

Inflammatory Arthritides of the Spine

Surgical versus Nonsurgical Treatment

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Ankylosing spondylitis and rheumatoid arthritis are disorders that cause marked alterations in the structure and function of the axial skeleton. Ankylosing spondylitis causes calcification of spinal structures causing limited motion. Rheumatoid arthritis causes synovial hypertrophy, joint destruction, and spinal instability. Surgical therapy for patients with ankylosing spondylitis corrects angular deformities with spinal osteotomies, and stabilization for spinal fractures. Spinal operative therapy for rheumatoid arthritis concentrates on correction of abnormal motion in the cervical spine. Advances in the medical therapy of spondyloarthritis have resulted in control of the inflammation of the axial skeleton halting the damage to spinal structures. The new biologic therapies for ankylosing spondylitis prevent progression of disease. Similarly, these same biologic therapies can also control the progression of rheumatoid arthritis including the cervical spine. The new medical therapies are very effective in preventing joint damage. The need for surgical intervention for patients with ankylosing spondylitis and rheumatoid arthritis will become a rare event in the setting of the new medical therapies for these inflammatory arthropathies.

Ankylosing spondylitis (AS) and rheumatoid arthritis (RA) are the most common inflammatory rheumatic disorders that damage the axial skeleton.⁴⁸ Classical AS affects the entire axial skeleton from the sacroiliac joints to the cervical spine.²⁵ Rheumatoid arthritis is more limited in its involvement affecting the cervical spine and the C1-C2 articulation.³⁴

Although AS and RA are mediated through similar inflammatory mediators, the effects on the axial skeleton are

remarkable in their difference.^{51,59} Ankylosing spondylitis initially causes inflammation of entheses, with local erosion of bone.³⁵ Subsequently, the reparative process results in calcification and ankylosis of axial joints and supporting structures, including ligaments and tendons. The spine becomes osteoporotic and brittle. Patients with AS are at risk for fracture, particularly of the cervical spine, resulting in devastating neurological injury.

Rheumatoid arthritis affects the synovial lining of the cervical apophyseal joints, as well as bursae, including those surrounding the C1-C2 articulation.^{7,52} Immunologic dysfunction results in the hypertrophy of synovial tissue causing erosion of articular cartilage and subchondral bone. Surrounding supportive structures are weakened also resulting in axial instability. For example, spinal cord compression occurs secondary to the subluxation of the C1-C2 articulation, which has become weakened by synovitis, affecting bursae cushioning the transverse cruciate ligament. In addition, synovial inflammation of the cervical apophyseal joints causes cartilaginous dissolution and capsular weakening causing subaxial subluxation. Patients with progressive cervical spine subluxation present with complaints characteristic of cervical myelopathy or nerve root compression.

Nonsurgical therapy for AS and RA was effective only partially in preventing spinal progression of these disorders.^{1,52,58,63} Therapies that controlled the peripheral arthritis of AS were ineffective in preventing the progression of spinal ankylosis. Axial disease seemed to follow its own natural history, completing its advance in no definite pattern. Some patients had only fused sacroiliac joints whereas others had total spinal ankylosis, independent of maximal medical therapy. Rheumatoid arthritis therapy directed at control of peripheral arthritis worked for cervical spine disease. However, the medical therapies for RA were only effective partially for controlling proliferative synovitis. Methotrexate, azathioprine, gold, penicillamine, and hydroxychloroquine are examples of the drug therapies for RA and AS. Progressive disease was resistant to a variety of these agents used in combination.

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Surgical therapy for spinal inflammatory disease was necessary in patients with progressive involvement characterized by instability or subluxation.^{23,27,41,43,70} Patients with AS who had fracture required surgical stabilization to prevent quadriplegia. Patients with angular deformities underwent osteotomies to improve functional stance. Patients with RA who had atlantoaxial or subaxial subluxation required surgical stabilization to prevent similar neurologic catastrophes.

We present the current improvements in medical and surgical therapies for RA and AS. Advances in the identification of the immunologic abnormalities associated with inflammatory rheumatic diseases have resulted in significant modifications in our understanding of the pathogenesis of these illnesses. A variety of specific cytokines (cell-to-cell chemical messengers) have the capability to mediate the destructive alterations that result in spinal arthritis. New biologic therapies directed at specific cytokines have stalled the progression of spinal disease in ankylosing spondylitis and rheumatoid arthritis. These novel medical therapies have the potential to arrest the progression of these illnesses making surgical correction of angular deformities or spinal instability a rare event. Newer surgical techniques for these patients have resulted in better outcomes with less operative risks.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory disease characterized by a variable symptomatic course and progressive involvement of the sacroiliac and axial skeletal joints. Ankylosing spondylitis is the prototype illness of seronegative spondyloarthritis (SA). Seronegative spondyloarthritis is characterized by enthesopathy, axial skeletal disease, the presence of a genetic factor on patient's cells, human leukocyte antigen (HLA)-B27, the absence of rheumatoid nodules, and rheumatoid factor in serum (seronegative). These illnesses include AS, psoriatic spondylitis, reactive arthritis, and enteropathic arthritis.

Ankylosing spondylitis affects about 1% of Caucasians, a number equal to the prevalence of RA. Human leukocyte antigen-B27 is present in more than 90% of Caucasian patients with AS compared with 8% of the healthy Caucasian population.⁶⁴ The male-to-female ratio of people who have the disease is in the range of 3:1. Women tend to be less symptomatic, to develop less severe disease, and to have more cervical spine disease.

The pathogenesis of AS is unknown. However, synovitis of the joints and enthesitis of tendon attachments plays a considerable role in the damage that occurs in the axial skeleton. Ankylosing spondylitis is a disease of the synovial and cartilaginous joints of the axial skeleton including symphysis pubis, spinal apophyseal joints, and sacroiliac joints. The large appendicular joints, hips,

shoulders, knees, elbows, and ankles also are affected in 30% of patients. Ankylosing spondylitis inflammation is characterized by ankylosis of joints and ossification of ligaments surrounding the vertebrae (syndesmophytes) and other entheses, such as the pelvis and heels, as opposed to the joint erosion associated with RA.

