RHEUMATOID ARTHRITIS: CURRENT PHARMACOLOGIC TREATMENT AND ANESTHETIC CONSIDERATIONS

DEEPA REDDY[*], LANDON W. TROST[*], TRAVIS LEE[*],
AMIR R. BALUCH[**] AND ALAN D. KAYE[***]

Introduction

Rheumatoid arthritis (RA) is a disorder characterized by acute and chronic systemic inflammation that primarily involves the joints, but may also affect many tissues and organs, including blood vessels, heart, skin, lungs, and muscles. The onset and severity of disease is variable and usually insidious. RA initially presents with fatigue, musculoskeletal pain, and stiffness and only after weeks to months does it progress to involve joints. Generally, the small joints are affected first, particularly the small bones of the hands. Later larger joints are affected, becoming swollen, warm, and painful[1]. Morning stiffness or stiffness upon inactivity are symptoms of RA and indicate active disease. The patient usually describes slowness or difficulty moving when getting out of bed or after staying in one position too long. Both sides of the body are involved and symptoms decrease with movement[2]. Since there are no specific laboratory tests, the diagnosis of RA it is made based on clinical features. Four of the seven criteria listed in Table 1 confirm the diagnosis[1].

* Medical Student, Tulane University School of Medicine, New Orleans, Louisiana, USA.
**MD, Anesthesia Resident, University of Miami School of Medicine, Miami, Florida, USA.
***MD/PhD, Professor and Chairman, Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX.
  The author and editor have no relationships with pharmaceutical companies or products to disclose, nor do they discuss off-label or investigative products in this lesson, USA.

Table 1
Clinical Features of Rheumatoid Arthritis

Morning stiffness ≥ 1 hour and present for > six weeks
Swelling of three or more joints for > six weeks
Swelling of wrist metacarpophalangeal or proximal interphalangeal joints > six weeks
Symmetric joint swelling
Hand X-ray changes typical of RA. Include erosions or unequivocal bony decalcification
Rheumatoid subcutaneous nodules
Positive rheumatoid factor

Rheumatoid arthritis is initially a clinical diagnosis after recognition of several of the above features.

Patients with RA are affected differently by the disease. Some may have mild onset disease with no severe symptoms, whereas others have progressive disability for life[1].

Currently, treatment strategies focus on alleviating active inflammation, because no curative treatment exists. The aim is to limit joint destruction. Recommended drug therapies include analgesics, NSAIDs, glucocorticoids, DMARDs, and anticytokines, used separately or in combination. Other conditions that affect individuals with RA include infections, renal impairment, lymphomas, and cardiovascular disease[3]. Iatrogenic effects of therapy may also play a role in the complications that arise with RA, associated with chronic use of non-steroidal anti-inflammatory drugs and steroids[1]. Mortality due to RA alone is low but may increase two-fold because of complications. Lifespan may decrease 7-10 years[4].

Epidemiology

RA affects about 1% of the world's population[1]. No population is immune but women are affected two to three times as often as men. The peak age of onset is between 30 and 55. Annually, the incidence of RA is 30 per 100,000 people. Due to the fact that women are affected more than

men, the prevalence of RA in women over the age of 65 is around 5%[5]. Risk factors for the development of RA include smoking, obesity, concurrent infections, advancing age, female gender, and genetic inheritance, while oral contraceptives and some dietary constituents may be protective.

Causative Factors

RA is a common disorder that has plagued people for centuries[6]. Many possible causative agents have been identified, yet the etiology of disease is still unknown. Women are affected by RA predominately more often than men and a possible reason includes the effects of estrogen on the immune system via a T-suppressor cell pathway.

It is believed that a genetic component to RA may exist. Supporting evidence includes an increased incidence in individuals carrying an epitope in the third hypervariable region of the HLA-DRB chains. Although there is still uncertainty in the etiology of RA, HLA genotyping may help predict relative risk, disease severity, and response to therapy.

Serum rheumatoid factor, an immunoglobulin with anti-IgG Fc specificity, is another genetic component that can be found in patients with RA. Rheumatoid factor is highly characteristic of RA, but is not specific, so clinicians do not rely solely on this finding for diagnosis[1]. Twin studies have also shown that there is a hereditary component involved with RA as monozygotic twins have a higher incidence of RA than dizygotic twins[7,8]. The relationship has held true for first degree relatives: they have a 1.5 increased risk of developing RA than individuals in the general population[9]. Another significant correlation is the link between RA and other diseases believed to have an autoimmune pathogenesis. There is overlap between alleles of RA, lupus erythematosis, inflammatory bowel disease, multiple sclerosis, and ankylosing spondylitis[10].

Environmental factors, such as smoking, have also been implicated in causation. Some studies have suggested that cigarette smoking

enhances the development of RA[11]. Cigarette smoking is also associated with more severe disease, where smokers with at least a 25 or more pack-year history are more likely to be seropositive, have nodules, or have more radiographically apparent erosions[12,13].

Infection is yet another environmental factor and may offer further explanation as to the possible etiology of RA. One of the prime suspects for a microbial trigger to RA is the Epstein Barr virus (EBV). In 1975 an antibody in the sera of RA patients was shown to react with an Epstein Barr nuclear antigen[14,15]. Since then further findings have linked RA and EBV, one of which is that EBV is a polyclonal activator of B lymphocytes, including those that express rheumatoid factor. Other agents that have been suggested in the development of RA include mycoplasma, proteus mirabilis, parvovirus, and retrovirus[1]. Further studies may elucidate the exact role these microorganisms play in the etiology of RA.

