The Capstone Committee for Mark L. Jacques, M.D. Certifies that this is the approved version of the following capstone:

GOUT: An Aeromedical Clinical Practice Guideline

Committee:

Robert Johnson, MD, MPH, MBA, Supervisor

Richard Jennings, MD, MS

Prashanth Sunkureddi, MD

Dean, Graduate School

GOUT: An Aeromedical Clinical Practice Guideline

by

Mark L. Jacques, M.D.

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Dedication

This work is dedicated to all of the men and women who have served in and will serve in the United States military during the war on terror. It is especially dedicated to the pilots and crew members of the United States Army who have inspired me to pursue a career in Aerospace Medicine.

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I would like to formally acknowledge all of my capstone committee members for their guidance and support with this project.

GOUT: An Aeromedical Clinical Practice Guideline

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Mark L. Jacques, MD, MPH

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Supervisor: Robert Johnson

Through the completion of this capstone project, I am demonstrating the significance of gout in the United States of America, and in particular in the arena of aerospace medicine today. I have created a current clinical practice guideline that allows for the efficient delivery of excellent acute and long term care to flight personnel afflicted with gout. This guideline addresses diagnosis, management, follow up and prevention strategies for dealing with gout. Standardization of management of this disease throughout the aerospace community will have multiple benefits for flight personnel with gout, aeromedical practitioners and the general public.

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CHAPTER 1: INTRODUCTION

The role of the aeromedical specialist truly exemplifies that of a public health practitioner. The aeromedical practitioner, through providing individually focused and tailored medical care to air crew members, helps to ensure the safety and well being of the greater public at large. Healthy pilots and crew members help ensure the safety of passengers in aircraft as well as the public on the ground below. The role of the aeromedical specialist is not to prevent crewmembers from flying, but to ensure that they are doing so safely. There are well established guidelines and aeromedical guidance for dealing with a variety of acute and chronic health conditions in crew members. These guidelines are designed to allow crew members to continue on with their aviation duties despite medical issues, as long as the safety of the greater public is not placed at risk. These guidelines help in determining not only which medical conditions are compatible with aviation duties, but also which forms of medical therapy are also compatible with flight status. There is currently a shortage of aeromedical guidance when it comes to dealing with crew members afflicted with gout. Gout is a type of inflammatory arthritis that ultimately results from elevated uric acid levels in the serum. With the appropriate conditions, the uric acid precipitates out of the serum, depositing as monosodium urate crystals in various locations of the body. This deposition of crystals causes the acute and chronic signs and symptoms of the disease. The clinical symptoms of this disease as well as the various therapies available for treating this disease can potentially affect a crew member's ability to carry out their aviation duties safely. Therefore, appropriate medical management of these crew members through the institution of appropriate practice guidelines is needed and important.

A. HISTORICAL PERSPECTIVE

Gout is a common inflammatory arthritis with a rich and extensive history. The appearance of gout dates back to the early Egyptians. It is one of the first diseases to be recognized as a clinical entity, first identified in 2640 BC. Hippocrates in the 5th century BC referred to gout as the unwalkable disease because its often associated lower extremity involvement makes it difficult to walk during an acute attack (Nuki & Simkin, 2006). He also noted an association between gout and lifestyle, referring to it as the arthritis of the rich; an idea that is still perpetuated today. Six centuries later, Galen was the first to describe soft tissue masses, or tophi, as a component of gout and recognized a hereditary component to the disease. Later on, in the 6th century AD, a Byzantine physician, Alexander of Tralles, is credited with being the first to use the drug colchicine as a specific treatment for gout (Nuki & Simkin, 2006). In 1679, Antoni van Leeuwenhoek was the first to describe the microscopic appearance of crystals derived from a gouty tophus. In the late 1700's, uric acid was identified as the crystal constituent of gouty tophi, as well as certain types of kidney stones. Both of these entities can be seen as part of the clinical presentation of chronic gout (Nuki & Simkin, 2006). As a result, the link between gout and uric acid was being solidified. In 1847, a method for the measurement of uric acid in the urine and in the serum, known as the thread test, was introduced. This was the effort of Sir Alfred Baring Garrod and was the first clinical chemical test ever to be employed. Years later, in 1931, his son, Sir Archibald Garrod, was among the first to suggest that gout was the result of some inborn error in one of the many metabolic pathways of the human body. Finally, in 1988 George Hitchings and Gertrude Elion were awarded the Nobel Prize in medicine for the development of the xanthine oxidase inhibitor, allopurinol. Allopurinol would prove to be an extremely beneficial drug in the management and treatment of gout (Nuki & Simkin, 2006).

Gout is interesting not only from the perspective of its own rich history but also for the possible role it played in the history of the United States of America. For example, William Pitt was a British statesman during the time of the American Revolution. He believed that the Americans were true sons of England and should be treated as such. He felt the Americans should not be taxed unfairly without their consent. Unfortunately, Pitt suffered from gout which caused him to be absent from Parliamentary proceedings from time to time. It was during two of these very absences that the English Parliament passed the Stamp Act of 1765 and the Tea Act of 1773, both of which Pitt opposed. These two well-known Parliamentary actions inflamed the Americans and helped fuel their desire for and commitment to a free state. In addition, there are reports of a number of the founding fathers of the United States having been afflicted with gout and how this may have helped to promote solidarity among them. Benjamin Franklin, Thomas Jefferson and John Hancock were among the most famous historical American figures known to have suffered from gout. The rich history of this disease is easily apparent, but the importance of it extends beyond history into the present (Nuki & Simkin, 2006).