The usual patient with AS is a man from 15 to 40 years of age with a moderate degree of intermittent aching lumbar spine pain. Back pain occurs in 90% to 95% of patients with increased discomfort experienced in the morning and with periods of inactivity. The mode of onset is variable. A majority of patients with AS develop pain in the lumbosacral region with a small number of patients with peripheral root joint arthritis (shoulder, hip) as the initial manifestation of disease. Patients with AS also may develop radicular pain mimicking acute lumbar disc herniation. Pseudosciatica is a syndrome associated with radicular pain in the absence of disc herniation. This disorder occurs secondary to inflammation of the attachment of the piriformis muscle to the sacroiliac joint. Contraction of the piriformis muscle causes sciatic nerve compression. The symptoms are reversed when sacroiliac inflammation is controlled.

Physical examination reveals flattening of the lumbar spine and loss of normal lordosis. Motion of the axial skeletal is limited particularly in hyperextension and lateral bending. Percussion over the sacroiliac joints elicits pain. Measurements of spinal motion, including Schober's test⁴⁶ (lumbar spine motion), lateral bending, chest expansion (thoracic costovertebral motion), and occiput to wall (cervical spine motion) monitor progression of disease. Thoracic spine disease causes decreased motion at the costovertebral joints, reduced chest expansion, and impaired pulmonary function. Cervical spine evaluation includes measurement of all planes of motion. Peripheral joint examination includes range of motion (ROM) measurements of the hips and shoulders.

Laboratory tests add little for the diagnosis of AS. Erythrocyte sedimentation rate (ESR) is increased in 80% of patients with active disease. C-reactive protein levels may be increased if ESR is normal.⁶⁸ Antinuclear antibody and rheumatoid factor are characteristically absent in patients with AS. Human leukocyte antigen testing is positive in 90% of patients with AS but also is present in patients with other SA (psoriatic spondylitis, enteropathic spondylitis, and reactive arthritis). Human leukocyte antigen testing is not diagnostic for AS.

Radiographic changes of AS in the sacroiliac joints and lumbosacral spine are important in making a diagnosis but may be difficult to determine in the early stages of the disease.⁴⁸ The areas of the spine most frequently affected include the sacroiliac, zygapophyseal, discovertebral, and costovertebral joints. The disease involves the sacroiliac

joints with the lumbar, thoracic and cervical spine in ascending order. Sacroiliitis is a bilateral, symmetrical process in AS. Erosions of the joints in the lower $\frac{1}{3}$ occur first. A widening of the joint is noted. In the final stages of sacroiliitis, complete ankylosis with total obliteration of the joint space occurs. In the lumbar spine, osteitis of the vertebral bodies causes a loss of the normal concavity of the anterior vertebral surface. Calcification of the annulus fibrosus and anterior and posterior longitudinal ligaments emerges. Thin, vertically oriented calcifications at the edges of the vertebral bodies are named syndesmophytes. Bamboo spine is the name given to the spine of patients with AS with extensive syndesmophytes encasing the axial skeleton. For most circumstances, plain roentgenograms of the axial skeleton are adequate to identify the characteristic findings of AS. Magnetic resonance images (MRIs) with fat saturation or contrast-enhanced images are able to detect early inflammatory lesions in the sacroiliac joints and the lumbar spine.⁸ An MRI scan is not required to make a diagnosis of AS. However, MRI scans identify early lesions of AS before their appearance on plain roentgenograms. Longitudinal MRI scans can document response to therapy and resolution of areas of active inflammation in the spine.³⁸

The diagnosis of AS is based on the presence of radiographic evidence of sacroiliitis and the clinical criteria of low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved with rest (Appendix 1).⁷⁴ Other classification systems are used for the diagnosis of SA in general.^{2,25}

Spinal Fracture

Alterations to the spinal column directly related to the inflammation of AS puts the spinal cord and roots at risk of injury. Loss of normal flexibility of the spine occurs secondary to ankylosis of spinal joints and ligaments. The brittle spine is prone to fracture. The most common location for fracture is the cervical spine, although thoracic and lumbar spine fractures occur.¹⁵ The lower cervical spine (C6-C7) is the most frequent location for fracture, which often is associated with a fall. The onset of neurologic dysfunction may be delayed for weeks after initial trauma. The diagnosis of fracture may be delayed because of the difficulty of detecting fractures in osteoporotic bone with plain roentgenograms. An MRI evaluation of these patients may identify the location of the fracture.²⁴ Neurologic deficits may persist despite surgical intervention in as many as 85.7% of patients.⁶² A mortality rate from 35% to 50% may be found in elderly patients with AS who have complete cord lesions or who develop pulmonary complications.³²

Spondylodiscitis is a destructive lesion of an intervertebral disc and the surrounding vertebral bodies. The cause

of these lesions is localized inflammation or minor trauma. The lesion causes new-onset localized pain in the spine. These patients with AS uncharacteristically improve with bed rest. Magnetic resonance imaging evaluation reveals increased activity in the central portion of the vertebral endplate confirming the area as one of enthesitis (Fig 1). External mobilization is effective in stabilizing the destructive lesion in most circumstances. Surgical fusion is reserved for more severely affected patients.

Atlantoaxial Subluxations

Instability of the C1-C2 articulation occurs in the setting of AS but less often than it does in RA. Patients with AS have symptoms and signs of nerve impingement more frequently than patients with RA in the setting of instability secondary to the immobilized state of the calcified structures surrounding the spine. In a study of 103 patients with AS, 21% had atlantoaxial subluxations. Five of the 22 patients with subluxation required surgical fusion.⁶⁰

