# Critical care challenges in orthopedic surgery patients

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***Objectives:*** **To review common and life-threatening complications resulting in intensive care unit admission for patients undergoing orthopedic surgery procedures. To identify specific diagnostic techniques and treatment modalities that may improve the outcome of critically ill orthopedic surgery patients.**

***Design:*** **A review of the current literature regarding the care of orthopedic surgery patients was performed.**

***Results:*** **Orthopedic surgery patients are vulnerable to a number of complications, particularly pulmonary complications related to scoliosis surgery, embolic complications of joint arthroplasty, and complications related to the use of opioids and sedatives in an elderly population. They also are susceptible to transfusion-related complications such as transfusion-related acute lung injury and transfusion-associated circulatory overload. Specific strategies for management of these complex patients are identified.**

***Conclusions:*** **Orthopedic surgery patients represent a significant and growing proportion of patients in intensive care units. They develop unique complications, and management of these complications requires understanding of preoperative co-morbidities, intraoperative management, and early recognition and treatment of postoperative complications. Prevention and early identification of these complications are the most efficacious routes to improving outcomes in this patient population. (Crit Care Med 2006; 34[Suppl.]:S191–S199)**

**Key Words: orthopedic surgery; acute lung injury; transfusion-related acute lung injury; air embolism; fat embolism; thromboembolism; pain management; complications; anticoagulation; ketamine; dexmedetomidine**

There are approximately 37 million surgeries performed in the United States each year, with orthopedic surgery accounting for approximately 6% of the total number of procedures (1). Orthopedic surgery is performed in both outpatient and inpatient settings in response to degenerative changes, traumatic injury, congenital aberrations, infectious pathogeneses, and malignant compromise. The goal of surgery in the orthopedic patient is to relieve pain, increase mobility, and improve function. Except for multiple trauma patients, most orthopedic surgical patients are older and often present with a variety of co-morbid conditions.

Increased surgical volume, improved perioperative care, and technological advances continue to decrease the complication rate after orthopedic surgery. The overall complication rate after major joint replacement is 5–8.6% (2, 3), and serious complications occur in 1–20% of adults undergoing corrective surgery for scoliosis (4). Complications after orthopedic surgery can be grossly divided into five categories: those resulting in 1) airway compromise, 2) pulmonary dysfunction, 3) circulatory compromise, 4) management of acute or chronic pain, and 5) those associated with special groups of patients, especially the elderly.

Recent advances in surgical and anesthetic techniques have dramatically reduced intraoperative mortality, but an aging population and increasing number of co-morbidities necessitate more vigilance and care in the postoperative period. The increasing complexity of orthopedic procedures, especially those involving joint arthroplasty and spine instrumentation, have resulted in increasing numbers of orthopedic patients requiring critical care.

## General Concerns in Orthopedic Surgery Patients

Based on nonnewborn hospital admissions, orthopedic surgery patients comprise approximately 6% of the total surgical volume in the United States. In general, orthopedic surgery patients are thought to have a low perioperative mortality rate. Bhattacharyya et al. (1) recently reviewed risk factors for mortality after inpatient orthopedic surgery. Data from the National Hospital Discharge Survey show that inpatient mortality rate is 0.92% (0.49% if acute hip fractures are not included). This is significantly lower than the general surgery mortality rate of 2.7% or that following polytrauma, which approaches 18% (5). However, the peak age for admission after orthopedic surgery is 70 yrs old, and there is a significant correlation between advanced age and mortality. The mortality rate for any orthopedic procedure increases with age; for patients >90 yrs old, mortality is 4.8%. An important factor with advancing age is hip fracture. An analysis of hospital admissions in 1998 showed 3.1% of patients with acute hip fracture died (1). This accounts for nearly half of the deaths in the orthopedic surgery patients in the study.

*Risk Assessment*. Preoperative risk factors for death in patients undergoing orthopedic surgery include chronic renal failure, metastasis to bone, age of >70 yrs, congestive heart failure, osteomyelitis, chronic obstructive pulmonary disease, and atrial fibrillation. Critical risk factors for postoperative risk factors summarized in Table 1 are: chronic renal failure, congestive heart failure, chronic obstructive pulmonary disease, hip fracture, and age of >70 yrs old. As in other studies of critically ill patients, renal failure is a major contributor to mortality.

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Table 1. Risk factors for mortality after orthopedic surgery

| Risk Factor | Associated Mortality, % |
|---|---|
| Chronic renal failure | 9.2 |
| Congestive heart failure | 5.75 |
| Acute hip fracture | 3.07 |
| Chronic obstructive pulmonary disease | 2.74 |
| Age of >70 yrs | 1.99 |

Adapted from Bhattacharyya et al (1).

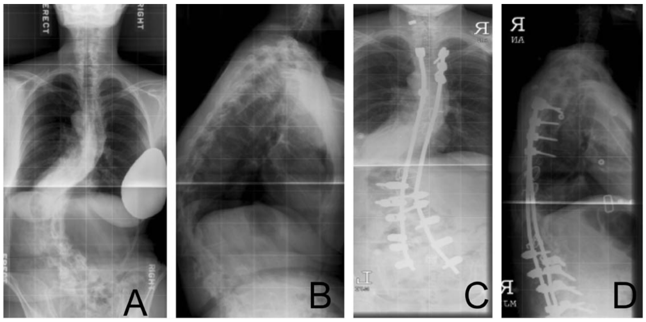


Figure 1. Frontal and lateral radiographs of a patient with severe kyphoscoliosis. *A* and *B*, preoperative; *C* and *D*, postoperative. Note the substantial correction of both kyphosis and scoliosis with placement of rods. Radiographs courtesy of Serena Hu, MD.

Of note, coincidence of hypertension was protective for the orthopedic surgery patient, an observation also noted by Iezzoni et al (6). In the postoperative setting, 19% of patients with acute myocardial infarction died, 27.6% of patients with acute renal failure died, 19.3% of patients with pulmonary embolism died, and 8% of patients with stroke died. Pneumonia occurred in 1.1% of patients and resulted in a mortality rate of 8.6%. Patients requiring surgery for tumor resection had an overall mortality of 5.2%, and infection carried a 1.6% mortality (1).

Approximately 200,000 total hip replacements are performed each year for degenerative joint disease. Improvements in perioperative care in general, and deep venous thrombosis (DVT) prophylaxis in particular, have reduced morbidity and mortality three-fold. U.S. National Institutes of Health data indicate there is a 1% risk of death after elective total hip replacement. The range for mortality after acute hip fracture is 0.6–24% in various studies (7). There is increased risk for mortality after acute hip fracture in patients with advanced age. Patients of >85 yrs in age have a 3.75% risk of death after total hip arthroplasty (THA), and after acute hip fracture, there is an associated 6.2% risk of death (7). Approximately 350,000 total knee replacements are performed in the United States each year (8). Patients receiving bilateral knee replacements are at increased risk of DVT and are typically of advanced age.

