifestyle modifications that minimize joint stress and promote overall well-being. Low-impact exercises, such as swimming or cycling, can help maintain joint flexibility without exacerbating pain. Additionally, maintaining a healthy weight can reduce joint strain and improve mobility.

### **Supportive Care**

Supportive care, including physical therapy and occupational therapy, can enhance daily functioning and improve the quality of life for individuals with MED. These therapies focus on strengthening muscles, improving joint flexibility, and developing strategies for managing pain and fatigue.

## **Multiple Epiphyseal Dysplasia (MED) — Epidemiology**

The incidence of autosomal dominant MED is estimated to be at least 1 in 10,000 newborns

The prevalence estimates range from about 1 in 20,000 to 1 in 10,000 individuals

The recessive form of MED has an unknown incidence, but it is considered rarer than the dominant form

Both dominant and recessive forms may be underdiagnosed, especially in mild cases that present later in life

MED affects males and females equally

Symptoms typically begin in childhood, with diagnosis often made during childhood, although some mild cases may not be diagnosed until adulthood

Clinical features include joint pain (especially hips and knees), waddling gait, early-onset osteoarthritis, and sometimes mild short stature

The recessive form is distinguished by additional skeletal malformations such as clubfoot, scoliosis, and double-layered patella

## **Differential Diagnoses**

1. Spondyloepiphyseal Dysplasia (SED)
   1. Involves both spine (vertebrae) and epiphyses.
   2. Presents with short trunk dwarfism, scoliosis, and early arthritis.
   3. Radiographs show vertebral abnormalities not typical in MED.
2. Legg-Calvé-Perthes Disease
   1. Avascular necrosis of the femoral head in children.
   2. Presents with hip pain and limp but without generalized epiphyseal involvement.
3. Other Multiple Skeletal Dysplasias
   1. Spondyloepimetaphyseal Dysplasia (SEMD): Involves metaphyses and epiphyses with more severe skeletal abnormalities.
   2. Metaphyseal Dysplasia: Primarily affects metaphyses, sparing epiphyses.
   3. Osteochondrodysplasias with overlapping features.
4. Juvenile Idiopathic Arthritis (JIA)
   1. Presents with joint pain, swelling, and stiffness.
   2. Unlike MED, JIA is inflammatory and may show joint effusions and erosions on imaging.
5. Early-Onset Osteoarthritis
   1. Can mimic symptoms of MED but usually lacks the characteristic epiphyseal abnormalities on X-rays.
6. Recessive Multiple Epiphyseal Dysplasia (rMED)
   1. Distinguished by more severe skeletal malformations including hands, feet, scoliosis, clubfoot, and double-layered patella.
7. Other Genetic Disorders with Epiphyseal Involvement
   1. Fairbank disease (a synonym for some forms of MED).
   2. Disorders involving collagen genes (COL9A1, COL9A2, COL9A3), COMP, MATN3 mutations.

**PROGNOSIS**

## Functional Outcomes

* Many patients maintain a full, active life with appropriate medical care, physical therapy, and symptom management.
* Joint pain and stiffness may limit some physical activities, but with treatment, most individuals achieve reasonable mobility and independence.
* Muscle weakness and joint deformities can worsen with age, potentially requiring surgical interventions.

## Surgical Prognosis

* Surgical procedures such as realignment osteotomies, guided growth (hemiepiphysiodesis), patella excision, and joint replacements can improve function and reduce pain.
* Total joint replacements (hip, knee, shoulder) are often needed in adulthood due to advanced arthritis.
* Studies show good functional outcomes and implant survivorship after bilateral hip and knee arthroplasties in MED patients, with significant pain reduction and improved mobility over long-term follow-up (average 7 years).
* Careful preoperative planning and multidisciplinary postoperative rehabilitation are vital for optimal results.

## Recessive MED Prognosis

* The recessive form tends to have more severe skeletal abnormalities, including clubfoot, scoliosis, and double-layered patella.
* Despite these additional features, stature is generally within the normal range before puberty, and adult height is only slightly reduced.
* Joint pain and arthritis develop similarly but may be accompanied by more complex deformities.

## **Doctor-Patient Conversation on Multiple Epiphyseal Dysplasia (De-Identified)**

## Doctor:

Hello! I understand you have some concerns about your child's joint pain and growth. Can you tell me more about what you've noticed?

## Parent:

Yes, doctor. My child has been complaining of joint pain, especially in the knees and hips, after playing or exercise. They also seem to tire easily and sometimes walk with a bit of a waddle.

## Doctor:

Thank you for sharing. Based on your description and the tests we’ve done, your child has a condition called Multiple Epiphyseal Dysplasia, or MED. It’s a genetic disorder that affects the growth of the ends of the bones, which are important for joint development.

## Parent:

What causes this? Is it something we did?

## Doctor:

No, this is a genetic condition, meaning it’s caused by changes in certain genes that affect cartilage and bone growth. It’s not due to anything you did during pregnancy or after birth. Sometimes it runs in families, but it can also occur as a new change.

## Parent:

What does this mean for my child’s future?

## Doctor:

Children with MED often experience joint pain and stiffness, and their bones may develop a bit differently, which can cause some deformities or difficulty moving certain joints. Many children have normal or slightly shorter height. Over time, some may develop early arthritis, but with proper care, many lead active lives.

## Parent:

Is there a treatment?

## Doctor:

There’s no cure, but we can manage symptoms. Physical therapy can help maintain joint mobility and strength. Pain can be managed with medications like ibuprofen. In some cases, surgery might be needed to correct bone deformities or improve joint function.

## Parent:

Will my child be able to do normal activities?

## Doctor:

Yes, with appropriate management, most children can participate in many activities. We encourage staying active but avoiding repetitive high-impact activities that might worsen joint pain.

## Parent:

How often will we need to see you?

## Doctor:

Regular follow-ups are important to monitor your child’s growth, joint health, and to adjust treatment as needed. We’ll also coordinate care with physical therapists and possibly orthopedic surgeons if surgery becomes necessary.

## Parent:

Is there anything else we should watch for?

## Doctor:

Keep an eye on increasing joint pain, swelling, or difficulty moving joints. Also, if your child develops any new symptoms like back pain or changes in posture, let us know.

## Parent:

Thank you, doctor. This helps me understand what’s going on.

## Doctor:

You’re welcome. We’re here to support you and your child every step of the way.

**REFERENCES**

[Multiple Epiphyseal Dysplasia | Johns Hopkins Medicine](https://www.hopkinsmedicine.org/health/conditions-and-diseases/multiple-epiphyseal-dysplasia)

[Multiple Epiphyseal Dysplasia: Causes, Symptoms, Treatment](https://www.medicoverhospitals.in/diseases/multiple-epiphyseal-dysplasia/)

### [**https://medicalcitykidsortho.com/multiple-epiphyseal-dysplasia/**](https://medicalcitykidsortho.com/multiple-epiphyseal-dysplasia/)

<https://www.nemours.org/conditions-treatments/multiple-epiphyseal-dysplasia/about-multiple-epiphyseal-dysplasia.html>

### **Hurler syndrome**

**Definition and description**

Hurler syndrome is the most severe form of mucopolysaccharidosis type 1 (MPS 1). It’s an autosomal recessive condition.

MPS 1 is a condition where your body doesn't have enough enzymes to break down sugar molecules (glycosaminoglycans, formerly called mucopolysaccharides). The condition causes skeletal/joint abnormalities, distinct facial characteristics, issues with cognitive development, heart and lung (respiratory) problems and an enlarged liver and spleen.

Hurler syndrome is a lysosomal storage condition. When your body is unable to break down molecules normally, they accumulate in lysosomes. Lysosomes are the parts of your cell that control molecular waste management (the storage, recycling and digestion of molecules). When there’s too much toxic molecular buildup in your cells, the cells quickly die or don’t function properly, which causes symptoms of the condition.

Life expectancy for children diagnosed with Hurler syndrome is short due to life-threatening symptoms.

### **Types of mucopolysaccharidosis type I**

There are three types of Mucopolysaccharidosis type I (MPS I), including:

* Hurler syndrome.
* Hurler-Scheie syndrome.
* Scheie syndrome.

These types fall on a spectrum based on severity. On one side of the spectrum is Hurler syndrome, which is the most common, most severe and has life-threatening complications. On the other side of the spectrum are Hurler-Scheie syndrome (intermediate form) and Scheie syndrome (mild form). Your child's healthcare provider will most likely call the less severe forms of MPS I “attenuated MPS I.”

Hurler-Scheie and Scheie syndromes have symptoms that match Hurler syndrome, but the progression of the condition is slower. You might see symptoms when your child turns six or seven years old with attenuated MPS I, as opposed to seeing symptoms shortly after birth with Hurler syndrome.

When symptoms of attenuated MPS 1 show up, how they impact the person diagnosed with the condition varies greatly. People with attenuated MPS I can have a normal lifespan and children with Hurler syndrome have a short lifespan.

The main difference between the three types of MPS I is that Hurler syndrome causes major developmental delays during early childhood and affects a child’s intelligence significantly. Hurler syndrome also causes your child’s cognitive abilities to decline over time. Attenuated MPS I can affect a child’s intelligence but not at the same rate as Hurler syndrome.

Hurler syndrome can affect any child since it's the result of a genetic mutation that occurs randomly. If you have a history of mucopolysaccharidosis type I (MPS I) in your family, you’re at an increased risk of having a child with Hurler syndrome.

Hurler syndrome affects an estimated 1 in every 100,000 newborns and affects males and females equally. Less severe forms of mucopolysaccharidosis type I (MPS I) affect nearly 1 out of every 500,000 newborns.

Hurler syndrome affects many aspects of your child’s growing body. Symptoms can cause physical characteristics that are unique to the condition, like an enlarged head, cloudy eyes and facial features such as widely spaced eyes, large forehead, a flat nasal bridge and enlarged lips. Physical symptoms can also affect how your child’s bones grow, which could lead to them having a short stature.

The condition also affects your child’s internal organs, like their heart and lungs. Your child might have recurrent ear, sinus and pulmonary infections or eventually need breathing assistance or surgery to repair symptomatic damage to their organs.

Symptoms of Hurler syndrome are life-threatening and treatment can improve your child’s life expectancy with early diagnosis and treatment.

If you plan on becoming pregnant and want to understand your risk of having a child with a hereditary condition like Hurler syndrome, talk to your healthcare provider about genetic testing.

### **Symptoms of Hurler syndrome**

Symptoms of Hurler syndrome range in severity and are unique to each person diagnosed with the condition. Symptoms begin in early childhood and continue through adolescence.

A symptom of Hurler syndrome that sets it apart from other levels of mucopolysaccharidosis type I (MPS 1) is early childhood developmental delays and a progressive decline in how your child can learn and retain information. Mild cases of MPS 1 don’t affect a child’s intelligence.

Symptoms of Hurler syndrome could include:

* Heart valve problems (cardiomyopathy).
* Hearing loss.
* Buildup of cerebrospinal fluid around your child's brain (hydrocephalus).
* Enlarged organs like connective tissues, tonsils, muscles, heart, liver and spleen.
* Vision problems (glaucoma).
* Joint problems (tight muscles, carpal tunnel and joint disease).
* Respiratory infections, sleep apnea and difficulty breathing.
* Hernias.

#### **Physical characteristics**

During a child’s first year, physical symptoms of Hurler syndrome will appear. These characteristics include:

* Short stature.
* Bones forming incorrectly (dysostosis).
* Rounding curve of your child's upper back (thoracic-lumbar kyphosis).
* Excessive hair growth.

### **What causes Hurler syndrome?**

A mutation of the *IDUA* gene causes Hurler syndrome. The *IDUA* gene is responsible for creating lysosomal enzymes, which break down waste in cells. When the *IDUA* gene doesn't create enough enzymes, toxic waste collects in cells, causing them to die or not function properly. When your cells can’t get rid of waste, symptoms of Hurler syndrome occur.

### **How is Hurler syndrome inherited?**

Hurler syndrome is hereditary, which means you can get the condition from your parents. Hereditary conditions aren't the result of something your parent did while pregnant.

Cells form in your parent’s reproductive organs via one fertilized cell from the sperm and one from the egg. The cells divide and copy themselves with half the amount of DNA as the original cell. During this process of cell division, genetic mutations can occur randomly as cells re-type the instruction manual word for word. Any time there's a typo (genetic mutation), the genetic code for part of your DNA is incomplete. As a result, your cells don’t have the instructions they need to form and function properly.

## **Diagnosis and Tests**

Prenatal screening tests, like amniocentesis or chorionic villus sampling, can diagnose your child with Hurler syndrome while you’re pregnant. Both tests examine whether or not there are any genetic abnormalities within your baby’s DNA.

After your baby is born, their healthcare provider will diagnose Hurler syndrome with a physical examination to look for symptoms of the condition and enzyme activity assays to confirm the diagnosis. They'll also ask if you know of any family members who have mucopolysaccharidosis conditions, since it’s hereditary.

Additional tests, like an X-ray of your child's bones, echocardiogram of their heart, and blood and urine tests might be necessary to confirm the diagnosis.

## **Management and Treatment**

Treatment for Hurler syndrome focuses on preventing and managing symptoms of the condition:

* **Enzyme replacement therapy (ERT):** Replacing damaged enzymes can prevent symptoms from getting worse and has the potential to reverse complications. Your child's healthcare provider will schedule regular shots of alpha L-iduronidase (aldurazyme) early after a diagnosis. The frequency of the shots depend on the severity of your child's diagnosis and is a lifelong treatment option.
* **Hematopoietic stem cell transplant (HSCT):** For children under two years old (and some over two years old, by the supervision of their provider) diagnosed with Hurler’s syndrome, HSCT can prolong life expectancy in severe cases, prevent disease progression, preserve cognitive function and reduce symptoms that affect their body (somatic). Stem cells from donors with functioning enzymes that are found in bone marrow (hematopoietic cells) replace damaged cells in a child via chemotherapy.

Other types of treatment options for Hurler syndrome include:

* Surgery to alleviate symptoms, like repairing or replacing heart valves, cornea replacement, repairing bone growth abnormalities or repairing hernias.
* Physical, occupational and/or speech therapy.
* Receiving supplemental oxygen using a CPAP machine.
* Using hearing aids.
* Taking medicine to reduce pain associated with symptoms.

## **Approved Treatments**

## a) Enzyme Replacement Therapy (ERT)

* Drug: Laronidase (Brand name: Aldurazyme)
* Mechanism: Recombinant human alpha-L-iduronidase replaces the deficient enzyme, facilitating breakdown of accumulated GAGs.
* Administration: Weekly intravenous infusions, lifelong treatment.
* Indications: Used in all forms of MPS I, especially attenuated forms and as adjunct therapy in Hurler syndrome.
* Benefits: Improves respiratory function, reduces liver and spleen size, improves joint mobility, and overall quality of life.
* Limitations: Does not cross the blood-brain barrier effectively, so neurological symptoms may persist.

Side Effects:

* Infusion-related reactions (fever, chills, rash, flushing)
* Hypersensitivity or allergic reactions (rare anaphylaxis)
* Headache, nausea, vomiting
* Respiratory symptoms during infusion (cough, wheezing)
* Rarely, development of antibodies against the enzyme

## b) Hematopoietic Stem Cell Transplantation (HSCT)

* Description: Transplantation of donor stem cells capable of producing functional IDUA enzyme.
* Indications: Gold standard for patients with Hurler syndrome diagnosed and treated before 2 to 2.5 years of age.
* Benefits: Can halt neurological decline by providing enzyme-producing cells in the central nervous system, improve survival, and reduce somatic symptoms.
* Limitations: Requires suitable donor, carries risks of transplant-related morbidity and mortality.

Side Effects and Risks:

* Graft-versus-host disease (GVHD)
* Infection risk due to immunosuppression
* Transplant rejection
* Organ toxicity (liver, lungs)
* Long recovery period

## 2. Other Treatments

* Orthopedic Surgery: For joint contractures and skeletal deformities.
* Supportive Surgeries: Myringotomy (ear tubes), hernia repair, adenoidectomy/tonsillectomy.
* Future/Emerging Therapies: Gene therapy and substrate reduction therapies are under investigation

## **PROCEDURES AND TIMELINE**

## Diagnosis and Initial Evaluation

* Prenatal screening: Amniocentesis or chorionic villus sampling can detect genetic abnormalities before birth.
* Postnatal diagnosis: Physical exam, enzyme activity assays, genetic testing, and imaging (X-rays, echocardiogram) confirm diagnosis.
* Timing: Diagnosis is usually made in infancy or early childhood, often between ages 3 to 8 years for symptoms, but earlier diagnosis improves prognosis.

## 2. Enzyme Replacement Therapy (ERT) — Ongoing Weekly Infusions

* Start: As soon as diagnosis is confirmed, ideally before significant organ damage.
* Procedure: Weekly intravenous infusions of laronidase (Aldurazyme) lasting several hours.
* Duration: Lifelong treatment.
* Purpose: Reduces glycosaminoglycan (GAG) accumulation, improves somatic symptoms (lung function, organ size, joint mobility).
* Limitation: Does not cross the blood-brain barrier, so neurological symptoms may persist.

## 3. Hematopoietic Stem Cell Transplantation (HSCT)

* Timing: Best performed before 2 to 2.5 years of age, prior to cognitive impairment. Early transplant improves survival and neurological outcomes.
* Preparation: Chemotherapy (with or without radiation) to destroy diseased marrow cells, lasting days to weeks.
* Transplant: Infusion of donor stem cells (from sibling, unrelated donor, or umbilical cord blood) into the bloodstream.
* Recovery: Hospital stay of weeks to months, followed by prolonged outpatient recovery and monitoring for complications (e.g., graft-versus-host disease).
* Benefits: Halts neurological decline, improves survival, reduces somatic symptoms.
* Limitations: Does not fully reverse bone, corneal, cardiac valve, or CNS damage; residual disease burden may remain.

## 4. Supportive and Surgical Interventions

* Orthopedic surgeries: For joint contractures and skeletal deformities (timing individualized based on severity).
* Other surgeries: Adenotonsillectomy, hernia repair, myringotomy, corneal transplant as needed.
* Timing: Performed as symptoms arise, often during childhood.

## 5. Follow-Up and Long-Term Care

* Lifelong multidisciplinary follow-up to monitor organ function, neurodevelopment, and manage complications.
* Genetic counseling recommended for families.

#### **Are there complications from the treatment?**

In some cases, people with Hurler syndrome may have complications related to the anesthetic given during surgical procedures. This happens because your child might have symptoms that cause breathing difficulties and their provider could have trouble securing an IV if they have tight muscles, joints or tissues (contractures).

The timing of treatment is important for it to be effective, especially for hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT). If symptoms relating to cognitive development are present, it might be too late for the treatment to work at its full potential.

Before your child begins treatment, talk with their healthcare provider about possible side effects or complications that could arise.

## **Outlook / Prognosis**

Prognosis is poor for children diagnosed with Hurler syndrome. It’s common for children diagnosed with Hurler syndrome to have a short life expectancy of about 10 years due to the severe symptoms of the condition affecting their heart and lungs. Early diagnosis and treatment can prolong their life with hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT).

Children diagnosed with an intermediate or mild form of mucopolysaccharidosis type I (MPS 1) normally live into their early 20s and 30s with treatment. Early death is often from respiratory failure.

If your child’s diagnosis is less severe and treatment begins early, a normal lifespan is possible.

#### **Is there a cure for Hurler syndrome?**

There's no known cure for Hurler syndrome, but treatment prolongs life expectancy and alleviates dangerous symptoms of the condition.

## **Prevention**

You can’t prevent Hurler syndrome because it’s the result of an inherited genetic mutation. To understand your risk of having a child with a genetic condition, talk to your healthcare provider about genetic testing if you plan on becoming pregnant.

### **When should my child see their healthcare provider?**

If you notice your child has symptoms of Hurler syndrome, especially if they miss developmental milestones or have trouble seeing or hearing, contact their healthcare provider for an examination.

Visit the emergency room or call 911 immediately if your child has difficulty breathing, an irregular heartbeat or if they pass out regularly (symptoms of cardiomyopathy).

## **Epidemiology**

### Frequency

United States

The estimated incidence of severe mucopolysaccharidosis type I (MPS I) is about 1 in 100,000 newborns. Attenuated MPS I is less common and occurs in about 1 in 500,000 newborns.

International

The birth prevalence of mucopolysaccharidosis type I (MPS I) in England and Wales from 1981-2003 was 1.07 cases per 100,000 births.

### Mortality/Morbidity

Lifespan in mucopolysaccharidosis type I (MPS I) encompasses a wide range. Death in early childhood can occur in the more severe form and can range to an adulthood lifespan in the attenuated form.

### Race

Mucopolysaccharidosis type I (MPS I) is inherited as autosomal recessive and equally affects both sexes.

## **Differential Diagnoses**

* Hunter Syndrome (Mucopolysaccharidosis Type II)
* Sanfilippo Syndrome (Mucopolysaccharidosis Type III)
* Morquio Syndrome (Mucopolysaccharidosis Type IV)
* Maroteaux-Lamy Syndrome (Mucopolysaccharidosis Type VI)
* Sly Syndrome (Mucopolysaccharidosis Type VII)

## **Question and Answer Set**

## 1. What is Hurler syndrome?

Hurler syndrome, also known as mucopolysaccharidosis type I (MPS I), is a rare inherited lysosomal storage disorder caused by deficiency of the enzyme alpha-L-iduronidase. This leads to accumulation of glycosaminoglycans (GAGs) in tissues, causing progressive physical and cognitive decline

## 2. What causes Hurler syndrome?

It is caused by mutations in the IDUA gene on chromosome 4, leading to absent or deficient alpha-L-iduronidase enzyme activity. The disorder is inherited in an autosomal recessive manner

## 3. How common is Hurler syndrome?

Hurler syndrome affects about 1 in 100,000 live births worldwide, affecting males and females equally and all ethnicities

## 4. What are the main symptoms of Hurler syndrome?

Symptoms usually appear in the first year of life and include coarse facial features (large head, flat nose, enlarged lips), developmental delay, skeletal abnormalities, joint stiffness, recurrent respiratory infections, heart disease, corneal clouding, hearing loss, and hepatosplenomegaly

## 5. How is Hurler syndrome diagnosed?

Diagnosis is based on clinical features, enzyme activity assays showing deficient alpha-L-iduronidase, and genetic testing to identify mutations in the IDUA gene

## 6. What treatments are available for Hurler syndrome?

* Enzyme Replacement Therapy (ERT) with laronidase to reduce GAG accumulation and improve somatic symptoms.
* Hematopoietic Stem Cell Transplantation (HSCT), ideally before 2–2.5 years of age, to improve neurological outcomes.
* Supportive care including surgeries for airway management, hernia repair, and orthopedic interventions

## 7. What is the prognosis of Hurler syndrome?

Without treatment, children with Hurler syndrome often do not survive beyond 10 years of age. Early HSCT and ERT improve survival and quality of life but do not fully reverse all symptoms

## 8. Can Hurler syndrome be prevented?

Genetic counseling and prenatal testing are recommended for families with a history of MPS I to assess the risk and consider early diagnosis

## 9. What complications are associated with Hurler syndrome?

Complications include severe cognitive decline, heart failure, respiratory difficulties, skeletal deformities, vision and hearing loss, and recurrent infections

## 10. Is Hurler syndrome the same as Scheie syndrome?

No, Scheie syndrome is a milder form of MPS I with later onset and less severe symptoms. Hurler syndrome is the most severe form

## **Genomic Data**

## Gene Involved

* Gene: IDUA (iduronidase, alpha-L-)
* Location: Chromosome 4, band p16.3
* Function: Encodes the enzyme alpha-L-iduronidase, essential for degradation of glycosaminoglycans (GAGs). Deficiency leads to GAG accumulation causing Hurler syndrome.

## Mutation Spectrum

* Over 500 variants in the IDUA gene have been reported globally, including nonsense, missense, frameshift, splice site, insertions, and deletions.
* More than 300 distinct mutations are catalogued in mutation databases such as the Leiden Open Variation Database (LOVD) and Human Genetic Mutation Database (HGMD).
* Common severe mutations include:
  + p.W402X: A nonsense mutation causing premature stop codon; prevalent in Northern Europe, UK, North America (~50% frequency).
  + p.Q70X: Another nonsense mutation common in Russia and Scandinavia (~50% frequency).
  + p.P533R: Frequent in Mediterranean populations and North Africa.
  + p.G51D: Common in Italy.
* Many patients are homozygous or compound heterozygous for two null (severe) mutations, correlating with the severe Hurler phenotype.
* Missense mutations and splice site variants also contribute to attenuated forms (Hurler-Scheie and Scheie syndromes).

## Genotype-Phenotype Correlations

* Severe phenotypes (Hurler syndrome) are mostly associated with two null mutations (nonsense, frameshift, splice site).
* Attenuated phenotypes often have at least one missense mutation allowing residual enzyme activity.
* Some mutations are population-specific, reflecting founder effects.

## Genetic Testing and Diagnosis

* Molecular genetic testing of the IDUA gene is standard for confirming diagnosis and carrier detection.
* Testing includes sequencing all exons and intron-exon boundaries, plus deletion/duplication analysis.
* Over 90% of patients have two identifiable pathogenic variants.

## **Doctor-Patient Conversation on Hurler Syndrome (De-Identified)**

## Doctor:

The tests indicate that your child has a rare genetic condition called Hurler syndrome, also known as Mucopolysaccharidosis Type I. It’s caused by a deficiency of an enzyme called alpha-L-iduronidase, which leads to a buildup of certain substances in the body.

## Parent:

What does that mean for my child?

## Doctor:

Because the enzyme is missing or not working properly, complex sugars called glycosaminoglycans accumulate in various tissues and organs. This causes symptoms such as developmental delay, joint stiffness, coarse facial features, enlarged liver and spleen, and sometimes heart and lung problems.

## Parent:

Is this condition inherited? Could we have prevented it?

## Doctor:

Hurler syndrome is inherited in an autosomal recessive pattern, meaning both parents carry a gene mutation but are usually healthy themselves. It’s not caused by anything you did or didn’t do.

## Parent:

What treatments are available?

## Doctor:

Treatment options include enzyme replacement therapy (ERT), which can help reduce some symptoms by providing the missing enzyme. Another important treatment is hematopoietic stem cell transplantation (HSCT), which can slow or prevent some of the neurological decline if done early.

## Parent:

Is there a cure?

## Doctor:

Currently, there is no cure. However, early treatment can significantly improve quality of life and slow disease progression. Treatments are most effective when started before significant symptoms develop.

## Parent:

What can we expect moving forward?

## Doctor:

Your child will need ongoing care from a multidisciplinary team including genetics, neurology, cardiology, and physical therapy. We will monitor development closely and manage symptoms as they arise.

## Parent:

Are there any risks or side effects with the treatments?

## Doctor:

ERT is generally well tolerated but requires regular infusions. HSCT carries risks like infection and graft-versus-host disease but can be life-saving. We will discuss these in detail if you decide to proceed.

## Parent:

What support is available for families?

## Doctor:

There are support groups and resources through national MPS societies that can provide information and connect you with other families. We’ll also help coordinate social and psychological support.

## Parent:

Thank you for explaining everything.

## Doctor:

You’re welcome. We’ll work together to give your child the best care possible. Please feel free to ask any questions anytime.

REFERENCES

<https://www.ncbi.nlm.nih.gov/books/NBK1162/>

[Hurler Syndrome, Hurler-Scheie Syndrome, and Scheie Syndrome (Mucopolysaccharidosis Type I) Clinical Presentation: History, Physical, Causes](https://emedicine.medscape.com/article/1599374-clinical?form=fpf)

[Mucopolysaccharidosis Type I: Hurler Syndrome - Symptoms & Causes](https://my.clevelandclinic.org/health/diseases/24000-hurler-syndrome)

### **Morquio syndrome**

**Definition and description**

Morquio syndrome, also known as mucopolysaccharidosis IV (MPS IV), is a condition that causes bone growth abnormalities and symptoms throughout your body that worsen over time. This means it’s progressive. The condition is genetic. It occurs when large sugar molecules (glycosaminoglycans or GAGs, formerly called mucopolysaccharides) can’t be broken down due to not having enough enzyme activity.

#### **Types of Morquio syndrome**

There are two types of Morquio syndrome that have similar symptoms but a different genetic cause:

* Type A: Deficiency of N-acetyl-galactosamine-6-sulfatase or *GALNS*.
* Type B: Deficiency of beta-galactosidase or *GLB1*.

Both types have different treatment options, so identifying the type is important.

Morquio syndrome affects an estimated 1 in 200,000 to 300,000 people in the United States. About 95% of cases are type A.

### **Symptoms of Morquio syndrome**

Morquio syndrome symptoms appear from infancy to early childhood and increase in severity over time. Symptoms can affect the skeleton and include:

* Coarse facial features.
* Flexible joints.
* Growth abnormalities of the spine, chest, ribs, hips and wrists.
* Knock knees (genu valgum).
* Misaligned cervical vertebrae (odontoid process).
* Short stature.
* Scoliosis or kyphosis.

Symptoms can also affect other parts of the body and cause:

* Cloudy eyes and vision loss.
* Dental problems from thin tooth enamel.
* Enlarged liver (hepatomegaly).
* Hearing loss and ear infections.
* Hernias.
* Pain in areas where there are bone growth abnormalities.
* Sleep apnea.
* Upper respiratory infections.

Severe symptoms of Morquio syndrome can be life-threatening and include:

* Airway blockages.
* Compressed spinal cord (paralysis).
* Heart valve abnormalities.

Morquio syndrome doesn’t affect a person’s intelligence.

### **What causes Morquio syndrome?**

Having two genetic changes (mutations) in either the *GALNS* (type A) gene or the *GLB1* (type B) genes causes Morquio syndrome. These genes produce enzymes that break down large sugar molecules called glycosaminoglycans (GAGs) or mucopolysaccharides.

When mutations target the *GALNS* or *GLB1* genes, your enzymes don’t have the instructions they need to do their job. This means they have little to no activity. As a result, sugar molecules accumulate in your lysosomes. These are places inside of cells that recycle or break down molecules. For this reason, Morquio syndrome is also known as a lysosomal storage disorder.

The accumulation of sugar molecules targets tissues and organs but mostly affects your bones, where you’ll experience symptoms.

### **Who does Morquio syndrome affect?**

Morquio syndrome can affect anyone since it’s a genetic condition. You can inherit the condition from genes you receive from both of your parents during conception (autosomal recessive). If you inherit the condition, your parents are carriers of the gene but don’t experience symptoms of the condition.

## **Diagnosis and Tests**

A diagnosis usually begins when symptoms become apparent, usually during early childhood. Your child’s provider will perform a physical examination and order an X-ray to look closely at their bones. Your child’s provider will also order additional tests like:

* A urine test (pee test) to identify if their glycosaminoglycan levels are high.
* A blood test to identify the gene responsible for their symptoms (genetic test) and the activity of an enzyme in their body.

## **Management and Treatment**

Treatment for Morquio syndrome addresses symptoms of the condition since there’s no cure. Treatment could include:

* Cornea replacement (penetrating keratoplasty) for cloudy eyes.
* Enzyme replacement therapy for type A.
* Physical therapy to improve mobility.
* Surgery to decompress bones and stabilize cervical vertebrae and the spinal cord.
* Surgery to remove tonsils and adenoids to open the airway.
* Using a wheelchair or assisted mobility devices.
* Using hearing aids or ventilation tubes in the ears.

## **Treatment, Drug Information, and Side Effects**

## 1. Enzyme Replacement Therapy (ERT)

* Drug: Elosulfase alfa (Vimizim) is the FDA-approved enzyme replacement therapy for Morquio A syndrome.
* Mechanism: Provides the deficient enzyme N-acetylgalactosamine-6-sulfatase to reduce glycosaminoglycan (GAG) accumulation.
* Administration: Weekly intravenous infusions.
* Benefits: Improves endurance, respiratory function, and reduces some systemic symptoms.
* Limitations: Limited effect on bone and cartilage lesions; does not reverse established skeletal abnormalities.

Side Effects:

* Infusion-related reactions (fever, chills, rash, headache)
* Hypersensitivity or allergic reactions (rare anaphylaxis)
* Nausea, vomiting, abdominal pain
* Fatigue and dizziness
* Respiratory symptoms during infusion (cough, wheezing)

## 2. Hematopoietic Stem Cell Transplantation (HSCT)

* Description: One-time treatment where donor stem cells produce the missing enzyme.
* Benefits: Potential to slow skeletal disease progression more effectively than ERT.
* Limitations: High-risk procedure with potential mortality, requires specialized centers and suitable donors.
* Side Effects and Risks: Graft-versus-host disease, infection, organ toxicity, transplant rejection.

## 3. Surgical Interventions

* Often necessary to manage skeletal complications and life-threatening conditions such as:
  + Cervical spine decompression and fusion to prevent spinal cord compression.
  + Orthopedic surgeries (e.g., femoral osteotomy) to preserve joint function and mobility.
  + Surgery to relieve severe tracheal obstruction, a major cause of mortality.
* Surgery improves quality of life but carries risks related to anesthesia and respiratory complications due to airway abnormalities.

## 4. Supportive Therapies

* Physical and occupational therapy to maintain mobility and function.
* Use of orthotic devices and mobility aids.
* Respiratory support and monitoring.
* Genetic counseling for families.

## 5. Emerging Therapies

* Gene therapy is under investigation but not yet clinically available.
* New surgical techniques for tracheal obstruction show promise in improving survival.

## **Procedures and Timeline**

## 1. Diagnosis and Initial Evaluation

* Usually diagnosed in early childhood when skeletal abnormalities and symptoms become apparent.
* Diagnosis confirmed by biochemical tests (urinary keratan sulfate), enzyme assays, and genetic testing.
* Early diagnosis is critical to initiate treatment promptly.

## 2. Enzyme Replacement Therapy (ERT)

* Start: As soon as diagnosis is confirmed, ideally early in life.
* Procedure: Weekly intravenous infusions of elosulfase alfa (Vimizim) over approximately 4 hours.
* Duration: Lifelong therapy.
* Benefits: Improves endurance, respiratory function, and reduces systemic symptoms.
* Side Effects: Infusion-related reactions (fever, rash, headache), hypersensitivity.

## 3. Surgical Interventions

* Timing: Usually performed during childhood and adolescence as symptoms progress.
* Common Procedures:
  + Cervical spine decompression and fusion: To treat instability and prevent spinal cord compression.
  + Orthopedic surgeries: Femoral osteotomy and other procedures to preserve joint function and mobility.
  + Tracheal surgery: To relieve severe airway obstruction, a major cause of morbidity and mortality.
  + Other supportive surgeries: Hernia repair, adenoidectomy, and tonsillectomy as needed.
* Surgery improves quality of life but carries risks due to airway and cardiac involvement.

## 4. Hematopoietic Stem Cell Transplantation (HSCT)

* Consideration: In select cases, HSCT may be performed to provide a permanent source of enzyme.
* Timing: Usually in childhood, but not standard due to risks and variable efficacy on skeletal disease.
* Limitations: Does not fully correct bone and cartilage lesions.

## 5. Supportive and Multidisciplinary Care

* Physical and occupational therapy to maintain mobility.
* Respiratory monitoring and support.
* Regular cardiac, ophthalmologic, and audiologic evaluations.
* Genetic counseling for families.

## **Staging**

1. Severe (Rapidly Progressing) Phenotype
   1. Onset: Symptoms appear within the first year of life, often before 1 year of age.
   2. Features: Marked short stature, severe skeletal dysplasia (kyphoscoliosis, odontoid hypoplasia, pectus carinatum), joint laxity, progressive spinal instability, hip dysplasia, and early loss of ambulation.
   3. Non-skeletal involvement: Significant respiratory compromise, cardiac valve disease, corneal clouding, hearing loss, hepatomegaly.
   4. Prognosis: Reduced life expectancy, often into the second or third decade without treatment.
2. Attenuated (Slowly Progressing) Phenotype
   1. Onset: Symptoms appear later, sometimes in the second decade of life.
   2. Features: Milder skeletal abnormalities, slower progression of joint and spinal deformities, better preservation of mobility.
   3. Non-skeletal involvement: Less severe or delayed onset of respiratory, cardiac, and ocular complications.
   4. Prognosis: Longer life expectancy and better quality of life with supportive care.

## Key Clinical and Radiological Features Used in Assessment

* Skeletal manifestations:
  + Short stature, kyphoscoliosis, genu valgum (knock knees), pectus carinatum (protruding chest), hip dysplasia, platyspondyly (flattened vertebrae), odontoid hypoplasia causing cervical instability.
* Non-skeletal manifestations:
  + Corneal clouding, hearing loss, cardiac valve thickening/regurgitation, respiratory compromise (tracheomalacia, obstructive sleep apnea), hepatomegaly, dental abnormalities.
* Functional status:
  + Endurance, mobility, respiratory function, neurological status.

## Biomarkers and Diagnostic Tools in Staging

* Urinary and blood keratan sulfate (KS) levels:
  + Elevated in early childhood; levels correlate with disease severity and progression.
* Enzyme activity assays:
  + Confirm diagnosis but do not predict severity.
* Genetic testing:
  + Over 100 mutations in the GALNS gene; genotype-phenotype correlations suggest some mutations associate with severe or attenuated forms.
* Imaging:
  + Radiographs and MRI assess skeletal abnormalities and spinal cord compression risk.

## **Morquio Syndrome (Mucopolysaccharidosis Type IV) — Epidemiology**

## Incidence and Prevalence

* Morquio A syndrome (MPS IVA):
  + Incidence varies widely by region:
    - 1 per 76,000 births in Northern Ireland
    - 1 per 201,000 births in Australia
    - 1 per 216,000 births in British Columbia (Canada)
    - 1 per 450,000 births in Portugal
    - 1 per 625,000 births in Japan
    - 0.11 per 100,000 live births in the United States
    - 0.15 per 100,000 live births in Brazil
    - 1.10 per 100,000 live births in Mexico
  + Morquio A is the third most common mucopolysaccharidosis (MPS) in India, the US, and much of Europe; second most common behind MPS II in Southern and Eastern Europe.
  + Estimated point prevalence ranges from about 1 per 217,000 (UAE) to 1 per 1,664,000 (Japan).
  + Median worldwide birth prevalence is approximately 1 per 1,500,000, though estimates vary widely due to diagnostic and reporting differences.
* Morquio B syndrome (MPS IVB):
  + Much rarer than Morquio A.
  + In the US, only 3 patients registered between 1995–2015.
  + Estimated incidence in Brazil is about 0.003 per 100,000 live births.

## **Outlook / Prognosis**

At first, symptoms of Morquio syndrome may be mild, but you can expect them to get worse as your child gets older. Treatment can help to keep your child more comfortable and may prevent life-threatening outcomes.

#### **What is the average life expectancy for someone diagnosed with Morquio syndrome?**

The life expectancy of people diagnosed with Morquio syndrome varies based on the severity of the condition. Your child’s healthcare provider will give you their outlook based on their situation. Symptoms that cause early death include breathing difficulties and a compressed spinal cord.

Children with severe symptoms could have a life expectancy into adolescence. People who have mild symptoms have a life expectancy into middle adulthood, up until age 60.

## **Prevention**

There’s no way to prevent Morquio syndrome since it’s a genetic condition. Reach out to your healthcare provider about genetic testing to understand your risk of having a child with a genetic condition.

### **When should I see my healthcare provider?**

Symptoms that affect the spinal cord and airways are most severe and require immediate attention. Visit the emergency room if your child has trouble breathing or can’t move a part of their body (paralysis).

Always monitor your child’s symptoms, especially after surgery to check for infections. Contact your child’s provider if they experience pain, swelling or a clear to yellow fluid drains from their surgical site.

**Differential diagnoses**

* Spondyloepiphyseal Dysplasia (SED)
* Perthes Disease (Avascular necrosis of the femoral head)
* Brachyolmia (Types 1, 2, 3)
* Rickets (Vitamin D deficiency-related bone disease)
* Juvenile Idiopathic Arthritis (JIA)
* Other Mucopolysaccharidoses (MPS types I, II, VI, VII)
* Multiple Epiphyseal Dysplasia
* Achondroplasia (in some cases)

**Genomic Data**

## Gene and Genetic Basis

* Morquio syndrome type A (MPS IVA) is caused by mutations in the GALNS gene, which encodes the enzyme N-acetylgalactosamine-6-sulfatase.
* Deficiency of this enzyme leads to accumulation of glycosaminoglycans (GAGs), causing skeletal abnormalities and multisystem involvement.
* Morquio syndrome type B (MPS IVB) is caused by mutations in the GLB1 gene, affecting beta-galactosidase enzyme.

## Mutation Spectrum in GALNS (MPS IVA)

* Over 400 mutations in the GALNS gene have been identified worldwide.
* A comprehensive review reported 277 unique GALNS alterations from 1,091 published alleles, with most mutations being missense variants.
* Approximately 48% of patients are homozygous for a GALNS mutation, 39% are compound heterozygous, and 13% have only one identified mutation.
* Mutations are highly heterogeneous and often population-specific, with some founder effects reported in British/Irish, Japanese, Colombian, and Spanish populations.
* The mutations cause varying degree

## **Morquio Syndrome (Mucopolysaccharidosis IV) — Q&A**

## 1. What is Morquio Syndrome?

Morquio Syndrome, or Mucopolysaccharidosis IV (MPS IV), is a rare genetic disorder caused by the body’s inability to break down certain sugar molecules called glycosaminoglycans (GAGs) due to enzyme deficiencies. This leads to progressive bone and tissue abnormalities

## 2. What are the main symptoms of Morquio Syndrome?

Symptoms include abnormal bone growth causing short stature, joint laxity, spinal deformities (kyphoscoliosis), pectus carinatum (protruding chest), airway obstruction, and progressive skeletal dysplasia. Other complications include heart valve disease, hearing loss, and corneal clouding

## 3. How is Morquio Syndrome diagnosed?

Diagnosis involves clinical evaluation, radiographic imaging showing skeletal abnormalities, and enzyme activity tests or genetic testing to identify mutations causing the enzyme deficiency

## 4. Is there a cure for Morquio Syndrome?

Currently, there is no cure. Treatment focuses on managing symptoms and improving quality of life through enzyme replacement therapy (ERT), surgery, and supportive care

## 5. What is Enzyme Replacement Therapy (ERT) and how does it help?

ERT involves intravenous infusions of the missing enzyme (elosulfase alfa) to reduce GAG accumulation. It has been shown to improve endurance, respiratory function, and reduce urinary GAG levels. Treatment should start as early as possible.

## 6. What surgical treatments are used?

Surgical interventions may include decompression and fusion of cervical vertebrae to stabilize the spine, orthopedic surgeries to correct hip deformities, and procedures to relieve airway obstruction such as tonsillectomy or tracheostomy in severe cases

## 7. What are the risks during anesthesia or surgery?

Patients with Morquio Syndrome have difficult airways and may have pulmonary and cardiac dysfunction, making anesthesia and surgery high risk. These procedures should be performed by experienced teams familiar with the disease

## 8. What other supportive treatments are recommended?

Physical therapy to maintain mobility, respiratory support (e.g., CPAP for sleep apnea), vaccinations to prevent respiratory infections, and multidisciplinary care involving geneticists, orthopedists, cardiologists, and pulmonologists

## 9. How does Morquio Syndrome affect life expectancy?

Life expectancy varies widely depending on severity and management. Early diagnosis and treatment can improve outcomes, but progressive skeletal and respiratory complications may reduce lifespan

## 10. Is genetic counseling recommended?

Yes, genetic counseling is important for affected families to understand inheritance patterns and recurrence risks

REFERENCES

[Morquio Syndrome: Symptoms & Causes](https://my.clevelandclinic.org/health/diseases/morquio-syndrome)

<https://www.medicalnewstoday.com/articles/what-is-morquio-syndrome>

<https://patient.info/doctor/morquios-syndrome>

**MARFAN SYNDROME**

**DEFINITION AND DESCRIPTION**

Marfan syndrome is an inherited disorder that affects connective tissue — the fibers that support and anchor your organs and other structures in your body. Marfan syndrome most commonly affects the heart, eyes, blood vessels and skeleton.

People with Marfan syndrome are usually tall and thin with unusually long arms, legs, fingers and toes. The damage caused by Marfan syndrome can be mild or severe. If your aorta — the large blood vessel that carries blood from your heart to the rest of your body — is affected, the condition can become life-threatening.

Treatment usually includes medications to keep your blood pressure low to reduce the strain on your aorta. Regular monitoring to check for damage progression is vital. Many people with Marfan syndrome eventually require preventive surgery to repair the aorta.

**Causes**

Marfan syndrome is caused by a defect in the gene that enables your body to produce a protein that helps give connective tissue its elasticity and strength.

Most people with Marfan syndrome inherit the abnormal gene from a parent who has the disorder. Each child of an affected parent has a 50-50 chance of inheriting the defective gene. In about 25% of the people who have Marfan syndrome, the abnormal gene comes from neither parent. In these cases, a new mutation develops spontaneously.

**Risk factors**

Marfan syndrome affects men and women equally and occurs among all races and ethnic groups. Because it's a genetic condition, the greatest risk factor for Marfan syndrome is having a parent with the disorder.

**SYMPTOMS**

The signs and symptoms of Marfan syndrome can vary greatly, even among members of the same family, because the disorder can affect so many different areas of the body. Some people experience only mild effects, but others develop life-threatening complications.

Marfan syndrome features may include:

* Tall and slender build
* Disproportionately long arms, legs and fingers
* A breastbone that protrudes outward or dips inward
* A high, arched palate and crowded teeth
* Heart murmurs
* Extreme nearsightedness
* An abnormally curved spine
* Flat feet

### **When to see a doctor**

If you think that you or your child may have Marfan syndrome, talk to your doctor or pediatrician. If your doctor suspects a problem, you'll likely be referred to a specialist for further evaluation.

**COMPLICATIONS**

Because Marfan syndrome can affect almost any part of your body, it may cause a wide variety of complications.

### **Cardiovascular complications**

The most dangerous complications of Marfan syndrome involve the heart and blood vessels. Faulty connective tissue can weaken the aorta — the large artery that arises from the heart and supplies blood to the body.

* **Aortic aneurysm.** The pressure of blood leaving your heart can cause the wall of your aorta to bulge out, like a weak spot in a tire. In people who have Marfan syndrome, this is most likely to happen at the aortic root — where the artery leaves your heart.
* **Aortic dissection.** The wall of the aorta is made up of layers. Dissection occurs when a small tear in the innermost layer of the aorta's wall allows blood to squeeze between the inner and outer layers of the wall. This can cause severe pain in the chest or back. An aortic dissection weakens the vessel's structure and can result in a rupture, which may be fatal.
* **Valve malformations.** People who have Marfan syndrome can have weak tissue in their heart valves. This can produce stretching of the valve tissue and abnormal valve function. When heart valves don't work properly, your heart often has to work harder to compensate. This can eventually lead to heart failure.

### **Eye complications**

Eye complications may include:

* **Lens dislocation.** The focusing lens within your eye can move out of place if its supporting structures weaken. The medical term for this problem is ectopia lentis, and it occurs in more than half the people who have Marfan syndrome.
* **Retinal problems.** Marfan syndrome also increases the risk of a detachment or tear in the retina, the light-sensitive tissue that lines the back wall of your eye.
* **Early-onset glaucoma or cataracts.** People who have Marfan syndrome tend to develop these eye problems at a younger age. Glaucoma causes the pressure within the eye to increase, which can damage the optic nerve. Cataracts are cloudy areas in the eye's normally clear lens.

### **Skeletal complications**

Marfan syndrome increases the risk of abnormal curves in the spine, such as scoliosis. It can also interfere with the normal development of the ribs, which can cause the breastbone to either protrude or appear sunken into the chest. Foot pain and low back pain are common with Marfan syndrome.

### **Complications of pregnancy**

Marfan syndrome can weaken the walls of the aorta, the main artery that leaves the heart. During pregnancy, the heart pumps more blood than usual. This can put extra stress on the aorta, which increases the risk of a deadly dissection or rupture.

## **Diagnosis**

Marfan syndrome can be challenging for doctors to diagnose because many connective tissue disorders have similar signs and symptoms. Even among members of the same family, the signs and symptoms of Marfan syndrome vary widely — both in their features and in their severity.

Certain combinations of symptoms and family history must be present to confirm a diagnosis of Marfan syndrome. In some cases, a person may have some features of Marfan syndrome, but not enough of them to be diagnosed with the disorder.

### **Heart tests**

If your doctor suspects Marfan syndrome, one of the first tests he or she may recommend is an echocardiogram. This test uses sound waves to capture real-time images of your heart in motion. It checks the condition of your heart valves and the size of your aorta. Other heart-imaging options include computerized tomography (CT) scans and magnetic resonance imaging (MRI).

If you are diagnosed with Marfan syndrome, you'll need to have regular imaging tests to monitor the size and condition of your aorta.

### **Eye tests**

Eye exams that may be needed include:

* **Slit-lamp exam.** This test checks for lens dislocation, cataracts or a detached retina. Your eyes will need to be completely dilated with drops for this exam.
* **Eye pressure test.** To check for glaucoma, your eye doctor may measure the pressure inside your eyeball by touching it with a special tool. Numbing eye drops are usually used before this test.

### **Genetic testing**

Genetic testing is often used to confirm the diagnosis of Marfan syndrome. If a Marfan mutation is found, family members can be tested to see if they are also affected. You may want to talk to a genetic counselor before starting a family, to see what your chances are of passing on Marfan syndrome to your future children.

**Treatment**

While there is no cure for Marfan syndrome, treatment focuses on preventing the various complications of the disease. To accomplish this, you'll need to be checked regularly for signs that the damage caused by the disease is progressing.

In the past, people who had Marfan syndrome often died young. With regular monitoring and modern treatment, most people with Marfan syndrome can now expect to live a more normal life span.

### **Medications**

Doctors often prescribe blood pressure lowering drugs to help prevent the aorta from enlarging and to reduce the risk of dissection and rupture.

### **Therapy**

The vision problems associated with a dislocated lens in your eye often can be corrected with glasses or contact lenses.

* **Aortic repair.** If your aorta's diameter reaches about 2 inches (50 millimeters) or if it enlarges rapidly, your doctor may recommend an operation to replace a portion of your aorta with a tube made of synthetic material. This can help prevent a life-threatening rupture. Your aortic valve may need to be replaced as well.
* **Scoliosis treatment.** When there is significant scoliosis, a consultation with a spine expert is necessary. Bracing and surgery are needed in some cases.
* **Breastbone corrections.** Surgical options are available to correct the appearance of a sunken or protruding breastbone. Because these operations are often considered to be for cosmetic purposes, your insurance might not cover the costs.
* **Eye surgeries.** If parts of your retina have torn or come loose from the back of your eye, surgical repair is usually successful. If you have cataracts, your clouded lens can be replaced with an artificial lens.

**Lifestyle and home remedies**

You may need to avoid competitive sports and certain recreational activities if you're at increased risk of aortic dissection or rupture. Increases in blood pressure, common in activities such as weightlifting, place extra strain on the aorta. Less intense activities — such as brisk walking, bowling, doubles tennis or golf — are generally safer.

## **Outlook / Prognosis**

If you have Marfan syndrome, you can expect a lot of medical appointments and need to have a thorough understanding of your body. MFS affects everyone differently, so you’ll have your own journey with the syndrome. You’ll work closely with your team of healthcare providers to manage MFS as it changes.

Due to increased knowledge of MFS and advanced medical treatments, people with MFS live much longer than they did before the 1970s. The life expectancy of someone with MFS is now almost the same as it is for people without MFS. But life expectancy is significantly lower in males than in females.