B. LITERATURE REVIEW

The literature search for this capstone project consisted of an examination of current peer-reviewed primary care, preventive medicine, aeromedical and rheumatologic sources. A focus was placed specifically on the most recent data in terms of epidemiology and treatment; data from the last 5 years was targeted. Resources were obtained through the use of the University of Texas Medical Branch electronic library including OVID, PubMed, and the Cochrane Library. Aeromedical data was obtained through the use of the Aerospace Medical Association (AsMA) and American Society of

Aerospace Medicine Specialists (ASAM) websites. The Federal Aviation Administration (FAA) and the National Transportation Safety Board (NTSB) resources were additionally researched in developing this capstone. United States Army Aeromedical recommendations regarding this topic were also reviewed.

CHAPTER 2: CHARACTERIZATION OF GOUT

A. EPIDEMIOLOGY

Today, the significance of this disease cannot be overstated. Gout is the most common inflammatory arthritis among men in the United States, and it affects more than 1% of the total adult population in this country. Additionally, the prevalence of this disease is increasing. This increase is being seen, not just within the confines of the United States, but rather worldwide (Mikuls & Saag, 2006). Epidemiologic studies show that between 1978 and 1996, the age-adjusted and sex-adjusted annual incidence rate of gout in the United States rose from 20.2/100,000 persons to 45.9/100,000 persons. Of note, this was an increase in the rate of primary gout. Therefore, this increase cannot be explained by an increase in the use of medications, such as certain diuretic classes, that are known to contribute to the development of gout (Saag & Choi, 2006). More recently, gouty arthritis accounted for almost 4 million outpatient office visits in the United States in 2002. The prevalence has nearly doubled over the last two decades, and currently gout affects more than 5 million Americans (Lee et al., 2006). The National Health and Nutrition Examination Survey III (NHANES III) described the overall prevalence of self-reported, physician diagnosed gout to be 2% in women older than 50 years and men older than 30 years (Eggebeen, 2007).

This increase in disease prevalence is multifactorial, with both genetic and environmental components. It is due to a combination of lifestyle choices, changing demographics of our population and an increased prevalence of medical conditions and treatments that contribute to the development of gout. These factors include sex, age, diet and certain medication use, among others. As a result, certain demographic groups are at a higher risk for the development of gout based on the presence of many of these

behavioral, biological and medical risk factors (Saag & Choi, 2006). In terms of sex, men are at an increased risk for the development of gout compared to women. However, it should be noted that the sex distribution becomes more equalized with increasing age. It is known that estrogen has a uricosuric effect, meaning that it facilitates excretion of uric acid via the kidneys. This equalization of distribution across sexes with increasing age may be due to the diminishing effects of estrogen in women with increasing age (Saag & Choi, 2006). In terms of age, the prevalence of gout increases with increasing age, in both men and women. Additional findings regarding the epidemiology of gout discovered through NHANES III showed the prevalence increase with increasing age resulted in 9% of men and 6% of women older than 80 years of age being affected (Saag & Choi, 2006). In terms of diet, there are certain foods and drinks that have been identified as increasing one's risk of developing disease. Alcohol has classically been linked to gout. Research shows that alcohol intake is proportional to the risk of gout. There are, however, differences among the classes of alcohol, with beer having the greatest risk for the development of gout. Its high purine content increases urate production in the body, and it also decreases normal urate elimination via the kidneys. Distilled liquor poses the next greatest risk, followed ultimately by wine. In fact, some studies show that minimal to moderate consumption of wine poses no risk at all (Choi et al., 2004a). Studies also show that consumption of certain purine-rich foods such as meat increases the risk of developing gout. The intake of high-purine vegetables has much less significant impact. Also, the intake of dairy products appears to be associated with a decreased risk for developing gout (Choi et al., 2004b). Many of these dietary risk factors are quite common in the Western diet of today. As a result, there are studies that show a marked disparity in the rates of gout between Asia, where the traditional diet is relatively low in purines, and Western Europe, where it is higher (Choi et al., 2004b). However, as much of the world begins incorporating more elements of a Western type diet, an increasing amount of gout is beginning to be seen. Examples of this include

increasing rates of gout in areas such as Taiwan (Chen et al., 2003) and New Zealand (Klemp et al., 1997). In terms of medication use, increased use of certain diuretics for blood pressure control and increased use of low dose aspirin therapy for the promotion of cardiovascular health may be adding to the increasing prevalence of gout (Saag & Choi, 2006). The mechanisms of these medications leading to an increased risk of gout will be discussed later. These contributing factors are many of the factors that we see increasing in frequency across our society as a whole in this country. All of these risk factors ultimately will result in elevated serum uric acid levels in the population. As the pathophysiology of gout is discussed, the relevance of this increase in serum uric acid will be apparent.

Studies show that hypertension has a positive correlation with hyperuricemia. This correlation has even been shown among the pediatric population. As many as 50% of untreated hypertensive persons have hyperuricemia. Many times the hyperuricemia may even precede the hypertension (Saag & Choi, 2006). A recent study, which has accounted for several confounding variables, such as dietary factors, obesity, diuretic use and renal failure, has confirmed that hypertension is associated with an increased risk for gout (Choi et al., 2005b). Additionally, it has also been shown that hyperuricemia is a risk factor for the presence of coronary artery disease (Wannamethee et al., 1997). Hyperuricemia has likewise been shown to be an independent risk factor for acute myocardial infarction (Krishman et al., 2006).