Pathogenesis

Although much about the etiology of RA seems uncertain, it is believed that RA is initiated by an arthritogenic microbial antigen acting on an immunogenetically susceptible host[1]. The origin of the arthritogenic antigen is currently unknown, yet it is still able to cause disease by activating an immune response. Once the host is attacked, the first event to occur is the activation of CD4+ helper T-cells which then release local inflammatory mediators and cytokines. Soon thereafter, endothelial cells of synovial capillaries are triggered, with the expression of intercellular adhesion molecule-1 (ICAM-1). This in turn leads to the migration and attachment of other inflammatory cells to the affected joint. While CD4+ cells are being activated, B cells are also triggered, which results in antibody production in the affected joints[1]. In 80% of patients with RA, autoantibodies to the Fc portion of autologous IgG, also known as rheumatoid factors are formed[1]. However, these factors are not diagnostic for RA because they may not be identified in some patients but found in other disease states. The circulating immune complexes are mostly localized within the inflamed cartilage activating complement and

enhance the synovial inflammatory reaction[1]. The synovium in RA organizes into invasive tissue, that if left untreated, can degrade cartilage and bone and eventually lead to the destruction of the joint.

Clinical Manifestations

The clinical picture of RA varies with a majority of patients presenting initially with a slow and insidious disease. The symptoms that predominate during this preliminary phase are musculoskeletal pain, stiffness, and swelling of many joints[16]. Sites of early arthritis are typically localized in the metocarpophalangeal and proximal interphalangeal joints of the fingers, interphalangeal joints of the thumbs, the wrists, and metocarpophalangeal joints of the toes. Other joints that also may be affected initially include joints of the upper and lower limbs, such as the elbows, shoulders, ankles, and knees[17,18]. Uncommonly the upper spine may be involved, but the lumbosacral region and hips are usually spared. As noted above, morning stiffness is typical. In about 10% of individuals with RA the onset of disease is acute and presents with severe symptoms and polyarticular involvement developing within a few days[1]. But the typical clinical picture presents with progressive joint involvement over a period of months to years, with initial minimal limitation of motion that in time becomes more severe. The course of RA may be fast or slow and fluctuates over a period of years, with the majority of the damage incurring in the first 4 or 5 years following disease onset. One-fifth of patients have periods when their symptoms partially or completely resolve!

Radiographic hallmarks of RA are joint effusions and juxta-articular osteopenia with erosions and narrowing of the joint space with the loss of articular cartilage[1]. With continued destruction of ligaments, tendons, and joint capsules, characteristic deformities are produced on imaging which include, radial deviation of the wrist, ulnar deviation of the fingers, and flexion-hyperextension abnormalities of the fingers[1]. However, with time, extensive destruction occurs and the severity of erosions may reach a level beyond which further progression of the RA cannot be assessed radiographically[19].

Diagnosis

Laboratory tests to diagnose RA definitively do not exist, but genetic tests are available to test for susceptibility. These factors do not guarantee that patients will develop the disease, but the chances for the possibility of occurrence are much greater than in the general population. The majority of individuals who have RA are positive for both HLA-DR beta and rheumatoid factor. These genetic factors are clearly major determinants for RA, however clinicians cannot rely solely on these factors for diagnosis. Synovial fluid in the inflamed joint can also be analyzed for leukocytosis of neutrophils or lymphocytes, low glucose and complement levels, and protein levels approaching those in plasma[20]. This test is nonspecific for RA, yet it may be used as a means to confirm the presence of inflammatory arthritis. Clinical features aid in the confirmatory diagnosis.

Current and New Therapies

Appropriate treatment early in the course of RA is essential to maintain joint function. The longer active disease persists, the less likely the patient is to respond to therapy[21]. Evidence has shown that early treatment can control synovitis and may slow, or even stop, radiographic progression of disease[16]. The goals of treatment include controlling signs and symptoms of RA, restoring physical function to joints, and preventing joint damage. If joint damage already exists then the goals are to ameliorate or halt progressive disease[22]. However, despite all the current therapies available it may not be possible to achieve complete remission[6].

Pharmacologic Therapy (Table 2)

Drug therapy is a mainstay in treatment options. The goals of pharmacologic therapy are to induce remission and prevent further loss of joint tissues or function in daily activities[22]. Physicians can manage their patients by manipulating the order in which they administer drugs,

adjusting dosages, and offering different combinations. There are five main drug classes that are currently used for treatment and they include analgesics, nonsteroidal anti-inflammatory drugs (NSAIDS), glucocorticoids, disease-modifying antirheumatic drugs (DMARDS), and anticytokine therapies.

Analgesics provide pain relief from mild to moderate arthritis. Included in this class are acetaminophen, tramadol, capsaicin, and narcotics. Due to the fact these drugs do not exhibit any anti-inflammatory properties, they are usually combined with NSAIDs, glucocorticoids, DMARDS, and anticytokine therapies.

Nonsteroidal anti-inflammatory drugs have both analgesic and anti-inflammatory properties but do not change disease outcomes[23]. The drugs in this class include ibuprofen, aspirin, naproxen, and indomethacin. They inhibit COX-1 and COX-2, which block prostaglandin synthesis. NSAIDs are useful for treating the symptoms of RA, but are unable to prevent the development of progressive disease. Although NSAIDs are essential to the treatment of RA, they can cause severe GI distress and ulcers. On the other hand, selective COX-2 inhibitors are also just as useful in the treatment of RA, but have a lower severity of these adverse GI side effects. These drugs include celecoxib and valdecoxib and are similar to the NSAIDs except that they do not have the same corrosive effects on the GI lining. However, when administering these drugs, the patients' medical history must be assessed to ascertain that cardiovascular disease is not significant. COX-2 inhibitors are associated with reduced PGI2 production by vascular endothelium with little or no inhibition of potentially thrombotic platelet thromboxane A2 production. This, in turn, predisposes to endothelial injury, which can increase ischemic cardiovascular events[24]. Since there is still uncertainty about the safety of COX-2 inhibitors, administration of these drugs should be decided on a case by case basis.