Cardiovascular impairment is still the most common cause of death in MFS. This is mainly due to sudden death in undiagnosed cases of MFS. It’s also more likely to affect people who get a late MFS diagnosis.

#### **MFS and mental health**

Several aspects of living with Marfan syndrome can impact your mental health and quality of life, like:

* The chronic nature of MFS and the need for lifelong treatment
* The ways MFS affects your appearance
* Chronic pain and fatigue
* Limits on physical activity, which are often social interactions
* Family planning stressors

Because of this, you may be at higher risk of:

* Anxiety
* Depression
* Experiencing bullying
* Social isolation

Caregivers and family members of people with MFS are also at risk of these mental health issues.

Be sure to seek help from a mental health specialist (like a psychologist) if you’re experiencing distress related to MFS. Your mental health is just as important as your physical health. Joining a support group may also help.

## **Epidemiology**

The estimated incidence of MFS has ranged from 1 in 5000 to 2-3 in 10,000 persons.The mutation in the fibrillin gene causes pleiotropic effects; thus, a wide range of phenotypic features is derived from a single gene mutation. Several other diseases have presentations similar to MFS, making it exceedingly difficult to determine the exact incidence.

**GENOMIC DATA**

Molecular genetic testing can be performed to assist in making the diagnosis of MFS in the following two clinical situations:

* First, if the specific *FBN1* mutation is known in an individual diagnosed with MFS, this information can be applied to help diagnose family members
* Second, linkage analysis can be performed in families with several individuals who are affected with MFS to assess involvement in the remaining undiagnosed relatives

It is known that the *FBN1* locus is associated with MFS; however, it is possible that other genes may cause a marfanoid habitus with phenotypic manifestations similar to those seen in MFS. The role of molecular genetics testing in the sporadic case is minor. In general, the diagnosis is made on a clinical basis using the previously described Ghent criteria

## **Medical Therapy**

The majority of medical therapy as it relates to MFS has targeted the prevention of cardiovascular compromise, which is the most likely cause of demise in this patient population.Beta blockers and afterload-reducing agents are used to reduce stress on the aortic and mitral valves and the aortic root.

Given that patients with MFS often have abnormal or prosthetic valves, all patients must receive routine antibiotic prophylaxis before undergoing procedures that could produce bacteremia. Researchers have demonstrated that the entire aorta, and especially the root, is stiffer than normal in patients with MFS.

Beta blockers have been given in attempts to decrease the onset and rate of aortic root dilatation and dissection. Studies have demonstrated a synergistic effect with regard to the reduction of aortic stiffness, decreased vascular resistance, and improved cardiac compliance when nitroprusside and beta blockers are used concomitantly.

Beta blockade is used because it is believed to reduce both inotropy and chronotropy and thereby reduce the stress on the aortic root. Nitroprusside reduces overall systemic vascular resistance, which serves to reduce overall afterload and stress on the heart. Further long-term data are needed to establish whether and to what extent these effects translate into decreased morbidity and mortality.

Some evidence suggests that angiotensin-receptor blockers (ARBs) may be useful in MFS. In a systematic review and meta-analysis comparing beta-blocker therapy with ARB therapy in patients with MFS (N = 1449; nine trials), Wang et al found that ARB-only therapy was not inferior to beta blockade alone and that combining the two approaches yielded superior therapeutic effects without significant adverse effects.

Calcium-channel blockers (eg, verapamil) and angiotenson-coverting enzyme inhibitors (ACEIs) have also been investigated with respect to potential effects on cardiovascular physiology in patients with MFS.

Scoliosis is the most common major skeletal deformity encountered in patients with MFS that necessitates intervention. No specific medicinal intervention exists to treat scoliosis. Nonoperative means of treatment (eg, bracing) may be attempted but are usually unsuccessful. Scoliosis occurs in approximately 50-70% of patients with MFS and differs from idiopathic adolescent scoliosis with regard to curve pattern, progression, and symptoms.The double major right thoracic–left lumbar curve is the most common type among patients with MFS, whereas a single pattern is usually seen in the idiopathic type. Pelvic obliquity is uncommon in both types, however.

Unfortunately, these patients often have an earlier onset of scoliosis with severely rigid, painful, and deforming curves, as well as a high incidence of curve progression. The curve progression may average 7-10° per year after the onset of scoliosis, and the curve often progresses rapidly in the early adolescent period during maximal vertebral growth. This is also in contrast to the idiopathic type, which is typically not painful and is not as progressively deforming as the scoliosis in patients with MFS. Scoliosis, in combination with poor musculature and chest deformities, can cause significant respiratory compromise, which mandates early detection and prevention, if possible, in this patient population.

Nonoperative intervention for the scoliosis typically involves observation followed by the use of a thoracolumbosacral orthosis (TLSO) if the curve is mild and reveals signs of progression. Bracing is controversial; many surgeons believe that the bulk of curves in patients with MFS progress regardless of bracing and thus require operative intervention to prevent worsening deformity.

For patients with curves less than 25°, observation and serial radiographs every 3-4 months is the recommended management. When the curve is in the range of 25-40°, Milwaukee bracing or an underarm TLSO is used. This may be a bridge to future surgical intervention. Bracing is only used in patients with mild curves (ie, 25-40°) and no sagittal plane deformity (ie, thoracic lordosis or lumbar kyphosis). Bracing is not indicated for curves that are rigid, large, or associated with sagittal deformities.

## **Marfan Syndrome Treatment Drugs and Their Side Effects**

## 1. Allopurinol

* Use: Recently designated by the European Medicines Agency (EMA) as the first orphan drug for Marfan syndrome treatment, specifically targeting the prevention and management of aortic aneurysm development.
* Status: Currently in preclinical and planned clinical trial phases; not yet widely used for Marfan syndrome but repurposed from gout treatment.
* Common Side Effects (from gout use):
  + Rash, itching
  + Gastrointestinal upset (nausea, diarrhea)
  + Rare but serious hypersensitivity reactions (Stevens-Johnson syndrome)
  + Liver enzyme abnormalities
  + Kidney function monitoring recommended
* Note: Safety and efficacy for Marfan syndrome patients are still under investigation.

## 2. Beta-Blockers (e.g., propranolol)

* Use: Standard treatment to reduce heart rate and blood pressure, thereby decreasing stress on the aorta and slowing its enlargement.
* Benefits: Lower risk of aortic dissection and rupture.
* Common Side Effects:
  + Fatigue, dizziness
  + Cold extremities
  + Bradycardia (slow heart rate)
  + Depression or mood changes (rare)
  + Sexual dysfunction (rare)
* Monitoring: Regular cardiovascular check-ups needed.

## 3. Angiotensin Receptor Blockers (ARBs) (e.g., losartan)

* Use: Alternative or adjunct to beta-blockers; shown to reduce aortic root dilation in some patients by blocking angiotensin II effects.
* Common Side Effects:
  + Dizziness, headache
  + Elevated potassium levels
  + Fatigue
  + Rare allergic reactions
* Monitoring: Blood pressure and kidney function tests recommended.

## 4. Other Medications

* Pain Management: NSAIDs or other analgesics may be used for musculoskeletal pain.
* Anticoagulants: If valve replacement surgery is performed, lifelong anticoagulation (e.g., warfarin) may be necessary, with associated bleeding risks.

## Surgical Treatments (Non-Drug)

* Aortic root repair or replacement (valve-sparing or valve replacement surgery) to prevent rupture.
* Orthopedic surgeries for scoliosis or chest deformities.
* Eye surgeries for lens dislocation or retinal issues.

## **Doctor-Patient Conversation on Marfan Syndrome (De-Identified)**

## Doctor:

Good morning! I see you’ve come in to discuss your recent diagnosis. How are you feeling about it?

## Patient:

Good morning, doctor. Honestly, I’m a bit overwhelmed. I’ve just been told I have Marfan syndrome, but I don’t fully understand what it means.

## Doctor:

That’s completely understandable. Marfan syndrome is a genetic disorder that affects the connective tissue in your body. This tissue supports many parts of your body, including your bones, heart, eyes, and blood vessels.

## Patient:

What kind of problems can it cause?

## Doctor:

People with Marfan syndrome often have features like tall stature, long arms and fingers, and flexible joints. More importantly, it can affect your heart and aorta, which is the main artery from your heart. The aorta can become enlarged and at risk of serious complications like dissection or rupture if not monitored and managed properly.

## Patient:

That sounds serious. What can be done to manage it?

## Doctor:

Management involves a team approach including cardiologists, geneticists, orthopaedic surgeons, and eye specialists. Medications such as beta-blockers or angiotensin receptor blockers like losartan can help reduce stress on your aorta and slow its enlargement.

## Patient:

Are there lifestyle changes I should make?

## Doctor:

Yes, it’s important to avoid strenuous activities, especially contact sports, heavy lifting, or exercises that raise your blood pressure significantly. Regular follow-ups with imaging to monitor your aorta are essential.

## Patient:

Will I need surgery?

## Doctor:

Some patients eventually require surgery to repair or replace the aortic root if it becomes too enlarged. Orthopaedic surgeries may also be needed for joint or spine issues. But with careful monitoring and treatment, many people live active lives.

## Patient:

Is this condition inherited? What about my family?

## Doctor:

Marfan syndrome is inherited in an autosomal dominant pattern, meaning there’s a 50% chance of passing it to your children. Genetic counseling can help you understand this better and discuss testing for family members.

## Patient:

What about my vision? I’ve heard it can affect the eyes too.

## Doctor:

Yes, eye problems like lens dislocation and nearsightedness are common. Regular eye exams are important to catch and manage these issues early.

## Patient:

How often will I need to see doctors?

## Doctor:

Initially, every 6 to 12 months for cardiac imaging and clinical assessments, then possibly less often if stable. But it depends on your individual situation.

## Patient:

This is a lot to take in. Is there support available?

## Doctor:

Absolutely. There are support groups and resources to help you cope emotionally and connect with others living with Marfan syndrome. Psychological support can be very helpful.

## Patient:

Thank you, doctor. I feel better knowing there’s a plan.

## Doctor:

You’re welcome. We’ll work together to manage your condition and maintain your quality of life. Please don’t hesitate to reach out with any questions.

REFERENCES

<https://emedicine.medscape.com/article/1258926-treatment>

[Marfan syndrome - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/marfan-syndrome/diagnosis-treatment/drc-20350787)

[Marfan Syndrome: Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/17209-marfan-syndrome#outlook-prognosis)

<https://web.ub.edu/en/web/actualitat/w/primer-medicament-orfe-sindrome-marfan>

**PERTHES DISEASE**

**DEFINITION AND DESCRIPTION**

Legg-Calve-Perthes (LEG-kahl-VAY-PER-tuz) disease is a childhood condition that occurs when blood supply to the ball part (femoral head) of the hip joint is temporarily interrupted and the bone begins to die.

This weakened bone gradually breaks apart and can lose its round shape. The body eventually restores blood supply to the ball, and the ball heals. But if the ball is no longer round after it heals, it can cause pain and stiffness. The complete process of bone death, fracture and renewal can take several years.

To keep the ball part of the joint as round as possible, doctors use a variety of treatments that keep it snug in the socket portion of the joint. The socket acts as a mold for the fragmented femoral head as it heals.

Legg-Calve-Perthes disease (LCPD) goes by various other names, including:

* Perthes disease.
* Perthes syndrome.
* Legg Calve.
* Legg-Perthes.
* Calve-Perthes.
* Coxa plana.

Estimates suggest Legg-Calve-Perthes disease affects around 1 in 12,000 children worldwide. It’s five times more common in male kids than female kids.

#### **What age is Legg-Calve-Perthes most common?**

Perthes disease is most common in kids ages 5-7. But it can affect kids as young as 2 or as old as 12.

#### **Is Legg-Calve-Perthes disease permanent?**

Perthes syndrome triggers a process of degeneration and regeneration in your child’s femur bone, which can last several years. The condition is temporary, but it can cause permanent changes.

#### **Can Perthes disease cause problems later in life?**

If the shape of your child’s femur head changes a lot, it might not fit properly in their hip socket anymore. Treatment can help, but if it continues not to fit, they can develop hip problems later in life.

### **causes Legg-Calve-Perthes disease**

Perthes disease develops when blood supply to the head of the femur bone temporarily slows or stops. This is called ischemia. Since the bone depends on blood supply for oxygen and nutrients, it starts to die and break down without them. This process is called avascular necrosis (osteonecrosis).

Normally, ischemia might happen if a blood vessel gets blocked or compressed. Artery disease or a blood clot might block it from the inside, or swelling might compress it from the outside. But researchers don’t know what causes ischemia in LCPD. It’s possible that different things cause it in different kids.

### **signs and symptoms of Legg-Calve-Perthes disease**

Signs and symptoms of Perthes develop over time and often with no clear beginning. You or your child might start to wonder what’s up when symptoms appear and don’t seem to ever get better.

Early symptoms might include:

* **A limp**. Your child may favor one leg while walking to keep weight off the affected side. A limp often appears before your child notices any pain. They may not know why they’re limping.
* **Hip pain**. If your kid has pain, it’s most likely to occur early in the disease process, when the bone has lost its blood supply and it’s starting to degenerate. Pain worsens with activity.
* **Referred pain.** Some kids may feel pain in their knees, thighs, pelvises or abdomens instead.
* **Leg cramps.** Kids may experience muscle spasms in the leg muscles connected to their hip joints.

Later signs and symptoms of LCPD may include:

* **Trendelenburg gait**. This is an abnormal walking pattern that’s characteristic of hip problems. Weak hip muscles cause the pelvis to tilt downward on the affected side as your child walks.
* **Limited range of motion**. Your child may have difficulty rotating their hip. They may not be able to open their thighs outward or turn their knees inward as far as they used to.
* **Muscle atrophy**. You may notice loss of muscle mass in your child’s thighs and buttocks.
* **Leg length discrepancy**. One leg may appear shorter than the other.

#### **Risk factors**

Research suggests that about half of kids who develop LCPD have some type of blood clotting disorder. Another suggested cause is a traumatic injury or repetitive strain injury that caused enough swelling to cut off blood flow to the bone. Around 10% of cases seem to relate to an inherited gene mutation.

Factors that may increase your child’s risk of developing Legg-Calve-Perthes include:

* Delayed skeletal growth.
* Low birth weight.
* Short stature.
* Abnormal teeth.
* Low socioeconomic status.
* Secondhand smoke exposure.
* Blood clotting disorders.
* HIV infection.
* Involvement in sports or gymnastics.
* Inherited mutations in the *COL2A1* gene.

### **How will Perthes disease affect my child?**

While Legg-Calve-Perthes is active, the head of your child’s femur bone in their hip socket will go through a process of degeneration (breakdown) and then regeneration (rebuilding). The breakdown phase may take up to a year, and the rebuilding and remodeling phase may last two to five years.

Some kids have more tissue loss than others. This might be because they have more severe ischemia, or it lasts longer, or they use their bone too much while it’s weakened, causing additional damage. In some kids, the rounded heads of their femurs collapse and flatten. This makes them fit poorly in their hip sockets.

When the bone begins to rebuild, it has another chance to restore its proper shape and fit. But different kids have different amounts of regrowth. Some femurs never recover their former size and shape. Others may overgrow the hip socket. Your healthcare provider will try to influence these outcomes.

Some kids might need to immobilize their hips in a cast for some time. Others might need surgery. These treatments can help the bone regrow correctly. Kids who continue to have poorly fitted hip joints will have ongoing symptoms. Hip dysplasia (a poor fit) can lead to complications like arthritis later in life.

## **Diagnosis**

During the physical exam, your healthcare professional might move your child's legs into various positions to check range of motion and see whether any of the positions cause pain.

### **Imaging tests**

These types of tests, which are vital to the diagnosis of Perthes disease, might include:

* **X-rays.** Initial X-rays may not show changes in the hip. It can take 1 to 2 months after symptoms begin for the changes related to Perthes disease to become clear on X-rays. Your healthcare professional will likely recommend several X-rays over time to track the progression of the disease.
* **MRI.** This technology uses radio waves and a strong magnetic field to make very detailed images of bone and soft tissue inside the body. MRIs often can visualize bone damage caused by Perthes disease more clearly than X-rays can, but MRI isn't always needed.

**Treatment**

In Perthes disease, the complete healing process can take several years. The types of treatment recommended depend on the:

* Age when symptoms began.
* Stage of the disease.
* Amount of hip damage.

As Perthes disease gets worse, the ball part of the joint, called the femoral head, weakens and breaks apart. During healing, the socket part of the joint can serve as a mold. This can help the weakened femoral head keep its round shape.

For this molding to work, the femoral head must sit snugly within the socket. Sometimes a child wears a special type of leg cast that spreads the legs widely apart for 4 to 6 weeks to keep the bone in the right position.

Some children need surgery to help keep the ball of the joint snug within the socket. This procedure might involve making wedge-shaped cuts in the thigh bone or pelvis to align the joint again.

Surgery generally isn't needed for children younger than 6. In this age group, the hip socket is naturally more moldable, so the ball and socket usually continue to fit together well without surgery.

### **Other treatments**

Some children, especially very young ones, might need only conservative treatments or observation. Conservative treatments can include:

* **Activity restrictions.** Children with Perthes disease should not run, jump or take part in other high-impact activities that might speed up hip damage.
* **Crutches.** Sometimes, your child may need to avoid bearing weight on the affected hip. Using crutches can help protect the joint.
* **Physical therapy.** As the hip stiffens, the muscles and ligaments around it may shorten. Stretching exercises can help keep the hip more flexible.
* **Anti-inflammatory medicines.** Your healthcare professional might recommend infants' or children's medicines that you can buy without a prescription, such as ibuprofen (Advil, Motrin, others) to help relieve your child's pain.

## **Treatment Drugs and Their Side Effects**

## 1. Bisphosphonates

* Use: Bisphosphonates (BPs) are used experimentally to prevent femoral head deformity by inhibiting osteoclastic bone resorption during the fragmentation phase of the disease
* Effectiveness: Some clinical and animal studies suggest BPs reduce deformity and improve pain and gait, but consistent clinical evidence is lacking, and more research is needed
* Side Effects: Common side effects of bisphosphonates (from general medical knowledge) include gastrointestinal upset, hypocalcemia, and rarely osteonecrosis of the jaw. Specific side effects in children with LCPD are not well documented due to limited studies

## 2. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

* Examples: Ibuprofen (Advil, Motrin), Naproxen (Aleve)
* Use: NSAIDs are used to relieve pain and reduce inflammation in affected joints
* Side Effects: Potential side effects include gastrointestinal irritation, stomach ulcers, kidney function impairment, and increased bleeding risk with prolonged use.

## 3. Other Medications

* Over-the-counter pain relievers: Often recommended for mild pain management, especially in younger children
* No corticosteroids or other specific drugs are routinely used as primary treatment due to the nature of the disease.

## **Legg-Calve-Perthes Disease Staging**

## 1. Waldenström Stages (Radiographic Disease Stages)

These stages describe the natural progression of the disease and are used to time treatment:

* Stage 1: Initial (Necrosis)
  + Ischemia causes bone death and sclerosis of the femoral head.
* Stage 2: Fragmentation
  + Resorption of necrotic bone, fibrovascular invasion, and fragmentation of the femoral head.
* Stage 3: Reossification
  + New bone formation replaces resorbed bone.
* Stage 4: Healed/Residual
  + Bone remodeling completes; femoral head shape stabilizes.

The average duration of these stages is roughly 5 months (initial), 9 months (fragmentation), and 19 months (reossification and healing)[6](https://posna.org/physician-education/study-guide/legg-calve-perthes-disease)[7](https://www.orthopaedia.com/legg-calve-perthes-disease/).

## 2. Catterall Classification (Prognostic)

Based on the extent of femoral head epiphyseal involvement on X-ray:

| Grade | Description | Prognosis |
| --- | --- | --- |
| I | Very anterior involvement; no metaphyseal involvement | Excellent prognosis at any age |
| II | Anterior involvement < 50%; possible metaphyseal involvement | Good prognosis if <4 years old; 50% good if >4 years |
| III | Anterior involvement > 50%; frequent metaphyseal involvement | Poor prognosis |
| IV | Total epiphyseal involvement; metaphyseal involvement | Poor or bad prognosis |

This classification helps predict long-term outcomes

## 3. Herring Lateral Pillar Classification (Widely Used Prognostic System)

Based on the height of the lateral pillar of the femoral head during the fragmentation stage (about 6 months after symptom onset):

* Group A: No loss of lateral pillar height.
* Group B: Lateral pillar height maintained >50%.
* Group B/C Border: Narrow or poorly ossified lateral pillar with about 50% height.
* Group C: Lateral pillar height <50% (significant collapse).

This classification has the best interobserver reliability and correlates well with prognosis and treatment decisions

## 4. Stulberg Classification (Outcome Classification)

Used after healing to predict long-term hip function and arthritis risk:

| Class | Description | Outcome |
| --- | --- | --- |
| I | Normal, congruent hip | No arthritis |
| II | Spherical head but with minor deformities | No arthritis |
| III | Ovoid or mushroom-shaped femoral head | Mild to moderate arthritis |
| IV | Flat femoral head but congruent joint | Mild to moderate arthritis |
| V | Flat femoral head with incongruent joint | Severe arthritis before age 50 |

## **Legg-Calve-Perthes Disease Procedures and Timelines**

## Disease Progression and Staging

* The disease progresses through stages: initial ischemia and necrosis, fragmentation (about 6 months after symptoms start), reossification, and healing over several years
* The fragmentation stage is a key point for assessment and treatment decisions, often around 6 months after symptom onset

## Treatment Goals

* Control pain and symptoms.
* Restore and maintain hip range of motion.
* Contain the femoral head within the acetabulum to allow proper remodeling and prevent deformity

## **Conservative (Non-Surgical) Procedures and Timeline**

* Initial Phase (Early disease, especially in children under 6-7 years):
  + Activity modification and symptom management.
  + Use of NSAIDs for pain relief.
  + Physical therapy to maintain hip motion.
  + Limited weight-bearing or use of crutches.
  + Abduction braces or orthoses to keep the femoral head well-seated in the socket.
  + Sometimes a special leg cast (e.g., Petrie cast) is applied for 4 to 6 weeks to maintain hip positioning
* Duration: Conservative treatment and monitoring can last several years, as the bone slowly heals and remodels

## **Surgical Procedures and Timeline**

* Surgery is generally considered for:
  + Older children (typically over 7-8 years).
  + Severe cases with significant femoral head involvement or poor prognostic signs (e.g., lateral pillar group B or C).
  + Cases where conservative treatment fails to maintain femoral head containment
* Common Surgical Procedures:
  + Femoral osteotomy: Wedge-shaped cut in the femur to realign the femoral head into the acetabulum.
  + Pelvic osteotomy: Reshaping or repositioning of the pelvis to improve femoral head coverage.
  + Surgery aims to improve joint congruency and promote better femoral head remodeling
* Post-Surgery:
  + Immobilization and physical therapy follow surgery.
  + Recovery and remodeling continue over months to years

**Complications**

Children who have had Perthes disease are at higher risk of developing hip arthritis in adulthood — especially if the hip joint has poor healing. If the ball-and-socket joint doesn't fit together well after healing, the joint can wear out early.

In general, children who are diagnosed with Perthes disease after age 6 are more likely to develop hip conditions later in life. The younger the child is at the time of diagnosis, the better the chances for the hip joint to heal in a typical, round shape.

## **Outlook / Prognosis**

If your child has developed Legg-Calve Perthes, you can expect a healthcare journey of several years, with different phases in it. This will intrude on their childhood, to some extent — less for some than others. But when it’s over, most can return to their activities without limitations or ongoing symptoms.

If your child is younger than 7, they’re more likely to recover fully with conservative treatments. If they’re older than 7, they’re more likely to need surgery. Kids who don’t get the right treatment at the right time, and whose femur bones remain deformed, can develop hip osteoarthritis later in life.

## **Prevention**

Unfortunately, no. There are no known ways to prevent Perthes disease.

### **What questions should I ask my healthcare provider about Perthes disease?**

If your child has Legg-Calve-Perthes, you’ll probably have many questions about their treatment and expected prognosis. Your provider will do their best to forecast what to expect for your child.

You might want to ask:

## What stage is the disease in?

LCPD progresses through four stages:

1. Initial/Necrosis: Blood supply to the femoral head is disrupted, causing bone death and inflammation. This stage lasts several months up to 1 year.
2. Fragmentation: The body absorbs dead bone and forms new bone; the femoral head is soft and at risk of flattening. This stage can last 1 to 3 years.
3. Reossification: New stronger bone forms, filling in areas of bone loss. This is often the longest stage, lasting 2-3 years.
4. Healed/Remodeling: Bone regrowth is complete; the femoral head shape stabilizes, though deformities may remain. This stage determines long-term outcome.  
   The exact stage is determined by clinical and radiographic assessment

## How severe is it?

Severity depends on:

* The extent of femoral head involvement (partial or total).
* The degree of femoral head collapse or deformity during fragmentation.
* The child’s age at onset (younger children generally have better prognosis).
* Whether the femoral head remains well-contained within the hip socket.  
  Classification systems like the Herring lateral pillar and Catterall grades help estimate severity and prognosis

## How should we adjust my child’s lifestyle or activities?

* Limit high-impact activities and weight-bearing to reduce stress on the femoral head, especially during the fragmentation stage.
* Use crutches or assistive devices as recommended to offload the hip.
* Encourage gentle range-of-motion exercises and physical therapy to maintain hip mobility and muscle strength.
* Avoid activities that cause pain or limp worsening.
* Most children can gradually return to normal activities after healing, often within 2-5 years

## What factors may have contributed to their condition?

* The exact cause is unknown.
* It involves temporary loss of blood supply (ischemia) to the femoral head leading to bone death.
* Some studies suggest a possible genetic predisposition.
* Other potential factors include trauma, coagulation abnormalities, or environmental influences, but none are definitively proven

## What symptoms or changes should we look out for during treatment?

* Persistent or worsening limp.
* Hip, thigh, or knee pain, especially after activity.
* Decreased hip range of motion or stiffness.
* Signs of femoral head flattening or subluxation on follow-up X-rays.
* Any increase in pain or new symptoms should prompt medical review to adjust treatment

## What should I tell my child about what to expect?

* The disease progresses slowly and healing can take several years.
* They may need to limit some activities and use crutches or braces temporarily.
* Pain and limping may come and go during treatment.
* Most children eventually recover well, especially if treated early.
* Some changes in hip shape may remain, but treatment aims to keep the hip as healthy as possible for the future.
* Encourage patience and reassure them that doctors and therapists will help them through the process

**Differential diagnoses to consider are:**

* Septic arthritis: Infection of the hip joint causing acute pain, swelling, and systemic symptoms.
* Osteomyelitis: Bone infection that can mimic early LCPD symptoms and radiographic changes.
* Transient synovitis (Coxitis fugax): A common cause of hip pain and limp in children, usually self-limited and less severe than LCPD.
* Multiple epiphyseal dysplasia (MED): A genetic disorder affecting the growth of epiphyses, which can resemble LCPD radiographically.
* Slipped capital femoral epiphysis (SCFE): A condition where the femoral head slips off the neck, often in adolescents, presenting with limp and hip/knee pain.
* Juvenile idiopathic arthritis: Chronic joint inflammation that can cause hip pain and swelling.
* Meyer’s dysplasia and spondyloepiphyseal dysplasia: Skeletal dysplasias that may mimic LCPD on imaging.
* Chondroblastoma: A benign bone tumor affecting the epiphysis.
* Hip dysplasia: Abnormal development of the hip joint that can cause similar symptoms.
* Other causes of osteonecrosis: Including sickle cell disease, corticosteroid use, leukemia, Gaucher disease, and other systemic conditions causing secondary avascular necrosis.

**Epidemiology**

Legg-Calve-Perthes disease usually occurs between the ages of 3 to 12 years old, with the highest rate of occurrence at 5 to 7 years. It affects 1 in 1200 children under the age of 15. Legg-Calve-Perthes disease occurs most commonly in male patients, with a male to female ratio between 4:1 and 5:1. It is bilateral in 10% to 20% of affected cases. When it occurs bilaterally, it is usually asymmetrical and discovered in different stages of the disease. If it is symmetrical, the examiner must consider multiple epiphyseal dysplasias as the culprit. Caucasians and Asians are more commonly affected. It is also more prevalent in urban areas in patients with lower socioeconomic status. Risk factors for Legg-Calve-Perthes disease include:

* Ten percent familial (there is a delayed bone age by about 2 years)
* HIV (Up to 5% of HIV patients have avascular necrosis of the hip)
* Factor V Leiden and other inherited coagulopathies
* Thrombophilias (increased clotting)
* Hypofibrinolysis (decreased ability to dissolve clots)
* Secondhand smoke exposure (OR=5)
* Low socioeconomic status
* Birth weight less than 2.5 kg in boys
* Short stature

**GENOMIC DATA**

COL2A1 gene: Some familial cases of LCPD have been linked to mutations in the *COL2A1* gene, which encodes type II collagen, a key protein in connective tissues. Specific missense mutations in *COL2A1* have been identified in affected families, suggesting a possible autosomal dominant inheritance pattern in rare cases. However, many researchers currently believe *COL2A1* variants do not cause most LCPD cases

* TRPS1 gene: Novel mutations in the *TRPS1* gene have been reported in some families with LCPD, indicating a potential role in disease development
* Coagulation gene variants: Mutations in coagulation-related genes, such as Factor V Leiden (G1691A) and Factor II (prothrombin), have been associated with increased risk of LCPD, suggesting hypercoagulability may contribute to the ischemic process causing femoral head necrosis
* Inflammatory gene polymorphisms: Certain polymorphisms in the IL-6 gene have been linked to increased susceptibility in some populations
* Other genetic factors: Mutations in *COL1A1* (associated with osteogenesis imperfecta) have been rarely reported in patients presenting with LCPD-like features, indicating possible overlap with other connective tissue disorders
* Multifactorial etiology: Overall, LCPD is considered multifactorial, involving a combination of genetic predisposition, environmental influences (e.g., passive smoking), metabolic factors, and possibly epigenetic changes
* Prevalence: LCPD affects about 29 per 100,000 children under 15, most commonly in white populations

## **Doctor-Patient Conversation on Perthes Disease (De-Identified)**

## Doctor:

Hello! I understand your child has been experiencing some hip pain and limping. Can you tell me more about what you’ve noticed?

## Parent:

Yes, doctor. My child has been limping for a few weeks and sometimes complains of pain in the hip and thigh. The pain seems worse after activity.

## Doctor:

Thank you for sharing. Based on the symptoms and the imaging we’ve done, your child has a condition called Perthes disease. It affects the hip joint, specifically the ball at the top of the thigh bone called the femoral head.

## Parent:

What exactly happens in Perthes disease?

## Doctor:

In Perthes disease, the blood supply to the femoral head is temporarily disrupted. Without enough blood, part of the bone dies—a process called avascular necrosis. This weakens the bone, and it can become flattened or misshapen due to pressure and weight-bearing.

## Parent:

Is this permanent? Will my child be in pain forever?

## Doctor:

The good news is that over time, usually one to two years, the dead bone is gradually replaced with new, healthy bone. However, during this time, the hip can be painful and stiff. The goal of treatment is to protect the hip, reduce pain, and keep the femoral head as round as possible to maintain joint function.

## Parent:

What kind of treatment will my child need?

## Doctor:

Treatment varies depending on the severity and your child’s age. It can include activity modification to reduce stress on the hip, physical therapy to maintain range of motion, and sometimes bracing or casting. In more severe cases, surgery may be needed to help the hip joint develop properly.

## Parent:

Will my child be able to walk and play normally again?

## Doctor:

Most children recover well, especially with early and appropriate treatment. The hip usually regains good function, though some children may have long-term changes or arthritis later in life.

## Parent:

How long will this process take?

## Doctor:

The disease process and healing can take several years. We will monitor your child regularly with clinical exams and imaging to track progress and adjust treatment as needed.

## Parent:

Is there anything I should watch for or avoid?

## Doctor:

Avoid activities that put excessive weight or impact on the hip, like running and jumping, especially during flare-ups. Swimming and gentle exercises are usually encouraged. Also, watch for worsening pain, decreased movement, or limping that gets worse.

## Parent:

Thank you, doctor. This helps me understand what to expect.

## Doctor:

You’re welcome. We’ll work together to support your child’s recovery and keep you informed every step of the way. Please reach out if you have any concerns.

REFERENCES

[Legg-Calve-Perthes (Perthes Disease): Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/legg-calve-perthes-disease)

[Legg-Calve-Perthes disease - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/legg-calve-perthes-disease/symptoms-causes/syc-20374343)

<https://www.ncbi.nlm.nih.gov/books/NBK513230/#article-24174.s9>

<https://emedicine.medscape.com/article/1248267-overview#a5>

### **Achondroplasia**

**Definition**

In the early stages of development, much of the fetal skeleton is made up of cartilage tissue, which turns into bone. Achondroplasia occurs when cartilage tissue doesn't develop in the bones of your arms and legs. This genetic disorder leads to short-limb dwarfism with the upper parts of arms and legs shorter than the lower portions of those limbs (rhizomelic shortening).

### **Achondroplasia and skeletal dysplasia (dwarfism)**

Achondroplasia is the most common form of skeletal dysplasia, which is the umbrella term used to identify hundreds of conditions that affect the growth of bones and cartilage. Achondroplasia specifically targets bone growth in your arms and legs.

### **Is achondroplasia hereditary?**

* Most cases of achondroplasia are not inherited. Anyone can be affected by achondroplasia. Around 80% of individuals with achondroplasia have parents of normal height and are born with a new gene alteration (de novo mutation). It is rare that these parents will have another child with achondroplasia.
* Only one parent needs to pass down the gene for a child to be born with achondroplasia (autosomal dominant). There is a 50% chance of a person with achondroplasia and a partner who does not have achondroplasia having a child with the disorder.
* If both parents have achondroplasia, there is a 25% chance that the child will be born with homozygous achondroplasia, which leads to stillbirth or death shortly after birth.

About 1 in 15,000 to 1 in 40,000 individuals are born with achondroplasia.

### **How does achondroplasia affect my child’s body?**

Infants born with achondroplasia normally have weak muscle tone (hypotonia), which could delay motor skill development. There’s is also a high risk of spinal cord compression and upper respiratory blockages among infants, which increases the risk of health complications.

It is common for people with achondroplasia to have breathing problems, recurrent ear infections and be prone to obesity.

All children with achondroplasia should be carefully monitored regularly by a healthcare provider to treat or prevent any symptoms that may arise.

### **What causes achondroplasia?**

Achondroplasia is caused by a gene mutation in the receptor that converts cartilage to bone during fetal development.

### **Symptoms of achondroplasia**

* Bones are shortened (thigh, upper arm).
* Short hands and feet.
* Large separation between third and fourth fingers.
* Maximum height of 4-ft.
* Head larger than normal.
* Prominent forehead.
* Flat nose.
* Delayed development in infants (sitting, crawling, walking).

### **What are the long-term effects of achondroplasia on your body?**

* Back and leg pain.
* Breathing problems (apnea).
* Obesity.
* Recurring ear infections.
* Curved spine.
* Bowed legs.
* Excess fluid on your brain (hydrocephalus).
* Obstructive sleep apnea.

## **Diagnosis and Tests**

Doctors can use ultrasounds to detect achondroplasia before birth if your baby’s arms and legs appear shorter than average and if their head is large. Most cases of achondroplasia aren't confirmed until after birth.

* X-ray.
* Physical examination.
* Prenatal examination (if one or both parents are affected).
* Genetic testing (FGFR3 gene).
* MRI or CT scan to identify muscle weakness or spinal cord compression.

## **Management and Treatment**

There is no specific treatment for achondroplasia other than managing symptoms. Monitoring height, weight and head circumference is recommended during early diagnosis in infants to track growth progress.

No, there's no cure for achondroplasia, but almost everyone who's diagnosed is able to live a full and healthy life.

Management of achondroplasia is focused on taking care of potential complications, which may include:

* Weight management and encouraging healthy eating habits to prevent obesity.
* Surgery (ventriculoperitoneal shunt) to decrease fluid pressure on your brain or to correct a life-threatening complication called craniocervical junction compression.
* Surgery to remove adenoids and tonsils.
* Growth hormones.
* Use of continuous positive airway pressure (CPAP) nasal mask for apnea.
* Ear tubes or antibiotics to prevent ear infections.
* Support for socialization.
* Much research is being done on medications that might help increase height by a few inches.

## **Achondroplasia "staging" or progression:**

* Present at birth: Achondroplasia is a genetic disorder caused by a mutation in the FGFR3 gene, leading to abnormal cartilage formation and impaired endochondral ossification, primarily affecting the long bones of the arms and legs
* Clinical features manifest early: These include rhizomelic shortening (shortening of the proximal limbs), large head with frontal bossing, midface hypoplasia, trident hands, spinal curvature abnormalities (kyphosis, lordosis), and characteristic radiographic findings
* Complications develop over time: Children may experience delayed motor milestones, bowed legs, spinal stenosis, hydrocephalus, ear infections, and sleep apnea. Adults may develop obesity, nerve compression symptoms, and psychosocial issues
* No progressive staging system: Unlike diseases with defined stages, achondroplasia is a static genetic condition with lifelong manifestations and potential complications that may evolve or require management at different ages.
* Management focuses on monitoring and treating complications rather than disease stages, including surgical interventions for spinal stenosis or hydrocephalus, physical therapy, and supportive care

## **Achondroplasia Treatment Drugs and Their Side Effects**

## 1. Vosoritide (Voxzogo)

* Description:  
  Vosoritide is an FDA-approved drug for children aged 2 years and older with achondroplasia. It is a modified C-type natriuretic peptide (CNP) analog that counteracts the overactive FGFR3 receptor responsible for impaired bone growth in achondroplasia. By promoting chondrocyte proliferation and endochondral ossification, it helps increase growth velocity and improve linear bone growth.
* Administration: Daily subcutaneous injections.
* Side Effects:
  + Injection site reactions (pain, redness, swelling)
  + Hypotension (low blood pressure)
  + Mild gastrointestinal symptoms (nausea, vomiting)
  + Possible mild headache or dizziness
  + Long-term safety is still under study, requiring regular monitoring.

## 2. Growth Hormone Therapy

* Description:  
  Growth hormone (GH) therapy is sometimes used off-label to improve growth velocity in children with achondroplasia, especially if they have coexisting GH deficiency. It can modestly increase height but does not significantly alter final adult stature.
* Administration: Regular subcutaneous injections.
* Side Effects:
  + Injection site reactions
  + Headaches
  + Joint and muscle pain
  + Risk of increased intracranial pressure (rare)
  + Possible glucose intolerance or insulin resistance
  + Requires careful monitoring by endocrinologists.

## 3. Symptom-Directed Treatments (Non-Drug)

* While not drugs, important supportive treatments include:
  + Adenoidectomy/tonsillectomy or CPAP/BiPAP for obstructive sleep apnea.
  + Myringotomy with pressure equalizing tubes for middle ear dysfunction and hearing loss.
  + Surgical interventions for spinal stenosis, kyphosis, or limb deformities.

## **Surgical Care**

Most of the orthopedic problems encountered in patients with achondroplasia are related to the spine. Craniocervical stenosis, thoracolumbar kyphosis, spinal stenosis, angular deformities of the lower extremities, and lengthening of the short extremities are the orthopedic problems commonly addressed in achondroplasia.

### **Treatment of spinal canal stenosis**

Wide multilevel laminectomies extending to the pedicles and lateral recesses with foraminotomies may be necessary. Extradural removal of herniated disk material is performed as necessary. To prevent recurrence, decompression usually extends from the lower thoracic spine to the sacrum. Maintaining the integrity of facet joints is necessary to prevent postlaminectomy instability. If instability does occur, anterior fusion may be necessary.

To obtain successful results, it is important to ensure that laminectomies are carried out to the appropriate extent, which should be three levels cephalad to the proximal extent of compression, distal to the second sacral level, and lateral to the facet joints. The results of this more extensive approach are encouraging.

### **Treatment of thoracolumbar kyphosis**

For the child who has not begun to walk, treatment of thoracolumbar kyphosis consists of mere observation because spontaneous resolution frequently occurs. Reports exist that demonstrate the efficacy of early prohibition of unsupported sitting.If wedging of the apical vertebra persists after independent ambulation (typically, wedging of T12 or L1), an extension-type thoracolumbosacral orthosis should be used.

## **Outlook / Prognosis**

The majority of people living with achondroplasia have a normal life span and normal intelligence, regardless of delayed development in infancy. Though complications from achondroplasia are a possibility, taking care of symptoms can help prevent serious health problems from occurring later in life.

## **Prevention**

Since achondroplasia is a rare genetic condition that's often the result of a new gene mutation, there's no way to prevent those random cases. If a parent has achondroplasia, the chance to pass it on could be significantly decreased through preimplantation genetic testing. If you’re interested in learning more, please speak with your OB/GYN provider.

**Living With**

Children diagnosed with achondroplasia can lead healthy and full lives. After treating your child’s medical needs, focus on providing a welcoming environment for your child to thrive by:

* Eliminating physical challenges to promote independence (use of a step stool, extending light switches).
* Providing emotional and educational support (to prevent bullying in school).
* Engaging with groups and organizations in the dwarfism community.

### **When should I contact my healthcare provider?**

Staying regular with checkups during infancy and throughout childhood can prevent many symptoms of achondroplasia from occurring.

Contact your healthcare provider during early infancy if your child isn’t meeting height benchmarks for their age or you’re seeing developmental delays in physical goals, like sitting, crawling and walking.

If your child’s having problems breathing, frequently gets ear infections, has back and leg pain or is at risk of obesity, seek treatment from a healthcare professional.

## **Differential Diagnosis of Achondroplasia**

* Hypochondroplasia  
  A milder form of FGFR3-related skeletal dysplasia with less severe short stature and less pronounced radiographic changes than achondroplasia.
* Thanatophoric Dysplasia  
  A severe, often lethal skeletal dysplasia caused by different *FGFR3* mutations, characterized by extremely short limbs, narrow thorax, and underdeveloped lungs.
* Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans (SADDAN) Syndrome  
  A rare disorder involving severe skeletal abnormalities, developmental delay, and skin changes, also caused by *FGFR3* mutations.
* Pseudoachondroplasia  
  A distinct skeletal dysplasia with short stature but normal facial features and different radiographic findings, including epiphyseal abnormalities.
* Metaphyseal Dysplasias (e.g., Schmid type, Cartilage-Hair Hypoplasia)  
  Differentiated by clinical presentation and radiographic features, often involving metaphyseal irregularities.
* Achondrogenesis  
  A group of lethal skeletal dysplasias with severe bone hypoplasia and distinct radiographic features.
* Chondroectodermal Dysplasia (Ellis-van Creveld Syndrome)  
  Characterized by short limbs, polydactyly, and cardiac defects.
* Metatropic Dysplasia  
  Severe skeletal dysplasia with progressive spinal deformities.
* Asphyxiating Thoracic Dystrophy (Jeune Syndrome)  
  Characterized by a small thoracic cage causing respiratory issues.
* Osteogenesis Imperfecta  
  A connective tissue disorder causing brittle bones but with different clinical and radiographic features.
* Spondyloepiphyseal Dysplasia Congenita  
  A skeletal dysplasia affecting spine and epiphyses with short trunk dwarfism.
* Fibrochondrogenesis, Chondrodysplasia Punctata, Kniest Dysplasia  
  Rare skeletal dysplasias with distinctive radiographic findings.

## **Achondroplasia Epidemiology**

Prevalence:  
Achondroplasia is the most common skeletal dysplasia causing disproportionate short stature, yet it remains a rare disease. The estimated global prevalence ranges from 1 to 9 individuals per 100,000 persons in the general population

Birth Incidence:  
The worldwide birth prevalence is approximately 4.6 to 4.7 per 100,000 births (roughly 1 in 20,000 to 1 in 30,000 live births) This estimate comes from a systematic review and meta-analysis covering studies from 1950 to 2019 involving over 48 million births

Geographic and Ethnic Variation:  
Higher birth prevalence rates have been reported in North Africa, sub-Saharan Africa, and the Middle East compared to Europe and the Americas, suggesting possible influences of ethnicity, genetics, or environmental factors including urbanization and pollution  
In Europe, prevalence estimates are around 3.6 to 3.7 per 100,000 births

Gender Distribution:  
Achondroplasia occurs with equal frequency in males and females

Population Estimates:  
Approximately 150,000 people worldwide are estimated to have achondroplasia, representing about 80% of individuals with dwarfism globally. In the United States, about 10,000 individuals are affected

Inheritance and Genetics:  
Achondroplasia is inherited in an autosomal dominant pattern, but about 80% of cases result from de novo mutations

Mortality and Morbidity:  
Mortality is increased compared to the general population, especially in early childhood due to brainstem compression and respiratory complications. Morbidity includes recurrent ear infections, spinal stenosis, and respiratory problems

## **Genomic Data of Achondroplasia**

* Causative Gene:  
  Achondroplasia is caused by mutations in the *FGFR3* (Fibroblast Growth Factor Receptor 3) gene located on chromosome 4p16.3
* Common Mutations:  
  More than 99% of achondroplasia cases are caused by one of two point mutations in *FGFR3* that result in a glycine-to-arginine substitution at codon 380 (G380R) in the transmembrane domain of the FGFR3 protein
  + The most frequent mutation is a G-to-A transition at nucleotide 1138 (G1138A).
  + A less common mutation is a G-to-C transversion at the same nucleotide (G1138C)
* Molecular Mechanism:  
  These gain-of-function mutations cause the FGFR3 receptor to be overly active, leading to excessive inhibition of chondrocyte proliferation and differentiation in the growth plate. This disrupts normal endochondral ossification, resulting in shortened bones and the characteristic features of achondroplasia
* Inheritance Pattern:  
  Achondroplasia is inherited in an autosomal dominant manner, but over 80% of cases arise from new (de novo) mutations, frequently associated with advanced paternal age
* Animal Models:  
  Mouse models with the human *FGFR3* G380R mutation replicate the human achondroplasia phenotype, including limb shortening and craniofacial abnormalities, and are used to study disease mechanisms and test therapies

## **QUESTION AND ANSWERS SET**

## What is achondroplasia?

Achondroplasia is the most common genetic bone disorder causing disproportionate short stature. It results from a mutation in the *FGFR3* gene that affects cartilage conversion to bone during fetal development, leading to short arms and legs, a large head, and a normal-sized torso

## How common is achondroplasia?

About 1 in 15,000 to 1 in 40,000 individuals are born with achondroplasia worldwide

## What causes achondroplasia?

Achondroplasia is caused by a mutation in the *FGFR3* gene. Most cases are due to new (de novo) mutations, meaning parents are typically average height and unaffected. It is inherited in an autosomal dominant pattern, so a parent with achondroplasia has a 50% chance of passing it to their child

## How is achondroplasia diagnosed?

Diagnosis can be made prenatally by ultrasound detecting short limbs and large head, and confirmed by genetic testing (amniocentesis or chorionic villus sampling). After birth, diagnosis is based on physical exam, growth patterns, X-rays, and sometimes genetic testing

## What are the common symptoms and complications?

* Short limbs with normal torso length
* Large head with prominent forehead
* Flattened nasal bridge
* Bowed legs and spinal curvature (lordosis or kyphosis)
* Poor muscle tone and loose joints in infants
* Frequent ear infections and hearing loss
* Sleep apnea and breathing problems
* Obesity risk
* Delayed motor milestones (e.g., walking)

## Is there a cure for achondroplasia?

No, there is no cure. Treatment focuses on managing symptoms and complications to improve quality of life

## What treatments are available?

* Monitoring growth, head size, and development
* Managing ear infections promptly to prevent hearing loss
* Surgery for spinal stenosis, bowed legs, or kyphosis if needed
* Growth hormone therapy has limited effect on final height
* Newer drugs like vosoritide may increase growth velocity in children (approved recently)

## What is the life expectancy and outlook?

People with achondroplasia usually have a normal lifespan but may face increased risks from complications like spinal cord compression and respiratory problems. With proper care, most lead full, healthy lives

## What is the inheritance risk for children

If one parent has achondroplasia, there is a 50% chance their child will inherit the condition. If both parents have achondroplasia, there is a 25% chance of a lethal form called double dominance, 50% chance of achondroplasia, and 25% chance of average stature

## Which specialists should be involved in care?

A multidisciplinary team including pediatricians, orthopedic surgeons, genetic counselors, neurosurgeons, and dentists may be needed depending on complications

## Is achondroplasia considered a disability?

While people with achondroplasia can live normal lives, they may qualify for disability benefits due to physical challenges

## **Diagnostic Considerations**

In addition to the conditions listed in the differential diagnosis, other problems to be considered include the following:

* Thanatophoric dwarfism
* Achondrogenesis
* Chondroectodermal dysplasia (Ellis-van Creveld syndrome[)](https://emedicine.medscape.com/article/949591-overview)
* Metatrophic dwarfism
* Asphyxiating thoracic dysplasia
* Chondrodysplasia punctata (Conradi disease)
* Pseudoachondroplastic dysplasia
* Metaphyseal chondrodysplasia (Schmid type)

The diagnosis of achondroplasia in the fetus is made with certainty when one or both parents have this condition. In situations where the parents have normal stature, the diagnosis may only be suspected on the basis of the observation of disproportionately short limbs in the fetus on ultrasonography (US). In most cases, the specific diagnosis cannot be made with certainty until birth. Caution should be exercised in counseling the family.

The diagnosis should be confirmed at birth by means of radiography. The measurements, including arm span, occipital frontal circumference, body length, and ratio of upper body to lower body, should be documented.

## Differential Diagnoses

* [Diastrophic Dysplasia](https://emedicine.medscape.com/article/1257787-overview)
* [Spondyloepiphyseal Dysplasia](https://emedicine.medscape.com/article/1260836-overview)

## **Guidelines for Achondroplasia**

* Cranial magnetic resonance imaging (MRI) is recommended to identify spinal cord compression due to foramen magnum stenosis.
* Foramen magnum decompression is recommended for managing spinal cord compression due to foramen magnum stenosis associated with neurologic symptoms, abnormal neurologic findings, and central respiratory disorders.
* An MRI cranial examination is recommended to identify ventricular enlargement with neurologic symptoms (hydrocephalus).
* Shunt surgery is recommended for managing ventricular enlargement associated with neurologic symptoms (hydrocephalus).
* Simple sleep studies and polysomnography (PSG) are selected for diagnosis of sleep apnea on the basis of circumstances.
* Noninvasive positive-pressure ventilation (PPV) is suggested for managing obstructive sleep apnea (OSA).
* Surgical treatment (tonsillectomy or adenoidectomy) is suggested when OSA is present with tonsillar or adenoid hypertrophy.
* Spinal decompression is recommended for managing spinal canal stenosis associated with neurologic symptoms.
* Delayed speech is observed in 25% of cases of achondroplasia.
* Leg lengthening should be possible after the age of 12 years, under informed consent.

Vosoritide, a biologic analogue of C-type natriuretic peptide (CNP), is approved to prevent the inhibition of mineralization of chondrocytes caused by the mutation in the fibroblast growth factor receptor 3 (FGFR3) gene (*FGFR3)*.

REFERENCES

[Achondroplasia: Symptoms, Treatment, Causes & Diagnosis](https://my.clevelandclinic.org/health/diseases/22183-achondroplasia)

<https://emedicine.medscape.com/article/1258401-overview#a6>

<https://www.ncbi.nlm.nih.gov/books/NBK559263/#article-17089.s9>

**BAKER CYST**

**DEFINITION**

A Baker cyst is a fluid-filled growth behind the knee. It causes a bulge and a feeling of tightness. Also called a popliteal (pop-luh-TEE-ul) cyst, a Baker cyst sometimes causes pain. The pain can get worse when with activity or when fully straightening or bending the knee.

