To my wife Kim
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Abstract of Dissertation Presented to the Graduate School
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RISK OF TENDON RUPTURE AFTER QUINOLONE USE IN A U.S. MILITARY
POPULATION

By

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August 2007

Chair: Lyle D. Reid
Major: Pharmaceutical Sciences

Non-battle related injuries are the greatest cause of morbidity and mortality in the US military. Within the category of non-battle injuries, musculoskeletal injuries are the leading cause of disability. Tendon ruptures in particular, require long rehabilitation programs and can result in permanent disability. The consequence of tendon rupture is degradation in unit readiness and operational effectiveness. Case reports and case studies have linked tendon ruptures with quinolone antibiotic usage in the civilian population.

This retrospective cohort study utilized a Department of Defense administrative database to estimate the risk of tendon rupture in active duty personnel associated with quinolone use compared with the use of cephalosporin antibiotics. It identifies an induction period from quinolone exposure to tendon rupture while also identifying risk factors that are associated with an increased risk of tendon ruptures. Data from military personnel June 2005 through May 2006 were collected. Internal validity was confirmed using macro-level assessment techniques. Survival analysis was used to estimate the hazard function and the Cox proportional hazards model was employed to produce hazard ratios for the main treatment and other independent risk factors.
There was a significant increase in the risk of tendon ruptures over a 60-day period between active duty personnel who used quinolones compared to those who used cephalosporins (HR=1.65, 95%CI 1.33-2.04). The risk was highest during the 26 to 35 day window which marked the average induction period. Risk factors were days of supply (HR=1.02, 95%CI 1.018-1.022); military occupation (HR=1.53, 95%CI 1.24-1.89); age (HR=1.02, 95%CI 1.01-1.03); provider specialty (HR=2.40, 95%CI 1.92-2.99); Marine Corps service (HR=1.65, 95%CI 1.20-2.28); GI/GU antibiotic indication (HR=1.25, 95%CI 0.99-1.57).

This is the first study to identify an increased risk of tendon rupture from quinolone use in a demographically diverse population. The risk is elevated upon the first day of therapy and increases incrementally until it reaches its maximum between days 26-35. The risk of tendon rupture is augmented by advancing age, length of treatment, and working in a physically demanding occupation. These findings are important as they provide evidence that a significant portion of this debilitating injury is avoidable by identifying specific risk factors and incorporating them into the patient care plan.
CHAPTER 1
INTRODUCTION

Background

The United States Army Medical Department (AMEDD) has a three-pronged mission in today’s military. Its leaders must ensure that the United States Army (USA) can project and sustain a healthy and medically protected force. The AMEDD must be able to deploy a trained and equipped medical force that supports the Army transformation and it must manage the care of the Soldier and the military family. Disease and non-battle injury (DNBI) is the one of the largest threats to these objectives(1).

The contribution of disease to DNBI has continued to fall due to immunization programs, appropriate chemoprophylaxis, and a heightened command emphasis on hygiene and other public health initiatives(1). Non-battle injuries (NBI) are now the greatest cause of morbidity and mortality in the US military(1). Within NBI, the leading cause of disability in the U.S. military is musculoskeletal injuries. Among MS injuries, tendonopathies are a common group of conditions ranging from tendonitis to a complete tear or rupture of the tendon(2).

The occurrence of tendonopathies in the U.S. military has been difficult to quantify, but is believed to be quite common. Tendon ruptures, in particular, require long rehabilitation programs and can result in a permanent disability. This lengthy rehabilitation time has the unwanted consequence of degrading unit readiness and operational effectiveness. Case reports and case-control studies have linked tendon ruptures with quinolone antibiotic usage in the civilian population (3). This risk factor has not been evaluated in a military population.

The use of quinolone antibiotics is of particular importance as it is an avoidable risk factor. This novel class of antibacterial medications is widely used throughout the world. As more quinolones have been synthesized, their spectrum of actively has widened. As their bacterial
coverage has increased, so has their inclusion in treatment recommendations for many kinds of infections, ranging from anaerobic, skin/soft tissue, and upper/lower respiratory tract infections. These new treatment indications have increased the frequency of their use, and the potential for increases in previously poorly recognized adverse events such as connective tissue disorders. Quinolones are contraindicated in children under the age of twelve due to connective tissue toxicity seen in juvenile animal studies. Connective tissue disorders include chondrotoxicity and tendonopathies. The first report of quinolone associated tendonitis in adults was published in 1983, while case reports of tendon ruptures began appearing in the early 1990s(4-6). It is recognized that most tendonopathy is seldom traceable to a single factor(7). The degenerative process that precedes tendon rupture probably emanates from a variety of different pathways and causative factors, many of which are unavoidable to the active duty soldier.

The term induction period is the epidemiologic term used to explain the period of time from causal action until disease initiation(8). Quinolone use is one postulated causal factor that may lead to the initiation of tendon rupture. There is a cascade of intrinsic steps post quinolone exposure, that may lead to the characteristic tendon lesion, but at the end of this relatively quick process (days) we do not see an immediate occurrence of tendon rupture. Data pertaining to a detailed induction period for tendon ruptures related to quinolone use, which includes the induction periods for the other component causes is lacking. For clarification, the epidemiologic term latent period is the time interval between disease occurrence and detection(8). The cellular process that leads to a weakened tendon non-withstanding, the occurrence of tendon rupture, and its detection is rapid, thus the latent period at the end of the induction period is minor. The induction period plus the latent period is sometimes referred to as the lag time. The lag time is the time from quinolone usage until a tendonopathy has been diagnosed.
Traditionally epidemiologic studies try to identify and induction period by selecting a set of induction periods and calculating the corresponding set of risk estimates. The estimates would ideally reach a peak when the selected induction period matches the actual induction period. If a pattern emerges, (rising estimates then falling estimates) that would be evidence that the induction period with the highest estimate would be the best estimate. If no pattern emerges then this method may not be reliable since any peak may be random variability. Instead of selecting a set of arbitrary induction periods and looking for a pattern in their risk estimates, the use of the hazard function within the survival analysis model framework, may provide better estimates of the induction period.

This study of quinolone antibiotics identifies an avoidable exposure risk factor, establishes a defined average induction period, and describes various other important risk factors for developing a tendon rupture.

**Need for Study**

Ensuring the U.S. military is ready to execute its mission is the responsibility of leaders at all levels. Maintaining or increasing military readiness is of paramount concern and must continually be re-evaluated to identify possible opportunities for improvement. Non-traumatic musculoskeletal injuries effect military readiness more than any other medical condition (9-12). Musculoskeletal injuries are frequent occurrences in all branches of the military. They are often found in combat units due to the physical nature of their occupation(13-15). Economically speaking, musculoskeletal injuries account for the largest impact on direct health care costs to the active duty force(10). Tendon ruptures are musculoskeletal injuries that 1) impact unit readiness because they require long-term rehabilitation, and 2) affect senior leaders more so than younger military personnel (3, 16).
Tendon ruptures have been associated with quinolone antibiotic use in case reports and case-control studies(5, 6, 17-22). Identification of an avoidable risk factor for tendon ruptures will help increase unit readiness and decrease the resources currently utilized treating musculoskeletal injuries. Additionally, the identification of a specific tendon rupture average induction period, post treatment initiation, will enable better counseling of patients in order to reduce tendon rupture risk. The identification of other risk factors for tendon rupture will enable clinicians to pinpoint patients that are at an increased risk and tailor their antibiotic therapy accordingly. Information from active duty soldiers is the best way to provide answers to these issues.

**Purpose of the Study**

This study utilized a large Department of Defense computer database, which contains encounter and pharmacy data, to estimate the risk of tendon rupture in active duty military personnel associated with quinolone antibiotic usage compared with the use of cephalosporin antibiotics. Connective tissue disorders have not been described in patients using the cephalosporin class of antibiotics. It also identifies the average induction period from quinolone exposure to tendon rupture using time to event analytic techniques. Lastly, risk factors that are associated with an increased risk of tendon ruptures, and are relevant to the active duty force, are identified and their risk estimated.

One of the major recommendations of the DoD’s Injury Surveillance and Prevention work group for preventing and controlling injuries in the military services, was to ensure adequate injury research to support prevention programs(1, 22). Treating this epidemic of injuries in a scientific way allows researchers to employ study designs and methods that yield reliable and valid results, which can be turned into action plans by military leaders. It takes this command involvement to bring about the needed changes to reduce lost duty time and shortened careers.
**Main Research Question**

Estimate the risk of tendon rupture from using a quinolone antibacterial medication relative to an antibacterial medication, in a military population

**Objectives**

This study uses formal Pharmacoepidemiologic and time at risk methods to estimate the risk of tendon rupture outcomes due to quinolone exposure relative to cephalosporin exposure in an active duty military population. It also estimates the hazard function in order to identify the average induction period in the exposure to outcome pathway while determining important risk factors for an individual using quinolone antibiotics.

This study addresses four specific objectives:

1) Estimate the risk of tendon rupture from quinolone use, relative to a cephalosporin medication, while adjusting for relevant risk factors and accounting for time at risk.

2) Investigate whether the risk of tendon ruptures from quinolone use varies over time.

3) Identify the average induction period within the study interval.

4) Identify other major risk factors that affect an active duty military individuals’ estimated risk for tendon rupture.
CHAPTER 2
LITERATURE REVIEW

Injury

The realization after Operations Desert Shield/Storm (the Persian Gulf War) that within DNBI, non-battle injuries were becoming the major source for morbidity and mortality in the U.S. Armed Forces, resulted in a request in 1994 from The U.S. Army Office of the Surgeon General (OTSG). The OTSG asked the Armed Forces Epidemiological Board (AFEB) for guidance on surveillance, prevention, and control of injuries in military populations. In response, the AFEB formed the Department of Defense (DoD) Injury Surveillance and Prevention Work Group (ISP) to gather information on injuries in the military and make recommendations for future surveillance and prevention based on their findings. The final report of their findings was published in 1996 and was sent to the Surgeons General of the three military medical departments for implementation in 1997. Ultimately, in 1999, the ISP’s work was collected and published as the Atlas of Injuries in the U.S. Armed Forces. This extensive text showed that injuries, not illnesses, have the largest negative effect on the health of military personnel. The Atlas of Injuries in the U.S. Armed Forces graphically illustrates three major facts in the identification of the injury problem. First, injuries are the leading cause of death, disabilities, hospitalizations, and outpatient visits in the military services, relative to other causes of morbidity and mortality. Second, sports, falls, training-related injuries, and motor vehicle accidents, are the leading causes of injury-related morbidity. Third, unintentional injuries (accidents/mishaps), in particular motor vehicle crashes, are the leading cause of death for all services.

The DoD ISP, after studying the issue, concluded, among other findings, that musculoskeletal (MS) injuries are the leading cause of disability in the military(1, 14). They are
responsible for 51% of diagnoses resulting in disability discharge from the USA (9). These musculoskeletal injuries and their resulting chronic conditions account for a large proportion of DoD disability cost. MS conditions are the leading cause of Veterans Administration (VA) disability payments (lifetime costs of $485 million to newly disabled Army personnel in 1993) (9). Injuries and their MS sequelae are the leading causes of hospitalization in the DoD (14). Wojik, et al. (2004) published a paper in the American Journal of Industrial Medicine that looked at disease and non-battle injuries based on Persian Gulf War admission rates (23). They found that musculoskeletal and connective tissue diagnoses accounted for 12.6% (1,718) of the total non-battle related injuries during operation Desert Shield and operation Desert Storm. Gordon, et al. (2000) in their article entitled ‘Hospitalization Due to Injuries in the Military’ published in the American Journal of Preventative Medicine, evaluated the current data and found combat injuries represent a small part of the injury problem in the U.S. Military. Most injuries in the military occur in similar ways to those in the civilian world, where injuries are recognized as a leading cause of morbidity, disability, and death in society as a whole. Data from the first Gulf War suggest that injuries and musculoskeletal conditions accounted for 39% of all hospitalizations during the operation and less than 5% of all hospitalizations were combat related. Musculoskeletal and connective tissue disorders (ICD code group 710-739) comprised 14% of all hospitalizations, many of which were the chronic or recurrent effects of injuries that occurred before deployment. In 1992, the musculoskeletal diagnosis group accounted for 28.1 (Army), 9.7 (Navy), 12.0 (Airforce) per 1000 person-years, this represented the number one reason for hospitalization in the Army, second in the Navy and second in the Airforce. Results from studies concerning NBI injuries in other conflicts support these MS injury trends (24, 25).
MS injuries associated with physical training and athletic/sports injuries are a major cause of training time loss and are the major contributor to the occurrence of nonfatal injuries(9).

In the Army and Airforce athletic/physical training injuries are more common than motor-vehicle injuries and correspond to an incidence rate of 3.2 / 1000 in the Army and 2.2 in the Airforce from hospitalization data(12). Lauder et al. (2000) studied sports and physical training injury hospitalizations in the U.S. Army and published their findings in the American Journal of Preventative Medicine. Since injuries are the leading health problem in the military service, Lauder looked at the amount of injuries caused by sports and physical training in the Army. They found that during the six-year study period there were 13,861 hospital admissions for injuries resulting from sports and Army physical training. The rates were 38 and 18 per 10,000 person-years for men and women respectively. Sports injuries resulted in 29,435 lost duty days each year. Musculoskeletal injuries were responsible for 82% of all sports or physical training injuries(12). This finding demonstrates a direct impact on military readiness. Risk factors for injury during military training are, female gender, BMI, smoking, ethnicity, flat feet, illness or injury in the past year, no previous military experience and baseline fitness level. Ankle injuries, which include Achilles tendon ruptures, were the 3rd most common injury diagnosis. The study’s major finding was that sports and physical training are responsible for a large number of lost duty days per year. It is of interest that the majority of these injuries were musculoskeletal in nature and resulted in a direct reduction of military readiness.

Musculoskeletal injuries are frequent occurrences in all branches of the military. They are often found in combat units due to the physical nature of their occupation(13-15). Non-traumatic tendon ruptures are musculoskeletal injuries that 1) impact unit readiness because they require
long-term rehabilitation, and 2) affect senior leaders more so than younger military personnel (16).

**Incidence of Tendon Ruptures in the U.S. Military**

The Department of Army (DA) through the Center for Health Promotion and Prevention Medical (CHPPM) published a report in it’s Medical Surveillance Monthly Report (MSMR), on spontaneous ruptures of the Achilles tendon, (16). This study chronicles incidence rates and trends for non-traumatic Achilles tendon ruptures among active duty service members between January 1998 and May 2001. In 2001, non-traumatic Achilles tendon ruptures occurred at a rate of 51.3 per 100,000 person-years(3). In this sample, non-traumatic tendon ruptures from all anatomic sites summed to 165 per 100,000 person years (3). This incidence rate is higher than the 6 to 18 per 100,000 person years seen in studies utilizing a civilian population sample(21, 26-29). This study identifies older individuals, Black race, and male gender as subgroups at highest risk. The increased incidence in older military personnel compared to more junior ones illustrates a disproportionate impact on senior leaders. An important finding of this study is the identification of a trend of increasing rates of tendon ruptures of all kinds during the study period. Achilles tendon ruptures had the sharpest increase starting at 22.7 per 100,000 person years in 1998. Also of import is the observed higher incidence rate in a military population compared to a civilian one.

Now that the general toll of MS and in particular non-traumatic tendon rupture injuries in the military has been reviewed, it is time to study specific causes of MS injuries and apply preventative measures to reduce their occurrences. Injuries must not be thought of as unpreventable random events, but as a predictable result of many risk factors. Important risk factors can be identified and controlled, which will lead to a reduction in injuries and the resulting morbidity and mortality. Tendon ruptures are important injuries that are associated
with many risk factors. Identification of an avoidable risk factor for non-traumatic tendon rupture will help increase unit readiness and decrease the resources currently utilized treating non-traumatic musculoskeletal injuries.

**Pathogenesis of Tendonopathy**

Tendon tissue is a matrix that is well suited to perform its major function of transferring force from muscle to bone. It is not a static tissue and is constantly being remodeled to adapt to the frequency and force applied. The term tendonopathy refers to disorders primarily affecting tendons, including chronic pain, inflammation, and tendon rupture. Tendonitis is characterized by chronic pain and the assumption of an inflammatory response to the tendon injury.

Spontaneous tendon rupture describes ruptures that occur without any noticeable preceding clinical symptoms. This is a misnomer as healthy tendons have much higher tensile strength than is required for normal activities. Because of this, tendon ruptures are rarely spontaneous and must be related to at least some degree of tenocyte degeneration. The cause and nature of this pathological degeneration is not settled. Many systemic diseases may compromise tendon strength and elasticity, or result in an inflammatory process.

There are two main theories that attempt to explain tendon ruptures. The first is the mechanical hypothesis, which says that repetitive micro-trauma or a single physiological load that strains the tissue above a certain percentage of length causes tendon ruptures. The second theory relies on the tendon vasculature. According to this theory, injury occurs as a result of diminished blood flow to the tendon because of aging, vascular disease, physical disuse, or trauma. In reality, most tendonopathies are probably a combination of mechanical and vasculature in nature and are initiated by a variety of different causative factors that lead to the degenerative process.
Tendon Rupture Risk Factors

Identification and avoidance of a risk factor for non-traumatic tendon ruptures will help increase unit readiness and decrease the resources currently utilized treating non-traumatic musculoskeletal injuries. Overall, risk factors for tendon injuries are listed in table 1. Increasing age, male gender, and Afro-American ethnicity, have been associated with an increased risk of non-traumatic tendon ruptures in military personnel (3). Case reports and observational studies of non-military personnel treated with quinolone antibiotics have demonstrated an increased risk of tendon rupture(19-22, 30-34). Other associated risk factors include renal dysfunction/dialysis/transplantation, rheumatic disease, gout, diabetes mellitus, sports participation, hyperparathyroidism, and hypoparathyroidism(18). Case-control studies have reinforced these factors linked to an increased risk of non-traumatic tendon ruptures (5, 6, 19-22, 30, 35, 36).

Quinolones

Quinolone antibiotics were first developed in the early 1960s with the introduction of nalidixic acid (2). The first-generation quinolones have bactericidal activity over most common Gram-negative bacteria(37). In the 1980s, with the introduction of norfloxacin, the first fluorinated quinolone derivatives began to appear(38). These second-generation quinolones include norfloxacin, ciprofloxacin, and ofloxacin, among others, and exhibit an increased, yet still mainly Gram-negative, antibacterial spectrum. In the following years, more second-generation quinolones have been created with more balanced broad-spectrum activity that encompass some Gram positive as well as Gram negative coverage. Temafloxacin, grepafloxacin, and sparfloxacin, are a few of the more recent second-generation quinolones. During the 1990s, a third generation was synthesized with levofloxacin being the most popular member. This generation is characterized by an enhanced Gram-positive and atypical pathogen
coverage, which makes it suitable for infections of the respiratory tract, while still maintaining the basic quinolone Gram-negative activity. Most recently, a fourth generation has been designated. This group is distinguished by an increased anaerobe coverage. This coverage is added to the third generation, which includes moxifloxacin and gatifloxacin. There are several organizational methods used to classify quinolone antibiotics based on their structure and activity relationships (SARs). The four-generation categories used here were developed by the Paul-Ehrlich-Society or Chemotherapy (PEG) and are commonly employed to reflect both the drugs chemical and functional characteristics. Some researchers have utilized different category representations to accentuate the distinction between either the original quinolone chemical entities and their subsequent fluorinated offspring or the unique functionalities of the different SARs. The former distinction is becoming obsolete with the synthesis of newer quinolones with fluorine atoms at different positions or the absence of fluorinated derivatives altogether. Throughout this study, the term quinolone will be used to describe all non-fluorinated and fluorinated quinolone derivatives.