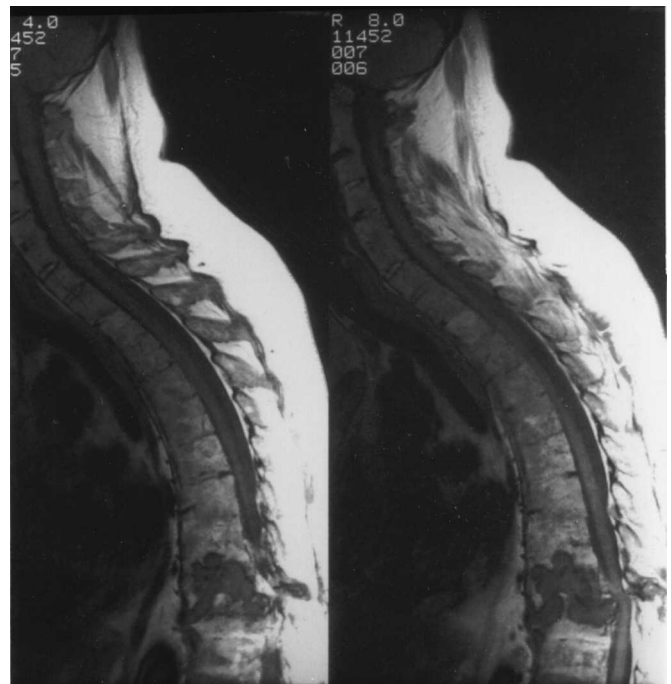


Fig 1A–B. (A) A T1-weighted sagittal MRI of the thoracic and cervical spine of this 62-year-old man with a 30-year history of ankylosing spondylitis reveals pseudoarthrosis in the thoracic spine with compression of the thoracic spinal cord. (B) A T1-weighted MRI of the same 62-year-old man demonstrates calcification of the anterior and posterior longitudinal ligament. The spinal canal is maintained in the cervical region. Reprinted with permission from Borenstein DG, Wiesel SW, Boden SD. *Low Back and Neck Pain: Comprehensive Diagnosis and Management*. Ed 3. Philadelphia, PA: Saunders; 2004:316.

Nonsurgical Treatment

Major advances have been reported in the medical literature for nonsurgical treatments of AS. The goals of these therapies are to control pain and stiffness, to reduce inflammation, to maintain function, and to prevent deformity. Therapies that have beneficial effects for AS include physical therapy, nonsteroidal anti-inflammatory drugs, and disease-modifying drugs, including tumor necrosis factor (TNF) inhibitors.

Physical Therapy

Physical therapies include a spectrum of interventions including patient education, individualized or group supervised or unsupervised exercises, massage, and temperature modalities. Patients are taught proper posture and mobilizing and breathing exercises to prevent the tendency to stoop forward and lose chest motion.⁷⁵ Patients are instructed to use a flat pillow for sleeping to prevent forward flexion of the neck and upright chair for sitting. Patients with AS benefit from supervised individualized exercises with improved ROM and function.⁴² Difficulty exists in separating the benefits of physical therapy from other interventions in randomized clinical trials.⁷⁷ Use of braces, splints, and corsets should be avoided. Greater disability associated with AS motivates patients to do exercises more frequently than individuals less disabled.²⁹

Nonsteroidal Anti-Inflammatories, Cyclo-oxygenase-II Inhibitors, and Other Disease-modifying Drugs

Medications to control pain and inflammation are useful to the patient with AS. Nonsteroidal anti-inflammatory drugs (NSAIDs) have antipyretic, analgesic, and anti-inflammatory characteristics. Nonsteroidal anti-inflammatory drugs, including cyclo-oxygenase-II (COX-II) inhibitors, currently are available for the treatment of spinal disorders. Nonsteroidal anti-inflammatory drugs are effective at decreasing pain and improving movement.⁵² Cyclo-oxygenase-II inhibitors, including celecoxib, have similar efficacy to standard NSAIDs for AS with less gastrointestinal toxicity.²⁶ Concerns have been raised regarding the cardiovascular effects of the COX-II inhibitors. The cardiovascular effects may include hypertension, edema, and thrombotic events associated with myocardial infarction and stroke. The size of this effect remains to be determined. In addition, the cardiovascular toxicities vary with the individual agents. The effects of NSAIDs to slow progression of ankylosis of the spine may relate to the use of continuous, fixed doses. 2-year randomized controlled trial has shown the benefit of continuous NSAID therapy to prevent radiographic alterations of the axial skeleton in AS patients.⁷⁸

Disease-Modifying Drugs are medications that alter the pathologic mechanisms that cause joint destruction and calcification of musculoskeletal structures. In AS, axial structures are responsive to certain drugs whereas peripheral joints may respond to different agents. Sulphasalazine and methotrexate have been studied for effects on axial and peripheral joints. Sulphasalazine decreases disease affects on peripheral joints but does not benefit axial disease.²⁰ Methotrexate has little effect on axial or peripheral disease.⁵⁸ In a 24-week, placebo-controlled trial with patients given methotrexate 10 mg weekly or a placebo, patients with AS did not obtain benefit in axial or peripheral disease with the active treatment.⁶³ The limitation of this study is the low dose of weekly methotrexate. Methotrexate is given orally to doses of 25 mg weekly. Higher doses may have a greater effect on joint inflammation.

Tumor Necrosis Factor Inhibitors

A major recent advance in the medical treatment of AS is the advent of the tumor necrosis factor (TNF) inhibitors. The TNF inhibitors have shown the control of disease-associated inflammation. Tumor necrosis factor is a pro-inflammatory cytokine produced by monocytes and activated macrophages. Tumor necrosis factor increases production of collagenase and superoxide radicals; mediates fever, anemia, and cachexia; improves vasodilation and vascular permeability; and activates platelets. The biologic activity of TNF is mediated by specific transmembrane receptors on inflammatory cells. A TNF molecule cross-links with two receptors to initiate a response. The extracellular portions of the TNF receptors are shed by cells and act as functional antagonists of TNF. The degree of TNF-mediated inflammation depends on the balance between TNF and its soluble receptor.

The TNF inhibitors include etanercept, infliximab, and adalimumab. Etanercept and infliximab have been studied for the treatment of AS. Adalimumab is used for the treatment of RA. Efficacy data for adalimumab in AS will need future studies done in order to become meaningful scientifically. Etanercept is a dimeric fusion protein consisting of 2 copies of the extracellular receptor ligand for TNF linked by the constant portion of human immunoglobulin G. Infliximab is a chimeric human-murine antibody directed at TNF. This antibody consists of an Fc human constant portion of IgG combined with a Fab murine variable region with binding properties for TNF. Etanercept 25 mg is injected subcutaneously twice weekly or 50 mg once weekly. Infliximab is infused every 8 weeks after an induction period. Infliximab is administered at a dose of 5 mg/kg.