A Baker cyst is usually the result of a problem with the knee joint, such as arthritis or a cartilage tear. Both conditions can cause the knee to produce too much fluid.

Although a Baker cyst may cause swelling and discomfort, treating the underlying problem that is causing it usually provides relief.

### **Baker cyst symptoms**

The most obvious symptom of a Baker cyst is the bump that forms behind your knee. Other common Baker cyst symptoms include:

* Knee pain.
* Stiffness.
* Trouble bending your knee as far as you usually can (a limited range of motion).
* Swelling in your knee or on your leg around it.

Some people with a Baker cyst don’t experience symptoms. You might not know you have one until a healthcare provider notices while they’re diagnosing other issues or conditions that affect your knee.

Baker cysts can sometimes cause swelling and discoloration in your lower leg that can be similar to the symptoms of a blood clot. **A blood clot is an emergency. Visit a healthcare provider right away if you think you might have a blood clot**. Your provider can check out your symptoms and determine if it’s a Baker cyst or a blood clot.

### **What causes Baker cysts?**

Anything that damages your knee joint can cause swelling and trigger a Baker cyst. The most common causes are different types of knee arthritis and injuries.

The most common forms of arthritis that cause Baker cysts include:

* Osteoarthritis.
* Rheumatoid arthritis.
* Gout.

If you experience a knee injury, the damage can cause swelling in your knee that leads to a Baker cyst. Knee injuries that cause Baker cysts include:

* Repetitive strain injuries (overuse injuries).
* Meniscus tears.
* Hyperextensions.
* Sprains.
* Dislocations.
* Bone fractures.

Injuries that damage your [knee ligaments](https://my.clevelandclinic.org/health/body/21596-knee-ligaments) can cause Baker cysts, including:

* ACL tears.
* MCL tears.
* LCL tears.
* PCL tears.

#### **Baker cyst risk factors**

Anyone can develop a Baker cyst, especially if you have arthritis or experience an injury. Some groups of people are more likely to have a Baker cyst, including:

* People 35 to 70 years old.
* Athletes.
* People who put lots of pressure on their knees at work or during a hobby.
* People with arthritis.

### **Baker cyst complications**

The most common complication of a Baker cyst is rupturing (breaking). A ruptured Baker cyst happens when the sac around the cyst fills up with fluid too fast or with too much pressure and bursts. If you’ve ever accidentally filled up a water balloon too quickly, you know what can happen if fluid flows into a thin, rubbery container with too much pressure — it pops.

A ruptured Baker cyst can cause other symptoms in your knee and lower leg, including:

* Sharp, stabbing pain in your knee or calf.
* Swelling in your calf and lower leg.
* A feeling like water is running down your leg (but inside your body).
* Nerve damage.
* Compartment syndrome (painful extra pressure in your muscles).

## **Diagnosis and Tests**

A healthcare provider will diagnose a Baker cyst with a [physical exam](https://my.clevelandclinic.org/health/diagnostics/17366-physical-examination). They’ll examine your leg and look for a lump on the back of your knee. Tell your provider when you first noticed the bump and if you’re experiencing any other symptoms. If you hurt your knee, tell your provider what you were doing before the injury.

Your provider might use a few imaging tests to diagnose a Baker cyst, including:

* X-rays.
* Ultrasound.
* Magnetic resonance imaging (MRI).

## **Management and Treatment**

Usually, your healthcare provider will treat the cause of a Baker cyst rather than the cyst itself. The cyst will usually go away when the damage in your knee that caused it has healed. Which treatments you’ll need depends on which injury or condition you have.

#### **RICE method**

Most minor injuries can be treated with the RICE method:

* **Rest:** Stop the physical activity that caused the injury to avoid making it worse.
* **Ice:** Apply an ice pack or cold compress for 10 to 15 minutes every hour for the first day after your injury. After one day, you can apply ice every three to four hours. Don’t apply ice directly to your skin (wrap the ice pack in a towel or washcloth).
* **Compression:** Compression helps reduce blood flow to your injured knee and reduces swelling. Apply a compression bandage or wrap around your knee. You can also wear compression pants to help keep pressure on your knee.
* **Elevation:** If possible, lift your knee and lower leg above the level of your heart. Support your leg with pillows, blankets or cushions.

#### **Medications**

Your healthcare provider might suggest medications to relieve pain and reduce swelling.

Most people can take over-the-counter (OTC) NSAIDs (ibuprofen, aspirin and naproxen) or acetaminophen (Tylenol®). Don’t take these medications for more than 10 days in a row without talking to your provider.

Your provider might suggest prescription corticosteroids or cortisone shots.

#### **Physical therapy**

Your provider might suggest physical therapy if you’re recovering from an injury or have arthritis. A physical therapist will show you stretches and exercises that strengthen the muscles around your affected knee.

#### **Knee surgery**

You might need knee surgery to repair torn cartilage or ligaments in your knee, or if you fractured a bone.

It’s rare, but you may need surgery to drain or remove a Baker cyst if it’s causing severe pain or making it hard to use your knee.

Your surgeon will tell you which type of surgery you’ll need and what to expect while you’re recovering.

## **Baker's Cyst Treatment Drugs and Their Side Effects**

## 1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

* Purpose: Reduce pain, inflammation, and swelling associated with Baker’s cyst.
* Common Drugs: Ibuprofen (Advil, Motrin), Naproxen (Aleve).
* Side Effects:
  + Gastrointestinal irritation, ulcers, or bleeding
  + Kidney damage with long-term use
  + Increased blood pressure
  + Possible allergic reactions, especially in people with asthma or certain heart/kidney conditions
* Notes: Should not be used for more than 10 days consecutively without medical advice

## 2. Corticosteroid Injections

* Purpose: Injected directly into the knee joint to reduce inflammation and swelling, which may reduce cyst size and relieve pain.
* Side Effects:
  + Temporary pain or discomfort at injection site
  + Risk of joint infection (rare)
  + Possible weakening of tendons or cartilage with repeated injections
  + Elevated blood sugar levels temporarily
* Notes: May not prevent cyst recurrence; usually reserved for persistent or severe symptoms

## 3. Prescription Painkillers (for ruptured cysts)

* Purpose: Control pain when the cyst ruptures and causes calf pain and swelling.
* Common Drugs: Combination of paracetamol and codeine.
* Side Effects:
  + Drowsiness, constipation, nausea (common with codeine)
  + Risk of dependency with prolonged use
* Notes: Used short-term under medical supervision

## Additional Treatments (Non-Drug)

* Ice application to reduce swelling
* Rest and elevation of the leg
* Knee supports or braces
* Physical therapy to strengthen muscles and improve knee function
* Aspiration (draining fluid) or surgery if conservative treatments fail

## **Baker's Cyst Procedures and Timelines**

## 1. Conservative (Non-Surgical) Treatment

* Initial approach: Most Baker’s cysts resolve on their own as the underlying knee condition improves.
* Methods:
  + Rest, activity modification (avoiding high-impact activities)
  + Ice application to reduce swelling and pain
  + Compression and elevation of the leg
  + NSAIDs for pain and inflammation relief
  + Physical therapy focusing on strengthening muscles around the knee and improving range of motion
* Timeline: Symptoms often improve within a few weeks to months, depending on the healing of the underlying joint problem

## 2. Aspiration and Corticosteroid Injection

* Procedure: Under ultrasound guidance, fluid is drained from the cyst using a needle (aspiration). A corticosteroid injection may follow to reduce inflammation.
* Purpose: Provides symptom relief and reduces cyst size temporarily.
* Limitations: Cysts often recur after aspiration.
* Recovery: Usually quick, with symptom relief within days to weeks.
* Timeline: May require repeat procedures if cyst recurs

## 3. Surgical Treatment

* Indications: Surgery is reserved for large, persistent cysts causing significant pain, nerve or vascular compression, or when underlying knee pathology (e.g., meniscal tear) needs correction.
* Types of surgery:
  + Arthroscopy: Minimally invasive surgery to repair intra-articular knee problems causing cyst formation.
  + Excision: Open or arthroscopic removal of the cyst itself.
  + Surgical techniques include posterior, posteromedial, or medial intra-articular approaches to remove or close the cyst.
* Recovery: Varies by procedure and patient; may take several weeks to months. Physical therapy is often required postoperatively.
* Timeline: Surgery is considered after failure of conservative treatments over weeks to months and if symptoms persist or worsen

## **Outlook / Prognosis**

How long a Baker cyst lasts depends on what caused it. Most Baker cysts go away as soon the swelling goes down and your knee starts to heal, usually within a few weeks.

It’s possible for a Baker cyst to go away on its own. But you should always visit a healthcare provider as soon as you notice any new lumps or growths on your body. Even if you don’t need treatment, a provider needs to diagnose a Baker cyst and make sure it’s not something more serious.

As your knee heals, the fluid in the cyst is absorbed back into your body. Follow your provider’s suggestions to help your knee heal and to prevent any more damage.

## **Prevention**

The best way to prevent a Baker cyst is to prevent knee injuries. During sports or other physical activities:

* Wear the right protective equipment.
* Don’t “play through the pain” if your knee hurts during or after physical activity.
* Give your body time to rest and recover after intense activity.
* Stretch and warm up before playing sports or working out.
* Cool down and stretch after physical activity.

Follow these general safety tips to reduce your risk of an injury:

* Make sure your home and workspace are free from clutter that could trip you or others.
* Always use the proper tools or equipment at home to reach things. Never stand on chairs, tables or countertops.
* Use a cane or walker if you have difficulty walking or have an increased risk of falls.

### **When should I see my healthcare provider?**

Visit a healthcare provider as soon as you notice a lump on your leg. It’s important to get it diagnosed

**QUESTION AND ANSWER SET**

## Do I have a Baker cyst or another issue?

A Baker’s cyst is a fluid-filled swelling behind the knee that often causes a noticeable lump, knee stiffness, pain, or tightness. Diagnosis is usually clinical, confirmed by ultrasound or MRI if needed. However, symptoms like calf swelling and pain can mimic serious conditions such as deep vein thrombosis (blood clot), so medical evaluation is essential to differentiate. If you have a lump behind your knee with pain or swelling, see a healthcare provider for proper diagnosis

## What caused the cyst?

Baker’s cysts form due to excess synovial fluid accumulating in the popliteal bursa behind the knee. This excess fluid is usually caused by an underlying knee problem such as:

* Osteoarthritis (wear-and-tear joint disease)
* Rheumatoid arthritis or other inflammatory arthritis
* Knee injuries like meniscus tears or ligament damage
* Overuse or trauma to the knee
* Sometimes cysts develop without a clear cause, especially in children

## Which treatments will I need?

Treatment focuses on relieving symptoms and addressing the underlying knee condition:

* Rest, ice, compression, and elevation (RICE)
* Nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce pain and inflammation
* Physical therapy to improve knee strength and flexibility
* Aspiration (draining fluid) and corticosteroid injections may be used if symptoms persist or cyst is large
* Surgery is rarely needed and reserved for persistent or complicated cases

## Will I need surgery?

Most people with Baker’s cysts do not need surgery. Surgery is considered only if:

* The cyst is very large, painful, or causing nerve or blood vessel compression
* There is an underlying knee problem requiring surgical repair (e.g., meniscus tear)
* Conservative treatments fail to relieve symptoms over weeks to months

## How long will the Baker cyst last?

The duration varies depending on the underlying cause and treatment:

* Many cysts improve or resolve within weeks to months with conservative care as the knee condition improves.
* Cysts can recur if the underlying joint problem persists.
* If untreated, cysts may remain stable or enlarge over time.
* Aspiration provides temporary relief but cysts often refill.
* Surgery may provide longer-term resolution but requires recovery time of several weeks to months

## **Baker's Cyst Differential Diagnosis**

## 1. Deep Vein Thrombosis (DVT)

* Presents with calf pain, swelling, warmth, and redness, similar to a ruptured Baker’s cyst.
* DVT is a medical emergency and must be ruled out promptly.

## 2. Popliteal (Baker’s) Cyst Rupture (Pseudothrombophlebitis Syndrome)

* Ruptured cyst can cause acute calf pain, swelling, redness, and a sensation of fluid running down the leg, mimicking DVT.

## 3. Popliteal Artery Aneurysm

* A pulsatile mass behind the knee that can cause swelling and pain.
* Distinguished by Doppler ultrasound.

## 4. Lipoma or Soft Tissue Tumors

* Soft, movable lumps that may occur in the popliteal fossa.
* Usually painless and less firm than cysts.

## 5. Hemangioma or Vascular Malformations

* Present as slowly enlarging masses, may be painful, and can limit motion.

## 6. Meniscal or Chondral Pathology

* Meniscus tears or cartilage damage can cause joint effusion and secondary cyst formation.
* Positive McMurray test may indicate meniscal injury.

## 7. Muscle or Tendon Disorders

* Tendinitis or bursitis around the knee can cause localized swelling and pain.

## 8. Infection or Septic Arthritis

* Acute onset with fever, severe pain, swelling, and limited motion.
* Requires urgent treatment.

## 9. Other Cystic Lesions

* Ganglion cysts or synovial cysts unrelated to the knee joint.

## **Baker's Cyst Epidemiology** The incidence of Baker’s cyst varies widely, reported between 5% and 38% in different populations. In a study of 399 patients with knee pain, the prevalence of Baker’s cyst was 25.8%, and the frequency increases with age. Another large series of knee MRIs found prevalence rates in adults ranging from 5% to 19%

Children aged 4 to 7 years (often primary cysts without underlying joint disease)

Adults aged 35 to 70 years (usually secondary to intra-articular knee conditions)

Associated Conditions:  
Baker’s cysts are commonly associated with degenerative or inflammatory knee diseases such as:

Osteoarthritis (seen in about 21-42% of patients with OA)

Meniscal tears (especially medial meniscus)

Rheumatoid arthritis (up to 48% prevalence in RA patients)

Other causes include ligament injuries, chondromalacia, chronic synovitis, and trauma  
No strong gender predilection is noted. Prevalence may vary based on population studied and diagnostic methods used.  
Many Baker’s cysts are asymptomatic and found incidentally on imaging. Symptomatic cysts causing pain or swelling represent a subset of cases  
In children, Baker’s cysts are less common (about 6.3% on MRI) and often resolve spontaneously without intervention

## **Doctor-Patient Conversation on Baker’s Cyst (De-Identified)**

## Doctor:

Hello! I understand you’ve noticed a lump behind your knee and some discomfort. Can you tell me more about your symptoms?

## Patient:

Yes, doctor. I’ve had this swelling behind my knee for a few weeks. It feels tight and sometimes painful, especially after I’ve been active or standing a long time.

## Doctor:

That sounds like it could be a Baker’s cyst, which is a fluid-filled swelling behind the knee. It often develops when the knee produces excess fluid, usually because of arthritis or a cartilage injury.

## Patient:

Is it dangerous? Will it go away on its own?

## Doctor:

A Baker’s cyst itself usually isn’t dangerous and sometimes it does go away by itself, especially if the underlying knee problem improves. However, it can cause discomfort and limit knee movement.

## Patient:

What causes it to form?

## Doctor:

It forms when joint fluid leaks into a small sac called a bursa behind your knee, creating the cyst. Conditions like osteoarthritis, rheumatoid arthritis, or a meniscus tear often trigger this excess fluid production.

## Patient:

How do you diagnose it?

## Doctor:

I can often diagnose it by examining the lump behind your knee. Sometimes we use ultrasound or MRI to confirm the diagnosis and rule out other issues like blood clots or tumors.

## Patient:

What treatments are available?

## Doctor:

For mild symptoms, we usually start with conservative measures:

* Rest and avoid activities that worsen symptoms
* Applying ice packs to reduce swelling
* Over-the-counter pain relievers like ibuprofen or acetaminophen
* Compression wraps or knee supports

If symptoms persist or the cyst is large and painful, we might:

* Drain the cyst fluid with a needle (aspiration), often guided by ultrasound
* Inject corticosteroids to reduce inflammation
* Recommend physical therapy to strengthen muscles and improve knee function

Surgery is rarely needed and usually reserved for cases where the underlying knee problem requires repair or if the cyst keeps coming back.

## Patient:

What if the cyst bursts?

## Doctor:

If a Baker’s cyst ruptures, fluid can leak down into your calf, causing swelling, redness, and pain. This can mimic a blood clot, so it’s important to seek medical advice promptly if that happens.

## Patient:

Is there anything I can do to prevent it?

## Doctor:

Managing the underlying knee condition is key. Keeping a healthy weight, avoiding excessive strain, and treating arthritis or injuries early can help prevent cyst formation.

## Patient:

Thank you, doctor. I’ll try these treatments and keep an eye on it.

## Doctor:

You’re welcome. Let’s schedule a follow-up to see how you’re doing, and don’t hesitate to contact me if your symptoms worsen or change.

REFERENCES

<https://www.ncbi.nlm.nih.gov/books/NBK430774/>

[Baker Cyst: Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/15183-bakers-cyst)

[Baker cyst - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/bakers-cyst/symptoms-causes/syc-20369950)

<https://www.nhs.uk/conditions/bakers-cyst/treatment/>

### **Ehlers-Danlos syndrome**

**Definition**

Ehlers-Danlos syndrome (EDS) is a condition that affects the connective tissues in your body.

Connective tissues support your organs and hold parts of your body in place. They’re made of two proteins: collagen and elastin. EDS affects your body’s ability to produce collagen the way it should. People with EDS have weaker collagen. This means their connective tissue isn’t as strong or supportive as it should be.

Ehlers-Danlos syndrome can affect any connective tissue in your body, including your:

* Cartilage.
* Bones.
* Blood.
* Fat.

Depending on where EDS affects your connective tissue, you might experience symptoms in your:

* Skin.
* Joints.
* Muscles.
* Blood vessels.

Ehlers-Danlos syndrome is a genetic disorder. Talk to a healthcare provider about testing for EDS if someone in your biological family has it (an immediate relative like a biological parent, grandparent or sibling).

#### **Types of Ehlers-Danlos syndrome**

Healthcare providers classify Ehlers-Danlos syndrome into 13 types based on where it affects you and the symptoms it causes.

The most common types cause symptoms like loose or unstable joints and fragile skin that tears easily. Some rare types of Ehlers-Danlos syndrome can cause fatal complications — especially vascular Ehlers-Danlos syndrome (EDS that affects your blood vessels).

Your provider will tell you which type of EDS you have and which treatments you’ll need to manage your symptoms.

Experts estimate that 1 in 5,000 people has Ehlers-Danlos syndrome.

### **Ehlers-Danlos syndrome symptoms**

Each type of Ehlers-Danlos syndrome has its own symptoms, but the most common EDS symptoms include:

* Overly flexible (hypermobile) joints — it might feel like your joints are loose or unstable.
* Soft skin that’s thinner and stretches more than it should.
* Bruising easily or more often than usual.
* Unusual scarring or taking unusually long to heal after a cut or small wound.
* Joint and muscle pain.
* Fatigue (feeling tired all the time).
* Difficulty concentrating.

### **What causes Ehlers-Danlos syndrome?**

A genetic mutation causes Ehlers-Danlos syndrome. Genetic mutations are changes to your DNA sequence that happen during cell division when your cells make copies of themselves. If part of your DNA sequence is in the wrong place, isn’t complete or is damaged, you might experience symptoms of a genetic condition.

Even though we know it’s caused by a genetic mutation, healthcare providers can’t always identify the exact mutation that causes Ehlers-Danlos syndrome in someone.

Experts have identified more than 20 different genetic mutations that can cause Ehlers-Danlos syndrome. They all affect your body’s ability to produce collagen. Which specific mutation you have determines which parts of your body are affected.

#### **Ehlers-Danlos syndrome risk factors**

Some types of Ehlers-Danlos syndrome are inheritable. This means biological parents can pass the mutations to their children. Other types happen somatically — they happen randomly and can’t be passed through generations of a family.

You may have an increased risk of EDS if one or both of your biological parents have it. Similarly, if you have EDS, you might pass the mutation that caused it to your biological children.

Talk to a healthcare provider about your risk of inheriting or passing on Ehlers-Danlos syndrome in your biological family. Your provider might suggest genetic counseling. Genetic counselors can help you determine your risk for developing or passing on certain conditions.

### **Complications of Ehlers-Danlos syndrome**

Dislocations are the most common complication of Ehlers-Danlos syndrome. A dislocation is the medical term for bones in one of your joints being pushed out of their usual place. Never try to push a joint back into place on your own if you think you have a dislocation. Go to the emergency room (ER) right away. You may need surgery to repair a dislocation.

Some types of Ehlers-Danlos syndrome can cause life-threatening complications. Vascular Ehlers-Danlos syndrome can cause blood vessels to rupture (tear). This can lead to dangerous internal bleeding and stroke.

People with these types of Ehlers-Danlos syndrome also have a higher risk of organ rupture. The most common types of organ rupture are intestines and a pregnant woman’s [uterus](https://my.clevelandclinic.org/health/body/22467-uterus).

Your risk of complications depends on which type of EDS you have. Complications can include:

* Problems with the valves that push blood through your heart.
* Severe spine curvature (scoliosis).
* Thin corneas in your eyes.
* Bowed (curved) limbs.
* Teeth and gum problems.

## **Diagnosis and Tests**

A healthcare provider will diagnose Ehlers-Danlos syndrome with a physical exam and by discussing your medical history. They’ll examine your skin and joints and ask you about your symptoms. Tell your provider when you first noticed symptoms or if any activities make them worse.

Most people with Ehlers-Danlos syndrome don’t have a known genetic mutation, so providers usually diagnose it based on your symptoms and medical history.

## **Management and Treatment**

Your healthcare provider will suggest treatments for Ehlers-Danlos syndrome that help you manage your symptoms and prevent dangerous complications. Which treatments will work for you depends on which type of EDS you have and how your connective tissue is affected.

Some common Ehlers-Danlos syndrome treatments include:

* Wearing sunscreen and using mild soaps to protect your skin.
* Physical therapy to strengthen the muscles around your joints.
* Wearing braces for extra joint support.

People with Ehlers-Danlos have an increased risk of dislocated joints and other joint injuries. Your provider might suggest you avoid:

* Strenuous (heavy) lifting.
* High-impact exercise.
* Contact sports.

## **Treatment Drugs and Their Side Effects**

## 1. Pain Management Medications

* Over-the-counter pain relievers:
  + *Acetaminophen (Tylenol)*, *Ibuprofen (Advil, Motrin)*, *Naproxen (Aleve)* are commonly used to manage mild to moderate pain.
  + Side effects:
    - Acetaminophen: Liver toxicity in overdose.
    - NSAIDs (ibuprofen, naproxen): Gastrointestinal irritation, ulcers, kidney impairment, increased bleeding risk.
* Stronger pain medications:
  + Opioids (e.g., morphine, oxycodone) may be prescribed for severe pain but carry risks of dependence, sedation, constipation, and respiratory depression.
* Neuropathic pain agents:
  + Antiseizure medications like gabapentin, pregabalin, and tricyclic antidepressants (e.g., amitriptyline) can help with nerve-related pain.
  + Side effects: Drowsiness, dizziness, dry mouth, weight gain.

## 2. Medications for Vascular Ehlers-Danlos Syndrome (vEDS)

* Beta-blockers:
  + *Metoprolol*, *propranolol*, and *celiprolol* (off-label in some regions) reduce heart rate and vascular stress to lower risk of arterial rupture.
  + Side effects: Fatigue, dizziness, low blood pressure, cold extremities.
* Angiotensin Receptor Blockers (ARBs):
  + *Losartan*, *irbesartan* help lower blood pressure and vascular strain.
  + Side effects: Dizziness, hyperkalemia, kidney function changes.

## 3. Medications for Mental Health and Comorbidities

* Selective Serotonin Reuptake Inhibitors (SSRIs):
  + *Sertraline (Zoloft)*, *paroxetine (Paxil)* to manage anxiety and depression common in EDS patients.
  + Side effects: Nausea, sexual dysfunction, insomnia or drowsiness.
* Tricyclic Antidepressants (TCAs):
  + Used for neuropathic pain and depression (e.g., amitriptyline).
  + Side effects: Dry mouth, constipation, sedation, weight gain.

## 4. Emerging and Adjunctive Treatments

* Low-Dose Naltrexone (LDN):
  + Investigated for chronic pain and inflammation modulation in EDS.
  + Side effects: Generally well tolerated; occasional sleep disturbances or vivid dreams.
* Muscle relaxants:
  + Used to relieve muscle spasms.
  + Side effects: Drowsiness, dizziness.

## **Procedures for EDS and Their Timelines**

## 1. Conservative Management (Initial Approach)

* Physical therapy: To strengthen muscles and stabilize joints, prevent dislocations.
* RICE (Rest, Ice, Compression, Elevation): For acute injuries or swelling.
* Medications: Pain control and management of comorbidities.
* Timeline: Ongoing, lifelong management; can start immediately after diagnosis.

## 2. Surgical Joint Stabilization

* Indications: Recurrent joint dislocations, severe instability, or joint damage not controlled by conservative care.
* Procedures: Ligament repair or reconstruction, joint fusion, or replacement.
* Risks: Poor wound healing, tissue fragility, bleeding, scar tissue formation.
* Timeline: Surgery scheduled after thorough evaluation; recovery can be prolonged (weeks to months) due to healing challenges.

## 3. Spinal Surgery (e.g., Laminectomy, Spinal Fusion)

* Indications: Spinal instability, nerve compression, degenerative disc disease, Chiari malformation, or craniocervical instability.
* Procedures:
  + *Laminectomy:* Removal of part of vertebra to relieve nerve pressure.
  + *Minimally invasive lumbar fusion:* Fusing vertebrae to stabilize spine, reduce pain and nerve damage.
* Advantages: Minimally invasive techniques reduce tissue trauma and recovery time.
* Timeline:
  + Surgery duration varies by procedure.
  + Recovery typically takes several weeks to months.
  + Use of advanced imaging and navigation improves outcomes.

## 4. Vascular Surgery

* Indications: Repair of ruptured or fragile blood vessels in vascular EDS.
* Risks: High due to fragile vessels and bleeding tendency.
* Timeline: Emergency or planned; recovery depends on complexity.

## Surgical and Anesthetic Precautions

* Preoperative preparation:
  + Inform surgical and anesthesia teams about EDS diagnosis.
  + Pre-op imaging (cervical spine flexion-extension X-rays, echocardiogram).
  + Avoid prolonged or extreme positioning to prevent joint dislocations.
  + Consider allergies and mast cell activation issues; premedicate if needed.
* Intraoperative care:
  + Use minimal tissue retraction and gentle handling.
  + Avoid tourniquets or minimize their use.
  + Use subcuticular stitches and adhesive dressings to aid healing.
* Postoperative care:
  + Close monitoring for bleeding, wound healing problems, and pain management.
  + Tailored rehabilitation with physical therapy.

## **Outlook / Prognosis**

You should expect to manage Ehlers-Danlos syndrome symptoms for the rest of your life. There’s no cure for EDS. But you should be able to participate in all your normal activities once you learn how to manage your symptoms. You might have to avoid some forms of intense physical activity (like contact sports).

Ehlers-Danlos syndrome affects everyone differently. What you experience depends on which type of EDS you have and the severity of your symptoms. Ask your provider what to expect based on your unique situation.

Most types of Ehlers-Danlos syndrome don’t affect or lower your life expectancy.

If you have EDS that affects your blood vessels (vascular Ehlers-Danlos syndrome), you might have an increased risk of experiencing a stroke or other fatal vascular issues.

Even if you have vascular Ehlers-Danlos syndrome, your healthcare provider will help you find a combination of treatments and lifestyle changes that help you lead a safe, healthy life. Talk to your provider about what to expect and which signs or symptoms of dangerous complications you should watch for.

## **Prevention**

No, you can’t prevent Ehlers-Danlos syndrome. Because you can’t control the genetic mutations that cause it, there’s no way to prevent EDS. Talk to your healthcare provider about genetic counseling if you’re worried about passing EDS (or any other genetic condition) on to your biological children.

## **Living With**

Monitor your symptoms and visit a healthcare provider if you notice any changes. Your provider will tell you how often you need regular visits in the future to track any changes in your body. They’ll help you change your treatments as needed.

Avoid playing high-impact sports. Intense physical activity like contact sports increases your risk of a joint injury (especially dislocations).

### **When should I see my healthcare provider?**

Visit a healthcare provider if you notice any changes in your body that make your skin or joints feel weaker or loose. See a provider if you notice that you’re bruising or bleeding more often than you used to.

Got to the emergency room or call 911 (or your local emergency number) if you or someone with you has symptoms of a stroke.

To recognize the warning signs of a stroke, remember to think, **BE** **FAST**:

* Be watchful for a sudden loss of balance.
* Look out for sudden loss of vision in one or both eyes. Are they experiencing double vision?
* Ask the person to smile. Look for a droop on one or both sides of their face, which is a sign of muscle weakness or paralysis.
* A person having a stroke often has muscle weakness on one side. Ask them to raise their arms. If they have one-sided weakness (and didn’t have it before), one arm will stay higher while the other will sag and drop downward.
* Strokes often cause a person to lose their ability to speak. They might slur their speech or have trouble choosing the right words.
* Time is critical, so don’t wait to get help! If possible, look at your watch or a clock and remember when symptoms start. Telling a healthcare provider when symptoms start can help the provider know what treatment options are best for you.

**QUESTION AND ANSWER SET**

## Do I have Ehlers-Danlos syndrome or another condition?

EDS is diagnosed primarily through clinical evaluation of symptoms such as joint hypermobility, skin elasticity, and family history. For hypermobile EDS (hEDS), the most common type, there is no definitive genetic test, so diagnosis relies on meeting specific clinical criteria including generalized joint hypermobility, musculoskeletal symptoms, and exclusion of other disorders. Other types like classical or vascular EDS can be confirmed with genetic testing. A healthcare provider will perform a detailed physical exam and may order genetic tests or imaging to rule out other conditions

## Which type of EDS do I have?

There are 13 recognized types of EDS, with hypermobile (hEDS) being the most common, followed by classical (cEDS) and vascular (vEDS) types. Each type has distinct features:

* hEDS: Joint hypermobility, pain, fatigue, mild skin symptoms, no genetic test available.
* cEDS: More prominent skin involvement—stretchy, fragile skin, wide scars, joint hypermobility.
* vEDS: Fragile blood vessels and organs, risk of rupture.  
  Diagnosis of type is based on clinical features and, for some types, genetic testing

## Which treatments will I need?

* Pain management: Over-the-counter pain relievers (acetaminophen, NSAIDs), stronger meds if needed.
* Physical therapy: To strengthen muscles and stabilize joints, prevent dislocations.
* Bracing: To support unstable joints.
* Cardiovascular management: Blood pressure control in vascular EDS to reduce vessel stress.
* Surgery: Reserved for severe joint damage or vascular complications but carries risks due to tissue fragility.
* Lifestyle adjustments: Avoid high-impact activities, maintain healthy weight, and manage fatigue

## Which symptoms or changes should I watch out for?

* Increasing joint pain, frequent dislocations or subluxations.
* Skin changes: increased bruising, slow wound healing, abnormal scarring.
* Signs of vascular problems (especially in vEDS): unexplained chest or abdominal pain, sudden severe headaches, or neurological symptoms.
* Fatigue, dizziness, gastrointestinal issues, and autonomic symptoms like rapid heart rate upon standing.
* Any new or worsening symptoms should prompt medical review

## How often will I need follow-up visits?

* Follow-up frequency depends on your symptoms and EDS type.
* Regular monitoring by a multidisciplinary team is recommended, often every 6 to 12 months.
* More frequent visits may be needed if you have vascular EDS or severe joint complications.
* Cardiovascular screening (echocardiogram) is advised periodically, especially for vascular and classical types

## Should I consider genetic counseling if I want to have biological children?

* Yes. Genetic counseling is strongly recommended, especially if you have a confirmed diagnosis of classical, vascular, or other genetically identifiable types of EDS.
* Counseling helps assess inheritance risks, discuss prenatal testing options, and plan for family health.
* For hypermobile EDS, where no specific gene is known, counseling focuses on symptom management and family history evaluation

## **Differential Diagnoses**

* Joint Hypermobility Syndrome (JHS):  
  Considered by many experts as overlapping or synonymous with hEDS; diagnosis is clinical and by exclusion of other disorders.
* Marfan Syndrome:  
  A connective tissue disorder with tall stature, arachnodactyly, cardiovascular involvement (aortic root dilation), and lens dislocation. Distinguished by genetic testing and specific clinical features.
* Loeys-Dietz Syndrome:  
  Characterized by arterial tortuosity, aneurysms, hypertelorism, and cleft palate. Genetic testing for *TGFBR1* and *TGFBR2* mutations differentiates it from EDS.
* Osteogenesis Imperfecta:  
  Presents with bone fragility and fractures; may have blue sclerae and dentinogenesis imperfecta. Distinguished by bone density studies and genetic testing.
* Turner Syndrome:  
  A chromosomal disorder (45,X) with short stature and joint laxity; diagnosed by karyotyping.
* Cartilage-Hair Hypoplasia Syndrome:  
  A rare skeletal dysplasia with short stature and immunodeficiency.
* Muscular Hypotonia (Kyphoscoliotic Type EDS):  
  Presents with muscle weakness and severe scoliosis; genetic testing helps differentiate.
* Fibromyalgia and Chronic Pain Syndromes:  
  Often misdiagnosed in patients with hEDS due to widespread pain and fatigue but lack connective tissue abnormalities.
* Other Heritable Connective Tissue Disorders:  
  Including arterial tortuosity syndrome, lateral meningocele syndrome, and others with overlapping features.

## **Epidemiology**

Overall Prevalence:  
EDS is estimated to affect approximately 1 in 5,000 people worldwide when all subtypes are combined, though this may be an underestimation due to underdiagnosis, especially of hypermobile EDS (hEDS)

Hypermobile EDS (hEDS): The most common subtype, accounting for about 90% of EDS cases, affects roughly 1 in 500 to 1 in 5,000 people. It is considered a rare disorder but likely underdiagnosed

Classical EDS (cEDS): Estimated to affect about 1 in 20,000 to 1 in 40,000 people

Vascular EDS (vEDS): Much rarer, with prevalence estimates between 1 in 50,000 to 1 in 200,000 people

Other rare subtypes: Such as kyphoscoliotic and dermatosparaxis types, affect fewer than 1 in 1,000,000 individuals globally

No clear racial predominance, though some data suggest Whites may be more frequently diagnosed

Sex distribution is roughly equal overall, but some reports indicate a higher diagnosis rate in females, especially for hEDS (female-to-male ratio up to 8:1 in some studies)

Clinical features often become recognizable in childhood or young adulthood, but diagnosis may be delayed.  
EDS is increasingly recognized as a multisystemic disorder, with links to cardiovascular, gastrointestinal, neurodevelopmental, and psychiatric conditions  
The combined prevalence of HSD and hEDS may be as high as 1 in 600 to 1 in 900, suggesting these connective tissue disorders are more common than previously thought

**GENOMIC DATA**

* Key Genes Involved:
  + COL5A1 and COL5A2: Mutations cause classical EDS (cEDS) by affecting type V collagen.
  + COL3A1: Mutations cause vascular EDS (vEDS), a severe autosomal dominant form characterized by fragile blood vessels and organs. Over 600 unique pathogenic variants have been documented, including glycine substitutions and splice-site mutations that disrupt collagen type III assembly.
  + Other genes: Include *ADAMTS2*, *AEBP1*, *B3GALT6*, *B4GALT7*, *C1R*, *C1S*, *CHST14*, *COL12A1*, *COL1A1*, *COL1A2*, *DSE*, *FKBP14*, *PLOD1*, among others, linked to various rare EDS subtypes.
  + Mutations can be dominant or recessive, and include missense, nonsense, splice-site, exon duplications/deletions, and complex structural variants.
* Variant Databases:  
  The Ehlers-Danlos Syndrome Variant Database (hosted on the Leiden Open Variation Database, LOVD) catalogs detailed genetic variants linked to EDS, aiding diagnosis and research. This resource is continuously updated with new mutations and genotype-phenotype correlations.
* Genotype-Phenotype Correlations:
  + In vEDS, different types of *COL3A1* variants (e.g., glycine substitutions vs. haploinsufficiency mutations) influence disease severity and clinical course.
  + Splice-site variants often lead to earlier onset and more severe manifestations.
  + Some mutations cause dominant-negative effects, severely destabilizing collagen triple helix formation.
* Diagnostic Challenges:
  + Some pathogenic variants may be missed by standard exome sequencing due to complex gene regions (e.g., *TNXB* locus).
  + Comprehensive genetic analysis may include sequencing of introns, promoters, and transcript studies.
  + Genetic testing is critical for confirming diagnosis, guiding management, and genetic counseling.
* Inheritance:  
  Most EDS types are inherited in an autosomal dominant manner, but some rare types are autosomal recessive.

## **Doctor-Patient Conversation on Ehlers-Danlos Syndrome (De-Identified)**

## Doctor:

Hello! I understand you’ve been experiencing joint pain and some unusual flexibility. Can you tell me more about your symptoms?

## Patient:

Yes, doctor. I’ve always been very flexible — I can bend my fingers and joints more than most people. Lately, I’ve been having frequent joint pain, some dislocations, and I feel tired a lot.

## Doctor:

Thank you for sharing. Your symptoms, including joint hypermobility and pain, are consistent with a group of conditions called Ehlers-Danlos Syndromes, or EDS. These are genetic connective tissue disorders that affect the strength and elasticity of your joints and skin.

## Patient:

Is this something serious? What causes it?

## Doctor:

EDS is caused by changes in genes that affect collagen, an important protein in connective tissues. This leads to joints that are more flexible but also more prone to injury, skin that may be stretchy or fragile, and sometimes other systemic issues.

## Patient:

How is it diagnosed?

## Doctor:

Diagnosis is based on your medical history, physical examination, and specific criteria including joint hypermobility scores. Genetic testing can confirm some types of EDS, but not all. Sometimes it takes seeing specialists familiar with EDS to make an accurate diagnosis.

## Patient:

Is there a cure?

## Doctor:

Currently, there is no cure for EDS. Treatment focuses on managing symptoms, preventing injuries, and improving quality of life. This includes physical therapy to strengthen muscles around joints, pain management, and sometimes braces or supports.

## Patient:

What should I avoid?

## Doctor:

It’s important to avoid activities that put excessive strain on your joints or risk injury. Low-impact exercises like swimming or cycling are usually recommended. Also, learning how to protect your joints during daily activities helps reduce dislocations.

## Patient:

Are there other health issues I should be aware of?

## Doctor:

Some people with EDS experience problems like easy bruising, slow wound healing, digestive issues, or cardiovascular concerns. We’ll monitor for these and coordinate care with other specialists as needed.

## Patient:

How often should I see a doctor?

## Doctor:

Regular follow-ups are important to monitor symptoms and adjust management. Having a multidisciplinary team including rheumatologists, physiotherapists, and pain specialists can be very helpful.

## Patient:

Is there support available?

## Doctor:

Yes, there are patient organizations and support groups that provide education and community. They can be a great resource for coping and learning more about living with EDS.

## Patient:

Thank you, doctor. I feel better knowing there’s a plan.

## Doctor:

You’re welcome. We’ll work together to manage your symptoms and improve your daily life. Please reach out anytime you have concerns or new symptoms.

REFERENCES

[Ehlers-Danlos Syndrome: Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/17813-ehlers-danlos-syndrome)

[Ehlers-Danlos syndrome - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/ehlers-danlos-syndrome/symptoms-causes/syc-20362125)

<https://emedicine.medscape.com/article/1114004-overview#a6>

<https://www.nhs.uk/conditions/ehlers-danlos-syndromes/>

**FIBROMYALGIA**

**DEFINITION AND DESCRIPTION**

Fibromyalgia is a long-term condition that involves widespread body pain. The pain happens along with fatigue. It also can involve issues with sleep, memory and mood. Researchers think that fibromyalgia affects the way the brain and spinal cord process painful and non painful signals. That increases your overall sensitivity to pain.

Symptoms often start after a triggering event. Triggers can include injuries, surgery, infections or emotional stress. Or the symptoms can build up over time, with no single event to trigger them.

Women are more likely to get fibromyalgia than are men. Many people who have fibromyalgia also have:

* Headaches.
* Jaw and facial pain due to temporomandibular joint (TMJ) disorders.
* Irritable bowel syndrome.
* Anxiety.
* Depression.

There's no cure for fibromyalgia. But medicines and other treatments can help control the symptoms. Exercise, talk therapy and techniques that lower stress also may help.

## **Causes**

With fibromyalgia, many researchers think nerves are affected in a way that causes the brain and spinal cord to change. This change involves an irregular rise in levels of certain chemicals in the brain that signal pain.

In addition, the brain's pain receptors seem to develop a sort of memory of the pain. They can start to overreact to painful and nonpainful signals.

Many factors likely lead to these changes, including:

* **Genes.** Fibromyalgia tends to run in families. So certain gene changes might make you more likely to get the condition.
* **Infections.** Some illnesses appear to trigger fibromyalgia or make it worse.
* **Physical or emotional events.** Sometimes, fibromyalgia can be triggered by a physical event, such as a car accident. Ongoing stress also may trigger the condition.

## **Risk factors**

Risk factors for fibromyalgia include:

* **Being assigned female at birth.** Fibromyalgia is more common in women than in men.
* **Family history.** You may be more likely to get fibromyalgia if a parent or sibling also has the condition.
* **Other medical conditions.** Your risk of fibromyalgia rises if you have osteoarthritis, rheumatoid arthritis, lupus or obesity.

## **Symptoms**

The main symptoms of fibromyalgia include:

* **Widespread pain.** Fibromyalgia pain often is described as a constant dull ache that has lasted for at least three months. The pain is considered widespread if it happens on both sides of the body and above and below the waist.
* **Fatigue.** People with fibromyalgia often wake up tired, even though they say they sleep for a long time. Often, the pain disrupts sleep. Many people with fibromyalgia have other sleep disorders. These include restless legs syndrome and sleep apnea.
* **Thinking-related troubles.** A symptom known as "fibro fog" makes it harder to pay attention and focus on mental tasks.

Fibromyalgia often happens with other conditions, such as:

* Irritable bowel syndrome.
* Chronic fatigue syndrome.
* Migraine and other types of headaches.
* Interstitial cystitis, also called painful bladder syndrome.
* TMJ disorders.
* Anxiety.
* Depression.
* Postural tachycardia syndrome.
* Post-COVID syndrome, also known as long COVID.

## **Diagnosis**

To find out if you have fibromyalgia, your healthcare professional starts by asking you about your symptoms and health history. You also get a physical exam. Your care team checks for the main sign of fibromyalgia: widespread pain throughout the body for at least three months.

You must have pain in at least four of these five areas:

* **Left upper region,** including the shoulder, arm or jaw.
* **Right upper region,** including the shoulder, arm or jaw.
* **Left lower region,** including the hip, buttock or leg.
* **Right lower region,** including the hip, buttock or leg.
* **Axial region,** which includes the neck, back, chest or stomach area.

### **Tests**

You might need blood tests or imaging tests. These tests can help find out if a condition other than fibromyalgia is the cause of your symptoms.

Other conditions that can cause ongoing pain and tiredness include:

* Rheumatoid arthritis.
* Lupus.
* Myalgic encephalomyelitis/chronic fatigue syndrome.

You also may need tests to find conditions that can happen along with fibromyalgia. For example, your doctor may recommend an overnight sleep study if sleep apnea is suspected.

## **Treatment**

In general, treatments for fibromyalgia include both medicine and other techniques. The goal is to lessen your symptoms and improve your overall health. No one treatment works for all symptoms, so it can help to try a few.

### **Medicines**

Medicines can help ease the pain of fibromyalgia and improve sleep. Common choices include:

* **Pain relievers.** Nonprescription pain relievers such as acetaminophen (Tylenol, others), ibuprofen (Advil, Motrin IB, others) or naproxen sodium (Aleve, others) may be helpful. Your doctor may recommend you take them along with other medicines. Opioid medicines are not recommended. They can lead to side effects, dependence and pain that gets worse over time.
* **Antidepressants.** These medicines may help even if you don't have depression with fibromyalgia. Duloxetine (Cymbalta) and milnacipran (Savella) may help ease fibromyalgia pain and fatigue. Your doctor may prescribe amitriptyline or the muscle relaxant cyclobenzaprine to help with pain or sleep.
* **Anti-seizure medicines.** Epilepsy medicines often help ease some types of pain. Pregabalin (Lyrica) is used as a fibromyalgia treatment. And gabapentin (Gralise, Neurontin) sometimes helps ease fibromyalgia symptoms.

### **Other therapies**

Other treatments can help reduce the effect that fibromyalgia has on your body and your life. Examples include:

* **Physical therapy.** A physical therapist can teach you exercises to boost your strength, flexibility and stamina. Water-based exercises might be especially helpful.
* **Occupational therapy.** An occupational therapist can help you make changes to your work area or the way you do certain tasks. The changes cause less stress on your body.
* **Counseling.** Talking with a counselor can help strengthen your belief in your abilities. It also can teach you ways to deal with stressful situations. It can be especially helpful to see a counselor who is trained in cognitive behavioral therapy.

## **Fibromyalgia Treatment Drugs and Their Side Effects**

## FDA-Approved Medications for Fibromyalgia

1. Pregabalin (Lyrica)
   1. Use: Reduces nerve pain and improves sleep and fatigue.
   2. Mechanism: Binds to calcium channels in nerve cells, decreasing pain signal transmission.
   3. Common Side Effects:
      1. Dizziness
      2. Drowsiness
      3. Dry mouth
      4. Weight gain
      5. Swelling of hands and feet (edema)
      6. Blurred vision
      7. Constipation
      8. Difficulty concentrating or balance problems
2. Duloxetine (Cymbalta)
   1. Use: An antidepressant that helps reduce pain and improve mood and fatigue.
   2. Mechanism: Serotonin-norepinephrine reuptake inhibitor (SNRI) that modulates pain pathways in the central nervous system.
   3. Common Side Effects:
      1. Nausea
      2. Dry mouth
      3. Fatigue
      4. Dizziness
      5. Insomnia
      6. Increased sweating
      7. Constipation
3. Milnacipran (Savella)
   1. Use: Similar to duloxetine, reduces pain and fatigue.
   2. Mechanism: SNRI that increases serotonin and norepinephrine levels.
   3. Common Side Effects:
      1. Nausea
      2. Headache
      3. Constipation
      4. Increased heart rate
      5. High blood pressure
      6. Insomnia
      7. Sweating

## Other Commonly Used Medications (Off-Label)

* Gabapentin: Similar to pregabalin, used for nerve pain. Side effects include dizziness and drowsiness.
* Muscle Relaxants (e.g., Cyclobenzaprine): Help relieve muscle spasms and improve sleep; side effects include drowsiness and dry mouth.
* Antidepressants (other than duloxetine/milnacipran): Such as amitriptyline, fluoxetine, sertraline; used to manage pain, sleep, and mood symptoms. Side effects vary by drug but often include sedation, dry mouth, and gastrointestinal upset.
* NSAIDs: May be used for mild pain relief but are generally less effective for fibromyalgia pain.
* Opioids (e.g., tramadol): Sometimes prescribed short-term for severe pain but have risks of dependence and side effects like sedation and constipation.

## **Self-care**

Self-care is key as you take charge of fibromyalgia.

* **Manage stress.** Work with your healthcare team on a plan to save your energy and manage stress. Give yourself time each day to relax. That may mean learning how to say no to others without guilt. But try not to change your whole routine. People who quit work or drop all activity tend to do worse than those who stay active. Try stress management techniques such as deep-breathing exercises or mindfulness meditation. Think about joining a fibromyalgia support group too. It helps you meet people who understand what you're going through.
* **Get quality sleep.** Fatigue is one of the main symptoms of fibromyalgia, which makes sleep crucial. Adults should aim to get at least seven hours of rest a night. Keep your bedroom cool, dark and quiet at night. Try to go to bed and get up at the same time each day. And limit daytime napping.
* **Exercise regularly.** At first, exercise may make your pain worse. But if you start slowly and become more active over time, it often relieves symptoms. Talk with your doctor or another member of your healthcare team if you're not active already. They may recommend aerobic exercises that get your heart pumping such as walking, swimming, biking and water aerobics. A physical therapist can help you develop a home exercise program too. Stretching, good posture and relaxation exercises also are helpful.
* **Pace yourself.** Keep your activity on an even level. If you do too much on your good days, you may have more bad days. Likewise, don't do too little on the days when your symptoms flare.
* **Practice other healthy habits.** Eat nutritious foods. Do not use tobacco products. Limit caffeine. Do something that you find fun and fulfilling every day.

## **Alternative medicine**

Complementary and alternative treatments to help manage pain and stress aren't new. Some, such as meditation and yoga, have been practiced for thousands of years. Their use has become more popular, especially with people who have chronic illnesses such as fibromyalgia.

Some of these treatments do appear to safely relieve stress and reduce pain. Talk with a member of your healthcare team before you try a new complementary or alternative treatment.

* **Acupuncture.** Acupuncture is a Chinese technique. A trained practitioner places very fine needles through the skin to various depths. According to Western theories of acupuncture, the needles cause changes in blood flow and levels of brain chemicals called neurotransmitters. Some studies suggest that acupuncture helps relieve fibromyalgia symptoms.
* **Massage therapy.** This is one of the oldest methods of healthcare still in practice. It involves the use of different techniques to move the body's muscles and soft tissues. Massage can reduce heart rate, relax muscles and improve the range of motion in joints. It also can boost the amount of natural pain-relieving chemicals the body makes. It often helps relieve stress and anxiety too.
* **Yoga and tai chi.** These practices combine meditation, slow movements, deep breathing and relaxation. Both have been found to be helpful in controlling fibromyalgia symptoms.

## **Complications**

The pain, fatigue, and poor sleep linked with fibromyalgia can affect your personal life and career. It also can be stressful to live with a condition that's often misunderstood by others. That can lead to mental health conditions such as depression and anxiety.

## **Outlook / Prognosis**

You should expect to manage fibromyalgia symptoms for a long time — maybe for the rest of your life. Some people with fibromyalgia experience fewer flare-ups with milder symptoms after they find treatments that work for them. Ask your provider how often you need follow-up appointments to adjust your treatments or to adjust any medications you’re taking.

Fibromyalgia is a real condition that has a real impact on your life. Some days it might feel like “it’s all in your head,” but it’s not. Talk to your provider or a mental health professional if you need help managing stress and other emotional symptoms.

### **Complications of fibromyalgia**

People with fibromyalgia are more likely to be hospitalized because of pain, fatigue or mental health symptoms. You’re also more likely to experience memory problems and have trouble concentrating.

Talk to your provider as soon as you notice any changes in your symptoms, especially if you feel like they’re affecting your memory or mental health.

## **Prevention**

Because experts don’t know what causes fibromyalgia, you can’t prevent it.

Maintaining your overall health can help reduce the severity of fibromyalgia symptoms:

* Manage stress as well as you can.
* Follow a diet and exercise plan that’s healthy for you.
* Get enough sleep and practice good sleep hygiene.

### **When should I see my healthcare provider?**

Visit a healthcare provider if you’re experiencing new symptoms like pain, fatigue or changes in your mental health, including:

* Depression or suicidal thoughts.
* Headaches or migraines.
* Memory problems or you feel like your brain is “foggy.”
* Sleep problems.