The most commonly used glucocorticoids are prednisone or prednisolone. Glucocorticoids may be administered orally, intravenously, or by intraarticular injection. The actions of these drugs on joint pain are much greater than NSAIDs and analgesics but they come with many side

effects including adrenal suppression, ulcers, and osteoporosis[25]. When deciding on whether or not to initiate therapy with glucocorticoids, other medical conditions which may possibly increase the risk of glucocorticoid drug toxicity should be assessed. These conditions include established hypertension or diabetes, preexisting cataracts or glaucoma, and significant risk factors for osteoporosis[26]. Furthermore, the physician should explain potential side effects, the importance of limiting the duration and dosage of glucocorticoids, directed use, the difficulty in ceasing use of steroids, as well as the danger of long-term use and abrupt cessation. All patients receiving long-term glucocorticoid therapy should wear a medical alert bracelet. Finally, all patients should be counseled on smoking cessation and/or cholesterol reduction in order to curtail cardiovascular risk factors[26].

DMARDs are disease-modifying antirheumatic drugs that encompass a large group of drugs that reduce the progression of joint erosion. These drugs have slow onsets and no analgesic activity. DMARDs include gold compounds, penicillamine, hydroxychloroquine, cyclophosphamide, and methotrexate. The actions of these drugs are probably related to reduction of phagocytosis and immune responses[22].

The last class of drugs available to treat RA is anticytokine therapies. The action of these drugs is still unknown, but it is thought that they act by decreasing the inflammatory response in affected joints. Examples of these drugs include anti-tumor necrosis factor alpha agents, etanercept, infliximab, and adalimumab and the interleukin-1 receptor antagonist, ankinra. There are, however, case reports stating that the anti-TNF-alpha agents may induce leukosytoclastic vasculitis and even neurologic manifestations, with resolution after the drus are removed. These drugs are newer treatments and in the future additional biological therapies will probably become available[27,28].

All of these drug therapies are useful in the treatment of RA and when administered in combination have a greater ability for relief. When choosing a treatment regimen for a patient one should take into consideration the severity of the disease, possible adverse effects of treatment, convenience to the patient, and patient preferences[29].

Table 2
Medications Used to Treat Rheumatoid Arthritis

Several classes of drugs have been used to treat rheumatoid arthritis. They are associated with many side effects.

Drug	Mechanism of Action	Side Effects and Precautions
Acetaminophen	Reversibly inhibits COX, mostly in the CNS	Hepatotoxicity at high doses
Aspirin	Irreversibly inhibit COX-1 and COX-2. Block prostaglandin synthesis	Gastric upset, GI and duodenal ulcers, hyperventilation, tinnitus, Reye's syndrome
Ibuprofen	Reversible inhibitor of COX-1 and COX-2. Block prostaglandin synthesis	Renal damage, aplastic anemia, GI distress, ulcers
Celecoxib	Selective reversible inhibitor of COX-2	Renal toxicity, less GI irritation than NSAIDs, possible risk of cardiovascular events
Prednisone	Decrease production of leukotrienes and prostaglandins by inhibiting phospholipase A2 and expression of COX-2	Iatrogenic Cushing's syndrome
Methotrexate	Unknown	Contraindicated in pregnancy, ulcerative stomatitis, leucopenia, nausea, abdominal distress
Gold Salts	Alters the morphology and functional capabilities of macrophages and may also alter lysosomal enzyme activity	Dermatitis, stomatitis, maybe toxic to kidney
Azathioprine	Interferes with DNA synthesis	Contraindicated in pregnancy, bone marrow suppression, anemia, skin rashes, fever, diarrhea, nausea
Infliximab	Neutralizes the biological activity of TNF-alpha	Increased incidence of lymphoma

Adapted and modified from Guidelines for monitoring in drug therapy in Rheumatoid Arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum, 39:723, 1996.

Clinically Relevant Organ System Issues

Many complications may arise with RA. One such complication is cervical joint destruction that may lead to vertebral subluxation. Although rare, the anesthesiologist must be cognizant of this potential situation. Among all the joints in the spine, the atlanto-axial (C1-C2) joint is most prone to subluxation. The atlas (C1) can move anteriorly, posteriorly, vertically, or laterally relative to the axis (C2). Abonormal anterior movement on C1 is the most common type of subluxation, whereas the least common is vertical movement in relation to the axis[30,31]. Intervertebral joints in the cervical spine become involved by extension of the inflammatory process from adjacent neurocentral joints and chronic cervical instability initiated by apophyseal joint destruction[32]. Usually the severity and involvement of cervical spinal disease is related to the progression of peripheral joint erosions especially in individuals with hand, feet, hip, and knee erosions[33,34]. The symptoms associated with atlanto-axial subluxation are pain radiating superiorly towards the occiput, slowly progressive spastic quadriparesis, sensory abnormalities, and transient episodes of medullary dysfunction[35,36]. These symptoms can cause changes in levels of consciousness, "drop" attacks, sensation of the head falling forward upon flexion of the cervical spine, loss of sphincter control, respiratory dysfunction, dysphagia, vertigo, convulsions, hemiplegia, dysarthria, nystagmus, or peripheral paresthesias without evidence of peripheral nerve disease or compression[37]. If such neurological signs are present, immediate attention needs to be taken to distinguish the origin of the symptoms and assess for the appropriate treatment of the underlying condition. Treatment for cervical subluxation is essential and is based on whether or not spinal cord compression exists. Usually patients with subluxation without signs of spinal cord compression are offered medical therapy, whereas patients with subluxation and signs of spinal cord compression require surgical intervention. Medical therapy for RA patients with cervical subluxation mostly consists of prescription of stiff collars for stability. The benefits of this treatment are prevention of severe injury or death associated with small falls, whiplash injuries, and intubation[38]. Fiberoptic intubation with the collar in place may be required to prevent further cervical injury. Surgical therapy offered to patients with atlanto-

axial subluxation is usually C1-C2 fusion. This treatment may prevent superior migration of the odontoid and decrease the risk of further progression of cervical spine instability[39]. Complications of this complex procedure include infection and progressive subluxation that may require reoperation[40].