Etanercept has been studied in randomized clinical trials of patients with AS with active disease. In trials ranging from 16 to 40 weeks, etanercept decreased clinical

symptoms and signs of AS.^{9,35} Improvements include decreased morning stiffness, decreased spinal pain, decreased erythrocyte sedimentation rate, decreased C-reactive protein, and improved functioning and chest expansion. In one study, at 4 months, 75% of the etanercept group had improvement versus 30% of the placebo group.³⁵ Improvement was sustained for the 10-month period. No serious toxicities were reported during the study. In a randomized study of 30 patients with AS observed for 18 weeks, 57% of the actively treated patients had decreased swollen joints and functional improvement. Recurrence of symptoms occurred 3 weeks after the treatment was discontinued.²⁴ No severe adverse events were reported in bacterial infections or reactivation of latent tuberculosis. In a large clinical trial of 277 patients with AS, 59% of patients who received etanercept reported decreased inflammation, pain, and improved function versus 28% in the placebo group.²² Few adverse events occurred in this trial.

Infliximab is effective for the treatment of AS, as shown in a 12-week, placebo-controlled, randomized, multicenter trial.¹⁰ In 53% of the actively treated patients had reduction in inflammation in sacroiliac joints, spine and peripheral joints as documented by MRI. Acute phase reactants were reduced. In another randomized, controlled trial of 40 patients with AS treated with infliximab 5 mg/kg, significant clinical improvement also was shown.⁷³ The level of serious adverse reactions was small.

Recent guidelines have been published listing characteristics of patients with AS who are appropriate candidates for TNF inhibitor treatment and the measures to monitor the improvement of these patients.¹¹ Tumor necrosis factor treatment is indicated for individuals with refractory, severe, and active disease. Individuals who do not obtain adequate control of disease with one TNF drug may respond to another of the TNF agents.¹³ The questions that remain are those associated with the discontinuation of medication. In addition, the key question of whether TNF treatment prevents the development of syndesmophyte formation and ankylosis remains to be determined.

Surgical Treatment

Surgical treatment for AS is required in patients for whom nonsurgical treatment has failed. These are patients who have not had the opportunity to receive the benefits of the new TNF inhibitors. Patients with AS who are candidates for surgery are those with severe deformity that impedes vision, walking, eating, abdominal compression, or respiratory function. Patients who have spinal instability related to spondylodiscitis or spinal fracture require surgical intervention.⁷⁰ Atlantoaxial subluxations are rare compared with their frequency associated with RA.

A number of nonspinal considerations are important to consider before surgical intervention for patients with AS. These considerations include osteoporosis, respiratory function, intubation, and nutritional status. Bone mineral density of the spine frequently is diminished, making fixation of instrumentation more difficult. The ankylosis of costovertebral joints limits chest expansion. Involvement of the cervical spine and temporomandibular joints may make intubation problematic. Patients with AS have a systemic inflammatory disease. These patients with AS may have decreased nutritional status, slowing postoperative healing.

The outcomes of surgical intervention for patients with spondyloarthritis has improved not solely based on the improvement of surgical techniques. The advent of spinal cord monitoring, improved imaging techniques, an array of spinal instrumentation, and medical advances in anesthesia and critical care units have resulted in long-term benefits in patients with AS.²⁷

Angular Deformity

Spinal surgery may be required to modify the lumbar, thoracic, or cervical regions of the spine. Historically, spinal surgery to correct deformities included lumbar osteotomies at three levels through the articular processes with resection of the spinous processes resulting in 90° of improvement with postoperative fixation with a plaster immobilization.⁶⁷ This procedure was limited because of anterior syndesmophytes that were an obstacle to mobilization. Subsequently, other techniques were developed including posterior polysegmental osteotomies with stabilization with internal fixation rods.⁴³ This resulted in improved spinal position spread over several segments. Simmons⁶⁷ described a method of local anesthesia to do osteotomies at the L3-L4 levels under the conus in which posterior osteotomy followed by an osteoclasty of the ankylosed anterior longitudinal ligament under continuous intraoperative neurologic monitoring. Originally, fixation was obtained with prolonged immobilization in a Böhler corset. This technique has been supplanted with internal fixation with pedicled screws and rod or cable systems.⁷⁰

Cervical angular disorders related to AS are a rare cause of surgical neck problems evaluated by spine surgeons.⁸² Patients with “chin-on-chest” deformities with kyphotic deformity at the cervicothoracic junction are candidates for cervical osteotomy. The entire spine needs evaluation for sagittal plane deformities because of the presence of corresponding angular abnormalities in the thoracic and lumbar spine.¹⁴ The amount of correction is determined by observing the patient upright with full extension of the hips and knees. A goniometer measures the angle between the patient’s head and the vertical position. The angle is transposed to a lateral roentgenogram, estimating the de-

gree of correction at the C7 to T1 interspace. The osteotomy typically is done at the cervicothoracic junction, at a level at which vertebral arteries are not at risk of kinking.²⁸ Portions of the C7 lamina, superior portion of T1, and inferior portion of C6 are resected. Adequate room for the exiting C8 nerve roots is obtained by resecting portions of the lateral masses. Correction techniques of cervical deformities use local or general anesthesia, halo casting, or internal fixation through Luque or Hartshill rectangles with or without sublaminar wires or cervical lateral mass and thoracic pedicled screws.^{41,50,51,65}

Fractures

The combination of stiffness and osteoporosis produce fracture patterns that differ from those related to regular traumatic injuries. The fracture line goes entirely through the vertebral body and ossified ligaments in a transverse direction resulting in increased risk of instability.⁷⁰ Patients with fractures secondary to hyperextension injuries of the spine are at greater risk of instability and neurologic damage.⁶⁹ Preventing damage to the spinal cord is of prime concern in patients with AS who have a cervical spine fracture. No consensus exists regarding the optimal therapy for these patients.¹² Conservative treatment with immediate immobilization is appropriate with the patients without neurologic deficits. The need for surgical stabilization of these lesions is related to the frequency of early or late neurologic sequelae.^{31,36} Current surgical practice attempts to gain adequate stability of the spine with anterior and posterior fusion to counteract the potential of loss of fixation because of the loss of screw purchase in osteoporotic bone. Internal fixation provides immediate stability, allowing more rapid rehabilitation. However, surgical therapy may be associated with intraoperative nerve damage with progression to complete quadriparesis. Patients with quadriparesis of a few hours' duration usually do not benefit from surgical stabilization and are at risk for postoperative complications.³

Spondylodiscitis frequently is associated with local trauma that causes a stress fracture through an endplate or apophyseal joint. A consideration must be given for infectious discitis before surgical intervention. Surgical stabilization is achieved by anterior grafting and plate fixation.⁷⁰ An alternative is combined anterior grafting with posterior fixation by pedicled screws and rods or by trans-laminar screws.