## **QUESTIONS AND ANSWERS SET**

## Do I have fibromyalgia or another condition?

Fibromyalgia is suspected if you have widespread musculoskeletal pain lasting at least three months, accompanied by symptoms such as fatigue, sleep disturbances, cognitive difficulties ("fibrofog"), and sometimes mood disorders. Diagnosis is clinical, based on your history and physical exam, and by excluding other conditions that can cause similar symptoms (e.g., rheumatoid arthritis, thyroid disease, lupus). There is no single definitive test for fibromyalgia. Your healthcare provider will evaluate your symptoms and may perform tests to rule out other diseases.

## Which tests will I need?

There is no specific test to diagnose fibromyalgia, but your doctor may order blood tests to exclude other causes of your symptoms, such as:

* Complete blood count (CBC)
* Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) to check for inflammation
* Thyroid function tests
* Rheumatoid factor and anti-CCP antibodies (to rule out rheumatoid arthritis)
* Antinuclear antibody (ANA) test (to rule out lupus)
* Vitamin D levels
* Celiac disease serology if indicated
* Sleep study if sleep apnea is suspected

## Which treatments will work best for me?

Fibromyalgia treatment is individualized and often multimodal, including:

* Medications: Such as pregabalin, duloxetine, milnacipran, or others to reduce pain and improve sleep.
* Physical therapy: Gentle aerobic exercise and stretching to improve function and reduce pain.
* Cognitive-behavioral therapy (CBT): To manage pain coping strategies and mood.
* Lifestyle changes: Stress reduction, sleep hygiene, pacing activities.
* Your healthcare provider will work with you to find the best combination based on your symptoms and response.

## How often will I need follow-up appointments to adjust my treatments?

* Initially, follow-ups may be every 4 to 6 weeks to monitor symptom response and medication side effects.
* Once stable, visits may be spaced to every 3 to 6 months.
* More frequent visits may be needed if symptoms worsen or new treatments are started.
* Regular communication with your provider helps optimize your care.

## Should I work with a mental health professional?

* Yes, many people with fibromyalgia experience anxiety, depression, or mood disorders, which can worsen pain and fatigue.
* Mental health professionals can provide cognitive-behavioral therapy (CBT) or other therapies to help manage stress, improve coping, and enhance quality of life.
* Integrating mental health care is an important part of comprehensive fibromyalgia management.

## Does this mean my family members are more likely to develop fibromyalgia?

* Fibromyalgia can run in families, suggesting a genetic predisposition, but it is influenced by multiple factors including environment and stress.
* Having a family member with fibromyalgia increases your risk somewhat, but it does not guarantee you will develop it.
* Early recognition and management of symptoms can improve outcomes.

## **Differential Diagnosis**

The differential diagnosis includes rheumatologic conditions, such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, spondyloarthropathies, polymyalgia rheumatica, and myopathies. Fibromyalgia should be considered in patients with other rheumatologic diagnoses who do not respond well to treatment of their primary condition. Based on the history and examination findings, other diagnoses to consider include Lyme disease, hepatitis, hyperthyroidism, hypothyroidism, hyperparathyroidism, and neurologic conditions such as multiple sclerosis and other disorders that cause neuropathic pain. The Choosing Wisely initiative recommends against testing for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and relevant examination findings. Medication adverse effects can rarely cause diffuse pain, including from statins, opioids, bisphosphonates, and aromatase inhibitors.

## **Fibromyalgia Epidemiology** Fibromyalgia affects approximately 3% to 10% of the general population worldwide, with estimates commonly around 2% to 4% in many countries[1](https://accessmedicine.mhmedical.com/content.aspx?sectionid=288489560&bookid=3495&preview=false)[4](https://emedicine.medscape.com/article/329838-overview)[5](https://en.wikipedia.org/wiki/Fibromyalgia). Some regional studies report higher prevalence, such as up to 13% in parts of the Middle East[7](https://pmc.ncbi.nlm.nih.gov/articles/PMC11765407/). In the United States, prevalence estimates range from about 2% to 6% depending on the study and diagnostic criteria used Women are affected 7 times more often than men, with about 80-90% of diagnosed cases being female[1](https://accessmedicine.mhmedical.com/content.aspx?sectionid=288489560&bookid=3495&preview=false)[3](https://www.moregooddays.com/post/fibromyalgia-by-numbers-key-statistics-you-need-to-know)[5](https://en.wikipedia.org/wiki/Fibromyalgia). Recent data suggest the female-to-male ratio may be closer to 60:40 when considering symptoms in the general population, indicating men may be underdiagnosed or underreported Fibromyalgia is most frequently diagnosed in adults aged 20 to 50 years, with peak diagnosis often occurring between 40 and 60 years. Juvenile fibromyalgia is also recognized but less common Fibromyalgia occurs across all ethnic groups and cultures, with no strong racial predilection[4](https://emedicine.medscape.com/article/329838-overview). Prevalence rates vary due to differences in diagnostic criteria, awareness, and healthcare access. Fibromyalgia is more common in individuals with:

Lower socioeconomic status and education levels

Comorbid conditions such as depression, anxiety, sleep disorders, and autoimmune diseases (e.g., lupus, rheumatoid arthritis)

History of physical or emotional trauma  
Fibromyalgia is the second most common disorder seen by rheumatologists, affecting about 15% of their patients. It causes chronic widespread pain, fatigue, and disability, often leading to reduced work capacity and quality of life. The economic burden in the US alone is estimated at over $9 billion annually  
The average time from symptom onset to diagnosis is about 5 to 6 years, with patients often consulting multiple specialists before diagnosis

## **Genomic Data**

## Identified Genetic Biomarkers

* + DYRK3 (dual-specificity tyrosine phosphorylation-regulated kinase 3)
  + RGS17 (regulator of G protein signaling 17)
  + ARHGEF37 (Rho guanine nucleotide exchange factor 37)  
    These genes are involved in ion homeostasis, cell signaling, and neurobiological functions, all of which are disrupted in FM

## Genomic Signatures and Patient Subgroups

* High-throughput RNA sequencing of peripheral blood mononuclear cells from FM patients revealed distinct genomic expression patterns, suggesting FM is a heterogeneous disease with multiple molecular subtypes. These include:
  + A subgroup with altered extracellular matrix gene expression and downregulated RhoGDI signaling
  + A subgroup with reduced inflammatory mediator expression but increased lysosomal biogenesis pathways
  + A subgroup with overexpression of acute inflammation pathways and transcriptional dysregulation  
    This heterogeneity may explain differences in symptoms and treatment responses among patients
* Several studies have identified altered immune and inflammatory signatures in FM, including:
  + Underexpression of pro-inflammatory cytokines like IL-6, IL-8, and MIP-1α/β compared to healthy controls
  + Presence of autoimmune-related gene signatures, such as increased Th17 cells and type I interferon pathways
  + Hypomethylation of genes involved in stress response and DNA repair, suggesting epigenetic contributions

## Genetic Susceptibility and Environmental Interaction

* Certain genotypes (e.g., Met/Met at specific loci) may increase susceptibility to FM following physical or emotional stress, highlighting a gene-environment interaction in disease development

## **Doctor-Patient Conversation on Fibromyalgia (De-Identified)**

## Doctor:

Hello! I understand you’ve been experiencing widespread pain and fatigue. Can you tell me more about your symptoms?

## Patient:

Yes, doctor. I’ve had pain all over my body for several months now. It’s like a constant aching, and I feel tired all the time. Sometimes I have trouble sleeping and concentrating.

## Doctor:

Thank you for sharing. Your symptoms are consistent with fibromyalgia, a chronic condition that causes widespread musculoskeletal pain along with fatigue, sleep disturbances, and cognitive difficulties often called “fibro fog.”

## Patient:

What causes fibromyalgia? Is it something serious?

## Doctor:

The exact cause isn’t fully understood, but it involves abnormal processing of pain signals in the brain and nervous system. Genetics, stress, infections, and other factors can contribute. While it’s not life-threatening, fibromyalgia can significantly impact quality of life.

## Patient:

How is it diagnosed?

## Doctor:

Diagnosis is based on your medical history, symptom patterns, and ruling out other conditions. There are no specific blood tests for fibromyalgia, but we may do some tests to exclude other causes of your symptoms.

## Patient:

What treatments are available?

## Doctor:

Treatment focuses on symptom management and improving function. This includes:

* Medications like certain antidepressants, anticonvulsants, or pain relievers
* Physical therapy and gentle exercise to improve strength and reduce pain
* Cognitive-behavioral therapy to help manage stress and coping
* Sleep hygiene and relaxation techniques

## Patient:

Will the pain ever go away?

## Doctor:

Fibromyalgia symptoms can fluctuate. Many people learn to manage their symptoms effectively and maintain a good quality of life. It often requires a combination of treatments tailored to your needs.

## Patient:

Are there lifestyle changes I can make?

## Doctor:

Yes, regular low-impact exercise like walking or swimming, stress reduction, balanced diet, and good sleep habits can help. Avoiding overexertion and pacing activities is important.

## Patient:

Is fibromyalgia hereditary?

## Doctor:

There is some genetic predisposition, meaning it can run in families, but environmental factors also play a big role.

## Patient:

What should I do if symptoms worsen?

## Doctor:

Keep a symptom diary and let me know if pain, fatigue, or other issues increase. We can adjust your treatment plan as needed.

## Patient:

Thank you, doctor. I’m glad to have a clearer understanding.

## Doctor:

You’re welcome. We’ll work together to find the best approach for you. Please reach out anytime you have questions or concerns.

REFERENCES

[Fibromyalgia: Symptoms, Diagnosis & Treatment](https://my.clevelandclinic.org/health/diseases/4832-fibromyalgia#outlook-prognosis)

[Fibromyalgia - Diagnosis & treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/fibromyalgia/diagnosis-treatment/drc-20354785)

<https://www.hopkinslupus.org/lupus-treatment/common-medications-conditions/fibromyalgia-medications/>

<https://www.ncbi.nlm.nih.gov/books/NBK274463/table/introduction.t1/>

<https://www.aafp.org/pubs/afp/issues/2023/0200/fibromyalgia.html>

**NEUROFIBROMATOSIS**

**DESCRIPTION**

Neurofibromatosis type 1 (NF1) is a genetic condition that causes changes in skin pigment and tumors on nerve tissue. Skin changes include flat, light brown spots and freckles in the armpits and groin. Tumors can grow anywhere in the nervous system, including the brain, spinal cord and nerves. NF1 is rare. About 1 in 2,500 is affected by NF1.

The tumors often are not cancerous, known as benign tumors. But sometimes they can become cancerous. Symptoms often are mild. But complications can occur and may include trouble with learning, heart and blood vessel conditions, vision loss, and pain.

Treatment focuses on supporting healthy growth and development in children and early management of complications. If NF1 causes large tumors or tumors that press on a nerve, surgery can reduce symptoms. A newer medicine is available to treat tumors in children, and other new treatments are being developed.

**Causes**

Neurofibromatosis type 1 is caused by an altered gene that either is passed down by a parent or occurs at conception.

The NF1 gene is located on chromosome 17. This gene produces a protein called neurofibromin that helps regulate cell growth. When the gene is altered, it causes a loss of neurofibromin. This allows cells to grow without control.

**Risk factors**

The biggest risk factor for neurofibromatosis type 1 (NF1) is a family history. For about half of people who have NF1, the disease was passed down from a parent. People who have NF1 and whose relatives aren't affected are likely to have a new change to a gene.

NF1 has an autosomal dominant inheritance pattern. This means that any child of a parent who is affected by the disease has a 50% chance of having the altered gene.

**Symptoms**

Neurofibromatosis type 1 (NF1) usually is diagnosed during childhood. Symptoms are seen at birth or shortly afterward and almost always by age 10. Symptoms tend to be mild to moderate, but they can vary from person to person.

Symptoms include:

* **Flat, light brown spots on the skin, known as cafe au lait spots.** These harmless spots are common in many people. But having more than six cafe au lait spots suggests NF1. They often are present at birth or appear during the first years of life. After childhood, new spots stop appearing.
* **Freckling in the armpits or groin area.** Freckling often appears by ages 3 to 5. Freckles are smaller than cafe au lait spots and tend to occur in clusters in skin folds.
* **Tiny bumps on the iris of the eye, known as Lisch nodules.** These nodules can't easily be seen and don't affect vision.
* **Soft, pea-sized bumps on or under the skin called neurofibromas.** These benign tumors usually grow in or under the skin but can also grow inside the body. A growth that involves many nerves is called a plexiform neurofibroma. Plexiform neurofibromas, when located on the face, can cause disfigurement. Neurofibromas may increase in number with age.
* **Bone changes.** Changes in bone development and low bone mineral density can cause bones to form in an irregular way. People with NF1 may have a curved spine, known as scoliosis, or a bowed lower leg.
* **Tumor on the nerve that connects the eye to the brain, called an optic pathway glioma.** This tumor usually appears by age 3. The tumor rarely appears in late childhood and among teenagers, and almost never in adults.
* **Learning disabilities.** It's common for children with NF1 to have some trouble with learning. Often there is a specific learning disability, such as trouble with reading or math. Attention-deficit/hyperactivity disorder (ADHD) and speech delay also are common.
* **Larger than average head size.** Children with NF1 tend to have a larger than average head size due to increased brain volume.
* **Short stature.** Children who have NF1 often are below average in height.

### **When to see a doctor**

See a healthcare professional if your child has symptoms of neurofibromatosis type 1. The tumors are often not cancerous and are slow growing, but complications can be managed. If your child has a plexiform neurofibroma, a medicine is available to treat it.

## **Diagnosis**

To diagnose neurofibromatosis type 1 (NF1), a healthcare professional begins with a review of your personal and family medical history and a physical exam.

Your child's skin is checked for cafe au lait spots, which can help diagnose NF1.

If other tests are needed to diagnose NF1, your child may need:

* **Eye exam.** An eye exam can reveal Lisch nodules, cataracts and vision loss.
* **Imaging tests.** X-rays, CT scans or MRIs can help identify bone changes, tumors in the brain or spinal cord, and very small tumors. An MRI might be used to diagnose optic gliomas.
* **Genetic tests.** Genetic testing for NF1 can help support the diagnosis. Genetic tests also can be done in pregnancy before a baby is born. Ask a member of your healthcare team about genetic counseling.

For a diagnosis of NF1, at least two symptoms of the condition must be present. A child who has only one symptom and no family history of NF1 is likely to be monitored for any other symptoms. A diagnosis of NF1 is usually made by age 4.

**Treatment**

There isn't a cure for neurofibromatosis type 1 (NF1), but symptoms can be managed. Generally, the sooner someone is under the care of a specialist trained in treating NF1, the better the outcome.

### **Monitoring**

If your child has NF1, often yearly age-appropriate checkups are recommended to:

* Check your child's skin for new neurofibromas or changes in existing ones.
* Check for signs of high blood pressure.
* Check your child's growth and development. This includes measuring height, weight and head circumference to compare to growth charts for children who have NF1.
* Look for signs of early puberty.
* Look for any skeletal changes.
* Check your child's learning development and progress in school.
* Get a complete eye exam.

Contact your healthcare team right away if you notice any changes in symptoms between visits. Many complications of NF1 can be treated effectively if therapy starts early.

### **Medicine**

Selumetinib (Koselugo) is a treatment approved by the U.S. Food and Drug Administration for plexiform neurofibroma in children. The medicine can shrink the size of a tumor. Clinical trials of similar medicines are currently being done for children and adults.

### **Surgery and other procedures**

Surgery to remove tumors may be needed to treat serious symptoms or complications of NF1. Symptoms can be relieved by removing all or part of tumors that are compressing nearby tissue or damaging organs.

### **Cancer treatment**

Cancers related to NF1 are treated with standard cancer therapies, such as surgery, chemotherapy and radiation therapy. Early diagnosis and treatment are the most important factors for a good outcome.

### **Potential future treatments**

Researchers are testing gene therapies for neurofibromatosis type 1 (NF1). Potential new treatments could include replacing the NF1 gene to restore the function of neurofibromin.

#### **side effects of the treatment**

Each type of treatment comes with possible side effects. Your healthcare provider will discuss side effects with you before you begin treatment.

Possible side effects of surgery include:

* Bleeding.
* Infection.
* Neurofibromas returning after removal.
* Nerve damage.

Side effects of chemotherapy include:

* Fatigue.
* Diarrhea or constipation.
* Hair loss.
* Loss of appetite.
* Nausea and vomiting.

## **Treatment Drug Information and Their Side Effects**

## 1. Mirdametinib (Gomekli)

* Indication: Approved by the FDA in February 2025 for adults and pediatric patients (2 years and older) with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN) that cannot be completely removed surgically.
* Mechanism: MEK kinase inhibitor that blocks enzymes involved in tumor growth, shrinking tumors and slowing progression.
* Efficacy: Clinical trials showed tumor shrinkage of ≥20% in 41% of adults and 52% of children, with many maintaining response for over a year.
* Common Side Effects:
  + Rash
  + Diarrhea
  + Fatigue
  + Nausea
  + Elevated liver enzymes
  + Muscle pain
  + Possible cardiac effects requiring monitoring
* Notes: Oral medication taken continuously until disease progression or unacceptable toxicity.

## 2. Selumetinib (Koselugo)

* Indication: FDA-approved since 2020 for pediatric patients (2 years and older) with NF1 and symptomatic, inoperable plexiform neurofibromas.
* Mechanism: MEK inhibitor similar to mirdametinib, targeting tumor growth pathways.
* Efficacy: Demonstrated an overall response rate of 66% in clinical trials, with sustained tumor shrinkage.
* Common Side Effects:
  + Vomiting
  + Rash
  + Abdominal pain
  + Diarrhea
  + Nausea
  + Fatigue
  + Musculoskeletal pain
  + Fever
  + Headache
  + Eye toxicity (retinal vein occlusion, impaired vision)
  + Elevated creatine phosphokinase
* Monitoring: Requires regular cardiac and ophthalmologic assessments due to potential toxicities.

## **Outlook / Prognosis**

Neurofibromatosis doesn’t usually affect your life expectancy. The location of the tumors can make certain aspects of your daily routine difficult without assistance, like hearing and seeing, for example. Complications can lead to possible life-threatening outcomes, like cancer, if left untreated.

## **Prevention**

There’s no known way to prevent neurofibromatosis. If you plan on starting a family, talk to a healthcare provider about genetic counseling to learn more about the risks of having a child with a genetic condition.

## **Complications**

Complications of neurofibromatosis type 1 (NF1) vary, even within the same family. Generally, complications occur when tumors affect nerve tissue or press on internal organs.

Complications of NF1 include:

* **Neurological symptoms.** Trouble with learning and thinking are the most common neurological symptoms associated with NF1. Less common complications include epilepsy and the buildup of excess fluid in the brain.
* **Concerns with appearance.** Visible signs of NF1 can include widespread cafe au lait spots, many neurofibromas in the facial area or large neurofibromas. In some people this can cause anxiety and emotional distress, even if they're not medically serious.
* **Skeletal symptoms.** Some children have bones that didn't form as usual. This can cause bowing of the legs and fractures that sometimes don't heal. NF1 can cause curvature of the spine, known as scoliosis, that may need bracing or surgery. NF1 also is associated with lower bone mineral density, which increases the risk of weak bones, known as osteoporosis.
* **Changes in vision.** Sometimes a tumor called an optic pathway glioma develops on the optic nerve. When this happens, it can affect vision.
* **Increase in symptoms during times of hormonal change.** Hormonal changes associated with puberty or pregnancy might cause an increase in neurofibromas. Most people who have NF1 have healthy pregnancies but will likely need monitoring by an obstetrician who is familiar with NF1.
* **Cardiovascular symptoms.** People who have NF1 have an increased risk of high blood pressure and may develop blood vessel conditions.
* **Trouble breathing.** Rarely, plexiform neurofibromas can put pressure on the airway.
* **Cancer.** Some people who have NF1 develop cancerous tumors. These usually arise from neurofibromas under the skin or from plexiform neurofibromas. People who have NF1 also have a higher risk of other forms of cancer. They include breast cancer, leukemia, colorectal cancer, brain tumors and some types of soft tissue cancer. Screening for breast cancer should begin earlier, at age 30, for women with NF1 compared to the general population.
* **Benign adrenal gland tumor, known as a pheochromocytoma.** This noncancerous tumor produces hormones that raise your blood pressure. Surgery often is needed to remove it.

## **Diagnostic Considerations**

* Café-au-lait spots
* Legius syndrome (*SPRED1* -related café-au-lait spots and freckles)
* McCune-Albright syndrome
* Acoustic neuroma
* Brainstem syndromes
* Spinal injury

## **Differential Diagnoses**

* Brainstem Gliomas
* Cauda Equina and Conus Medullaris Syndromes
* Low-Grade Astrocytoma
* Meningioma
* Neurofibromatosis Type 2
* Spinal Cord Hemorrhage
* Spinal Cord Infarction
* Spinal Epidural Abscess

## **Epidemiology**

The estimated incidence of neurofibromatosis type 1 (NF1) is 1 in 3000, but the actual frequency may be higher because of less than complete ascertainment of mildly affected individuals. Approximately half of affected individuals represent first cases in the family as a result of a new genetic event or mutation.

### Race-, sex-, and age-related demographics

All races and ethnic backgrounds are affected equally. However, evidence indicates that the risk for optic nerve glioma is lower in African Americans than in Caucasians and Hispanics.

Males and females are affected equally with this autosomal dominant condition. However, one study showed that female patients with NF1-associated optic glioma were twice as likely to undergo brain magnetic resonance imaging for visual symptoms and three times more likely to require treatment for visual decline than their male counterparts.

Scoliosis may be especially severe in young girls compared to their male counterparts.

Although the genetic change causing NF1 is present at conception, clinical manifestations may appear slowly over many years.

Diagnosis often is made earlier in children born to an NF1-affected parent; the clinical criteria for diagnosis are fulfilled more easily, and the clinician may be more attuned to this possible diagnostic concern.

If an at-risk individual reaches the age of 10 years without meeting the diagnostic criteria for NF1, he or she is unlikely to be affected.

## **Neurofibromatosis Genomic Data**

* Gene: *NF1* (Neurofibromin 1)
* Chromosomal Location: Chromosome 17q11.2
* Gene Size: Large gene with 60 exons
* Protein: Neurofibromin, a tumor suppressor involved in regulating cell growth via the RAS/MAPK pathway

## Mutation Spectrum

* Over 4,000 unique DNA variants and more than 8,600 public variants reported in the *NF1* gene variant database (LOVD)[1](https://www.lovd.nl/nf1).
* Variants include:
  + Frameshift mutations (insertions/deletions causing premature stop codons)
  + Nonsense mutations (premature stop codons)
  + Missense mutations (single amino acid changes)
  + Splice-site mutations affecting RNA processing
  + Large deletions and copy number variations (including microdeletions)
* Many mutations lead to loss of function of neurofibromin, causing uncontrolled cell proliferation and tumor formation.

## Genetic Characteristics

* Most *NF1* mutations are de novo (new in the patient), but about 50% of cases are inherited in an autosomal dominant manner.
* Mosaicism (presence of mutation in some but not all cells) can occur, leading to variable clinical severity even within families
* Genotype-phenotype correlations are complex; some large deletions are associated with more severe phenotypes including skeletal and neurological manifestations.

## Clinical Implications

* Mutations cause Neurofibromatosis type 1 (NF1), characterized by café-au-lait spots, neurofibromas, Lisch nodules, skeletal abnormalities, and increased tumor risk.
* Genetic testing is crucial for diagnosis, prognosis, and genetic counseling.
* Comprehensive testing includes sequencing and copy number variation analysis to detect point mutations and large deletions

## **QUESTIONS AND ANSWERS**

## What’s causing my symptoms?

Your symptoms are caused by a mutation in the NF1 gene on chromosome 17, which produces a protein called neurofibromin that normally helps regulate cell growth. When this gene is altered, neurofibromin is nonfunctional or absent, leading to uncontrolled growth of nerve tissue cells and the development of benign tumors called neurofibromas, skin pigment changes (café-au-lait spots), and other features of neurofibromatosis type 1 (NF1)

## What’s the risk that my future children will inherit this condition?

NF1 follows an autosomal dominant inheritance pattern, meaning only one copy of the altered gene is enough to cause the disorder. If you have NF1, each of your children has a 50% chance of inheriting the mutated gene and developing the condition. This risk applies whether the mutation was inherited from a parent or occurred spontaneously in you

## What type of treatment do you recommend?

Treatment focuses on managing symptoms and complications:

* Surgical removal of tumors causing pain or functional impairment.
* Newer medications like MEK inhibitors (e.g., mirdametinib, selumetinib) may shrink plexiform neurofibromas.
* Regular monitoring for complications such as vision problems, learning disabilities, skeletal abnormalities, and hypertension.
* Supportive therapies including physical therapy, pain management, and educational support for learning difficulties

## Are there side effects of the treatment?

Yes, especially with newer drug therapies:

* MEK inhibitors can cause rash, diarrhea, fatigue, nausea, elevated liver enzymes, muscle pain, and require monitoring for cardiac and eye toxicity.
* Surgical risks include bleeding, nerve damage, and incomplete tumor removal.
* Supportive treatments generally have fewer side effects but require ongoing management

## How often should I schedule follow-up appointments?

Follow-up frequency depends on your symptoms and complications but typically includes:

* Regular clinical evaluations every 6 to 12 months.
* More frequent visits if tumors are growing, vision is affected, or other complications arise.
* Imaging and specialist assessments as needed to monitor tumor size and organ involvement

## Are there any clinical trials available for me?

Yes, ongoing clinical trials are investigating new treatments for NF1, including novel targeted therapies and improved surgical techniques. Your healthcare provider or specialized NF centers can provide information about current trials appropriate for your age, symptoms, and tumor types

## Do I need to see a fertility specialist?

Most people with NF1 can have children without special fertility concerns. However, because of the 50% inheritance risk, genetic counseling is recommended before pregnancy to discuss reproductive options and risks. A fertility specialist or genetic counselor can help you understand testing, prenatal diagnosis, and assisted reproductive technologies if desired

## **Doctor-Patient Conversation on Neurofibromatosis (De-Identified)**

## Doctor:

Hello! I understand you’ve come in to discuss some skin changes and other symptoms you’ve been noticing. Can you tell me more about them?

## Patient:

Yes, doctor. I’ve noticed several small bumps on my skin, some café-au-lait spots, and sometimes I experience some numbness and tingling in my arms and legs.

## Doctor:

Thank you for sharing. Based on your symptoms and examination, it’s possible you have a condition called Neurofibromatosis, which is a genetic disorder that causes tumors to grow on nerve tissue.

## Patient:

Is this serious? What causes it?

## Doctor:

Neurofibromatosis is caused by mutations in specific genes that regulate cell growth. There are different types, mainly NF1 and NF2. NF1 is more common and often presents with skin findings like café-au-lait spots and neurofibromas, which are benign nerve tumors. NF2 primarily affects hearing and balance due to tumors on the auditory nerves.

## Patient:

Will these tumors become cancerous?

## Doctor:

Most neurofibromas are benign, but there is a small risk that some tumors can become malignant. Regular monitoring is important to detect any changes early.

## Patient:

What symptoms should I watch for?

## Doctor:

Watch for rapid growth of lumps, new neurological symptoms like weakness, pain, changes in vision or hearing, or headaches. If you notice any of these, please seek medical attention promptly.

## Patient:

How is Neurofibromatosis diagnosed?

## Doctor:

Diagnosis is based on clinical criteria including skin findings, family history, and sometimes genetic testing. Imaging studies like MRI can help evaluate internal tumors.

## Patient:

Is there a cure?

## Doctor:

There is no cure currently, but treatments focus on managing symptoms and complications. Surgery may be needed to remove problematic tumors, and other therapies are available for specific issues.

## Patient:

Can my children inherit this?

## Doctor:

Yes, Neurofibromatosis is inherited in an autosomal dominant pattern, meaning a 50% chance of passing the mutation to offspring. Genetic counseling can help you understand the risks and options.

## Patient:

What kind of follow-up care will I need?

## Doctor:

Regular check-ups with a multidisciplinary team including dermatologists, neurologists, and geneticists are important. We’ll monitor for tumor growth and manage any complications.

## Patient:

Thank you, doctor. What should I do next?

## Doctor:

I’ll arrange for genetic testing and imaging studies, and we’ll set up a follow-up plan. Meanwhile, keep track of any new symptoms and maintain regular health check-ups.

## Patient:

I appreciate your help.

## Doctor:

You’re welcome. We’re here to support you. Please don’t hesitate to reach out with any concerns.

REFERENCES

[Neurofibromatosis: What It Is, Symptoms, Types & Treatment](https://my.clevelandclinic.org/health/diseases/neurofibromatosis)

[Neurofibromatosis type 1 - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/neurofibromatosis-type-1/diagnosis-treatment/drc-20350495)

<https://emedicine.medscape.com/article/1177266-guidelines?form=fpf>

<https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-mirdametinib-adult-and-pediatric-patients-neurofibromatosis-type-1-who-have-symptomatic>

### **Duchenne muscular dystrophy**

**Definition**

Duchenne muscular dystrophy (DMD) is a condition that weakens skeletal and heart muscle that quickly gets worse with time. It’s the most common form of muscular dystrophy.

Most cases of DMD are inherited as an X-linked recessive trait (passed on through the mother, who is a carrier), but approximately 30% of cases are due to new genetic changes (mutations) that happen randomly and aren’t inherited.

Duchenne muscular dystrophy mainly affects boys, but girls who are carriers for DMD can sometimes have milder symptoms.

Symptoms of muscle weakness usually appear by the age of 2 years to 4 years, but sometimes, are noted as late as 6 years.

Duchenne muscular dystrophy affects about 1 in 3,600 male live-born infants. It’s the most common type of severe hereditary myopathies (disorders of skeletal muscles).

Yes, Duchenne muscular dystrophy is ultimately fatal. Most people with the condition die from lung or heart issues caused by it.

### **Symptoms of Duchenne muscular dystrophy**

Symptoms of Duchenne muscular dystrophy (DMD) most often appear between the ages of 2 and 4 years, though they can begin as early as infancy or be noticed later in childhood.

DMD causes muscle weakness that worsens over time, so common symptoms include:

* Progressive muscle weakness and atrophy (loss of muscle bulk) that begins in your child’s legs and pelvis. It occurs less severely in their arms, neck and other areas of their body.
* Calf muscle hypertrophy (increase in muscle size).
* Difficulty climbing up stairs.
* Difficulty walking gets worse over time.
* Frequent falls.
* Waddling gait (walk).
* Toe walking.
* Fatigue.

Other common symptoms of DMD include:

* Cardiomyopathy.
* Breathing difficulties and shortness of breath.
* Cognitive impairment and learning differences.
* Delayed speech and language development.
* Developmental delay.
* Scoliosis (spine curvature).
* Short stature (height).

About 2.5% to 20% of girls who are carriers of DMD may have symptoms that are usually milder.

### **What causes Duchenne muscular dystrophy?**

Duchenne muscular dystrophy (DMD) is caused by a change (mutation) in the gene that gives instructions for a protein called dystrophin. Dystrophin is a critical part of the dystrophin-glycoprotein complex (DGC), which plays an important role as a structural unit of muscle.

In DMD, both dystrophin and DGC proteins are missing, which ultimately leads to the death (necrosis) of muscle cells. People with DMD have less than 5% of the normal quantity of dystrophin needed for healthy muscles.

As people with DMD age, their muscles can’t replace the dead cells with new ones, and connective and adipose (fat) tissue gradually replaces muscle fibers.

Duchenne muscular dystrophy has X-linked recessive inheritance, but about 30% of cases happen spontaneously without a family history of the condition.

X-linked means the gene responsible for DMD is located on the X chromosome, one of two sex chromosomes. Males have an X and Y chromosome, and females have two X chromosomes.

Genes, like chromosomes, usually come in pairs. Recessive means that when there are two copies of the responsible gene, both copies must have a disease-causing change (pathogenic variant or mutation) for a person to have the condition. Since males only have one X chromosome, if that chromosome has the genetic variant that causes DMD, they’ll have DMD.

## **Diagnosis and Tests**

If your child is experiencing symptoms of Duchenne muscular dystrophy (DMD), your child’s healthcare provider will likely perform a physical exam, neurological exam and muscle exam. They’ll ask detailed questions about your child’s symptoms and medical history.

If your child’s provider suspects that your child may have DMD, they’ll likely order the following tests:

* **Creatine kinase blood test**: Your muscles release creatine kinase when they’re damaged, so elevated levels may indicate DMD. Levels typically peak by age 2 and can be more than 10 to 20 times above the normal range.
* **Genetic blood test**: A genetic blood test that looks for a complete or near-complete absence of the dystrophin gene can confirm the diagnosis of DMD.
* **Muscle** **biopsy**: Your child’s provider may take a small sample of their muscle tissue from a muscle in their thigh or calf. A specialist will then look at the sample under a microscope to look for signs of DMD.
* **Electrocardiogram (EKG)**: As DMD almost always affects your heart, your child’s provider will likely perform an EKG to look for characteristic signs of DMD and to check the health of your child’s heart.

## **Management and Treatment**

There’s currently no cure for Duchene muscular dystrophy (DMD), so the main goal of treatment is to manage symptoms and improve quality of life.

Supportive therapies for DMD include:

* **Corticosteroids**: Corticosteroids, such as prednisolone and deflazacort, are beneficial for delaying muscle strength loss, improving lung function, delaying scoliosis, slowing the progression of cardiomyopathy (heart weakness) and prolonging survival.
* **Medication to treat cardiomyopathy**: Early treatment with ACE inhibitors and/or beta-blockers may slow the progression of cardiomyopathy and prevent the onset of heart failure.
* **Physical therapy**: The main goal of physical therapy for DMD is to prevent contractures (permanent tightening of your muscles, tendons and skin). This usually involves certain stretching exercises.
* **Surgery to help treat scoliosis and contractures**: Surgery to release contractures may be necessary for severe cases. Surgery to correct scoliosis may improve lung and breathing function.
* **Exercise**: Your child’s healthcare provider will likely recommend gentle exercise to avoid muscle atrophy due to a lack of use. This is usually a combination of swimming pool and recreation-based exercises.

Other supportive therapies for DMD include:

* Mobility aids, such as braces, canes and wheelchairs.
* Tracheostomy and assisted ventilation for respiratory failure.

With improvement in supportive care over the years, the life expectancy of DMD has significantly improved over the past few decades.

There are many new drugs currently undergoing clinical testing that show promise in treating DMD. Some newer treatments that employ “exon skipping” (patching over a missing or mutated part of the dystrophin gene) have recently received FDA (Food and Drug Administration) approval. These treatments are applicable only to a minority of cases that have very specific mutations. Although these treatments increase dystrophin protein amount in muscle, meaningful gain in strength and physical function has not yet been shown.

## **Treatment Drugs and Their Side Effects**

## FDA-Approved Drugs for DMD

1. Agamree (vamorolone)
   1. Type: Steroid-like anti-inflammatory drug
   2. Use: Reduces inflammation and muscle damage with fewer steroid side effects than traditional corticosteroids.
   3. Side Effects: May include adrenal suppression, weight gain, mood changes, but generally better tolerated than prednisone.
2. Amondys 45 (casimersen)
   1. Type: Exon-skipping therapy targeting exon 45 mutations
   2. Use: Helps produce a shortened but functional dystrophin protein in patients amenable to exon 45 skipping.
   3. Side Effects: Possible injection site reactions, headache, fever, cough.
3. Duvyzat (givinostat)
   1. Type: Histone deacetylase (HDAC) inhibitor
   2. Use: Oral drug aiming to reduce muscle inflammation and slow disease progression.
   3. Side Effects: Gastrointestinal symptoms (nausea, diarrhea), fatigue, potential blood count changes; requires monitoring.
4. Elevidys (delandistrogene moxeparvovec)
   1. Type: Gene therapy
   2. Use: Single infusion delivering a functional dystrophin gene to muscle cells in children aged 4 and older.
   3. Side Effects: Infusion reactions, liver enzyme elevations, immune responses; long-term effects under study.
5. Emflaza (deflazacort)
   1. Type: Corticosteroid
   2. Use: Slows muscle degeneration and improves strength.
   3. Side Effects: Weight gain, bone thinning, mood swings, increased infection risk.
6. Exondys 51 (eteplirsen)
   1. Type: Exon-skipping therapy targeting exon 51 mutations
   2. Use: Promotes production of truncated dystrophin protein.
   3. Side Effects: Injection site reactions, headache, nausea.
7. Viltepso (viltolarsen)
   1. Type: Exon-skipping therapy targeting exon 53 mutations
   2. Use: Similar to Exondys 51 but for exon 53 mutations.
   3. Side Effects: Injection site reactions, headache, cough.
8. Vyondys 53 (golodirsen)
   1. Type: Exon-skipping therapy targeting exon 53 mutations
   2. Use: Same exon target as Viltepso; helps produce functional dystrophin.
   3. Side Effects: Injection site reactions, headache, fever.

## Emerging and Investigational Therapies

* Dyne-251: Next-generation exon 51 skipper showing higher dystrophin expression and favorable safety in trials.
* WVE-N531: Exon 53 skipper with promising dystrophin production and muscle health improvements in Phase II.
* Ataluren (Translarna): Protein restoration therapy for nonsense mutation DMD (nmDMD); pending FDA decision. Side effects include gastrointestinal symptoms and headache.

## **Duchenne Muscular Dystrophy (DMD) Staging**

## 1. Diagnosis Stage (Infancy/Childhood)

* Symptoms often appear between ages 2 and 5.
* Early signs include delayed motor milestones (walking, crawling), large calves (pseudohypertrophy), difficulty standing up (positive Gowers’ sign), and abnormal gait.
* Elevated creatine kinase (CK) levels and genetic testing confirm diagnosis.

## 2. Early Ambulatory Stage (Childhood)

* Muscle weakness primarily affects hips, thighs, shoulders, and pelvis.
* Children may have difficulty climbing stairs, running, or rising from the floor.
* Walking is still possible but may be awkward or waddling.
* Fatigue and frequent falls are common.

## 3. Late Ambulatory Stage (Late Childhood/Adolescence)

* Weakness progresses to lower legs, forearms, neck, and trunk muscles.
* Walking becomes increasingly difficult; fatigue worsens.
* Use of leg braces or walking aids may begin around ages 8-10.
* Wheelchair use often starts between ages 10-12.
* Scoliosis and bone fragility may develop.

## 4. Early Non-Ambulatory Stage (Adolescence/Young Adult)

* Loss of independent walking; full-time wheelchair use.
* Progressive weakness in arms and hands affects self-care.
* Respiratory muscles weaken; pulmonary function declines.
* Cardiac involvement (cardiomyopathy) may appear.

## 5. Late Non-Ambulatory Stage (Adulthood)

* Severe muscle wasting and contractures.
* Respiratory failure and cardiac complications are major causes of morbidity and mortality.
* Increased risk of infections such as pneumonia.
* Supportive care focuses on quality of life and symptom management.

## **Duchenne Muscular Dystrophy (DMD) Procedures and Timelines**

## 1. Diagnosis and Early Monitoring

* Timeline: Usually diagnosed in early childhood (ages 2-5) based on symptoms, elevated creatine kinase, and genetic testing.
* Procedures: Genetic testing to confirm mutation; baseline cardiac and pulmonary evaluations.
* Follow-up: Regular monitoring every 6-12 months to assess disease progression and organ function.

## 2. Physical Therapy and Mobility Support

* Timeline: Begins soon after diagnosis and continues lifelong.
* Procedures:
  + Physical therapy to maintain muscle strength and prevent contractures.
  + Use of braces (e.g., ankle-foot orthoses) from around age 5-8 to support ankles and prevent deformities.
  + Standing frames or walkers to promote bone health and circulation.
  + Gradual transition to wheelchair use, typically by age 12, starting with long distances and progressing to full-time use.

## 3. Pharmacologic Treatment

* Corticosteroids (Prednisone, Deflazacort):
  + Start typically between ages 4-6 to slow muscle degeneration.
  + Side effects require monitoring (weight gain, bone health).
* Newer therapies: Exon-skipping drugs (eteplirsen, golodirsen, viltolarsen, casimersen) approved for specific mutations; gene therapy (delandistrogene moxeparvovec) emerging.
* Timeline: Medications started early and continued long-term; response monitored every few months.

## 4. Cardiac and Respiratory Care

* Timeline: Cardiac monitoring begins early (around diagnosis) and continues regularly (annually or more often).
* Procedures:
  + Echocardiograms and ECGs to monitor heart function.
  + Medications like ACE inhibitors or beta-blockers started if cardiac involvement was detected.
  + Pulmonary function tests beginning around age 6 and repeated regularly.
  + Non-invasive ventilation (e.g., BiPAP) initiated as respiratory muscles weaken, often in adolescence.

## 5. Surgical Interventions

* Spinal Surgery:
  + Indicated for scoliosis, typically developing after loss of ambulation (around 10-15 years).
  + Recovery may take several months; surgery improves sitting balance and respiratory function.
* Other orthopedic surgeries: For contractures or fractures as needed.

## 6. Multidisciplinary Care and Supportive Therapies

* Occupational therapy, speech therapy, nutritional support, and psychosocial support are integrated throughout disease progression.
* Regular assessments to adjust interventions and assistive devices.

## **Outlook / Prognosis**

The prognosis is often poor for people with Duchenne muscular dystrophy (DMD). It leads to progressively worsening disability, and most children with DMD need to use a wheelchair by the age of 12. DMD ultimately results in death at an early age.

People with Duchene muscular dystrophy often die from the condition by the age of 25 years. However, advances in supportive care have resulted in many people living longer.

Death often occurs as a result of respiratory (breathing) or heart complications. Other causes of death include pneumonia, aspiration (breathing in a foreign object, such as food) or airway obstruction.

## **Prevention**

As Duchenne muscular dystrophy (DMD) is an inherited condition, there’s nothing you can do to prevent it. About a third of cases happen randomly without a family history of the condition.

If you’re concerned about the risk of passing on DMD or other genetic conditions before trying to have a biological child, talk to your healthcare provider about genetic counseling. In some situations, prenatal testing may be able to diagnose DMD in early pregnancy.

## **Living With**

If you’re taking care of someone with Duchenne muscular dystrophy (DMD), it’s important to advocate for them to ensure they get the best medical care and access to therapy that can help them have the best quality of life.

You and your family may also want to consider joining a support group to meet others who can relate to your experiences.

### **When should my child see their healthcare provider**

If your child has been diagnosed with Duchenne muscular dystrophy, they’ll need to see their team of healthcare providers regularly to receive treatment and monitor symptoms.

## **Differential Diagnoses**

1. Becker Muscular Dystrophy (BMD)
   1. Similar to DMD but with later onset and slower progression.
   2. Caused by mutations in the same dystrophin gene but usually producing partially functional dystrophin.
   3. Muscle biopsy and genetic testing help distinguish BMD from DMD.
2. Limb-Girdle Muscular Dystrophy (LGMD)
   1. A heterogeneous group of disorders affecting proximal muscles of hips and shoulders.
   2. LGMD 2A (calpainopathy) can clinically mimic DMD but usually has slower progression and different genetic cause (CAPN3 mutations).
   3. Muscle biopsy, immunohistochemistry, and genetic testing differentiate LGMD from DMD.
3. Emery-Dreifuss Muscular Dystrophy (EDMD)
   1. Characterized by early contractures, muscle weakness, and cardiac conduction defects.
   2. Genetic testing identifies mutations in emerin or lamin A/C genes.
4. Congenital Muscular Dystrophy (CMD)
   1. Presents at birth or early infancy with hypotonia and weakness.
   2. Genetic and muscle biopsy studies differentiate CMD from DMD.
5. Spinal Muscular Atrophy (SMA)
   1. A motor neuron disease causing progressive muscle weakness.
   2. Distinguished by genetic testing for SMN1 gene deletions and clinical features like absent reflexes and fasciculations.
6. Polymyositis and Dermatomyositis
   1. Inflammatory myopathies with muscle weakness and elevated muscle enzymes.
   2. Muscle biopsy shows inflammation; autoimmune markers may be positive.
7. Other Neurological Disorders
   1. Conditions such as motor neuron disease, multiple sclerosis, or metabolic myopathies may present with weakness but have distinct clinical and laboratory features.

## **Epidemiology**

### United States statistics

The incidence of MD varies, depending on the specific type of MD under consideration. Duchenne MD is the most common MD and is sex-linked, with an inheritance pattern of 1 case per 3500 live male births.One third of cases occur as a result of spontaneous new mutations. Becker MD is the second most common form, with an incidence of 1 case per 30,000 live male births.Other types of MD are rare. For example, limb-girdle dystrophy occurs in only 1.3% of patients with MDs.

### International statistics

The incidence internationally is similar to that of the US for most of the dystrophies, except for the oculopharyngeal type, which is more common in French Canadians than in other groups.Distal MD tends to occur in Sweden.

**RECOMMENDATIONS**

The developmental screenings take place at well-child visits at 9, 18, 30, and 48 months of age. The following motor skills are typically acquired at earlier ages, and their absence at these ages signifies delay:

* 9-month visit - Roll to both sides, sit well without support, and demonstrate motor symmetry without established handedness; ability to grasp and transfer objects hand to hand
* 18-month visit - Sitting, standing, and walking independently; ability to grasp and manipulate small objects; mild motor delays undetected at the 9-month screening visit may now be apparent
* 30-month visit - Most motor delays will have already been identified and more subtle gross motor, fine motor, speech, and oral motor impairments may emerge; progressive neuromuscular disorders may manifest as a loss of previously attained gross or fine motor skills
* 48-month visit - Elementary school skills, with emerging fine motor, handwriting, gross motor, communication, and feeding abilities that promote

## **Genomic Data**

## Gene Information

* Gene symbol: *DMD*
* Gene name: Dystrophin
* Chromosome: X chromosome (Xp21.2)
* Function: Codes for dystrophin, a protein critical for maintaining muscle fiber membrane stability.

## Mutation Spectrum

* The *DMD* gene is one of the largest human genes, with over 40,000 reported variants in public databases.
* Approximately 9,900 unique DNA variants have been documented, affecting over 60,000 individuals worldwide.
* Mutations include:
  + Large deletions (~60-70% of cases), often spanning one or more exons.
  + Duplications (~10% of cases).
  + Small mutations such as point mutations, small insertions/deletions, splice-site mutations (~20% of cases).
  + Nonsense mutations causing premature stop codons are common among small mutations.
* The majority of mutations cause frameshifts leading to absent or nonfunctional dystrophin protein, resulting in Duchenne muscular dystrophy (DMD).
* In-frame mutations that allow production of partially functional dystrophin cause Becker muscular dystrophy (BMD), a milder form.

## Genotype-Phenotype Correlations

* The reading-frame rule explains that out-of-frame mutations typically cause DMD, while in-frame mutations cause BMD.
* Exceptions exist, and ongoing research investigates genetic modifiers that influence disease severity and progression.
* Modifier genes related to inflammation, fibrosis, and muscle regeneration (e.g., *CD40*, *ACTN3*, *THBS1*) have been identified, affecting clinical variability.

**QUESTION AND ANSWERS SET**

## 1. What is Muscular Dystrophy?

Muscular dystrophy refers to a group of more than 30 genetic conditions that cause progressive muscle weakness and wasting due to mutations affecting muscle structure and function. Symptoms worsen over time and vary by type.

## 2. What causes Muscular Dystrophy?

MD is caused by genetic mutations that impair proteins essential for muscle cell stability and repair, such as dystrophin in Duchenne muscular dystrophy (DMD). These mutations can be inherited or arise spontaneously (*de novo*).

## 3. What are the common symptoms?

* Progressive muscle weakness, often starting in proximal muscles (hips, shoulders).
* Difficulty walking, climbing stairs, or rising from the floor.
* Muscle wasting and sometimes pseudohypertrophy (enlarged calves).
* In advanced stages, respiratory and cardiac muscles may be affected.

## 4. How is Muscular Dystrophy diagnosed?

* Clinical evaluation including physical and neurological exams.
* Blood tests showing elevated creatine kinase (CK) levels.
* Genetic testing to identify mutations.
* Muscle biopsy may be performed to examine muscle tissue.

## 5. What treatments are available?

* No cure currently exists; treatment focuses on symptom management and improving quality of life.
* Corticosteroids (e.g., prednisone, deflazacort) slow muscle degeneration.
* New medications like eteplirsen and golodirsen target specific genetic mutations in DMD.
* Physical therapy, orthopedic interventions, and respiratory support are important.
* Experimental therapies, including gene therapy, are under development.

## 6. What is the prognosis?

* Varies by type of MD.
* Duchenne muscular dystrophy often leads to loss of ambulation by early teens and reduced life expectancy (often into the 20s or 30s).
* Some types, like oculopharyngeal MD, have milder symptoms and normal life expectancy.

## 7. Is Muscular Dystrophy inherited?

* Most types are inherited in an X-linked, autosomal dominant, or autosomal recessive manner depending on the specific gene involved.
* Some cases arise from new mutations without family history.

## 8. Can newborns be screened for Muscular Dystrophy?

* Newborn screening for some neuromuscular disorders is becoming more common, but routine screening for MD is not universal.
* Early diagnosis can improve management and outcomes.

## 9. What complications can occur?

* Respiratory failure due to weakened breathing muscles.
* Cardiomyopathy and heart failure.
* Skeletal deformities like scoliosis.
* Swallowing difficulties and risk of aspiration pneumonia.

## 10. How often should patients be monitored?

* Regular multidisciplinary follow-up including neurology, cardiology, pulmonology, and physical therapy.
* Frequency depends on disease stage and complications.

## **Doctor-Patient Conversation on Duchenne Muscular Dystrophy (De-Identified)**

## Doctor:

Hello! I understand you’ve come to discuss your son’s muscle weakness and some difficulties he’s been having. Can you tell me more about what you’ve noticed?

## Parent:

Yes, doctor. He’s about 5 years old and lately he’s been having trouble running and climbing stairs. He sometimes uses his hands to push himself up from the floor. We’re worried because he seems weaker than other kids his age.

## Doctor:

Thank you for sharing. Based on your description and the examinations, your son likely has Duchenne Muscular Dystrophy, or DMD. It’s a genetic condition that causes progressive muscle weakness, especially in muscles near the trunk like hips and shoulders.

## Parent:

What causes this condition?

## Doctor:

DMD is caused by a mutation in the gene responsible for producing dystrophin, a protein essential for muscle strength and integrity. Without enough dystrophin, muscle fibers gradually break down and weaken over time.

## Parent:

Is there a cure?

## Doctor:

Currently, there is no cure for DMD. However, treatments can help slow the progression of muscle weakness and improve quality of life. These include corticosteroid medications, physical therapy, and supportive devices like braces.

## Parent:

What kind of treatments would my son need now?

## Doctor:

At this stage, corticosteroids such as prednisolone or deflazacort are commonly prescribed to help maintain muscle strength and delay loss of walking ability. Physical therapy is important to maintain joint flexibility and prevent contractures. We may also recommend ankle splints or braces to support his legs.

## Parent:

Will he be able to walk normally?

## Doctor:

Children with DMD usually start to lose the ability to walk between ages 10 and 12, but this varies. Our goal is to help him maintain mobility and independence as long as possible.

## Parent:

What other health issues should we watch for?

## Doctor:

DMD can also affect the heart and lungs over time. We will monitor his heart function regularly and may start medications like ACE inhibitors to protect the heart. Respiratory support may become necessary as the disease progresses.

## Parent:

Is this condition inherited? Could our other children have it?