Another difficulty that may arise with progressive RA disease is complications associated with cardiac involvement including pericarditis, myocardidits, and atherosclerosis. The incidence of pericarditis associated with RA varies greatly. Most RA patients with pericarditis are asymptomatic with echocardiographic evidence of pericardial effusions of no clinical significance[41]. On the other hand, patients with symptomatic pericarditis usually have active rheumatoid disease and other extraarticular manifestations. Therefore for the most part management of this condition should be linked to control of RA[41]. Myocarditis is a rare complication and can present in either interstitial or granulomatous forms. The granulomatous variety is highly specific for RA, where as the interstitial form is more related to SLE. Granulomatous involvement of the endocardium can cause mitral insufficiency, while involvement of the conduction system can induce atrioventricular block[20]. Atherosclerosis is the most common cardiovascular event affecting patients with RA. The risk of sudden death and myocardial infarction appear to be increased[42]. The potential mechanisms for myocardial infarction include changes in the endothelium due to circulating immune complexes, cytokines, or C-reactive protein, hypercoaguable state due to increased plasma levels of fibrinogen, von Willebrand factor, plasminogen activator inhibitor, and other acute phase reactants, and direct vascular injury due to dyslipidemia associated with glucocorticoid therapy or rheumatoid vasculitis[42-44]. The most important treatment option for RA induced atherosclerosis is strict control of inflammation with the use of aggressive therapy[45].

Lung disease may also be associated. Etiology can be related to treatment-induced lung disease or infection secondary to immunosuppression. Treatment-induced lung disease may arise from the use of DMARDS. Methotrexate has been shown to cause pulmonary complications the most common being acute interstitial pneumonitis[46].

The etiology of the acute pneumonitis may be due to a hypersensitivity-type mechanism[47]. Pneumonitis has also been associated with the use of gold-salts, which occurs after the ingestion of about 500 mg of gold. Patients usually present with cough and dyspnea, which resolves after the removal of treatment[48]. Although rare, obliterative bronchiolitis has been related to the use of d-penicillamine and has a poor prognosis with an estimated mortality rate of 50 percent[49].

Upper airway disease is common in patients with long-standing RA disease. Early symptoms of upper airway disease may include hoarse voice, pain upon swallowing, tenderness of the throat, pain on coughing or speaking, or exertional dyspnea. These symptoms are due to obstruction of the upper airway secondary to cricoarytenoid and laryngeal involvement. These symptoms may not be apparent until significant obstruction is present. If the airway was already distorted or swollen, emergent situations may result in complete obstruction arise if airway edema develops secondary to repeated or failed intubation attempts. Intubation can also be further complicated by RA induced cervical spine instability, and should be performed without excessive neck flexion[50].

Anesthetic Considerations and Management

Preoperative Evaluation

Systemic Effects

The systemic effects of rheumatoid arthritis must be considered preoperatively. Malnutrition, poor wound healing, and anemia are often present in this population secondary to multiple drug ingestion. The ultimate cause of the anemia should be evaluated since NSAIDs predispose to gastrointestinal bleeds. Furthermore, the presence of anemia may mean there is also hypovolemia and hypoproteinemia, as well.

Since cardiovascular disease is the leading cause of death in RA patients, the cardiac system (pericardial thickening, effusions, arteritis, cardiac valve fibrosis, rheumatoid nodules in the cardiac conduction system) must be given particular attention. Pericardial disease commonly

manifests itself if the RA patients has a cardiovascular disorder, but up to 45% of patients with pericardial involvement may not be symptomatic[51]. An echocardiogram may be ordered if clinically indicated from the cardiovascular examination. For example, suspicion of a cardiac tamponade may warrant an echocardiogram and possibly placement of a pericardial window.

Long-standing rheumatoid arthritis may compromise the respiratory system. Pulmonary hypertension may be present secondary to an underlying pulmonary vasculitis. Pleural disease, lung nodules, interstitial pulmonary fibrosis, and obliterative bronchiolitis may be present. Review of chest radiographs, restrictive changes with decreased lung volumes and vital capacity, and ventilation/perfusion mismatch are tolls used to diagnose underlying pulmonary pathology.

The renal and hepatic systems may be compromised. An amyloidosis or vasculitis may impair renal function. Vasculitis may damage hepatic tissue which may present as hypoalbuminemia and elevated hepatic transaminases. Hepatotoxic effects of nonsteroidal anti-inflammatory agents may manifest with increased alkaline phosphatase[52]. Immunosuppressant medications such as penacillamine, methotrexate, and azathiprine, may retard wound healing. If a rheumatoid arthritis patient is using chronic steroid treatment for pain, perioperative supplementation will most likely be required **[Table 3]**. Reviewing general symptoms of adrenal insufficiency is recommended, although these symptoms present in a variety of diseases **[Table 4]**.

Table 3

Suggested Corticosteroid Regimen [adapted from 53]

Supplemental steroid administration is often used for patients who have received steroids previously. One proposed scheme is presented.

Day of surgery	Give hydrocortisone 100 mg intramuscularly and every 6 hours thereafter. Add maintenance dose, if any.
Postop day 1-3	Follow same regimen as day of surgery
Postop day 4	Discontinue hydrocortisone treatment. Continue maintenance dose, if any.

Adapted and modified from Eisele, JH. Connective Tissue Diseases: Benumof JL, ed. Anesthesia and Uncommon Diseases. 4th ed. New York: W.B. Saunders Company; 398-

421, 1998.