Surgery of the spine is performed for correction of degenerative disease, trauma, congenital malformations, infection, and malignancy. Procedures include osteotomies, stabilization, and distraction. Scoliosis affects 4% of the population. Muscular dystrophy and cerebral palsy are common causes of scoliosis. Surgery is performed when the Cobb angle (a measure of the severity of the spinal deformity) exceeds 50 degrees in the thoracic spine and 40 degrees in the lumbar spine. The goal of surgery is to slow or stop the progression of cardiopulmonary disease. If untreated, idiopathic scoliosis is often fatal in the fourth or fifth decades of life as a result of pulmonary hypertension or respiratory failure (9). Patients with scoliosis often develop restrictive lung disease and are at risk for chronic hypercapnia and pulmonary hypertension. Duchenne muscular dystrophy occurs in 1/3,300 male births. Patients with Duchenne muscular dystrophy often have intellectual impairment, dysrhythmias, cardiomyopathy, and sensitivity to neuromuscular blockers. These patients exhibit prolonged action of nondepolarizing neuromuscular blocking agents and hyperkalemic response to succinylcholine (9). Figure 1 demonstrates preoperative and postoperative radiographs of a patient with severe scoliosis.

As opposed to lower limb surgery, spine surgery has a relatively low prevalence of DVT (<1%) (10). Major complications of spine surgery include pneumonia, respiratory failure, prolonged postoperative intubation, congestive heart failure, myocardial infarction, stroke, and delirium. Minor complications include atelectasis, ileus, dural tear, atrial fibrillation, and urinary retention. Positioning during surgery may predispose patients to venous air embolism in the seated position. Patients in the prone position have increase intraabdominal pressure that can lead to respiratory insufficiency and increased epidural venous pressure. This may predispose patients to the development of an epidural hematoma (7).

## Predictors of Intensive Care Unit Admission

Admission to the intensive care unit (ICU) may be anticipated in patients who have multiple-level spine surgery, preexisting myelopathy, pulmonary disease, cardiovascular disease, hypertension, or diabetes. Other factors include patients with possible airway edema or those who have had massive transfusion. It is also suggested by Nahtomi-Shick et al. (11) that ICU admission can be predicted by complexity of surgery and amount of intraoperative fluid administered. More complex surgeries frequently have more blood loss and resuscitation, resulting in net positive fluid balance, edema, and more difficult pain management issues. A retrospective study reviewed adult patients undergoing corrective spine surgery between 1986 and 1992 and found no correlation between the Cobb angle, approach (anterior vs. posterior), and the frequency of complications. They did find that smoking was a risk factor for minor pulmonary complications, which occurred in 46% of the patients in the study, without a significant difference in the morbidity or mortality (12). Nahtomi-Shick et al. (11) also identified factors associated with ICU admission after orthopedic surgery. Predictors of ICU length of stay were age, American Society of Anesthesiology status, surgical procedure, and fluid administration. Patients who had an ICU length of stay of >1 day had greater intraoperative blood loss and resultant greater fluid administration and net positive fluid balance. This study supports previous findings that more complex surgical procedures on the spine result in an increased rate of complications (11).

Primary or secondary malignancy involving bone may result in infection, pleural effusion, and pulmonary toxicity or myocardial injury from chemotherapy. The malignant process may result in hypercalcemia or syndrome of inappropriate antidiuretic hormone, frequently associated with small cell lung cancer. Often, patients with cancer have chronic pain that is exacerbated by acute surgical insult (9).

## Issues in Airway Management

Orthopedic surgery can affect patency of the airway in a number of ways. Patients with rheumatoid arthritis, temporomandibular joint disease, and ankylosing spondylosis often present with difficult to manage airways. Direct laryngoscopy is often contraindicated due to exacerbation of symptoms or known atlantoaxial subluxation. Rheumatoid arthritis affects approximately 1% of the population (13). It is not uncommon for patients with rheumatoid arthritis to have silent C1-C2 instability and difficulty with neck extension. This instability can pose significant difficulty when establishing a secure airway (14). Prone positioning for posterior spine procedures may result in significant facial edema and potential airway obstruction due to soft-tissue edema. Anterior cervical spine surgery may result in localized edema or hematoma. Cervical spine fusion may result in carotid injury, upper airway edema, recurrent laryngeal nerve injury, vertebral artery compromise, or Horner-Bernard syndrome due to stellate ganglion injury if dissection occurs at the C7-T2 level (7). These issues can both affect initial airway management for surgery and lead to postextubation complications.

Airway assessment involves patient examination and discussion with the surgeon regarding the stability of the cervical spine. Distracting injuries or use of narcotics may invalidate a focused physical examination of the cervical spine for tenderness or pain with movement when evaluating a patient with suspected cervical spine injury. Radiologic studies of the cervical spine must be carefully reviewed for C1–2 abnormalities. Genetic disorders, like Duchenne muscular dystrophy, can be associated with macroglossia (9). It is also important to bear in mind the findings of Ezri et al. (15), who identified three risk factors associated with difficult intubation in the morbidly obese (body mass index >40): patients with documented obstructive sleep apnea, pretracheal soft tissue in excess of 28 mm identified with ultrasound, and a neck circumference of >50 cm were found to be difficult to intubate by experienced laryngoscopists. Although the study was small, they did not find that thyromental distance, Mallampati score, mouth opening, limitation in neck range of motion, or abnormalities in upper teeth were predictive of difficult laryngoscopy.

Anterior cervical spine surgery is performed to treat degenerative changes, abscess formation, tumor resection, or to repair traumatic injury and accounts for approximately 65% of cervical spine surgery (16). Serious complications are rare, although potentially lethal in as much as they usually involve airway obstruction (16). The overall rate of complications after anterior cervical spine surgery is approximately 6%. Major complications may be the result of esophageal or pharyngeal perforation, pharyngeal edema, hematoma, or angioedema that can result in airway obstruction (16). Minor complications after anterior cervical spine surgery include dysphagia, hoarseness, sore throat, and vocal cord paralysis due to recurrent laryngeal nerve paralysis (16). Emery et al. (17) reviewed seven reports of airway compromise after anterior cervical spine surgery. They concluded that multiple-level anterior cervical spine surgery for myelopathy and patients with a history of heavy tobacco use are at risk for airway compromise. Myelopathy typically requires more extensive surgery and may therefore be associated with more blood loss and more necessary resuscitation (18).

A retrospective review of 311 patients undergoing anterior cervical spine surgery identified four risk factors for airway complications (16). Exposure of three or more vertebral levels, exposures involving C2 through C4, operative blood loss of >300 mL, and operative time of >5 hrs are risk factors statistically associated with airway complications. Of note, airway class, thyromental distance, smoking history, body mass index, myelopathy, and other medical co-morbidities (including chronic obstructive pulmonary disease) were not associated with airway complications in this study. About 33% of the airway complications required reintubation. The mean time to airway complications necessitating reintubation was 24 hrs and was 36 hrs for development of respiratory insufficiency (16). This study suggests that prophylactic intubation of ≤24 hrs may not reduce the prevalence of postoperative respiratory insufficiency.