**Mechanism of Action**

Quinolones exert their antibacterial activity through the inhibition of bacterial topoisomerase II. This interference of this DNA gyrase enzyme leads to inhibition of DNA synthesis in nuclei and mitochondria. The specific binding reactions to topoisomerase II and the subsequent damage to bacterial DNA are beyond the scope of this text, but this mechanism of action makes quinolones rapidly bactericidal. As a class, they exhibit concentration-dependent killing, which makes them highly effective and clinically useful in treating a range of bacterial infections. Quinolones are commonly used in the treatment of diseases ranging from urinary tract infections, sexually transmitted diseases, respiratory infections, gastrointestinal infections,
skin and soft tissue infections, and bone infections. They are also used empirically to treat fever in neutropenic cancer patients and for prophylaxis in many surgical procedures.

**Drug Safety Overview**

Quinolones have an important toxicity and adverse effect profile that has been demonstrated in animals as well as in humans.

Pharmaceutical manufacturers routinely do preclinical toxicity studies in animals. The results of these studies are usually not published in peer-reviewed journals, which make them difficult to evaluate. The relevance of these studies becomes smaller as human information, from clinical studies becomes available. Still, animal studies are important as they produce a range of possible toxicities that give the clinical investigator forewarning of what to look for in human patients.

Human trials have established quinolones to be a relatively safe and well-tolerated class of antimicrobials. The overall adverse event rate in most clinical trials is very similar to the control group whether the group was a placebo or another antimicrobial. This should not be implied to mean that they do not have a unique safety risk profile that is consequential when weighted against the possible benefits of quinolone therapy.

**Connective Tissue Toxicity**

Connective tissue toxicity is a well-known adverse effect that has been noted to occur in all quinolones so far tested. Effects on connective tissue are broken down into chondrotoxicity and tendonopathies.

**Animal Chondrotoxicity**

Ingham et al. (1977) first described chondrotoxicity in quinolones, consisting of articular lesions in the cartilage of juvenile dogs. Young beagle dogs were given pipemidic acid orally for 1-15 days at doses of 200-1000 mg/kg. Lameness occurred by way of gait abnormalities within
the first 3-7 days after starting the treatment. Upon inspection, articular cartilage lesions were identified in major joints such as the hip, wrist, elbow, ankle, and shoulder. Lesions were also detected in the distal growth plates (epiphyses) of the humerus, femur, proximal tibia, and tarsal bone in rats. These lesions started as blisters before progressing to ulcerative erosions, which were considered irreversible. When these lesions were examined histologically they revealed a general necrosis of chondrocytes. It has been postulated that quinolones directly or indirectly damage collagen fibrils, which leads to hyperhydration and osmolality changes in the cartilage matrix. These changes predispose the cartilage to blister formation from the mechanical pressure of body weight while ambulating. The clinical recovery, in the form of a reduction in lameness, took place over a 2 to 3 week period after cessation of the drug, although cartilage lesions were still present up to 3 months. Dogs between 2.5 to 5 months old were most at risk for the toxic effect. Following this study, other investigations replicated the toxicity of this compound as well as uncovering the same adverse effects in all other available quinolones across many different species of laboratory animals. Because of the propensity of quinolones to induce toxic lesions in the articular cartilage of distinctly juvenile animals, quinolones have been restricted from use by children and growing adolescents.

**Human Chondrotoxicity**

Chondrotoxicity caused by quinolones has only been directly demonstrated in juvenile animal models. Because of the resulting arthropathies identified in animals, these drugs are restricted in children under the age of twelve. Consequently, clinical evidence of this side effect is small due to their limited use in children as well as the fact that cartilage lesions are not always associated with clinical symptoms. The general deficit of clinical evidence should not be used to minimize the effect of irreversible cartilage toxicity, as clinical symptoms may arise over a long period of time. The best evidence of clinical arthropathies in humans comes from the use of
quinolones in children with cystic fibrosis. In this international review of 2,030 courses of ciprofloxacin treatment in 1,795 children, the incidence of arthralgia was 1.5% (39). All cases resolved without intervention. Case reports of arthralgia have been reported with quinolones other than ciprofloxacin, including nalidixic acid, pefloxacin and norfloxacin (4, 40, 41).

**Animal Tendon Toxicity**

Tendon tissue is also affected by quinolone use. Starting with Kato et al. (1997) researchers have consistently found structural changes in tendon and tendon associated tissues in rats. Edema and mononuclear cell infiltration in the inner sheath of the Achilles tendon, and infiltration surrounding the adjacent synovial membrane and joint space marked the tendon lesions induced by quinolones early trials. Later, Sendzik et al. (2005) showed that the final event in the pathogenesis of quinolone induced tendonopathies is in fact apoptosis of tenocytes, which leads to necrosis of the tendon tissue. In a study comparing the effects of 10 different quinolones on rat Achilles tendon tissue, Kashida and Kato, (1997) showed that there is a difference in the toxic potential within the drug class. Pefloxacin and fleroxacin were the most toxic while sparfloxacin, norfloxacin, and ciprofloxacin, resulted in less lesion formations. The researchers suggested that this difference in toxicity is more a result of pharmacokinetics, as pefloxacin and fleroxacin have higher absorption rates than the other quinolones.

**Etiology of Connective Tissue Toxicity**

Early reports attempting to describe the mechanism for quinolone induced connective tissue toxicity centered on their inhibition of DNA synthesis in nuclei and mitochondria via their interference with the topoisomerase II enzyme. Even though quinolones have a low affinity for eukaryotic DNA several studies showed that quinolones may target chondrocytes and tenocytes more so than other cell types thus initiating the typical lesions. Later, different evidence pointed toward the inhibition of synthesis, rather than the stimulated degradation of collagen. This
hypothesis, first put forth by Schroter-Kermani et al. (1992), and reinforced by several others, was evidenced by several factors. These researchers showed that quinolones were responsible for compositional changes in individual proteoglycans and glycosaminoglycans in rats and dogs. These changes along with the inhibition of soluble prostaglandins work to reduce chondrogenesis. Original research done by Stahlman et al. (1993) diverged from these two hypotheses by showing that the primary event in quinolone chondrotoxicity is the negative effect they have on magnesium-dependent integrins in articular cartilage. This brings the basis of quinolone toxicity to a long known characteristic of quinolones known as chelation. Chelation occurs when metallic and nonmetallic substances combine to form stable chelate complexes. This attribute is well known for its effect on the pharmacokinetics of quinolones as their absorption is reduced if di- or trivalent-metal cations are present in the GI tract when quinolones are orally administered. Typically, magnesium (Mg$^{2+}$), aluminium (Al$^{3+}$), or calcium (Ca$^{2+}$), containing agents such, as antacids or vitamin supplements, form poorly absorbed chelated compounds probably consisting of quinolone molecules and metal cations. Stahlman’s findings hinted that by forming stable chelate complexes, systemically within the connective tissue, with magnesium, quinolones affected the electrolytic balance, impaired a specific family of integrins, and eventually caused degeneration of the collagen matrix and irreversible articular damage.

This hypothesis has become the accepted mechanism for quinolone induced connective tissue toxicity for several reasons. Both tendon and cartilage tissues are characterized by low vascularization and similar matrix components. Because of the poor vascularization any change in nutrient or electrolyte balance in the surrounding environment can not be corrected quickly. This vascular isolation enhances the chances that chelate complexes formed by quinolones will deprive important integrin proteins of magnesium, which will lead to chondrocytes and tenocytes
losing integrity and releasing harmful inflammatory radicals into the local cellular area. This notion has been reinforced by the fact that animals fed a magnesium deficient diet develop similar lesions as the ones induced by quinolones. Shakibael et al. (1999) and Lozo, et al. (2002) demonstrated that rats fed a magnesium deficient diet while treated with quinolones had a higher occurrence of degenerative alterations in tenocytes than rats fed a normal magnesium diet. Recently Pouzaud, et al. (2003) showed that the toxic effects of quinolones on tendon cells were partially related to reactive oxygen species production (ROS). Increased ROS contributed to the damage of cartilage and tendon microstructure seen in rabbit tendon cells. This increased ROS production may be directly caused by quinolones, or may result from cellular proteolytic activity caused by the magnesium deficient degenerative process. Quinolone induced connective tissue toxicity is mostly likely a degenerative process that results from a variety of different microenvironment pathways. Its pathological features are similar in both cartilage and tendon tissues indicating that quinolone induced chrondrotoxicity and quinolone-induced tendonopathy are probably different clinical manifestations of the same toxic effect on cellular components of connective tissue structures. Animal and human models have shown it to be an accepted, identifiable, toxicity that differs in intensity across different age groups and individual quinolone compounds.

**Human Tendonopathy**

**Case reports**

Tendonopathies linked to quinolone use usually involve tendonitis that may or may not progress to a tendon rupture. The first report of tendonitis related to quinolone use was in 1983 and involved two post renal transplantation patients who developed tendonitis while being treated with norfloxacin(4). Since then, there have been over a thousand case reports to various
governmental surveillance agencies associating most quinolones with tendonopathies (2, 18, 42-45).

Dependin upon the source of case reports used, review articles have show that roughly half of these tendonopathies are tendon ruptures (18, 44, 45). Characterizations of spontaneous tendon ruptures post quinolone therapy are numerous, dating back to 1992 when seven patients with Achilles tendonitis, including 3 with rupture following quinolone therapy were reported (5). Since then tendon rupture has been accepted as an infrequent but important adverse reaction to quinolone therapy.

The most common injury site is the Achilles occurring in about 90% of the cases and 40% of these occurred bilaterally (18, 35, 43, 44, 46). The Achilles tendon is probably affected the most because it is the main weight-bearing tendon. Ruptures have also occurred at the triceps tendon, flexor tendon (finger), thumb, patellar, supraspinal tendon, quadriceps, subscapularis, and rotator cuff tendon (2, 18, 21, 44).

Overall, the mean time of onset of tendonopathies has been estimated to be 17 days with half occurring within the first six days post initiation of quinolone therapy. Rupture of a tendon had a mean onset of 25 days but the median was 6 days. Case reports show that tendonopathies have occurred as soon as 2 hours post treatment initiation and as late as 6 months after the medication has been discontinued (2, 18, 21, 31, 44, 47).

Pefloxacin induced tendonopathies account for 37% of case reports while ciprofloxacin was implicated in 25%. Norfloxacin is responsible for 11%, levofloxacin 8%, and ofloxacin 6% (44). In one case tendonopathy symptoms were eliminated by lowering the dose of norfloxacin, and upon rechallenge at the higher dose, the symptoms reappeared (4). Diagnosis was mostly by physical examination and treatment usually involved discontinuing the
medication. Anti-inflammatory pain medications, physical therapy, immobilization, and surgery were all documents interventions to treat the tendonopathy. Recovery took a mean of 59 days and lingering sequelae of swelling, bruising, difficulty in walking, decreased flexion, and pain were reported(44). The mean age for case reports is 59 years with a range of 28 to 92 years. Men seem to be affected more than women by 2:1.

Interestingly, reviews in the Netherlands, Sweden, and Switzerland all show sharp national increases in tendonopathies when a newer third or fourth generation quinolone was added to the national formulary (18, 29, 45). The increases were characterized by large jumps in tendon ruptures that were not attributed to young active males but to older patients that were administered a corticosteroid in conjunction with the quinolone for a respiratory tract problem(18, 29). The new generations of quinolones, with their increased Gram-positive coverage, have become the drug of choice for upper respiratory tract infections such as community acquired pneumonia. This increase in cases may be due to the increased prescribing of quinolones because of their increased inclusion in treatment recommendations or because of a yet undetected, enhanced connective tissue toxicity of the newer quinolones. The exposure rate to quinolones was estimated at 2% in the Dutch case review study.

It is worth noting here that the incidence of tendon rupture also increased, mostly due to a doubling of the occurrence of Achilles tendon ruptures, in the U.S. military from 1999 to the end of the Medical Surveillance Monthly Report (MSMR) incidence study in 2001 (3).

Cohort studies

Two cohort studies helped solidify the estimated incidence rate of quinolone induced tendon disorders in otherwise healthy individuals. The rate is characteristically low at 0.14 and 0.4% respectively(35, 48). Van der Linden et al. (1999) employed a retrospective cohort study design using data from the Integrated Primary Care Information system (IPCI). The IPCI
contained computerized patient records from general practitioners throughout the Netherlands monitoring about 250,000 patient records. In the end, this study was woefully underpowered to find an association as after patients were excluded for various reasons they were left with n=1,841 in the quinolone group and n= 9,406 in the control group. There was a significant nested finding for ofloxacin and Achilles tendonitis of RR 10.1 (95%CI: 2.2-46.0). Ofloxacin treatment was associated with an increased risk of 15 cases per 100,000 days. The increased risk of tendonopathy attributed to quinolone therapy was 0.4%(35). Another study completed in England compared the results of five observational cohort studies that reported the safety of ciprofloxacin, norfloxacin, ofloxacin, azithromycin, and cefixime. The three quinolones were compared to the macrolide and cephalosporin safety findings. All samples were less than n=10,000. The average rate was 0.14 % in the quinolone group and 0.03% for the other antibiotics. Of note, there were four tendon ruptures in the quinolone group and zero in the non-quinolone group(48).

Case-control studies

More recently, three case control studies have been completed. The first centered on the risk of Achilles tendonopathy in general and the other two on Achilles tendon rupture in particular.

In the first study, researchers from the Netherlands conducted a nested case-control design of quinolone users whose records were contained in the IMS Health database (UK MediPlus). This database contains data from general practice (GP) visits on a source population of 2 million. The researchers established four categories of exposure to quinolones: current use, recent use, past use, and no use. Current use was defined as day 1 of drug therapy through 30 days past the calculated end date. Recent use was between 30 to 90 days post therapy end date, and past use was greater than 90 days after the calculated end date. Analyzing the data using logistic
regression they adjusted for age, sex, number of GP visits, use of a corticosteroid, calendar year, obesity, and history of musculoskeletal disorders. The cohort contained 46,776 patients of which 704 were cases. Cases were 61% female and had a mean age of 56 years. Significant covariates included age, number of GP visits, gout, obesity, and use of corticosteroids. The overall adjusted relative risk (RR) for Achilles tendon disorders for current use of quinolones was a modest but significant 1.9 (95% CI: 1.3-2.6). Recent and past use was comparable to no use. Other important results were that patients over the age of 60 had an Achilles tendon disorder current use RR of 3.2 (95% CI: 2.1-4.9). When the tendon disorder was stratified, the RR of Achilles tendon rupture in current use patients over 60 year old was 7.1 (95% CI: 1.7-29.1) and similarly the RR for tendonitis was 3.1 (95% CI: 2.0-3.8). This study reinforces results from case reports and smaller cohort studies that this adverse event is relatively small with an excess risk of 3.2 cases per 1,000 patient years in this study. The risk was highest in patients over the age of 60 with concomitant use of corticosteroids(19).

In the second population-based case-control study, the same research group utilized the General Practice Research Database (GPRD) from the United Kingdom to carry out a similar research project. This study’s main objective was to quantify the risk of Achilles tendon rupture from quinolone use, and to report on concomitant risk factor(20). The GPRD contains GP entered medical information on approximately eight million residents of the United Kingdom, of these 50,000 persons were randomly selected to act as controls. This study design and methods are similar to the previous research article with a few differences. Adjustments were used for age, sex, cortical steroid use, history of musculoskeletal related disorders, disorders of lipid metabolism, organ transplants or hemodialysis, and number of GP visits. They also performed a stratification analysis by age, sex, and concomitant use of cortical steroids. The researchers
identified 1,367 occurrences of Achilles tendon rupture from January 1, 1988 to January 1, 1999 that after review were included in the study. The identification of exposure was broken into current, recent, and past use of quinolones defined the same as in the previous study. The cases were 69.4% male and had a mean age of 48 years. The use of quinolones was significantly lower in males compared to females and higher in patients between 60 and 79 and over 80 years old compared to patients 59 and younger. Exposure to any quinolone was 4.5% of cases and 2.0% of controls. The overall Odds Ratio (OR) for Achilles tendon rupture was 4.3 (95% CI: 2.4-7.8) for current exposure and 2.4 (95% CI: 1.5-3.7) for recent exposure. When the results were stratified by age the OR was 6.4 (95% CI: 3.0-13.7) for patients between 60 to 79 years and 20.4 (95% CI: 4.6-90.1) in patients over 80 years. This study found no cases of Achilles tendon rupture in patients under the age of 60 after exposure to quinolones. The OR in the non-cortical steroid stratification associated with current exposure was 5.3 (95% CI: 1.8-15.2) and ballooned to 17.5 (95% CI: 5.0-60.9) and 18.4 (95% CI: 1.4-240.2) in the current and recent quinolone and steroid users group. This analysis utilized only oral cortical steroid use, even though injectable steroids are sometimes used in tendonitis treatment. Lastly, the overall absolute risk of Achilles tendon rupture was 5.5 in patients 60-79 years and 3.5 in patients 80 years and older per 100,000 person-years. The attributable risk percent was 2.2% and 6.3% respectively.

The third case-control study completed by Seeger, DS et al. (2005), investigated the association between Achilles tendon rupture (ATR) and quinolone exposure(36). Secondarily, they attempted to quantify and account for other risk factors related to ATR. The researchers utilized the Ingenix Research Database, sourced from United Healthcare to conduct a nested case-control study. The population included patients with commercial as well as Medicare supplement health insurance. Case selection was stringent in order to reduce misclassification
bias. Cases were persons with both a diagnosis and a procedure (surgical or non-surgical) related to ATR occurring between 1 January 1997 and 30 June 2001. All cases were affirmed through medical record review. Controls were randomly sampled from the same database at a 20:1 control to case ratio. The controls were categorized by age (0-17, 18-59, 60+ years) to achieve nearly the same distribution as the cases. Exposure and risk factors were created from medical and pharmacy claims data over six months prior to the index or case date. When evaluating cases, this study found that 55% of potential cases were confirmed to have been ATR. The potential cases that were not ATR tended to be diagnostic rule-outs or cases of trauma or procedure related to the Achilles tendon but not associated with ATR. In all there were 947 cases and 18,940 controls. The association between quinolone antibiotics and ATR was not significant (OR=1.2; 95% CI=0.9-1.7). The association was stronger but still not significant, with higher cumulative exposure to quinolones (OR=1.5; 95% CI=1.0-2.3). Risk factors for ATR included; trauma (OR=17.2; 95% CI=14.0-20.2), male gender ((OR=3.0; 95% CI=2.6-3.5), injected corticosteroid injection (OR=2.2; 95% CI=1.6-2.9), obesity (OR=2.0; 95% CI=1.2-3.1), rheumatoid arthritis (OR=1.9; 95% CI=1.0-3.7), skin or soft tissue infections (OR=1.5; 95% CI=0.9-2.3), oral corticosteroids (OR=1.4; 95% CI=1.0-1.8), and non-quinolone antibiotics (OR=1.2; 95% CI=1.1-1.5)(36). This study suggested that the risk of ATR after quinolone use is not different among quinolones or from that associated with corticosteroids. The researchers also found no potentiation of ATR risk among persons exposed to corticosteroids and quinolones. The main result of this study was to identify trauma, obesity, arthritis, male gender, and injected steroids as risk factors for ATR. The associations in this study between tendonopathies (tendonitis, TR) are consistent with a causal pathway that puts tendonitis or other tendonopathies as an intermediate stage that eventually progresses to tendon rupture(21, 36).
General Safety Review

Gastrointestinal toxicity

The most common adverse effects reported by humans are gastrointestinal in nature. Studies testing gastric emptying and intestinal motility in animals suggest that quinolones do not have a direct effect on the gastrointestinal (GI) tract. Even after long-term use, no histological toxicity has been shown in the GI tract of animals taking quinolones. Vomiting has been demonstrated in animal and human models and is believed to be a central effect, as opposed to a direct irritation of the gastrointestinal mucosa. Diarrhea is a common side effect in animals and humans given quinolones. This effect is believed to be from the increased release of toxins from pathogenic bacteria whose concentration tends to grow when normal intestinal flora are destroyed by the antibiotic medication. Nausea, vomiting, abdominal pain, and diarrhea have been described in all quinolones. The frequency of GI side effects, ranging from 0.8 to 6.8% in clinical trials, is not generally higher than other antimicrobials.