## Doctor:

DMD is inherited in an X-linked pattern, meaning it mainly affects boys. Girls can be carriers and may have mild symptoms. Genetic counseling can help your family understand the risks and options for testing.

## Parent:

What kind of support is available for us?

## Doctor:

There are multidisciplinary teams including neurologists, physiotherapists, cardiologists, and respiratory specialists who will work with you. Support groups and counseling services can also provide emotional and practical help.

## Parent:

Thank you, doctor. What are the next steps?

## Doctor:

We’ll arrange for genetic testing to confirm the diagnosis, start corticosteroid treatment, and set up physical therapy. We’ll also schedule regular follow-ups to monitor his progress and adjust care as needed.

## Parent:

I appreciate your help and guidance.

## Doctor:

You’re welcome. We’re here to support your son and your family every step of the way. Please don’t hesitate to contact me with any questions or concerns.

REFERENCES

[Duchenne Muscular Dystrophy (DMD): Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/23538-duchenne-muscular-dystrophy-dmd)

<https://emedicine.medscape.com/article/1259041-guidelines?form=fpf>

<https://www.ncbi.nlm.nih.gov/books/NBK482346/#article-20747.s10>

**MYASTHENIA GRAVIS**

**DEFINITION AND DESCRIPTION**

Myasthenia gravis (my-us-THEE-nee-uh GRAY-vis) causes muscles under your voluntary control to feel weak and get tired quickly. This happens when the communication between nerves and muscles breaks down.

There's no cure for myasthenia gravis. Treatment can help with symptoms. These symptoms can include weakness of arm or leg muscles, double vision, drooping eyelids, and problems with speaking, chewing, swallowing and breathing.

This disease can affect people of any age, but it's more common in women younger than 40 and in men older than 60.

**Symptoms**

Muscle weakness caused by myasthenia gravis gets worse when the affected muscle is used. Because symptoms usually get better with rest, muscle weakness can come and go. However, the symptoms tend to progress over time. They usually reach their worst within a few years after the disease begins.

Myasthenia gravis may affect any of the muscles that you can control. Certain muscle groups are more commonly affected than others.

### **Eye muscles**

In more than half the people who develop myasthenia gravis, their first symptoms affect the eyes. Symptoms include:

* Drooping of one or both eyelids, called ptosis.
* Double vision, called diplopia, which may be horizontal or vertical, and improves or resolves when one eye is closed.

### **Face and throat muscles**

In about 15% of people with myasthenia gravis, the first symptoms involve face and throat muscles. These symptoms can:

* **Make speaking difficult.** Your speech might sound soft or nasal, depending on which muscles are affected.
* **Cause problems with swallowing.** You might choke easily, making it difficult to eat, drink or take pills. Sometimes, liquids you're trying to swallow come out your nose.
* **Affect chewing.** The muscles used for chewing might tire halfway through a meal. This is especially true if you've been eating something hard to chew, such as steak.
* **Change facial expressions.** For example, your smile might look like a snarl.

### **Neck and limb muscles**

Myasthenia gravis also can cause weakness in the neck, arms and legs. Weakness in the legs can affect how you walk. Weak neck muscles make it hard to hold up the head.

### **When to see a doctor**

Talk to your health care provider if you have problems:

* Breathing.
* Seeing.
* Swallowing.
* Chewing.
* Walking.
* Using your arms or hands.
* Holding up your head.

**Causes**

### **Antibodies**

Your nerves communicate with your muscles by releasing chemicals, called neurotransmitters, that fit into places on the muscle cells, called receptor sites, at the nerve-muscle junction.

In myasthenia gravis, the immune system makes antibodies that block or destroy many of your muscles' receptor sites for a neurotransmitter called acetylcholine (as-uh-teel-KOH-leen). With fewer receptor sites available, your muscles receive fewer nerve signals. This causes weakness.

Antibodies also can block a protein called muscle-specific receptor tyrosine kinase (TIE-roh-seen KIE-nays), sometimes referred to as MuSK. This protein helps form the nerve-muscle junction. Antibodies against this protein can lead to myasthenia gravis.

Antibodies against another protein, called lipoprotein-related protein 4 (LRP4), can play a part in this condition. Research studies have found other antibodies and the number of antibodies involved will likely grow over time.

Some people have myasthenia gravis that isn't caused by antibodies blocking acetylcholine, MuSK or LRP4. This type of myasthenia gravis is called seronegative myasthenia gravis, also known as antibody-negative myasthenia gravis. In general, researchers believe that this type of myasthenia gravis still comes from a problem with autoimmunity, but the antibodies involved just can't be found yet.

### **Thymus gland**

The thymus gland is a part of your immune system. This gland is located in the upper chest beneath the breastbone. Researchers believe that the thymus gland makes or helps produce the antibodies that block acetylcholine.

The thymus gland is large in babies and small in healthy adults. In some adults with myasthenia gravis, however, the thymus gland is larger than usual. Some people with myasthenia gravis also have tumors of the thymus gland, called thymomas. Usually, thymomas aren't cancerous, also known as malignant. But thymomas can become cancerous.

### **Other causes**

Rarely, mothers with myasthenia gravis have children who are born with myasthenia gravis. This is called neonatal myasthenia gravis. If treated immediately, children usually recover within two months after birth.

Some children are born with a rare, hereditary form of myasthenia gravis, called congenital myasthenic syndrome.

Factors that can make myasthenia gravis worse include:

* Fatigue.
* Illness or infection.
* Surgery.
* Stress.
* Some medicines — such as beta blockers, quinidine gluconate, quinidine sulfate, quinine (Qualaquin), phenytoin (Dilantin), certain anesthetics and some antibiotics.
* Pregnancy.
* Menstrual periods.

**Complications**

Complications of myasthenia gravis are treatable, but some can be life-threatening.

### **Myasthenic crisis**

Myasthenic crisis is a life-threatening condition. It happens when the muscles that control breathing become too weak to work. Emergency treatment and mechanical assistance with breathing are needed. Medicines and therapies that filter the blood help people to breathe on their own.

### **Thymus gland tumors**

Some people with myasthenia gravis have a tumor in the thymus gland. The thymus is a gland under the breastbone that is part of the immune system. Most of these tumors, called thymomas, aren't cancerous.

### **Other disorders**

People with myasthenia gravis are more likely to have the following conditions:

* **Underactive or overactive thyroid.** The thyroid gland in the neck secretes hormones that regulate the metabolism. If the thyroid is underactive, you might have problems dealing with cold, weight gain and other issues. An overactive thyroid can cause problems dealing with heat, weight loss and other issues.
* **Autoimmune conditions.** People with myasthenia gravis might be more likely to have autoimmune conditions, such as rheumatoid arthritis or lupus.

## **Diagnosis**

Your health care provider will look at your symptoms and medical history and conduct a physical examination. Your provider might use several tests, including:

### **Neurological examination**

Your provider may check your neurological health by testing:

* Reflexes.
* Muscle strength.
* Muscle tone.
* Senses of touch and sight.
* Coordination.
* Balance.

Tests to help confirm a diagnosis of myasthenia gravis might include:

### **Ice pack test**

If you have a droopy eyelid, your provider might put a bag filled with ice on your eyelid. After two minutes, your provider removes the bag and analyzes your droopy eyelid for improvement.

### **Blood analysis**

A blood test might show nontypical antibodies that interrupt the receptor sites where nerves signal your muscles to move.

### **Repetitive nerve stimulation**

In this nerve conduction study, providers attach electrodes to your skin over the muscles to be tested. Small pulses of electricity run through the electrodes. These pulses measure whether the nerve can send a signal to the muscle.

During this test, the nerve is tested several times to see if its ability to send signals gets worse with fatigue. Results from this test help inform a diagnosis of myasthenia gravis.

### **Single-fiber electromyography (EMG)**

This test measures the electrical activity traveling between your brain and your muscle. It involves inserting a fine wire electrode through your skin and into a muscle to test a single muscle fiber.

### **Imaging**

Your provider might order a CT scan or an MRI to check if there's a tumor or other problem with your thymus.

### **Pulmonary function tests**

These tests measure whether your condition is affecting your breathing.

**Treatment**

Various treatments, alone or together, can help with symptoms of myasthenia gravis. Your treatment will depend on your age, how severe your disease is and how fast it's progressing.

### **Medications**

* **Cholinesterase inhibitors.** Medicines such as pyridostigmine (Mestinon, Regonal) improve communication between nerves and muscles. These medicines aren't a cure, but they can improve muscle contraction and muscle strength in some people.

Possible side effects include gastrointestinal upset, diarrhea, nausea, and too much salivation and sweating.

* **Corticosteroids.** Corticosteroids such as prednisone (Rayos) block the immune system, making it less able to produce antibodies. Use of corticosteroids over a long period of time, however, can lead to serious side effects. These include bone thinning, weight gain, diabetes and higher risk of some infections.
* **Immunosuppressants.** Your provider also might prescribe other medicines that change your immune system. These medicines could include azathioprine (Azasan, Imuran), mycophenolate mofetil (Cellcept), cyclosporine (Sandimmune, Gengraf, others), methotrexate (Trexall) or tacrolimus (Astagraf XL, Prograf, others). These medicines, which can take months to work, might be used with corticosteroids.

Side effects of immunosuppressants, such as higher risk of infection and liver or kidney damage, can be serious.

### **Intravenous therapy**

The following therapies are usually used for a short time to treat symptoms that suddenly get worse or before surgery or other therapies.

* **Plasmapheresis (plaz-muh-fuh-REE-sis).** This procedure uses a filtering process that's like dialysis. Your blood is put through a machine that removes the antibodies that block transmission of signals from your nerve endings to your muscles. However, the good effects from this procedure usually last only a few weeks. Having several procedures can lead to problems finding veins for the treatment.

Risks of plasmapheresis include a drop in blood pressure, bleeding, heart rhythm problems or muscle cramps. Some people have an allergic reaction to the solutions used to replace the plasma.

* **Intravenous immunoglobulin (IVIg).** This therapy provides your body with typical antibodies, which alters your immune system response. Benefits are usually seen in less than a week and can last 3 to 6 weeks.

Side effects, which usually are mild, can include chills, dizziness, headaches and fluid retention.

* **Monoclonal antibody.** Rituximab (Rituxan) and eculizumab (Soliris) are medicines given by vein for myasthenia gravis. These medicines are usually used when other treatments don't work. They can have serious side effects.

### **Surgery**

Some people with myasthenia gravis have a tumor in the thymus gland. If you have a tumor, called a thymoma, you'll need surgery to remove the thymus gland, called thymectomy.

Even if you don't have a tumor in the thymus gland, removing the gland might improve your symptoms. However, the benefits of this surgery can take years to develop.

The thymectomy can be performed as an open surgery or as a minimally invasive surgery. In open surgery, the surgeon splits the central breastbone, called the sternum,) to open the chest and remove the thymus gland.

Minimally invasive surgery to remove the thymus gland uses smaller cuts, called incisions. It might also involve:

* **Video-assisted thymectomy.** In one form of this surgery, surgeons make a small opening in the neck or a few small openings in the side of the chest. They then use a long, thin camera, called a video endoscope, and small instruments to see and remove the thymus gland.
* **Robot-assisted thymectomy.** In this form of thymectomy, surgeons make several small openings in the side of the chest. They use a robotic system to remove the thymus gland. This system includes a camera arm and mechanical arms.

These procedures might cause less blood loss, less pain, lower mortality rates and shorter hospital stays compared with open surgery.

## **Treatment Drugs and Their Side Effects**

## 1. Cholinesterase Inhibitors

* Example: Pyridostigmine (Mestinon, Regonal)
* Use: Improve communication between nerves and muscles by preventing breakdown of acetylcholine, enhancing muscle contraction and strength.
* Side Effects:
  + Gastrointestinal upset (stomach cramps, diarrhea, nausea)
  + Excess salivation and sweating
  + Muscle twitching
* Notes: Often the first medication prescribed; effects last a few hours, requiring multiple daily doses.

## 2. Corticosteroids

* Example: Prednisone (Rayos, Prednisolone)
* Use: Suppress the immune system to reduce production of antibodies attacking the neuromuscular junction.
* Side Effects:
  + Weight gain
  + Mood swings
  + Bone thinning (osteoporosis)
  + Increased risk of infections
  + Diabetes risk with long-term use
* Notes: Usually started at high doses and tapered; often given every other day to minimize side effects.

## 3. Immunosuppressants

* Examples: Azathioprine (Imuran), Mycophenolate mofetil (Cellcept), Cyclosporine, Methotrexate, Tacrolimus
* Use: Modulate or suppress immune response to decrease antibody production.
* Side Effects:
  + Increased infection risk
  + Liver or kidney toxicity
  + Nausea, loss of appetite, fatigue
* Notes: May take months to show benefits; require regular blood tests for monitoring.

## 4. Monoclonal Antibodies and Complement Inhibitors

* Examples:
  + Eculizumab (Soliris)
  + Ravulizumab (Ultomiris)
  + Efgartigimod (Vyvgart)
  + Rozanolixizumab (Rystiggo)
  + Zilucoplan (Zilbrysq)
* Use: Target specific immune pathways to reduce autoantibody-mediated damage.
* Side Effects:
  + Infusion or injection site reactions
  + Headache, nausea
  + Increased risk of meningococcal infections (vaccination required before treatment)
* Notes: Newer FDA-approved therapies for generalized or refractory myasthenia gravis.

## 5. Intravenous Therapies

* Plasmapheresis: Removes circulating antibodies from the blood temporarily.
* Intravenous Immunoglobulin (IVIG): Provides normal antibodies to modulate immune response.
* Side Effects:
  + Headache, chills, fever
  + Risk of allergic reactions
* Notes: Used for rapid symptom control, myasthenic crisis, or pre-surgery.

## 6. Surgical Treatment

* Thymectomy: Surgical removal of the thymus gland, which may reduce symptoms in some patients, especially if a thymoma (tumor) is present.

## **Procedures and Timelines**

## 1. Initial Medical Therapy

* Pyridostigmine (Cholinesterase Inhibitor):
  + Onset: 15–30 minutes after oral dose.
  + Dosage adjusted over days to weeks based on symptom control.
  + Used continuously to improve muscle strength.
* Corticosteroids (e.g., Prednisone):
  + Starting dose: 60–100 mg/day for 2–4 weeks or slow titration.
  + Onset: 2–4 weeks to see improvement.
  + Maintenance with slow tapering; monitoring for side effects ongoing.

## 2. Immunosuppressive Therapies

* Azathioprine, Mycophenolate Mofetil, Cyclosporine, Methotrexate:
  + Onset: 1–12 months for clinical benefit.
  + Dosing titrated gradually; requires regular blood monitoring.
  + Used as steroid-sparing agents or for refractory cases.

## 3. Rapid Immunomodulatory Procedures

* Plasmapheresis (Plasma Exchange):
  + Typically 5 sessions every other day.
  + Onset: Improvement within 1–2 weeks.
  + Used for myasthenic crisis or preoperative stabilization.
  + Effects last weeks to months; repeated treatments may be necessary.
* Intravenous Immunoglobulin (IVIG):
  + Dose: 2 g/kg divided over 2–5 days.
  + Onset: Improvement often within days, lasting 3–6 weeks.
  + Used for crisis or maintenance therapy.

## 4. Monoclonal Antibody Therapies

* Rituximab:
  + Dose: Weekly infusions for 4 weeks; repeat cycles as needed.
  + Onset: 1–3 months for effect.
  + Used in refractory MG.
* Eculizumab and Ravulizumab:
  + Dosing involves weekly induction then maintenance every 2 weeks (eculizumab) or every 8 weeks (ravulizumab).
  + Onset: 2–4 weeks.
  + Requires meningococcal vaccination prior to treatment.

## 5. Surgical Treatment

* Thymectomy:
  + Indicated especially if thymoma present or in generalized MG.
  + Clinical improvement may take 6–12 months post-surgery.
  + Can reduce medication requirements and improve symptoms long term.

**Lifestyle and home remedies**

To help you make the most of your energy and cope with the symptoms of myasthenia gravis:

* **Adjust your eating routine.** Try to eat when you have good muscle strength. Take your time chewing your food, and take a break between bites of food. You might find it easier to eat small meals several times a day. Also, try eating mainly soft foods and avoid foods that require more chewing, such as raw fruits or vegetables.
* **Use safety precautions at home.** Install grab bars or railings in places where you need support, such as next to the bathtub or next to steps. Keep your floors clean, and move area rugs. Outside your home, keep paths, sidewalks and driveways cleared of leaves, snow and other debris that could cause you to trip.
* **Use electric appliances and power tools.** To save your energy, try using an electric toothbrush, electric can openers and other electrical tools to perform tasks.
* **Wear an eye patch.** If you have double vision, an eye patch can help. Try wearing one to write, read or watch television. Switch the eye patch to the other eye regularly to help reduce eyestrain.
* **Plan.** If you have chores, shopping or errands to do, plan the activity for when you have the most energy.

## **Diagnostic Considerations**

Myasthenia gravis (MG) can mimic other diagnoses in elderly persons and vice versa. Examples of such pathology include diagnoses such as congestive heart failure, pulmonary embolism, and acute myocardial infarction.

## **Differential Diagnoses**

* Amyotrophic Lateral Sclerosis in Physical Medicine and Rehabilitation
* Basilar Artery Thrombosis
* Botulism
* Brainstem Gliomas
* Cavernous Sinus Syndromes
* Chronic Myelogenous Leukemia (CML)
* Ciguatera Toxicity
* Congenital Myasthenic Syndrome
* Dermatomyositis
* Diphtheria
* Graves Disease
* Guillain-Barre Syndrome
* Kearns-Sayre Syndrome
* Lambert-Eaton Myasthenic Syndrome (LEMS)
* Miller-Fisher Syndrome
* Multiple Sclerosis
* Myocardial Infarction
* Neurosarcoidosis
* Organophosphate Toxicity
* Polymyositis
* Pulmonary Embolism (PE)
* Tetrodotoxin Toxicity
* Thyroid Ophthalmopathy
* Tick-Borne Diseases
* Tolosa-Hunt Syndrome

## **Prognosis**

Given current treatment, which combines cholinesterase inhibitors, immunosuppressive drugs, plasmapheresis, immunotherapy, and supportive care in an intensive care unit (ICU) setting (when appropriate), most patients with myasthenia gravis (MG) have a near-normal life span. Mortality is now 3–4%, with principal risk factors being age older than 40 years, short history of progressive disease, and thymoma; previously, it was as high as 30–40%. In most cases, the term gravis is now a misnomer.

Morbidity results from intermittent impairment of muscle strength, which may cause aspiration, increased incidence of pneumonia, falls, and even respiratory failure if not treated.In addition, the medications used to control the disease may produce adverse effects.

Today, the only feared condition arises when the weakness involves the respiratory muscles. Weakness might become so severe as to require ventilatory assistance. Those patients are said to be in a myasthenic crisis.

The disease frequently presents (40%) with only ocular symptoms. However, the extraocular is almost always involved within the first year. Of patients who show only ocular involvement at the onset of MG, only 16% still have exclusively ocular disease at the end of 2 years.

In patients with generalized weakness, the nadir of maximal weakness usually is reached within the first 3 years of the disease.

## **Epidemiology**

In the United States in 2021, the overall incidence of myasthenia gravis (MG) was 3.2 per 100,000 with similar estimates for males and females (3.2 vs. 3.1 per 100,000, respectively).Total prevalence was estimated to be 37.0 per 100,000 with sex-specific estimates being comparable at 37.3 and 36.7 per 100,000 for males and females, respectively. These figures suggest that cases of MG are increasing, likely due to increased awareness and diagnosis of the disease.

Approximately 15%–20% of patients with MG experience crisis in their lifetime, typically within the first 2 years of the diagnosis.

Fifty years ago, estimates of mortality in the MG crisis ranged from 50% to 80%.Currently, the overall in-hospital mortality rate is 2.2%, being higher in the MG crisis (4.47%).

### Age-related demographics

MG can occur at any age. Female incidence peaks in the third decade of life, whereas male incidence peaks in the sixth or seventh decade. The mean age of onset is 28 years in females and 42 years in males.

Transient neonatal MG occurs in infants of myasthenic mothers who acquire anti-AChR antibodies via placental transfer of IgG. Some of these infants may suffer from transient neonatal myasthenia due to effects of these antibodies.

Most infants born to myasthenic mothers possess anti-AChR antibodies at birth, yet only 10-20% develop neonatal MG.

## **Genomic Data**

* Human Leukocyte Antigen (HLA) Region:
  + Strongly associated with MG susceptibility.
  + Specific alleles such as HLA-DQA1, HLA-DRB1, and HLA-B show significant links to MG risk.
  + Different HLA alleles are implicated in early-onset MG (EOMG) versus late-onset MG (LOMG), indicating genetic heterogeneity.
* Non-HLA Genes:
  + PTPN22: A gene involved in immune regulation, associated with increased MG risk.
  + TNIP1: Linked to thymoma-associated MG and early-onset MG.
  + CTLA4: Variants near this gene reduce its expression, affecting immune checkpoint regulation.
  + CHRNA1 and CHRNB1: Genes encoding subunits of the acetylcholine receptor; certain variants reduce their expression, contributing to disease.
  + TNFRSF11A, SFMBT2, FAM76B, ZBTB10: Other loci identified by genome-wide association studies (GWAS) linked to MG susceptibility.
* Epigenetic Modifications:
  + DNA methylation changes in genes such as CAMK1D and CREB5 influence gene expression relevant to neuromuscular junction function.
  + Aberrant epigenetic regulation may disrupt synaptic homeostasis, contributing to MG pathogenesis.

## **QUESTIONS AND ANSWERS SET**

## What is likely causing my symptoms?

Myasthenia gravis is caused by an autoimmune process where your immune system produces antibodies that block or disrupt the communication between nerves and muscles. This leads to muscle weakness, often starting with eyelid drooping or difficulty with eye movements, and can progress to affect other voluntary muscles. The thymus gland may be abnormal or enlarged in some cases, contributing to the disease

## What tests do I need?

Diagnosis involves several tests:

* Blood tests to detect antibodies against acetylcholine receptors (AChR), anti-MuSK, or other related antibodies. About 85% of MG patients have detectable AChR antibodies
* Electromyography (EMG): Repetitive nerve stimulation and single-fiber EMG assess nerve-to-muscle signal transmission and are sensitive diagnostic tools
* Ice pack test: Applying ice to a droopy eyelid may temporarily improve muscle strength, supporting diagnosis
* Imaging (CT or MRI): To check for thymus abnormalities or thymoma
* Occasionally, a medication trial with pyridostigmine or corticosteroids may be used if tests are inconclusive

## What course of action do you recommend?

Treatment typically begins with cholinesterase inhibitors (e.g., pyridostigmine) to improve muscle strength. If symptoms are moderate to severe, immunosuppressive therapies such as corticosteroids or other immunosuppressants may be started. In some cases, thymectomy (surgical removal of the thymus) is recommended. For acute worsening or myasthenic crisis, therapies like plasmapheresis or intravenous immunoglobulin (IVIG) are used

## What are the alternatives to the approach you're suggesting?

Alternatives depend on disease severity and patient factors:

* If immunosuppressants are contraindicated, symptomatic treatment with cholinesterase inhibitors alone may be used.
* Newer biologic therapies targeting specific immune pathways (e.g., monoclonal antibodies) may be options for refractory cases.
* Some patients may opt for watchful waiting if symptoms are mild and stable.
* Physical therapy and lifestyle modifications can complement medical treatment

## I have other health conditions. How can I best manage them together?

Managing MG alongside other conditions requires coordination:

* Inform your providers about all medications to avoid drug interactions that may worsen MG.
* Monitor for infections closely, as immunosuppressive treatments increase risk.
* Adjust treatments for comorbidities considering MG symptoms and therapies.
* Regular follow-up with neurology and your other specialists is important for integrated care

## Are there restrictions I need to follow?

* Avoid medications known to exacerbate MG symptoms (e.g., certain antibiotics, beta-blockers, magnesium).
* Manage stress and avoid excessive heat or fatigue, which can worsen muscle weakness.
* Follow vaccination recommendations, especially if on immunosuppressants.
* Discuss exercise plans with your provider to maintain strength without overexertion

## **Doctor-Patient Conversation on Myasthenia Gravis (De-Identified)**

## Doctor:

Hello! I understand you’ve been experiencing muscle weakness and some vision problems. Can you tell me more about your symptoms?

## Patient:

Yes, doctor. I’ve noticed my eyelids drooping, especially by the end of the day, and sometimes I have double vision. Lately, I’ve also felt my arms and legs get weak after using them for a while.

## Doctor:

Thank you for sharing. These symptoms are characteristic of myasthenia gravis, which is a chronic autoimmune neuromuscular disease that causes weakness in the voluntary muscles.

## Patient:

What causes this condition?

## Doctor:

In MG, your immune system produces antibodies that interfere with communication between nerves and muscles, leading to muscle weakness. Most patients have detectable antibodies, but some, called seronegative, do not, which can make diagnosis more challenging.

## Patient:

How do you diagnose MG?

## Doctor:

We use a combination of clinical examination, blood tests for antibodies, and specialized tests like single fiber electromyography (SFEMG) to assess nerve-muscle transmission. Imaging may also be done to check the thymus gland.

## Patient:

What treatments are available?

## Doctor:

Treatment often includes medications that improve nerve-muscle communication, such as acetylcholinesterase inhibitors. Immunosuppressive drugs can reduce antibody production. In some cases, therapies like plasma exchange or intravenous immunoglobulin (IVIG) are used. Thymectomy surgery may be considered if a thymoma is present.

## Patient:

Are there side effects to these treatments?

## Doctor:

Yes, many treatments can suppress your immune system, increasing infection risk. Other side effects depend on the specific medication. We carefully balance benefits and risks and monitor you closely.

## Patient:

Can I still live a normal life?

## Doctor:

Many people with MG lead active lives with proper treatment and lifestyle adjustments. Symptoms can fluctuate, so it’s important to avoid triggers like stress, infections, and overheating.

## Patient:

What should I do if symptoms worsen suddenly?

## Doctor:

If you experience sudden worsening of weakness, especially difficulty breathing or swallowing, seek emergency care immediately, as this can be a myasthenic crisis requiring urgent treatment.

## Patient:

How often will I need to see you?

## Doctor:

Regular follow-ups help us monitor your condition and adjust treatment. We’ll also discuss any new symptoms or concerns you have.

## Patient:

Thank you, doctor. I feel more hopeful knowing there are treatments.

## Doctor:

You’re welcome. We’ll work together to manage your MG and maintain your quality of life. Please reach out anytime you need support.

REFERENCES

[Myasthenia gravis - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/myasthenia-gravis/diagnosis-treatment/drc-20352040)

<https://www.nhs.uk/conditions/myasthenia-gravis/treatment/>

<https://emedicine.medscape.com/article/1171206-medication?form=fpf>

<https://myasthenia.org/blog/2025/02/27/my-mg-story-danielles-journey-with-seronegative-myasthenia-gravis/>

### **Myositis**

**Definition**

Myositis is a disease that makes your immune system attack your muscles. It causes chronic inflammation — swelling that comes and goes over a long time. Eventually, this inflammation makes your muscles feel increasingly weak. It can also cause muscle pain.

Myositis is a type of myopathy. Myopathy is a general term that refers to diseases that affect the muscles that connect to your bones (skeletal muscles). Different forms of myositis affect different groups of muscles throughout your body. Myositis usually affects the muscles you use to move, including muscles in your:

* Arms and shoulders.
* Legs and hips.
* Abdomen and spine (your trunk).

Other people with myositis experience muscle weakness on or near their:

* Eyes.
* Esophagus.
* Diaphragm.

Experts aren’t certain what causes myositis, and there’s no cure for it. Your healthcare provider will treat the symptoms you’re experiencing. They’ll also recommend exercises like stretching and physical movements that can help strengthen your affected muscles between episodes of myositis symptoms.

Visit a healthcare provider if you feel weak, have trouble moving or notice new pain or rashes on your skin. Go to the emergency room if you have trouble breathing or swallowing.

#### **Types of myositis**

A healthcare provider will diagnose a type of myositis based on your symptoms and the location of your affected muscles. There are a few different forms of myositis, including:

* Polymyositis.
* Dermatomyositis.
* Inclusion of body myositis.

##### **Polymyositis**

Polymyositis affects multiple muscles at the same time. It usually causes symptoms in muscles on or near the center of your body.

Polymyositis develops gradually over time. It typically affects adults. Females are twice as likely to develop polymyositis than males.

If you have polymyositis, you might have trouble performing movements you usually can, including:

* Standing up after sitting.
* Climbing stairs.
* Lifting objects.
* Reaching over your head.

##### **Dermatomyositis**

Dermatomyositis is a form of myositis that affects your skin in addition to your muscles.

Some cases take months to develop, but dermatomyositis can develop quickly. The sooner you begin treatment, the more likely it is you can avoid having severe complications.

In rare cases, dermatomyositis can be fatal, especially in the first year after symptoms start. It can also increase your risk of developing certain kinds of cancer.

Anyone can experience dermatomyositis. If it affects children, it’s known as juvenile dermatomyositis.

##### **Inclusion body myositis**

Inclusion body myositis is a degenerative muscle disease. It usually affects people older than 50.

Inclusion body myositis causes muscle weakness in your extremities (your hands and your legs below your knees). It can also affect the muscles in your throat that help you swallow. Around 30% of people with inclusion body myositis develop dysphagia (difficulty swallowing).

If you have inclusion body myositis, it might be hard to:

* Use your hands and fingers to do precise tasks like buttoning a shirt.
* Grip something small.
* Walk or stand.
* Swallow.

### **Symptoms of myositis**

Myositis symptoms include:

* Muscle weakness.
* Joint or muscle pain.
* Fatigue.
* Swelling.
* Trouble breathing or swallowing.
* Arrhythmia (if the myositis affects your heart).

During an episode of symptoms, you might have trouble moving or doing certain activities you usually can. You might get tired faster, or feel like you can’t control your arms, hands or legs.

Different types of myositis have different symptoms. Your provider will tell you what to expect and which symptoms you’ll experience.

### **What causes myositis?**

Experts don’t know for sure what causes myositis. It can occur on its own, but it’s sometimes triggered by other health conditions.

Myositis is an autoimmune disease. Autoimmune diseases are the result of your immune system accidentally attacking your body instead of protecting it. It’s unclear why your immune system does this. Some people with other autoimmune diseases are more likely to develop myositis, including:

* Lupus.
* Rheumatoid arthritis.
* Scleroderma.

Some people develop myositis after they have a viral infection, including:

* The common cold.
* Influenza (the flu).
* HIV.

## **Diagnosis and Tests**

A healthcare provider will diagnose myositis with a physical exam and tests. They’ll examine your symptoms and ask you how it feels when you do certain movements or motions. You might need a few tests, including:

* Blood tests.
* MRI (magnetic resonance imaging).
* EMG (electromyography).
* A muscle biopsy.

**Management and Treatment**

There’s no cure for myositis. Your provider will treat your symptoms to reduce their impact on your daily routine. Their goal will be to treat your symptoms until the myositis goes into remission (when there’s little or no inflammation in your muscles). Typical treatments for myositis include:

* Corticosteroids.
* Immunosuppressants.
* Intravenous immunoglobulin.

Your provider or physical therapist will give you stretches and exercises to keep your affected muscles flexible and strong. This can help reduce pain and stiffness and how much you’re affected by future episodes.

## **Treatment Drugs and Their Side Effects**

## 1. Corticosteroids (e.g., Prednisone)

* Use: First-line treatment to rapidly reduce muscle inflammation.
* Mechanism: Suppresses immune system activity to decrease muscle damage.
* Side Effects:
  + Weight gain
  + Mood changes
  + Bone thinning (osteoporosis)
  + Increased infection risk
  + High blood pressure
  + Diabetes risk with long-term use
* Notes: Often started at high doses and tapered gradually to minimize side effects.

## 2. Methotrexate

* Use: Steroid-sparing immunosuppressant, often combined with corticosteroids.
* Mechanism: Inhibits immune cell proliferation.
* Side Effects:
  + Liver toxicity (elevated liver enzymes, cirrhosis)
  + Bone marrow suppression (low blood counts)
  + Pulmonary toxicity (rare but serious)
  + Nausea, fatigue
* Notes: Requires regular blood tests and folic acid supplementation; contraindicated in pregnancy.

## 3. Azathioprine

* Use: Immunosuppressant to reduce steroid dose and maintain remission.
* Side Effects:
  + Bone marrow suppression
  + Liver toxicity
  + Increased infection risk
  + Nausea
* Notes: Dose titrated gradually; regular monitoring needed.

## 4. Mycophenolate Mofetil

* Use: Alternative immunosuppressant, especially in patients intolerant to methotrexate or azathioprine.
* Side Effects:
  + Gastrointestinal upset (diarrhea, nausea)
  + Increased infection risk
  + Blood count abnormalities
* Notes: Regular monitoring required.

## 5. Intravenous Immunoglobulin (IVIG)

* Use: For patients with refractory disease or dermatomyositis; FDA-approved for dermatomyositis.
* Side Effects:
  + Headache
  + Fever, chills
  + Allergic reactions
  + Rarely, kidney dysfunction or thromboembolism
* Notes: Given as monthly infusions over several days; effects may take weeks to months.

## 6. Rituximab

* Use: Monoclonal antibody targeting B cells, used in refractory cases.
* Side Effects:
  + Infusion reactions (fever, chills)
  + Increased risk of infections
  + Rarely, progressive multifocal leukoencephalopathy (PML)
* Notes: Administered as two doses two weeks apart; monitoring essential.

## 7. Other Immunosuppressants

* Tacrolimus, Cyclosporine, Cyclophosphamide:
  + Used in specific cases, especially with lung involvement (interstitial lung disease).
  + Side effects include kidney toxicity, hypertension, increased infection risk, and nausea.
  + Require close monitoring.

## **Procedures and Timelines**

## Diagnostic Procedures and Typical Timeline

1. Initial Evaluation and Blood Tests (Weeks 0–1)
   1. Medical history and physical exam: Assess muscle weakness, rash, and systemic symptoms.
   2. Blood tests: Measure muscle enzymes (creatine kinase, aldolase), inflammatory markers, and myositis-specific autoantibodies.
   3. Elevated muscle enzymes provide early clues but can be normal in some subtypes.
2. Electromyography (EMG) and Nerve Conduction Studies (Weeks 1–2)
   1. Detect abnormal electrical activity in muscles indicating inflammation or damage.
   2. Helps distinguish myositis from nerve disorders.
3. Imaging: MRI of Muscles (Weeks 1–3)
   1. Identifies areas of muscle inflammation and edema.
   2. Guides selection of biopsy site.
   3. Helps differentiate myositis subtypes based on inflammation patterns.
4. Muscle and/or Skin Biopsy (Weeks 2–4)
   1. Gold standard for diagnosis.
   2. Muscle biopsy shows inflammation, muscle fiber damage, and specific features depending on subtype (e.g., inclusion bodies in IBM).
   3. Skin biopsy may be done if dermatomyositis skin rash is present.
   4. Biopsy results can take 1–2 weeks after sampling.
5. Additional Testing (Weeks 3–6)
   1. Chest X-ray or High-Resolution CT: To screen for interstitial lung disease (ILD), common in some myositis types.
   2. Pulmonary function tests: Assess lung involvement.
   3. Cancer screening: Recommended especially in dermatomyositis due to associated malignancy risk.
   4. Swallowing evaluation: If dysphagia is reported, tests like videofluoroscopy or FEES may be performed.

## **Outlook / Prognosis**

There’s no cure for myositis, but in most cases, treatment can put it into remission. Most people with myositis have it for the rest of their lives.

People with myositis have an increased risk of developing rhabdomyolysis.

Some cases of myositis can be fatal. Around 5% of people with dermatomyositis die within a year of their diagnosis. This is why it’s important to get your symptoms examined by a healthcare provider as soon as you notice them.

## **Prevention**

There’s nothing you can do to prevent myositis. Because experts aren’t sure what causes it, there’s no way to know who’ll develop it or when you’ll first experience symptoms.

**When should I see my healthcare provider?**

Visit a provider right away if you experience new muscle weakness, pain or other symptoms — especially if they don’t get better in a few days. Talk to your provider if your symptoms are getting worse or spreading.

Go to the emergency room if you experience any of the following symptoms:

* You can’t move a part of your body you usually can.
* You’re having trouble breathing.
* You’re having trouble swallowing.

## **Differential Diagnosis**

1. Muscular Dystrophies
   1. Genetic disorders causing progressive muscle weakness.
   2. May show inflammation on biopsy, complicating differentiation from inflammatory myopathies.
   3. Family history and genetic testing aid diagnosis.
2. Inclusion Body Myositis (IBM)
   1. Often misdiagnosed as PM but typically affects older adults (>45 years).
   2. Characterized by asymmetric weakness, especially finger flexors and quadriceps.
   3. Poor response to immunosuppressive therapy.
   4. Muscle biopsy shows rimmed vacuoles and protein aggregates.
3. Myasthenia Gravis
   1. Autoimmune disorder causing fluctuating muscle weakness due to impaired neuromuscular transmission.
   2. Distinguished by fatigability, antibody testing, and electrophysiology.
4. Metabolic and Toxic Myopathies
   1. Examples: Hypokalemia, hypothyroidism, statin-induced myopathy, alcohol-related myopathy.
   2. Often reversible with correction of underlying cause or drug cessation.
5. Infectious Myositis
   1. Bacterial, viral, or parasitic infections causing muscle inflammation.
   2. Usually acute/subacute onset with systemic signs of infection.
6. Other Autoimmune and Systemic Diseases
   1. Sarcoidosis, eosinophilic myositis, systemic lupus erythematosus (SLE), vasculitis.
   2. May present with muscle inflammation but have distinct systemic features.
7. Neuropathic Disorders and Motor Neuron Disease
   1. Disorders affecting nerves rather than muscle directly; EMG and clinical features help differentiate.
8. Other Myopathies
   1. Dysferlinopathy, Pompe disease, mitochondrial myopathies, McArdle disease.
   2. Diagnosed with genetic testing, enzyme assays, and muscle biopsy.

## **Epidemiology**

## Incidence and Prevalence

The incidence of idiopathic inflammatory myopathies (IIM), which include polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM), ranges from about 0.2 to 10 new cases per 100,000 people per year, depending on age group and geographic region.

A peak incidence occurs in people aged 45 to 64 years, with about 8 to 10 new cases per 100,000 per year in this group. Younger (25–44 years) and older (65+) populations have lower incidence rates of about 3 to 5 per 100,000 per year

Prevalence estimates vary widely, from approximately 2 to 25 cases per 100,000 population, with some U.S. data suggesting 14 to 21 cases per 100,000

In Africa, prevalence estimates are similar, around 11.5 per 100,000 for IIM and PM subtypes

## Age and Sex Distribution

Most patients are diagnosed in middle age, with a mean age around 50 years. Juvenile dermatomyositis (JDM) occurs in children with a mean age of about 13 years

Women are affected two to three times more often than men in polymyositis and dermatomyositis, whereas inclusion body myositis affects men about 1.5 to 2 times more than women

People of Sub-Saharan African descent have a higher risk, approximately three times greater than those without such ancestry

No specific geographic area shows markedly higher prevalence, indicating a relatively uniform global distribution with some ethnic variation.

Patients with IIM frequently require specialist care, with most visiting internal medicine or neurology departments

Hospitalization and emergency room visits are common, reflecting disease severity and complications.

## **Genomic Data**

Human Leukocyte Antigen (HLA) Region:

* + The strongest genetic risk locus for IIM lies within the major histocompatibility complex (MHC), particularly specific HLA alleles.
  + Different HLA variants associate with distinct clinical subgroups and autoantibody profiles, suggesting genetically defined disease subsets.
  + For example, the 8.1 ancestral haplotype (AH) is a well-known risk factor in Caucasian populations, especially linked to juvenile-onset myositis.
* Non-HLA Genes:
  + Genome-wide association studies (GWAS) have identified multiple non-HLA loci associated with IIM, including:
    - PTPN22, STAT4, TYK2, NAB1, FAM167A-BLK, DGKQ, YDJC—genes involved in immune regulation and signaling.
    - WDFY4, linked to clinically amyopathic dermatomyositis, affects NF-κB signaling pathways.
  + Some of these genes overlap with other autoimmune diseases, indicating shared pathogenic pathways.
* Somatic Mutations and Cancer-Associated Myositis:
  + Somatic mutations and loss of heterozygosity in genes like TRIM33 (encoding TIF1γ) have been reported in tumors from patients with cancer-associated myositis, suggesting a link between genetic alterations in tumors and autoimmune activation.
* Mitochondrial DNA Variation:
  + Rare mitochondrial DNA variants have been implicated in sporadic inclusion body myositis (sIBM), indicating a role for mitochondrial dysfunction.
* Gene Expression Patterns:
  + Studies of gene expression in muscle, blood, and skin samples reveal dysregulation of interferon signaling and other immune pathways.
  + These expression signatures help differentiate IIM subtypes and may serve as biomarkers.

**QUESTION AND ANSWERS SET**

## 1. What is Myositis?

Myositis refers to a group of rare autoimmune diseases characterized by inflammation of the muscles, leading to muscle weakness, fatigue, and sometimes skin rash (in dermatomyositis). It includes polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), and immune-mediated necrotizing myopathy (IMNM).

## 2. What are the key symptoms of Myositis?

* Symmetrical muscle weakness, especially in the shoulders, upper arms, hips, and thighs.
* Muscle pain or tenderness.
* Fatigue and difficulty performing daily activities.
* Skin rash in dermatomyositis (heliotrope rash, Gottron’s papules).
* Possible involvement of swallowing muscles, respiratory muscles, and joints.

## 3. How is Myositis diagnosed?

Diagnosis is based on a combination of clinical features, laboratory tests, and specialized investigations:

* Elevated muscle enzymes: Creatine kinase (CK), aldolase, lactate dehydrogenase (LDH), and transaminases (ALT/AST).
* Electromyography (EMG): Shows characteristic muscle electrical abnormalities such as short, low-amplitude motor unit potentials, fibrillations, and repetitive discharges.
* Muscle biopsy: Shows inflammation, muscle fiber necrosis, regeneration, and immune cell infiltration.
* Myositis-specific autoantibodies: Presence supports diagnosis and helps subtype classification.
* Imaging (MRI): Detects muscle inflammation and guides biopsy.
* Clinical criteria: The Bohan and Peter criteria and the newer 2017 EULAR/ACR classification criteria are used to support diagnosis and classification.

## 4. What are the diagnostic criteria for Polymyositis?

A diagnosis of polymyositis is considered if a patient has:

* Symmetrical proximal muscle weakness (shoulders, hips, trunk).
* Elevated serum muscle enzymes (CK, aldolase, LDH, ALT/AST).
* Characteristic EMG findings.
* Muscle biopsy showing endomysial inflammation and muscle fiber necrosis/regeneration.
* Positive myositis-specific autoantibodies may support diagnosis.
* Other systemic signs like fever or arthritis may be present.

## 5. What tests will my doctor order?

* Blood tests for muscle enzymes and autoantibodies.
* Electromyography to assess muscle electrical activity.
* Muscle MRI to detect inflammation.
* Muscle biopsy for histopathological confirmation.
* Imaging of lungs and heart if systemic involvement suspected.
* Pulmonary function tests if respiratory muscles are involved.

## 6. How are different types of myositis classified?

* Polymyositis: Muscle inflammation without skin rash.
* Dermatomyositis: Muscle inflammation with characteristic skin rash.
* Inclusion Body Myositis: Typically affects older adults with asymmetric weakness; diagnosed by biopsy.
* Immune-Mediated Necrotizing Myopathy: Severe muscle necrosis with minimal inflammation.

Classification uses clinical features, autoantibodies, biopsy, and imaging guided by EULAR/ACR criteria.

## 7. What is the role of autoantibodies in myositis?

Autoantibodies such as anti-Jo-1 and others are myositis-specific and help in diagnosis, prognosis, and identifying associated complications like interstitial lung disease.

## 8. Can myositis be mistaken for other diseases?

Yes, diagnosis requires ruling out other causes of muscle weakness such as muscular dystrophies, metabolic myopathies, neuropathies, and drug-induced myopathies.

## **Doctor-Patient Conversation on Myositis (De-Identified)**

## Doctor:

Hello! I understand you’ve been experiencing muscle weakness and fatigue. Can you tell me more about your symptoms?

## Patient:

Yes, doctor. Over the past few months, I’ve noticed that it’s getting harder to climb stairs and lift things. My muscles feel weak and sometimes sore.

## Doctor:

Thank you for sharing. Based on your symptoms and initial tests, it appears you may have myositis, which is an inflammation of the muscles that causes weakness.

## Patient:

What causes myositis?

## Doctor:

Myositis can be caused by autoimmune diseases, infections, medications, or sometimes it occurs without a clear cause. The immune system mistakenly attacks your muscle tissue, leading to inflammation and weakness.

## Patient:

How is it diagnosed?

## Doctor:

Diagnosis involves blood tests to check muscle enzymes like creatine kinase, antibody tests, electromyography to assess muscle function, and sometimes a muscle biopsy. Imaging like MRI can also help detect inflammation.

## Patient:

What treatments are available?

## Doctor:

Treatment usually starts with corticosteroids to reduce inflammation. Other immunosuppressive medications may be added to control the immune response. Physical therapy is important to maintain muscle strength and function.

## Patient:

Are there side effects to these medications?

## Doctor:

Yes, corticosteroids can cause weight gain, mood changes, high blood pressure, and increased infection risk. Immunosuppressants also carry infection risks and require monitoring. We will carefully manage these effects.

## Patient:

Will my muscles get better?

## Doctor:

Many patients improve with treatment, especially if started early. Some may have a chronic course and require long-term management. Physical therapy and regular follow-up are key.

## Patient:

What should I watch for?

## Doctor:

Report any worsening weakness, difficulty swallowing or breathing, or new symptoms promptly, as these may require urgent care.

## Patient:

How often will I need to see you?

## Doctor:

Initially, frequent visits to monitor treatment response and side effects, then less often as your condition stabilizes.

## Patient:

Thank you, doctor. I appreciate your help.

## Doctor:

You’re welcome. We’ll work together to manage your myositis and maintain your quality of life. Please contact me anytime with concerns.

REFERENCES

[Myositis: Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/24170-myositis)

<https://emedicine.medscape.com/article/1168167-differential?form=fpf>

<https://www.myositis.org/about-myositis/diagnosis/>

**TENDINITIS**

**DEFINITION AND DESCRIPTION**

Tendinitis is inflammation of the thick fibrous cords that attach muscle to bone. These cords are called tendons. The condition causes pain and tenderness just outside a joint.

Tendinitis can occur in any tendon. But it's most common around shoulders, elbows, wrists, knees and heels.

Most tendinitis can be treated with rest, physical therapy and medicine to reduce pain. Long-lasting tendon inflammation can cause a tendon to tear. A torn tendon might need surgery.

**Types**

Achilles tendinitis

Golfer's elbow

Patellar tendinitis

Tennis elbow

**Symptoms**

Symptoms of tendinitis tend to occur where a tendon attaches to a bone. Symptoms often include:

* Pain, often described as a dull ache, especially when moving the hurt limb or joint
* Tenderness
* Mild swelling

### **When to see a doctor**

Most cases of tendinitis respond to self care. See your health care provider if your symptoms don't lessen after a few days and if they get in the way of daily activities.

**Causes**

Tendinitis can be caused by a sudden injury. But repeating the same movement over time is a much more likely cause. Most people develop tendinitis because their jobs or hobbies involve motions that they repeat, over and over. This puts stress on tendons.

Moving correctly is especially important when having to repeat movements for sports or a job. Moving incorrectly can overload the tendon and lead to tendinitis.

**Risk factors**

Risk factors for developing tendinitis include age, having jobs that involve doing the same motion over and over, doing physical activities with poor form, and taking certain medicines.

### **Age**

As people get older, their tendons become less flexible — which makes them easier to injure.

### **Work**

Tendinitis is more common in people, such as gardeners and manual laborers, whose jobs involve:

* Repeated motions
* Awkward positions
* A lot of overhead reaching
* Vibration
* Forced movements

### **Activities**

When doing physical activities, the following can increase the risk of tendinitis:

* Sudden increase in amount or difficulty of training
* Poor equipment, such as old shoes
* Hard surfaces, such as concrete or gym floors
* Too little recovery time after an injury or too little time to get used to the activity again after time off
* Poor posture or body movements

### **Medical condition and medications**

Certain medical conditions, such as diabetes, can increase the risk of tendinitis. Medications that may increase risk include:

* Antibiotics known as fluoroquinolines
* Corticosteroids such as cortisone
* Aromatase inhibitors, used to lower breast cancer risk

## **Diagnosis**

Usually, a physical exam alone can diagnose tendinitis. X-rays or other imaging tests might be used to rule out other conditions that could be causing the symptoms.

**Treatment**

The goals of tendinitis treatment are to relieve pain and reduce irritation. Self-care, including rest, ice and pain relievers, might be all that's needed. But full recovery might take several months.

### **Medications**

Medicines used to treat tendinitis include:

* **Pain relievers.** Aspirin, naproxen sodium (Aleve), ibuprofen (Advil, Motrin IB, others) or acetaminophen (Tylenol, others) may relieve tendinitis pain. Some of these drugs can cause stomach upset, or kidney or liver problems. Creams containing pain relievers can be applied to the skin. These products can help relieve pain and avoid the side effects of taking these drugs by mouth.
* **Steroids.** A steroid shot around a tendon might help ease the pain of tendinitis. These shots aren't for tendinitis lasting more than three months. Repeated steroid shots can weaken a tendon and increase the risk of the tendon tearing.
* **Platelet-rich plasma.** This treatment involves taking a sample of your own blood and spinning the blood to separate out the platelets and other healing factors. The solution is then injected into the area of chronic tendon irritation. Though research is still going on to find the best way to use platelet-rich plasma, it has shown promise in the treatment of many chronic tendon conditions.

### **Physical therapy**

Physical therapy exercises can help strengthen the muscle and tendon. Eccentric strengthening, which emphasizes contraction of a muscle while it's lengthening, is an effective treatment for many chronic tendon conditions.

### **Surgical and other procedures**

In situations where physical therapy hasn't resolved symptoms, your health care provider might suggest:

* **Dry needling.** This procedure, usually performed with ultrasound to guide it, involves making small holes in the tendon with a fine needle to stimulate factors involved in tendon healing.
* **Surgery.** Depending on the severity of your tendon injury, surgical repair may be needed, especially if the tendon has torn away from the bone.

## **Drug Information and Side Effects**

## Common Medications Used to Treat Tendinitis

1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
   1. Examples: Ibuprofen (Advil, Motrin), Naproxen (Aleve, Naprosyn), Aspirin
   2. Use: Reduce inflammation and relieve pain associated with tendinitis. Can be taken orally or applied topically as creams or gels.
   3. Side Effects:
      1. Gastrointestinal upset (stomach pain, nausea, ulcers)
      2. Increased risk of kidney or liver problems with prolonged use
      3. Possible increased risk of cardiovascular events with long-term use
      4. Topical NSAIDs have fewer systemic side effects but may cause local skin irritation.
2. Acetaminophen (Tylenol)
   1. Use: Pain relief, but does not reduce inflammation.
   2. Side Effects:
      1. Generally well tolerated
      2. Risk of liver damage with high doses or chronic use.
3. Corticosteroid Injections
   1. Use: Given around the affected tendon to quickly reduce inflammation and pain, especially if symptoms persist beyond 3 months.
   2. Side Effects:
      1. Possible weakening of the tendon with repeated injections
      2. Increased risk of tendon rupture
      3. Local pain and irritation at injection site
      4. Rare systemic effects if used frequently.
4. Platelet-Rich Plasma (PRP) Therapy
   1. Use: Involves injecting concentrated platelets from the patient’s own blood to promote tendon healing, mainly for chronic tendinitis.
   2. Side Effects:
      1. Mild pain or swelling at injection site
      2. Infection risk is low but possible
      3. Still under research; not universally accepted.