Techniques for airway assessment include documentation of endotracheal tube cuff leak pressure at the time of intubation and again on completion of the procedure. This should be done while the patient is well sedated. After suctioning of the oral and hypopharynx, the air is withdrawn from the endotracheal cuff. A manometer and hand ventilation system capable of delivering >30 cm $H_2O$ of pressure is used to deliver positive pressure ventilation while auscultating the trachea at the level of vocal cords. The pressure required to force air around the endotracheal tube is referred to as the cuff leak. A study by Jaber et al. (19) is the only study to quantify endotracheal cuff leak as a predictor of postextubation stridor. Their recommendation was that a cuff leak of <130 mL or <12% of tidal volume is a predictor of postextubation stridor. The authors used an ICU ventilator set in the assist/control mode to standardize the delivery of the breath and reduce interobserver variability during auscultation.

In patients who require reintubation, care should be taken to have all the equipment immediately available that may be required for difficult intubation. In settings with cervical spine abnormalities, awake, fiberoptic intubation is the approach of choice, as long as adequate oxygenation and ventilation can be maintained. If direct laryngoscopy is difficult or impossible, then the American Society of Anesthesiologists Difficult Airway Algorithm should be followed (20).

## Respiratory Complications

Both preexisting medical conditions and complications associated with specific surgical procedures may lead to respiratory complications in orthopedic surgery patients. Assessment of the pulmonary system must focus on evidence of preexisting lung injury or pulmonary disease, pneumonia, and severity of scoliosis. Factors associated with postoperative mechanical ventilation requirements include preexisting neuromuscular disease, severe restrictive pulmonary dysfunction with a vital capacity of <35% predicted, congenital heart defects, right ventricular failure, obesity, anterior thoracic spine surgery involvement, and blood loss of >30 mL/kg (12). It is not always a co-morbid condition that predisposes the patient to pulmonary dysfunction. High doses of opiates are often required to treat acute surgical pain, resulting in the predictable side effects of central respiratory depression, monotonous respiratory pattern, and cough suppression.

Although any patient undergoing general anesthesia and surgery is at risk for pulmonary complications, it is apparent that corrective spine surgery has the highest prevalence. Postoperative complications in spine surgery occur with a prevalence of 7% and include acute respiratory distress syndrome, pneumonitis, pulmonary embolism, stroke, and death (9). Anderson et al. (21) found a 35% complication rate after spine surgery for nonidiopathic scoliosis. Although routine preoperative pulmonary function testing is controversial, patients with a preoperative vital capacity of <35% predicted will likely require postoperative ventilation.

Kyphoscoliosis results in reduced vital capacity, reduced functional reserve capacity, and a restrictive pulmonary disease pattern. The severity of pulmonary impairment is influenced by the scoliosis angle, number of vertebrae involved, cephalad location of the curvature, and degree of loss seen in thoracic kyphosis. Pulmonary impairment is manifested by decreased arterial oxygen tension due to pulmonary shunting. There is significant controversy regarding the degree of improvement in pulmonary function after scoliosis surgery. One study found that patients who had an anterior component to their surgery had worse pulmonary function testing variables at 3 mos but improved function at 2 yrs (9). Patients who had posterior correction only had a trend for improved function at 3 months but no significant difference from the anterior/combined group at 2 yrs.

Scoliosis surgery is more likely to have immediate pulmonary complications if the curvature is >60 degrees. Reduced vital capacity is the first manifestation of restrictive lung disease in this population. As the disease progresses, gas exchange is affected by ventilation/perfusion mismatch, alveolar hypoventilation, an increased dead space, and an increased alveolar-arterial gradient. Prolonged periods of hypoxemia result in pulmonary hypertension and hypercapnia and eventual respiratory failure. Surgery for scoliosis is performed to slow disease progression and prevent complications. Complications may arise in the preoperative period, as scoliosis patients are very sensitive to premedications resulting in respiratory depression (7).

Patients undergoing surgical procedures lasting >3 hrs under general anesthesia have a three-fold increase in pulmonary complications. Complications present as atelectasis, pleural effusion, pneumonia, and congestive heart failure. Acute lung injury and transfusion-related acute lung injury or transfusion-related circulatory overload may occur in patients requiring significant transfusion.

*Transfusion-Related Acute Lung Injury*. Transfusion-related acute lung injury (TRALI) was coined in 1983 by Popovsky et al (22). TRALI is the leading cause of transfusion-related mortality in the United States. TRALI is defined as acute hypoxemia with noncardiogenic pulmonary edema after blood product transfusion. TRALI has been reported after administration of all plasma-containing blood products. Whole blood, packed red blood cells, fresh frozen plasma, platelets concentrates, cryoprecipitate, and intravenous immunoglobulin have all been associated with TRALI (23). Table 2 describes the diagnostic criteria for TRALI.

Table 2. Definitions of acute lung injury (ALI) and transfusion-related acute lung injury (TRALI)

| | |
|---|---|
| ALI | Acute onset |
| | Pulmonary artery occlusion pressure of <18 mm Hg *or* no clinical evidence of left atrial hypertension |
| | Frontal chest radiograph with bilateral infiltrates |
| | Ratio of $Pa_{O_2}$:$F_{IO_2}$ of <300 mm Hg *or* room air saturation of <90% |
| TRALI | Transfusion of at least one plasma-containing blood product |
| | Diagnosis of ALI from above criteria |
| | Onset of ALI during transfusion *or* within 6 hrs of transfusion |
| | If no other ALI risk factors than transfusion, TRALI diagnosed |
| | If other risk factors for ALI are present, the patient's clinical course determines new ALI is either due to transfusion alone or in concert with alternative risk factor |

Adapted from Toy et al (23).

TRALI presents with cough, dyspnea, and fever. Both hypertension and hypotension have been described. Manifestation of TRALI can occur during transfusion or up to 6 hrs after transfusion has occurred. Patients typically require, at least, supplemental oxygen. In the first and largest series of patients with TRALI, 72% of patients required mechanical ventilation (22). Eighty-one percent of patients have resolution of symptoms in the first 96 hrs, but mortality rate is 5–8% (acute respiratory distress syndrome carries a 30–50% rate of mortality) (23). TRALI is commonly misdiagnosed as volume overload and treated with diuretics before confirmatory diagnosis is made. The prevalence of TRALI is 0.08–0.16% per patient transfused and 0.014–0.02% per unit transfused (23).