Neurotoxicity

Neurotoxicity is a common finding in animal models. While the mechanism of action is unknown, the administration of quinolones to rats has led to convulsive seizures. Studies have advanced two possible explanations that entail the inhibition of the γ-aminobutyric acid (GABA) inhibitory neurotransmitter or a decrease in CNS magnesium concentration probably caused by the chelating of quinolones and metal cations. There is currently no model to predict the seizure potential of each individual quinolone.

In humans neurotoxicity can be divided into minor Central Nervous System CNS side effects and the more severe events that require discontinuation of therapy. Minor reactions consist of headache, dizziness, tiredness, and sleeplessness along with some reports of vision distortion, bad dreams, and restlessness. The more serious reactions occur at a rare >.05% rate
and include depression, grand mal seizures, psychotic reactions, and hallucinations. The medication dose is related to CNS adverse effects as higher doses increase the incidence in safety studies (bowie et al. 1989).

**Phototoxicity**

Phototoxicity has been shown, in animal models, to occur in all quinolones. This toxicity is related to the compound’s relative photoinstability and degradation process that induces the creation of tissue damaging free radicals. This degradation process caused by UV radiation, has also been shown to be photomutagenic and photocarcinogenic in some quinolones.

Clinical manifestations of phototoxicity include mild erythema to severe bullous eruptions in areas of the skin exposed to UV radiation. All quinolones have exhibited this side effect to one degree or another. The interesting point in the evaluation of the likelihood for individual quinolones to cause phototoxicity is that it can be estimated by measuring the rates of compound degradation when exposed to UV radiation. The higher the degradation rate the more extensive the cellular damage will be. Quinolones such as fleroxacin, lomefloxacin, and sparfloxacin have the highest phototoxic potential. Hypersensitivity reactions have an incidence rate of 0.4 to 2.1% and include erythema, pruritus, urticaria, rash, among other skin reactions. These are reported separately in clinical trials but may be a result of low level phototoxic reactions.

**Nephrotoxicity**

Nephrotoxicity in the form of crystalluria in neutral or alkaline pH conditions has been demonstrated in rats and monkeys administered norfloxacin or ciprofloxacin. These two drugs are slightly soluble in neutral or high pH environments found in these animals’s urine whereas human urine has a lower pH, which reduces the risk.
**Opthalmotoxicity**

Ocular toxicity has been demonstrated in feline retinas when treated with nalidixic acid and to a lesser extent when treated with norfloxacin. No other quinolone has been reliably found to have ophthalmotoxicity.

**Cardiotoxicity**

Cardiotoxicity in the form of hypotension, tachycardia, bradycardia, and dysrhythmias, has been induced after intravenous injection in cats and dogs. A more recently identified adverse effect related to newer quinolones is the prolongation of the QT interval. This effect has been produced in dogs administered newer quinolone compounds such as sparfloxacin or moxifloxacin.

The most common cardiovascular side effect, in humans, of most quinolones is either hypotension or tachycardia upon initiation of systemic treatment. One of the most severe consequences of quinolone therapy is the inducement of a pronounced QT-interval prolongation, which can lead to a dangerous polymorphic ventricular tachycardia called *torsade de pointes*. Grepafloxacin was withdrawn from the market due to the inducement of this cardiovascular adverse event, while sparfloxacin and moxifloxacin both carry warning. Generally, the safety of any quinolone not reported to cause QT-prolongation should not be assumed pending ongoing post marketing surveillance studies.

**Reproductive Toxicity**

Reproductive and developmental toxicity has been accessed in animals with mostly negative results. While there are toxic changes that have been observed in rats, rabbits, dogs, and monkeys, during the organogenesis period, these changes have not resulted in any irreversible overt teratogenicity either peri- or postnatal. Due to these toxic changes in animal studies, quinolones are not considered safe to use during human pregnancy. In rat models,
several quinolones induced fertility disorders in males. This male reproductive toxicity consists of histopathological changes in the testes that led to impaired spermatogenesis.

Genotoxicity

Quinolones exhibit some genotoxicity through their affinity, although at several magnitudes less than bacterial enzymes, for eukaryotic topoisomerases. Many studies in animals have shown that quinolones with increased Gram-positive antibacterial coverage are generally more toxic to mammalian DNA. While these results reveal DNA damage and induction of mutations and chromosomal aberrations there has been no indication of a carcinogenic effect even after life-long animal drug exposure.

Large Administrative Health Care Databases

Large administrative health care databases have been developed primarily for financial accountability and planning reasons. Health care administrative databases have recorded huge amounts of clinical information in diverse settings throughout the world. The ability of these databases to link multiple aspects of care for an individual patient in a longitudinal fashion have solidified them as the main source of population-based pharmacologic research and health policy evaluation. These databases have different features, such as the number of variables collected, size of data, and length of follow-up, depending upon its intended use. Examples of common health care administrative databases used for drug utilization and quality improvement research are the Group Health Cooperative of Puget Sound, the Manitoba Health Service Commission, the Medicaid Management Information System, and the Medicare database(49). The advantages of using a health care database are quick access to a large well defined population and the ability to select both cases and controls, or exposures to the drug of interest (Hartzema in press). Disadvantages stem from the fact that the normal everyday health care that is captured does not take place in a controlled environment. During patient encounters and subsequent coding of
diagnostic information, there are many opportunities for error, biases, and misunderstandings to occur. The use of administrative databases for health research is widespread, but less consideration has been paid to the validity of the health care information stored within them.

**Database Validation Methods**

When evaluating the validity of health care databases there are two central components that must be examined. First, the external validity of the database should be explored to show the extent that results abstracted from a database can be generalized to other settings. Next, the internal validity ought to be scrutinized to judge if the information measures what it purports to measure. When studying databases this quality of internal validity is more specifically referred to as measurement validity. Evaluating measurement validity is accomplished by investigating the consistency of the subject database compared to either external clinical records, or particular data files internal to the subject database.

**External Validity**

Database external validity is a subjective area where the question of whether the information obtained from a health care database is representative of different health care settings and different health care environments in the world at large. This evaluation is usually referred to as generalizability and is lacking in objective methods to calculate a quantifiable appraisal. The most voiced concern generally centers on the differences in the various demographics covered by the database population. How generalizable is the Medicaid database, when its population is poor, unemployed, and less educated, when compared to a large health insurance database where their population is more middle-class, employed, and better educated. Carson, et al. (2000), postulated that this seeming deficiency in generalizability can be a problem in descriptive studies but less of one in more analytical research. Their rationale is that in analytical studies the researcher is comparing treatment and control groups taken from the same
population and so are subject to the same biases and unknown confounders (50). Because of this, comparing incidence rates between different health care databases can be problematic but relative statistics such as the risk ratio or odds ratio are generally considered more generalizable (50).

**Measurement Validity**

**Data vs. Source information consistency**

The agreement between the source information and the computer data that it came from, is the benchmark for gauging measurement validity. This analysis rests on the assumption that the source information is accurate and complete. The results of this comparison of data external from the database to data within the database should be in good agreement with each other.

Many evaluations of health care databases using this method have shown that socio-demographic data, names of dispensed drugs, and other non-clinical records are very consistent with what is in the medical record (50-57). Agreement of >90% should be expected. Clinical data, on the other hand, can be more erratic. Concordance has ranged from 58% to near 100% in assessments of diagnosis and surgical procedures in several large administrative health care databases (54, 58, 59). Overall agreement between computerized health data and the records from which they were derived should be good, but just because they are broadly consistent does not mean individual diagnosis codes can not vary markedly (60-62). Other external information besides the patient record can also be used to examine external consistency. Patient interviews have been used in several assessments as the source information. Like its use in other areas, patient recall bias can cause substantial discrepancies and result in undependable agreement (59).

**Internal data consistency**

When an external source of information, such as the patient record, is not available, internal validation methods have been used. This method of evaluating the internal consistency
of a database entails cross-comparing information from different fields to identify any inconsistencies. This is done in a cross-sectional way or by comparing entries over time in a longitudinal fashion. This approach to validation has been utilized effectively in research concerning diagnosis verification, disease incidence, and adverse drug event appraisals(63-66). An illustration of this approach to validate the diagnosis code of Type II Diabetes may be the presence of an elevated FBG or HbA1c laboratory result. Likewise, the existence of hypoglycemic medication prescriptions in the patient’s pharmacy profile would reinforce the Diabetes diagnosis entry. These three parameters, diagnosis code, laboratory result, and pharmacy entry, are all in different subsystems of the same larger health care database and taken together reflect the consistency of the entered data.

Pharmacoepidemiologic studies using this method have shown an increase in the predictive value of case ascertainment. In their study, Gerstman et al. (1990) demonstrated an increase from 42% to 65% for probable deep venous thromboembolism and from 70% to 97% for possible deep venous thromboembolism in the predictive value of case ascertainment. They did this by requiring evidence of outpatient anticoagulant use within six months of hospitalization(67).

Internal descriptive research done on the Medicaid databases has proved useful in assessing validity. Hennessy et al. (2002) looked at four categories of potential data errors in datasets provided by the Computerized On-line Medical Pharmaceutical Analysis and Surveillance System (COMPASS) from six Medicaid states and covering a defined time period(68). COMPASS is a Medicaid program data vendor that provides software and services related to drug utilization reviews (DURs) within the Medicaid program. The categories included: incomplete claims for certain time periods; absence of an accurate indicator of
inpatient hospitalizations; missing hospitalizations for those aged 65 years and older; and
diagnostic codes in demographic groups in which those conditions should be rare. By reviewing
the data over time the researchers were able to see if there were missing blocks or gaps in claims
data. Next, they compared claims for inpatient hospitalizations in a defined time-period with the
number reported by the US Centers for Medicare & Medicaid Services (CMS). Thirdly, they
looked at the consistency of the data sets over time by examining the trend of the number of
hospitalizations per enrollee stratified by age group. Specifically, they hypothesized that
hospitalizations should increase among adults as their age increases. An evaluation of this trend
as adults reached the age of 65 and beyond was used as an indicator of consistency of claims in
this age group. Lastly, an exploration of the overall validity of diagnosis and demographic data
was done by identifying disorders that were expected to be found predominantly in a particular
demographic group. They specified female specific disorders in females, complications of
childbirth and pregnancy, and lung cancer in those aged 40 years and older. Their hypothesis
was that the number of disease-demographic matches would far exceed the number of
mismatches. The presentation of this analysis shows the quality of the data using longitudinal
graphs to depict missing data and trends in the data using stratification by age group. The
accuracy of the diagnosis can be judged by displaying the code along with patient demographics
over time and comparing to expected results (68). The authors called this kind of internal data
assessment macro-level validity.

Administrative health care databases are often made up of separately maintained data files
that are linkable to an individual patient file. This allows the examination of consistency of
diagnostic information, which is especially important in a cohort studies that seek to identify
specific medical disorders. Preferable there should be a high level of concordance between the
different data files within a database since the source information should be the same. Even if
the source data is unavailable, by using these cross-comparison and longitudinal techniques, it is
still possible to describe the internal validity of large administrative health care databases.

Table 2-1. Tendonopathy risk factors

<table>
<thead>
<tr>
<th>Extrinsic</th>
<th>Intrinsic</th>
<th>Systemic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupation</td>
<td>Age</td>
<td>Inherited disorders</td>
</tr>
<tr>
<td>Sports</td>
<td>Vascular perfusion</td>
<td>Endocrine disorders</td>
</tr>
<tr>
<td>Physical load</td>
<td>Nutrition</td>
<td>Metabolic disorders</td>
</tr>
<tr>
<td>Training errors</td>
<td>Anatomical variants</td>
<td>Rheumatological diseases</td>
</tr>
<tr>
<td>Shoes and equipment</td>
<td>Joint laxity</td>
<td>Medication</td>
</tr>
<tr>
<td>Environment (temp, surface)</td>
<td>Muscle weakness</td>
<td>Quinolones</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2-2. Common quinolones grouped by PEG® classifications

<table>
<thead>
<tr>
<th>Generation</th>
<th>Generic name</th>
<th>Spectrum/use</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>norfloxacin</td>
<td>Mainly Gram-negative / urinary tract infections</td>
</tr>
<tr>
<td>Second</td>
<td>ciprofloxacin</td>
<td>Gram-negative, moderate Gram positive / broad oral and systemic use</td>
</tr>
<tr>
<td>Third</td>
<td>levofloxacin</td>
<td>Improved Gram-positive, ‘atypical’ / respiratory tract and many others</td>
</tr>
<tr>
<td>Fourth</td>
<td>moxifloxacin</td>
<td>Improved Gram-positive and ‘atypical’ plus anaerobic / respiratory tract and many others</td>
</tr>
</tbody>
</table>

@Paul-Ehrlich-Society of Chemotherapy(69)

Table 2-3. Quinolone toxicities leading to market withdrawal or decreased clinical significance

<table>
<thead>
<tr>
<th>Quinolone</th>
<th>Reason for Discontinued Development or Market Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>enoxacin</td>
<td>inhibition of cytochrome p450</td>
</tr>
<tr>
<td>pefloxacin</td>
<td>phototoxicity, tendonopathies, etc.</td>
</tr>
<tr>
<td>fleroxacin</td>
<td>phototoxicity, CNS effects</td>
</tr>
<tr>
<td>sitafloxacin</td>
<td>phototoxicity</td>
</tr>
<tr>
<td>temafloxacin</td>
<td>hemolytic uremic syndrome</td>
</tr>
<tr>
<td>lomefloxacin</td>
<td>phototoxicity</td>
</tr>
<tr>
<td>sparfloxacin</td>
<td>phototoxicity, QT prolongation</td>
</tr>
<tr>
<td>tosufloxacin</td>
<td>thrombocytopenia, nephritis</td>
</tr>
<tr>
<td>trovafloxacin</td>
<td>hepatotoxicity, CNS effects</td>
</tr>
<tr>
<td>grepafloxacin</td>
<td>QT prolongation, arrhythmia, nausea</td>
</tr>
<tr>
<td>clinafloxacin</td>
<td>phototoxicity, inhibition of cytochrome p450</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>Type</td>
<td>Incidence Range (%)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.8-6.8</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>0.9-4.7</td>
</tr>
<tr>
<td>Serious reactions</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Skin/hypersensitivity</td>
<td>0.4-2.1</td>
</tr>
<tr>
<td>Phototoxicity</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Renal</td>
<td>0.5-4.5</td>
</tr>
<tr>
<td>Hematological</td>
<td>0.5-5.3</td>
</tr>
<tr>
<td>Musculoskeletal/rheumatological</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Cumulative incidences</td>
<td>4.4-20</td>
</tr>
</tbody>
</table>

Modified from Christ and Esch (1994)
CHAPTER 3
METHODS

This study utilizes a retrospective cohort design employing one study drug group and one comparator drug group. Statistical analysis includes the estimation of general epidemiologic measures of association between the two groups expressed as relative hazards. The proportional hazards (Cox regression) model is used to evaluate the overall relative hazard and time at risk of tendon ruptures from quinolone exposure in U.S. active duty military personnel, compared to a cephalosporin exposed group(70, 71).

Exposure, outcome, and demographic information were abstracted from the relevant data fields in the eligibility, pharmacy, and encounter databases contained under the M2 query system. Exposure to the quinolone class of antibiotics was selected because of its demonstrated toxicity to connective tissues and specifically, its propensity to weaken tendons. Exposure to the cephalosporin class of antibiotics was selected as a comparator group due to its similarity of clinical use to quinolones and because of the absence of any documented connective tissue toxicity. By using this design, the risk of tendon rupture from quinolones was estimated while the distribution of unmeasured confounding factors associated with the use of an antibiotic drug was roughly equal in each group.

Lastly, the survival analysis model was used for two main reasons. The first rationale relates to the effect of the primary predictor variable on the shape of the hazard function. Next, it allows determination of which combination of explanatory variables effect the shape of the hazard function. This elucidates the effect that exposure has on the hazard of tendon rupture, as well as the effects of other co-variables. Secondly, the modeling of the hazard function provides the estimation of the instantaneous risk for a notional individual. This produces an estimated risk of tendon rupture after starting a quinolone, which is a function of the explanatory variables in
the model. This process will also shed light on the induction time where the hazard of tendon rupture continues onward for an unknown time after discontinuance of the drug.

**Population Description**

**U.S. Military Demographics**

This information describes members in the military community for fiscal year 2003 and before. Active Duty service branches include the Department of Defenses (DoD’s) Army, Navy, Marine Corps, and Air Force.

**Overview**

The total number of military personnel is over 3.2 million strong, including Active Duty military personnel (1,419,061); Department of Homeland Security (DHS) Active Duty Coast Guard members (38,389), DoD Ready Reserve and DHS Coast Guard Reserve members (1,167,101); and DoD appropriated-fund civilian personnel (650,714). DoD and DHS Coast Guard Active Duty members comprise the largest portion of the military force (44.5%), supplemented by Ready Reserve members (35.6%) and DoD civilian personnel (19.9%).

**Active Duty**

**Branches:** The Army has the largest number of Active Duty members (493,563) followed by the Navy (376,970), the Air Force (370,945), and the Marine Corps (177,583). There are also 38,389 Active Duty members in the DHS’s Coast Guard. The total 1,419,061 DoD Active Duty service contingent in 2003 is 30.1% smaller than it was in 1993, when there were 2,029,300 Active Duty members. Since 1990, the number of DoD Active Duty service members has declined by 9.6% Marine Corps; 30.1% Air Force; 32.2% Army, and 34.3% Navy.

**Ranks:** The Active Duty force has one officer for every 5.2 enlisted personnel. In order, the Air Force has one officer for every 4.0 enlisted personnel, Army has one for every 5.2, the Navy has one for every 5.9, and the Marine Corps has one for every 8.5.
Women: Women comprise 213,059, or 15% of the DoD Active Duty force. The percent of women in the Active Duty population has continued to grow since 1990. It has gone from 11.5% officers and 10.9% enlisted to 15.3% officers and 15% enlisted in 2003.

Minorities: Over one-third (35.8%), or 507,418, of Active Duty members identify themselves as a minority. Classifications include African American, Hispanic American, Native American, Alaskan Native, Asian American, Pacific Islander, or multi-racial.

Location: While the Active Duty population is spread throughout the world, it can be divided into three basic areas. Active Duty members are assigned to the United States and its territories (84.5%), Europe (8.0%), and East Asia (6.6%). The states with the largest Active Duty populations are California (166,397), Virginia (140,575), and Texas (116,638).

Age: Close to half of the Active Duty force is 25 years old or younger (47.4%). The next largest group is 26 to 30 (18.1%), followed by 31 to 35 (13.8%), 36 to 40 (12.3%) and 41 and above (8.4%). The average age of the Active Duty force is 28.2. The average age for officers is 34.5 and 27.0 for enlisted personnel.

Education: 86.1% of officers have a Bachelor’s degree or higher while only 3.7% of enlisted members do. Most (94.0%) enlisted members have a high school diploma and/or some college experience.

Marital status: Over half (52.3%) of Active Duty members are married. A majority (68.8%) of officers are married while slightly less than half (49.2%) of enlisted personnel are married. In addition, 6.7% of the DoD Active Duty force is in dual-military marriages.

Dependents: There are fewer Active Duty members (1,419,061) than their associated family members (1,924,174). Just over one-third (37.3%) of Active Duty members are married with children while 6.1% are single parents.
Patient Selection

Inclusion Criteria

Information on study measures was abstracted from the M2 database for patients 18 years and older and serving on active duty in the U.S. military at the time of receiving medical care. All visits for outpatient services from June 1, 2005 to May 31, 2006 were reviewed for study inclusion. Study patients were identified in the Pharmacy Detail Transaction Service (PDTS) data file by the annotation of a quinolone antibiotic in the medication brand name field and/or the generic name field. Identification also included The American Hospital Formulary Service (AHFS) classification number field for quinolone antibiotics and/or AHFS therapeutic class description field. Lastly, the Generic Code Number (GCN) field, which is specific to the generic ingredient, dosage form, and drug strength, was used for patient recognition. The GCN is the same regardless of manufactures and/or package size. Identified patients were followed forward from the day the quinolone prescription was dispensed (day 0) to day 60. Quinolone exposed patients had their records reviewed sixty days pre-drug exposure and sixty days past the 60-day study period cutoff. Review identified any previous quinolone exposure or co-morbid disease states related to connective tissue disorders.