Surgical complications

Complications associated with AS spinal surgeries are potentially life threatening. Stretching of the spine can result in lengthening of the aorta resulting in tears and bleeding.⁴⁹ Loosening of pedicle screws can occur secondary to

osteoporotic bone. Epidural hematomas may cause spinal cord or nerve root compression. Patients with surgical corrections are at risk of developing spinal stenosis.⁷² In the cervical region, patients are at risk of developing nerve root compression or quadraparesis.⁵⁰

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic, systemic, inflammatory disease that causes pain, heat, swelling, and destruction in synovial joints. The joints characteristically affected by RA are small joints of the hands and feet, wrists, elbows, hips, knees, ankles, and the cervical spine. A majority of patients with RA have cervical spine disease manifested as neck pain, headaches, or arm numbness. Signs of cervical spine disease include decreased neck motion with stiffness, undue prominence of the spinous process of the axis (C2), and neurologic dysfunction including paresthesias, spasticity, incontinence, and quadriplegia. The diagnosis of RA is made in the setting of a history of persistent joint inflammation in the appropriate joints and the presence of specific serum antibodies (rheumatoid factor).

The prevalence of RA is approximately 1% of the United States population. The condition occurs in all age groups, but is most common in those between 40 and 70 years of age. The male-to female prevalence ratio is 1:3. Symptoms of cervical spine disease occur in 40% to 80% of patients with RA.

The pathogenesis of RA is unknown. Rheumatoid arthritis is a chronic immune-mediated disease whose initiation and perpetuation are dependent on T lymphocyte response to unknown antigens.⁵⁹ A number of abnormalities occur secondary to this lymphocytic activation that are beyond the scope of this article. Reviews of our current knowledge are available in the medical literature. Increased numbers of CD4+ lymphocytes that activate B lymphocytes to produce immunoglobulin frequently are found in synovium from patients with RA. The activation of macrophages results in the production of monokines TNF- α , and interleukin (IL)-1. These factors attract additional lymphocytes and neutrophils. Angiogenesis factors result in the growth of new capillaries. Synovial cells cause tissue destruction by release of activated metalloproteinases, including procollagenase and progelatinase. The inflammatory response is also enhanced by the production of arachidonic acid metabolites.

Patients with RA develop joint pain, heat, swelling, and tenderness. The joint involvement is additive and symmetrical. The joints at greatest risk of being affected by the disease process include the proximal interphalangeal, metacarpal-carpal, wrist, elbow, hip, knee, ankle, and metatarsophalangeal joints. In the axial skeleton, the cervical spine is most frequently affected. Patients have joint pain and stiffness, which are most severe in the morning.

Activity improves symptoms. This phenomenon—stiffness of a joint with rest—occurs frequently with active disease. As a component of systemic inflammation, afternoon fatigue, anorexia, and weight loss are common complaints.

Cervical Subluxation

Neck movement frequently precipitates or aggravates neck pain that is aching and deep in quality. Atlantoaxial disease is experienced in the upper part of the cervical spine, and pain radiates over the occiput into the temporal and frontal regions with increasing disease of the C1-C2 joint. Occipital headaches frequently are associated with active rheumatoid involvement of the cervical spine. Other symptoms of C1-C2 subluxation include a sensation of the head falling forward with flexion of the neck, loss of consciousness or syncope, incontinence, dysphagia, vertigo, convulsions, hemiplegia, dysarthria, nystagmus, or peripheral paresthesias.³⁴ Peripheral joint erosion is a harbinger of C1-C2 subluxation. Development of cervical subluxation occurs in patients who have joint erosions of the hands and feet, serum rheumatoid factor, and subcutaneous nodules.

Pain associated with RA in the subaxial segments of the cervical spine is located in the lateral aspects of the neck and clavicles (C3-C4) and over the shoulders (C5-C6). Neurologic symptoms include paresthesias and numbness. The paresthesias have a burning quality that may be attributed to an entrapment neuropathy (carpal tunnel syndrome) but this pain is sufficiently different, not to be confused with joint pain. Patients with sensory symptoms alone may have their symptoms ascribed to arthritis, delaying the diagnosis of cervical myelopathy.⁸¹

Physical examination of a patient with RA reveals diffuse peripheral joint involvement characterized by heat, swelling, boggy tenderness, and loss of motion. Nodules over the extensor surfaces are noted in 20% of patients with RA. Examination of the cervical spine may show tenderness with palpation over the bony skeleton and limitation of all spinal movements. Inspection may show fixation of the head tilted down and to one side. This lateral tilt is caused by the asymmetrical destruction of the lateral atlantoaxial joints. The normal cervical lordosis also may be absent. With the neck flexed, the spinous process of the axis may be prominent in the midline of the neck of the patient with atlantoaxial subluxation. Patients with subaxial subluxation may have abnormalities in the upper extremities. For example, compression of C6-C8 segments causes distinctive numb, clumsy hands and tactile agnosia.¹⁷ Neurologic abnormalities are seen in approximately 7% of patients with RA.

Abnormal laboratory findings include anemia, elevated ESR, and increases in serum globulin levels. Thrombocy-

tosis is found in patients with active RA. Rheumatoid factors (antibodies directed against host antibodies) are present in 80% of patients with RA. Antinuclear antibodies are present in 30% of patients with RA. C-reactive protein, an acute-phase reactant, may be helpful when obtained in a serial manner to predict those individuals who are at increased risk for joint deterioration and as a measure of response to treatment. Individuals with persistent elevations in C-reactive protein are at risk of progressive cervical spine subluxations.³³ Synovial fluid analysis shows an inflammatory fluid characterized by poor viscosity, increased numbers of white blood cells, a decreased glucose level, and an increased protein level.