The pathogenesis of TRALI is not completely understood, but there are two compelling theories. Both theories use a "two-hit" hypothesis model, in which the first hit is the underlying condition of the patient, with the second hit being transfusion of blood products. The first hit is the priming of pulmonary neutrophils, and the second hit activates the primed white blood cells that release oxygen radicals that cause capillary leak leading to pulmonary edema. The two theories differ in the origin of the second hit (23). The first theory implicates transfused antibodies to human leukocyte antigens (class I and II) that set an inflammatory cascade into motion. The problem with the first theory is an absence of antibody found in donor or recipient in >10% of the TRALI cases. The second theory states that cellular breakdown products, biologically active lipids, incite neutrophil activation. The limitation to the second theory is that fresh frozen plasma has been associated with TRALI, and fresh frozen plasma has no cellular component. It is possible that these theories are not exclusive of one another. There is a definite association between multiparous donors and the prevalence of TRALI. This is likely due to human leukocyte antigen antibodies that have developed to the fetus *in utero*. This theory is further supported by the increased prevalence of TRALI seen in transfusion between close relatives (23).

Diagnosis of TRALI is typically clinical and one of exclusion (Table 2). The differential diagnosis includes acute respiratory distress syndrome, acute lung injury, congestive heart failure, and pulmonary embolism. Once cardiogenic pulmonary edema and blood group incompatibility are ruled out, TRALI should be suspected. Pulmonary edema fluid will show a high protein content, as opposed to hydrostatic pulmonary edema seen in left atrial hypertension, in which the protein concentration relative to plasma protein is low. Complete blood count may demonstrate leukopenia or thrombocytopenia. A chest radiograph typically shows bilateral interstitial infiltrates. As seen in acute lung injury, the ratio of $Pa_{O_2}$ to $F_{IO_2}$ will be <300 (23). Leukocyte reduction has been proposed as a preventive measure. However, it is thought that antibodies and not the leukocyte are responsible for the majority of TRALI cases. Furthermore, antibodies are not removed by leukocyte filtration (23). Treatment of TRALI begins with correct diagnosis and discontinuing diuretics if the patient is being erroneously treated for volume overload. Supplemental oxygen and respiratory support are often needed. The ventilation strategy should be that of lung protective ventilation outlined by the Acute Respiratory Distress Syndrome Network study (24). Symptoms typically show resolution in the first 24 to 96 hrs.

*Fat Embolism Syndrome.* Fat embolism syndrome (FES) occurs most commonly during orthopedic surgery. FES is a triad of symptoms including respiratory distress, neurologic changes, and petechial rash. Surgical procedures most commonly associated with FES are THA, total knee arthroplasty, and femur intramedullary rod placement. The pathogenesis of FES is not well understood, but there are two leading theories: biochemical and mechanical. The biochemical theory proposes that free fatty acids in the circulation directly injure pneumocytes. A large pulmonary fat burden may result in pulmonary hypertension, right ventricular dysfunction, and resultant hypoxemia. The mechanical theory states that small fat droplets ($<10$ μm) enter the circulation, pass through the pulmonary capillaries or pass through a patent foramen ovale, and deposit in the end organs where the deposition results in local cellular and organ dysfunction.

Diagnosis of FES is based on identification of major and minor criteria. Major diagnostic criteria are respiratory distress, change in neurologic status, and petechial rash; minor criteria are pyrexia, renal insufficiency, hyperbilirubinemia, and tachycardia. Signs and symptoms may manifest immediately or in 24–48 hrs. Respiratory distress is almost always present, and neurologic changes occur in 86% of patients. Petechial rash is pathognomonic for FES but occurs in only 40% of patients. Other symptoms include dyspnea, fever, cough, hemoptysis, chest pain, hypoxia, alveolar hemorrhage, and altered consciousness. The Schonfeld scoring system can be used to diagnose FES (25). Thrombocytopenia may or may not be present, and bronchoalveolar lavage often reveals characteristic fat-laden macrophages. Despite treatment, which is supportive, mortality ranges from 5% to 33%. Heparin and steroids have not shown efficacy in the treatment of FES (7). Table 3 describes the diagnostic criteria for FES.

**Table 3.** The Schonfeld criteria for the diagnosis of fat embolism syndrome (FES)

| Criteria | Points[a] |
|---|---|
| Petechiae | 5 |
| Chest radiograph changes | 4 |
| Hypoxemia | 3 |
| Fever | 1 |
| Tachycardia | 1 |
| Tachypnea | 1 |
| Confusion | 1 |

[a]Fat embolism syndrome defined by a score of >5. Adapted from Schonfeld et al (25).

*Other Emboli: Cement, Air, and Thromboemboli.* Cement or polymethylmethacrylate (PMMA) is used to secure prosthetic joint hardware and for placement of antibiotic spacers in cases of infected hardware that require removal and direct antibiotic therapy. PMMA-related hypotension occurs in 33–100% of patients who have THA (26). The mechanism of hypotension is controversial. Proposed theories are anaphylactoid reaction to PMMA, direct vasodilation by PMMA monomers, and pulmonary emboli of air, PMMA, and fat. Whatever the mechanism, it is clear that intrapulmonary shunting is present in this syndrome. Ries et al. (26) in 1993 calculated a pulmonary shunt fraction of 28% that may persist for 48 hrs after insult. It is now clear that providing a ventilation hole in the femur, allowing a reduction in intramedullary pressure when PMMA is placed, decreases resultant hypotension (7). Patients with severe preexisting lung disease may be better served by the placement of noncement femoral prostheses.

Air embolism can occur when a venous structure is open to air and the heart is in a gravity-dependent position, thus creating a siphon. Prevention relies on maintenance of intravascular volume and pressure and on keeping the surgical field in a dependent position during surgery. Low intravascular volume predisposes patients to air embolism; it is not uncommon for older patients with multiple medical problems to be dehydrated and at greater risk for air embolism. Intraoperative diagnosis of air embolism can be made after a sudden decrease in blood pressure or oxygenation, characteristic changes in capnography (decreased end-tidal $CO_2$), or a mill-wheel murmur may be heard. Echocardiographic examination may demonstrate air in the right atrium, right ventricular strain, or gross ventricular impairment. Paradoxic emboli can manifest with cardiac ischemia or sudden change in mental status (if the patient is awake). Treatment involves placing the patient in left lateral decubitus position, administering 100% oxygen, and providing intravascular fluids and inotropic support to maintain right ventricular cardiac output. Aspiration of air from the right ventricle can be attempted using a multiple-orifice catheter placed in the right ventricle.

*DVT and Pulmonary Embolus.* DVT and pulmonary embolism (PE) are major contributors to morbidity and mortality in orthopedic surgery patients. A meta-analysis of nine studies that included 19 million patients and commented on prophylaxis and treatment of DVT in general surgery, found the prevalence increases four-fold with age. At 70 yrs of age, the prevalence of DVT is 200 in 100,000 persons (27). Whereas general surgery patients have a 25% rate of DVT, orthopedic surgery patients have the highest prevalence of DVT at 50–60%.

It is estimated that there are 600,000 cases of PE each year, whereas only 25% or 260,000 cases are diagnosed. PE carries a 30% rate of morbidity and mortality.