Table 4

Symptoms of Adrenal Insufficiency

The table below represents non-specific symptoms that may or may not present in a patient with adrenal insufficiency

Hypotension	Headache
Restlessnes	Fatigue
Weakness	Fever/Chills
Anorexia	Confusion
Nausea	Darkening skin
Vomiting	Tachycardic
Abdominal Pain	Tachypnea
Hyperpyrexia	Sweating

The following 14-point checklist (Table 5) has been recommended by Eisele, JH[53] to evaluate the operative risk in patients with rheumatoid arthritis since they may present with long standing chronic disease and nutrition/drug induced anemias. Furthermore, review of systems and physical/lab findings may commonly lead to echocardiographic testing related to rheumatoid arthritis induced pericarditis, myocarditis, valve abnormalities, or atherosclerosis. Recent general anesthesia may reveal prior complications or successful techniques used. Although past history may not predict the present difficulty of performing general anesthesia, a complicated anesthetic technique may influence current strategy (i.e., choosing between regional and general anesthesia). Drug therapy may help predict or direct investigation for underlying systemic effects such as GI bleeds due to NSAIDS or elevated glucose due to corticosteroids. A long history of drug use should make one more suspicious of complications from that medication compared to a more recently started regimen. Examination of the jaw/neck and laryngoscopy aids the anesthesiologist by allowing visualization of the airway anatomy and jaw mobility or immobility before surgery. Chest and skeletal X-rays help identify nodules, effusions, or bony abnormalities of the chest wall that may complicate breathing and oxygen exchange during the surgical

procedure. Pulmonary function tests (PFTs) can help determine if a restrictive pattern is present secondary to fibrosis and can help decide on the I:E ratio settings of the anesthesia machine. To rule out pericarditis or other cardiac pathologies (cardiac conduction abnormalities, valve abnormalities), and EKG and/or echocardiography may be performed. In this regard, patients with significant cardiac, pulmonary, or renal pathology may possess abnormal arterial blood gas (ABG) values, and an ABG should be taken to ascertain perioperative needs. Since these patients may also present with anemia or abnormal white blood cell and platelet count, a routine CBC should be used preoperatively and can guide the clinical anesthesiologist on the need for blood transfusion or additional testing/consultation. Urinalysis and creatinine clearance may help diagnose renal impairments secondary to an underlying amyloidosis, drug-induced nephropathy, or vasculitis. Finally, occult blood may suggest the possibility of a GI bleed secondary to drug usage such as NSAIDS **[Table 5]**.

Table 5
Preoperative Checklist
The following is a 14 point list of issues to evaluate preoperatively in the rheumatoid patient.

1	Recent general anesthesia	8	Blood gas
2	History of drug therapy	9	EKG
3	Check jaw/neck mobility	10	Hemoglobin/ESR
4	Laryngoscopy (indirect)	11	WBC/Platelets
5	Chest X-ray	12	Urinalysis
6	Skeletal X-ray	13	Occult blood in stool
7	Pulmonary function tests	14	Creatinine clearance

Adapted and modified from Eisele, JH. Connective Tissue Diseases: Benumof JL, ed. Anesthesia and Uncommon Diseases. 4th ed. New York: W.B. Saunders Company; 398-421, 1998.

Airway assessment

More than half of RA patients suffer from jaw pathology such as decreased mobility, crepitus, and tenderness[51]. The anesthesiologist

should evaluate the extent of mouth opening as well as palpate the temporomandibular joint for pain. A reduced aperture of the mouth may necessitate the use of a fiberoptic scope.

Arthritis is frequently found in the cricoarytenoid joint, and laryngeal involvement has been reported in up to 59% of patients with classic symptoms[54]. Extrathoracic airway obstruction may also be present. Hoarseness, dysphasia, shortness of breath, or wheezing are examples of signs and symptoms of obstruction. The anesthesiologist should be wary that some patients with cricoarytenoid joint arthritis may be asymptomatic. This type of arthritis may still allow aspiration of pharyngeal contents, while others with a more severe form may suffer from decreased mobility of the vocal cords, resulting in a narrowed glottic opening. Severe narrowing may even lead to laryngeal obstruction and stridor. An evaluation by an otolaryngologist may be indicated.

Cervical spine pathology presents its own set of complications. For example, excessive neck flexion may result in cord compression in patients with atlanto-axial involvement. Also, if the odontoid process is unstable and migrates rostrally, compression may be exaggerated. Subaxial involvement, or subluxation below C2, may predispose to spinal cord compression with extension of the neck. Reports of laryngeal deviation have been recorded[51]. Displacement of the larynx is possible. It may be angulated anteriorly, displaced caudally, or rotated to the right or left. The anesthesiologist may encounter difficulties with the placement of airway equipment such as the laryngeal mask airway if there are deviations in angulation. Avoiding the recommended "sniffing" position during intubation will help avoid cervical complications. The neutral position is tolerated by most airway lesions. This technique is improved by a carefully performed fiberoptic intubation which is generally preferred[51]. Recently, a study was performed to determine the optimal head position for these patients in order to avoid atlantoaxial subluxation. The authors concluded that when managing a patient with atlantoaxial subluxation, the protrusion position using a flat pillow and a donut-shaped pillow during general anesthesia reduced the anterior atlantodental interval and increased the posterior atlantodental interval. These findings imply that this protrusion position may be

advantageous in this patient population[55].

Routine perioperative radiographs of the neck are recommended by some because of the chance of cervical spine instability even in the absence of neurologic symptoms[56,57], yet others believe that performing these imaging studies on all rheumatoid patients would be expensive and unnecessary[58,59]. Need should be determined on a case by case basis. The presence of symptoms such as pain radiating to the occiput, paresthesias in the shoulders or arms with head movement, or sensory loss in the hands without pain may warrant radiographs. Further, radiographs may be taken in high risk patients such as the elderly, those with long-standing disease, cervical symptoms, erosive disease, subcutaneous nodules, general anesthetic cases, and cases where a non-supine position is necessary[51].