Beyond the scope of the disease itself, data indicate that the quality of treatment may be suboptimal in up to one-half of the patients with this disease (Mikuls et al., 2005). This is the case despite the fact that patients with gout have been shown to have more comorbidities than a comparative group of patients with osteoarthritis. Therefore, this is a patient population that we may want to maximize treatment.

These trends in the epidemiology of gout help to contribute to the importance of this disease in the field of aerospace medicine. This connection and relevance will be discussed later on.

B. PATHOPHYSIOLOGY

The pathophysiology of gout is well established and well understood on a macro level. Current research is optimizing our understanding of the intricacies of this disease and its effects. The root cause of the disease is an increased concentration of uric acid in the blood stream known as hyperuricemia. Hyperuricemia has a direct relationship with the risk for gout. Alterations in the normal physiological metabolism of purines can lead to increased uric acid concentrations. As purines are some of the basic building blocks of DNA and RNA, they are essential to our well-being and homeostasis. The breakdown of purines, through catabolism, results in the production of uric acid. As the uric acid is removed from the body through excretion, this allows a mechanism for the removal of nitrogenous wastes from the body; a necessary process (Pillinger et al., 2007). The amount of uric acid in the body is a balancing act. It is dependent upon dietary intake of purines, internal synthesis of purines and the excretion of purines from the body (Choi et al., 2005b). The state of hyperuricemia is defined by a level of serum uric acid greater than 6.5 milligrams per deciliter. Certain exogenous factors alluded to earlier can lead to a state of hyperuricemia. These include high purine diets, excessive consumption of alcohol, and the use of certain classes of medications such as aspirin and diuretics (Eggebeen, 2007). Hyperuricemia can result from overproduction of uric acid in the body; this accounts for about 10% of individuals with hyperuricemia. More commonly, it results from underexcretion of uric acid from the body via the kidneys; this accounts for about 90% of the individuals with hyperuricemia. You can also have a combination

of these two states (Choi et al., 2005b). Most patients with primary or idiopathic gout have a genetically reduced capability to excrete uric acid through the kidneys. This reduced excretory capacity, in and of itself, is usually not enough to cause gout. It is well established that only a small minority of people with hyperuricemia (serum uric acid level greater than 6.5 mg/dl) develop clinical manifestations of gout (Underwood, 2006). Under certain conditions, the possibility exists for the uric acid to precipitate out of the serum and deposit in various tissues of the body in the form of monosodium urate (MSU) crystals. This precipitation of urate crystals can be seen with a rapid fluctuation in the serum uric acid level of a patient. This shift can be an increase, as is seen when a patient suffers an acute gouty attack after the ingestion of a purine-rich meal. This shift can also be a decrease in the serum uric acid level, as is often seen when the hospitalization and resulting dietary restriction of a patient results in an acute gouty attack. The formation and deposition of these crystals is influenced by several factors including pH level in the body, temperature in the body and hydration status of the body (Eggebeen, 2007). Urate crystals can deposit in the joints, soft tissues and solid organs, such as the kidneys. It is this deposition of crystals, in combination with the host response to these crystals, which leads to the clinical manifestations of gout. The mere presence of crystals alone will not lead to symptoms. The body's own inflammatory response must be initiated for symptoms to occur. The symptoms encountered are dependant upon where these crystals deposit and can include arthritis, tophi formation and kidney abnormalities.

There has been a fair amount of recent research to attempt to discover the purpose of uric acid in the body. Recent evidence suggests that uric acid may be essential to maintaining the proper functioning of the immune system. Evidence points to the possibility of uric acid serving as a necessary substance which helps the body produce a full and adequate immune reaction in response to foreign invaders (Shi et al., 2003). Additionally, an interesting reason that uric acid has been the subject of ongoing research is that most mammals maintain very low levels of this substance in the serum. Primates,

including humans, tend to have higher levels of uric acid due to the absence of the enzyme uricase. This enzyme is present and functional in most mammals. It converts uric acid to a substance called allantoin, thereby decreasing the uric acid level in these mammals. The enzyme is also present in birds, although the selective advantage of this is not fully understood. In humans and the great apes this enzyme has become dysfunctional and inactivated. The uric acid as a result achieves much higher levels. Scientists have suggested that the loss of this enzyme and the corresponding higher levels of uric acid are actually beneficial to humans. They propose that uric acid may be a key to helping to maintain blood pressure during upright walking (Watanabe et al., 2002). There is experimental animal evidence to support this hypothesis (Mazzali et al., 2001). Additionally, given the likely link between uric acid and blood pressure regulation, scientists are currently investigating the hypothesis that lowering uric acid could potentially lower blood pressure levels.

Considerable research has also been conducted to investigate why certain individuals' kidneys fail to maintain appropriate levels of uric acid. It is known that the handling of urate by the kidneys involves multiple steps. "Glomerular filtration of the urate is followed by proximal tubule resorption of 99% of the filtered load, then resecretion of approximately 50% of the resorptate" (Pillinger et al., 2007, p. 218). There is one final resorption before excretion occurs. The end result is that only about 10-14% of the filtered uric acid is ultimately excreted in the urine (Terkeltaub et al., 2006). We do not yet know a great deal about the step of "resecretion." This is in fact the step that is the cause of the approximately 90% of hyperuricemia in the population. On the contrary, much information has been learned about the initial proximal tubule resorption of urate. The transporter protein responsible for this step and its corresponding gene have been identified (Pillinger et al., 2007). This protein is called URAT1. This protein is the target for drugs that are employed to increase excretion of uric acid through the kidneys

(Enomoto et al., 2002). Conversely, drugs that block this protein will result in an increased serum uric acid level.