Risk factors for development of PE are: advanced age, obesity, previous PE/DVT, cancer, bedrest, and major surgery. In addition, factor V Leiden is the most common hereditary blood disorder associated with venous thromboembolism (VTE) and PE (27). Virchow's triad consists of 1) stasis (supine position or general anesthesia), 2) intimal injury (vessel traction, ligatures, or tourniquets), and 3) hypercoagulability (venous stasis and decreased clearance or activate clotting factors) (28). Up to 50% of patients hospitalized with a lower limb fracture will develop a DVT, 10% of those patients will develop a PE. There is 2% mortality associated with acute PE after lower limb fracture. The occurrence of DVT after elective THR is 10–25%; the prevalence of PE after THR is approximately twice that for general surgery. Only those patients with hemodynamic instability or requiring respiratory support typically require ICU admission. Patients with shock after PE have the highest mortality (7).

Patients with acute hip fracture who are surgically repaired have a 40–45% rate of PE, 6–10% of which are fatal after acute hip fracture. Before routine postoperative treatment low molecular weight heparin, warfarin was shown to significantly reduce the prevalence of DVT and PE (28). A long plasma half-life and difficulty achieving therapeutic levels in a timely manner have prompted the use of shorter-acting and more titratable factor Xa inhibitors for postoperative VTE prophylaxis.

Total knee arthroplasty is one of the most frequently performed major orthopedic surgery procedures in the United States.

Table 4. Venous thromboembolism prophylaxis in orthopedic surgery patients[a]

| Hip or Knee Arthroplasty | Percutaneous Hip Fracture Pinning |
|---|---|
| Low molecular weight heparin | Low molecular weight heparin |
| Fondaparinux | Adjusted-dose Coumadin |
| Adjusted-dose Coumadin[b] | Unfractionated heparin |

[a]Treatment should be for ≥10 days in duration; [b]international normalized ratio target, 2.5; range, 2.0–3.0.

VTE, myocardial infarction, and infection are the major complications associated with this procedure. DVT occurs in up to 50% of unilateral total knee arthroplasty patients and up to 75% of bilateral total knee arthroplasty patients. These DVTs are typically distal (below the knee) and may not be of clinical significance, whereas symptomatic PE has a prevalence of 1.1% (29).

There are many modalities for diagnosis of PE. Although pulmonary angiogram is still the gold standard for diagnosis, it is now rarely used. Chest computerized tomographic angiography has a negative predictive value of 99.5% and is easily obtained (30). Ventilation-perfusion scan has low sensitivity and is difficult to perform in the critically ill patient, as intubated patients can participate only in the perfusion portion of the test. Plasma concentration of D-dimers and spiral computerized tomographic scan provide rapid results. Newer diagnostic modalities like echocardiography can demonstrate right ventricular dysfunction in patients without obvious hemodynamic instability. However, patients with <30% perfusion defect do not typically have echocardiographic evidence of right ventricular dysfunction (28). Severity of symptoms and hemodynamic instability often force a clinical diagnosis followed by diagnostic confirmation.

Proper treatment of PE relies on the patient presentation and patient history. The decision to anticoagulate a patient in the immediate postoperative period is not without profound risk, particularly in patients who have had spine surgery. Heparin prevents clot propagation or secondary clot formation, although it does not lyse formed clot. It is estimated that 15% of patients with massive PE had previous episodes, and 20% of those treated had signs of recurrent PE in the first 2 wks (28). Thrombolysis dissolves clot and restores pulmonary perfusion, which can reverse right ventricular dysfunction. Treatment provides symptomatic relief, restores hemodynamic stability, and improves pulmonary perfusion. Thrombolysis of pulmonary embolus reduces 30-day mortality from 11% to 5% (28, 29).

Prophylaxis for VTE is of paramount importance in the orthopedic surgery patient. There have been numerous studies evaluating prophylaxis for DVT in the postoperative period. In a sentinel study, aspirin provided a 20% risk reduction compared with placebo. Graded compression stockings have a 44% risk reduction, and sequential compression devices have an 88% risk reduction (27). Low-dose unfractionated heparin provides 68% risk reduction, and low molecular weight heparin provides 76% risk reduction.

Fondaparinux is a synthetic pentasaccharide that directly inhibits factor Xa. Low-dose unfractionated heparin and low molecular weight heparin inhibit factor Xa and thrombin. A meta-analysis of four randomized, double-blind, control trials comparing fondaparinux with enoxaparin (low molecular weight heparin) for the prevention of VTE in major orthopedic surgery found the prevalence of VTE through postoperative day 10 was significantly lower in those patients treated with fondaparinux. Likewise, the frequency of proximal and distal DVT was lower in the fondaparinux group. Also, the number of patients treated for VTE was significantly lower in the fondaparinux group. However, the prevalence of symptomatic VTE, fatal PE, and nonfatal PE did not show significant differences (30). Of note, there was no significant difference in major bleeding between the groups, and there were no reports of decreased platelets in either group (31). The study concluded that a once-daily dose of fondaparinux, 2.5 mg subcutaneously, initiated 6 hrs after completion of surgery significantly reduced the rate of VTE by 55% and rate of proximal DVT by 57% as compared with low molecular weight heparin. Superior efficacy may be explained by different mechanism of action, longer biological half-life, or earlier initiation of treatment (31).

The evidence-based guidelines of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy (32) have provided specific recommendations for VTE prophylaxis in orthopedic surgery (Table 4). There is also evidence for extended VTE prophylaxis in the setting of orthopedic surgery (33). An oral direct thrombin inhibitor (ximelagatran) is currently undergoing investigation for the prevention of VTE in patients undergoing major lower limb surgery (34).

## Cardiac and Circulatory Concerns

Other than myocardial ischemia, cardiac problems unique to orthopedic surgery typically involve autonomic dysfunction due to spinal cord compromise or cardiac dysfunction due to emboli. Advanced age and severity of co-morbid medical conditions can exacerbate acute circulatory compromise. Preservation of adequate perfusion pressure is important, not only for myocardial, cerebral, and renal perfusion, but also for perfusion of the spinal cord. Postoperative treatment of hypotension must consider adrenal insufficiency in the differential diagnosis.

Cardiac complications after THA have a prevalence of 2–10%, and postoperative myocardial infarction after noncardiac surgery has a mortality rate of up to 70%. The use of pulmonary artery catheters in hip revision surgery and bilateral THA has been suggested but never proven to change outcome. The purpose in bilateral THA surgery is to monitor right heart pressures during and after the first stage of the THA and determine how safe it is to proceed with the second stage of the operation (35). Emboli after THR procedures is very common and can cause acute and often sustained pressures across the pulmonary vasculature (36). The prevalence of postoperative electrocardiographic changes is 20%, although the significance of these changes is not known. There is a 4.8% rate of supraventricular tachycardias after THR. This is more likely to occur in an elderly patient with a history of pulmonary or cardiac disease (7). This population would be expected to benefit from appropriate use of perioperative beta blockers to reduce perioperative myocardial ischemia and infarction (37). Many patients undergoing orthopedic surgery have been treated with corticosteroids for rheumatoid arthritis or anti-inflammatory effects. A single dose of etomidate for induction during intubation may cause adrenal insufficiency in the susceptible patient (38). Although this may be an infrequent cause of hypotension, it is easily corrected with supplemental corticosteroids.