An approach to the airway using the laryngeal mask airway (LMA) or facemask plus oral airway can be maintained without excessive neck extension, but is not always easily performed. LMA insertion may be difficult in some patients and inexperienced users may cause excessive neck manipulation. Moreover, laryngeal deviation may lead to difficulties when conventional methods of laryngeal mask placement are employed, although the incidence of deviation is low (15 out of 710 fiberoptic intubations)[60].

Intraoperative Management

General Care

Patients with rheumatoid arthritis generally present for surgery due to joint pain or decreased functionality of their deformed joints that are unresponsive to medication; hence, many procedures are orthopedic. Current trends in anesthesia point to the use of regional anesthesia over general anesthesia whenever possible for many reasons. Complications from airway manipulation, intubations, and ventilatory agitations are avoided. Besides being safe, a regional approach allows for excellent

operating conditions, successfully blunts the neurohormonal stress response during surgery, and paves the way for a smooth transition into the postoperative period[51].

Positioning

Movements during anesthesia and neurovascular compression are special issues in the RA patient. Often times moderate amounts of sedation are used to help the patient tolerate maintenance of positioning. Generous padding is used during general anesthesia to prevent neurovascular compression whereas the awake patient is able to attain a comfortable position by him or herself. Sudden movements of the neck and torso are not well tolerated and should be avoided in these patients as the spines are brittle. This is especially true in those with ankylosing spondylitis. The use of narcotics for postoperative pain control may be necessary as joint stiffness and pain increase with immobilization[51].

Temperature Regulation and Invasive Monitoring

In a subpopulation of patients with rheumatoid arthritis, Raynaud's phenomena may occur. Temperature regulation is always important but, in this group of patients preventing hypothermia is vital as cold can precipitate arterial vasospasm of digital arteries and result in cyanosis and ischemic episodes. Invasive monitoring for orthopedic procedures on the rheumatoid patient provides much needed second-by-second information. Some of these surgeries, such as spine, pelvic acetabulum, and total hip replacement, are performed under induced hypotension to reduce intraoperative blood loss, which mandates the placement of a direct arterial monitor. Prompt recognition of embolism (by sudden decrease in end tidal CO_2, tachycardia, hypotension), as well as cement reactions, allows early treatment of these conditions (alerting the surgeon, fluid infusions, vasopressors administration). Methylmethacrylate resins may embolize and can also cause sudden decreases in vascular resistance due to metabolites. Hammering on joints during the surgeries may result in

lethal fat emboli. The use of a central venous catheter monitor during high risk cases such as complicated joint revisions, use of longstem prosthesis for hip or bilateral joint replacements may be advised[51].

Decreased joint mobility may create a challenge for placement of the arterial monitor. In these cases, a more proximal cannulation of the wrist or use of a different location such as the foot may be necessary. Along the same lines, cannulation of the internal jugular vein may be complicated by limited rotation or flexion of the neck and the risk of subluxation of cervical vertebrae. Vein location ultrasound techniques can expedite the process[51,61].

Blood conservation

Chronic anemia with low erythropoietin levels is a common finding and patients may benefit from erythropoietin and iron supplementation. Deliberate hypotension, cell salvage techniques, and tourniquet control (if amenable) may be applied. Additionally, extensive operations may require blood replacement and, since these patients are already at risk for bleeding, the anesthesiologist should have a high sensitivity for ordering blood products preoperatively[51,53].

Postoperative pain control

Optimal outcomes with higher patient satisfaction are a direct result of the anesthesiologist's active involvement in postoperative care, especially pain control. Regional anesthesia is preferred for this reason as it provides a smoother transition into the postoperative period. The technique allows for long-acting blocks for painful surgeries. Furthermore, the employment of continuous or demand analgesia by way of epidural, brachial plexus, or IV catheters is available[51]. A recent study demonstrated more effective pain control by using patient-controlled epidural anesthesia versus a pain control infusion pump[62]. Patients that had an infusion pump used significantly more acetaminophen, propoxyphene napsylate, and ketorolac after the pump was removed. In

addition, the infusion pump group experienced prolonged wound drainage, which is associated with a higher risk for infection.

Summary

A diagnosis of rheumatoid arthritis carries with it a lifelong progressive disease; however twenty percent of patients enjoy periods of partial to total remission. After remission, the disease will frequently plague previously unaffected joints. Life expectancy is reduced by an average of three to seven years. Complications of RA include vasculitis and amyloidosis affecting any vessel, including the aorta. Additionally, complications of therapy such as chronic NSAID use leading to GI bleeding and infections associated with long term steroid use, can add to the difficulties of the disease. The recent discovery and use of anticytokines and DMARDs has lead to greatly reduced symptomology associated with RA and greater patient comfort.

Side effects of drugs should be well understood including the risk of bleeding from NSAIDs. Management and surgical intervention of problems that arise from this disease vary dramatically. The anesthesiologist must be aware of airway pathologies, pain management techniques, and available pharmacology parameters.

References

1. COTRAN R, KUMAR V, COLLINS T: *Robbins Pathologic Basis of Disease*. 6th Ed. Philadelphia, PA: W.B. Saunders Company; 1248-1251, 1999.

2. LINEKER S, BADLEY E, CHARLES C, ET AL: Defining morning stiffness in rheumatoid arthritis. *J Rheumatol*; 26:1052-1057, 1999.

3. BERKANOVIC E, HURWICZ M, O'DELL JR: Therapeutic strategies for rheumatoid arthritis. *N Engl J Med*; 350(25):2591-2602, 2004.