## **Tendinitis Procedures and Timelines**

## Initial Self-Care and Conservative Treatment (First 2–3 Weeks)

* Rest: Avoid activities that stress the affected tendon for at least 2–3 days to reduce inflammation and pain.
* Ice: Apply ice packs wrapped in a cloth for 15–20 minutes every 2–3 hours during the first 2–3 days.
* Compression and Support: Use elastic bandages, braces, or splints to reduce swelling and support the tendon.
* Pain Relief: Over-the-counter NSAIDs (e.g., ibuprofen) or acetaminophen can be used to manage pain and inflammation.
* Gentle Movement: Once pain subsides, begin gentle range-of-motion exercises to prevent joint stiffness.

## Follow-up and Additional Treatments (If No Improvement After ~3 Weeks)

* Physical Therapy: Customized stretching and strengthening exercises to promote tendon healing and prevent recurrence.
* Corticosteroid Injections: Considered if symptoms persist beyond 3 weeks; injections reduce inflammation but are used cautiously due to risk of tendon weakening.
* Advanced Therapies:
  + Dry Needling: Ultrasound-guided needle insertion to stimulate healing.
  + Platelet-Rich Plasma (PRP) Injections: Injecting concentrated platelets to promote tissue repair; evidence mixed and considered experimental.
  + Extracorporeal Shock Wave Therapy: Non-invasive treatment to stimulate tendon healing.
  + Focused Aspiration of Scar Tissue (FAST): Minimally invasive procedure to remove scar tissue in chronic cases.

## Imaging and Diagnostic Procedures

* Ultrasound or MRI: Used if diagnosis is uncertain or symptoms persist beyond 6–12 weeks to assess tendon damage and rule out tears.
* X-rays: May be done to exclude bone involvement or other joint pathology.

## Surgical Intervention (Considered After 3–12 Months of Failed Conservative Treatment)

* Surgery is reserved for severe cases, such as tendon tears or chronic tendinopathy unresponsive to other treatments.
* Recovery from surgery may take several months and includes post-operative physical therapy.

## Expected Healing Timelines

* Mild Tendinitis: Improvement typically within 2–3 weeks with rest and conservative care.
* Moderate to Severe Tendinitis: May take several weeks to a few months for full recovery.
* Chronic Tendinopathy: Requires prolonged rehabilitation (3–12 months or longer) and possibly advanced therapies.
* Post-Surgical Recovery: Several months, including gradual return to activity.

## **Complications**

Without treatment, tendinitis can increase the risk of a tendon breaking down or tearing. A completely torn tendon might need surgery.

**Prevention**

To reduce the chance of developing tendinitis, follow these suggestions:

* **Ease up.** Avoid activities that place too much stress on your tendons, especially for long periods. If you have pain during an exercise, stop and rest.
* **Mix it up.** If one exercise or activity causes you pain, try something else. Cross-training can help you mix high-impact exercise, such as running, with lower impact exercise, such as biking or swimming.
* **Improve the way you move.** If how you do an activity or exercise is flawed, you could be setting yourself up for problems with your tendons. Consider taking lessons or getting professional instructions when starting a new sport or using exercise equipment.
* **Stretch.** After exercise, move your joints through full range of motion. The best time to stretch is after exercise, when your muscles are warmed up.
* **Move right in the workplace.** Make sure your chair, keyboard and desktop are positioned correctly for your height, arm length and the tasks you do. This will help protect your joints and tendons from stress.
* **Prepare your muscles to play.** Strengthening muscles used in your activity or sport can help them bear the load better.

## **Differential Diagnoses**

* Acute Compartment Syndrome
* Ankle Injury, Soft Tissue
* Bursitis
* Carpal Tunnel Syndrome in Emergency Medicine
* Deep Venous Thrombosis and Thrombophlebitis
* Diphyllobothriasis
* Gout and Pseudogout
* Hand Infections
* Plantar Fasciitis
* Reactive Arthritis
* Rheumatoid Arthritis (RA)
* Rotator Cuff Injury Management in the ED
* Knee Soft Tissue Injury (ACL, LCL, MCL, PCL) Management in the ED

## **Tendinitis Epidemiology**

## Prevalence and Incidence

Tendinitis and related upper extremity disorders have a projected prevalence of about 11.6% in working populations, with tendinitis alone accounting for approximately 3.5%

Tendinitis is more common in physically demanding jobs and less frequent in older age groups and those employed longer

In athletes, specific tendinopathies have high prevalence:

Patellar tendinopathy affects about 45% of volleyball players and 32% of basketball players

Achilles tendinopathy incidence in the general population is about 2.35 per 1000 person-years, with a lifetime incidence of 24% in competitive athletes and up to 40-50% in competitive runners

Tendinitis accounts for roughly 10% of all sport overuse injuries, notably causing anterior knee pain in young athletes

Prevalence is higher in workers with physically demanding jobs, such as textile workers studied in a large survey

Tendinitis is less frequent among older individuals and those with longer employment duration

Certain occupations like spine surgeons and coal miners report very high tendinopathy rates, up to 18% and 41%, respectively

North America leads the global tendinitis treatment market, reflecting high healthcare expenditure and advanced treatment adoption

Europe and Asia-Pacific regions are expected to see significant market growth due to increasing prevalence and improving healthcare infrastructure.

Worldwide, tendon ruptures occur at a rate of approximately 80 to 90 cases per 100,000 inhabitants annually, equating to 6–7 million cases per year

Tendinitis contributes significantly to work absenteeism; in the U.S., it leads to nearly 70,000 cases of missed work annually

The condition imposes a substantial economic burden due to treatment costs and lost productivity

## **Tendinitis Genomic Data**

## Genetic Factors Associated with Tendinitis and Tendon Injuries

1. Tenascin-C (TNC) Gene
   1. TNC encodes a glycoprotein involved in cell adhesion, signaling, proliferation, and migration, important for tendon structure and repair.
   2. Several studies found associations between polymorphisms in the TNC gene and Achilles tendinopathy:
      1. Variations in GT dinucleotide repeats (e.g., alleles with 12 or 14 repeats overrepresented in injured individuals, while 13 or 17 repeats underrepresented, suggesting protective effects).
      2. Specific single nucleotide polymorphisms (SNPs) such as rs2104772 and rs1330363 showed different allele frequencies in tendinopathy patients versus controls.
   3. These findings indicate TNC variants influence susceptibility to tendon injury and healing capacity
2. Collagen Genes (COL1A1, COL3A1, COL5A1, COL11A1, COL27A1)
   1. Collagens are major components of tendon extracellular matrix (ECM), critical for tendon strength and elasticity.
   2. Variants in collagen genes have been studied extensively:
      1. COL1A1: Some studies found no association with tendinopathy, but it remains a candidate gene due to its role in collagen type I synthesis.
      2. COL5A1: SNP rs12722 is linked to tendinopathy risk; genotype CC may be protective, while TT is associated with increased risk and reduced tendon elasticity.
      3. COL3A1, COL11A1, COL27A1: Mutations in these genes are linked to connective tissue disorders (e.g., Ehlers-Danlos syndrome) affecting tendon integrity and may influence tendinopathy susceptibility.
   3. Increased expression of COL1A1 and COL3A1 has been observed in tendinopathic tendons, indicating altered collagen remodeling
3. SPARC (Secreted Protein Acidic and Rich in Cysteine)
   1. SPARC influences type I collagen production in tendons and ligaments.
   2. Gene mutations reducing SPARC expression lead to lower collagen content and increased susceptibility to tendon and ligament injuries
4. Other Genes and Factors
   1. Variants affecting extracellular matrix remodeling, inflammation, and tendon homeostasis contribute to tendinopathy risk.
   2. Research is ongoing to identify additional genetic markers and their functional impact on tendon biology

**Lifestyle and home remedies**

To treat tendinitis at home, use rest, ice, compression and elevation. This treatment can help speed recovery and help prevent more problems.

* **Rest.** Avoid doing things that increase the pain or swelling. Don't try to work or play through the pain. Healing requires rest, but not complete bed rest. You can do other activities and exercises that don't stress the injured tendon. Swimming and water exercise may be good options.
* **Ice.** To decrease pain, muscle spasm and swelling, apply ice to the injured area for up to 20 minutes several times a day. Ice packs, ice massage or slush baths with ice and water all can help. For an ice massage, freeze a paper cup full of water so that you can hold the cup while applying the ice directly to the skin.
* **Compression.** Because swelling can cause loss of motion in an injured joint, wrap the area tightly until the swelling stops. Use wraps or elastic bandages.
* **Elevation.** If tendinitis affects your knee, raise the hurt leg above the level of your heart to reduce swelling.

Although rest is a key to treating tendinitis, not moving joints can cause them to become stiff. After a few days of resting the injured area, gently move it through its full range of motion to keep your joints flexible.

## **Doctor-Patient Conversation on Tendinitis (De-Identified)**

## Patient:

Good morning, doctor. I’ve been having pain and swelling around my elbow for the past few weeks. It hurts especially when I try to lift things or bend my arm.

## Doctor:

Thank you for sharing. Where exactly do you feel the pain? Did it start suddenly or gradually?

## Patient:

It’s mostly on the outside of my elbow. The pain started gradually after I started doing some heavy gardening and lifting.

## Doctor:

That sounds like it could be tendinitis, which is inflammation of the tendon where the muscle attaches to the bone. It’s common in people who overuse certain muscles or tendons.

## Patient:

Is it serious? What can I do to feel better?

## Doctor:

Tendinitis is usually not serious and often improves with proper care. I recommend resting the affected arm, applying ice to reduce swelling, and avoiding activities that worsen the pain.

## Patient:

Should I take any medications?

## Doctor:

Yes, over-the-counter pain relievers like ibuprofen or acetaminophen can help reduce pain and inflammation. If the pain persists, we might consider physical therapy or other treatments.

## Patient:

Do I need any tests?

## Doctor:

Usually, tendinitis is diagnosed based on your history and physical exam. If symptoms don’t improve or if we suspect other issues, imaging like ultrasound or MRI can be done.

## Patient:

How long will it take to get better?

## Doctor:

With rest and treatment, most people improve within a few weeks to a couple of months. It’s important to gradually return to activities and avoid overuse.

## Patient:

Is there anything I can do to prevent this in the future?

## Doctor:

Yes, warming up before activities, using proper techniques, and strengthening exercises can help prevent tendinitis. If your work or hobbies involve repetitive motions, taking regular breaks is important.

## Patient:

Thank you, doctor. I’ll follow your advice.

## Doctor:

You’re welcome. If the pain worsens or doesn’t improve, please come back for further evaluation.

REFERENCES

<https://emedicine.medscape.com/article/809692-overview#a6>

<https://www.nhs.uk/conditions/tendonitis/>

[Tendinitis - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/tendinitis/diagnosis-treatment/drc-20378248)

### **Tendinopathy**

**Definition**

Tendinopathy is any condition that affects a tendon, making it painful to use and reducing its functionality. Tendons are rope-like connective tissues that attach muscles to bones. Most people injure their tendons by overusing them — although other factors can contribute to weakening of your tendons. Tendinopathy can begin when a tendon injury can’t heal. Eventually, destructive changes begin to occur.

#### **Types of tendinopathy**

Tendinitis and tendinosis are two different types of tendinopathy. While they often begin in a similar way, they affect your tendons by different processes. They also have different treatment protocols.

**Tendinitis** is inflammation in your tendon. It’s usually an acute response to an injury. But it can become chronic if the injury doesn’t heal. If inflammation lasts too long, it can be destructive.

Chronic tendinitis can lead to:

* Scarring and micro-tearing
* Calcium deposits
* Tendinosis

**Tendinosis** is a breakdown of the collagen in your tendon, which makes it lose its strength and elasticity. It happens separately from inflammation. The process is progressive and lasting.

Untreated tendinosis can lead to:

* Muscle atrophy
* Tendon rupture
* Disability

##### **Tendinopathy in different tendons**

When symptoms first develop, most people don’t know what type of tendinopathy they have — only where it hurts. You might simply say that you have “shoulder tendinopathy” or “ankle tendinopathy.”

Tendinopathy is most common in your:

* Heel (Achilles tendon)
* Foot (posterior tibial tendon)
* Ankle (peroneal tendon)
* Knee (patellar tendon)
* Shoulder (supraspinatus tendon or rotator cuff)
* Elbow (lateral extensor or medial flexor tendons)
* Wrist (abductor and extensor tendons)

As many tendon injuries begin as sports injuries, it’s common to refer to a sore tendon by the name of the sport that can cause it. However, you may still develop this tendon injury without playing a sport.

Examples include:

* Tennis elbow
* Golfer’s elbow
* Swimmer’s shoulder
* Jumper’s knee

## **Symptoms of tendinopathy**

Tendinopathy is characterized by:

* Chronic tendon pain
* Reduced exercise tolerance
* Reduced functionality in the tendon

Depending on the type, it may also cause:

* Swelling, heat and discoloration
* Stiffness and reduced range of motion
* A crackling or grating sensation when the tendon moves

### **What causes tendinopathy**

It’s not always clear how tendinopathy develops, but it often starts with overusing your tendon. How much force your tendon can tolerate may differ from the next person. Athletes can strain their tendons by overtraining. People who aren’t regularly active can strain a tendon by suddenly increasing their activity. Any task repeated too often without enough rest in between can cause a repetitive strain injury.

Examples of repetitive tasks include:

* Scrubbing
* Typing
* Gardening
* Sewing
* Woodworking and carpentry
* Weight training

Factors that may contribute to straining your tendon include:

* High-intensity training
* Poor ergonomics or equipment
* Lack of flexibility
* Lack of strength
* Muscle imbalances
* Posture or gait abnormalities
* Too much weight on your tendon
* Certain autoimmune diseases

In addition, some medications can cause tendon damage as a side effect, including:

* Fluoroquinolones (a type of antibiotic)
* Corticosteroids
* Statins

When you strain your tendon, small tears in the fibers can form. Tendons are strong, but when they tear, they’re slow to heal. Acute inflammation (tendinitis) is your body’s way of starting the healing process. But if your tendon doesn’t get the rest it needs to heal, chronic tendinopathy can set in. Tendinitis might continue long-term, or tendinosis might begin the process of remodeling your tendon.

**Diagnosis and Tests**

If you have tendon pain with activity that lasts for several months, you have tendinopathy. But it’s important to find out what kind you have. A healthcare provider can diagnose your tendinopathy with a physical exam and imaging studies. They’ll ask about your symptoms, activities and any recent changes. They’ll examine your tendon and may follow up with imaging to look for signs of tissue changes.

## **Management and Treatment**

Treatment for different types of tendinopathy can vary, which is why it’s important to get an accurate diagnosis. Treatment can also vary by how long you’ve had tendinopathy and how far it’s progressed. Healthcare providers usually begin with conservative therapies, like rest, ice, anti-inflammatory medications and physical therapy. If these don’t help enough, they may suggest other interventions, such as:

* Therapeutic injections
* Minimally invasive tendon debridement
* Extracorporeal shockwave therapy (ESWT)
* Surgery

## **Tendinopathy Treatment Drug Information and Side Effects**

## 1. Corticosteroid Injections (Cortisone Shots)

* Use: Reduce inflammation and relieve pain in tendons affected by tendinopathy, especially when symptoms persist despite conservative care.
* Effectiveness: Pain relief typically begins within a week and can last several months.
* Common Side Effects:
  + Pain, swelling, and irritation at the injection site lasting up to 2 days (postinjection flare)
  + Bruising and skin discoloration or hypopigmentation, especially with superficial injections
  + Temporary increase in blood sugar levels, particularly important for diabetic patients
  + Facial flushing, headache, insomnia, and transient hypertension (systemic effects are usually mild)
* Serious but Rare Side Effects:
  + Tendon weakening or rupture (reported incidence ~0.1%), especially with repeated injections or injections into tendons under high stress (e.g., Achilles, patellar)
  + Infection risk at injection site (rare, but serious)
  + Accelerated osteoarthritis progression or bone injury in adjacent joints
  + Adrenal suppression or insufficiency with repeated use
* Precautions:
  + Avoid injections if there is an active infection
  + Limit number of injections at one site (commonly 3–5 max) with at least 2 weeks between injections to reduce tendon rupture risk
  + Rest the injected area for 24–48 hours post-injection to minimize complications

## 2. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

* Use: Oral or topical NSAIDs (e.g., ibuprofen, naproxen) are commonly used to reduce pain and inflammation in tendinopathy.
* Side Effects:
  + Gastrointestinal irritation, ulcers, bleeding risk with prolonged use.
  + Kidney or liver dysfunction in susceptible individuals.
  + Cardiovascular risks with long-term use.

## 3. Other Medications

* Acetaminophen: For pain relief without anti-inflammatory effect; generally well tolerated but risk of liver toxicity with overdose.
* Experimental Treatments: Platelet-rich plasma (PRP) injections and other biologics are being studied but not yet standard care.

## **Tendinopathy Procedures and Timelines**

## Phase 1: Pain Reduction and Initial Management (Weeks 0–3)

* Goal: Reduce pain and inflammation, protect the tendon from further overload.
* Methods:
  + Relative rest and activity modification to avoid aggravating movements.
  + Ice application and use of NSAIDs for symptom relief.
  + Isometric loading exercises (5 repetitions of 45 seconds, 2–3 times daily) at about 70% maximal voluntary contraction as pain allows.
* Expected Outcome: Pain reduction and prevention of muscle inhibition.

## Phase 2: Strengthening and Load Progression (Weeks 3–12)

* Goal: Restore muscle strength and tendon capacity gradually.
* Methods:
  + Progress to isotonic loading exercises (3–4 sets at 15RM progressing to 6RM every other day).
  + Eccentric strengthening exercises are commonly used to promote tendon remodeling.
  + Physical therapy focusing on progressive loading tailored to pain tolerance.
* Expected Outcome: Significant muscle strength gains typically take 6–8 weeks; tendon adaptation may require 3–4 months.

## Phase 3: Functional Rehabilitation and Return to Activity (After Week 12)

* Goal: Return to full function and prevent recurrence.
* Methods:
  + Functional and sport-specific rehabilitation once pain is well controlled and strength is adequate (e.g., 10RM strength equal bilaterally).
  + Gradual return to normal or athletic activities with ongoing load management.
* Expected Outcome: Reduced risk of recurrence and restoration of tendon load capacity.

## Additional Treatment Options (If Conservative Treatment Fails)

* Corticosteroid Injections: May provide short-term pain relief but carry risk of tendon weakening and rupture; generally reserved for persistent symptoms after several weeks of rehab.
* Dry Needling: Small needle punctures to stimulate healing; used in refractory cases.
* Shockwave Therapy: Non-invasive treatment to promote tendon healing.
* Platelet-Rich Plasma (PRP) Injections: Experimental therapy to enhance tissue repair.
* Surgery: Considered after 3–6 months of failed conservative treatment; includes debridement or repair of damaged tendon tissue.

### **Self-care**

Many times, tendon pain and injury can be treated at home. Self-care steps include:

* **Rest.** Avoid doing things that increase the pain or swelling. Don't try to work or play through the pain. Healing requires rest, but not complete bed rest. You can do other activities and exercises that don't stress the injured tendon. Swimming and water exercise may be good options.
* **Ice.** To decrease pain, muscle spasm and swelling, apply ice to the injured area for up to 20 minutes several times a day. Ice packs, ice massage, or slush baths with ice and water all can help. For an ice massage, freeze a paper cup full of water so that you can hold the cup while applying the ice directly to the skin.
* **Pain relievers.** Over-the-counter pain relievers such as ibuprofen (Advil, Motrin IB, others) or acetaminophen (Tylenol, others) may help reduce the pain caused by swelling in the tendon.

## **Outlook / Prognosis**

Recovery from acute tendinitis only takes a few days to weeks, but recovery from chronic tendinitis can take up to six weeks. Tendinosis recovery can take much longer — between two and six months. Recovery depends on being able to relieve the strain on your tendon long enough for healing to take place. Follow your healthcare provider’s advice on rest and exercise to ensure a smooth recovery.

## **Prevention**

You can’t prevent tendinopathy altogether. For example, accidents can happen to you while you’re playing or working. But you can take some steps to reduce your risk of tendinopathy.

To reduce your risk of tendinopathy, work with a trainer or coach. A change in how you play or a different way to stretch could help the same tendons.

## **Living With**

If you have tendinopathy:

* **Don’t:** Ignore your pain. You might be used to a certain level of soreness if you’re used to training or doing repetitive tasks. But if it persists or gets worse, see a healthcare provider.
* **Do:** Get a specific diagnosis. Tendinitis and tendinosis are not the same. Knowing what you’re dealing with will help you understand your treatment plan and what to expect from recovery.
* **Don’t:** Be impatient. Your tendon needs time to heal. Don’t try to use it again until your healthcare provider says it’s OK. Trying to cut your recovery time will only prolong it in the end.
* **Do:** Practice your physical therapy. As important as it is to rest your tendon, it’s equally important to rehabilitate the muscles connected to your tendon, and later, the tendon itself.
* **Don’t:** Lose heart. If conservative therapy doesn’t work, there are a variety of other treatments to try. Most people won’t need surgery for tendinopathy. But if you do, surgery can help.
* **Do:** Make some long-term changes. Now that you know how tendinopathy happened to you, try to avoid it in the future by adjusting your routine, technique, equipment or other factors.

## **Differential Diagnoses for Tendinopathy**

1. Bursitis
   1. Inflammation of the bursa near tendons causing pain and swelling.
   2. Example: Trochanteric bursitis mimics gluteal tendinopathy.
   3. Differentiated by tenderness, location and imaging.
2. Partial or Complete Tendon Tears
   1. Acute or chronic tears can present with pain and weakness.
   2. History of trauma or sudden onset helps distinguish from tendinopathy.
   3. Ultrasound or MRI confirms diagnosis.
3. Paratendinopathy (Tenosynovitis)
   1. Inflammation of the tendon sheath rather than the tendon itself.
   2. Common in De Quervain’s tenosynovitis (thumb/wrist).
   3. Diagnosed clinically and with ultrasound.
4. Nerve Entrapment or Neuropathy
   1. Conditions like carpal tunnel syndrome or sural nerve neuropathy cause pain and sensory changes overlapping with tendon symptoms.
   2. Electromyography (EMG) and nerve conduction studies aid diagnosis.
5. Joint Pathologies
   1. Osteoarthritis, rheumatoid arthritis, or gout near tendon insertions can cause pain mimicking tendinopathy.
   2. Imaging and blood tests help differentiate.
6. Stress Fractures or Bone Spurs
   1. Bone abnormalities near tendons can cause pain and limit function.
   2. X-rays or MRI identify these conditions.
7. Compartment Syndrome
   1. Acute compartment syndrome presents with severe pain and requires urgent diagnosis to prevent tissue damage.
8. Inflammatory or Systemic Diseases
   1. Systemic inflammatory conditions (e.g., polymyalgia rheumatica, systemic lupus erythematosus) can cause tendon pain.
   2. Systemic symptoms and blood tests guide diagnosis

## **Tendinopathies Epidemiology**

## Prevalence and Incidence

Tendinopathies are among the most common musculoskeletal disorders, accounting for over 30% of all orthopedic consultations worldwide

The prevalence of tendinopathy in the general population varies by tendon and activity level, with rates reported as:

3% prevalence for lateral epicondylitis (tennis elbow), but higher rates up to 18% in spine surgeons and 41% in coal miners due to occupational strain

Lower limb tendinopathy incidence around 11.8 per 1000 person-years and prevalence about 10.5 per 1000 person-years

Achilles tendinopathy (AT) incidence is approximately 2.35 per 1000 persons annually in the general population aged 21–60 years

Lifetime incidence of AT in competitive athletes reaches 24%, with up to 40–50% in competitive runners

Point prevalence of AT in university soccer players is about 21.9%

Age: Prevalence increases with age, highest in people over 45 years (about 8%) and lowest in those under 18 (about 2%)

Gender: No consistent difference in prevalence between males and females overall

Occupation and Activity: Physically demanding jobs and sports with repetitive tendon loading have higher prevalence. For example, coal miners and spine surgeons have markedly higher rates of tendinopathy (up to 41% and 18%, respectively)

Sports: Gymnastics and ball games show highest prevalence of Achilles tendinopathy (up to 17% and 6%, respectively). Recreational and amateur exercisers have lower prevalence than athletes

Geography: Prevalence varies slightly by region, with Oceania showing higher rates than Europe and America

Tendinopathies cause significant loss of working hours and economic burden globally, with over 30 million tendon-related procedures annually

In the US, tendinopathies result in tens of thousands of missed work days annually, affecting productivity and quality of life

## **Key Genes and Genetic Variants Associated with Tendinopathy**

1. COL5A1 (Collagen Type V Alpha 1 Chain)
   1. The most consistently implicated gene in tendinopathy susceptibility.
   2. Polymorphisms such as rs12722 influence tendon elasticity and risk:
      1. CC genotype is generally protective.
      2. TT genotype is associated with increased risk of chronic Achilles tendinopathy and reduced tendon flexibility.
   3. Variants affect mRNA stability and collagen fibril formation, impacting tendon strength.
2. Tenascin-C (TNC)
   1. Encodes an ECM glycoprotein involved in cell adhesion and tissue repair.
   2. Polymorphisms, including GT dinucleotide repeat variants, have been linked to Achilles tendon injuries.
   3. Certain alleles (e.g., 12 or 14 repeats) are overrepresented in tendinopathy patients, suggesting increased susceptibility.
3. Matrix Metalloproteinase 3 (MMP3)
   1. Enzyme involved in ECM remodeling and degradation.
   2. Variants in MMP3 gene have been associated with tendon injury risk and altered tendon healing.
4. Other Collagen Genes: COL1A1, COL3A1, COL12A1, COL14A1, COL11A1, COL11A2
   1. These genes encode fibrillar collagens critical for tendon structure.
   2. Some polymorphisms have been linked to tendinopathy, particularly in the elbow and rotator cuff tendons.
   3. For example, COL11A1 rs3753841 variant is associated with increased risk of elbow tendon pathology.
5. Estrogen-Related Receptor Beta (ESRRB)
   1. Genetic variants may influence tendon biology and injury risk, though evidence is emerging.
6. Epigenetic Factors
   1. DNA methylation and other epigenetic modifications affect gene expression in tendons and may contribute to tendinopathy development.

## **Doctor-Patient Conversation on Tendinopathy (De-Identified)**

## Doctor:

Hello! I understand you’ve been having some pain around your tendon. Can you tell me more about what you’re experiencing?

## Patient:

Yes, doctor. I have pain and stiffness near my Achilles tendon, especially when I start running or after resting. It sometimes feels swollen and tender.

## Doctor:

Thank you for sharing that. It sounds like you might have tendinopathy, which is an overuse injury causing degeneration and inflammation of the tendon. It’s quite common in people who increase their activity suddenly or repeat certain movements.

## Patient:

What exactly is causing my symptoms?

## Doctor:

Your symptoms are likely caused by tiny tears and degeneration in the tendon fibers due to repetitive strain. This leads to pain, swelling, and reduced function.

## Patient:

Could something else be causing this pain?

## Doctor:

Other possibilities include tendon tears, bursitis, or arthritis near the joint. We’ll do a thorough exam and may order imaging if needed to confirm the diagnosis.

## Patient:

What tests will I need?

## Doctor:

Usually, a physical exam is sufficient. If needed, we might do an ultrasound or MRI to look at the tendon structure and rule out tears.

## Patient:

What treatment options are available?

## Doctor:

Treatment typically starts with rest and avoiding activities that worsen the pain. Ice and over-the-counter anti-inflammatory medications can help. Physical therapy focusing on tendon strengthening and flexibility is very effective. In some cases, other therapies like shockwave treatment or injections may be considered.

## Patient:

Which treatment do you recommend for me?

## Doctor:

Given your symptoms, I recommend starting with rest, ice, and a physical therapy program tailored to gradually strengthen your tendon and improve flexibility. We’ll monitor your progress and adjust treatment as needed.

## Patient:

What are the chances of side effects from these treatments?

## Doctor:

Most treatments like physical therapy and ice have minimal side effects. Anti-inflammatory medications can sometimes cause stomach upset or other issues if used long-term. More advanced treatments like injections have small risks of infection or tendon weakening but are generally safe when done properly.

## Patient:

What happens if I don’t treat it?

## Doctor:

If untreated, tendinopathy can worsen, leading to chronic pain, reduced function, and in rare cases, tendon rupture, which is a more serious injury requiring surgery.

## Patient:

Thank you, doctor. I appreciate your explanation.

## Doctor:

You’re welcome. Please feel free to ask any questions as we go along. We’ll work together to get you back to your activities safely.

REFERENCES

[Tendinopathy: What It Is, Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/22289-tendinopathy)

<https://www.mayoclinic.org/diseases-conditions/tendinopathy/diagnosis-treatment/drc-20580691>

## **Muscle Strain**

**Description**

Muscle strains can be mild to severe. A grade 1 muscle strain only pulls and breaks a few fibers. But a grade 3 muscle strain tears all the way through.

A muscle strain, or pulled muscle, is a tear in your muscle fibers. It’s one of the most common soft tissue injuries. You can strain a muscle by pulling it too hard or using it too much, which weakens the fibers.

Muscle strains can be minor to major. A mild strain might only break tiny fibers within the fabric of your muscle, while a severe one can tear through it. Strains are painful, but most can heal with time and rest.

Your muscles are made of thousands of small fibers woven together. When you strain a muscle, the strands of fiber are stretched beyond their limit and tear apart. If you’ve ever tried to use an old bungee cord to hold something in place, you’ve seen this happen. New bungee cords have plenty of give and stretch. But if you use one for too long or suddenly jerk on it too hard, the fibers will start to pull apart.

### **Types of muscle strains**

Common types of muscle strains include:

* Abdominal muscle strain
* Back strain
* Groin muscle strain
* Hip flexor strain
* Calf muscle strain
* Hamstring strain

Healthcare providers also classify muscle strains as either acute or chronic.

* **Acute muscle strains.** These happen suddenly and cause immediate symptoms. You might pull a muscle with a sudden, forceful movement, or by twisting it.
* **Chronic muscle strains.** These develop gradually, and so do the symptoms. You can gradually tear a muscle by overusing it without giving it enough time to repair.

### **Muscle tears symptoms**

Symptoms of a pulled or torn muscle include:

* Muscle pain
* Muscle spasms
* Bruising
* Swelling
* Muscle weakness
* Limited range of motion
* Feeling a “pop” during the injury
* Seeing a gap or dent in the shape of the muscle

#### **What does a torn muscle feel like?**

A torn muscle feels sore when you try to use it. You can usually locate the pain in one spot. You may be able to connect it to a recent event or activity. If it’s a chronic muscle strain, you may develop pain gradually over a few days. If it’s an acute muscle strain, you’ll feel pain immediately, and it may even feel like tearing. You may also feel your muscle weaken, and you may feel that you can’t use it at all.

### **Causes of muscle strains**

Muscle strains happen when you tear the fibers of your muscle. This can happen suddenly or gradually.

Common causes of muscle strains include:

* **Acute injuries.** Muscle strains are often sports injuries, caused by sudden sprinting, twisting or jumping. But accidental muscle strains are also common in everyday life.
* **Repetitive strain injuries.** Repeating the same movement over and over, whether at work or a recreational activity, can strain your muscles over time.
* **Overtraining.** Training or laboring too hard or too long without letting your muscles rest weakens them. If they don’t have a chance to rebuild, they might break instead.
* **Undertraining.** Low flexibility and strength can cause muscles to strain with ordinary use. Not stretching or warming up before exercise can overstress your muscles before they’re ready.

#### **Risk factors of muscle strains**

Some muscles are more likely to tear than others. These are muscles that:

* **Cross more than one joint.** Muscles that cross joints often act to restrain other muscles when you move that joint. If the joint moves with too much force, these muscles feel the impact first.
* **Contract eccentrically.** Eccentric muscles stretch and lengthen when bearing a load. They absorb the impact of the load with controlled movements, like lowering a weight or walking downhill.
* **Have type II muscle fibers.** Muscles with higher concentrations of type II muscle fibers (fast-twitch fibers) are designed for short bursts of power and speed, so they use more force.

Other risk factors that can contribute to muscle strains include:

* **Muscle stiffness.** When muscles are tight and inflexible, the fibers break more easily.
* **Muscle imbalances.** Favoring some muscles over others can make the others too weak.
* **Previous injuries.** Muscles that have been torn before are more likely to tear again.

## **Diagnosis and Tests**

If you’ve pulled a muscle, you’ll probably have a pretty good idea of how it happened. A healthcare provider will start by asking you about when the pain started and what you were doing at the time. Then, they’ll examine the spot, which may have visible bruising and swelling if it’s been at least 24 hours since the injury. They’ll gently feel it for tenderness and test the muscle for strength and range of motion.

A physical exam is often enough to diagnose a pulled muscle. But in some cases, your provider might want to take an MRI to rule out other conditions, or to determine the extent of the tear and grade it.

#### **Muscle strain grades**

Healthcare providers also grade muscle strains by how severe they are.

* **Grade I.** If you have a mild muscle strain, you’ve stretched and pulled your muscle enough to cause minor damage, but it isn’t torn through. This is the most common type.
* **Grade II.** A moderate muscle strain has torn through some or even most of the muscle. This will affect your muscle strength and range of motion. It can take time to heal.
* **Grade III.** If you have a severe muscle strain, your muscle has torn all the way through. A complete muscle tear (muscle rupture) might need surgery to repair it.

## **Management and Treatment**

Most people can recover from a pulled muscle at home. Only a severe, grade III tear might need surgery. Surgery for a complete muscle tear means stitching the two ends of the muscle back together.

Home treatment for a muscle strain includes:

* **The RICE method.** **R**est, **i**ce, **c**ompression and **e**levation can help relieve pain and inflammation during the first few days of your recovery. After the first few days, you can start moving it again.
* **Crutches.** If your injury is in your lower body, you might need to use crutches to keep weight off the muscle when you walk. Your healthcare provider can guide you on how long to use them.
* **Pain relievers.** Anti-inflammatory medications, like NSAIDs, can help during the first few days of your recovery. After this, your healthcare provider might recommend switching medications.
* **Physical therapy.** It’s important to reintroduce gentle movement after the first few days of recovery. A physical therapist can guide you in specific exercises to rehabilitate your muscle.
* **Platelet-rich plasma injections.** This newer treatment uses platelets from your own blood to stimulate tissue repair. It’s still unproven, but some studies suggest it can speed up healing.

## **Treatment Drugs, Information, and Side Effects**

## 1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

* Examples: Ibuprofen (Advil, Motrin), Naproxen (Aleve), Diclofenac
* Use: Reduce pain, inflammation, and swelling during the acute phase of muscle strain.
* Common Side Effects:
  + Gastrointestinal irritation, ulcers, bleeding
  + Kidney or liver dysfunction with prolonged use
  + Increased cardiovascular risk with long-term use
* Notes: Often used for the first few days after injury; topical NSAIDs (e.g., diclofenac gel) may reduce systemic side effects.

## 2. Acetaminophen (Tylenol)

* Use: Pain relief without anti-inflammatory effects; alternative for patients who cannot tolerate NSAIDs.
* Side Effects:
  + Generally well tolerated
  + Risk of liver toxicity with overdose or chronic high doses.

## 3. Muscle Relaxants

* Examples: Cyclobenzaprine (Flexeril), Carisoprodol (Soma)
* Use: Prescribed for severe muscle spasms and stiffness associated with muscle strain.
* Side Effects:
  + Drowsiness, dizziness, dry mouth
  + Potential for dependence with long-term use
  + May impair coordination and alertness.

## 4. Topical Analgesics

* Examples: Methyl salicylate, Capsaicin, Lidocaine, Menthol-containing creams or gels
* Use: Provide localized pain relief with minimal systemic absorption.
* Side Effects:
  + Skin irritation or allergic reactions at application site.

## Expanded 5-Grade Classification (British Athletics Muscle Injury Classification - BAMIC)

| Grade | Description | Notes |
| --- | --- | --- |
| Grade 0 | MRI-negative muscle soreness (no structural damage) | Muscle soreness without tear |
| Grade 1 | Small muscle tear; mild strain | Minor fiber disruption; minimal functional loss |
| Grade 2 | Moderate muscle tear; partial disruption | Larger tear; moderate functional impairment |
| Grade 3 | Extensive muscle tear; severe partial disruption | Significant fiber disruption; severe functional loss |
| Grade 4 | Complete muscle tear or tendon rupture | Full-thickness tear; complete loss of function |

* Grades 1–4 are further subclassified by injury location:
  + a: Myofascial
  + b: Musculotendinous
  + c: Intratendinous
* This system is primarily MRI-based and used in elite sports medicine.

## Other Classification Notes

* + Grade 1: Little or no abnormality on imaging; <5% fiber rupture.
  + Grade 2: Partial rupture >5% of muscle fibers.
  + Grade 3: Complete rupture with muscle retraction.
* Clinical Features Across Grades:
  + Grade I: Mild pain, minimal swelling, no strength loss.
  + Grade II: Moderate pain, swelling, some strength loss, limited motion.
  + Grade III: Severe pain, swelling, loss of function, possible palpable defect

**Muscle Strains: Procedures and Timelines**

## Healing Phases and Timelines

| Phase | Duration | Biological Process | Treatment Focus |
| --- | --- | --- | --- |
| 1. Inflammatory (Destruction) | 1–3 to 5 days | Muscle fiber rupture, necrosis, immune cell infiltration (neutrophils, pro-inflammatory macrophages) | Rest, ice, compression, elevation (RICE), brief immobilization (3–7 days) to reduce bleeding and swelling |
| 2. Proliferation (Repair/Regeneration) | Starts ~2 days, peaks ~2 weeks, lasts up to 3 weeks or more | Satellite cells activate, new muscle fibers (myoblasts) form, fibroblasts produce connective tissue, angiogenesis | Gradual mobilization within pain limits, gentle range of motion and isometric exercises, avoid re-injury |
| 3. Remodeling (Maturation) | Begins soon after injury, can last months to over a year | Maturation and alignment of new muscle fibers and connective tissue, restoration of muscle strength and function | Progressive strengthening (eccentric/isotonic), proprioception, endurance training, functional rehabilitation |

## Recovery Time by Injury Grade

| Grade | Description | Typical Recovery Timeline | Notes |
| --- | --- | --- | --- |
| Grade I | Mild strain (<5% fibers torn) | 2–4 weeks | Return to activity usually within 3–6 weeks |
| Grade II | Moderate partial tear (~5–50% fibers) | 4–8 weeks to 2 months | Requires gradual rehab; may take several months |
| Grade III | Severe or complete tear | 3–6 months or longer; surgery may be needed | Immobilization (up to 6 weeks), then rehab; longer recovery, possible surgery |

## **Key Treatment Procedures and Recommendations**

* Initial 3 Days:
  + Apply RICE (Rest, Ice, Compression, Elevation)
  + Avoid anti-inflammatory medications initially to not interfere with healing
  + Brief immobilization to reduce bleeding and swelling
* After 3 Days to 3 Weeks:
  + Begin gentle mobilization and isometric exercises within pain limits
  + Cardiovascular conditioning with low-impact activities
  + Physical therapy focusing on restoring range of motion and preventing stiffness
* After 3 Weeks:
  + Progressive loading with eccentric and isotonic strengthening exercises
  + Proprioceptive and endurance training
  + Functional and sport-specific rehabilitation
* Return to Full Activity:
  + When pain-free active range of motion is restored
  + Strength is at least 90–100% compared to the uninjured side
  + Maintenance programs to prevent re-injury
* Surgery:
  + Reserved for complete tears or severe injuries not responding to conservative management
  + Post-surgical rehab may take several months

**DIFFERENTIAL DIAGNOSIS**

* Muscle Contusion (Bruise)
  + Caused by direct blunt trauma leading to bleeding within the muscle.
  + Presents with localized pain, swelling, and discoloration similar to strains but usually with a clear history of impact.
* Muscle Tear or Rupture
  + Severe muscle strain can progress to partial or complete muscle or tendon rupture.
  + Complete tears often show a palpable gap, significant weakness, and loss of function.
  + Imaging (ultrasound or MRI) helps differentiate.
* Tendon Injury or Tendinopathy
  + Tendon inflammation or degeneration can cause pain near muscle attachments, sometimes confused with muscle strain.
  + Tendon injuries may have a more localized tenderness over the tendon rather than muscle belly.
* Ligament Sprain
  + Injury to ligaments connecting bones, often near joints, can cause pain and swelling.
  + Sprains differ from strains as they involve ligaments, not muscles or tendons.
* Delayed Onset Muscle Soreness (DOMS)
  + Occurs 24–72 hours after unaccustomed or intense exercise.
  + Diffuse muscle pain and stiffness without focal tenderness or swelling typical of strains.
* Myofascial Pain Syndrome
  + Chronic muscle pain with trigger points causing referred pain.
  + Lacks acute injury history and swelling.
* Compartment Syndrome
  + Increased pressure within a muscle compartment causing severe pain, swelling, and possible nerve dysfunction.
  + Requires urgent diagnosis and treatment.
* Fracture or Bone Injury
  + Pain from underlying bone fractures or avulsion injuries can mimic muscle strain pain.
  + X-rays are needed to exclude fractures.
* Nerve Injury or Radiculopathy
  + Nerve root compression or peripheral nerve injury can cause muscle weakness and pain mimicking strain.
  + Neurological exams and imaging help differentiate.
* Infection or Inflammatory Myopathies
  + Rarely, infections (e.g., pyomyositis) or autoimmune muscle diseases can present with muscle pain and swelling.

### **When should I see a healthcare provider for a muscle strain?**

Check in with a healthcare provider if your muscle strain:

* **Seems severe.** If you heard or felt a “pop” when your muscle tore, if you can’t move your muscle at all, or if pain, bruising and swelling are severe, see a provider right away.
* **Isn’t improving.** If symptoms persist or get worse after a few days, your injury might not be as minor as you thought. It’s time to have a provider examine it.
* **Triggers new symptoms.** If you develop nerve-related symptoms like numbness, tingling, sudden weakness or difficulty controlling certain muscles, you may have nerve damage.

**You might want to ask:**

## Which muscle did I strain?

The specific muscle strain depends on your symptoms and injury location. Diagnosis is usually made by clinical examination, and sometimes imaging like MRI is used to identify the exact muscle and extent of injury.

## 2. What grade is my muscle strain (how bad is it?)

Muscle strains are graded as:

* Grade 1 (Mild): Minor tears, mild pain, little or no loss of strength. Heals in about 1-2 weeks to 8 weeks.
* Grade 2 (Moderate): Partial muscle tear, moderate pain, some loss of strength and function. Healing can take several weeks to a few months (up to 4 months).
* Grade 3 (Severe): Complete muscle tear, severe pain, major loss of function, often requires surgery. Recovery can take 4-6 months or longer.

## 3. What activities should I avoid during recovery?

* Avoid activities that cause pain or strain the injured muscle, especially heavy lifting, running, jumping, or sudden movements involving the affected muscle.
* During the initial inflammatory phase (first 3-7 days), rest and avoid putting stress on the muscle to prevent further injury.
* Gradually reintroduce movement and low-impact activities as pain allows, following your healthcare provider’s guidance.

## 4. How long should I rest, and when should I start moving again?

* Rest: Immobilization or relative rest is recommended for the first 4-6 days to allow initial healing and prevent rerupture.
* Early Movement: After this acute phase, start gentle, pain-free mobilization and physical therapy to promote regeneration and prevent stiffness.
* Return to Activity:
  + Grade 1 strains: Usually return to normal activity within 1-2 weeks, full healing up to 8 weeks.
  + Grade 2 strains: Gradual return over 3-6 weeks or longer, with physical therapy. Full healing may take several months.
  + Grade 3 strains: May require surgery and immobilization for 4-6 weeks, followed by extensive rehabilitation lasting several months.
* Avoid rushing back to intense activity to reduce risk of reinjury.

## **Outlook / Prognosis**

If you only have a minor (grade I) muscle strain, it should heal within a few weeks. Moderate (grade II) muscle strains may take several weeks to months to heal completely. A severe (grade III) muscle strain can take four to six months to heal after surgery. You may need to immobilize your muscle with a cast for up to six weeks before starting your rehabilitation program. Athletes will need to sit out the season.

Most people recover completely from a muscle strain, even a severe one. But how you treat your muscle during recovery can affect how well it heals. In some cases, the muscle might retain some scar tissue, which is stiffer and more brittle than healthy muscle tissue. This makes it easier to tear the muscle again. You might have to be more mindful of how you use your muscles in the future.

## **Prevention**

Some simple guidelines to help prevent muscle strains are:

* Condition your muscles with a daily fitness program.
* Stretch and warm up your muscles before using them.
* Check your technique when lifting weights or performing physical tasks.
* Pay attention to your posture and workplace ergonomics.

## **Epidemiology**

## Prevalence and Incidence

Muscle strains are very common injuries, especially in athletes and physically active populations. They account for approximately 10% to 55% of all sports injuries depending on the sport and level of activity

In professional male football (soccer) players, muscle injuries constitute about 31% of all injuries, with an average of 0.6 muscle injuries per player per season. A typical squad of 25 players can expect about 15 muscle injuries per season

The most commonly affected muscles are in the lower limbs: hamstrings (37%), adductors (23%), quadriceps (19%), and calf muscles (13%)

Muscle strains account for roughly 50% of athletic injuries overall

The incidence of muscle strains increases with age, particularly for calf muscle injuries, while hamstring and quadriceps strains do not show a clear age association

In the general adult population in the US, about 9.0% reported repetitive strain injuries in the past 3 months, which includes muscle strains among other musculoskeletal injuries

Muscle strains and related injuries are among the most common workplace injuries, with sprains and strains being the leading cause of lost workdays

Sports involving repetitive or explosive movements, such as soccer, basketball, and track and field, have higher muscle strain rates

Factors contributing to muscle strain include inadequate warm-up, poor flexibility, muscle fatigue, previous injury, and improper technique

Lack of rest and overtraining also increase risk

## **Doctor-Patient Conversation on Muscle Strain (De-Identified)**

## Doctor:

Good morning! What brings you in today?

## Patient:

Good morning, doctor. I think I’ve strained a muscle in my leg. It hurts when I move, and there’s some swelling.

## Doctor:

I’m sorry to hear that. Can you tell me how the injury happened? Did you feel a sudden sharp pain or a pop?

## Patient:

Yes, I was running and suddenly felt a sharp pain in my calf. Since then, it’s been sore and a bit swollen.

## Doctor:

Based on your description, it sounds like a muscle strain, which is an overstretch or tear of muscle fibers. We usually classify strains into three grades: mild, moderate, and severe.

## Patient:

How do you know how bad it is?

## Doctor:

I’ll examine the muscle for tenderness, swelling, and strength. Mild strains (Grade 1) cause minor pain and little loss of strength. Moderate strains (Grade 2) involve a partial tear and more pain and weakness. Severe strains (Grade 3) are complete tears and often require surgery.

## Patient:

What should I do now? Should I rest or keep moving?

## Doctor:

Initially, rest the muscle and avoid activities that cause pain. Apply ice to reduce swelling and take over-the-counter pain relievers like ibuprofen if needed. After a few days, start gentle movements and physical therapy to regain strength and flexibility.

## Patient:

How long will it take to heal?

## Doctor:

Healing time depends on the severity:

* Mild strains often improve within 1-2 weeks.
* Moderate strains may take several weeks to a few months.
* Severe strains can take several months and might need surgery.

## Patient:

Are there things I should avoid during recovery?

## Doctor:

Avoid heavy lifting, running, or sudden movements that stress the muscle until it’s healed. Gradually return to activity as pain allows, guided by your therapist.

## Patient:

What happens if I don’t treat it properly?

## Doctor:

If untreated or if you return to activity too soon, you risk worsening the injury or causing a chronic problem. Proper rest and rehabilitation are key to full recovery.

## Patient:

Thank you, doctor. I’ll follow your advice.

## Doctor:

You’re welcome. If the pain worsens or you notice swelling or bruising increasing, please come back for further evaluation.

REFERENCES

https://www.hopkinsmedicine.org/-/media/orthopaedic-surgery/documents/patient-guides/muscle-strain.pdf

[Muscle Strains: Causes, Symptoms, Treatment & Recovery](https://my.clevelandclinic.org/health/diseases/22336-muscle-strains)

<https://www.cdc.gov/nchs/data/nhsr/nhsr189.pdf>

<https://www.health.harvard.edu/staying-healthy/muscle-strain-a-to-z>

### **MUSCLE SPRAIN**

**DEFINITION AND DESCRIPTION**

A sprain is an injury that happens when one of your ligaments is stretched or torn.

Ligaments are bands of tissue that connect bones throughout your body. They’re like ropes that hold your muscles and bones together and prevent them from moving too far. Ligaments also make sure your joints only move in the direction(s) they’re supposed to.

Sprains happen when ligaments around one of your joints are damaged. Visit a healthcare provider if you notice pain, swelling or it’s hard to use or put weight on a joint — especially if you’ve experienced a fall, injury or accident.

#### **Types of sprains**

Any joint supported by ligaments can be sprained. The most commonly sprained joints are:

* Ankle sprains (including high ankle sprains).
* Wrist sprains.
* Knee sprains.
* Finger sprains (sometimes called jammed fingers).
* Thumb sprains.

Sprains are very common. They’re one of the most common injuries, especially among athletes.

### **Sprain symptoms**

The most common sprain symptoms include:

* Pain.
* Swelling.
* Bruising or discoloration.
* Instability (feeling like you can’t put weight on the joint or move comfortably).
* Reduced range of motion (it’s hard or painful to move the joint as far as usual).

### **What causes sprains?**

Anything that forces your joint to move too much or too far can cause a sprain. The most common causes include:

* Sports injuries.
* Falls.
* Slipping and catching yourself suddenly.
* Rolling an ankle or twisting a knee while walking, running or jumping.
* Repetitive strain injuries (overusing a joint or performing a repetitive motion for work, a sport or a hobby).

#### **Risk factors for sprains**

Anyone can experience a sprain, but some people are more likely to sprain a joint, including:

* Athletes.
* Workers with physically demanding jobs.
* People who have a hobby or activity that makes them perform repetitive motions.

Exercise habits that can increase your injury risk (especially sprains) include:

* Suddenly increasing your workout or activity intensity.
* Starting a new sport or activity without the proper equipment or training (working out with poor form or wearing the wrong kind of shoes, for example).
* Playing the same sport year-round with no offseason.

## **Diagnosis and Tests**

A healthcare provider will diagnose a sprain with a physical exam. Your provider will examine your injured joint. Tell them when you first noticed symptoms, especially if you know exactly what caused the injury.

Healthcare providers grade sprains based on their severity:

* Grade 1 sprain (mild): Very little or no tearing in your ligament.
* Grade 2 sprain (moderate): Your ligament is partially torn, but not all the way through.
* Grade 3 sprain (severe): Your ligament is completely torn.

You might need imaging tests to take pictures of your joint and the tissue around it. These tests can show damage inside your joint and help diagnose other injuries like bone fractures. Your provider might use:

* X-rays.
* Ultrasound.
* Magnetic resonance imaging (MRI).