A more complex issue is that of spinal shock. Spinal trauma often results in spinal shock that begins immediately after injury and may last for up to 3 wks. Loss of sympathetic tone occurs below the level of the lesion, and hypotension is common when the lesion is at or above T6 due to splanchnic vasodilation. Bradycardia may occur if the lesion involves the cardiac accelerator fibers arising from T2 to T6. Hypotension resulting from sympathectomy is best treated with vasopressors, and those refractory to catecholamines may be responsive to vasopressin. Cervical spine injuries involving C4–8 typically spare the diaphragm but result in intercostal and abdominal muscle paralysis, which leads to inadequate cough, paradoxic breathing pattern, reduction in vital capacity, and functional residual capacity. Patients with spinal shock are at high risk for VTE as a result of venous stasis, gastric reflux due to loss of upper esophageal sphincter tone, and hyperkalemia in response to succinylcholine administration. Autonomic dysfunction occurs 3–6 wks after spinal cord injury. When injury occurs above T7, extremes of hypertension and tachycardia may result from stimulation of nerves below the level of the injury (9).

Prone positioning may increase the likelihood of venous air embolism, as the surgical site may be above the level of the right atrium. During general anesthesia, an already increased alveolar-arterial oxygen gradient may be exaggerated due to regional hypoventilation and intrapulmonary shunting (9). Cardiovascular assessment should include transthoracic echocardiogram for those patients with chronic hypoxemia.

## Pain Management Concerns

Orthopedic surgery is associated with complex pain management problems. This population is often opioid-dependent, and this dependency creates significant postoperative challenges and complications. Both opiate withdrawal and severe respiratory depression may occur in the same patient in a single hospitalization. It is estimated that chronic back pain accounts for 15 million office visits per year, generating a cost of $50–100 billion per year (39). Fear of tolerance, dependence, addiction, and abuse may result in under-treating pain. Concerns for opiate-related side effects, both major and minor, often result in inadequate pain control reports by patients after hospital admission. Current trends and literature support a multimodal treatment approach to pain management.

Orthopedic surgery patients who require admission to the ICU more than likely will have postoperative surgical pain, and opiates are the mainstay of pain treatment, both acute and chronic. Sedation and analgesia in the ICU is often achieved with continuous intravenous infusions of opiates and sedatives. There is ample evidence that controlling pain reduces the likelihood of the development of chronic pain pathways (40), systemic catecholamine levels, blood glucose abnormalities, and inflammation and that it promotes wound healing. However, for patients requiring mechanical ventilation, continuous infusion of analgesics and sedatives may result in: 1) ventilator-associated pneumonia, 2) upper gastrointestinal hemorrhage, 3) bacteremia, 4) barotrauma, 5) venous thromboembolic disease, 6) cholestasis, and 7) sinusitis (41). Two recent studies indicate that daily interruption of continuous infusion of analgesics and sedatives reduce duration of mechanical ventilation, ICU length of stay, and the complications related to prolonged mechanical ventilation listed above (42).

Treatment of pain with opiates is only part of the multimodal approach to pain management. This approach utilizes nonpharmacologic and pharmacologic methods, such as ice packs, to treat pain. Pharmacologic treatment draws on many drug classes to harness their synergistic effects in an effort to reduce single-class side effects. An example of this strategy is using acetaminophen or paracetamol, nonsteroidal anti-inflammatory drugs, opiates, alpha agonists, tricyclic antidepressants, and neuroleptics to provide pain relief in a patient with acute on chronic pain exacerbation. Although nonsteroidal anti-inflammatory drugs are synergistic with narcotics, they can be associated with inhibition of bone regeneration, acute renal failure, and platelet inhibition leading to bleeding (9). Nontraditional medications used in treatment of pain include dexmedetomidine (a sedative analgesic) and ketamine.

*Ketamine.* Ketamine acts at multiple receptors. It acts centrally as an *N*-methyl-D-aspartate receptor antagonist that modulates perception of nociceptive pain. Ketamine also acts at the delta, kappa, and mu opioid receptors and on calcium and sodium channels. There is conflicting evidence surrounding the use of low-dose ketamine as an analgesic adjunct. Kafali et al. (43) showed that postoperative morphine requirements were lower in those patients who received a single preoperative dose of ketamine before abdominal surgery. Fitzgibbon and Viola (44) demonstrated improved pain control with low-dose ketamine in patients who had opiate-resistant neuropathic pain. However, a study by Jaksch et al. (45) failed to show lower postoperative morphine requirements in patients undergoing lower limb arthroscopic surgery. Low-dose ketamine may act in synergy with narcotic infusion; the net benefit is a reduction in the rate of narcotic infusion. Side effects are rare at low doses (2–5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), but they can include dysphoria, hallucinations, increased secretions, tachycardia, and hypertension due to inherent sympathomimetic properties.

*Dexmedetomidine.* Dexmedetomidine is a central-acting alpha-2 receptor agonist that produces sedation and analgesia without respiratory depression. Side effects are uncommon and include hypertension with rapid administration, bradycardia due to nodal blockade, and hypotension due to alpha-2 agonist effects. There is limited data about longer-term use of this agent, and it is currently indicated only for use up to 24 hrs. There are ongoing studies to identify if dexmedetomidine has efficacy for longer-term analgesia and sedation in the ICU.

*Regional Anesthetic Techniques.* Regional analgesia in the form of spinal anesthesia, epidural catheters, and peripheral nerve blocks and catheters are commonly used in management of the orthopedic surgery patient. The benefits of regional anesthesia may include reduction in the total amount of narcotics administered, reduced prevalence of VTE, earlier ambulation, and shorter length of stay. Intraoperative neuraxial anesthesia is associated with decreased ICU admission in high-risk orthopedic surgery patients (46). However, a survey of Medicare patients undergoing THA did not identify lower morbidity or mortality when neuraxial anesthesia was used (47).

Serious complications related to epidural catheters may occur during anticoagulation. The prevalence of epidural hematoma due to epidural catheter placement is 1 in 150,000 epidural and 1 in 220,000 spinal anesthetics performed. Vigilance should be maintained during concurrent epidural catheter presence, anticoagulation, platelet inhibition, or platelet dysfunction. Presumptive diagnosis of an epidural hematoma should be made if deterioration in neurologic function or severe back pain is noted. Confirmation of hematoma must be made by myelogram or computerized tomographic scan, and paraplegia is the likely result of delays in treatment. Epidural hematomas must be surgically decompressed in the first 12 hrs or neurologic function is unlikely to return (48). Minor complications of epidural anesthesia include hypotension, decreased and masking of more serious symptoms like bleeding, compartment syndrome, or nerve damage.