The cephalosporin group in this study consisted of patients fitting the same inclusion criteria as above. The singular difference is that this group was selected based on their exposure to any cephalosporin antibiotic medication. Cephalosporin exposure was chosen as the comparator group because it is an antibiotic class with similar treatment uses as quinolones. Cephalosporins have not been implicated in any connective tissue toxicities in animals or humans. There are no cases in the literature of cephalosporin-induced tendonopathies or tendon ruptures. It is intended that by choosing to compare patients that have been exposed to quinolones to patients exposed to cephalosporins that unknown or unmeasured differences in our
sample patients will be similar in both the study and control group thus reducing biases inherent in a nonrandomized study. Cephalosporin exposed patients had their records reviewed 60-days pre-drug exposure and 60-days past the 60-day study cutoff. Review identified any previous quinolone exposure or co-morbid disease states related to connective tissue disorders.

**Exclusion Criteria**

Patients possessing the ‘E’ code in the injury and poisoning category of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) defined disease codes, signifying an external cause of the injury (ICD-9-E800-E999) were excluded from selection into any of the study groups.

There are diseases and health states that have been shown to, possibly, predispose patients to connective tissue disorders. After initial patient selection, both study groups were screened to allow identification and exclusion of patients possessing any of these conditions. Exclusion of patients with arthropathies and related disorders (ICD-9-710-719), neoplasms (ICD-9-140-239), presence of HIV (ICD-9-042), alcohol dependency (ICD-9-303), drug abuse (ICD-9-304), organ transplant (ICD-9-V42), hemodialysis (ICD-9-V42), diabetes mellitus (ICD-9-250) to reduce confounding the outcome. As expected the occurrence of these conditions were low or absent, as all but alcohol dependency is reason for a change from active to inactive service.

This study will utilized the concept of a New User design posited by Ray and associates (72, 73)

**Data Source**

The Executive Information and Decision Support (EIDS) Program Office

EIDS is the centralized data store for the Military Health System (MHS). EIDS collects, processes, and manages nearly 100 terabytes of military health data through a powerful suite of decision-support tools that enable effective management of MHS health care operations. EIDS
has active interfaces around the globe in order to manage the receipt, processing, and storage of billions of health care records that characterize MHS operations and performance.

**The Military Health System Management Analysis and Reporting Tool (M2)**

The M2 is a powerful ad-hoc query tool used to obtain summary and detailed views of population, clinical, and financial data from all MHS regions. M2 includes Military Treatment Facility (MTF) and commercial network claims data integrated with eligibility and enrollment data. This integrated data enhances support to healthcare managers across the MHS. M2 allows users to perform trend analyses, conduct patient and provider profiling studies, and conduct business case analyses to maximize health plan efficiency. In a recent pilot information pull, taken from the M2 system for the FY 2005, there were 111-million prescriptions for the entire DoD population, 10-million prescriptions for active duty military, 1.3-million prescriptions for quinolones, and 0.9-million for cephalosporins.

**Data Validity**

The M2 databases contain eligibility, diagnosis, dispensing, and administrative information for the Military Health Service (MHS). The repository presently includes only outpatient data for both institutional (military health facility) and non-institutional (commercial network) health care providers. The goal of the M2 is to provide a system that is easily queried to enhance the decision making process of the DoD health care managers. It has not been validated in a meaningful way through a published peer-reviewed validation study, as such, this study undertooke a limited validation study to build confidence in the use of the M2 for research purposes. Since the M2 has global coverage and researchers are not given access to individual patient identification information, the ability to validate M2 through comparison with external data “i.e” the patient medical record, is not possible. Due to this, the present study performed an internal consistency validation process along the same lines as the Medicaid descriptive analysis.
performed by Hennessy, 2003(68). This process utilized the three different databases, or Universes in Microsoft Object terminology, to perform cross-checks of pertinent data fields.

**Database Characteristics**

The M2 is the query module for the MHS medical data repository. Data contained in the repository comes from clinical databases used in military treatment facilities worldwide and from commercial health care facilities that are part of the MHS network. The M2 links eligibility, demographic, diagnosis, and prescription data, through the patient specific military eligibility identification number. Because of this, an individual patient’s eligibility and medical information can be retrieved from each of the three universes and combined in a common report.

**Internal Validity**

Macro-level data quality assessment was used in this study to judge the consistency and validity of data in the absence of external records for comparison(68).

**Incomplete Data**

Descriptive statistics were used to depict the magnitude of missing data in several important fields across all three universes. The following variables were examined for missing data: 1) patient demographics (gender, age, race) in the eligibility, clinical care, and pharmacy universes, 2) military status (active or dependent), 3) diagnosis codes (ICD-9-CM), 4) drug quantity, 5) days of supply 6) military occupation specialty code. Missing data was handled in the analytic phase by exclusion and description if necessary. Patients with exposure information but missing diagnosis data were necessarily excluded from this study.

**Longitudinal Data Integrity**

In order to examine the data over time the total number of prescriptions in the MHS was abstracted from M2 and graphed, by month, over a five-year period (FY 2002-06). This gave a gross indication of the consistency of M2 over that period.
Diagnosis vs. Demographics

One disease diagnose was selected and cross-checked with demographic information that one would commonly expect to occur together. For the fiscal years 2002-06 the percent coherence between normal pregnancy delivery in females (ICD-9-CM 650.00) and benign prostate hyperplasia ICD-9-CM 600.00 – 600.91), was generated and plotted.

Diagnosis and Drugs

One disease state was cross-checked versus the medication usually prescribed to treat it. Coherence levels were generated yearly for fiscal years 2002-06 for the following ICD-9-CM drug combination: Type I diabetes (ICD-9-250.01 and any insulin product on the DoD uniform formulary (UF).

Drugs and Diagnosis

The algorithm from the previous paragraph was reversed for the examination of drug data. All patients with a prescription for insulin in M2 during the FYs 2002-06 were cross-checked with the ICD-9-CM code 250.00 for any type diabetes.

All cross-checks generated the percent matched or coherence of the information between the different data fields. In the study by Hennessy et.al, 2003, the data was considered valid if the percent coherence was equal or greater than 80%(68). This study utilized this rule in judging the validity of the M2 information system.

The Variables

Dependant Variable

Tendon Rupture: The outcome variable of interest is the occurrence of a tendon rupture in the study group at a specified time (t) from drug exposure until the end of a sixty-day study interval. All patients are censored at 60 days. The occurrence was expressed in a binary fashion by the presence or absence of the appropriate ICD-9-CM entry in the patient’s M2 computerized
record. The ICD-9-CM codes of interest are; 727.6 rupture of tendon, non-traumatic, 727.60 non-traumatic rupture of unspecified tendon, 727.61 rupture of rotator cuff, 727.62 tendon of biceps, 727.63 extensor tendons of hand and wrist, 727.64 flexor tendons of hand and wrist, 727.65 quadriceps tendon, 727.66 patellar tendon, 727.67 Achilles tendon, 727.68 other tendons of foot and ankle, 727.69 other tendon ruptures.

**Predictor Variable**

**Treatment:** Exposure to a quinolone medication in the study group, or exposure to a cephalosporin medication in the comparator group is the main explanatory variable of interest. The quinolone group exposure status, is the recorded dispensing of a valid prescription for an oral quinolone antibacterial medication in the outpatient PDTS sub-database of M2. Exposure time in this cohort was calculated in person-days. Quinolone antibiotics used in exposure data include: moxifloxacin, ciprofloxacin, gemifloxacin, levofloxacin, norfloxacin, and gatifloxacin. The comparator group exposure was the recorded dispensing of a valid prescription of an oral cephalosporin antibacterial medication in the outpatient PDTS sub-database of M2. Exposure time was calculated in person-days starting at the date of a valid prescription dispensing. Time at risk continues for 60-days post prescription dispensing for quinolone and cephalosporin groups. Cephalosporin medications used in exposure data include: cefazolin, cefuroxime, ceftazidime, cefepime, cefdinir, ceftriaxone, cefditoren, and cefixime proxetil.

**Additional Covariates:**

**Gender:** Male or female

**Race:** Expressed as White, Black, Other

**Military grade:** Categorized as officer or enlisted

**Military occupation specialty (MOS):** Taken from DoD operational MOS codes and collapsed into two main groups; 1) Direct 2) support
**Age:** Years at time medication was dispensed

**Concomitant corticosteroid:** outpatient use, grouped as yes or no

**Days of medication supply:** calculated locally at the time of dispensing = #of pills / daily direction for use

**Service:** Branch of military, Army, Navy, Air Force, Marine Corps

**Provider specialty:** Specialty of the provider that wrote the prescription for the treatment medication divided into primary care and specialty care.

**Medication diagnosis:** Recorded diagnosis leading to antibiotic use. Categories are; 1) upper respiratory infection 2) gastrointestinal/genitourinary and 3) soft tissue/bone infections.

**Analysis**

**Descriptive Statistics**

Demographic and related explanatory variables expressed in a continuous fashion were analyzed via means and their standard deviations, while categorical variables are presented as proportions.

**General Measures of Association**

Due to the cohort study design, only probabilities that condition on exposure status can be estimated. Conditional probabilities for tendon rupture that is categorized as yes or no and occur within a sixty-day period, given exposure (P^TR | E)) and non-exposure (P^TR | Ŕ)) were used to calculate unadjusted Relative Rate Ratio (RR), Excess Risk (ER), and Attributable Risk (AR) in quinolone versus cephalosporins groups.

Using the conditional baseline probabilities from Table 3-2 the following unadjusted measures of association may be estimated.

\[
\text{Estimated Relative Risk (RR^)} = \frac{a/(a+b)}{c/(c+d)}
\]

(3-1)
Excess Risk (ER^) = \frac{a}{a+b} - \frac{c}{c+d} \quad (3-2)

Attributable Fraction (AFc^) = \frac{RR - 1}{RR} \quad (3-3)

**Hazard Function**

When either the population at risk or the incidence rate changes substantially over the study time-period it becomes necessary to stratify time into shorter intervals to adequately capture this effect. The incidence proportion which is a cumulative measure used in closed cohorts and the more flexible incidence rate which is an average rate over the risk time interval and can be used in both closed or open cohorts, are both summary measures for the entire time interval and thus do not explain within-interval risk changes. If a study has a large population with plentiful outcomes, it is possible to measure the outcomes over smaller and smaller time intervals. A plot of the incidence rates over the associated interval on which the incidence rate was based reveals a graph of the changes in the incidence rate over time. By reducing the intervals to their hypothetical limit it yields the hazard function, \( h(t) \). The hazard function is interpreted as the instantaneous incidence rate. The hazard function can be linked mathematically to the cumulative incidence proportion through the following equation (74):

\[
h(t) = \frac{dI(t) / d(t)}{(1 - I(t))} \quad (3-4)
\]

Here the total interval of interest is \([0,T]\) where \( T \) equals 60-days in this study. The link between the hazard function at \( h(t) \) for \( 0 \leq t \leq T \) and the incidence proportion \( I(t) \), over the interval \([0,t]\) is demonstrated. This connection assumes that an incident case is no longer at risk after incurring the outcome of interest and that this is the only way that an individual can cease to be at risk. In the above equation \( dI(t) / d(t) \) represents the slope of \( I(t) \) at time \( t \). The
denominator \((1 - I(t))\), accounts for the proportion of the population still at risk at time \(t\). The benefit of using the hazard function is its ability to extract dynamic information from a plot of the function as compared to other methods that measure association over preconceived time intervals assuming a linear risk over time. Whereas \(I(t)\) measures the cumulative incidence from time \(= 0\) to time \(= t\), \(h(t)\) measures the incidence rate at exactly time \(t\).

**Relative Hazard**

As has been previously described the exposure variable of interest in this study is binary in nature. Thus in each sample there are two incidence proportions of interest. These are \(I_E(t)\) and \(I_U(t)\) reflecting the interval \([0, t]\) within \([0, T]\), for the exposed and unexposed respectively. This is also true for the hazard functions for the two groups e.g. \((h_E(t)\) and \(h_U(t)\)). Since the RR and Odds Ratio (OR) are measures of relative difference in incidence between the exposed and unexposed, they can be written as:

\[
RR(t) \approx OR(t) = \frac{I_E(t)}{I_U(t)}
\]  

(3-5)

The hazard function can also be used to measure the relationship between exposure and incidence by:

\[
RH(t) = \frac{h_E(t)}{h_U(t)}
\]  

(3-6)

\(RH(t)\) stands for the Relative Hazard at time \(t\). Using the hazard function, we can produce a relative hazard that provides an instantaneous measure of how exposure to the study medication affects the incidence of tendon ruptures.

The \(RH(t)\) can vary widely at different \(t\)'s within \([0, T]\), so that at certain times \(RH(t)\) can be larger than one, reflecting an increasing risk, or below one, signifying a decreasing risk. It is
these swings in risk that are captured by utilizing the hazard function and masked when using the RR or OR.

If the assumption is made that the relative impact of exposure on the instantaneous incidence rate remains constant over the interval \([0,T]\), then the hazard functions in the exposed and unexposed will be proportional to each other. Thus the \(RH(t)\) will remain constant throughout the \([0,T]\) interval and \(RH(t) = RH\). This assumption is called the proportional hazards model which allows comparison of the \(RH(t)\), \(RR(t)\), and \(OR(t)\). Importantly in this study, since the incidence of tendon rupture at baseline over \([0,T]\) is likely small then \(RR(t) \approx OR(t) \approx RH(t) \equiv RH\). If the proportional hazard assumption is valid in this study then there should be little difference between \(RH\), \(RR\), or \(OR\) as a measure of the relative difference in tendon rupture between those exposed to quinolone therapy and those exposed to cephalosporins or in the unexposed control group.

Figure 3 uses notional data with a constant \(RH\) of two and a low incidence rate to show the relationship between the three measures of association over time.

This study utilized the hazard function to graph the change in incidence over time after exposure to the study medication. This allows identification of the time, post therapy initiation, of the greatest risk of tendon rupture. This also allows the calculation of the \(RH\) as the main measure of relative association.

**Modeling the Hazard Function**

In the current study, we are modeling two distinct groups or subpopulations. The two groups have exposure \((X)\) at two different levels \((X = x_0, X = x_1,\) corresponding to \(x_0 = \) cephalosporin exposure, \(x_1 = \) quinolone exposure. The dependent variable is the hazard of tendon rupture at time \(t\) for each level of exposure. The simplest model includes only two groups and has the form:
\[ h(t \mid x) = ch(t \mid x_0) \] (3-7)

The hazard of tendon rupture when exposed to quinolones at time \( t \) equals the hazard of tendon rupture with no exposure multiplied by some constant \( c \). This model assumes that the hazard at time \( t \) for both groups is proportional. The constant \( c \) is the previously discussed relative hazard (RH). If RH is less than one then the hazard of tendon rupture at time \( t \) is less in the quinolone group than in the cephalosporin group. Conversely, if the RH is greater than one the hazard of tendon rupture at time \( t \) is greater in the quinolone group compared to the cephalosporin group.

A more generalized form of equation 3-7 can be written to include other relevant covariates. This allows the simplest two-group proportional hazard model, which allows the addition of other independent variables that affect the shape of the hazard function:

\[ h(t / X) = h_0(t) \exp(\beta x) \] (3-8)

The exponentiated component of this equation is a linear combination of explanatory variables and can be interpreted as the risk score for the individual represented by the model. The risk score contains variates and factors. Variates are stated in numerical form and are usually measured on the continuous scale, e.g. age. Factors are represented by a limited set of values called levels e.g. gender.

The advantages of utilizing the proportional hazards model in this study are threefold: 1) It allows estimation of the baseline hazard function, \( h_0(t) \), (all explanatory variables = 0). 2) It allows estimation of Relative Hazard coefficients, which are similar to the Relative Risk/Rate ratios, or Odds Ratio, in measuring association between exposure and outcome. 3) Provides an insight into how the hazard changes over time in any exposure group during the time interval.
Time-Dependent Exposure

The need to stratify by time when using logistic regression highlights the main advantage of using the proportional hazard model. The Cox regression model assumes proportional hazards and controls for the effect of time at risk, before considering the association between risk factors and outcome (70, 71).

In order for the results from logistic regression and Cox regression to differ it is necessary for 1) time at risk be associated with the outcome and 2) time at risk be associated with exposure. In simpler terms, this means that the risk is changing over time. In the present study, as in most epidemiologic studies, the length of exposure is assumed to effect the risk of the outcome occurring. The use of the proportional hazards model in this study rests on the time at risk effecting exposure. Since the exposure levels will change during the follow-up period as a person first takes the medication then stops taking it, often after a 7-10 day period, but the individual will remain at risk as the drug levels decline in the body and onward to some, as yet, unspecified time. Since exposure levels do change in this study, then by definition there will be association between time at risk and exposure, thus time at risk confounding will occur.

Variables whose values change over time are known as time-dependent variables. In this study, the exposure variable will change over time, but because of the inability to specifically track this change, through blood levels etc., the use of a time-varying coefficient will be used.

In the proportional hazards model the time*exposure variable is assumed to be constant. This allows the interpretation of this coefficient as the log-hazard ratio where it is constant over time. In this instance, if this ratio is in fact a function of time then the coefficient of the exposure variable is called a time-varying coefficient. In other words, this model allows the hazard to change over time in a way that is not proportional to the baseline group. Time is affecting exposure and outcome in the quinolone group differently than in the cephalosporin group.
This assertion of a time-varying coefficient results in a non-proportional hazard model and can be difficult to fit. This difficulty can be overcome by 1) specifying a unique distribution chosen to model the variable; 2) stratification by the identified variable or 3) use piece-wise regression.

This study first stratified by the chosen variable in order to graph the resulting hazard function. If the variable was found to vary with time, by way of the time*variable interaction term being significant, then the piece-wise regression technique was employed to model the variable. This technique keeps the proportional hazard assumption intact and results in more accurate risk estimates (hazard ratios) being produced from the different regression equations that model the different ‘pieces’ of the study interval. The resulting piece-wise regression models was tested for selection using the Akaike’s information criterion (AIC) on the basis of their resulting -2logL test statistic.

The Cox Proportional Hazards Regression Models utilized for this study were the following:

Study model 1 Cox regression equation for demographic variables

$$ h_i(t) = h_0(t) \exp(\beta_2x_2 + \beta_3x_3 + \beta_4x_4) $$ (3-9)

Study model 2 Cox regression equation for 60-day interval

$$ h_i(t) = h_0(t) \exp(\beta_1x_1 + \beta_2x_2 + \ldots + \beta_{11}x_{11}) $$ (3-10)

Study model 3 Cox regression equation with treatment*time variable

$$ h_i(t) = h_0(t) \exp(\beta_1x_1 + \beta^*x_1(t) + \ldots + \beta_{11}x_{11}) $$ (3-11)

Study model 4 Cox regression equation with three risk windows

$$ h_i(t) = h_0(t) \exp(\beta_1x_1^{(1)} + \beta_2x_1^{(2)} + \beta_3x_1^{(3)} + \beta_{21}x_2 + \ldots + \beta_{11}x_{11}) $$ (3-12)

Equation components are defined below:
h(t): Hazard of tendon rupture at time $t$ conditioned on quinolone exposure and controlling for covariates.

X: Treatment variable.

$h_0(t)$: Baseline hazard at time ($t$).

$x_1$: Days 1-60, treatment, a factor with two levels. Cephalosporin=0, quinolone=1.

$x_2$: Age, a continuous variable.

$x_3$: Gender, a factor with two levels. Male=0, female=1.

Race, a factor with 3 levels.

$x_4$: White=0, Black=1.

$x_5$: White =0, Other=2.

Military Occupation Specialty (MOS), a factor with 2 levels.

$x_6$: Support = 0, Direct = 1.