## **Management and Treatment**

After you see a provider for a diagnosis, you should be able to treat sprain symptoms at home by following the R.I.C.E. method:

* **Rest**: Avoid the activity that caused your injury. Try not to use the injured part of your body while it heals.
* **Ice**: Apply a cold compress to your injury 15 minutes at a time, a few times a day. Wrap ice packs in a towel or thin cloth so they’re not directly touching your skin.
* **Compression**: Wrap an elastic bandage around your injured joint to help reduce swelling. Your provider can show you how to apply a compression wrap safely.
* **Elevation**: Keep your joint above the level of your heart as often as you can.

Over-the-counter NSAIDs (aspirin or ibuprofen) or acetaminophen can reduce pain and inflammation. Talk to your provider before taking over-the-counter (OTC) pain medication for longer than 10 days.

Other treatments you may need include:

* A brace or splint that supports your joint and holds it in place.
* A walking boot.
* Crutches.
* Physical therapy.

It’s rare to need surgery after a sprain. You may need surgery for a severe sprain or other injuries like a broken bone or dislocation. Some people need surgery if they’ve sprained the same joint multiple times.

You should start feeling better gradually after you start treating your symptoms. The most important part of healing after a sprain is to avoid using that joint or putting more stress on it. Ask your provider how much you can use your joint while you’re recovering.

## **Muscle Strains Treatment Drugs and Side Effects**

## 1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

* Examples: Ibuprofen (Advil, Motrin), Naproxen (Aleve), Diclofenac
* Use: Reduce pain, inflammation, and swelling, especially in the acute phase of muscle strain.
* Side Effects:
  + Gastrointestinal irritation, ulcers, bleeding
  + Kidney or liver dysfunction with prolonged use
  + Increased cardiovascular risk with long-term use
  + Possible allergic reactions
* Notes: Often recommended for the first few days after injury; topical NSAIDs (e.g., diclofenac gel) may reduce systemic side effects.

## 2. Acetaminophen (Paracetamol, Tylenol)

* Use: Pain relief without anti-inflammatory effect; alternative for those who cannot tolerate NSAIDs.
* Side Effects:
  + Generally well tolerated
  + Risk of liver toxicity with overdose or chronic high doses

## 3. Muscle Relaxants

* Examples: Cyclobenzaprine (Flexeril), Carisoprodol (Soma), Methocarbamol (Robaxin), Baclofen (Lioresal)
* Use: Prescribed for muscle spasms and stiffness associated with muscle strain.
* Side Effects:
  + Drowsiness, dizziness, dry mouth
  + Potential for dependence with long-term use
  + May impair coordination and alertness
* Notes: Should be used short-term and under medical supervision.

## 4. Topical Analgesics

* Examples: Methyl salicylate (Arthricare), Capsaicin, Lidocaine, Menthol-containing creams or gels
* Use: Provide localized pain relief with minimal systemic absorption.
* Side Effects:
  + Skin irritation or allergic reactions at application site

## **Muscle Strains: Procedures and Timelines**

## Diagnosis

* Physical Examination: Usually sufficient to diagnose muscle strain based on symptoms and clinical signs.
* Imaging: MRI may be used in moderate to severe cases to assess the extent and grade of the tear.

## Treatment Procedures and Timeline by Severity

| Grade | Description | Timeline and Treatment Procedures |
| --- | --- | --- |
| Grade I | Mild strain (<5% fibers torn) | Heals within a few weeks (typically 2–4 weeks). |
|  |  | Home treatment: RICE (Rest, Ice, Compression, Elevation), gradual return to activity. |
| Grade II | Moderate partial tear (5–50% fibers) | Healing may take several weeks to months. |
|  |  | Immobilization may be brief; physical therapy starts after initial rest to regain strength and function. |
| Grade III | Severe or complete tear | Recovery can take 4–6 months or longer, sometimes requires surgery. |
|  |  | Immobilization with cast/splint for up to 6 weeks; surgical repair if complete rupture; intensive rehabilitation post-immobilization. |

## Healing Phases and Rehabilitation

1. Inflammatory Phase (0–3 to 5 days):
   1. Goal: Minimize bleeding and swelling using RICE and brief immobilization (3–7 days).
   2. Avoid anti-inflammatory meds initially to not interfere with healing.
2. Proliferation Phase (2 days to ~3 weeks):
   1. Satellite cells regenerate muscle fibers; fibroblasts produce connective tissue.
   2. Begin gentle mobilization, isometric exercises within pain limits.
   3. Cardiovascular conditioning with low-impact activities.
3. Remodeling Phase (Weeks 3 to months):
   1. Progressive loading with eccentric and isotonic strengthening exercises.
   2. Proprioceptive and endurance training.
   3. Functional and sport-specific rehab before full return.

## **Outlook / Prognosis**

You should expect to make a full recovery. Sprains are usually temporary injuries, and shouldn’t have a long-term impact on your health or ability to stay active.

Spraining a joint can make you more likely to injure it again in the future. Ask your provider about your unique risk and what you can do to prevent future sprains.

Your sprain recovery time will depend on which joint is sprained and how severe it was. Most sprains take a few weeks to heal. More severe (grade 3) sprains can take a few months. Your healthcare provider will tell you what to expect.

## **Prevention**

There might not be any way to prevent a sprain, especially if you’re an athlete.

During sports or other physical activities:

* Wear the proper protective equipment.
* Don’t “play through the pain” if something hurts during or after physical activity.
* Give your body time to rest and recover after intense activity.
* Stretch and warm up before playing sports or working out.
* Cool down and stretch after physical activity.

Follow these general safety tips to reduce your risk of an injury:

* Make sure your home and workspace are free from clutter that could trip you or others.
* Always use the proper tools or equipment at home to reach things. Never stand on chairs, tables or countertops.
* Use your cane or walker if you have difficulty walking or have an increased risk of falls.

## **When should I see my healthcare provider?**

Visit a healthcare provider if you’ve experienced an injury and have sprain symptoms. Talk to your provider if you’ve started treating a sprain and your symptoms aren’t improving after a few days (or if they’re getting worse).

Go to the ER if you experience any of the following:

* Extreme pain.
* Swelling that’s getting worse.
* Discoloration.
* Numbness.

## **Differential Diagnoses**

1. Muscle Contusion (Bruise)
   1. Caused by direct trauma causing bleeding within the muscle.
   2. Presents with localized pain, swelling, and bruising similar to strains but usually with a clear history of impact.
2. Muscle Tear or Rupture
   1. Partial or complete tear of muscle fibers or tendon.
   2. Severe pain, swelling, loss of function, and sometimes a palpable gap.
   3. MRI or ultrasound may be needed for confirmation.
3. Tendon Injuries (Tendinopathy or Rupture)
   1. Tendon inflammation or tears can mimic muscle strain, especially near muscle insertions.
   2. Tendon ruptures may cause loss of muscle function.
4. Ligament Sprain
   1. Injury to ligaments connecting bones, often near joints.
   2. Pain, swelling, and instability differ from muscle strain.
5. Delayed Onset Muscle Soreness (DOMS)
   1. Diffuse muscle pain and stiffness after unaccustomed exercise, without swelling or loss of strength.
6. Myofascial Pain Syndrome
   1. Chronic muscle pain with trigger points causing referred pain.
7. Compartment Syndrome
   1. Severe pain, swelling, and neurological symptoms due to increased pressure in muscle compartments; a medical emergency.
8. Fracture or Avulsion Injury
   1. Bone fractures or tendon avulsions can cause localized pain and swelling.
   2. X-rays help exclude fractures.
9. Nerve Injury or Radiculopathy
   1. Nerve compression or injury causing pain, weakness, or sensory changes mimicking muscle strain.
10. Infection or Inflammatory Myopathies
    1. Rarely, infections (pyomyositis) or autoimmune muscle diseases cause muscle pain and swelling.

## **Muscle Strains Epidemiology**

## Incidence and Prevalence

Muscle strains constitute a substantial proportion of sports injuries, accounting for about 31% of all injuries in professional male football (soccer) players

On average, a professional football player sustains 0.6 muscle injuries per season, meaning a squad of 25 players can expect approximately 15 muscle injuries per season

Muscle strains cause about 27% of total injury-related absence in professional football teams.

The majority (92%) of muscle strains affect four major lower limb muscle groups: hamstrings (37%), adductors (23%), quadriceps (19%), and calf muscles (13%)

About 16% of muscle strains are reinjuries, which tend to cause longer absences than initial injuries

Injury severity distribution in professional football:

Minimal (1–3 days absence): ~13%

Mild (4–7 days): ~25%

Moderate (8–28 days): ~51%

Severe (>28 days): ~11%

Mean absence per muscle injury is approximately 14 to 17 days, varying by cohort and injury severity

Injury incidence is six times higher during match play compared to training (8.7 vs. 1.37 injuries per 1000 hours)

Muscle strain incidence increases with age, particularly for calf muscle injuries; hamstring and quadriceps strains do not show a clear age association

Most muscle injuries occur in non-contact situations (over 90%) such as sudden acceleration or deceleration

Muscle strains are also common in other sports and occupational settings, often resulting from overuse or acute overload

Sprains and strains, including muscle strains, are among the most common workplace injuries, with around 628,000 sprains occurring annually in the US

Approximately 25,000 laborers sprain an ankle daily, highlighting the high frequency of soft tissue injuries including muscle strains

## **Muscle Strain Genomic Data**

1. ACTN3 (Alpha-Actinin-3) – R577X (rs1815739)
   1. One of the most studied polymorphisms related to muscle function and injury.
   2. The R allele is associated with power and sprint performance; the X allele leads to deficiency of alpha-actinin-3 protein, potentially increasing susceptibility to muscle damage and slower recovery.
   3. Variants influence muscle fiber type composition and response to eccentric exercise.
2. AMPD1 (Adenosine Monophosphate Deaminase 1) – rs17602729
   1. Polymorphism linked to muscle metabolism and fatigue.
   2. The TT genotype is associated with metabolic myopathy, early fatigue, cramps, and increased injury risk, especially in soccer players.
3. ACE (Angiotensin-Converting Enzyme) – rs4646994
   1. Insertion/deletion polymorphism influences muscle efficiency and repair.
   2. Certain genotypes may predispose to injury or affect recovery.
4. CKM (Creatine Kinase Muscle) – rs8111989
   1. Variants affect muscle energy metabolism and susceptibility to injury.
5. MLCK (Myosin Light Chain Kinase) – rs2849757 and rs2700352
   1. Polymorphisms linked to muscle contraction regulation and injury risk.
6. COL1A1, COL5A1, MMP3
   1. Genes involved in collagen synthesis and extracellular matrix remodeling, influencing muscle and tendon structural integrity and injury susceptibility.
7. TNF (Tumor Necrosis Factor) – rs1800629 and IL6 (Interleukin 6) – rs1800795
   1. Inflammatory cytokine gene variants influencing muscle inflammation and repair after injury.
8. IGF2 (Insulin-like Growth Factor 2) – rs680
   1. Plays a role in muscle growth and regeneration.

### **sprains vs. strains**

Sprains and strains are similar injuries — the difference is what’s damaged.

Sprains happen when a ligament is torn or damaged, usually when one of your joints moves further than it should.

Muscle strains happen when one of your muscles is torn. People also sometimes call strains pulled muscles or muscle tears. Providers sometimes call tendon tears strains.

Sprains and strains are both common sports injuries. Visit a healthcare provider if you’re experiencing pain, swelling and can’t move a joint or muscle as well as you usually can.

## **Doctor-Patient Conversation on Muscle Sprain (De-Identified)**

## Doctor:

Hello! What brings you in today?

## Patient:

Hi doctor. I twisted my ankle while playing football, and it’s swollen and painful. I think I sprained a muscle there.

## Doctor:

Thanks for telling me. Just to clarify, a sprain is an injury to a ligament, which connects bones, while a strain is an injury to a muscle or tendon. From your description, it sounds like you may have a ligament sprain in your ankle.

## Patient:

Oh, I didn’t know that. What does that mean for my injury?

## Doctor:

A ligament sprain means the fibers of the ligament have been stretched or torn. The severity can range from mild stretching to a complete tear.

## Patient:

How do you know how bad it is?

## Doctor:

I’ll examine your ankle for swelling, bruising, tenderness, and stability. Sometimes we use imaging like an X-ray to rule out fractures or an MRI if the injury is severe.

## Patient:

What should I do now?

## Doctor:

For now, follow the R.I.C.E. protocol:

* Rest the ankle and avoid putting weight on it.
* Ice the area for 15-20 minutes every 2-3 hours to reduce swelling.
* Compression with an elastic bandage can help control swelling.
* Elevation of the ankle above heart level also reduces swelling.

## Patient:

How long will it take to heal?

## Doctor:

Mild sprains usually heal within 1-3 weeks. Moderate sprains may take 4-6 weeks, and severe sprains can take several months and might require physical therapy or sometimes surgery.

## Patient:

When can I start moving or playing again?

## Doctor:

Start gentle movement as pain allows after a few days, usually with guidance from a physiotherapist. Return to sports only when you regain strength, stability, and full range of motion to prevent reinjury.

## Patient:

What happens if I don’t treat it properly?

## Doctor:

Ignoring a sprain or returning to activity too soon can cause chronic instability, repeated injuries, or arthritis later on.

## Patient:

Thank you for explaining. I’ll follow your advice.

## Doctor:

You’re welcome. If your pain worsens or you notice numbness, severe swelling, or inability to move your foot, please come back immediately.

**References**

[Sprains: Types, Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/sprains)

<https://emedicine.medscape.com/article/95444-medication?form=fpf>

### **Frozen shoulder**

**Definition**

Frozen shoulder is a painful condition in which your shoulder movement becomes limited. Another name for frozen shoulders is adhesive capsulitis.

Frozen shoulder occurs when the strong connective tissue surrounding your shoulder joint (called the shoulder joint capsule) becomes thick, stiff and inflamed. The joint capsule contains the ligaments that attach the top of your upper arm bone (humeral head) to your shoulder socket (glenoid), firmly holding the joint in place. This is more commonly known as a ball-and-socket joint.

The condition is called “frozen” shoulder because the more pain you feel, the less likely you’ll use your shoulder. Lack of use causes your shoulder capsule to thicken and become tight, making your shoulder even more difficult to move — it’s “frozen” in its position.

## **Symptoms of frozen shoulder (adhesive capsulitis)**

Healthcare providers divide frozen shoulder symptoms into three stages:

* **The “freezing” stage:** In this stage, your shoulder becomes stiff and is painful to move. The pain slowly increases. It may worsen at night. Inability to move your shoulder increases. This stage lasts from six weeks to nine months.
* **The “frozen” stage:** In this stage, pain may lessen, but your shoulder remains stiff. This makes it more difficult to complete daily tasks and activities. This stage lasts for two to six months.
* **The “thawing” (recovery) stage:** In this stage, pain lessens, and your ability to move your shoulder slowly improves. Full or near full recovery occurs as typical strength and motion return. The stage lasts from six months to two years.

### **Cause of frozen shoulder (adhesive capsulitis)**

Researchers don’t know exactly why frozen shoulders develop. The condition occurs when inflammation causes your shoulder joint capsule to thicken and tighten. Thick bands of scar tissue called adhesions develop over time, and you have less synovial fluid to keep your shoulder joint lubricated. This makes it more difficult for your shoulder to move and rotate properly.

#### **Risk factor for frozen shoulders**

The following risk factors increase your likelihood of developing frozen shoulder:

* **Age:** Frozen shoulder most commonly affects adults between the ages of 40 and 60 years old.
* **Sex:** The condition affects females more often than males.
* **Recent shoulder injury:** Any shoulder injury or surgery that results in the need to keep your shoulder from moving (for example, by using a shoulder brace, sling, shoulder wrap, etc.) increases your risk of frozen shoulder. Examples include a rotator cuff tear and fractures of your shoulder blade, collarbone or upper arm.
* **Diabetes:** Between 10% and 20% of people with diabetes develop frozen shoulders.
* **Other health diseases and conditions:** This includes stroke, hypothyroidism (underactive thyroid gland), hyperthyroidism (overactive thyroid gland), Parkinson’s disease and heart disease. Stroke is a risk factor for frozen shoulders because movement of your arm and shoulder may be limited. Researchers aren’t sure why other diseases and conditions increase the risk of developing frozen shoulders.

## **Diagnosis and Tests**

To diagnose frozen shoulder (adhesive capsulitis), your healthcare provider will discuss your symptoms and review your medical history. They’ll also perform a physical exam of your arms and shoulders. They’ll:

* Move your shoulder in all directions to check your range of motion and if there’s pain with movement. This type of exam, in which your provider moves your arm, is called determining your “passive range of motion.”
* Watch you move your shoulder to see your “active range of motion.”
* Compare the two types of motion. People with frozen shoulders have a limited range of both active and passive motion.

Your provider will likely order shoulder X-rays to make sure the cause of your symptoms isn’t due to another problem with your shoulder, like arthritis. You usually don’t need advanced imaging tests like magnetic resonance imaging (MRI) and ultrasound to diagnose frozen shoulders. But your provider may request them to look for other problems, like a rotator cuff tear.

## **Management and Treatment**

Frozen shoulder treatment usually involves pain relief methods until the initial phase passes. You may need therapy or surgery to regain motion if it doesn’t return on its own.

Some simple adhesive capsulitis treatments include:

* **Hot and cold compresses.** These help reduce pain and swelling.
* **Medicines that reduce pain and swelling.** These include nonsteroidal anti-inflammatory drugs (NSAIDs), like ibuprofen (Advil®, Motrin®) and acetaminophen (Tylenol®). Your healthcare provider may prescribe other painkiller/anti-inflammatory drugs. You can manage more severe pain and swelling with steroid injections. Your provider will inject a corticosteroid, like cortisone, directly into your shoulder joint.
* **Physical therapy.** A physical therapist can teach you stretching and range-of-motion exercises.
* **Home exercise program.** Your healthcare provider can show you exercises you can do at home.
* **Transcutaneous electrical nerve stimulation (TENS).** Use of a small, battery-operated device that reduces pain by blocking nerve impulses.

If these noninvasive treatments haven’t relieved your pain and shoulder stiffness after about a year, your provider may recommend other procedures. These include:

* **Manipulation under anesthesia:** During this surgery, you’ll be put to sleep and your provider will force movement of your shoulder. This will cause your joint capsule to stretch or tear to loosen the tightness. This will lead to an increase in your range of motion.
* **Shoulder arthroscopy:** Your provider will cut through the tight parts of your joint capsule (capsular release). They’ll insert small, pencil-size instruments through small cuts (incisions) around your shoulder.

Providers often use these two procedures together to get better results.

## **Treatment Drugs and Their Side Effects**

## 1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

* Common Drugs: Ibuprofen (Advil, Motrin), Naproxen (Aleve), Diclofenac
* Use: Reduce pain and inflammation in the shoulder joint. Often first-line treatment for frozen shoulder symptoms.
* Side Effects:
  + Gastrointestinal irritation, ulcers, bleeding
  + Kidney or liver dysfunction with prolonged use
  + Increased cardiovascular risk with long-term use
  + Allergic reactions in some patients
* Notes: Available over-the-counter or by prescription; topical forms may reduce systemic side effects

## 2. Corticosteroid Injections

* Use: Injected directly into the shoulder joint, corticosteroids reduce inflammation and improve range of motion, especially effective in the early (freezing) phase of frozen shoulder. Often combined with a local anesthetic like lidocaine for immediate pain relief.
* Procedure: Performed under local anesthesia, sometimes with imaging guidance; takes less than 30 minutes.
* Duration of Relief: Weeks to months.
* Side Effects:
  + Temporary pain or tenderness at injection site
  + Risk of tendon weakening or rupture with repeated injections
  + Possible infection (rare)
  + Elevated blood sugar levels, especially in diabetics
  + Facial flushing, headache, insomnia (transient systemic effects)
* Notes: Usually limited to a few injections to avoid complications

## 3. Acetaminophen (Paracetamol)

* Use: Pain relief without anti-inflammatory effects; often used when NSAIDs are contraindicated.
* Side Effects:
  + Generally well tolerated
  + Risk of liver toxicity with overdose or chronic high doses

## 4. Other Pain Relievers

* Occasional Use: Narcotics or stronger pain medications may be prescribed for severe pain, especially post-therapy or at night.
* Side Effects: Risk of dependence, sedation, constipation, and other opioid-related adverse effects

## **Procedures and Timelines**

## Frozen Shoulder Stages

Frozen shoulder (adhesive capsulitis) typically progresses through three clinical stages over 1 to 3 years:

| Stage | Duration | Characteristics |
| --- | --- | --- |
| Freezing | 6 weeks to 9 months | Increasing shoulder pain and progressive loss of motion; pain is often severe. |
| Frozen | 4 to 12 months (can last up to 9 months) | Pain may lessen but stiffness and limited range of motion persist, making daily activities difficult. |
| Thawing | 6 months to 2 years or more | Gradual improvement in shoulder movement and function; pain continues to fade. |

## Treatment Procedures by Stage

## 1. Conservative Treatments (All Stages, Especially Early)

* Pain Management: NSAIDs, acetaminophen, and corticosteroid injections to reduce pain and inflammation.
* Physical Therapy: Gentle stretching and strengthening exercises tailored to each stage to restore motion and function. Early physical therapy after shoulder injury may reduce risk.
* Home Exercises: External rotation stretches, forward flexion, and crossover arm stretches to improve flexibility.

## 2. Hydrodilatation (If Conservative Treatment Fails)

* A procedure where sterile fluid is injected into the shoulder joint capsule under imaging guidance to stretch and expand the capsule, improving motion.
* Usually performed by radiologists or orthopedic specialists.

## 3. Manipulation Under Anesthesia (MUA)

* Performed during the frozen stage if stiffness persists despite conservative treatment.
* Under general anesthesia, the shoulder is forcibly moved to break adhesions and stretch the capsule.
* Often combined with physical therapy post-procedure to maintain gains.

## 4. Shoulder Arthroscopy (Capsular Release)

* Minimally invasive surgery to cut tight portions of the joint capsule.
* Usually combined with MUA for better outcomes.
* Followed by intensive physical therapy for 6 weeks to 3 months.
* Surgery is reserved for refractory cases after prolonged conservative management.

## Recovery Timelines

| Procedure/Treatment | Expected Recovery Time | Notes |
| --- | --- | --- |
| Conservative Management | Up to 1–3 years for full or near-full recovery | Most patients improve without surgery |
| Corticosteroid Injection | Weeks to months of symptom relief | Often combined with physical therapy |
| Hydrodilatation | Weeks to months | May speed up recovery in resistant cases |
| Manipulation Under Anesthesia | 6 weeks to 3 months | Requires commitment to post-procedure rehab |
| Arthroscopic Capsular Release | 6 weeks to 3 months | Good long-term outcomes; diabetic patients may have residual stiffness |

## **Capsulitis (Frozen Shoulder) Staging**

## 1. Freezing (Painful) Stage

* Duration: Approximately 6 weeks to 9 months
* Characteristics:
  + Gradual onset of shoulder pain, often severe and worsening over time
  + Pain at rest and with movement, especially at the extremes of motion
  + Night pain frequently disrupts sleep
  + Progressive loss of active and passive shoulder range of motion
  + Capsular pattern of restriction: external rotation most limited, followed by abduction and internal rotation
* Clinical Note: Pain predominates in this stage; stiffness begins to develop.

## 2. Frozen (Adhesive/Stiffening) Stage

* Duration: About 4 to 12 months (can last up to 9 months or more)
* Characteristics:
  + Pain may decrease or plateau but stiffness and limited range of motion become more prominent
  + Significant restriction of shoulder movement in a capsular pattern
  + Difficulty performing daily activities due to stiffness
  + Pain mainly at end ranges of motion
* Clinical Note: Stiffness predominates; pain is less intense than in freezing stage.

## 3. Thawing (Resolution) Stage

* Duration: 6 months to 2 years or more
* Characteristics:
  + Gradual improvement in shoulder mobility and function
  + Pain continues to decrease or resolves completely
  + Progressive restoration of range of motion
  + Some patients may not regain full normal motion
* Clinical Note: Recovery phase; functional improvements occur slowly.

## **Differential Diagnosis**

1. Osteoarthritis of the Glenohumeral Joint
   1. Degenerative joint disease causing pain and limited motion.
   2. Usually presents with joint space narrowing on X-ray and may have crepitus.
2. Calcific Tendinitis / Acute Calcific Bursitis
   1. Calcium deposits in rotator cuff tendons causing acute pain and inflammation.
   2. Often identified by characteristic calcifications on X-ray.
3. Rotator Cuff Pathologies
   1. Tendinopathy, partial or full-thickness tears causing pain and weakness.
   2. Active movement is painful, but passive range of motion often preserved, unlike frozen shoulder where both are limited.
4. Parsonage-Turner Syndrome (Brachial Neuritis)
   1. Acute onset of severe shoulder pain followed by muscle weakness and atrophy.
   2. Neurological symptoms help differentiate.
5. Locked Posterior Shoulder Dislocation
   1. History of trauma with shoulder locked in internal rotation.
   2. Requires imaging for diagnosis.
6. Proximal Humeral Fracture
   1. Trauma history with localized pain, swelling, and deformity.
   2. Confirmed by X-ray.
7. Acromioclavicular (AC) Joint Arthropathy
   1. Pain localized to AC joint, worsened by cross-body adduction.
8. Biceps Tendinopathy or Tendon Rupture
   1. Anterior shoulder pain with tenderness over biceps tendon.
9. Subacromial/Subdeltoid Bursitis
   1. Inflammation causes pain with overhead activities.
10. Cervical Radiculopathy
    1. Neck pain radiating to the shoulder with neurological signs.
11. Autoimmune or Systemic Diseases
    1. Rheumatoid arthritis, systemic lupus erythematosus causing shoulder pain and stiffness.
12. Malignancy
    1. Rarely, tumors around the shoulder can mimic symptoms.

## **Epidemiology**

Frozen shoulder syndrome (FSS) usually affects patients aged 40-60 years. The incidence of FSS is not precisely known; however, it is estimated that 2% to 5% of the general populationdevelops the disease over their lifetime. Women tend to be affected more often than men, and there is no predilection for race. In general, bilateral shoulder involvement is rarely simultaneous and instead occurs sequentially.

Diabetes mellitus is an independent risk factor for FSS. A meta-analysis by Zreik concluded that diabetic patients are 5 times more likely to develop adhesive capsulitis compared with non-diabetic controls. They reported a 13.4% overall mean prevalence of adhesive capsulitis in patients with diabetes, and a 30% mean prevalence of diabetes in a population with adhesive capsulitis. Zreik found no significant difference in the prevalence of the disorder with type 1 versus type 2 diabetes, or between patients on insulin therapy and those on oral hypoglycemic agents.

Thyroid disease has also been linked to FSS. A meta-analysis by Chuang et al found significantly higher rates of hypothyroidism (odds ratio [OR] = 1.92, *P* = 0.02) and subclinical hypothyroidism (OR = 2.56, *P*< 0.00001) in patients with FSS than in those without FSS.A nationwide longitudinal population-based study from Taiwan concluded that hyperthyroidism is an independent risk factor for FSS, with an adjusted hazard ratio of 1.22.

**Outlook / Prognosis**

Simple treatments, like the use of pain relievers and shoulder exercises, in combination with a cortisone injection, are often enough to restore motion and function within a year or less. Even left completely untreated, range of motion and use of your shoulder continue to get better on their own, but often over a slower course of time. Full or nearly full recovery is seen after about two years.

## **Prevention**

You can reduce your risk of frozen shoulder if you start physical therapy shortly after any shoulder injury in which shoulder movement is painful or difficult. Your orthopedic surgeon or physical therapist can develop an exercise program to meet your specific needs.

## **Genomic Data**

1. WNT7B Gene
   1. The strongest and most consistently replicated genetic association with frozen shoulder involves variants near the WNT7B gene.
   2. WNT7B is implicated in tissue fibrosis and repair processes; it is highly expressed in the anterior capsule tissue of patients undergoing surgery for frozen shoulder.
   3. Variants at this locus confer approximately a six-fold increased risk of developing frozen shoulder, a stronger association than many known clinical risk factors.
2. Other Genetic Loci
   1. Weaker but notable associations have been found near the POU1F1 and MAU2 genes.
   2. These loci may influence cellular and developmental pathways contributing to capsular fibrosis and stiffness.
3. Heritability and Family History
   1. Studies show a heritability estimate of about 42%, with first-degree relatives of frozen shoulder patients having a 4-fold increased risk compared to controls.
   2. Family and twin studies support a substantial genetic predisposition.
4. Human Leukocyte Antigen (HLA)-B27
   1. Some immunological studies suggest higher prevalence of HLA-B27 positivity in frozen shoulder patients, indicating possible immune-mediated components.
5. Gene Expression Profiles
   1. Frozen shoulder synovial tissues show altered expression of genes involved in fibrosis, inflammation, chondrogenesis (e.g., MMP2, IGF1, SOX9, COL2A1), and neural growth factors (NGF, NGFR), suggesting complex molecular pathways in disease pathogenesis.

## **Questions and Answers Set**

## 1. What is frozen shoulder (capsulitis)?

Frozen shoulder, also known as adhesive capsulitis, is a condition where the shoulder joint becomes painful and stiff, leading to a gradual loss of both active and passive range of motion

## 2. What are the symptoms of frozen shoulders?

Symptoms include progressive shoulder pain, especially at night, and a gradual decrease in shoulder movement, particularly loss of external rotation. Patients often have difficulty with overhead activities, dressing, grooming, and fastening items behind the back

## 3. How long does frozen shoulder last?

Frozen shoulder is generally self-limiting but can last from 6 months up to 2 years or more, with some sources reporting symptom resolution anywhere from 6 months to 11 years. Some patients may never fully recover

## 4. What are the stages of frozen shoulder?

There are three overlapping stages:

* Freezing stage: Increasing pain and stiffness (6 weeks to 9 months)
* Frozen stage: Pain decreases but stiffness remains (4 to 12 months)
* Thawing stage: Gradual improvement in motion and reduction in stiffness (6 months to 2 years or more)

## 5. How is frozen shoulder diagnosed?

Diagnosis is mainly clinical, based on history and physical exam showing limited active and passive shoulder motion, especially external rotation. Imaging (X-ray, ultrasound, MRI) is rarely needed but may be used to exclude other conditions

## 6. What treatments are available for frozen shoulder?

* Pain relief: NSAIDs, acetaminophen, corticosteroid injections
* Physiotherapy: Range-of-motion and stretching exercises, manual therapy
* Procedures: Hydrodilatation, manipulation under anesthesia, arthroscopic capsular release for refractory cases
* Most patients improve with conservative treatment over time

## 7. What exercises help frozen shoulder?

Common exercises include:

* Pendulum swings
* Wall slides
* External rotation stretches with a stick  
  These exercises should be gentle and pain-free, performed regularly to improve mobility

## 8. When should I see a specialist?

If pain and stiffness persist despite initial treatments like steroid injections and physiotherapy, or if symptoms severely limit daily activities, referral to an orthopedic shoulder specialist is advised

## 9. Can frozen shoulder come back?

Recurrence is rare. Most patients do not experience a second episode of frozen shoulder in the same shoulder

## 10. Is frozen shoulder related to other medical conditions?

Yes, frozen shoulder is more common in people with diabetes, thyroid disorders, and after shoulder injuries or surgeries

## **Doctor-Patient Conversation on Frozen Shoulder (Adhesive Capsulitis) (De-Identified)**

## Doctor:

Good morning! What brings you in today?

## Patient:

Good morning, doctor. My shoulder has been hurting for a while, and I can’t move it like I used to. It feels stiff, and the pain sometimes wakes me up at night.

## Doctor:

I’m sorry to hear that. How long have you been experiencing this pain and stiffness?

## Patient:

I’m not exactly sure when it started, but it’s been getting worse over the past few months.

## Doctor:

Have you noticed if the pain is constant or does it come and go? And how would you describe the pain—sharp, dull, or something else?

## Patient:

The pain comes and goes, but it’s mostly a dull ache. Sometimes it feels sharp when I try to move my arm too much.

## Doctor:

Do you have trouble with any specific activities, like reaching overhead, dressing, or putting on a seatbelt?

## Patient:

Yes, it’s hard to reach behind my back or put on my coat. Even brushing my hair is difficult.

## Doctor:

Based on your symptoms, it sounds like you might have a condition called frozen shoulder, or adhesive capsulitis. This happens when the capsule around your shoulder joint becomes thickened and tight, limiting movement and causing pain.

## Patient:

What causes frozen shoulder?

## Doctor:

It can develop after an injury, surgery, or sometimes without a clear cause. It’s more common in people with diabetes or thyroid problems. The condition usually progresses through phases: painful freezing, stiff frozen, and then thawing where motion gradually improves.

## Patient:

What can be done to treat it?

## Doctor:

Treatment focuses on relieving pain and restoring movement. This includes:

* Physical therapy and gentle stretching exercises
* Pain relief with medications like NSAIDs
* In some cases, corticosteroid injections to reduce inflammation
* A procedure called hydrodilatation, where fluid is injected into the joint to stretch the capsule
* Surgery is rarely needed but considered if other treatments fail

## Patient:

How long will it take to get better?

## Doctor:

Frozen shoulder can last from several months up to a couple of years. Many people improve with treatment, but some may have lingering stiffness.

## Patient:

Is there anything I should avoid?

## Doctor:

Avoid forcing painful movements; gentle, consistent exercises are best. Rest during painful flare-ups but try to keep the shoulder moving within your comfort zone.

## Patient:

What if I don’t get treatment?

## Doctor:

Without treatment, the pain and stiffness may persist longer and impact your daily activities. Early intervention can help speed recovery.

## Patient:

Thank you, doctor. I’d like to start treatment and learn exercises I can do at home.

## Doctor:

That’s a good plan. I’ll refer you to a physical therapist and we can discuss pain management options. We’ll monitor your progress and adjust treatment as needed.

REFERENCES

[Frozen Shoulder (Adhesive Capsulitis): Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/frozen-shoulder-adhesive-capsulitis)

[Frozen shoulder - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/frozen-shoulder/symptoms-causes/syc-20372684)

<https://www.aafp.org/pubs/afp/issues/2011/0215/p417.html>

<https://emedicine.medscape.com/article/1261598-overview#a7>

<https://www.raleighsurgerycenter.com/orthopedic-surgery-center-nc/frozen-shoulder-surgery-6-important-answers-to-your-question/>

<https://wexnermedical.osu.edu/orthopedics/shoulder/frozen-shoulder>

### **CHRONIC LOW BACK PAIN**

**Definition and description**

Chronic low back pain (CLBP) is defined as lower back pain lasting for longer than 12 weeks or 3 months, even after an initial injury or underlying cause of acute low back pain has been treated.

Lower back pain affects the lumbar region of your spine or back. It can result from many different injuries and conditions. Most often, the cause is an injury to muscles or tendons in your back.

Nearly everyone experiences lower back pain at some point in their lives. The pain can range from mild to severe. For most, it’s temporary. But long-lasting (chronic) lower back pain is also common — up to 23% of adults worldwide have chronic lower back pain. In extreme cases, lower back pain can make it difficult or impossible to walk, sleep, work or do everyday activities.

Given how common it is, it may be hard to tell if you should be worried about your lower back pain. Trust your gut and reach out to a healthcare provider if something feels off — or if the pain keeps you from going about your usual activities.

## **Symptoms and Causes**

Lower back pain affects the lumbar region of your spine or back. It can result from many different injuries and conditions.

### **Symptoms of lower back pain**

Lower back pain can involve a wide spectrum of symptoms. Lower back pain may:

* Come on suddenly or appear gradually.
* Happen after a specific event, like bending over to pick something up. You may hear a “pop” when it happens.
* Have an unknown trigger.
* Feel sharp or dull and achy.
* Come and go or be persistent.
* Radiate down to your buttock or down the back of your leg (sciatica).
* Feel worse in certain positions (like bending over or crouching down) and get better when lying down.

Other symptoms of lower back pain can include:

* **Stiffness**: It may be tough to move or straighten your back. Getting up from a seated position may take a while, and you might feel like you need to walk or stretch to loosen up. You may notice a decreased range of motion.
* **Posture problems**: Many people with back pain find it hard to stand up straight. You may stand “crooked” or bent, with your torso off to the side rather than aligned with your spine. Your lower back may look flat instead of curved.
* **Muscle spasms**: After a strain, muscles in your lower back can spasm or contract uncontrollably. Muscle spasms can cause extreme pain and make it difficult or impossible to stand, walk or move.

If you have severe pain and/or lower back pain that keeps you from doing daily activities, reach out to a healthcare provider.

### **What causes low back pain?**

Many injuries and conditions can cause lower back pain. This kind of pain is so common because your lumbar (low back) vertebrae (bones) do a lot to support your body, including:

* Providing stability for the rest of your spine.
* Serving as a point of attachment for many muscles and ligaments that allow you to walk, run, sit, lift and move your body in all directions.
* Supporting most of your body’s weight.
* Functioning as the center of your body’s balance.

With all these important functions, any issue with the structures in your lower back can lead to pain. Specific causes of lower back pain include:

* **Strains and sprains**: Strains and sprains are the most common causes of back pain. You can injure muscles, tendons or ligaments by lifting something too heavy or not lifting safely. Some people strain their back by sneezing, coughing, twisting or bending over.
* **Spinal fractures**: The bones in your lumbar spine can break during an accident, like a car crash or a fall. Certain conditions (like osteoporosis) increase your risk of fractures. Spondylolysis is a specific type of stress fracture or crack in spinal bones. It’s common in young athletes.
* **Disk problems**: Spinal disks have the important job of providing a cushion between your vertebrae. Disks can bulge from their position in your spine and press on a [nerve](https://my.clevelandclinic.org/health/body/22584-nerves) (pinched nerve). They can also tear (herniated disk). With age, disks can get flatter and offer less protection (degenerative disk disease).
* **Structural issues**: A condition called spinal stenosis happens when your spinal column is too narrow for your spinal cord. Something pinching your spinal cord (like vertebral bone spurs) can cause severe sciatic nerve pain and lower back pain. Lumbar scoliosis can also lead to pain, stiffness and difficulty moving. Another structural issue that can cause low back pain is spondylolisthesis. It happens when a vertebra slips out of place, resting on the bone below it.
* **Arthritis**: Osteoarthritis is the most common type of arthritis to cause lower back pain. Ankylosing spondylitis, another type of arthritis, causes lower back pain, inflammation and stiffness in your spine.
* **Disease**: Spine tumors, infections and several types of cancer can cause back pain. Other conditions can cause back pain, too, like kidney stones and an abdominal aortic aneurysm. Chronic inflammatory conditions, like fibromyalgia, can also result in lower back pain.

#### **Other temporary causes of low back pain**

Other common temporary causes of lower back pain include:

* **Menstrual cramps**: Some menstruating people experience lower back pain or lower back cramps during their period.
* **Pregnancy**: Pregnancy can cause lower back pain, especially in the second and third trimesters. This is often due to hormonal changes, increasing weight from your uterus and fetus, and a changing center of gravity.
* **Back labor**: This is pain and discomfort in your lower back that happens during labor. It often occurs when the fetus is facing your belly instead of your back

**Risk factors for low back pain**

Some people are more likely to have lower back pain than others. Risk factors for lower back pain include:

* **Age**: People over 30 are more likely to experience back pain. Vertebral disks wear away with age. As the disks weaken and wear down, pain and stiffness can result.
* **Weight**: People who have a body mass index (BMI) greater than 25 (have overweight or obesity) are more likely to have back pain. Excess weight puts pressure on joints and disks. Increasing weight in pregnancy can also put pressure on your lower back.
* **Poor core strength**: Weakened abdominal muscles can’t properly support your spine, which can lead to back strains and sprains.
* **Overall health**: People who smoke, drink excess alcohol and/or get limited physical activity have a higher risk of back pain.
* **Occupation and hobbies**: Jobs and activities that require heavy lifting or frequent bending can increase your risk of a back injury. Lower back pain is also very common in athletes.
* **Mental health conditions**: Studies show there’s a connection between depression and back pain. But it’s difficult to tell for sure if depression can cause back pain.

## **Common Causes of Chronic Back Pain**

Chronic back pain is usually age-related, but it can also result from an injury. The most common causes include:

Arthritis of the spine — the gradual thinning of the cartilage inside the spine

Spinal stenosis — narrowing of the spinal canal that may lead to nerve pain

Disk problems, such as a herniated or bulging disk

Myofascial pain syndrome — muscle pain and tenderness without clear cause

In some cases, it is difficult to pinpoint the cause of chronic back pain.

“If your doctor has explored all diagnostic and treatment options they are comfortable with, consider seeking a second opinion from a back pain specialist,” Van recommends.

It is important to understand the source of your pain as much as possible, and to consider every available, reasonable option. People with back pain should not feel rushed into settling for an invasive, irreversible surgical procedure. Surgery can be helpful for many people, but it is usually considered a last resort after more conservative options have been exhausted. Surgery can correct structural abnormalities contributing to back pain, but it does not guarantee pain relief, and it may even worsen the pain, Van warns. If the source of the pain is not known or can’t be treated, the best strategy is to collaborate with your doctor on a pain management plan that reduces the severity and frequency of flare-ups and focuses on goals for function and quality of life.

## **Diagnosis and Tests**

Your healthcare provider will ask about your symptoms and medical history and do a physical exam. Your provider may recommend a variety of tests to check your spine for injuries and assess your health in other ways. Tests may include:

* **Spine X-ray**: This test uses radiation to produce images of your bones.
* **MRI**: This test uses a magnet and radio waves to create pictures of your bones, muscles, tendons and other soft tissues.
* **CT scan**: This test uses X-rays and a computer to create 3D images of your bones and soft tissues.
* **Electromyography (EMG)**: This test assesses the function of your nerves and muscles. It checks for neuropathy (nerve damage), which can cause pain, tingling and [numbness](https://my.clevelandclinic.org/health/symptoms/21015-numbness).
* **Blood tests or urine tests**: Blood tests can detect genetic markers for some conditions that cause back pain (like ankylosing spondylitis). Urine tests check for kidney stones, which cause pain in your flank (the sides of your lower back).

Because there are so many possible causes of low back pain, it may take time to find the correct diagnosis.

## **Management and Treatment**

Treatment for chronic low back pain is grouped into three wide categories: monotherapies, multidisciplinary therapy, and reductionism.

* Monotherapies: do not work or have limited effectiveness (eg, analgesics, non-steroidal anti-inflammatory drugs, muscle relaxants, antidepressants, physiotherapy, manipulative therapy and surgery).
* Multidisciplinary therapy based on intensive exercises improves physical function and has modest effects on CLPB.
* The reductionist approach, meaning the pursuit of a pathoanatomical diagnosis with the view to target-specific treatment, should be implemented when a specific diagnosis is essential. Searching a pathoanatomical diagnosis has been criticized on the grounds that it ignores the psychosocial aspects of chronic pain. However, advocates of reductionism have persisted, as monotherapies and multidisciplinary therapy to date, have not provided a good solution to chronic low back pain.

Imaging: Conventional investigations often do not reveal the cause of pain however joint blocks and discography can identify zygapophysial joint pain (in 15%–40%), sacroiliac joint pain (in about 20%) and internal disc disruption (in over 40%). Zygapophysial joint pain can be relieved by radiofrequency neurotomy; techniques are emerging for treating sacroiliac joint pain and internal disc disruption.

**Multidisciplinary Approach**

In patients who have already failed a course of conservative treatment, multidisciplinary rehabilitation programmes result in better outcomes with respect to long term pain and disability compared with usual care or physical treatments. Patients in these programmes also have increased odds of being at work compared with patients receiving physical treatment.

### **What are the treatments for lower back pain?**

Many cases of mild to moderate lower back pain get better with rest, ice and over-the-counter (OTC) pain relievers. After a few days of rest, you should be able to get back to your normal activities. Staying active increases blood flow to the area and helps you heal.

If your back pain is severe and/or happens after a traumatic accident, like a fall, you should seek medical treatment as soon as possible.

Other treatments for lower back pain depend on the underlying cause, severity and how long you’ve had pain. They may include:

* **Medications**: Your healthcare provider may recommend nonsteroidal anti-inflammatory drugs (NSAIDs) or prescription medications to relieve pain. They may also prescribe [muscle relaxers](https://my.clevelandclinic.org/health/treatments/24686-muscle-relaxers) in certain situations to relieve back spasms.
* **Physical therapy (PT)**: PT can strengthen your muscles so they can better support your spine. PT also improves flexibility and helps you avoid another injury. PT can also help with posture, alignment and body mechanics to reduce back pain.
* **Hands-on manipulation**: Several “hands-on” treatments can relax tight muscles, reduce pain and improve posture and alignment. Depending on the cause of the pain, you may need osteopathic manipulation or chiropractic adjustments. Massage therapy can also help with back pain relief and restore function.
* **Injections**: Your provider may recommend lumbar epidural steroid injections to help manage chronic lower back pain.
* **Surgery**: Some lower back injuries and conditions require surgical repair. There are several types of surgery for low back pain, including many minimally invasive techniques.

It may take time to find the best treatment for you, especially if you have chronic lower back pain. Your provider will be by your side throughout the process.

## **Nonsurgical Treatments for Chronic Back Pain**

### **Physical Therapy and Home Exercise Program**

Exercise is the foundation of chronic back pain treatment. It’s one of the first treatments you should try, under the guidance of your physician and spine physical therapist. However, one set of exercises does not work for everyone, says Van. Prescribed exercises can and should be tailored to your specific symptoms, condition and comfort level. Maintaining your exercise routine regularly at home is even more important than the work you do during the physical therapy — a consistent regimen is the key to maintaining the spine’s strength and stability.

Physical therapy for chronic back pain may include:

Core strengthening

Stretching and flexibility exercises

Retraining posture

Testing the limits of pain tolerance

Aerobic exercises at a comfortable pace

### **Mindfulness and Meditation**

Chronic back pain is both physically and emotionally straining. To manage the frustration, irritability, depression and other psychological aspects of dealing with chronic pain, you may get referred to a rehabilitation psychologist. This specialist may recommend meditation, yoga, tai chi and other cognitive and relaxation strategies to boost your conscious control over your nervous system and its response to activity.

### **Diet Change**

Some diets are highly inflammatory, especially those high in trans fats, refined sugars and processed foods. Consult with your doctor to see if your diet could be contributing to your chronic back pain and how you could change it. Maintaining a healthy weight could also help lessen back pain by reducing pressure on your spine. Referral to a nutrition specialist is the best way to get personalized advice for strategies to access more balanced foods and to develop eating habits that support your health goals.

### **Lifestyle Modifications**

There are many ways to adapt and adjust your behavior and activity that can significantly improve chronic back pain before even considering medications or procedures.

“Listen to your body and learn to pace yourself,” suggests Van. Take breaks when doing strenuous chores, and make several trips or ask for help when carrying heavy or multiple objects such as groceries. Take note of the activities that worsen your pain and avoid them, if possible, while engaging more with activities you find comfortable and enjoyable. Not only could this help your back feel better, but it may also prevent the underlying condition from advancing. It’s also important to consider minimizing harmful habits like smoking, which is proven to heighten pain and delay healing. Focus on one realistic goal that you can achieve comfortably and consistently before addressing another lifestyle change.

### **Injection-based Treatments**

Trigger point injections, epidural steroid injections, nerve blocks, nerve ablations and other types of injection-based procedures are available for chronic back pain. These procedures are considered when the source of the pain is known, and they can sometimes help rule out certain causes if the treatment does not work. Injections may stop or lessen pain for a while, but they are not intended as long-term solutions and shouldn’t be used in isolation. The goal of injection-based treatments is to improve pain control and maximize your participation in regular gentle activity such as physical therapy and home exercises.

### **Alternative Treatments**

Acupuncture, massage, biofeedback therapy, laser therapy, electrical nerve stimulation and other nonsurgical spine treatments can make a difference for chronic back pain. Overall, the potential benefits of these strategies far outweigh their potential risks, so they are worth exploring. Talk to your spine specialist about alternative treatments that could help you.

### **Pharmacologic Treatments**

All kinds of medicines (topical, oral, injectable) are used to help manage chronic back pain, including anti-inflammatories, muscle relaxants, nerve pain medications and even antidepressants.However, any medication can have unwanted side effects. Work with your doctor to explore medication strategies that directly address the cause of your pain (if it is known). Find the lowest effective dose to minimize side effects, and use medications only for as long as they are helpful and well-tolerated.

“Opioid medications are not recommended as a first-line strategy for chronic back pain,” Van says. “They are most helpful in the short term for acute pain, like after a traumatic accident or surgery, because they act to shut down pain signaling temporarily without addressing a root cause of pain, like inflammation. Past the expected healing period, opioids should be phased out and nonopioid medications should be maximized to achieve pain control long term. Prolonged use of opioids is so stigmatized because it inevitably leads to medication tolerance, escalating to higher and riskier doses, physical dependence and habit formation.”

Opioids should be prescribed only after first-line and second-line pain medications have been tried without providing relief. If you find yourself relying on opioids to get through the day and you have not been offered many alternatives, it may be time to seek a second opinion.

## **Chronic Low Back Pain Treatment: Drug Information and Side Effects**

## 1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

* Examples: Ibuprofen (Advil, Motrin), Naproxen (Aleve), Diclofenac
* Use: First-line treatment to reduce pain and inflammation.
* Common Side Effects:
  + Gastrointestinal irritation, ulcers, bleeding
  + Kidney or liver dysfunction with prolonged use
  + Dizziness, headache, and possible cardiovascular risks
* Notes: Should be taken as directed; long-term use requires monitoring.

## 2. Acetaminophen (Paracetamol)

* Use: Pain relief without anti-inflammatory effects; alternative if NSAIDs contraindicated.
* Side Effects:
  + Generally well tolerated
  + Risk of liver toxicity with overdose or chronic high doses.

## 3. Muscle Relaxants

* Examples: Cyclobenzaprine (Flexeril), Metaxalone (Skelaxin), Tizanidine (Zanaflex)
* Use: Reduce muscle spasms associated with low back pain.
* Side Effects:
  + Drowsiness, dizziness, dry mouth
  + Fatigue and possible impairment of coordination
* Notes: Usually prescribed for short-term use due to sedation risks.

## 4. Antidepressants

* Examples: Amitriptyline, Nortriptyline, Duloxetine
* Use: Particularly helpful for chronic low back pain with neuropathic features or depression.
* Side Effects:
  + Dry mouth, constipation, blurred vision
  + Weight gain, sleepiness, urinary problems
  + Rarely heart and lung issues
* Notes: Benefits may take several weeks to manifest.

## 5. Anticonvulsants (Neuropathic Pain Agents)

* Examples: Gabapentin, Pregabalin, Carbamazepine
* Use: For nerve-related pain or radiculopathy associated with chronic low back pain.
* Side Effects:
  + Drowsiness, dizziness, weight changes
  + Confusion, depression, headaches
* Notes: Should be used under medical supervision.

## 6. Opioids

* Examples: Codeine, Oxycodone, Morphine, Hydrocodone, Tramadol
* Use: Reserved for short-term use in severe pain unresponsive to other treatments.
* Side Effects:
  + Nausea, constipation, drowsiness, dizziness
  + Risk of dependence, tolerance, hormonal changes
  + Depression, sexual dysfunction with long-term use
* Notes: Use with caution and under close medical supervision.

## 7. Topical Analgesics

* Examples: Lidocaine patches, Capsaicin creams, NSAID gels
* Use: Localized pain relief with minimal systemic absorption.
* Side Effects:
  + Skin irritation or allergic reactions at application site.

## **Chronic Low Back Pain: Differential Diagnosis**

## 1. Non-Specific Low Back Pain

* Most common category (~90% of cases)
* No identifiable specific pathology; often related to muscular strain, ligamentous injury, or degenerative changes without nerve involvement.