Characteristic roentgenographic changes of RA in peripheral joints include soft tissue swelling, bony erosion without reactive sclerotic bone, joint space narrowing, and periarticular osteopenia. Radiographic evaluation of the cervical spine includes anteroposterior (AP), lateral with flexion and extension, oblique, and open-mouth frontal projection xrays.

Radiographic Evaluation

The radiographic criteria for the diagnosis of RA cervical spine disease as proposed by Bland et al⁶ are the following: (1) atlantoaxial subluxation of 2.5 mm or more; (2) multiple subluxation of C2-C3, C3-C4, C4-C5, and C5-C6; (3) narrow disc spaces with little or no osteophytosis; (4) erosion of vertebrae, especially vertebral plates; (5) odontoid, small, pointed, eroded loss of cortex; (6) basilar impression; (7) apophyseal joint erosion and blurred facets; (8) cervical spine osteoporosis; (9) wide space (more than 5 mm) between the posterior arch of the atlas and the spinous process of the axis (flexion to extension); and (10) secondary osteosclerosis, atlantoaxial occipital complex, which may indicate local degenerative change. The normal distance between the odontoid and atlas is 2.5 mm in women and 3.0 mm in men, as measured from the posteroinferior aspect of the tubercle of C1 to the nearest point on the odontoid.⁵⁷ The posterior atlanto-odontoid interval is the remaining distance between the posterior surface of the odontoid process and the anterior edge of the posterior ring of the atlas. Patients with RA with a posterior interval of more than 14 mm did not have neurologic deficits. Posterior subluxation may also occur if the atlas “jumps” over the axis resting in a dorsal position, resulting in posterior subluxation. Vertebrobasilar artery insufficiency associated with neurologic dysfunction is a manifestation of this form of subluxation.

Upward translocation occurs when the bony and ligamentous integrity of the atlanto-occipital articulations is disrupted. Disease of the occipital condyles, lateral masses of the atlas, and lateral articulations of the axis results in bony erosions or collapse. Erosion of the lateral apophy-

seal joints allows for a rotational head tilt. The open-mouth view may show narrowing of the atlanto-occipital and atlantoaxial joints and erosion of the odontoid. Subluxation occurs when the lateral masses of the atlas are displaced more than 2 mm with respect to those of the axis. Bony erosion is the most important factor in the development of severe lateral subluxation.

In addition to changes in the upper cervical spine, radiographic abnormalities, including subaxial subluxation, apophyseal joint narrowing, and disc space narrowing, occur in the lower cervical spine. Subaxial subluxation is present in instances of more than 3.5 mm malalignment. The stability of flexion and extension of the lower cervical spine depend on the integrity of the anterior and posterior longitudinal ligaments. Greater than 3.5 mm of malalignment is indicative of a mechanically unstable spine. Multiple subluxations may occur, producing a "staircase" appearance on lateral radiographs. Anterior subluxation is more frequent than posterior subluxation. Subaxial subluxation is most notable on a lateral flexion view of the cervical spine. Apophyseal joint disease includes narrowing, erosions, and sclerosis. Disc destruction in the cervical spine is associated with disc space narrowing and is caused by extension of erosive disease from uncovertebral joints or by ongoing trauma to vertebral end plates secondary to instability. The final stage of apophyseal disease is fibrous ankylosis of one or more levels, which rarely may simulate the appearance of ankylosing spondylitis.

Computed tomography and Magnetic Resonance Imaging

Computed tomography (CT) is a useful radiographic technique for detecting the extent of bony destruction of structures that may not be easily observed with plain roentgenograms. A CT scan detects the position of an eroded odontoid process that may not be seen on open-mouth roentgenograms.

Magnetic resonance imaging (MRI) is a noninvasive method that is useful in detecting soft tissue abnormalities in the cervical spine of patients with RA. Magnetic resonance imaging is able to detect pannus around the odontoid and alterations in the substance of the spinal cord. Magnetic resonance imaging also may be useful in documenting the response of pannus to treatment or the status of the spinal cord in the postoperative state. Compared with CT and plain roentgenograms, MRI with plain roentgenograms shows cystic lesions and odontoid erosions and vertical atlantoaxial subluxations more often, shows anterior subluxations as often, and shows lateral subluxations less often.⁵⁷

Rheumatoid arthritis is a clinical diagnosis based on history of joint pain, distribution of joint involvement, and characteristic laboratory abnormalities (rheumatoid fac-

tor). Criteria for the classification of RA were published by the American College of Rheumatology (Appendix 2).⁴

Nonsurgical Treatment

The treatment of RA has gone through a paradigm shift with the advent of new drug therapies directed at control of the factors that mediate the immunologic destruction of joints.^{18,44} The previous approach involved an initial nonsurgical approach with few medications prescribed until definite erosions were documented. The treatment for control of generalized RA included a regimen of patient education, physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying drugs (sulfasalazine, hydroxychloroquine), corticosteroids, and immunosuppressive agents (methotrexate). The American College of Rheumatology has reviewed the available therapies and has proposed new options for the treatment of RA.¹ These new guidelines include data supporting the use of the biologic agents in the treatment of RA.

Nonsteroidal Anti-Inflammatories, Cyclo-oxygenase-II Inhibitors, and Disease-modifying Drugs

Medications to control pain and inflammation are useful in the patient with RA (Table 1). The choice of agent is dependent on a number of factors, including drug half-life, formulation, dose range, and tolerability. Cyclo-oxygenase-II inhibitors are a class of nonsteroidal anti-inflammatory drugs that have efficacy equal to cyclo-oxygenase I and II inhibitors (aspirin, naproxen) with less gastrointestinal toxicity. Cyclo-oxygenase-II inhibitors are effective in rheumatoid arthritis and are associated with less gastrointestinal toxicities.⁶⁶ Additional studies are being done to determine the extent of cardiovascular events in patients with RA who take cyclo-oxygenase II inhibitors as well as other NSAIDs.

Patients who continue with joint inflammation or who have joint damage (joint space narrowing, bony erosions, or cysts), despite adequate nonsteroidal treatment, are candidates for disease-modifying drugs. Methotrexate at doses from 7.5 to 15 mg per week is effective in decreasing the inflammation of RA and also may slow disease progression. Methotrexate may be given all at once during the week. It is effective for a long duration of treatment.