Grade, a factor with two levels,

$x_7$: Officer=0, Enlisted=1.

$x_8$: Days of Supply, a continuous variable.

Provider Specialty, a factor with two levels.

$x_9$: Primary care (PC)=0, Secondary care (SC)=1.

Oral concomitant corticosteroid use, a factor with two levels.

$x_{10}$: no=0, yes=1.

Diagnosis leading to antibiotic treatment, a factor with three levels.

$x_{11}$: Upper respiratory infection (URI) = 0, Gastrointestinal/Genitourinary (GI/GU) = 1, Soft tissue/Bone infection (ST/BI) = 3.

Branch of Service, a factor with four levels.
$x_{12}$; Army = 0, Air Force (AF) = 1, Navy = 2, Marine Corps = 3.

$x_1(t)$ = interaction term consisting of the treatment variable and time (60 days).

$x_1^{(1)}$ = Days 1-25, treatment, a factor with two levels. Cephalosporin=0, quinolone=1.

$x_1^{(2)}$ = Days 26-35, treatment, a factor with two levels. Cephalosporin=0, quinolone=1.

$x_1^{(3)}$ = Days 36-60, treatment, a factor with two levels. Cephalosporin=0, quinolone=1.

**Power**

**General**

For general epidemiologic power calculations the incidence rates of tendon rupture calculated in a recent incidence study of active military were used (3). The rates ranged from 30.9 per 100,000 person-years for Achilles tendon ruptures to 120 per 100,000 person-years for all site tendon ruptures (3). The probability of making a type I error (alpha) equals 0.05 while the probability of making a type II error (beta) equals 0.20 (power equals 0.80). The estimated incidence in the quinolone group equals 0.004, and the estimated the effect size taken from a cohort of otherwise healthy Dutch subjects is RR=1.9 (35). The minimum required sample size is estimated at 22,520 person-years of follow-up time. The maximum required sample size is estimated at 52,135 person-years of follow-up time. The sample size calculation was performed using Epi Info(TM), database and statistics software for public health professionals, 4/26/2004 (75).

Secondary objectives involving analysis of subgroup populations, such as race or military occupation specialties, may or may not have sufficient power to adequately address their hypotheses. This is a retrospective study, the number of cases is static, as result, power was determined in a *post-hoc* fashion.
Survival Analysis

In survival analysis, it is the number of events that is most important. Accordingly, the first step in sample size calculation utilizing a survival analysis analytic method is to calculate the number of events that must be observed.

\[
d = \frac{(z_{\alpha/2} + z_\beta)^2}{\Theta^2}
\]

\[d=\text{required number of events, } \Theta = \text{risk estimate (effect size)}\]

Using a conservative risk estimate of RR=1.5 (Dutch cohort was 1.9(19)), and alpha = 0.05, beta = .20 (power equals .80), the number of events required, \(d= 79\).

A simplified equation for calculating the required number of subject to ensure the 79 cases are identified is the following.

\[n = \frac{d}{P(\text{event})}\]

\[d = \text{number of events from Equation 3-7.}\]

Using a conservative estimate of \(P(\text{event})\) from a recent study on Achilles tendon ruptures only, events is 0.309%, gives a maximum sample size requirement of 25,566, which is commiserate with the minimum sample size calculated based on a general measure of association (3).

These calculations are based on having an 80% chance of rejecting the null hypothesis if in fact it is false, e.g. having a power probability of 0.80 in detecting a statistically significant difference in outcome between groups if one truly exists.

Objectives, Research Questions, and Hypothesis

All hypothesis use \(\alpha = 0.05\)

65
Main Research Question

Estimate the risk of tendon rupture from using a quinolone antibacterial medication relative to a cephalosporin antibacterial medication, in a military population

Objective 1

Estimate the risk of tendon rupture from quinolone use, relative to a cephalosporin medication, while adjusting for relevant risk factors and accounting for time at risk.

Research Question 1

Is there a difference in risk of tendon rupture in active duty U.S. military personnel, from quinolone antibiotic use relative to cephalosporin antibiotic use, when adjusting for age, gender, race, military occupation, grade, provider specialty, days of medication supply, diagnosis related to antibiotic dispensing, branch of service, oral steroid status, and time at risk?

Research Question 1 Hypothesis

The null hypothesis is the regression coefficient in the quinolone exposed group relative to the cephalosporin exposed group will equal zero, after adjusting for age, gender, race, military occupation, grade, provider specialty, days of medication supply, diagnosis related to antibiotic dispensing, branch of service, oral steroid status, and time at risk. The alternative hypothesis is the regression coefficient is different from zero.

Ho: $\beta_1 = 0$

Ha: $\beta_1 \neq 0$

Note: $\beta_1 =$ treatment variable from equation 3-10.

Objective 2

Investigate whether the risk of tendon rupture from quinolone use varies over the 60-day study interval.
Research Question 2

Does the adjusted hazard function for each antibiotic treatment, support the proportional hazards model assumption?

Research Question 2 Hypothesis

The null hypothesis states that the interaction regression coefficient, created from the treatment and time variables, is not different from zero during the 60-day post exposure period, after adjusting for treatment, age, gender, race, military occupation, grade, provider specialty, days of medication supply, diagnosis related to antibiotic dispensing, branch of service, oral steroid status, and time at risk. The alternative hypothesis states that the adjusted interaction regression coefficient is different from zero over the 60-day period.

\[ \text{Ho: } \beta^* = 0 \]

\[ \text{Ha: } \beta^* \neq 0 \]

Note: \( \beta_1 \) = treatment variable from equation 3-11.

Objective 3

What is the average induction period from quinolone exposure to tendon rupture?

Research Question 3

Does model 4 (piece-wise model) fit better than Model 2 or 3? If so, at what interval, in days, is the hazard ratio of tendon rupture post-quinolone therapy at its highest?

Research Question 3 Hypothesis

The null hypothesis is that all of the time interval regression coefficients in the quinolone exposed group relative to the cephalosporin exposed group will equal zero, after adjusting for age, gender, race, military occupation, grade, provider specialty, days of medication supply, diagnosis related to antibiotic dispensing, branch of service, oral steroid status, and time at risk.
The alternative hypothesis is at least one of the time intervals regression coefficient is different from zero.

\[
\text{Ho: } \beta_A = \beta_B = \beta_C = 0 \\
\text{Ha: at least one } \beta \neq 0
\]

**Objective 4**

Identify other major risk factors that affect an active duty military individuals’ estimated risk for tendon rupture.

**Research Question 4**

What are the significant risk factors, other than quinolone treatment, for tendon rupture relevant to active duty military personnel?

**Research Question 4 Hypothesis**

The null hypothesis states that the age, gender, race, military occupation, grade, provider specialty, days of medication supply, diagnosis related to antibiotic dispensing, branch of service, and oral steroid status regression coefficients are equal to zero. The alternative hypothesis is that one or more covariate regression coefficients are not equal to zero.

\[
\text{Ho: } \beta_2 = \beta_3 = \ldots = \beta_{11} = 0 \\
\text{Ha: at least one } \beta \neq 0
\]

This study has been approved by the University of Florida Institutional Review Board #303-06, and the Brooke Army Medical Center (BAMC) Institutional Review Board C.2007.088d.
Figure 3-1. DoD population description

Figure 3-2. DoD active duty trend 1990-2003
Figure 3-3. Patient inclusion schematic

Figure 3-4. Illustration of RH(t), RR(t), and OR(t) where the hazard functions for both exposed and unexposed are constant.
<table>
<thead>
<tr>
<th>Demographic Variable</th>
<th>Active Duty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number</td>
<td>1,419,061</td>
</tr>
<tr>
<td>Ratio of officers to enlisted</td>
<td>1 to 5.2</td>
</tr>
<tr>
<td>Percent Women</td>
<td>15.0</td>
</tr>
<tr>
<td>Percent minorities</td>
<td>35.8</td>
</tr>
<tr>
<td>Percent located in the United States</td>
<td>84.5</td>
</tr>
<tr>
<td>Percent 25 years old or younger</td>
<td>47.4</td>
</tr>
<tr>
<td>Percent with bachelor’s degree or higher</td>
<td>16.9</td>
</tr>
<tr>
<td>Percent married</td>
<td>52.3</td>
</tr>
<tr>
<td>Percent in dual-military marriage</td>
<td>6.7</td>
</tr>
<tr>
<td>Number of dependents</td>
<td>1,924,174</td>
</tr>
<tr>
<td>Percent with children</td>
<td>43.4</td>
</tr>
<tr>
<td>Percent single parents</td>
<td>6.1</td>
</tr>
</tbody>
</table>
Table 3-2. Conditional probabilities

<table>
<thead>
<tr>
<th>Medication</th>
<th>TR</th>
<th>No-TR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>a</td>
<td>b</td>
<td>a + b</td>
</tr>
<tr>
<td>Unexposed</td>
<td>c</td>
<td>d</td>
<td>c + d</td>
</tr>
</tbody>
</table>

\[
P^{\text{TR} | E} = \hat{P}_1 = \frac{a}{a+b}, \quad P^{\text{TR} | \bar{E}} = \hat{P}_2 = \frac{c}{c+d}
\]
CHAPTER 4
RESULTS

Data Validity

Missing Data

The military occupation specialty (MOS) variable utilized in the proportional hazards regression model had an appreciable amount of missing data. Nearly 6.1% (6,518) of the military personnel in the study were without MOS observations out of the 107,334 total from both groups combined. There were 3,914 (6.6%) missing in the quinolone group and 2,606 (5.4%) in the cephalosporin sample. All 382 cases had a value included for the MOS variable (210 support and 172 direct).

Ten variables came from a combination of the medication and encounter databases. The medication database was almost bereft of missing data. The reason for this is the finding that the Pharmacy Data Transaction Service (PDTS) medication database prompts the pharmacy dispensing the medication to complete missing data fields prior to moving to the next screen. In some instances, the prescription cannot be filled unless all medication and demographic fields are completed. The MOS information came solely from the DEERs eligibility database, which resulted in the missing data.

Longitudinal Validity

The integrity of the data in the M2 database can be assessed by graphing the number of prescriptions per month and per year. This longitudinal analysis reveals any unusual spikes or downward trends that are irregular. These irregularities may represent blocks of missing data that constitute poor database integrity.

In Figure 4-1, the normal trend during the same month in different years steadily increases which signifies an increasing volume of prescriptions over time. It also shows the increase in
prescriptions within the DoD by year. This graph presents no identifiable blocks of missing data that would impugn the longitudinal validity this database, and lead to a conclusion of reduced integrity of the data.

**Diagnosis versus Demographics Validity**

This is a particularly important evaluation as the diagnosis information comes from two separate databases representing military purchased care, received in civilian facilities, and direct care, received on a military base. The gender information comes from another database file containing demographic information and functioning as a ‘membership’ database. Essentially, the validity assessed here is actually calculated from the coherence coming from the linking of three separate databases.

The coherence is very high for females and normal pregnancy deliveries (Table 4-1). The coherence remained stable and high over time as demonstrated by the stability of normal pregnancy deliveries over time (Figure 4-2). Both of these data presentations help reinforce the coherence of the sources within the M2 database.

Coherence was high when the diagnosis of benign prostate hyperplasia was cross-checked with gender (Table 4-2). The coherence remains consistently high over the five-year span.

**Diagnosis versus Drugs Validity**

The coherence characterized by Figure 4-4 and Table 4-3 is formulated from the three separate databases described above. The diabetes mellitus diagnosis codes were abstracted from the purchased care and direct care clinical databases within M2, while the prescription information was gathered from the prescription detail transaction service (PDTS) database. The coherence for the five years measured stays well above the *a priori* 80% threshold stipulated in this study.
These results are cautiously relayed in the next two sections with the understanding that the reliability of these results is affected by the appropriateness of prescribing and diagnosis coding. These terms (insulin and type 1 diabetes) were selected to minimized the misclassification error as it is a requirement to sustain life that exogenous insulin be administered to truly type I diabetes sufferers.

**Drug versus Diagnosis Validity**

Coherence between a prescription for insulin and a diagnosis for diabetes mellitus (any type) is above the 80% threshold for each of the five years evaluated. The greater amount of non-matching, drug versus diagnosis observations shows the difficulty for large administrative databases to have absolute coherence. Since all patients using insulin should have a diagnosis for some type of diabetes, this measure of internal consistency and reliability is crucial in interpreting results gained from using this database (Figure 4-5, Table 4-4).

**Patient Demographics**

Upon the completion of the cohort selection process, 107,334 active duty patients were included in this study. The quinolone study group contained 59,264 patients while the cephalosporin control group counted 48,070. In 2006, for active duty members only, there were 116,479 outpatient prescriptions dispensed for quinolones and 91,785 for cephalosporin antibiotics. There were 10,370,568 prescriptions dispensed DoD wide for active duty members.

On average, the quinolone treatment group was slightly older than the cephalosporin group (29.1±8.8 versus 28.7±8.4; p-value<.001) and the population of the DoD as a whole (28.2 years) (Table 4-5). The quinolone group contained a higher proportion of females than the cephalosporin group (28.3 versus 21.8; p-value<.001) and both had considerably more than the DoD population at large (15.0) (Table 4-5). The quinolone group, while still mostly White, has a
higher percentage of Black patients when compared to the cephalosporin group (18.2 versus 16.1; p-value<.001) (Table 4-5).

**Dependent Variable**

The dependent variable is the number of cases of tendon rupture from the dispensing date of the prescription for either a quinolone or cephalosporin, censored at 60-days. There were 255 cases of all-site tendon rupture in the quinolone group and 127 in the cephalosporin control group. Median time to rupture was twice as long in the quinolone group at 27 vs. 12 days. (Table 4-6)

There were fewer male cases of tendon ruptures when compared to the cephalosporin group, as well as a racial disparity. More Whites had tendon ruptures in the quinolone group, although this difference proved to be statistically non-significant (Table 4-6).

Table 4-7 gives an overview of the nature of the cases of tendon ruptures in both groups. Significant differences between cases in the treatment groups are highlighted by the median time to rupture (27 days versus 12 days; p-value<.001) and provider specialty ($\chi^2 = 27.02; p$-value<.001).

**Other Independent Variables**

Military occupation was divided into direct and support categories. There were predictably twice as many patients in the support occupations as in the direct occupations. There were missing data on this variable ranging from 6.1% in the quinolone group to 5.5% in the control group. Military rank was broken into officer and enlisted for the purpose of these analyses. The two treatment groups had similar proportions while having more officers and less enlisted than the military population as a whole. A small percentage of each group used outpatient steroids
The only continuous measure in this group is medication days of supply. The variable averaged just over 11 days in the quinolone group and just below 10 days in the control group. The most frequent days of supply, was 10 days followed by 30 in each treatment group.

**Research Question 1**

Is there a difference in risk of tendon rupture in active duty U.S. military personnel from quinolone antibiotic use relative to cephalosporin antibiotic use, after adjusting for age, gender, race, military occupation, grade, provider specialty, days of medication supply, diagnosis related to antibiotic dispensing, branch of service, oral steroid status, and time at risk?

Due to the significant p-value from Table 4-14 for the treatment regression coefficient, the null hypothesis for Research Question 1 was rejected.

\[ H_0: \beta_1 = 0 \]

\[ H_a: \beta_1 \neq 0 \]

The adjusted hazard ratio for the occurrence of tendon ruptures within sixty days of using a quinolone antibiotic compared to a cephalosporin antibiotic is 1.65 (95% confidence interval: 1.33 – 2.04) (Table 4-9b). Active duty soldiers, sailors, airmen, and marines have a 65% greater likelihood of incurring a tendon rupture during the first sixty day post quinolone exposure compared to the same period for cephalosporin use.

The absolute impact of quinolones compared to cephalosporins reflected by the excess risk is an additional 166 cases of tendon ruptures per 100,000 active duty military members.

Since the excess risk includes individuals who ruptured their tendons and were not exposed to quinolones it is important to estimate the risk to individuals characterized by the presence of...
solely quinolone use. By using the attributable risk or more precisely the attributable fraction, the answer to the question of how many cases in the quinolone group can be attributed to the quinolone exposure is answered. The attributable fraction is 0.39 in this study. Thus, 39% of the tendon ruptures, or 100 of 255 cases, in the quinolone group can be attributed to quinolone use. Stated differently, 100 cases of tendon rupture may have been avoided if they had been dispensed a cephalosporin instead of a quinolone.

**Research Question 2**

Does the adjusted hazard function for each antibiotic treatment support the proportional hazards model assumption?

The graph of the hazard function stratified by treatment and adjusted for model covariates illustrates the dynamic nature of the risk of tendon rupture over the 60-day post exposure period (Figure 4-6). This graph also shows the apparent violation of the proportion hazards assumption, which underpins the use of the Cox regression model. In other words, it appears that the risk of tendon rupture is not in relative proportion over time between the two treatment groups. The appearance of a proportional hazard violation is reinforced by adding a term representing the treatment and time interaction. The time-dependant covariate represented by this interaction term can then be tested for significance. The treatment by time interaction in this study is significant (p-value<.001). These two methods show that the effect of quinolones on tendon rupture is changing over time when compared to the cephalosporin group. Since exposure is dichotomous in this study, it is more exact to say that the quinolone coefficient varies over time differently than the cephalosporin coefficient.

Based on the significant p-value of the interaction term the Research Question 2 null hypothesis was rejected.
\[ H_0: \beta^* = 0 \]
\[ H_a: \beta^* \neq 0 \]

**Research Question 3**

At what interval, in days, is the hazard ratio of tendon rupture post-quinolone therapy at its highest?

To remedy the proportional hazard violation a Cox piece-wise regression analysis was utilized to model the ‘pieces’ of the hazard function that appear to be proportional. In plotting the relative hazard between the quinolone and cephalosporin groups at arbitrary 10-day ‘pieces’ or intervals it appears the risk of tendon rupture increases directly after being exposed to quinolones and becomes non-significant after day 30 (Figure 4-7). This estimation of risk is misleading because it ignores the unique time-varying nature of risk in the study.

By using the hazard function, stratified by treatment and adjusted for other model covariates, as a guide, an alternative to the equal intervals can be formulated to provide an improved risk profile for exposure to quinolones compared to cephalosporins. The intervals, post antibiotic dispensing, that best capture the effect modification of time were: 1) day 0 through 25; 2) day 26 through 35 and; 3) day 36 though 59. Since the hazard function remains generally proportional within these three intervals, it allows estimation of a less misleading hazard ratio for each interval. To reinforce the observation that the hazard function is proportional within each of the three intervals a treatment*time interaction term was tested for each of the intervals and was statistically non-significant.

The first interval, day 0–25, has a significant hazard ratio of 1.38 (95% confidence interval: 1.11–1.73), while the second interval’s (26 – 35) hazard ratio increases to 1.74 (95% confidence interval: 1.49 – 2.04). The last interval, formed from days 36 through 59, exhibited
no significant difference between the two treatment groups 1.00 (95% confidence interval: 0.60 – 1.65) (Figure 4-8).

The hazard function performs two important tasks in this analysis. First, it helps detect a treatment effect modified by time, which resulted in a violation in the proportional hazards assumption in this study and second, it helps determine the best way to overcome this violation and attain optimal estimates of the risk of tendon ruptures from quinolone use. Referring back to Figure 4-6 and 4-8, the risk progression over the 60-day study period comes into focus. First, in Figure 4-6, it appears the risk of tendon rupture in the quinolone group is increased immediately after the index date. This is confirmed in Table 4-8 by a significant hazard ratio of 1.38 (p-value=0.004; 95% confidence interval 1.11-1.73) for the first 25 days post exposure. Next, the hazard function shows a sizable increase in risk that diverges from the cephalosporin group around day 25. The ten day, 25 to 35, period measures the highest hazard ratio estimate (1.74; p-value<.001; 95% confidence interval 1.49-2.04) (Figure 4-8) in the quinolone group compared to the cephalosporin group. The hazard function then begins to diminish after day 35 where it approaches a comparable risk to the cephalosporin group, until the end of the study period. Lastly, the non-significant hazard ratio of 1.01 (p-value=0.886; 95% confidence interval 0.60-1.65) (Figure 4-8) from day 36 to 59 confirms the reduction of risk at the end of the study period.