4. WOLFE F, MITCHELL DM, SIBLEY JT ,ET AL: The mortality of rheumatoid arthritis. *Arthritis Rheum*; 37:481-494, 1994.

5. SPECTOR TD: Rheumatoid Arthritis. *Rheum Dis Clin North Am*; 16:513-537, 1990.

6. ROTHSCHILD BM, TURNER KR, DELUCA MA: Symmetrical erosive peripheral polyarthritis in the late Archaic period of Alabama. *Science*; 241:1498-1501, 1998.

7. SILMAN AJ, MACGREGOR AJ, WHITING S, ET AL: Twin concordance rates for rheumatoid arthritis: Results from a nationwide study. *Br J Rheumatol*; 32:903-907, 1993.

8. JONES MA, SILMAN AJ, WHITING S, ET AL: Occurrence of rheumatoid arthritis is not increased in the first degree relatives of a population based inception cohort of inflammatory polyarthritis. *Ann Rheum Dis*; 55:89-93, 1996.

9. MACGREGOR AJ, SNIEDER H, RIGBY AS, ET AL: Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum*; 43:30-37, 2000.

10. JAWAHEER D, SELDIN MF, AMOS CI, ET AL: A genomewide screen in multiplex rheumatoid arthritis families suggests genetic overlap with other autoimmune diseases. *Am J Hum Genet*; 68:927-936, 2001.

11. PADYUKOV L, SILVA C, STOLT P, ET AL: A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. *Arthritis Rheum*; 50:3085-3092, 2004.

12. SAAG KG, CERHAN JR, KOLLURI S, ET AL: Cigarete smoking and rheumatoid arthritis severity. *Ann Rheum Dis*; 56:463-469, 1997.

13. WOLFE F: The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis. *J Rheumatol*; 27:630-637, 2000.

14. TODA I: Autoantigens and Sjogren syndrome. *Cornea*; 21(2 Suppl 1): S13-16, 2002.

15. BLASCHKE S, SCHWARZ G, MONEKE D, ET AL: Epstein-Barr virus infection in peripheral blood mononuclear cells, synovial fluid cells, and synovial membranes of patients with rheumatoid arthritis. *J Rheumatol*; 27(4):866-873, 2000.

16. LEE DM, WEINBLATT ME: Rheumatoid arthritis. *Lancet*; 358:903-911, 2001.

17. FLEMING A, CROWN JM, CORBETT M: Early rheumatoid disease. I. Onset. II. Patterns of joint involvement. *Ann Rheum Dis*; 35:361-364, 1976.

18. JACOBY RK, JAYSON MIV, COSH JA: Onset, early stages and prognosis of rheumatoid arthritis: A clinical study of 100 patients with 11 year follow-up. *Br Med J*; 2:96-100, 1973.

19. KUPER IH, VAN LEEUWEN MA, VAN RIEL PL, ET AL: Influence of a ceiling effect on the assessment of radiographic progression in rheumatoid arthritis during the first 6 years of disease. *J Rheumatol*; 26:268-276, 1999.

20. NIWA Y, LIO A, NIWA G, ET AL: Serum albumin metabolism in rheumatic diseases: relationship to corticosteroids and peptic ulcer. *J Clin Lab Immunol*; 31:11-16, 1990.

21. ANDERSON JJ, WELLS G, VERHOEVEN AC, FELSON DT: Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. *Arthritis Rheum*; 43:22-29, 2000.

22. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum*; 46:328-346, 2002.

23. OFMAN JJ, BADAMGARAV E, HENNING JM, ET AL: Utilization of nonsteroidal anti-inflammatory drugs and antisecretory agents: a managed care claims analysis. *Am J Med*; 116:835-842, 2004.

24. CAUGHEY GE, CLEHAND LG, PENGLIS PS, ET AL: Roles of cyclooxygenase (COX-1) and COX-2 in prostanoid production by human endothelial cells: Selective up-regulation of prostacyclin synthesis by COX-2. *J Immunol*; 1667:2831-2838, 2001.

25. GOTZSCHE PC, JOHANSEN HK: Short-term low-dose corticosteroids vs placebo and nonsteroidal anti-inflammatory drugs in rheumatoid arthritis. *Cochrane Database Syst Rev*; CD000189, 2003.

26. Guidelines for monitoring drug therapy in rheumatoid arthritis: American college of Rheumatology Ad Hoc Committee on Clinical Guidelines. *Arthritis Rheum*; 39:723-731, 1996.

27. ST CLAIR EW, VAN DER H, SMOLEN JS, ET AL: Combination of infliximabl and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum*; 50:3422-3443, 2004.

28. SAMUELS J, SPIERA R: Newer therapeutic approaches to the vasculitides: biologic agents. *Rheum Dis Clin North Am*; 32(1):187-200, 2006.

29. Guidelines for monitoring drug therapy in rheumatoid arthritis: American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. *Arthritis Rheum*; 39:723-731, 1996.

30. KAUPPI M, SAKAGUCHI M, KONTTINENT YT, ET AL: Pathogenic mechanisms and prevalence of the stable atlantoaxial subluxation in rheumatoid arthritis. *J Rheumatol*; 23:831-834, 1996.

31. CHANG DJ, PAGET SA: Neurologic complications of rheumatoid arthritis. *Rheum Dis Clin North Am*; 19:955-973, 1993.

32. MARTEL W: Pathogenesis of cervical discovertebral destruction in rheumatoid arthritis. *Arthritis Rheum*; 20:1217-1225, 1977.

33. WINFIELD J, YOUNG A, WILLIAMS P, ET AL: Prospective study of the radiological change in hands, feet and cervical spine in adult rheumatoid disease. *Ann Rheum Dis*; 42:613-618, 1983.

34. COLLINS DN, BARNES CL, FITZRANDOLPH, RL: Cervical spine instability in rheumatoid patients having total hip or knee arthroplasty. *Clin Orthop*; 127-135, 1991.