The pathophysiology of how the deposition of monosodium urate crystals causes symptoms in gout has been extensively studied. Monosodium urate crystals promote inflammation in the body. They initiate the cascade of an ultimately self-limited response from the body to the presence of the crystals. This is accomplished through a variety of mechanisms. The recognition of the naked crystals via certain receptors which normally are involved in the recognition of foreign infectious pathogens is the primary trigger of the inflammatory response (Cronstein & Terkeltaub, 2006). This recognition then leads to ingestion of the crystals by the phagocytic cells. The crystals also serve as a site for the activation of the body's complement system, an innate defense system of the body usually reserved for protection against foreign substances. These processes result in the formation of a variety of chemical substances that further propagate the inflammatory response and recruit additional inflammatory cells to the site of the monosodium urate crystal deposition (Cronstein & Terkeltaub, 2006). The end result is the influx of neutrophils into the area. As already stated, acute gouty attacks are self-limited; they will eventually resolve, even without any treatment (Cronstein & Terkeltaub, 2006). This is most likely a result of, at least in part, the influx of monocytes that follows the influx of neutrophils during a gouty attack. These monocytes which are proinflammatory cells in response to the monosodium urate crystals eventually mature into macrophages. These macrophages are actually anti-inflammatory in response to the crystals, and they also ingest dying inflammatory neutrophils. In this way, it is believed that the macrophages are a key element in the self-limited nature of the body's inflammatory response during an attack of gout (Cronstein & Terkeltaub, 2006).

Overall, gout appears to be an easy clinical entity to treat; the etiology is well characterized, its pathophysiology is well understood, the disease is easily diagnosed and

effective, inexpensive therapies are available (Eggebeen, 2007). Despite these features of the disease, gout remains a significant health problem in the United States today.

C. Symptoms & Clinical Presentation

Gout can present with a classic acute gouty attack resulting from monosodium urate crystal deposition in a joint; but it can also present as chronic tophaceous gout. More precisely, gout is a spectrum of disease and can be described in four stages: asymptomatic hyperuricemia, intermittent acute gout, intercritical gout and advanced chronic tophaceous gout (Sunkureddi et al., 2006).

Asymptomatic hyperuricemia is common in the population of the United States. It may be present for years or even decades without any clinical manifestations. Most people with asymptomatic hyperuricemia do not progress to symptomatic gouty disease. Equally important regarding serum uric acid levels is that up to 20% of patients suffering an acute gouty attack may have serum uric acid levels considered to be normal.

Acute gouty attacks occur with rapid onset when the monosodium urate crystals precipitate out of the serum and into a joint. Although attacks are self-limited and may last for only a few days, they are extremely painful and can be completely debilitating and incapacitating. Additionally, in some cases it can take up to six weeks for symptoms to completely resolve. Acute attacks of gout typically affect only one joint, and in 50% of initial gouty attacks the metatarsophalangeal joint of the great toe is involved (Sunkureddi et al., 2006). This involvement of the great toe is formally known as podagra. With subsequent attacks, polyarticular involvement may be seen with the ankles, knees, wrists and hands becoming involved. During an attack, the affected joints are usually painful, swollen and erythematous. These symptoms usually begin in the early morning hours, when the body core temperature is lowest. Symptoms usually peak

within 24-48 hours after onset. There may be accompanying fever and elevated white blood cell count. An acute attack of gout can additionally present with acute bursitis, tenosynovitis or cellulitis (Eggebeen, 2007). Patients may be mistakenly treated for infectious cellulitis, thereby delaying the appropriate treatment of gout. The clinician needs to have a high index of suspicion for gout if a patient with a presumed cellulitis shows no improvement with antibiotic therapy.

Between acute attacks, patients will usually experience asymptomatic periods. These can be very long periods of time with no symptoms of the disease. These periods are called the intercritical periods (Sunkureddi et al., 2006). The fact that patients may experience such long symptom-free periods, combined with the fact that attacks are self-limited, may be a key contributing factor as to why care for the management of gout can often be suboptimal. Because of these facts, patients may not be so eager to seek care for attacks. Additionally, patients may be likely to demonstrate low adherence to therapy in the absence of discrete guidelines and management plans put forth by care providers.

With disease progression, the acute attacks usually become more frequent eventually resulting in chronic tophaceous gout. Chronic gouty arthritis may share similar musculoskeletal symptoms with rheumatoid arthritis. Tophi, or clusters of urate crystals in the soft tissues of the body, may also be present and would distinguish the clinical picture of gout from that of rheumatoid arthritis. Tophi can form anywhere in the body. Common sites for tophi include the elbow, wrist, fingers and pinna of the ears (Sunkureddi et al., 2006). Finally, with chronic gout, urate crystal deposition can occur in the kidneys, as well. This can lead to complications such as urate kidney stones, nephropathy and ultimately renal failure (Sunkureddi et al., 2006).

During an acute attack of gout, it is important that other conditions that may appear similar are ruled out. In particular, it is most important to ensure that a patient suspected of having an attack of gout is actually not suffering from septic arthritis. This is a condition where there is a bacterial infection within the affected joint. The

presentation of gout and septic arthritis can be similar, in that each may have joint pain, swelling, fever, erythema and an increased white blood cell count. The important difference is that an acute attack of gout is self-limited whereas an episode of septic arthritis can be extremely damaging to the joint involved and can have serious long-term sequelae. An episode of septic arthritis is in fact a true medical emergency. There are times when the only way to differentiate between septic arthritis and acute gout is through an arthrocentesis or "tapping the joint."