## 2. Mechanical Causes

* Lumbar muscular strain/sprain
* Degenerative Disc Disease
* Facet Joint Arthropathy
* Herniated Nucleus Pulposus (Disc Herniation)
* Spinal Stenosis
* Spondylolysis and Spondylolisthesis
* Compression Fractures (especially in osteoporosis)
* Sacroiliitis

## 3. Inflammatory and Systemic Causes

* Axial Spondyloarthritis / Ankylosing Spondylitis
* Rheumatoid Arthritis and other Connective Tissue Diseases
* Vertebral Osteomyelitis / Discitis
* Spinal Epidural Abscess
* Neoplasia / Malignancy (primary or metastatic spinal tumors)
* Chronic Pelvic Inflammatory Disease, Endometriosis, Prostatitis (referred pain)

## 4. Neurological Causes

* Radiculopathy due to nerve root compression
* Cauda Equina Syndrome (emergency)
* Spinal Cord Compression

## 5. Referred Pain from Visceral Organs

* Abdominal Aortic Aneurysm
* Renal Colic / Pyelonephritis
* Pancreatitis
* Biliary Colic
* Lung Disease (e.g., Pleuritis)

## 6. Other Causes

* Herpes Zoster (Shingles)
* Retroperitoneal Hemorrhage
* Coccyx Pain
* Achilles Tendon Injuries (can refer pain)

## **Chronic Low Back Pain Epidemiology**

## Global Prevalence

In 2020, approximately 619 million people worldwide were affected by low back pain (LBP), representing nearly 10% of the global population

The point prevalence of low back pain was estimated at about 7.5% globally in 2017, or around 577 million people

Prevalence is expected to increase due to population growth and aging, with projections estimating 843 million cases by 2050

Chronic low back pain prevalence increases linearly from the third decade of life (20s) up to around 60 years old

Prevalence in younger adults (24–39 years) is about 4.2%, rising to nearly 19.6% in those aged 20–59

Women tend to have a higher prevalence of chronic low back pain than men[1](https://pmc.ncbi.nlm.nih.gov/articles/PMC4603263/).

The greatest number of people living with LBP globally are currently in the 50–54 year age group

Age-standardized prevalence varies by region, with higher rates reported in:

Australasia (~11%)

Central Europe (~12.7%)

High-income North America (~10.4%)

Western Europe (~9.4%)

Lower prevalence regions include East Asia (~5.3%) and parts of sub-Saharan Africa (~6.4–7.4%)

Prevalence rates in Latin America, Middle East, and Asia range between 5% and 9% depending on the region

Although many experience low back pain, fewer than 1 in 3 people with chronic LBP have substantial disability affecting work, social, or self-care activities for 6 months or more

Low back pain is a leading cause of years lived with disability (YLDs) globally, contributing significantly to the global burden of disease

### **Prognosis for someone with lower back pain**

The prognosis (outlook) for someone with lower back pain depends on several factors, including:

* The underlying cause.
* The severity of the pain.
* How long the pain lasts.
* How your body responds to treatment.
* Your age and overall health.

Your healthcare provider will be able to give you a better idea of what to expect based on your unique situation. Most people with back strains and sprains recover and don’t have long-term health issues. But many people will have another episode within a year.

Some people have chronic back pain that doesn’t get better after several weeks. People with degenerative conditions such as arthritis and osteoporosis may have symptoms that get worse over time. Surgery and other treatments are often effective at helping people with a range of injuries and conditions live with less pain.

## **Prevention**

Not all causes of lower back pain are preventable. But you can take some steps to avoid injuries that cause lower back pain, including:

* **Maintaining a weight that’s healthy for you**: Excess weight puts pressure on your vertebrae and disks.
* **Strengthening your abdominal, hip and back muscles**: Pilates and other exercise programs strengthen core, hip and back muscles that support your spine.
* **Lifting safely**: To avoid injuries, lift with your legs, not your back. Hold heavy items close to your body. Try not to twist your torso while you’re lifting.
* **Warming up before physical activity or sports**: Do gentle stretches to warm up your body properly before exercise.

## **Living With**

Certain symptoms that happen alongside lower back pain can be warning signs of something more serious. You should see a healthcare provider right away if you have lower back pain and any of these symptoms:

* Numbness.
* Weakness in one or both legs.
* Problems peeing or pooping.
* Fever.
* Light-headedness or fainting.
* Severe abdominal pain.

While not as urgent, it’s a good idea to see a provider soon if you have lower back pain and any of these:

* History of cancer.
* Unexplained weight loss.
* Severe pain at night.
* You’re 55 or older and there’s no obvious reason for the back pain.
* You’re at increased risk of infection due to being immunocompromised

## **Doctor-Patient Conversation on Chronic Low Back Pain (De-Identified)**

## Doctor:

Good morning! What brings you in today?

## Patient:

Good morning, doctor. I’ve been having persistent lower back pain for several months now. It’s been affecting my daily activities and sleep.

## Doctor:

I’m sorry to hear that. Can you describe the pain for me? Is it sharp, dull, or burning? Does it radiate anywhere?

## Patient:

It’s mostly a dull ache, but sometimes it feels sharp. The pain sometimes radiates down my right leg.

## Doctor:

When did the pain start, and was there any injury or event that triggered it?

## Patient:

It started about six months ago. I don’t remember any specific injury, but it gradually got worse.

## Doctor:

Do you have any numbness, tingling, or weakness in your legs?

## Patient:

Yes, sometimes I feel tingling and numbness in my right foot.

## Doctor:

Have you noticed any changes in bladder or bowel control?

## Patient:

No, nothing like that.

## Doctor:

Have you tried any treatments so far?

## Patient:

I’ve taken some over-the-counter painkillers and tried to rest, but the pain keeps coming back.

## Doctor:

Thank you for sharing. Chronic low back pain can have many causes, including muscle strain, disc problems, or arthritis. We’ll do a thorough examination and may order imaging like an MRI if needed.

## Patient:

What treatment options are available?

## Doctor:

Treatment usually includes a combination of physical therapy, pain management with medications, and lifestyle modifications like exercise and posture correction. In some cases, injections or other interventions may be considered.

## Patient:

Are there any risks with these treatments?

## Doctor:

Medications can have side effects like stomach upset or drowsiness. Physical therapy is generally safe but may cause temporary soreness. We’ll tailor the plan to minimize risks and maximize benefits.

## Patient:

What if I don’t do anything?

## Doctor:

Without treatment, the pain may worsen and limit your activities further. Early management improves outcomes and quality of life.

## Patient:

How often will I need to follow up?

## Doctor:

We’ll start with regular visits to monitor your progress and adjust treatment. I’ll also provide guidance on when to seek urgent care if symptoms worsen.

## Patient:

Thank you, doctor. I appreciate your help.

## Doctor:

You’re welcome. We’ll work together to manage your pain and improve your function. Please reach out anytime you have concerns.

REFERENCES

[Low back pain](https://www.who.int/news-room/fact-sheets/detail/low-back-pain)

[Lower Back Pain: Causes, Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/7936-lower-back-pain)

<https://emedicine.medscape.com/article/310353-differential?form=fpf>

<https://www.hopkinsmedicine.org/health/conditions-and-diseases/back-pain/7-ways-to-treat-chronic-back-pain-without-surgery>

**SCOLIOSIS**

**DEFINITION AND DESCRIPTION**

Scoliosis is a side-to-side curve of the spine. It's most often diagnosed after age 10 or in the early teen years. The spine can curve to either side and in different parts of the back. Experts don't know the cause of most childhood scoliosis.

Most scoliosis is mild. But some curves get worse as children grow. If the curve gets very bad, scoliosis can cause pain and breathing problems. A bad curve of the spine can push on the lungs and make it hard to breathe.

Healthcare professionals watch growing children who have mild scoliosis with follow-up visits a few times a year. This most often involves X-rays and a physical exam to see if the curve is getting worse. Many people with scoliosis don't need treatment.

Some children may need to wear a brace to stop the curve from getting worse. Others may need surgery to correct the curves.

**Causes**

Experts don't know what causes the most common type of scoliosis. But the condition can run in families. The following may cause some types of scoliosis:

* Certain conditions of the muscles and nerves that let the body move, called neuromuscular conditions. Conditions include cerebral palsy or muscular dystrophy.
* Birth conditions that affect how the bones of the spine form.
* Surgery on the chest wall as a baby or surgery to remove bone over the back of the spine.
* Spinal cord conditions.

**Risk factors**

Risk factors for getting the most common type of scoliosis include:

* **Being age 10 or older.** Symptoms most often begin in the early teen years.
* **Being assigned female at birth.** Both sexes get mild scoliosis at about the same rate. But people assigned female at birth have a higher risk of the curve getting worse and needing treatment.
* **Having a family history.** Scoliosis can run in families. But most children with scoliosis don't have a family history of the condition.

**Symptoms**

Symptoms of scoliosis may include:

* Change in posture.
* Shoulders that aren't even.
* One shoulder blade that looks bigger than the other.
* Waist that isn't even.
* One hip higher than the other.
* One side of the rib cage pushing forward.
* One side of the back poking out when bending forward.

Most often with scoliosis, the spine rotates or twists as well as curving side to side. This causes the ribs or muscles on one side of the body to stick out farther than those on the other side.

### **When to see a doctor**

See your child's healthcare professional if you see signs of scoliosis in your child. A mild curve might form slowly and not cause pain. You and your child might not know it's there. Sometimes, teachers, friends and sports teammates are the first to notice a child's scoliosis.

## **Diagnosis**

To diagnose scoliosis, your child's healthcare professional may take a medical history and ask about recent growth. During the physical exam, the healthcare professional may have your child stand and bend forward from the waist, with arms hanging loosely. This is to see if one side of the rib cage stands out more than the other.

The healthcare professional also may do an exam to check the nervous system, called a neurological exam. The exam checks for:

* Muscle weakness.
* Numbness.
* Reflexes.

### **Imaging tests**

X-rays can confirm the diagnosis of scoliosis and measure the spinal curve. Children who are growing most often get X-rays every six months to see if the curve is getting worse. This might make the radiation from the X-rays a worry.

To reduce this risk, your healthcare professional may suggest a special type of X-ray imaging that uses much lower doses of radiation. Most medical centers that specialize in scoliosis care offer this type of imaging.

Some children get an X-ray of the hand to show how much more they'll grow. The X-ray of the hand shows whether the growth plates are open and still growing.

You might have an MRI if your healthcare professional suspects that an underlying condition, such as a spinal cord issue, is causing the scoliosis. MRI scans don't use radiation.

**Treatment**

Scoliosis treatment depends on the size of the curve and how much more the child is likely to grow. Even children with small curves may need regular checkups to see if the curve is getting worse as they grow. Older teenagers who have mild curves often don't need treatment.

A moderate or large spinal curve might need bracing or surgery. That may depend on:

* **How mature the child is.** If a child's bones have stopped growing, the risk of the curve getting worse is low. Braces have the most effect in children whose bones are still growing. A healthcare professional can check how mature the bones are with hand X-rays.
* **Size of curve.** Larger curves are more likely to get worse with time.
* **People assigned female at birth.** They have a higher risk of the curve getting worse than do people assigned male at birth.

### **Braces**

Children with moderate scoliosis whose bones are still growing may wear a brace. The brace most often won't cure scoliosis or reverse the curve. But it may keep a moderate curve from getting worse.

The most common type of brace is made of plastic. It forms to the body. This brace fits under the arms and around the rib cage, lower back and hips. It's hard to see under clothes.

Most children who have a brace wear it from 13 to 18 hours a day. A brace works better the more it's worn. Children who wear braces can take part in most activities. If they need to, children can take off the brace to play sports or do other physical activities.

Some braces are designed to be worn only at night. They may work for some types of scoliosis.

Children who have stopped growing may no longer need the brace. People assigned female at birth most often stop growing at age 14. People assigned male at birth most often stop growing at age 16. But the age varies from person to person.

### **Surgery**

Scoliosis can get worse over time. This is most likely in children who are still growing. For large curves, your healthcare professional might suggest scoliosis surgery to help straighten the curve and keep it from getting worse.

Surgical options include:

* **Spinal fusion.** In this procedure, surgeons join 6 to 12 of the bones in the spine, called vertebrae. Then they can't move by themselves. The surgeon puts pieces of bone or a bonelike material between the vertebrae.

Surgeons do this procedure through a cut in the back of the spine, called an incision. The fused area of the spine where the scoliosis was treated gets stiff. Most people can return to sports in 3 to 6 months after surgery.

The surgeon puts metal rods and special screws in the vertebrae to hold that part of the spine straight and still. That lets the old and new bone material fuse.

* **Vertebral body tethering.** Surgeons do this procedure through small cuts, called incisions. A surgeon puts screws along the outside edge of the spinal curve and threads a strong cord through the screws. Tightening the cord straightens the spine. As the child grows, the spine may straighten even more. This procedure lets the spine move as usual.
* **Expanding or growing rods.** If the scoliosis gets worse fast at a young age, surgeons can attach one or two rods along the spine. The rods expand, so they get longer as the child grows.

Some rods expand on their own. For other rods, a healthcare professional makes the rods longer every 3 to 6 months using a magnetic remote control in a clinic. Rods used more rarely need to be made longer with surgery twice a year.

Complications of spinal surgery may include infection or, rarely, nerve damage. The spine may keep curving above or below the site of the surgery.

## **Scoliosis Treatment: Drug Information and Side Effects**

## Common Medications Used in Scoliosis Symptom Management

| Drug Class | Examples | Purpose | Common Side Effects |
| --- | --- | --- | --- |
| Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) | Ibuprofen, Naproxen, Diclofenac | Reduce pain and inflammation | Stomach pain, nausea, gastrointestinal irritation, ulcers, kidney issues with prolonged use |
| Acetaminophen (Paracetamol) | Tylenol | Pain relief without anti-inflammatory effect | Nausea, stomach pain, liver toxicity in overdose |
| Muscle Relaxants | Cyclobenzaprine (sometimes used) | Reduce muscle spasms associated with scoliosis-related pain | Drowsiness, dizziness, dry mouth |
| Opioids (in severe cases) | Oxycodone, Morphine | For severe, refractory pain | Risk of dependence, constipation, sedation, nausea |
| Neuropathic Pain Agents | Gabapentin, Pregabalin | For nerve-related pain if present | Dizziness, drowsiness, weight gain |
| Corticosteroid Injections | Local injections (rarely used) | Reduce local inflammation and pain | Injection site pain, risk of infection, tendon weakening |

## Common Surgical Procedures for Scoliosis

| Procedure | Description | Typical Timeline and Recovery |
| --- | --- | --- |
| Posterior Spinal Fusion (Traditional Fusion) | Most common surgery; involves fusing 6–12 vertebrae using bone grafts and metal rods, screws, and hooks to straighten and stabilize the spine. | Surgery lasts 4–8 hours; hospital stay ~3–7 days; initial recovery 6–12 weeks; full recovery and fusion can take 6–12 months. |
| Vertebral Body Tethering (VBT) | Fusionless surgery using screws and a flexible tether to gradually straighten the spine while preserving motion; suitable for growing children. | Less invasive; quicker recovery than fusion; patients often resume activities within weeks; ongoing correction as child grows. |
| ApiFix System | Internal bracing system with adjustable hardware that corrects curvature and allows spine flexibility; minimally invasive. | Faster recovery than fusion; outpatient or short hospital stay; gradual curve correction over months. |
| Anterior Scoliosis Correction (ASC) | Surgery via a small incision on the side of the chest; used for certain curves; allows correction without stiffening the spine. | Recovery similar to VBT; less invasive than fusion; physical therapy needed post-op. |
| Thoracoplasty | Rib hump reduction by partial rib removal; often combined with spinal surgery. | Recovery depends on combined procedures; chest tube may be required post-op; hospital stay varies. |
| Expandable Rods (for young children) | Rods implanted to allow spine growth; lengthened every 3–6 months via surgery or remotely. | Multiple surgeries over years; initial recovery a few weeks per surgery. |

## Recovery and Rehabilitation Timeline

| Phase | Duration | Focus and Activities |
| --- | --- | --- |
| Hospital Stay | 3–7 days post-surgery | Pain control, early mobilization, wound care |
| Initial Recovery | 6–12 weeks | Gradual increase in activity, physical therapy begins |
| Intermediate Recovery | 3–6 months | Strengthening exercises, improved mobility |
| Full Recovery and Fusion | 6–12 months | Solid bone fusion (for fusion surgery), return to full activities including sports |
| Long-term Follow-up | Years | Monitoring for hardware issues, curve progression, and function |

## **Lifestyle and home remedies**

No activities are known to cause or fix scoliosis. Most people with scoliosis don't have to restrict what they do. Carrying a heavy backpack does not cause scoliosis.

Exercise or playing sports may improve overall health and well-being. A healthy diet with enough calcium and vitamin D also may help bone health. Physical therapy can help strengthen the back, ease pain and improve posture.

**Alternative medicine**

Studies don't show that the following treatments for scoliosis help fix the curve:

* A procedure that uses controlled force to move a joint past its range of motion, called spinal manipulation.
* Soft braces.
* Electrical stimulation of muscles.
* Dietary supplements.

**Complications**

Most people with scoliosis have a mild form. In a growing child, scoliosis can get worse. Worse scoliosis sometimes causes complications, including:

* **Breathing problems.** The spine may press against the lungs. This can make it harder to breathe.
* **Back problems.** People who get scoliosis as children may be more likely to have chronic back pain as adults. This is more often true for curves that are large and not treated.
* **Changes in how the body looks.** As scoliosis gets worse, it can cause body changes. These changes may include hips and shoulders that aren't even, ribs that stick out, being short, and a shift of the waist and trunk to the side.

## **Outlook / Prognosis**

Though scoliosis is often asymptomatic, symptoms may appear as your body ages and natural spine degeneration occurs. A healthcare provider can help you manage symptoms if they become bothersome.

Scoliosis can change the way your body looks depending on the degree of the spinal curve. This might be challenging for your emotional well-being. A mental health professional can help you manage how you feel about your body.

### **What’s the outlook for scoliosis?**

The outlook for scoliosis can vary depending on the type and severity. Most people can live normally, without any changes to their routines.

## **Prevention**

There’s no known way to prevent scoliosis.

If you have scoliosis, a healthcare provider might recommend strengthening your back and abdominal muscles with stretching and exercises. These can help prevent the curve in your spine from getting worse.

## **Living With**

Talk to your healthcare provider or physical therapist about what activities are safe to do. Most people with scoliosis can participate in physical activities and exercise. Routine movement can reduce the severity of symptoms. If an activity causes pain, listen to your body and stop.

#### **Can playing sports make scoliosis worse?**

Most cases of scoliosis are diagnosed during adolescence. This is the time when many children are eager to jump into team sports and athletic programs. As a parent or caregiver, you might wonder what activities are safe for your child.

Luckily, playing sports won’t make scoliosis worse. In fact, participating in sports that promote flexibility and core strength can reduce your child’s symptoms.

Sports that can help scoliosis include:

* **Swimming**: It can increase core strength, as it requires your child to use all of their muscles at once.
* **Gymnastics**: It can boost your child’s flexibility and improve core strength.

**Should certain sports be avoided with scoliosis?**

Talk to your child’s healthcare provider about what’s safe for them. Most sports, even weightlifting, are generally fine. However, if your child had back surgery, they should avoid contact sports. These include hockey, lacrosse, wrestling and football.

### **When should I see a healthcare provider?**

Contact a healthcare provider if:

* You believe you have signs or symptoms of scoliosis.
* Your treatment doesn’t seem to be working.
* Your symptoms get worse.

As a parent or caregiver, it’s important to contact a pediatrician if:

* A routine screening suggests your child may have scoliosis.
* Your child has signs or symptoms of scoliosis.
* Treatment isn’t helping your child or their symptoms get worse.
* You have a biological family history of scoliosis and want to keep an eye on your child’s development.

## **QUESTIONS AND ANSWERS**

## What type of scoliosis do I/does my child have?

Scoliosis is a sideways curvature of the spine that can appear as a C- or S-shaped curve. The main types include:

* Idiopathic scoliosis: The most common type, cause unknown, often diagnosed in adolescence.
* Congenital scoliosis: Caused by spinal defects present at birth.
* Neuromuscular scoliosis: Associated with neurological or muscular diseases like cerebral palsy or muscular dystrophy.
* Degenerative (adult-onset) scoliosis: Occurs due to aging-related changes like disc degeneration or osteoporosis.  
  Curvature location also matters:
* Thoracic scoliosis: Curve in the upper/mid back
* Lumbar scoliosis: Curve in the lower back
* Thoracolumbar scoliosis: Curve at the junction of thoracic and lumbar spine
* Curves can be dextroscoliosis (right-sided) or levoscoliosis (left-sided).  
  A healthcare provider will determine the exact type based on clinical exam and imaging.

## 2. What type of treatment do you recommend?

Treatment depends on the curve severity, age, symptoms, and progression risk:

* Mild scoliosis: Often requires no active treatment; monitoring and physical therapy to maintain flexibility and strength.
* Moderate scoliosis: May benefit from bracing to prevent progression, especially in growing children.
* Severe scoliosis: Surgery is considered if the curve is large (>45–50 degrees), progressive, or causing symptoms like pain or breathing issues.
* Physical therapy is recommended across all stages to improve posture, reduce pain, and enhance function.

## 3. Do I/does my child need surgery?

Surgery is generally reserved for:

* Curves greater than 45–50 degrees in adolescents or adults
* Progressive curves despite bracing
* Significant pain, functional impairment, or cardiopulmonary compromise
* Neurological symptoms caused by spinal cord or nerve compression  
  Your doctor will assess the curve size, progression, symptoms, and overall health to decide if surgery is necessary.

## 4. Are there side effects of the treatment?

* Bracing: Can cause skin irritation, discomfort, and emotional distress, but no long-term physical harm.
* Physical therapy: Generally safe; soreness may occur initially.
* Surgery: Risks include infection, bleeding, nerve injury, hardware complications, and reduced spinal flexibility. Recovery can take several months.
* Medications for pain or muscle spasms may cause side effects like gastrointestinal upset (NSAIDs), drowsiness (muscle relaxants), or dependency (opioids).

## 5. Should I/my child see a physical therapist?

Yes. Physical therapy is highly recommended to:

* Improve spinal flexibility and muscle strength
* Reduce back pain and discomfort
* Enhance posture and functional abilities
* Support overall spine health and potentially slow curve progression  
  A physical therapist will tailor exercises based on the scoliosis type and severity.

## 6. What types of physical activities are safe?

Most physical activities are safe and encouraged, including:

* Swimming
* Walking
* Yoga and Pilates (with modifications)
* Low-impact aerobic exercises
* Core strengthening exercises  
  Contact or high-impact sports may be limited depending on curve severity and symptoms. Always consult your healthcare provider or physical therapist for personalized advice.

## **Scoliosis Differential Diagnosis**

## 1. Structural and Neurological Disorders

* Syringomyelia: A fluid-filled cyst within the spinal cord that can cause scoliosis and neurological abnormalities.
* Spina Bifida: A congenital defect causing incomplete closure of the spinal canal, sometimes associated with scoliosis.
* Arnold-Chiari Malformation: A condition where brain tissue extends into the spinal canal, potentially causing scoliosis and neurological signs.
* Neuromuscular Disorders: Conditions like cerebral palsy, muscular dystrophy, or spina bifida can cause neuromuscular scoliosis with associated muscle weakness and gait abnormalities.

## 2. Functional and Postural Causes

* Leg Length Discrepancy: Unequal leg lengths can cause compensatory spinal curvature mimicking scoliosis (functional scoliosis).
* Postural Asymmetry: Poor posture or muscle imbalances causing apparent spinal curvature without structural vertebral rotation.
* Muscle Spasms: Acute muscle tightness can cause transient spinal curvature.

## 3. Other Spinal Conditions

* Scheuermann’s Disease: Juvenile kyphosis causing thoracic spine deformity, which can be mistaken for scoliosis.
* Spondylolisthesis: Forward slippage of a vertebra, sometimes causing spinal asymmetry.
* Disc Herniation or Degenerative Changes: Can cause localized spinal deformity or pain mimicking scoliosis.
* Congenital Vertebral Anomalies: Vertebral malformations present at birth causing spinal curvature.

## 4. Tumors and Infections

* Spinal Tumors: Both intraspinal and extraspinal tumors can cause deformity and neurological symptoms.
* Infections: Vertebral osteomyelitis or discitis can cause spinal deformity and pain.

## **Scoliosis Epidemiology**

## Global Prevalence

The prevalence of scoliosis worldwide varies widely, ranging from 0.11% to 5.2% depending on population characteristics, geographic location, and screening methods

A systematic review found the overall prevalence among children and adolescents to be approximately 3.1%, with idiopathic scoliosis accounting for about 1.7% and congenital scoliosis about 0.2%

In the United States, scoliosis affects about 2-3% of the population, corresponding to roughly 6 to 9 million people

In China, prevalence among children varies regionally from 0.11% in Beijing to 2.4% in Sichuan, with a pooled prevalence of about 1.02% and a female-to-male ratio of 1.54

Scoliosis can develop at any age but is most commonly diagnosed in:

Adolescents (11–18 years): This group accounts for approximately 90% of idiopathic scoliosis cases

Congenital scoliosis: Typically diagnosed in early childhood (0–3 years)

Adults: Prevalence increases with age due to degenerative scoliosis, reaching over 8% in adults over 25 years and up to 68% in those over 60 years

Females are more commonly affected by idiopathic scoliosis, with a female-to-male ratio ranging from 1.5:1 to 3:1

Congenital scoliosis affects males and females equally

Prevalence tends to be higher in Europe and the Americas compared to Asia

In Asia, prevalence rates vary by country and region, influenced by genetic and environmental factors

African-American populations show scoliosis prevalence with somewhat higher mean curve magnitudes compared to other races

Germany reports a high number of scoliosis cases relative to other countries

The most common curve location in idiopathic scoliosis is the thoracic region, with a prevalence around 3.89%, followed by thoracolumbar and lumbar regions

Most scoliosis cases present with mild curves (10°–19°), with fewer cases exhibiting more severe curvatures

## **Scoliosis Genomic Data**

## Heredity and Genetic Influence

* Idiopathic scoliosis (IS) has a strong genetic component, with family studies showing:
  + About 26–27% of patients have a relative with scoliosis.
  + Prevalence among first-degree relatives is significantly higher (7–16%) than in the general population.
  + Twin studies show higher concordance in identical (monozygotic) twins compared to fraternal (dizygotic) twins, indicating heritability estimated at around 38%.
* Genetic predisposition influences both risk and severity of scoliosis.

## Key Genes and Variants Associated with Scoliosis

| Gene / Variant | Role / Association | Notes |
| --- | --- | --- |
| LBX1 (rs11190870) | Transcription factor involved in spinal cord development | Strongly associated with adolescent idiopathic scoliosis (AIS) in multiple GWAS studies. |
| GPR126 (rs657507) | G-protein coupled receptor affecting cartilage formation | Linked to AIS susceptibility. |
| BNC2 (rs3904778) | Zinc finger protein involved in development | Associated with AIS in genome-wide association studies. |
| PAX1 | Regulates vertebral development | Mutations cause vertebral malformations; important in congenital scoliosis. |
| COL11A2 | Collagen gene involved in extracellular matrix | Variants enriched in severe AIS cases; related to connective tissue integrity. |
| Fibrillin-1 and Fibrillin-2 | Structural proteins of connective tissue | Mutations linked to scoliosis in Marfan syndrome and AIS. |
| HSPG2 (Perlecan) | Extracellular matrix protein | Rare damaging variants found in familial IS cases. |
| TTLL11 | Tubulin tyrosine ligase-like gene, involved in cilia function | Mutations linked to IS in familial studies; ciliary defects implicated in pathogenesis. |
| TBX6 | Transcription factor important in vertebral segmentation | Mutations cause congenital scoliosis in some patients. |
| LFNG | Glycosyltransferase involved in vertebral development | Mutations linked to spondylocostal dysostosis, a form of congenital scoliosis. |

## **Doctor-Patient Conversation on Scoliosis (De-Identified)**

## Doctor:

Good morning! What brings you in today?

## Patient:

Good morning, doctor. I recently found out I have scoliosis, and I’m worried about what it means and what I should do next.

## Doctor:

Thank you for sharing that. Can you tell me how you first noticed the scoliosis or what symptoms you have?

## Patient:

I noticed my shoulders and hips look uneven, and sometimes I have back pain. My doctor mentioned an abnormal curve in my spine on an X-ray.

## Doctor:

Scoliosis is a condition where the spine curves sideways. It can vary from mild to severe. Many people have mild scoliosis that doesn’t cause major problems, but it’s important to monitor the curve and symptoms.

## Patient:

What causes scoliosis?

## Doctor:

Most scoliosis cases are idiopathic, meaning the exact cause is unknown. It often develops during adolescence. Other causes can include congenital spine abnormalities or neuromuscular conditions.

## Patient:

What are my treatment options?

## Doctor:

Treatment depends on the severity of the curve, your age, and symptoms. Options include:

* Observation: Regular check-ups and imaging to monitor progression, especially if the curve is mild.
* Bracing: For moderate curves in growing adolescents to prevent worsening.
* Physical therapy: To improve posture, strength, and reduce pain.
* Surgery: Considered for severe curves or if scoliosis causes significant symptoms or progression.

## Patient:

What are the risks if I don’t treat it?

## Doctor:

If untreated, scoliosis can worsen over time, potentially leading to pain, decreased lung function, or physical deformity. However, many people live normal lives with mild scoliosis.

## Patient:

How often will I need to be monitored?

## Doctor:

For mild scoliosis, monitoring every 6 to 12 months is typical. If the curve progresses or symptoms worsen, we may recommend more frequent visits or treatment adjustments.

## Patient:

Can I still be active and play sports?

## Doctor:

Yes, most people with scoliosis can participate in sports and physical activities. Physical therapy can help you maintain flexibility and strength.

## Patient:

Thank you, doctor. I feel better knowing there’s a plan.

## Doctor:

You’re welcome. We’ll work together to manage your scoliosis and keep you healthy. Please don’t hesitate to ask questions anytime.

REFERENCES

[Scoliosis: What It Is, Types, Causes, Symptoms & Treatment & Types](https://my.clevelandclinic.org/health/diseases/15837-scoliosis#outlook-prognosis)

[Scoliosis - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/scoliosis/symptoms-causes/syc-20350716)

<https://www.aans.org/patients/conditions-treatments/scoliosis/>

<https://www.hopkinsmedicine.org/health/conditions-and-diseases/scoliosis>

**ACL TEAR**

**DEFINITION AND DESCRIPTION**

An ACL tear is an injury to the anterior cruciate ligament (ACL) in your knee.

The ACL is one of your knee ligaments. It connects your thigh bone (femur) to your shin bone (tibia). You have one ACL in each knee. It forms an “X” shape inside your knee with your posterior cruciate ligament (PCL). The ACL is closer to the front of your knee. The PCL is closer to the back of your knee.

Your ACL is like a strap that connects your bones and prevents your knee from bending or rotating too much. Anything that puts enough force on your knee to bend or twist it farther than its natural limit can injure or tear your ACL.

ACL tears are a common injury, especially among athletes. Visit a healthcare provider if your knee hurts, particularly if the pain started after an injury or physical activity.

#### **Types of ACL injuries**

Healthcare providers usually grade ACL injuries and tears. These grades are a quick way to describe the extent of your injury. ACL injury grades range from one (the least severe) to three (the most severe):

* **Grade one:** The injury stretched your ACL enough to damage it, but it’s still in one piece and holding your knee bones together.
* **Grade two:** The injury stretched your ACL so much that it was partially torn and loosened.
* **Grade three:** A complete tear — your ACL is in two pieces.

#### **What does an ACL tear feel like?**

Most people know the moment they tear their ACL. Sports injuries and other traumas that tear your ACL are usually obvious enough that you can say exactly when it happened.

People who experience an ACL tear usually feel or hear a pop in their knee. Your knee might give out (feel unstable and weak). ACL tears can be very painful, but some people only feel small discomfort. Visit a provider if you injured your knee — especially if you heard or felt a popping.

ACL injuries and tears are very common. The ACL is the most commonly injured knee ligament. Experts estimate that between 100,000 and 200,000 people in the U.S. tear an ACL each year.

**ACL tear symptoms**

The most common ACL tear symptoms include:

* Feeling or hearing a pop in your knee.
* Swelling.
* Pain (especially when you try to put weight on your knee).
* Weakness or feeling like your knee has given out.
* Losing your range of motion (how far you can move your knee).

### **What causes ACL tears?**

Anything that puts too much force on your knee can tear your ACL. ACL tears happen when your knee moves or twists more than it naturally can.

The most common causes of ACL tears include:

* Sports injuries.
* Car accidents.
* Falls.

#### **ACL tear risk factors**

Anyone can experience an ACL tear. They’re much more common among athletes, especially those who play sports that involve suddenly stopping, twisting or changing directions. Some sports that cause frequent ACL tears include:

* Soccer.
* Football.
* Basketball.
* Gymnastics.
* Lacrosse.

### **Complications of an ACL tear**

The injuries that cause ACL tears can damage other parts of your knee, too.

You might damage or tear your other knee ligaments during an ACL tear, including your:

* Medial collateral ligament (MCL).
* Lateral collateral ligament (LCL).
* Posterior cruciate ligament (PCL).

Other injuries that can occur at the same time as an ACL tear include:

* Bone fractures.
* Meniscus tears.
* Muscle strains.

## **Diagnosis and Tests**

A healthcare provider will diagnose an ACL tear with a physical exam and some tests. They’ll ask you about your symptoms and look at your knee. Tell your provider what you were doing right before you hurt your knee and when you first noticed symptoms.

Your provider might perform some movements or motions with your knee and leg. These tests might feel uncomfortable. Tell your provider if any position or motion hurts or makes your symptoms worse.

You’ll probably need at least one of a few imaging tests, including:

* X-rays.
* A computed tomography (CT) scan.
* Magnetic resonance imaging (MRI).

## **Management and Treatment**

Treatments can vary depending on your ACL tear grade and any other damage inside your knee.

Don’t play sports or do any activity that can put more stress on your knee. Follow the RICE method as soon as you notice pain or other symptoms:

* **Rest**: Avoid the activity that caused your injury. Don’t overuse your knee while it heals.
* **Ice**: Apply a cold compress or ice packs wrapped in a thin towel to your knee for 15 minutes at a time, a few times a day.
* **Compression**: You can wrap your knee in an elastic bandage to help reduce swelling.
* **Elevation**: Prop your knee and leg up above the level of your heart as often as you can.

Your provider will suggest treatments to manage your pain and other symptoms. You might need:

* Crutches.
* A brace that holds your knee in place.
* Over-the-counter (OTC) pain medicine like NSAIDs (nonsteroidal anti-inflammatory drugs) or acetaminophen.
* Physical therapy.

#### **Can an ACL tear heal on its own?**

A torn ACL can’t heal on its own, but it’s possible to live with it (especially if you have a low-grade tear). But if you’re an athlete or want to return to physical activity, you’ll need surgery to repair your ACL. Most people choose to have an ACL tear surgically repaired.

#### **ACL tear surgery**

Surgery to repair damage in your knees is usually an outpatient procedure, which means you can go home the same day. Your surgeon will perform a knee arthroscopy, a minimally invasive technique to repair the tear inside your knee. Ask your surgeon what to expect.

**ACL Tear Treatment: Drug Information and Side Effects**

## Drug Treatments for ACL Tear (Non-Surgical Management)

1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
   1. Examples: Ibuprofen, Naproxen
   2. Purpose: Reduce pain, inflammation, and swelling after injury.
   3. Side Effects:
      1. Gastrointestinal irritation, ulcers, bleeding risk
      2. Kidney dysfunction with prolonged use
      3. Increased cardiovascular risk in some patients
      4. Allergic reactions in rare cases
   4. Notes: Often used initially to manage symptoms before or alongside other treatments
2. Acetaminophen (Paracetamol)
   1. Purpose: Pain relief without anti-inflammatory effects.
   2. Side Effects:
      1. Generally well tolerated
      2. Risk of liver toxicity in overdose or chronic high doses
   3. Notes: Alternative when NSAIDs are contraindicated
3. Stronger Pain Medications (Occasionally Prescribed)
   1. Examples: Opioids (e.g., codeine) for short-term severe pain.
   2. Side Effects:
      1. Risk of dependence, sedation, constipation, nausea
   3. Notes: Used cautiously and for short durations only
4. Muscle Relaxants
   1. Sometimes prescribed to relieve muscle spasms around the knee.
   2. Side effects include drowsiness and dizziness.

## **ACL Tear Procedure and Timelines**

1. Anesthesia and Positioning
   1. Most patients receive regional anesthesia such as an epidural nerve block and a localized nerve block around the knee for postoperative pain control; general anesthesia may also be used.
   2. The patient lies supine with the leg positioned for full knee flexion and extension.
2. Arthroscopic Evaluation
   1. Small incisions (portals) are made around the knee.
   2. An arthroscope (tiny camera) is inserted to visualize the inside of the joint.
   3. The surgeon inspects the ACL tear and evaluates surrounding structures (menisci, cartilage) and repairs any additional damage.
3. Graft Harvesting
   1. A tendon graft is harvested from the patient (autograft) or taken from a donor (allograft).
   2. Common autograft sources include the hamstring tendons, patellar tendon (middle third), or quadriceps tendon.
   3. For hamstring graft, a small incision is made over the hamstring insertion, and tendons are carefully removed and prepared.
4. Tunnel Creation
   1. Small tunnels are drilled in the femur (thigh bone) and tibia (shin bone) at the anatomical ACL attachment sites.
   2. These tunnels allow passage and fixation of the graft.
5. Graft Passage and Fixation
   1. The prepared graft is pulled through the bone tunnels.
   2. It is secured with screws or other fixation devices in the femur and tibia.
   3. The knee is cycled through flexion and extension to remove slack and ensure proper graft tension.
6. Closure
   1. Incisions are closed with sutures and covered with dressings.

## Recovery Timelines

| Phase | Duration | Key Activities and Milestones |
| --- | --- | --- |
| Hospital Stay | 1–2 days (often outpatient) | Pain control, initial mobilization, wound care |
| Early Recovery | 0–2 weeks | Use of crutches, limited weight-bearing, gentle range of motion exercises |
| Rehabilitation Phase 1 | 2–6 weeks | Gradual increase in knee motion, muscle activation (quadriceps, hamstrings) |
| Rehabilitation Phase 2 | 6 weeks – 3 months | Strengthening exercises, balance training, increased weight-bearing and activity |
| Rehabilitation Phase 3 | 3–6 months | Advanced strengthening, proprioception, low-impact sports activities |
| Return to Sports | 6–9 months or longer | Gradual return to full sports participation after functional testing and surgeon clearance |

## **ACL Tear Genomic Data**

## Key Genes and Genetic Variants Associated with ACL Tears

| Gene / Variant | Role / Association | Notes and Evidence |
| --- | --- | --- |
| COL1A1 (rs1800012, rs1107946) | Collagen type I gene involved in ligament strength and structure | Protective and risk variants identified; associations stronger in European ancestry populations |
| COL3A1 | Collagen type III gene | AA genotype overrepresented in ACL-injured Polish skiers[1](https://www.sciencedirect.com/science/article/pii/S2059775421002303). |
| COL5A1 (rs12722) | Collagen type V gene affecting connective tissue integrity | Associated with increased ACL rupture risk, especially in females |
| COL12A1 | Collagen type XII gene | Linked to ACL rupture susceptibility |
| ELN (Elastin gene, rs2071307) | Maintains tissue elasticity | AA genotype more frequent in ACL-injured individuals; gender-specific differences noted |
| FMOD (Fibromodulin gene, rs7543148) | Regulates collagen fibrillogenesis | TT genotype less frequent in ACL-injured males |
| ACAN, BGN, DCN, LUM | Proteoglycans involved in extracellular matrix | Haplotypes associated with ACL tear susceptibility |
| GDF5, MMPs, VEGFA, KDR | Genes involved in tissue remodeling, angiogenesis | Various polymorphisms studied with mixed results |
| NGFB, HIF1A, IL-1B, IL-6, TNF | Inflammatory and growth factor genes | Potential modulators of injury risk and healing |

## Anatomical and Genetic Risk Factors

* Genetic factors influence anatomical traits such as:
  + Narrow intercondylar notch width
  + Steep posterior tibial slope
  + Joint laxity  
    These anatomical variations, which run in families, increase ACL injury risk

## **ACL Tear Epidemiology**

## Incidence and Prevalence

The overall incidence of ACL tears is estimated at 68.6 per 100,000 person-years in the general population

In the United States, approximately 95,000 ACL ruptures occur annually, with about 200,000 ACL-related injuries reported each year

Around 100,000 ACL reconstructions are performed annually in the U.S.

Globally, ACL injuries are common in athletes, especially those involved in sports requiring cutting, pivoting, and sudden deceleration (e.g., soccer, basketball, football, skiing)

## Age and Sex Distribution

ACL injury incidence peaks in:

Males: Ages 19–25 years (241 per 100,000 person-years)

Females: Ages 14–18 years (227.6 per 100,000 person-years

Females have a significantly higher risk of ACL tears compared to males, with rates ranging from 2.4 to 9.7 times greater when adjusted for athletic exposure

High school female athletes have about a 1.6-fold greater rate of ACL tears per athletic exposure compared to males

Among children and adolescents, ACL injuries constitute the majority of cruciate ligament injuries, especially in those over 16 years old

Approximately 70% of ACL injuries occur via non-contact mechanisms, such as sudden pivoting, braking, or awkward landings

Female athletes have a 4 to 6 times higher risk than males, likely due to anatomical, hormonal, biomechanical, and neuromuscular control differences

Sports most commonly associated with ACL injuries include soccer, basketball, football, baseball, and skiing, accounting for about 78% of ACL injuries

In pediatric populations, sports activities are the leading cause of ACL injuries (65%), with a higher proportion of injuries in females aged ≤16 years

A large study of ACL reconstructions across Denmark, Luxembourg, Norway, Sweden, the UK, and the US found soccer as the most common cause of ACL reconstruction, with rates ranging from 14.1% to 42.3%

ACL injuries account for about 6.4% of all reported knee injuries, with nearly half occurring during training sessions

## **Anterior Cruciate Ligament (ACL) Injury Differential Diagnoses**

## 1. Meniscal Injuries

* Meniscal tears often coexist with ACL injuries and can cause joint line tenderness, swelling, locking, or clicking.
* Unlike ACL tears, meniscal injuries may not cause significant instability but can cause mechanical symptoms.

## 2. Collateral Ligament Sprains

* Medial Collateral Ligament (MCL) sprain
* Lateral Collateral Ligament (LCL) sprain
* These cause localized pain and tenderness along the sides of the knee, with less anterior instability compared to ACL tears.

## 3. Posterior Cruciate Ligament (PCL) Injury

* PCL injuries cause posterior knee instability and differ from ACL injuries which cause anterior instability.
* Mechanism often involves direct blow to the anterior tibia.

## 4. Knee Dislocation

* High-energy injury often involves multiple ligament injuries including ACL.
* Presents with gross instability and possible neurovascular compromise.

## 5. Tibial Plateau Fracture

* Fracture of the proximal tibia can mimic ACL injury symptoms with pain, swelling, and limited motion.
* Requires imaging to differentiate.

## 6. Distal Femur Fracture

* May present with knee pain and swelling after trauma.

## 7. Patellar Dislocation or Subluxation

* Causes anterior knee pain and instability but differs in mechanism and clinical findings.

## 8. Synovial Plica Syndrome

* Causes anterior or medial knee pain and can mimic meniscal or ligamentous injury.

## 9. Osteochondral Injuries / Loose Bodies

* Cartilage or bone fragments within the joint cause pain, swelling, and mechanical symptoms.

## 10. Tendon Injuries

* Quadriceps or patellar tendon ruptures cause inability to extend the knee rather than instability.

## **Outlook / Prognosis**

It usually takes six to nine months to recover from a torn ACL. Competitive athletes may need a little longer than this to heal fully before they’re cleared to return to their sport.

Your provider will tell you when you can resume physical activities. Don’t return to playing sports or working out before your provider says it’s safe. If you resume activities before your ACL heals, you’re more likely to re-injure it.

**Prevention**

There might not be any way to prevent an ACL tear, especially if you’re an athlete. Sports injuries and accidents you can’t plan for usually cause ACL tears.

During sports or other physical activities:

* Wear the proper protective equipment.
* Don’t “play through the pain” if your knee hurts during or after physical activity.
* Give your body time to rest and recover after intense activity.
* Stretch and warm up before playing sports or working out.
* Cool down and stretch after physical activity.
* Offseason knee and lower body strengthening programs can help prepare your knee joints for the stress a sports season puts on them.

Follow these general safety tips to reduce your risk of an injury:

* Avoid planting your foot and pivoting over your knee. This is a common way athletes injure their ACL and meniscus.
* Make sure your home and workspace are free from clutter that could trip you or others.
* Always use the proper tools or equipment at home to reach things. Never stand on chairs, tables or countertops.
* Use your cane or walker if you have difficulty walking or have an increased risk of falls.

## **Living With**

### **Can you walk if your ACL is torn?**

Some people can walk with a torn ACL. But don’t force yourself to move or use your knee if it hurts. Visit a healthcare provider if you feel pain or have other knee injury symptoms. Putting more stress on your injured ACL can make a small tear worse.

### **When should I see my healthcare provider?**

Visit a healthcare provider as soon as possible after you injure your knee. Talk to your provider if you notice new symptoms or the pain is getting worse.

Go to the emergency room if you experience trauma like a car accident or serious fall. Traumas sometimes cause other injuries you may not notice right away.

## **QUESTION AND ANSWERS SET**

## Do I have a torn ACL or another injury?

A torn ACL typically presents with:

* A sudden, painful pop or popping sound at the time of injury
* Rapid knee swelling (effusion) within hours
* Feeling of instability or the knee "giving way"
* Inability to continue the activity or bear weight comfortably  
  Physical examination tests such as the Lachman test (most accurate early on) and pivot shift test (useful later) help confirm the diagnosis.  
  Imaging with MRI is the gold standard to visualize the ACL tear and assess for associated injuries (meniscus, cartilage).  
  Other injuries like meniscal tears, collateral ligament sprains, or fractures can mimic symptoms but usually have different clinical findings and imaging results

## 2. What grade is the tear?

ACL tears are graded based on severity:

* Grade 1: Mild sprain; ligament fibers stretched but intact
* Grade 2: Partial tear; some fibers torn but ligament partially intact
* Grade 3: Complete tear; ligament completely disrupted  
  Your healthcare provider will determine the grade via physical exam and MRI. Complete tears (Grade 3) usually cause significant instability, while partial tears may have milder symptoms

## 3. Should I get surgery?

Surgery is often recommended if:

* You have a complete ACL tear causing knee instability
* You are young, active, or participate in sports involving pivoting, jumping, or cutting
* There are associated injuries (meniscus or cartilage damage) needing repair
* You experience repeated episodes of knee giving way  
  Some patients with partial tears or low activity demands may be managed non-surgically with physical therapy and bracing.  
  Your doctor will discuss options based on your lifestyle, tear severity, and knee stability

## 4. How long will I need to wait before working out or playing sports again?

* After ACL reconstruction surgery, return to sports typically takes 6 to 9 months, sometimes longer, depending on rehabilitation progress and functional testing.
* Early phases focus on pain control, swelling reduction, and gentle range of motion.
* Strengthening and neuromuscular training progress gradually over months.
* Return to high-level sports requires meeting specific strength, stability, and functional criteria to reduce re-injury risk.
* If treated non-surgically, return to low-impact activities may be sooner, but pivoting sports might be limited due to instability

## 5. What’s the risk that I tear the same ACL again in the future?

* The risk of re-tearing the same ACL (graft failure or re-injury) after reconstruction is estimated at about 5–15%, higher in younger athletes and those returning to high-risk sports early.
* The risk of tearing the contralateral (opposite) ACL is also increased after an initial ACL injury.
* Proper rehabilitation, gradual return to sport, and neuromuscular training reduce re-injury risk.
* Early return to pivoting or cutting sports before full recovery increases the likelihood of re-tear

### **Will an ACL tear happen again?**

There’s a small chance you’ll tear the same ACL again in the future, even if you have surgery to repair it. Fewer than 10% of people who have a torn ACL tear that same ACL again. Talk to your provider or surgeon about what to expect.

### **Is an ACL tear “career-ending” for an athlete?**

Most ACL tears aren’t career-ending. Just make sure you don’t rush your recovery. Most people who experience a torn ACL can return to their sport with no long-term consequences. Rehabilitation after your surgery is the best way to restore your knee’s strength and flexibility. You’ll need to rehab your knee over time before you can return to your sport.

Ask your provider or surgeon if it’s safe for you to play the same sport again, and when you can resume practice or training.

## **Doctor-Patient Conversation on ACL Tear (De-Identified)**

## Doctor:

Hello! I understand you injured your knee recently. Can you tell me what happened and what symptoms you have?

## Patient:

Hi doctor. I was playing soccer and suddenly felt a pop in my knee. It swelled up quickly, and I have pain and difficulty walking.

## Doctor:

That sounds like a classic ACL injury. The Anterior Cruciate Ligament (ACL) is a key stabilizer in your knee, and when it tears, it often causes a popping sensation, swelling, and instability.

## Patient:

What exactly is torn? Can it be fixed?

## Doctor:

The ACL is a ligament inside your knee that helps keep it stable. Unfortunately, when the ACL tears, it usually can’t just be stitched back together because the tissue is often shredded. Instead, we perform an ACL reconstruction, which means we replace the torn ligament with a graft, often taken from your own tendon.

## Patient:

What are my treatment options?

## Doctor:

Treatment depends on your activity level, knee stability, and goals. Options include:

* Non-surgical management: Physical therapy and activity modification, especially if you have low activity demands and no instability.
* Surgical reconstruction: Recommended if you want to return to pivoting sports or have knee instability. Surgery involves replacing the torn ligament and requires a structured rehab program.

## Patient:

How long does recovery take after surgery?

## Doctor:

Recovery takes time. Typically, it’s a minimum of 9 months before returning to sports, and many experts recommend waiting 12 to 18 months to reduce the risk of re-injury. The biology of healing and graft incorporation requires patience.

## Patient:

What happens right after surgery?

## Doctor:

You’ll have swelling and soreness, and you’ll use crutches and a brace initially. Physical therapy starts early to regain motion and strength. Pain management and swelling control are important in the first week.

## Patient:

Are there risks or side effects?

## Doctor:

As with any surgery, there are risks such as infection, stiffness, or graft failure. But with proper rehab and precautions, most patients recover well and return to their previous level of activity.

## Patient:

Can I prevent ACL tears in the future?

## Doctor:

There are training programs that improve strength, flexibility, and movement patterns, especially for athletes. These can reduce the risk, particularly in female athletes who are at higher risk.

## Patient:

Thank you, doctor. What should I do next?

## Doctor:

We’ll confirm the diagnosis with an MRI if not already done, discuss your goals, and plan your treatment. If surgery is chosen, we’ll prepare you for the procedure and rehab. Meanwhile, avoid activities that cause instability or pain.

REFERENCES

https://emedicine.medscape.com/article/89442-overview

<https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/acl-tear-treatment-and-reconstruction>

<https://www.mayoclinic.org/diseases-conditions/acl-injury/diagnosis-treatment/drc-20350744>

<https://my.clevelandclinic.org/health/diseases/16576-acl-tear>