As outlined in the American Society of Regional Anesthesia 2003 Consensus Statement, the risks of hematoma after anticoagulation increases with traumatic needle placement (49). If a patient has an epidural catheter in place and requires systemic anticoagulation, it is recommended that the catheter be left in place and use discontinued. Removal of the catheter is considered safe 2 hrs after unfractionated heparin drip is stopped, 2 hrs before the first dose of low molecular weight heparin is administered, and when the international normalized ratio is <1.5 for those patients receiving warfarin therapy. There are no data on use of thrombolytics in the presence of neuraxial catheters. If a patient has taken antiplatelet medications, neuraxial blockade should not be performed for 7–10 days from the time of the last dose.

## Elderly Patients

Hip fracture occurs in one of every 50 persons >60 yrs of age. Postoperative confusion is common, occurring in 28–50% of patients. Delirium is a common postoperative complication in the elderly and occurs in 14–56% of hospitalized adults, with an associated 25–33% increase in mortality (50). Risk factors for delirium include: age of >70 yrs, increased duration of general anesthesia, low level of education, a second operation, postoperative infection, and respiratory complications. Advanced age, American Society of Anesthesiology class II or greater, and abnormal preoperative serum sodium are associated with late-onset cognitive dysfunction. In the ICU, these patients require multiple medications that may exacerbate their risk for delirium; benzodiazepines, anticholinergics, and poorly controlled pain are also associated with delirium (14). Prompt treatment and early mobility result in a decreased rate of complications.

Opiates in the elderly have a decreased volume of distribution and decreased plasma clearance. The alteration in pharmacokinetics is due to decreased lean body mass, decreased total body water, and increased percentage of body fat in the elderly patient. Although adequate pain control is associated with reduced prevalence of delirium and improved rehabilitation, opiate side effects of respiratory depression, delayed intestinal function, and altered sensorium can result in complications and prolonged hospitalization (14).

Other complications that may contribute to delirium include electrolyte abnormalities. Hyponatremia occurs in 4.4% of patients after THR and is associated with a 60-fold increase in perioperative mortality (7, 21, 51). Tierney et al. (51) studied nearly 14,000 patients and found a 4% rate of hyponatremia that was associated with a seven-fold increase in hospital mortality, regardless of underlying disease. Dehydration, hypotension, and underlying vascular disease predispose the elderly to risk of altered level of consciousness, ischemic stroke, myocardial ischemia, and renal hypoperfusion among other end organ problems.

## Reducing Complications in the ICU

There are several components of patient care that have been shown to reduce morbidity, mortality, and ICU length of stay. Although these components of care are not unique to orthopedic surgery patients, they are not exclusive of these patients and should be employed in the comprehensive care plan for each patient. The most publicized advance in perioperative risk reduction is that of perioperative beta blockade. In 1997, Wallace and Mangano (52) showed that perioperative beta blockers for patients with cardiac risk factors reduce the operative risks. A recent review by Lindenauer et al. (53) showed that beta blockade in high-risk patients is associated with a relative risk reduction; however, low-risk patients did not benefit from perioperative beta blockade.

There are several other management tactics that can have a significant effect on patient care. For example, van den Berghe et al. (54) demonstrated that intensive insulin therapy in critically ill patients results in a 4% reduction in mortality. Timely antibiotic administration will reduce infectious complications (55). Typically, patients in the ICU require sedation; Kress et al. (42) showed that daily interruption of continuous sedation led to shorter duration of mechanical ventilation and early discharge from the ICU. Other strategies include prevention of ICU-associated infections, including prevention of ventilator-associated pneumonia by elevating the head of the bed to 30 degrees, weaning patients from mechanical ventilation by using a weaning protocol, and appropriate use of antibiotics (56).

## Conclusion

The orthopedic surgery patients present unique challenges to the critical care physician. Their advanced age and co-morbidities make them particularly prone to complications of ICU care. Understanding the preoperative and intraoperative factors contributing to ICU admission and close communication with the orthopedic surgery and anesthesia teams will help identify potential problems and hopefully identify strategies for prevention. Life-threatening complications such as airway obstruction and emboli can be anticipated and prevented by understanding the risk factors commonly associated with patients undergoing major orthopedic procedures.

## REFERENCES

1. Bhattacharyya T, Iorio R, Healy WL: Rate of and risk factors for acute inpatient mortality after orthopaedic surgery. *J Bone Joint Surg Am* 2002; 84:562–572
2. Mahomed NN, Barrett J, Katz JN, et al: Epidemiology of total knee replacement in the United States Medicare population. *J Bone Joint Surg Am* 2005; 87:1222–1228
3. Kreder HJ, Deyo RA, Koepsell T, et al: Relationship between the volume of total hip replacements performed by providers and the rates of postoperative complications in the state of Washington. *J Bone Joint Surg Am* 1997; 79:485–494
4. Bradford DS, Tay BK, Hu SS: Adult scoliosis: Surgical indications, operative management, complications, and outcomes. *Spine* 1999; 24:2617–2629
5. Tornetta P III, Mostafavi H, Riina J, et al: Morbidity and mortality in elderly trauma patients. *J Trauma* 1999; 46:702–706
6. Iezzoni LI, Foley SM, Daley J, et al: Comorbidities, complications, and coding bias: Does the number of diagnosis codes matter in predicting in-hospital mortality? *JAMA* 1992; 267:2197–2203
7. Nazon D, Abergel G, Hatem CM: Critical care in orthopedic and spine surgery. *Crit Care Clin* 2003; 19:33–53
8. Kurtz S, Mowat F, Ong K, et al: Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. *J Bone Joint Surg Am* 2005; 87:1487–1497
9. Raw DA, Beattie JK, Hunter JM: Anaesthesia for spinal surgery in adults. *Br J Anaesth* 2003; 91:886–904
10. Fujita T, Kostuik JP, Huckell CB, et al: Complications of spinal fusion in adult patients