In order to aid clinicians in the diagnosis of gout, classification criteria have been proposed by the American College of Rheumatology. An arthrocentesis which shows monosodium urate crystals in joint fluid or the presence of tophi confirmed with examination are in and of themselves diagnostic of gout (Wallace et al., 1977). There are, however, ways a clinician can diagnose gout without direct examination of monosodium urate crystals from a patient. The presence of six of twelve other findings is also qualifying for a diagnosis of gout. These criteria include: 1) more than one attack of acute arthritis, 2) maximum inflammation developed within one day, 3) monoarthritis attack, 4) redness observed over affected joints, 5) first metatarsophalangeal joint pain or swelling, 6) unilateral first metatarsophalangeal joint attack, 7) unilateral tarsal joint attack, 8) tophus, 9) hyperuricemia, 10) asymmetric swelling within a joint on x-ray, 11) subcortical cyst without erosion on x-ray, and 12) monosodium urate monohydrate microcrystals in joint fluid during an attack (Wallace et al., 1977). The usefulness of these criteria to the general practitioner is supported by the fact that "several surveys suggest that arthrocenteses for crystal identification in gout are rarely performed except by rheumatologists" (Chen & Schumacher, 2006, p. 171). While it is possible to make a diagnosis of gout without an arthrocentesis using these criteria, the eventual performance of an arthrocentesis to identify the presence of monosodium urate crystals in the synovial fluid of the patient suspected of having gout is important for several reasons. Most importantly, there are several diseases which can mimic gout such as pseudogout,

rheumatoid arthritis and septic arthritis. The treatments of these diseases are very different, and without crystal identification the practitioner can not be certain that the patient truly has gout. Also, crystal identification can be performed with a relatively small amount of fluid which can be obtained relatively easily with the use of imaging-guided arthrocentesis. Finally, if the patient truly has gout, it becomes important to also address the additional health issue for which the patient may be at risk. These may not be risks associated with the other diseases which may mimic gout.

CHAPTER 3: TREATMENT OF GOUT

The treatment and management of gout involves treatment of both acute gouty attacks as well as the chronic management of gout and gout prophylaxis. Treatment and management also involves both the medical treatment of the disease as well as patient education regarding the importance of risk factor modification and appropriate lifestyle changes.

Treatment of acute gouty attacks is aimed at the reduction of the inflammatory reaction of the body to the monosodium urate crystals, thereby reducing pain, swelling and other symptoms of the attack. When it comes to the management of gout, there is a paucity of adequate placebo-controlled trials comparing the different treatment options available (Cronstein & Terkeltaub, 2006). Despite this, common treatment protocols have evolved. Anti-inflammatory drugs are extensively employed in an attempt to control the inflammation present. Non-steroidal anti-inflammatory drugs, or NSAID's, such as ibuprofen, naproxen and indomethacin are often used as the first line of therapy for the treatment of an acute attack of gout. There is data to support the use of generic NSAID's to provide relief of symptoms of an acute attack within 24 hours of their administration (Cronstein & Terkeltaub, 2006). As an additional benefit, NSAID's are also relatively inexpensive compared to other lines of treatment. Clinical studies suggest that there is not a significant difference between agents in this class of medication in terms of efficacy and effectiveness (Cronstein & Terkeltaub, 2006). One should keep in mind that although the use of these agents is quite common today, their use is not completely free of risk and treatment should be tailored to the individual patient. In particular, one must consider the risk of gastrointestinal side effects when employing these medications. Complications such as gastric and duodenal ulcers, as well as gastrointestinal bleeding, are well associated with the use of NSAID's. While all

NSAID's carry a risk of gastrointestinal complications, COX-2 inhibitors such as celecoxib may be better tolerated and should be considered, especially in patients with a history of gastrointestinal symptoms associated with previous NSAID use.

Beyond the NSAID agents, corticosteroids have also been employed in the treatment of acute gouty attacks. There is evidence that patients with contraindications to treatment with NSAID's showed good results when treated with short-term systemic corticosteroids for an acute attack of gout. Studies have shown benefits to both oral and intramuscular systemic corticosteroid use. Additionally, corticosteroids have also been used locally; intra-articular use of these agents by themselves has shown success in the treatment of monoarticular attacks (Cronstein & Terkeltaub, 2006). An added benefit of the use of intra-articular steroids is that the practitioner can simultaneously obtain synovial fluid for microscopic evaluation for the presence of MSU crystals. The procedure can be both diagnostic and therapeutic at the same time. The use of corticosteroids only within the affected joint will additionally help avoid some of the systemic side effects of oral or parenteral steroid use. Also, in an attempt to recruit the anti-inflammatory effect of endogenously produced corticosteroids, adrenocorticotropic hormone (ACTH) has been used successfully in patients with acute gouty attacks.