Indeed the model selection process, which uses the -2logL statistic to test for model fit illustrates that model 3 is a more adequate combination of explanatory variables (Equation 3-12, Table 4-21). Model 3 contains three treatment predictor variables that represent ‘windows’ of time at risk while Model 2 only includes one predictor variable or risk window, for treatment.

These results point to an average induction period that begins, immediately after exposure to quinolone antibiotics and extends through day 35 post exposure. The maximum risk of tendon
rupture from quinolone use occurs between days 26 through 35 compared to cephalosporin use. In other words, the risk of tendon rupture is increased by 38% from the first administration of the drug to around day 25, compared to cephalosporin use. After this interval, the risk increases by 74% starting around day 25 and lasting until roughly day 35. Finally, approximately 35 days after a patient is dispensed a prescription for a quinolone antibiotic their increased risk of tendon rupture compared to the cephalosporin group, falls to nearly zero.

Two of the three, interval regression coefficients, are shown to be significantly different from zero in Figure 4-8. Due to this, the null hypothesis for Research Question 3 was rejected.

\[ H_0: \beta_{AX_1}^{(1)} = \beta_{BX_1}^{(2)} = \beta_{CX_1}^{(3)} = 0 \]

\[ H_a: \text{at least one } \beta \neq 0 \]

The method of using Cox piece-wise regression to overcome the violation of the proportional hazards model assumption results in a better model fit for the effect of changing risk in this study.

**Research Question 4**

What are the significant risk factors, other than quinolone treatment, for tendon rupture relevant to active duty military personnel?

Several of the covariate regression coefficients are significantly different from zero (Table 4-14). Due to this, Research Question 4 null hypothesis was rejected.

\[ H_0: \beta_2 = \beta_3 = \ldots = \beta_{11} = 0 \]

\[ H_a: \text{at least one } \beta \neq 0 \]
Each of the remaining covariates is analyzed for their effect on tendon ruptures when adjusting for the other covariates. The hazard function for the modeled Cox equation, stratified by each independent dichotomous variable, is reviewed for the presence of any variable by time interaction. This both identifies the most important risk factors and optimizes the resulting hazard ratio.

**MOS:** Military occupation was subdivided into direct involvement characterized by more physically demanding jobs, and support, distinguished by its administrative and medical components. As can be ascertained from inspecting the hazard function, direct versus support occupations are generally in proportion throughout the study period (Figure 4-9). This is reinforced by a non-significant time dependent interaction term (p-value=0.096). There is a spike of tendon rupture cases in the direct group around day 25, but the support group is also increasing over the same interval. The overall hazard ratio of MOS is significant at HR=1.53 (p-value<.001; 95% confidence interval 1.24-1.89) (Table 4-7). An estimated 53% of tendon ruptures in this cohort are explained by having a military occupation that requires more physical exertion compared to supporting personnel. This makes intuitive sense as soldiers, sailors, airmen and marines who carry, lift, or patrol more should be more prone to orthopedic injuries.

**Branch:** Branch of service is a four category variable consisting of 1) Army 2) Air Force 3) Navy and 4) Marines. After adjusting for other covariates, there emerged one significant difference in risk between the Army and Marine Corps. The Marine Corps had a 65% higher risk of tendon rupture over the 60-day study period compared to the Army (p-value=0.002; HR=1.65; 95% confidence interval 1.20-2.28) (Table 4-9b). The Marine Corps has very little support personnel and is generally considered to be the most physically demanding branch in the
active duty force. This result coincides with the significant military occupational findings that more physical occupations result in an increase risk of tendon ruptures regardless of treatment.

Viewing the Marine Corps versus Army hazard functions reveal a relative increase in tendon ruptures for the Marines, which occur later when compared to the Army (Figure 5-10). The time-dependent interaction term is significant (p-value=0.028), meaning that the Marine Corps and Army hazard functions are not generally proportional over the 60-day study period. Further analysis of the risk profile for the Marine Corps when using the same interval as before, shows that the risk is highest from day 35 through day 50 (p-value 0.048; HR= 1.78; 95% confidence interval 1.04, 2.52) when compared to their Army counterparts.

**Provider Specialty**: Patients being seen by specialty care providers (internist, infectious disease, nephrologists, etc.) were almost two and a half times more likely to incur a tendon rupture than patients seeing a primary care provider (HR 2.40, p-value <.001; 95% confidence interval 1.92-2.99) (Table 4-9b). The hazard curve is generally proportional over the study period giving reassurance that the Cox regression model is appropriately estimating the hazard ratio (Figure 4-11). The test of proportionality time-dependant interaction term is non-significant (p-value=0.105). This variable seems to help explain the belief that sicker patients require specialty care and that sicker patients tend to have an array of related or unrelated health risk factors for tendon ruptures. The subgroup analysis of primary care versus orthopedic care was non-significant (p-value 0.457).

**Days of Medication Supply**: The days of supply explanatory variable consists of the number of days a patient is expected to take the medication assuming the directions are followed. An example of days of supply would be a prescription for 30 capsules with instructions to take twice a day. The days supply in this case would be 15. The most frequently prescribed days of
supply for antibiotics in this study were: 1(4.2%), 3(6.6%), 5(8.5%), 7(18%), 10(44%), 14(3.7), and 30(9.5). This is commensurate with prescribing guidelines for quinolones and cephalosporins.

The days of supply variable is significant (p-value<.001; HR=1.02; 95% confidence interval 1.018-1.022, Table 4-14). The result indicates there is a 2% increase in tendon rupture risk for every additional day of quinolone treatment. When the days of supply variable was stratified by exposure the result was a significant 3% increase in tendon ruptures per day in the quinolone group (p-value<.001, HR=1.03; 95% confidence interval 1.028-1.039, Table 4-15). This stratification also included a protective finding in the cephalosporin group (p-value<.001, HR=0.90; 95% confidence interval 0.854-0.957, Table 4-16)

For further insight, days of supply was categorized by the most frequent days of supply occurring in the quinolone sample. Inspection of the hazard ratios show that the longer a patient is on quinolones the higher their risk of tendon rupture becomes compared to patients taking cephalosporins. Patients prescribed quinolones for the most common 10-day regimen are 1.39 times more likely to experience a rupture, while patients on a 30-day supply are 2.7 times more likely to incur a rupture compared to patients prescribed cephalosporins (Figure 4-12).

Age: The continuous variable age is statistically significant (p-value = 0.002; HR 1.02; 95% confidence interval 1.001-1.029) (Table 4-14). It can be interpreted as increasing the risk of tendon rupture by 2% as a patient gets 1-year older or that in this sample every year older a person ages increases their risk by 2% compared to patients who received cephalosporins.

To illustrate the relationship between age and tendon ruptures the hazard ratio was calculated for four time intervals (Figure 4-13). The hazard ratio of incurring a tendon rupture over a 10-year span was 1.20, 20-year 1.43, 30-year 1.72, and 40-years 2.05. Having a 2%
increase in risk per year means that over a typical 20-year military career a soldier, sailor, airman, or marine has a 43% increase in their risk of tendon rupture merely from the effects of aging, which included reduced flexibility and a loss in vascular perfusion in tendon tissue.

**Diagnosis Leading to Antibiotic Treatment:** Quinolone and cephalosporin antibiotics have similar indications for use. These indications were divided into three main categories for analysis. The comparison group is upper respiratory infections (URI), followed by gastrointestinal / genitourinary (GI/GU) infections, and lastly, soft tissue / bone infections (ST/BI). GI/GU use came closest to being significant (p-value=0.058; HR=1.25; 95% confidence interval 0.99-1.57) (Table 4-14), when compared to URI. Specifically, patients prescribed quinolones and cephalosporins for GI/GU infections were 25% more likely to experience a tendon rupture when compared to patients who were prescribed these antibiotics for URI infections. Notably, treatment of ST/BI with quinolones or cephalosporins, was not an important explanation of tendon ruptures when compared to URI (p-value=0.590) (Table 4-14).

The hazard functions stratified by the treatment groupings show the similarity of the URI and ST/BI curves (Figure 4-14). The graph also reveals the slight increase in events in the GI/GU group between day 10 and day 20, compared to the URI group.

**Grade:** The explanatory variable grade is dichotomous, consisting of officers compared to enlisted military personnel. This variable is evenly distributed between the two treatment groups (enlisted 78.3 versus 77.5 and officer 21.7 versus 22.5,Table 4-8). Cases of tendon rupture are also evenly distributed between treatment groups (Table 5-7), indicated by the non-significant hazard ratio of 1.08 (p-value=0.529; 95% confidence interval 0.85 – 1.37, Table 4-14) when comparing officers to enlisted members according to the occurrence of tendon ruptures over time. Grade does not vary with time as its time interaction variable is also non-significant (p-
value=0.199). Officer and enlisted members of the military are not significantly different at any interval post exposure when compared to each other, even after viewing the baseline hazard function (Figure 4-15) and tailoring the intervals accordingly (day 30 through 40: p-value = 0.163; HR = 0.71; 95% confidence interval 0.45 – 1.20). The occurrence of tendon ruptures does not seem to be affected by whether a person is an officer or enlisted member of the armed forces in this study.

**Gender:** Gender has a non-significant hazard ratio over the 60-day study period, (p-value=0.165; HR=1.20; 95% confidence interval 0.93 – 1.54, Table 4-14). Upon viewing the hazard function for males and females it appears there may be a time-varying increase in risk occurring from day 25 to day 35 (Figure 4-16). The gender-time interaction term trends toward statistical significance but ultimately is non-significant (p-value = 0.068) signifying that the occurrence of tendon ruptures according to gender is generally proportional over the study period. The hazard ratios for the intervals from index to day 25 (p-value=0.374), from day 26 through 36 (p-value=0.157and from day 36 to 60 (p-value=1.00), are non-significant. Gender does not affect the occurrence of tendon ruptures in this study.

**Race:** The race variable is divided into three groups, 1) White, 2) Black, and 3) Other. Categorical comparisons utilizing the White category as the reference group versus Black (p-value=0.697) and Other group (p-value=0.218) based on tendon rupture occurrence, proved to be statistically non-significant (Table 4-14). When Black and the Other categories were combined and compared to Whites, the results were still non-significant (p-value=0.260).

The hazard function stratified by race illustrates the similarity of the risk of tendon rupture between the different race categories (Figure 4-17).
**Steroid:** The steroid explanatory variable describes whether a DoD member used oral steroids prior to, during, or promptly after the study period. The distribution is similar between treatment groups (Table 4-8) and between cases stratified by treatment group (Table 4-7). As such, steroid use is not an important independent variable in this study as revealed by its non-significant p-value ($p$-value=0.925; HR = 0.98) (Table 4-14), and hazard function which is nearly overlapping during the entire 60-day period (Figure 4-18).
Figure 4-1. Total DoD prescriptions by month and year

Figure 4-2. Normal pregnancy delivery in the DoD (ICD-9 650.00) by gender and year
### Table 4–1. Normal pregnancy delivery in the DoD (ICD-9-650.00) by gender and year*

<table>
<thead>
<tr>
<th>Year</th>
<th>NPD</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>63,184</td>
<td>63,181</td>
<td>71,805</td>
<td>68,881</td>
<td>59,981</td>
<td>59,800</td>
</tr>
<tr>
<td>Coherence (%)</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
</tr>
</tbody>
</table>

* includes entire DoD population; NPD = normal pregnancy delivery

### Figure 4-3. Benign prostate hyperplasia in the DoD (ICD-9-600.00 – 600.91) by gender and year

![Graph showing benign prostate hyperplasia by year and gender](image)

### Table 4-2. Benign prostate hyperplasia in the DoD (ICD-9-600.00 – 600.91) by gender and year*

<table>
<thead>
<tr>
<th>Year</th>
<th>BPH</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>8,011</td>
<td>7,985</td>
<td>8,487</td>
<td>10,725</td>
<td>10,767</td>
<td>15,792</td>
</tr>
<tr>
<td>Coherence (%)</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
</tr>
</tbody>
</table>

* includes entire DoD population; BPH = benign prostate hyperplasia
Figure 4–4. Diabetes mellitus type 1 versus insulin use in the DoD (ICD-9-250.01) by year

Table 4–3. Diabetes mellitus type 1 versus insulin in the DoD (ICD-9-250.01) by year*

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I DM</td>
<td>12,090</td>
<td>12,906</td>
<td>12,768</td>
<td>14,038</td>
<td>14,210</td>
</tr>
<tr>
<td>Insulin rxs</td>
<td>11,579</td>
<td>12,098</td>
<td>12,145</td>
<td>13,108</td>
<td>13,843</td>
</tr>
<tr>
<td>Coherence (%)</td>
<td>96</td>
<td>94</td>
<td>95</td>
<td>93</td>
<td>97</td>
</tr>
</tbody>
</table>

* includes entire DoD population not just active duty; ≥ one physician encounter for type 1 DM per fiscal year
Figure 4–5. Insulin use versus diabetes mellitus in the DoD (ICD-9-250.xx) by year

Table 4–4. Insulin use versus diabetes mellitus in the DoD (ICD-9-250.xx) by year*

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin rxs</td>
<td>593,529</td>
<td>638,242</td>
<td>662,790</td>
<td>693,532</td>
<td>721,029</td>
</tr>
<tr>
<td>Diabetes dx</td>
<td>552,335</td>
<td>603,485</td>
<td>604,589</td>
<td>670,142</td>
<td>701,287</td>
</tr>
<tr>
<td>Coherence (%)</td>
<td>92</td>
<td>94</td>
<td>90</td>
<td>96</td>
<td>97</td>
</tr>
</tbody>
</table>

* includes entire DoD population not just active duty;
### Table 4-5. Sample demographics

<table>
<thead>
<tr>
<th>N=107,334</th>
<th>quinolone</th>
<th>cephalosporin</th>
<th>p-value</th>
<th>DoD&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=59,264</td>
<td>n=48,070</td>
<td></td>
<td></td>
<td>n=1,419,061</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>70.7</td>
<td>78.2</td>
<td>&lt;.001&lt;sup&gt;c&lt;/sup&gt;</td>
<td>85.0</td>
</tr>
<tr>
<td>female</td>
<td>28.3</td>
<td>21.8</td>
<td></td>
<td>15.0</td>
</tr>
<tr>
<td>Age, year (mean±SD&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>29.1±8.8</td>
<td>28.7±8.4</td>
<td>&lt;.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28.2</td>
</tr>
<tr>
<td>White</td>
<td>72.7</td>
<td>75.1</td>
<td></td>
<td>64.2</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>18.2</td>
<td>16.1</td>
<td>&lt;.001&lt;sup&gt;c&lt;/sup&gt;</td>
<td>35.8</td>
</tr>
<tr>
<td>Other</td>
<td>9.1</td>
<td>8.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Department of Defense; <sup>b</sup> independent t-test; <sup>c</sup> chi-squared test; <sup>d</sup> Standard deviation

### Table 4-6. Case demographics

<table>
<thead>
<tr>
<th>N&lt;sup&gt;a&lt;/sup&gt;=382</th>
<th>quinolone</th>
<th>cephalosporin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=255</td>
<td>n=127</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (%)</td>
<td>66.7</td>
<td>33.3</td>
<td>&lt;.001&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>74.1</td>
<td>88.2</td>
<td>0.035&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>female</td>
<td>25.9</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>Age, year (mean±SD&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>31.6±9.9</td>
<td>30.0±8.7</td>
<td>&lt;.069&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>White</td>
<td>78.0</td>
<td>70.9</td>
<td></td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>13.3</td>
<td>22.0</td>
<td>0.706&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Other</td>
<td>8.6</td>
<td>7.1</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> total cases; <sup>b</sup> Standard deviation; <sup>c</sup> Chi-squared test; <sup>d</sup> Independent t-test; <sup>e</sup> test of difference in proportions
Table 4-7. Description of tendon rupture cases

<table>
<thead>
<tr>
<th></th>
<th>quinolone (n=255)</th>
<th>cephalosporin (n=127)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case (%)</td>
<td>66.7</td>
<td>33.3</td>
<td>&lt;.001&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median time to rupture (days)</td>
<td>27 (95%CI(22,29))</td>
<td>12 (95%CI(11,16))</td>
<td>&lt;.001&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Occupation (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>direct</td>
<td>44.3</td>
<td>46.5</td>
<td>0.692&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>support</td>
<td>55.7</td>
<td>53.5</td>
<td></td>
</tr>
<tr>
<td>enlisted</td>
<td>77.6</td>
<td>74.0</td>
<td>0.431&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Grade (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>officer</td>
<td>22.4</td>
<td>26.0</td>
<td></td>
</tr>
<tr>
<td>Steroid use (%)</td>
<td>7.8</td>
<td>6.3</td>
<td>0.585&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Days of supply, days (mean±SD)</td>
<td>16.9±30.4</td>
<td>8.2±2.6</td>
<td>0.001&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Provider Specialty (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care</td>
<td>61.6</td>
<td>87.4</td>
<td>&lt;.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Specialty care</td>
<td>38.4</td>
<td>12.6</td>
<td></td>
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<tr>
<td>Diagnosis leading to abx&lt;sup&gt;a&lt;/sup&gt; treatment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>65.5</td>
<td>66.9</td>
<td></td>
</tr>
<tr>
<td>GI/GU&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27.8</td>
<td>25.2</td>
<td>0.810&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ST/BI&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6.7</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Army</td>
<td>31.4</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td>Air Force</td>
<td>32.9</td>
<td>21.3</td>
<td></td>
</tr>
<tr>
<td>Navy</td>
<td>23.1</td>
<td>32.3</td>
<td></td>
</tr>
<tr>
<td>Branch of Service (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marines</td>
<td>12.5</td>
<td>11.8</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Antibiotic; <sup>b</sup> total cases; <sup>c</sup> Standard deviation; <sup>d</sup> Chi-squared test; <sup>e</sup> Independent t-test; <sup>f</sup> test of difference in proportions; <sup>g</sup> Kaplan-Meier estimator
<table>
<thead>
<tr>
<th></th>
<th>quinolone n=59,264</th>
<th>cephalosporin n=48,070</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment group (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Army</td>
<td>34.6</td>
<td>34.9</td>
<td></td>
</tr>
<tr>
<td>Air Force</td>
<td>32.5</td>
<td>30.4</td>
<td>&lt;.001&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Navy</td>
<td>19.8</td>
<td>21.3</td>
<td></td>
</tr>
<tr>
<td>Marines</td>
<td>13.1</td>
<td>13.4</td>
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<tr>
<td>direct</td>
<td>32.5</td>
<td>33.9</td>
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<tr>
<td><strong>Branch of Service (%)</strong></td>
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<tr>
<td>support</td>
<td>60.9</td>
<td>60.6</td>
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<td>unknown</td>
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<td>5.5</td>
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<tr>
<td>enlisted</td>
<td>78.3</td>
<td>77.5</td>
<td>0.004&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>officer</td>
<td>21.7</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td><strong>Occupation (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid use (%)</td>
<td>7.5</td>
<td>7.0</td>
<td>0.002&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Days of supply, days (mean±SD)</strong></td>
<td>11.1±9.2</td>
<td>9.8±6.4</td>
<td>&lt;.001&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Provider Specialty (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care</td>
<td>84.9</td>
<td>85.2</td>
<td>0.173&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Specialty care</td>
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<td></td>
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<tr>
<td>Diagnosis leading to abx&lt;sup&gt;a&lt;/sup&gt; treatment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>70.4</td>
<td>69.9</td>
<td></td>
</tr>
<tr>
<td>GI/GU&lt;sup&gt;c&lt;/sup&gt;</td>
<td>22.9</td>
<td>23.2</td>
<td>0.137&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>ST/BI&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6.7</td>
<td>6.9</td>
<td></td>
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</tbody>
</table>