more than 60 years of age. *Orthop Clin North Am* 1998; 29:669–678
11. Nahtomi-Shick O, Kostuik JP, Winters BD, et al: Does intraoperative fluid management in spine surgery predict intensive care unit length of stay? *J Clin Anesth* 2001; 13: 208–212
12. Weis JC, Betz RR, Clements DH III, et al: Prevalence of perioperative complications after anterior spinal fusion for patients with idiopathic scoliosis. *J Spinal Disord* 1997; 10:371–375
13. Lawrence RC, Helmick CG, Arnett FC, et al: Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998; 41: 778–799
14. Borgeat A, Ekatodramis G: Orthopaedic surgery in the elderly. *Best Pract Res Clin Anaesthesiol* 2003; 17:235–244
15. Ezri T, Gewurtz G, Sessler DI, et al: Prediction of difficult laryngoscopy in obese patients by ultrasound quantification of anterior neck soft tissue. *Anaesthesia* 2003; 58:1111–1114
16. Sagi HC, Beutler W, Carroll E, et al: Airway complications associated with surgery on the anterior cervical spine. *Spine* 2002; 27: 949–953
17. Emery SE, Smith MD, Bohlman HH: Upper-airway obstruction after multilevel cervical corpectomy for myelopathy. *J Bone Joint Surg Am* 1991; 73:544–551
18. Harris OA, Runnels JB, Matz PG: Clinical factors associated with unexpected critical care management and prolonged hospitalization after elective cervical spine surgery. *Crit Care Med* 2001; 29:1898–1902
19. Jaber S, Chanques G, Matecki S, et al: Post-extubation stridor in intensive care unit patients: Risk factors evaluation and importance of the cuff-leak test. *Intensive Care Med* 2003; 29:69–74
20. Benumof JL: Management of the difficult adult airway: With special emphasis on awake tracheal intubation. *Anesthesiology* 1991; 75:1087–1110
21. Anderson PR, Puno MR, Lovell SL, et al: Postoperative respiratory complications in non-idiopathic scoliosis. *Acta Anaesthesiol Scand* 1985; 29:186–192
22. Popovsky MA, Abel MD, Moore SB: Transfusion-related acute lung injury associated with passive transfer of antileukocyte antibodies. *Am Rev Respir Dis* 1983; 128:185–189
23. Toy P, Popovsky MA, Abraham E, et al: Transfusion-related acute lung injury: Definition and review. *Crit Care Med* 2005; 33:721–726
24. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome: The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342: 1301–1308
25. Schonfeld SA, Ploysongsang Y, DiLisio R, et al: Fat embolism prophylaxis with corticosteroids: A prospective study in high-risk patients. *Ann Intern Med* 1983; 99:438–443
26. Ries MD, Lynch F, Rauscher LA, et al: Pulmonary function during and after total hip replacement: Findings in patients who have insertion of a femoral component with and without cement. *J Bone Joint Surg Am* 1993; 75:581–587
27. Gutt CN, Oniu T, Wolkener F, et al: Prophylaxis and treatment of deep vein thrombosis in general surgery. *Am J Surg* 2005; 189:14–22
28. DePalo LR: Near-fatal pulmonary embolism. *Mt Sinai J Med* 2001; 68:370–377
29. Konstantinides S, Geibel A, Olschewski M, et al: Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: Results of a multicenter registry. *Circulation* 1997; 96:882–888
30. Swensen SJ, Sheedy PF Jr, Ryu JH, et al: Outcomes after withholding anticoagulation from patients with suspected acute pulmonary embolism and negative computed tomographic findings: A cohort study. *Mayo Clin Proc* 2002; 77:130–138
31. Turpie AG, Bauer KA, Eriksson BI, et al: Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: A meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 2002; 162:1833–1840
32. Geerts WH, Pineo GF, Heit JA, et al: Prevention of venous thromboembolism: The Seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004; 126(3 Suppl):338S–400S
33. Dobesh PP: Evidence for extended prophylaxis in the setting or orthopedic surgery. *Pharmacotherapy* 2004; 24(7 Pt 2):73S–81S
34. Colwell C, Mouret P: Ximelagatran for the prevention of venous thromboembolism following elective hip or knee replacement surgery. *Semin Vasc Med* 2005; 5:2660–2675
35. Kim YH, Oh SW, Kim JS: Prevalence of fat embolism following bilateral simultaneous and unilateral total hip arthroplasty performed with or without cement: A prospective, randomized clinical study. *J Bone Joint Surg Am* 2002; 84:1372–1379
36. Hagio K, Sugano N, Takashina M, et al: Embolic events during total hip arthroplasty: An echocardiographic study. *J Arthroplasty* 2003; 18:186–192
37. Fleisher LA: Preoperative cardiac evaluation. *Anesthesiol Clin North America* 2004; 22: 59–75
38. Malerba G, Romano-Girard F, Cravoisy A, et al: Risk factors of relative adrenocortical deficiency in intensive care patients needing mechanical ventilation. *Intensive Care Med* 2005; 31:388–392
39. Mahowald ML, Singh JA, Majeski P: Opioid use by patients in an orthopedics spine clinic. *Arthritis Rheum* 2005; 52:312–321
40. Ekman EF, Koman LA: Acute pain following musculoskeletal injuries and orthopaedic surgery: Mechanisms and management. *Instr Course Lect* 2005; 54:21–33
41. Schweickert WD, Gehlbach BK, Pohlman AS, et al: Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. *Crit Care Med* 2004; 32:1272–1276
42. Kress JP, Pohlman AS, O'Connor MF, et al: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000; 342:1471–1477
43. Kafali H, Aldemir B, Kaygusuz K, et al: Small-dose ketamine decreases postoperative morphine requirements. *Eur J Anaesthesiol* 2004; 21:916–917
44. Fitzgibbon EJ, Viola R: Parenteral ketamine as an analgesic adjuvant for severe pain: Development and retrospective audit of a protocol for a palliative care unit. *J Palliat Med* 2005; 8:49–57
45. Jaksch W, Lang S, Reichhalter R, et al: Perioperative small-dose S(+)-ketamine has no incremental beneficial effects on postoperative pain when standard-practice opioid infusions are used. *Anesth Analg* 2002; 94:981–986
46. Kaufmann SC, Wu CL, Pronovost PJ, et al: The association of intraoperative neuraxial anesthesia on anticipated admission to the intensive care unit. *J Clin Anesth* 2002; 14:432–436
47. Wu CL, Hurley RW, Anderson GF, et al: Effect of postoperative epidural analgesia on morbidity and mortality following surgery in medicare patients. *Reg Anesth Pain Med* 2004; 29: 525–533
48. Liu S, Carpenter RL, Neal JM: Epidural anesthesia and analgesia: Their role in postoperative outcome. *Anesthesiology* 1995; 82: 1474–1506
49. Horlocker TT, Wedel DJ, Benzon H, et al: Regional anesthesia in the anticoagulated patient: Defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med* 2003; 28:172–197
50. Inouye SK, Schlesinger MJ, Lydon TJ: Delirium: A symptom of how hospital care is failing older persons and a window to improve quality of hospital care. *Am J Med* 1999; 106:565–573
51. Tierney WM, Martin DK, Greenlee MC, et al: The prognosis of hyponatremia at hospital admission. *J Gen Intern Med* 1986; 1:380–385
52. Wallace A, Mangano DT: Use of beta-blockade to prevent death after noncardiac surgery. *West J Med* 1997; 166:203–204
53. Lindenauer PK, Fitzgerald J, Hoople N, et al: The potential preventability of postoperative myocardial infarction: Underuse of perioperative beta-adrenergic blockade. *Arch Intern Med* 2004; 164:762–766
54. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345:1359–1367
55. Silber JH, Rosenbaum PR, Trudeau ME, et al: Preoperative antibiotics and mortality in the elderly. *Ann Surg* 2005; 242:107–114
56. Saint S, Savel RH, Matthay MA: Enhancing the safety of critically ill patients by reducing urinary and central venous catheter-related infections. *Am J Respir Crit Care Med* 2002; 165:1475–1479