Colchicine is another alternative for the treatment of an acute gouty attack, particularly in those patients who are unable to receive treatment with NSAID's or corticosteroids. Colchicine is a medicine derived from the autumn crocus plant and has been used for over 2000 years as an anti-inflammatory medication (Cronstein & Terkeltaub, 2006). This medication has a number of different anti-inflammatory properties, thereby reducing and suppressing the body's normal response to monosodium urate crystals in the tissues. Oral colchicine appears to be most effective when it is administered during the first 24 hours of an acute attack. Typically, at presentation, the patient is given 0.6 milligrams of colchicine orally. This dose is then repeated hourly. The most common and dose-limiting side effects of colchicine are gastrointestinal, in

particular nausea, vomiting and diarrhea. The hourly dosing is continued until the patient begins to experience these side effects or until between six and eight doses have been administered (Cronstein & Terkeltaub, 2006). Most patients will experience a significant reduction in symptoms with the use of this type of colchicine regimen. This medication does have other, potentially more serious complications, such as bone marrow suppression, and therefore must be employed with caution and only when appropriate (Cronstein & Terkeltaub, 2006). Because of the common occurrence of side effects and resulting poor compliance by patients using this medication, currently colchicine is rarely used for the treatment of acute attacks of gout. Colchicine also has a role in the chronic treatment of gout; this aspect of the medication will be further discussed below as the chronic treatment of gout is reviewed.

Overall, there are several agents available for the treatment of an acute attack of gout. In general, these agents are targeted at controlling the body's inflammatory response to the presence of the monosodium urate crystals. Although there are few scientific studies comparing these therapies, all appear to exhibit effectiveness and therefore have a role in the treatment of this disease. Additionally, they all have characteristics that may limit their use in certain patient populations. The practitioner must tailor the therapy to the individual needs, benefits and risks of each patient.

The chronic treatment and management of gout involves the use of medication employed in an attempt to reduce the frequency and severity of future attacks. Equally as important is the concept of patient education and lifestyle changes in an attempt to improve modifiable risk factors for gout that may be present.

Colchicine can be used as a chronic prophylactic treatment to reduce the recurrence of acute attacks. An oral dose of "0.6 milligrams daily is effective and is usually continued until the serum uric acid level is below 6.0 milligrams/deciliter" (Sunkureddi et al., 2006, p. 42). Dosing may need to be adjusted in patients with renal insufficiency. The practitioner must be aware of the possibility of rhabdomyolysis and

painful axonal neuromyopathy with the chronic use of colchicine (Sunkureddi et al., 2006).

In attempting to control gout chronically, it is very important to address the issue of hyperuricemia and attempt to normalize the patient's uric acid level. The employment of urate-lowering agents is known to potentially reverse urate deposition in tissues, in addition to reducing the serum uric acid level (Sunkureddi et al., 2006). General recommendations for the use of these agents include a patient with tophi present, 2 or more acute attacks of gout per year, renal calculi or erosive arthritis seen on radiography (Sunkureddi et al., 2006). Allopurinol inhibits xanthine oxidase, a key enzyme in the metabolic pathway of urate production. The inhibition of this enzyme therefore blocks the production of urate in the body, lowering the serum uric acid level. It should be noted that when allopurinol therapy is started, usually at 300 milligrams per day orally, there is a risk of precipitating an acute attack of gout. It is recommended that the patient beginning allopurinol also be given prophylactic therapy with one of the NSAID's or colchicine (Sunkureddi et al., 2006). Allopurinol should never be initiated during an acute attack of gout. Also, if a patient is on chronic allopurinol therapy and experiences an attack of gouty arthritis, the allopurinol should be continued, not stopped. Allopurinol is contraindicated in patients on azathioprine therapy because of the risk of profound bone marrow suppression when these drugs are used in combination (Sunkureddi et al., 2006). Also, it must be noted that the use of allopurinol carries the risk of allopurinol hypersensitivity syndrome. This syndrome includes rash, hepatitis, eosinophilia, fever, renal failure and possible death. This risk is increased in patients with underlying renal insufficiency and those taking diuretics. Therefore, allopurinol should be started at a lower dose and titrated up slowly in these patients (Sunkureddi, et al., 2006). In addition, allopurinol can be titrated to achieve the desired effect of serum uric acid level below 6.0 milligrams per deciliter. Some patients will require daily doses of between 600 milligrams and 800 milligrams daily. Of course, as the dose is increased, so is the risk of

side effects. In addition to xanthine oxidase inhibitors, uricosuric agents have also been used in the chronic treatment of gout. These agents, typically probenecid, lower the serum uric acid level through the increased excretion of uric acid via the kidneys. This type of agent is used less frequently given that the relative efficacy is less compared to allopurinol. Additionally, if the presence of urate nephropathy, urate nephrolithiasis, gouty tophi, or a glomerular filtration rate (GFR) of less than 60 milliliters per minute is noted probenecid should be avoided and the patient should be treated with allopurinol (Sunkureddi, et al., 2006). Usually patients will continue on these medications indefinitely (Sunkureddi et al., 2006).

In addition to medical therapies, the practitioner must address the alteration of any modifiable risk factors that may be present in the patient presenting with gout. Education about the importance of diet in preventing recurrences is key. Patients should be instructed to limit or avoid specific foods with high purine content. In particular, purine-rich meats and seafood should be avoided. In contrast, purine-rich vegetables appear to be much less risk. Intake of dairy products may actually be preventive of attacks. Patients should be educated about the effects of drinking alcohol and how different types of alcohol can have a different impact on their gout. It has been shown that beer has the greatest effect, followed by distilled spirits, followed by wine. Patients should also be encouraged to decrease their weight and BMI when appropriate, as obesity increases the risk of gout. Decreased weight will often lead to a corresponding decrease in serum uric acid levels. Some studies show that a reduction in weight of 10 pounds can decrease one's risk of gout by as much as 30% (Saag & Choi, 2006). However, for most patients, lifestyle modification alone is usually not enough to obtain control of this disease. Also, the patient's medication history should be reviewed and potential precipitators of gout should be noted and changed when possible. In particular, the use of low dose aspirin and diuretic use should be addressed, as these increase one's risk for gout. Both appear to decrease uric acid secretion from the body via the kidneys, thereby increasing the

serum uric acid (Saag & Choi, 2006). Higher dose aspirin does not appear to pose this same risk. Finally, as previously discussed, hypertension has been shown to increase one's risk for the development of gout. Therefore, treatment should be instituted to normalize the patient's blood pressure. Of course, the use of diuretics should be minimized when possible, as these are an independent risk factor for hyperuricemia. On the contrary there are certain medications, used for concerns other than gout, which have been shown to reduce serum uric acid. For example, the use of losartan, an angiotensin II receptor antagonist used for hypertension, exerts a urate-lowering effect via its action within the renal tubule (Mikuls & Saag, 2006).