<sup>a</sup> Antibiotic; <sup>b</sup> Upper respiratory infection; <sup>c</sup> Gastrointestinal infection/Genital urinary; <sup>d</sup> Soft tissue/Bone infection; <sup>e</sup> Independent t-test; <sup>f</sup> Chi-squared test; <sup>g</sup> Test of difference in proportions; <sup>h</sup> Total number of patients
### Table 4–9. Model 1 regression parameters for demographic variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
<th>HR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95%CI&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;.001</td>
<td>1.025</td>
<td>1.014, 1.036</td>
</tr>
<tr>
<td>Gender, male&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.071</td>
<td>1.26</td>
<td>0.99, 1.61</td>
</tr>
<tr>
<td>Race&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.672</td>
<td>0.94</td>
<td>0.72, 1.24</td>
</tr>
<tr>
<td>Other</td>
<td>0.537</td>
<td>0.89</td>
<td>0.61, 1.29</td>
</tr>
</tbody>
</table>

* Model Summary

<table>
<thead>
<tr>
<th>-2logL&lt;sup&gt;c&lt;/sup&gt;</th>
<th>w/out covariates</th>
<th>8848.583</th>
<th>w/ covariates</th>
<th>8823.352</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-ratio(df)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>25.23(4)</td>
<td>p-value &lt;.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> HR = hazard ratio; <sup>b</sup> CI = Confidence interval; <sup>c</sup> -2 log likelihood; <sup>d</sup> Likelihood ratio (degrees of freedom); <sup>e</sup> reference female; <sup>f</sup> reference White

### Table 4-10. Treatment variable stratified by occupation

<table>
<thead>
<tr>
<th>Support</th>
<th>TR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>No TR</th>
<th>p-value</th>
<th>OR&lt;sup&gt;c&lt;/sup&gt;</th>
<th>95%CI&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>N&lt;sup&gt;a&lt;/sup&gt; = 65,239</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>quinolone</td>
<td>142</td>
<td>35,946</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cephalosporin</td>
<td>68</td>
<td>29,083</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> total number of secondary patients; <sup>b</sup> tendon rupture; <sup>c</sup> odds ratio; <sup>d</sup> confidence interval; <sup>f</sup> chi-squared test
Table 4-11. Treatment variable stratified by occupation

<table>
<thead>
<tr>
<th>TR</th>
<th>No TR</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>quinolone</td>
<td>113</td>
<td>19,149</td>
<td>&lt;.003</td>
<td>1.63f</td>
</tr>
<tr>
<td>cephalosporin</td>
<td>59</td>
<td>16,256</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) total number of secondary patients; \(^b\) tendon rupture; \(^c\) odds ratio; \(^d\) confidence interval; \(^f\) chi-squared test

Table 4-12. Treatment variable stratified by provider specialty

<table>
<thead>
<tr>
<th>TR</th>
<th>No TR</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>quinolone</td>
<td>157</td>
<td>50,152</td>
<td>&lt;.269</td>
<td>1.15</td>
</tr>
<tr>
<td>cephalosporin</td>
<td>111</td>
<td>40,839</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) total number of secondary patients; \(^b\) tendon rupture; \(^c\) odds ratio; \(^d\) confidence interval; \(^f\) chi-squared test

Table 4-13. Treatment variable stratified by provider specialty

<table>
<thead>
<tr>
<th>TR</th>
<th>No TR</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>quinolone</td>
<td>114</td>
<td>8,857</td>
<td>&lt;.001</td>
<td>4.91</td>
</tr>
<tr>
<td>cephalosporin</td>
<td>16</td>
<td>7,104</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) total number of secondary patients; \(^b\) tendon rupture; \(^c\) odds ratio; \(^d\) confidence interval; \(^f\) chi-squared test
Table 4-14. Model 2 full regression parameters for treatment and covariate effects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter(SE\textsuperscript{a})</th>
<th>$\chi^2$\textsuperscript{n}</th>
<th>p-value</th>
<th>HR\textsuperscript{b}</th>
<th>95%CI\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment, quinolone\textsuperscript{d}</td>
<td>0.501(0.110)</td>
<td>21.016</td>
<td>&lt;.001</td>
<td>1.65</td>
<td>1.33, 2.04</td>
</tr>
<tr>
<td>Days supply</td>
<td>0.018(0.003)</td>
<td>90.305</td>
<td>&lt;.001</td>
<td>1.02</td>
<td>1.018, 1.022</td>
</tr>
<tr>
<td>Gender, male\textsuperscript{e}</td>
<td>0.179(0.130)</td>
<td>1.924</td>
<td>0.165</td>
<td>1.20</td>
<td>0.93, 1.54</td>
</tr>
<tr>
<td>Grade, officer\textsuperscript{f}</td>
<td>0.076(0.121)</td>
<td>0.397</td>
<td>0.529</td>
<td>1.08</td>
<td>0.85, 1.37</td>
</tr>
<tr>
<td>Steroid</td>
<td>-0.019(0.197)</td>
<td>0.009</td>
<td>0.925</td>
<td>0.98</td>
<td>0.67, 1.44</td>
</tr>
<tr>
<td>Occupation, direct\textsuperscript{g}</td>
<td>0.424(0.107)</td>
<td>15.607</td>
<td>&lt;.001</td>
<td>1.53</td>
<td>1.24, 1.89</td>
</tr>
<tr>
<td>Age</td>
<td>0.018(0.132)</td>
<td>9.584</td>
<td>0.002</td>
<td>1.02</td>
<td>1.01, 1.03</td>
</tr>
<tr>
<td>Provider, specialty care\textsuperscript{h}</td>
<td>0.874(0.114)</td>
<td>59.310</td>
<td>&lt;.001</td>
<td>2.40</td>
<td>1.92, 2.99</td>
</tr>
<tr>
<td>AF</td>
<td>0.035(0.132)</td>
<td>0.070</td>
<td>0.791</td>
<td>1.04</td>
<td>0.80, 1.34</td>
</tr>
<tr>
<td>Branch\textsuperscript{i}</td>
<td>N</td>
<td>0.292(0.135)</td>
<td>4.658</td>
<td>0.113</td>
<td>1.24, 1.63</td>
</tr>
<tr>
<td>M</td>
<td>0.362(0.173)</td>
<td>4.398</td>
<td>0.002</td>
<td>1.65</td>
<td>1.20, 2.28</td>
</tr>
<tr>
<td>Race\textsuperscript{j}</td>
<td>Black</td>
<td>-0.055(0.142)</td>
<td>0.152</td>
<td>0.697</td>
<td>0.95, 1.25</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>-0.234(0.190)</td>
<td>1.516</td>
<td>0.218</td>
<td>0.79, 1.15</td>
</tr>
<tr>
<td>Antibiotic indication\textsuperscript{k}</td>
<td>GI/GU\textsuperscript{l}</td>
<td>0.222(0.117)</td>
<td>3.595</td>
<td>0.058</td>
<td>1.25, 1.57</td>
</tr>
<tr>
<td>ST/BI\textsuperscript{m}</td>
<td>0.109(0.203)</td>
<td>0.291</td>
<td>0.590</td>
<td>1.12</td>
<td>0.75, 1.66</td>
</tr>
</tbody>
</table>

Model Two Summary

-2logL\textsuperscript{o} \\
Model 1 8823.352  Model 2 8644.503

L-ratio(df)\textsuperscript{p} 178.849(15)  p-value <.001

\textsuperscript{a} standard error; \textsuperscript{b} hazard ratio; \textsuperscript{c} confidence interval; \textsuperscript{d} reference cephalosporin; \textsuperscript{e} reference female; \textsuperscript{f} reference enlisted; \textsuperscript{g} reference support; \textsuperscript{h} reference primary care; \textsuperscript{i} reference army; \textsuperscript{j} reference white; \textsuperscript{k} reference upper respiratory infection; \textsuperscript{l} gastrointestinal/genitourinary; \textsuperscript{m} soft tissue/bone infection; \textsuperscript{n} Chi-squared statistic; \textsuperscript{o} -2 log likelihood; \textsuperscript{p} likelihood ratio(degrees of freedom)
Table 4-15. Regression parameters stratified by treatment, adjusted for covariate effects, and reported based on study significance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quinolone strata</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=59,264</td>
<td>Parameter(SE(^a))</td>
</tr>
<tr>
<td>Days supply</td>
<td>0.033(0.003)</td>
</tr>
<tr>
<td>Occupation, direct (^g)</td>
<td>0.429(0.131)</td>
</tr>
<tr>
<td>Provider, specialty care  (^h)</td>
<td>1.27(0.130)</td>
</tr>
<tr>
<td>Branch, Marines (^d)</td>
<td>0.626(0.202)</td>
</tr>
<tr>
<td>Age</td>
<td>0.017(0.007)</td>
</tr>
</tbody>
</table>

\(^a\) standard error; \(^b\) hazard ratio; \(^c\) confidence interval; \(^g\) reference support; \(^h\) reference primary care; \(^n\) Chi-squared statistic; \(^d\) reference Army

Table 4-16. Regression parameters stratified by treatment, adjusted for all covariate effects, and reported based on study relevance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cephalosporin strata</th>
<th>Parameter(SE(^a))</th>
<th>(\chi^2)</th>
<th>p-value</th>
<th>HR(^b)</th>
<th>95%CI(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48,070</td>
<td></td>
<td>-0.101(0.029)</td>
<td>12.15</td>
<td>&lt;.001</td>
<td>0.90</td>
<td>0.85, 0.96</td>
</tr>
<tr>
<td>Days supply</td>
<td></td>
<td>0.410(0.184)</td>
<td>2.21</td>
<td>&lt;.026</td>
<td>1.51</td>
<td>1.05, 2.16</td>
</tr>
<tr>
<td>Occupation, direct (^g)</td>
<td></td>
<td>0.686(0.279)</td>
<td>6.04</td>
<td>&lt;.014</td>
<td>1.99</td>
<td>1.15, 3.43</td>
</tr>
<tr>
<td>Gender, male</td>
<td></td>
<td>0.253(.281)</td>
<td>0.081</td>
<td>&lt;.369</td>
<td>1.29</td>
<td>0.74, 2.34</td>
</tr>
</tbody>
</table>

\(^a\) standard error; \(^b\) hazard ratio; \(^c\) confidence interval; \(^g\) reference support; \(^n\) Chi-squared statistic; \(^d\) reference Army
Table 4-17. Regression parameters stratified by provider specialty, adjusted for all covariate effects, and reported based on study relevance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Secondary care strata</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N=14,854</td>
<td>Parameter(SE\textsuperscript{a})</td>
<td>$\chi^2$</td>
<td>p-value</td>
<td>HR\textsuperscript{b}</td>
<td>95%CI\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>Tx, quinolone\textsuperscript{d}</td>
<td>1.591(0.271)</td>
<td>34.61</td>
<td>&lt;.001</td>
<td>4.91</td>
<td>2.89, 8.34</td>
<td></td>
</tr>
<tr>
<td>Occupation, direct\textsuperscript{g}</td>
<td>0.256(0.198)</td>
<td>1.68</td>
<td>&lt;.196</td>
<td>1.29</td>
<td>0.88, 1.91</td>
<td></td>
</tr>
<tr>
<td>Days of Supply</td>
<td>0.024(0.005)</td>
<td>16.63</td>
<td>&lt;.001</td>
<td>1.024</td>
<td>1.012, 1.036</td>
<td></td>
</tr>
<tr>
<td>Antibiotic indication, GI/GU\textsuperscript{e}</td>
<td>0.468(0.204)</td>
<td>5.27</td>
<td>&lt;.022</td>
<td>1.60</td>
<td>1.07, 2.38</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} standard error; \textsuperscript{b} hazard ratio; \textsuperscript{c} confidence interval; \textsuperscript{g} reference support; \textsuperscript{n} Chi-squared statistic; \textsuperscript{d} reference cephalosporin; \textsuperscript{e} reference URI

Table 4-18. Regression parameters stratified by provider specialty, adjusted for all covariate effects, and reported based on study relevance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary care strata</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N=85,961</td>
<td>Parameter(SE\textsuperscript{a})</td>
<td>$\chi^2$</td>
<td>p-value</td>
<td>HR\textsuperscript{b}</td>
<td>95%CI\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>Tx, quinolone\textsuperscript{d}</td>
<td>0.155(0.125)</td>
<td>1.54</td>
<td>&lt;.215</td>
<td>1.17</td>
<td>0.91, 1.50</td>
<td></td>
</tr>
<tr>
<td>Occupation, direct\textsuperscript{g}</td>
<td>0.501(0.127)</td>
<td>15.55</td>
<td>&lt;.001</td>
<td>1.65</td>
<td>1.29, 2.12</td>
<td></td>
</tr>
<tr>
<td>Branch, Marines\textsuperscript{c}</td>
<td>0.535(0.193)</td>
<td>7.67</td>
<td>&lt;.0056</td>
<td>1.71</td>
<td>1.17, 2.50</td>
<td></td>
</tr>
<tr>
<td>Days of Supply</td>
<td>0.155(0.125)</td>
<td>66.79</td>
<td>&lt;.001</td>
<td>1.018</td>
<td>1.013, 1.022</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.021(0.007)</td>
<td>8.79</td>
<td>&lt;.003</td>
<td>1.021</td>
<td>1.007, 1.035</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} standard error; \textsuperscript{b} hazard ratio; \textsuperscript{c} confidence interval; \textsuperscript{g} reference support; \textsuperscript{n} Chi-squared statistic; \textsuperscript{d} reference cephalosporin; \textsuperscript{c} reference Army
### Table 4-19. Regression parameters stratified by occupation, adjusted for all covariate effects, and reported based on significance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Direct strata</th>
<th>Support strata</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=35,576</td>
<td>Parameter(SE(^a))</td>
<td>(\chi^2) (n) p-value</td>
</tr>
<tr>
<td>Tx, quinolone(^d)</td>
<td>0.473(0.164)</td>
<td>8.37 &lt;.004</td>
</tr>
<tr>
<td>Provider, specialty care(^h)</td>
<td>0.786(0.172)</td>
<td>20.81 &lt;.001</td>
</tr>
<tr>
<td>Branch, Marines(^e)</td>
<td>0.677(0.227)</td>
<td>8.85 &lt;.003</td>
</tr>
<tr>
<td>Days of Supply</td>
<td>0.027(0.006)</td>
<td>20.86 &lt;.001</td>
</tr>
</tbody>
</table>

\(^a\) standard error; \(^b\) hazard ratio; \(^c\) confidence interval; \(^h\) reference primary care; \(^n\) Chi-squared statistic; \(^d\) reference cephalosporin; \(^e\) reference Army

### Table 4-20. Regression parameters stratified by occupation, adjusted for all covariate effects, and reported based on significance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Support strata</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=65,239</td>
<td>Parameter(SE(^a))</td>
</tr>
<tr>
<td>Tx, quinolone(^d)</td>
<td>0.526(0.148)</td>
</tr>
<tr>
<td>Provider, specialty care(^h)</td>
<td>0.947(0.150)</td>
</tr>
<tr>
<td>Antibiotic Indication, GI/GU(^e)</td>
<td>0.545(0.149)</td>
</tr>
<tr>
<td>Days of supply</td>
<td>0.018(0.002)</td>
</tr>
<tr>
<td>Age</td>
<td>0.029(0.007)</td>
</tr>
</tbody>
</table>

\(^a\) standard error; \(^b\) hazard ratio; \(^c\) confidence interval; \(^h\) reference primary care; \(^n\) Chi-squared statistic; \(^d\) reference cephalosporin; \(^e\) reference URI
Table 4-21. Model selection for objective 3

Model Selection Summary

<table>
<thead>
<tr>
<th>Model</th>
<th>-2logLa</th>
<th>L-ratio(df)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 2</td>
<td>8644.503</td>
<td>121.290(18)</td>
</tr>
<tr>
<td>Model 3</td>
<td>8523.213</td>
<td>p-value &lt;.001</td>
</tr>
</tbody>
</table>

*a -2 log likelihood; b likelihood ratio(degrees of freedom)*

* Adjusted for model covariates; group 1 = cephalosporin, group 2 = quinolone

Figure 4-6. Hazard function stratified by treatment group*
Figure 4-7. Plotted treatment hazard ratio at 10-day intervals

<table>
<thead>
<tr>
<th>Interval</th>
<th>p-value</th>
<th>HR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 10</td>
<td>.001</td>
<td>1.62</td>
<td>1.31, 2.01</td>
</tr>
<tr>
<td>11 – 20</td>
<td>&lt;.001</td>
<td>1.67</td>
<td>1.30, 2.14</td>
</tr>
<tr>
<td>21 – 30</td>
<td>.005</td>
<td>1.43</td>
<td>1.07, 1.91</td>
</tr>
<tr>
<td>31 – 40</td>
<td>.274</td>
<td>1.24</td>
<td>0.85, 1.81</td>
</tr>
<tr>
<td>41 – 50</td>
<td>.889</td>
<td>1.04</td>
<td>0.60, 1.81</td>
</tr>
<tr>
<td>51 – 60</td>
<td>.956</td>
<td>1.01</td>
<td>0.31, 3.21</td>
</tr>
</tbody>
</table>
Figure 4-8. Treatment hazard ratio at three selected intervals

<table>
<thead>
<tr>
<th>Interval</th>
<th>p-value</th>
<th>HR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 25</td>
<td>0.004</td>
<td>1.38</td>
<td>1.11, 1.73</td>
</tr>
<tr>
<td>26 - 35</td>
<td>&lt;.001</td>
<td>1.74</td>
<td>1.49, 2.04</td>
</tr>
<tr>
<td>36 - 59</td>
<td>0.886</td>
<td>1.01</td>
<td>0.60, 1.65</td>
</tr>
</tbody>
</table>
* 1 = support, 2 = direct

Figure 4 - 9. Hazard function stratified by military occupation*
* Group 1 = Marine Corps; Group 2 = Army

* Group 1 = Air Force; Group 2 = Army

* Group 1 = Navy; Group 2 = Army

Figure 4–10. Hazard function stratified by branch*
Figure 4 - 11. Hazard function stratified by provider specialty *

* 1 = primary care, 2 = specialty care
*Stratified by treatment, quinolone group

<table>
<thead>
<tr>
<th>Days</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.03</td>
</tr>
<tr>
<td>3</td>
<td>1.11</td>
</tr>
<tr>
<td>5</td>
<td>1.18</td>
</tr>
<tr>
<td>7</td>
<td>1.26</td>
</tr>
<tr>
<td>10</td>
<td>1.39</td>
</tr>
<tr>
<td>14</td>
<td>1.59</td>
</tr>
<tr>
<td>30</td>
<td>2.70</td>
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Figure 4–12. Most frequent days of quinolone days of supply supply risk estimates
* 10 year interval; 20 year interval; 30 year interval; 40 year interval

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<th>Interval (yrs)</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
</tr>
</thead>
<tbody>
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<td>HR</td>
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<td>1.43</td>
<td>1.72</td>
<td>2.05</td>
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</tbody>
</table>

Figure 4–13. Age interval risk estimates
* Group 1 = URI; Group 2 = ST/BI
* Group 1 = URI; Group 2 = GI/GU

Figure 4-14. Hazard function stratified by antibiotic indication*

* Group 1 = enlisted, 2 = officers

Figure 4-15. Hazard function stratified by military grade*
* 1 = females, 2 = males

Figure 4-16. Hazard function stratified by gender*
* Group 1 = Black; Group 2 = White
Figure 4-17. Hazard function stratified by race

* Group 1 = Other; Group 2 = White

* 1 = no steroid, 2 = steroid
Figure 4-18. Hazard function stratified by steroid use
CHAPTER 5
DISCUSSION

**Objective 1**

Estimate the risk of tendon rupture from quinolone antibiotics use, relative to cephalosporin antibiotic use, while adjusting for relevant risk factors and accounting for time at risk.

This is the first study to demonstrate in a military population an association between quinolone use and an increase in this physically debilitating injury. The incidence of tendon rupture was 0.43% in the quinolone treated group and 0.26% in the cephalosporin group. The resulting risk ratio of the two treatment groups in terms of tendon rupture occurrence, while adjusting for other relevant risk factors, revealed that active duty personnel dispensed a prescription for a quinolone antibiotic were 1.65 times more likely to incur a tendon rupture during the 60-day post-exposure study interval.