35. STEVENS JC, CARTLIDGE NE, SAUNDERS M, ET AL: Atlanto-axial subluxation and cervical myelopthy in rheumatoid arthritis. *Q J Med*; 40:391-408, 1971.

36. NAKANO KK, SCHOENC WC, BAKER RA, ET AL: The cervical myelopathy associated with rheumatoid arthritis: Analysis of patients, with 2 postmortem cases. *Ann Neurol*; 3:144-151, 1978.

37. MAYER JW, MESSNER RP, KAPLAN RJ: Brain stem compression in rheumatoid arthritis. *JAMA*; 236:2094-2095, 1976.

38. KAUPPI M, ANTTILA P: A stiff collar for the treatment of rheumatoid atlantoaxial subluxation. *Br J Rheumatol*; 35:771-774, 1996.

39. AGARWAL AK, PEPPELMAN WC, KRAUS DR, ET AL: Recurrence of cervical spine instability in rheumatoid arthritis following previous fusion: can disease progression be prevented by early surgery? *J Rheumatol*; 19:1364-1370, 1992.

40. ZYGMUNT SC, CHRISTENSSON D, SAVELAND H, ET AL: Occipito-cervical fixation in rheumatoid arthritis – an analysis of surgical risk factors in 163 patients. *Acta Neurochir (Wien)*; 135:25-31, 1995.

41. TURESSON C, JARENROS A, JACOBSSON L: Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from a community based study. *Ann Rheum Dis*; 63:952-955, 2004.

42. VAN DOORNUM S, MCCOLL G, WICKS IP: Accelerated atherosclerosis: An extraarticular feature of

rheumatoid arthritis? *Arthritis Rheum*; 46:862-873, 2002.

43. WALLBERG-JONSSON S, CVETKOVIC JT, SUNDQVIST KG, ET AL: Activation of the immune system and inflammatory activity in relation to markers of atherothrombotic disease and atherosclerosis in rheumatoid arthritis. *J Rheumatol*; 29:875-882, 2002.

44. WALLBERG-JONSON S, CEDERFELT M, RANTAPAA S: Hemostatic factors and cardiovascular disease in active rheumatoid arthritis: an 8 year follow-up study. *J Rheumatol*; 27:71-75, 2000.

45. PARK YB, CHOI HK, KIM MY, ET AL: Effects of antirheumatic therapy on serum lipid levels in patients with rheumatoid arthritis: a prospective study. *Am J Med*; 113:188-193, 2002.

46. DAWSON JK, GRAHAM DR, DESMOND J, ET AL: Investigation of chronic pulmonary effects of low dose methotrexate in patients with rheumatoid arthritis: a prospective study incorporating HRCT scanning and pulmonary function tests. *Rheumatology (Oxford)*; 41:262-267, 2002.

47. BELZUNEGUI J, INTXAUSTI JJ, ET AL: Absence of pulmonary fibrosis in patients with psoriatic arthritis treated with weekly low dose methotrexate. *Clin Exp Rheumatol*; 19:727-730, 2001.

48. BLANCAS R, MORENO JL, MARTIN F, ET AL: Alveolar-interstitial pneumopathy after gold-salts compounds administration, requiring mechanical ventilation. *Intensive Care Med*; 24:1110-1112, 1998.

49. LIBBY D, WHITE DA: Pulmonary toxicity of drugs used to treat systemic autoimmune diseases. *Clin Chest Med*; 19:809-821, 1998.

50. KELLY CA: Rheumatoid arthritis: classical rheumatoid lung disease. *Baillieres Clin Rheumatol*; 7:1-16, 1993.

51. MATTI MV, SHARROCK NE: Anesthesia on the rheumatoid patient. *Rheum Dis Clin North Am*; 24(1):19-34, 1998.

52. MacKENZIE CR, SHARROCK NE: Perioperative medical considerations in patients with rheumatoid arthritis. *Rheum Dis Clin North Am*; 24(1):1-17, 1998.

53. EISELE JH: Connective Tissue Diseases: Benumof JL, ed. *Anesthesia and Uncommon Diseases*. 4th ed. New York: W.B. Saunders Company; 398-421, 1998.

54. GETERUD A, BAKE B, BERTHELSEN B, ET AL: Laryngeal involvement in rheumatoid arthritis. *Acta Orolaryngol*; 111:990-998, 1991.

55. TOKUNAGA D, HASE H, MIKAMI Y, ET AL: Atlantoaxial subluxation in different intraoperative head positions in patients with rheumatoid arthritis. *Anesthesiology*; 104(4):675-679, Apr 1006.

56. CROSBY ET, LUI A: The adult cervical spine: Implications for airway management [review]. *Can J Anaesth*; 37:77-93, 1990.

57. FRATER RA: Preoperative cervical spine radiography in rheumatoid arthritis [letter; comment]. *Clin Radiol*; 51:77, 1996.

58. CAMPBELL RS, WOU P, WATT I: A continuing role for pre-operative cervical spine radiography in rheumatoid arthritis? *Clin Radiol*; 50:157-159, 1995.

59. SHARP RJ: The cervical spine in rheumatoid arthritis [letter]. *Anaesthesia and Intensive Care*; 24:401-402, 1996.

60. WATTENMAKER I, CONCEPCION M, HIBBERED P, ET AL: Upper airway obstruction and perioperative management of the airway in patients managed with posterior operations on the cervical spine for rheumatoid arthritis. *J Bone Joint Surg Am*; 76:360-365, 1994.

61. SHARROCK NE, FIERRO LE: Jugular venous pulsations as the sole landmark for percutaneous internal jugular cannulation. *Br J Anaesth*; 55:1213-1216, 1983.

62. DeWEESE FT, AKBARI Z, CARLINE E: Pain control after knee arthroplasty: intraarticular versus epidural anesthesia. *Clin Orthop Relat Res*; (392):226-231, 2001.