CHAPTER 4: AEROMEDICAL RELEVANCE & CONCERNS

The role of the aeromedical specialist truly exemplifies that of a public health practitioner. Beyond the impact on the general public health, gout is an important medical issue in the field of aviation medicine. Acute flares of the disease can be incapacitating, severely limiting an aviator's ability to carry out his or her duty or even excluding them from flight duties altogether. Joint involvement and limited range of motion as a result of gout can impair an aviator's ability to properly operate an aircraft as well as effectively evacuate an aircraft in the event of an emergency. Long term sequelae of the disease, such as kidney stones and renal impairment may not be compatible with established requirements for flight duties. Additionally, the reality of caring for crew members with gout in remote locations during long deployment must be considered in the realm of military aviation. Some of the recognized therapies for the treatment of the illness may also be incompatible with flight status. Based on the epidemiology of this disease, it is likely that aerospace medicine specialists will be seeing more patients with gout in their practices. The data show us that the disease has a markedly higher prevalence in men compared to women. The Federal Aviation Administration's (FAA) active airmen count by sex shows the following as of March 4, 2008. In terms of first class airmen, there are 101,239 men and 4,532 women. In terms of second class airmen, there are 117,051 men and 6,586 women. Finally, in terms of third class airmen, there are 322,888 men and 23,566 women. It is easily apparent that this patient base is heavily skewed toward men. Gout not only has a predilection for men, it has a tendency to be found in older age groups. The aviation world is seeing a growing number of older pilots. Many foreign countries do not recognize 60 years old as the age limit for commercial pilots. The United States has recently followed suit, as it has increased the age limit for scheduled air carrier pilots to 65 years old. Therefore, it is reasonable that a

standard be set for the treatment and management of this disease in those individuals with flying duties. Proper management of these patients will not only be directly beneficial to them, but it will also benefit the public at large as it will further promote safe air travel. This will benefit people throughout the country, regardless of whether or not they have the disease, and regardless of whether or not they hold aviation duties.

First of all, it is important to state that a diagnosis of gout is not incompatible with an air crew member continuing their aviation duties. On the contrary, properly diagnosed and well managed gout should not prevent the airmen from continuing on with aviation duties. There may need to be temporary restriction from duties during acute attacks and certain therapies may be limited to crew members only when they are not carrying out their aviation duties. The point of proper and timely treatment, however, will be to help ensure a long and product aviation career for those crew members found to have gout.

Acute gouty attacks are intensely painful; some have said they are among the most painful conditions that patients can experience. Even as Hippocrates described gout as the unwalkable disease in the 5th century BC, it was already known that this disease could have a significant impact on the ability of those affected to carry out their normal activities. Because of this intense pain, as well as the other symptoms such as joint swelling and limited range of motion, resulting from the intense inflammatory reaction of an acute attack, air crew members should not be carrying out aviation related duties during an acute attack while these symptoms are present. Once the initial intensity of these symptoms is relieved and the crew member is no longer limited by them, a return to full aviation duties will be warranted, given that medications being used to control the disease are compatible with flight duties. Medications and their restrictions are discussed below.

The hierarchy of common treatments for gout has already been discussed. Some of these treatment options will impact the crew member's ability to safely carry out aviation duties more than others. When considering ability to carry out aviation duties

while on certain treatments, we must examine the side effects of these treatments and their ability to impair the skills needed for the safe operation of aircraft.

The non-steroidal anti-inflammatory drugs (NSAID's) are generally regarded as safe when taken in proper doses. The major negative effects of these drugs include gastroduodenal ulcer and the possibility of gastrointestinal bleeding. There use is acceptable for the treatment of gouty symptoms in crewmembers. Because they are generally employed during an acute attack, the symptoms of the acute attack itself would be the limiting factor in the crew member's ability to perform aviation duties rather than the use of the NSAID.

The use of corticosteroids carries with it its own risks and potential complications. Most notably with short term use, increases in blood sugar, hypertension, changes in mood and immune suppression leading to susceptibility to infection can occur. The FAA currently holds that the use of steroids, greater than 20 milligram equivalent of prednisone daily requires a deferral to the Aerospace Medical Certification Division (AMCD) (FAA, 2008). Therefore, the use of steroids greater than the 20 milligram equivalent of prednisone daily should incur a temporary grounding period, with a return to aviation duties after the discontinuation of the corticosteroid use. This would be an ideal situation to employ the use of intra-articular steroids for a monoarticular attack of gout. The side effects of systemic steroid administration could be avoided, a confirmatory arthrocentesis could be performed, and effective therapy could be delivered to the patient. The limiting factor in this scenario, of course, is the comfort level and ability of the practitioner to perform the procedure.

The use of allopurinol is acceptable to the FAA when used appropriately (Silberman, 2003). This is a valuable means of chronic control of gout in those who are experiencing frequent attacks.