Leflunomide is an oral pyrimidine inhibitor used for the treatment of RA.¹⁶ The dosage is 100 mg for 3 days, then 20 mg or 10 mg daily as tolerated. Toxicities include abnormal liver function tests and diarrhea. Leflunomide and methotrexate can be used together. Patients on these drugs need to be monitored closely for potential hepatotoxicity.

Systemic corticosteroids are effective controlling the inflammatory components of RA. Corticosteroids are the

TABLE 1. Drug Therapy for Inflammatory Spinal Disorders

Drug (chemical class)	Trade Name	Pill Size (mg)	Maximum Dose (mg/day or week)	Frequency (per day)
Salicylates				
Aspirin	Bayer	81, 325	5,200	4-6
	Ecotrin	325	5,200	
Substituted salicylates				
Diflunisal	Dolobid	250, 500	1,500	2
Propionic acid				
Ibuprofen	Motrin	200, 400, 600, 800	4,800	4-6
Naproxen	Naprosyn	220, 375, 500	1,500	2-3
Flurbiprofen	Ansaid	50, 100	300	2-3
Ketoprofen	Orudis	25, 50, 75, 200	300	1-4
Pyrole acetic acid				
Sulindac	Clinoril	150, 200	450	2-3
Indomethacin	Indocin	25, 50, 75SR	225	2-3
Benzeneacetic acid				
Diclofenac	Voltaren	25, 50, 75, 100SR	225	2-3
Diclofenac/Misoprostil	Arthrotec	50, 75, 200	225	2-3
Oxicam				
Piroxicam	Feldene	10, 20	20	1
Pyranocarboxylic acid				
Etodolac	Lodine	200, 300, 400XL, 500XL	1,600	2-4
Naphthylalkanone				
Nabumetone	Relafen	500, 750	2,000	2
COX-2 inhibitors				
Celecoxib	Celebrex	100, 200	400	2
Meloxicam	Mobic	7.5, 15	15	1-2
Disease-modifying antirheumatic drugs				
Hydroxychloroquine	Plaquenil	200	400	1-2
Sulfasalazine	Azulfidine	500	3,000	1-3
Penicillamine	Cupramine	125, 250	125-750	1-2
Leflunomide	Arava	10, 20, 100	20	1
Methotrexate	Rheumatrex	2.5, 5, 7.5	25	1/week
Azathioprine	Imuran	50	50-300	1
Etanercept	Enbrel	25, 50	100	1/week
Adalimumab	Humira	40	40	2 weeks
Infliximab	Remicaide	3 mg-10 mg/kg	10 mg/kg	8 weeks

most powerful and predictable remedy, inducing immediate relief of joint inflammation in RA. Corticosteroids at low doses (5 mg to 10 mg) have a modest effect on reducing the rate of radiologically detected joint destruction. A prospective trial demonstrated disease-modifying properties of 10 mg of prednisone over a 2-year period.⁷⁶ Corticosteroids also are associated with a wide range of toxicities, from hypertension and diabetes to cataracts and obesity.

Tumor Necrosis Factor (TNF) Inhibitors

Tumor necrosis factor inhibitors are available in the form of infliximab, etanercept, and adalimumab that inhibit the inflammatory effects of TNF. These therapies are efficacious in the treatment of RA.

Infliximab is added to methotrexate to limit the production of neutralizing antibodies to the murine component of

the agent. In a 30-week trial, infliximab and methotrexate together were more effective than methotrexate alone in patients with active RA.⁴⁷ In a 54-week study, infliximab at 3 mg/kg or 10 mg/kg and a stable dose of methotrexate prevented radiographic progression to a greater degree than methotrexate alone.⁴⁵

Etanercept is more effective than placebo in limiting joint activity in RA.⁵³ Etanercept also is effective and safe when added to methotrexate.⁷⁹ The therapeutic dose of this medication is 50 mg subcutaneously once a week. This drug also is effective during a 12-month period.⁵

Adalimumab is effective with methotrexate in decreasing joint activity.⁸⁰ The effective dose is 40 mg subcutaneously every 2 weeks. The concern with the anti-TNF therapies are the toxicities. Blocking TNF does increase the risk for serious infection. Tumor necrosis factor helps to maintain containment of organisms in granulomas. In-

hibition of TNF has been associated with the reactivation of tuberculosis.⁴⁰

Anakinra is a recombinant, nonglycosylated form of human IL-1 receptor antagonist. This agent works by competitively inhibiting IL-1 from binding to its receptor site. Anakinra is given as a daily subcutaneous injection of 100 mg. Anakinra has been shown to be an effective agent in combination with methotrexate in the improvement of RA.²¹

Nonsurgical treatment of RA cervical spine disease is supportive. Combination treatment used early in the course of RA can limit the development of atlantoaxial and vertical subluxations. Sulfasalazine, methotrexate, hydroxychloroquine, and prednisolone were more effective than a single disease-modifying drug with prednisolone in preventing cervical subluxation.⁵⁵ Soft cervical collars offer comfort but do not protect against progressive subluxations. Rigid collars can limit anterior subluxations but do not allow reduction of the subluxations in extension. Rigid collars are poorly tolerated by patients with RA with temporomandibular disease.³⁹ In a patient in whom surgery is a significant risk, cervical traction and immobilization with a Halo vest will result in stabilization of subaxial subluxation without progressive myelopathy.⁵⁶

Surgical Treatment

The role of surgery in the treatment of patients with RA with cervical spine disease, particularly those who are asymptomatic, is controversial. Approximately, 33% of patients with RA develop myelopathy. Against the potential for neurologic dysfunction are a mortality rate of 15% and a successful fusion rate of only 50%.