It is helpful from a public health and prevention standpoint to assess, in the quinolone exposed group, how much of the total risk of tendon rupture is actually due to quinolone exposure. In this study, 39% of the cases of tendon rupture that occur in individuals prescribed quinolones may be due to quinolones. More specifically, 100 of the 255 cases of tendon rupture, in the quinolone-exposed group, can be directly attributable to being prescribed a quinolone medication. This further translates into 168 cases of tendon rupture per 100,000 quinolone users.

The absolute difference between the two treatment groups is 166 cases per 100,000 personnel. In other words if all the quinolone users were instead prescribed cephalosporins 166 cases of tendon rupture might have been avoided. This information is particularly important because patients presenting with an infectious disease must be treated. The increase in the risk of tendon rupture seen in this study from quinolone use affects the decision to prescribe a
quinolone or cephalosporin if both are equally indicated. The reduction in unit readiness and cohesiveness caused by 166 to 168 tendon injuries requiring surgery and followed by long-term rehabilitation may be prevented by treating patients with cephalosporins instead of quinolones where appropriate, and by paying more attention to the specific adverse event risk factors and time line presented in this study.

Most of the studies examining the relationship between quinolone use and tendon rupture have been conducted in older populations. In two case-control studies (Van der Linden 2002, 2003), the relative risk of tendon rupture from quinolone use varied from 7.1 for those over the age of 60, to 4.3 for patients between 60 and 79, and 20.4 for those patients aged 80 and older (19, 20). The discovery of a robust finding of an increase in risk for patients ranging from 18 to 60 years old has not been previously reported. Larger relative risks in other studies may emanate from two probable areas. The first concerns advancing age, which has consistently been found to increase the risk of tendon rupture. Consequentially, age as a risk factor for tendon injury, will be reiterated as a meaningful result of this study in discussion of Objective 4. Next, is the fact that previous studies used a randomly assigned non-treatment control group for comparison while the present study utilized personnel who were treated with a class of antibiotics with similar indications for use as quinolones. By definition, the present study’s cephalosporin control group and quinolone group were both being treated for an infectious disease of some type. This study may have resulted in a better risk estimate, when compared to other comparable studies because the infectious diagnosis was effectively controlled by sample selection, while other studies ignored this possible effect modifier.

The use of quinolone antibiotics cannot and should not be eliminated from clinical use due to their importance in treating a variety of medically important conditions. What can be done is
to modify their use based on a more patient specific approach. This patient specific approach, which will be outlined in the discussion to follow, has the potential to reduce the incidence of a serious injury that not only takes military personnel out of their unit for long periods of time, but also may inflict life long morbidity on the affected person.

**Objective 2**

Investigate whether the risk of tendon rupture from quinolone use varies over the 60-day post exposure interval.

Exposure to quinolone antibiotics was shown in Objective 1 to increase the risk of tendon ruptures. Objective 2 seeks to analyze the model in order to provide the most accurate risk estimate. This is done by testing the proportional hazards assumption to determine if the risk of tendon rupture is varying over time. The proportional hazards model controls for the effect of time at risk prior to the consideration of the association between the predictor variables and the outcome variable. This model assumes that there is no interaction between time at risk and the predictor variables. In this study, the variability of the risk is verified by a significant exposure by time interaction term. This informs us that the initial risk estimate may be misleading because the risk is changing over the study period.

In order to increase the precision of the risk estimate the piecewise regression model, which entails breaking the 60-day study period in several pieces was utilized. This method restores the proportionality of the proportional hazards model. The resulting risk estimates, of 1.38, 1.74, and 1.01 occurring between days 1 to 25, 26-35, and 36 to 59 respectively, show that the risk of tendon rupture from quinolone use is changing over the 60-day post exposure interval and that the maximum risk is higher than 1.65.

This endeavor to identify time at risk variability is important for several reasons. First, it reveals that traditional risk estimates found in the literature are likely conservative in nature
because they fail to assess the true effect of time on the risk of tendon rupture. Second, it shows that the effect of time at risk on exposure can be quantified in the absence of medication strength or blood levels even when exposure is defined in a dichotomous fashion. Third, this analysis allows the identification of a risk ‘time-line’ that is beneficial in truly understanding how quinolone use effects the occurrence of tendon ruptures that may be useful in informing clinical practice for the purpose of increasing troop readiness.

**Objective 3**

Identify the period of maximum risk and average induction period within the study interval.

The term induction period is a more precise epidemiologic term to explain the ‘lag’ or post exposure follow-up time in this study. Induction period is the time from causal action until disease initiation, thus it has a definite biologic connotation. In this study, it is defined by risk. It is the time from the dispensing of a prescription for a quinolone to the increase in risk of tendon rupture when compared to the cephalosporin group. The literature on this topic points to a sequence of action of various causes that can lead to a ruptured tendon. Quinolone use is one postulated causal factor. Specifically, this study is not dealing with a general induction period for tendon rupture but with the induction period related to quinolone use, which includes the induction periods for the other component causes.

If only one analysis is conducted, using a single exposure period where the time window is misclassified (e.g. too long or too short) and may or may not contain the relevant window where risk is maximized, information concerning the time relation between exposure and outcome may be misleading. In this study, the estimated hazard ratio is 1.65 over the entire 60-day post-exposure period. The 60-day period is based on an assumption of the actual time at risk taken from previous studies on quinolone use. This study period surely contains portions of time when
the risk of tendon rupture is small or absent. This misclassification of the time at risk leads to the attenuation of the risk estimate during the relevant time at risk period.

Traditionally, epidemiologists will select a set of induction time assumptions and estimate the exposure effect for each interval. The peak risk estimate would then be assumed the closest to the true effect. If the set of induction time assumptions provide a pattern of effects “i.e” rising then falling, the middle of the largest risk estimate interval would be the best estimate of the induction period (76). The assumption of the time at risk from the beginning of exposure drives the selection of the study period. If a study period is selected that is different from the true time at risk, the resulting exposure measure is a misclassified version of the true exposure. This exposure misclassification will reduce the size of the risk estimate and under estimate the risk of tendon rupture from quinolone use.

By using the survival analysis technique of graphing the hazard function of the quinolone-exposed group, it allows for the more precise matching of the true time at risk with the assumed study time at risk period. This leads to a better maximum risk estimate and a better representation of the induction period.

The hazard function allows the identification of the time in days, post quinolone exposure that the quinolone effect on tendon ruptures is at its zenith. Creating three time intervals using piecewise regression, restores the proportional hazard violation, identifies the best risk estimate, and reveals the induction period. It also adjusts for the effects of other model covariates.

The average induction period starts at day one, and lasts until approximately day 35 after receiving a prescription for a quinolone. This coincides with the hypothesized etiology related to quinolone induced tendon ruptures where tendon weakening begins to occur upon the initial dose and lasts for an unknown amount of time after the cessation of therapy. The best estimate of
maximum risk, in a military population, is an increase of 74% compared to cephalosporin use, and occurs on average, between days 26 through 35. The risk model that includes three different intervals during the 60-day study period is statistically better than using a single 60-day post treatment model. The improvement in fit is modest when the 95% confidence intervals are scrutinized, as there is considerable overlapping in the risk estimates for the 60-day and three-piece models. Additional analysis is needed in this area to pinpoint the induction period with more precision. Further research will utilize the boot-strap statistical method to develop the most likely range of average induction periods which will a more statistical precision to estimation of the average induction period.

The classification of an average induction period has great value when conveyed to health care providers as it lends itself to the patient counseling process. Patients who will be taking quinolones can be counseled that physical exertion should be reduced for up to 35 days after exposure begins. This counseling may effectively help decrease tendon rupture cases. This can be particularly important because the negative effects of the infection for which they are receiving treatment will tend to subside before the time at risk for tendon rupture does. Soldiers, sailors, airmen, and marines will be back at work and undergoing normal physical fitness training after the infection related complications subside. Results from this study suggest a reduction in physical exertion for a longer period after quinolone therapy is may be indicated.

Objective 4

Identify other major risk factors that increase an active duty military individual’s risk of tendon rupture.

Tendon ruptures often require surgery and result in long periods of rehabilitation. The ability of this study to identify risk factors in a contemporary population that is diverse in terms of demographics and physical demands is extremely important. These results give the health
care provider more specific information that aids them in treating their patients in a way that will help avoid this debilitating condition. This in turn will help increase readiness in military units across the Department of Defense. Taken as a whole, the important independent risk factors from this study paint a picture of a physical demanding environment, advancing age, and longer exposure to quinolones, as contributing to more tendon ruptures.

The occupation of military personnel is an important contributor for tendon rupture. Military members who have more physically demanding jobs are 53% more likely to have a tendon rupture when compared to support personnel. This dove tails nicely with the finding that Marines are 65% more likely than Army personnel to develop a tendon rupture. The Marine Corps, have a higher proportion of their members involved in more physically demanding work than the other services. Marines typically rely on the Navy for certain support, transportation, and medical services.

These two situations support the notion that military personnel engaged in more physically demanding occupations are more susceptible to musculoskeletal injuries. This supports the recommendation that military personnel prescribed a quinolone antibiotic to treat their infection, and are classified as having a physically demanding occupation should be given a longer period of reduced physical exertion (up to 35 days) to avoid tendon ruptures or other musculoskeletal injuries. These high-risk patients should be screened for the use of an alternative antibiotic such as a cephalosporin, if possible.

One of the key findings from Lum (2002) is the impact to the military from the finding that tendon ruptures are more frequent as military personnel advance in age(3). This study reinforces those findings and extends them by quantifying a 2% increase in risk for every year older a service member ages. A typical 20-year military career increases a service member’s risk of
tendon rupture by 43%. This is a prominent finding due to the reality that senior leaders from both the NCO and Officer Corps, are at a higher risk than junior personnel when involved in similar occupations or physical exertion. The long recovery time required post tendon rupture requires that senior leaders be taken away from their units for long periods. This kind of disproportionate risk between junior and senior personnel can reduce readiness, as there are less senior leaders available to step in when one is undergoing a long rehabilitation phase during tendon rupture recovery.

A question often asked by clinicians is whether a shorter length of treatment will lead to a lower risk of adverse events while longer treatment duration leads to a higher risk of adverse events. This study suggests that longer length of treatment with a quinolone is associated with a higher risk for tendon rupture when compared to treatment with cephalosporins. Every day of medication therapy results in a 2% increase in risk. A typical 3-day regimen for a urinary tract infection has a 6% increase while a 30-day regimen for prostatitis carries a 72% increase compared to treatment with cephalosporins. These findings should encourage health care providers to ensure they are prescribing the minimum length of treatment. Extra days of unneeded quinolone treatment may expose patients to an unnecessary increase in risk.

Another category of patients that should be monitored more closely are those referred for secondary or specialty care. These patients are 2.4 times more likely to experience a tendon rupture when compared to patients who are seen and treated by primary care providers. This may be seen through the lens of a Berkson’s bias explanation where by people with multiple conditions or risk factors are over represented in the secondary health care provider’s patient population(77-79). Generally, the literature supports the notion that persons referred to secondary health care providers are more likely to be sicker than patients who are seen and
treated by primary care providers (80). The result is that referred patients have more, and a wider array, of health problems, including musculoskeletal injuries than non-referred patients. In this study, it is not related to longer treatment regimens or an older patient clientele as both primary and secondary patients have comparable days of supply and age values. This information should alert secondary care providers to be vigilant to the fact that rare adverse events, like tendon ruptures from quinolone use, are more likely to happen in their patient population. The risk is compounded if a secondary health care provider is seeing an older patient or one that has a physically demanding military occupation or one that may require treatment with a quinolone.

The main infectious disease diagnoses with indications for quinolone use can be broadly broken into upper respiratory tract infections (URI), gastrointestinal/genitourinary (GI/GU), and soft tissue/bone infections (ST/BI). Of these three divisions, only GI/GU approaches the threshold of being an important high-risk group for tendon rupture. Patients who are prescribed a quinolone for a GI/GU infectious diagnosis have an approximately 25% increase in their likelihood of experiencing a tendon rupture compared to patients with URIs. While the increase in risk is low, it should be followed-up in later studies because the type of infectious disease diagnosis may help identify patients who are at increased risk for musculoskeletal injuries. These patients may benefit from a different antibiotic or longer periods of reduced physical exertion post quinolone treatment.

**Limitations**

The M2 query software system that was used to recall results from the Military Health System clinical data repository has not been extensively used for research purposes. Because of this, there have been no published peer-reviewed investigations into the validity of the data. A comparison of the data with paper records was not possible due to the expansiveness of the Military Health System. Consequently, patient information that was not entered into the
Another limitation related to the inability to compare the database records with the paper patient record is the occurrence of ‘rule-out’ entries for tendon rupture. The rupture of a tendon is a serious injury that would necessitate continued management by the military health care system. Patients identified in this study by having a diagnosis for a tendon rupture were required to have more than one diagnosis entry to limit possible misclassification error. There is no reason to assume that the occurrence of ‘rule-out’ diagnoses would favor one treatment group over the other.

A significant limitation of naturalistic observational designs is the lack of randomization. The absence of randomization produces the potential for selection bias, which may lead to any differences between the two treatment groups to be the result of this systematic error that is unrelated to treatment. Because of the large sample size, the two groups differ in many characteristics. Characteristics that are different at baseline between treatment groups and are related to tendon ruptures are days of supply, military occupation, age, provider specialty, military branch, and diagnosis leading to antibiotic treatment. Multivariate analysis was used to attenuate the confounding produced by selection bias on the primary predictor variable. The measurement and inclusion of important aspects of this population related to their demographics and health care surrounding their being treated with antibiotics was accomplished in order to adjust for pre-existing differences between subjects in the two treatment groups. This
multivariable analysis helps to identify and control for the affect of selection bias, which enhances the confidence in the results.

Even though the implementation of an observational study design is a limitation, it is also an asset. The results of an observational study still provide a realistic estimate of the risk of tendon rupture in the real world day-to-day military, with potential effect modifiers identified and adjusted for in a multivariable model. Specifically, randomized clinical trials comparing the risk cannot be conducted on quinolone induced tendon ruptures because of the large sample size required to find a noteworthy result from an outcome with such a small incidence in the population. To study adverse events, which occur in less than 1% of the population, like tendon ruptures, observational studies are uniquely well suited to provide meaningful results.

The two treatment groups in this study came from an active duty military population. Military Personnel are screened prior to entry for congenital or chronic maladies that may render them unable to perform active duty service. On average military personnel are more physically fit, than their civilian counterparts(82). These and other differences between active duty military and civilian communities may limit the generalizability of the obtained point estimates from this study to the US Military.

Military members, who seek out medical care, usually present at the local medical facility during sick call hours in the early morning prior to the start of their duty day. If the treating physician decides that they are indeed ill, he or she may provide the patient with quarter’s paperwork. Quarter’s paperwork informs the patient’s unit that he/she is ill and requires a modified duty schedule. These modifications range from light duty (no physical training) to confinement to quarters for a specified length of time. This may affect the timing of the occurrence of tendon ruptures post quinolone exposure. Quinolone antibiotics likely weaken
tendon tissue resulting in a higher probability of a rupture occurring during physical exertion. When a patient receives quarter’s he/she is less likely to participate in physically demanding actions. This may lower the incidence of tendon rupture immediately following the patient’s diagnosis prompting quinolone therapy. The practice of giving quarters may reduce the risk of tendon rupture from quinolone use and result in a longer induction period.

**Recommendations**

1. Health care providers should consider the use of cephalosporin antibiotics in place of quinolones if indicated or if the clinical presentation allows.

2. If quinolones are required to treat a patient’s infection, make certain that the length of treatment is optimized to reduce the risk of tendon rupture.

3. When prescribing a quinolone, the health care provider should understand a reduced duty profile might be necessary for up to 35 days after starting therapy.

4. Military members who are prescribed quinolones should be asked about their military occupation specialty. Patients with physically intensive occupations should be given profiles to avoid extreme physical exertion for up to 35 days after starting therapy.

5. Secondary and specialty health care providers should be made aware of the increased vulnerability of their patient population to tendon ruptures. Information concerning alternate antibiotic medications with similar indications and the need for a reduction in extreme physical exertion should be provided.

6. Care should be taken to develop an individual risk profile, including age, occupation specialty, indication for quinolone use, length of treatment, and branch of service, for each patient when prescribing quinolones. Patients at high risk should be prescribed a different antibiotic if possible or given reduced duty status if quinolone use is necessary.

**Conclusion**

This is the first study to identify an increased risk of tendon rupture from quinolone use in a large demographically diverse population. The risk is elevated upon the first day of therapy and increases incrementally each day until it reaches its maximum between days 26-35. The risk of tendon rupture is augmented by advancing age, length of treatment, and working in a physically demanding environment. These findings are important as they provide evidence that a
significant portion of this physically debilitating injury is potentially avoidable by identifying specific risk factors and incorporating them into the overall patient care plan.

Injuries are the single most significant medical impediment to the U.S. Army’s ability to project and sustain a healthy and medically protected force(1). This dissertation identifies quinolone antibiotics and other independent characteristics as risk factors for a debilitating type of musculoskeletal injury. It also recommends ways to reduce the lost duty time and shortened military careers that result from tendon ruptures.
LIST OF REFERENCES


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42. Stahlmann R: Children as a special population at risk--quinolones as an example for xenobiotics exhibiting skeletal toxicity. Arch Toxicol 2003; 77(1):7-11


52. Kashner TM: Agreement between administrative files and written medical records: a case of the Department of Veterans Affairs. Med Care 1998; 36(9):1324-36


71. Cox D, Oakes D: Analysis of Survival Data. 1984


74. Jewell N: Statistics for Epidemiology. 2004

75. CDC: Epi Info(TM)Database and statistics software for public health professionals. 2004

76. Rothman KG, S: Modern Epidemiology. 1998; 2nd Edition:297-300


BIOGRAPHICAL SKETCH

Patrick M. Garman was born on March 15, 1968 in Troy, Ohio. The second of three boys, he grew up in Miami County Ohio and graduated from Miami East High School in 1986. He earned his B.S. in pharmacy from Ohio Northern University (ONU) in 1991. He was also a member of the Bowling Green University Army Reserve Officer Training Corps (ROTC) and received a commission as a 2nd Lieutenant in the Medical Service Corps.

Upon graduating in May 1991 with his degree in pharmacy, Patrick entered the active duty Army. After completion of his Officer Basic Course, he spent his initial two assignments serving as the director of pharmacy at Fort Irwin, California and Baumholder Health Clinic Baumholder Germany. During his tour of duty in Germany, he was selected to the Army’s Long-Term Health Education and Training program (LTHET) which afforded him the opportunity to attend The Ohio State University and attain the Doctor of Pharmacy degree.

His first assignment after graduation in July 2000 was as the Director of Pharmacy in the 121st General Hospital, Seoul Republic of South Korea. From there, he was assigned in July 2002 as the Pharmacy Consultant to the Commander of the United States Army Medical Material Agency (USAMMA), Fort Detrick Maryland. During this assignment, he was the point man for the Department of Defense in the distribution of the Anthrax and Small Pox vaccines for Operation Enduring Freedom (Afghanistan) and Operation Iraqi Freedom (Iraq). This tour of duty ended with another selection into the Army’s LTHET program and his assignment at the University of Florida, College of Pharmacy’s graduate program in Pharmacy Health Care Administration to pursue Doctor of Philosophy degree.

Upon completion of his Ph.D. program, Patrick will be assigned to the U.S. Army Military Vaccine Agency (MILVAX) as the Deputy Director for Scientific Affairs. MILVAX is located at the Army Surgeon Generals Office in Falls Church, Virginia. He has attained the rank of
Lieutenant Colonel during his 16 years of active duty service. Patrick has been married to Kim Garman for 15 years and they have four children: Keye, age 10; Kenna, age 9; Bella, age 19 months; and Kitrick, age 2 months.