Surgical intervention is indicated in patients with RA with intractable pain and neurologic deficit, vertebral artery compromise, or evidence of increased signal intensity within the spinal cord on T1-weighted MRI sequences. A posterior atlanto-dental interval of 14 mm or less is a measurement of patients at considerable risk for paralysis.⁷ Patients with isolated atlantoaxial subluxations and no neurologic deficit can be observed. Other forms of subluxations must be evaluated with concern regarding neural impingement and adequate space in the spinal canal.⁶¹ Long-term followup studies in patients with RA who have atlantoaxial subluxation and pain but without neurologic deficits reported a lower mortality with surgical stabilization with posterior fusion than those treated nonoperatively.⁷¹

Posterior arthrodesis is required for reducible atlantoaxial subluxations (Fig 2). This procedure stabilizes the joint and results in resorption of pannus.³⁷ Excessive pannus resection is not required with adequate stabilization. Irreducible subluxations may require a transoral approach for decompression and posterior fusion. Patients with ver-



Fig 2. A postoperative lateral view of the cervical spine in a 56-year-old woman with more than a 20-year history of RA increasing neck pain and dysesthesias in her arms shows the presence of surgical wires stabilizing her C1-C2 spinous processes. She has had resolution of her symptoms for the 5 years after the procedure. Reprinted with permission from Reprinted with permission from Borenstein DG, Wiesel SW, Boden SD. *Low Back and Neck Pain: Comprehensive Diagnosis and Management*. Ed 3. Philadelphia, PA: Saunders; 2004:316.

tical subluxations require tong traction to reduce subluxations, transoral anterior decompression, and occipitofusion to prevent recurrent cranial settling. A number of techniques may be used for stabilization of C1-C2 abnormalities including Brooks fusion, trans-articular C1-C2 screw placement, and occipital-cervical arthrodesis.²⁸

Subaxial subluxation requires stabilization.²³ One approach is posterior stabilization of the subluxated segment. The posterior approach is preferred when multiple levels are subluxated. An alternative approach is anterior decompression and fusion. This approach consists of corpectomy, decompression, and strut graft fusion with or with-

out instrumentation. Laminoplasty also has been suggested as a surgical technique for subaxial subluxation in patients with less severe RA.⁵⁴

Atlantoaxial rotatory (lateral) subluxations occurs secondary to C1-C2 joint damage allowing rotation of the cranium. This subluxation is progressive and may result in permanent fixed torticollis that is painful. This subluxation requires halo traction to correct the subluxations and occiput-to-axis fusion. These patients remain in a halo vest for 10 to 12 weeks postoperatively.

Progressive spinal disease may occur despite successful surgical stabilization of cervical spine segments. In a study of 83 RA patients treated with cervical spine surgery, 17 showed recurrent subluxation at between 1 to 17 months after their procedure. Seven individuals required additional surgery at the same level.¹⁹

DISCUSSION

The current status of treatment for inflammatory spine disease is in flux. A number of new medical therapies are under active clinical investigation and have the potential to prevent the destruction of skeletal structures. Although these new therapies offer great hope for individuals with these disorders, many questions remain regarding their use. These biologic therapies prevent progression of disease, but do not offer a true remission of the disorders. The activity of disease returns in a duration of weeks to months after the medications are discontinued. The time for initiation of these expensive therapies is also debated. Are they cost effective? Outcome measures to determine efficacy and improved function are insensitive in detecting improvements. The general consensus is that the new biological therapies are effective. How that statement results in improved lives remains to be determined.

Surgical therapy for patients with AS and RA is reserved for those individuals with progressive, severe disease. Most of the patients reported in the literature were treated with medical regimens before the availability of the new biologic, immune-modifying drugs. Angular deformities in AS and subluxation in RA occurred in the absence of medical therapy or in individuals resistant to usual medical therapy. These patients not only were devastated by their inflammatory diseases but also were in poor general health. Systemic disease caused a generalized inflammation categorized by a catabolic status associated with poor wound healing and decreased bone mineral density. The patients who required surgery most urgently were at greatest risk of having poor outcomes. In addition, once neurologic damage occurred, surgical therapy did not guarantee an improved outcome. Surgical intervention at best might stabilize a deficit or at worse might cause complete quadriplegia. Therefore, the ideal surgical candidate

is the patient without neurologic deficits who is asymptomatic or has a minimal amount of pain.

Surgical treatment for inflammatory diseases of the spine consists of salvage procedures for spinal instability and malformation. These procedures should become obsolete. Medical treatment for AS and RA has gone through major advances with biologic therapies. The era of marked joint destruction should be behind us. The need for surgical intervention should diminish substantially. The spinal surgeon who completes these procedures should have experience with patients with inflammatory arthritis. These procedures should be accomplished at medical centers with services of multiple specialists who are capable of treating patients with severe disabilities.

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APPENDIX 1. MODIFIED NEW YORK DIAGNOSTIC CRITERIA FOR ANKYLOSING SPONDYLITIS*

Clinical Criteria

- Lower-back pain and stiffness for > 3 months that improves with exercise but is not relieved with rest
- Limited lumbar spine motion in frontal and sagittal planes
- Limitation of chest expansion

Radiographic Criteria

- Requires either bilateral sacroiliitis > Grade 2 or unilateral sacroiliitis > Grade 3

*DEFINITE ankylosing spondylitis = one clinical criterion plus one radiographic criterion and PROBABLE ankylosing spondylitis = three clinical criteria and no radiologic criteria or one radiologic criterion and no clinical criteria

APPENDIX 2. AMERICAN RHEUMATISM ASSOCIATION 1987 REVISED CRITERIA FOR THE CLASSIFICATION OF RHEUMATOID ARTHRITIS

1. Morning stiffness

- Morning stiffness in and around the joints lasting at least 1 hour before maximal improvement

2. Arthritis of three or more joint areas
 - At least three joint areas simultaneously have soft tissue swelling or fluid (not bony overgrowth)
3. Arthritis of hand joints
 - At least one area swollen (as defined above) in a wrist, metacarpophalangeal, or proximal interphalangeal joint
4. Symmetrical arthritis
 - Simultaneous involvement of proximal interphalangeal, metacarpophalangeal, or metatarsophalangeal joints is acceptable without absolute symmetry
5. Rheumatoid nodules
 - Subcutaneous nodules over bony prominences, extensor surfaces, or juxta-articular regions observed by a physician
6. Serum rheumatoid factor
 - Demonstration of abnormal amounts of serum factor by any method for which the result has been positive in less than 5% of normal control subjects
7. Radiographic changes
 - Radiographic change typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs; must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)