Beyond the role of medication, it is imperative that the aeromedical practitioner address the issue of lifestyle modification, and other modifiable risk factors, with the

aircrew member affected with gout. It is important that a medication history be reviewed and that any medications that increase the risk for gout be identified and discontinued if possible. Specifically, the use of thiazide diuretics, most likely for blood pressure control, should be identified and a different antihypertensive medication should be employed. There are several medications acceptable to the FAA for treatment of hypertension. They include all Food and Drug Administration (FDA) approved diuretics, alpha-adrenergic blocking agents, beta-adrenergic blocking agents, calcium channel blocking agents, angiotension converting enzyme (ACE inhibitors) agents, and direct vasodilators. There are several agents (such as, reserpine, guanethidine, guanadrel, guanabenz, and methyldopa) which are not acceptable to the FAA (FAA, 2007). When employing antihypertensives, dosage levels should be the minimum necessary to obtain optimal clinical control. Medications should not be modified to influence the certification decision (FAA, 2007). Additionally, history of aspirin use should be examined. Low dose aspirin use has been shown to increase serum uric acid levels. This effect appears to be greater with low dose aspirin use than aspirin used at higher doses. Although, the risk of gout from the increase in uric acid seen with aspirin is yet to be determined, the clinician should consider the discontinuation of low dose aspirin use.

Dietary risk of gout should be discussed thoroughly with the airman. The contribution of diet to the development of gout should be clearly explained. The airman should be instructed to avoid, or at least limit, the consumption of purine-rich meats and seafood. Total protein intake and purine-rich vegetables appear to have no association with gout. Consumption of low-fat dairy products should be promoted as the risk of gout is decreased with increased dairy consumption (Choi et al., 2004b). Alcohol use must also be addressed. The role of alcohol as a risk factor for the development of gout should be reviewed with the aviator. It should be explained that beer consumption, and to a lesser extent hard liquor consumption, has been shown to increase one's risk for the development of gout in a dose-responsive manner (Choi et al., 2004a). The areas of diet

and alcohol intake are two areas that a motivated airman can have a significant impact in terms of overall reduction of the risk of further gouty attacks.

Another important modifiable risk factor that needs to be addressed with the crew member with gout is that of obesity. It is known that an increased BMI is associated with an increased risk for gout. Weight gain over time is associated with an increased risk for the disease, while weight loss appears to be protective. In one study, a weight loss of more than only 10 pounds was associated with 30% reduction in the development of gout (Choi et al., 2005a).

Finally, the importance of blood pressure must not be overlooked. The air crew member's blood pressure should be optimized, as it has been shown that hypertension is associated with hyperuricemia.

CHAPTER 5: DISCUSSION & CONCLUSION

There is an important and inherent link between aerospace medicine and the health and well-being of the public. For pilots, crewmembers, passengers and those on the ground maintaining safety in aviation is essential. An aspect of such safety is ensuring the health of airmen and treating disease in a standardized manner that will not affect their ability to perform their duties safely. It is important that we develop these standards given that in the realm of civil aviation there is a paucity of guidelines for the management of many diseases in flight personnel. Gout is one of those diseases where no guidelines currently exist.

There are several aspects of gout which make it important that a guideline be in place for the management of this disease. The aeromedical specialist must be aware of the pathophysiology and the growing burden of disease associated with gout. The practitioner must be familiar with the diagnosis of and management options available for gout. In terms of management, there are new options on the horizon. Febuxostat is a xanthine oxidase inhibitor that, unlike allopurinol, is metabolized by the liver which may be very beneficial to patients with renal disease (Pillinger et al., 2007). Additionally, rasburicase is a recombinant bacterial uricase that may prove effective in the treatment of gout (Pillinger et al., 2007). Finally, the treating specialist needs to also be aware of the growing linkages of hyperuricemia and other disease states such as coronary artery disease and hypertension.

The clinical guideline for the management of gout, which is the result of this capstone project, will serve to educate the aeromedical specialist about these issues and other aspects of the disease. It will be submitted to the American Society of Aerospace Medical Specialists for potential use by aeromedical providers throughout the country.

Its use will improve the quality and standardization of care provided to airmen with gout. This will ultimately improve the safety of the aviation community and the public at large.

APPENDIX A: AEROMEDICAL CLINICAL PRACTICE GUIDELINE

OVERVIEW:

Gout is a significant and growing problem within the United States today. It is currently the most common inflammatory arthritis among men and affects more than 1% of the total adult population in this country. It affects 2% of women over the age of 50 and men over the age of 30. The prevalence of the disease is increasing worldwide, as well as within the United States. The prevalence has nearly doubled over the last 20 years in this country. Gout now affects more than 5 million Americans and accounts for over 4 million outpatient office visits annually. The risk for gout increases with increasing age and, the disease affects more men than women across all age groups.

At the root cause of gout is an increase in the concentration of uric acid in the blood stream known as hyperuricemia. Hyperuricemia has a direct causal relationship with the risk for gout. As the catabolism of purines in the body lead to the formation of uric acid, the amount of uric acid in the body is dependant upon dietary intake of purines, internal synthesis of purines in the body and excretion of purines from the body. Most commonly, hyperuricemia results from underexcretion from the body rather than overproduction of uric acid. When hyperuricemia is present (a serum uric acid level greater than 6.5 mg/dl), the possibility exists for uric acid to precipitate out of the serum and deposit in various tissues of the body in the form of monosodium urate (MSU) crystals. The formation of these crystals is dependant upon several factors including pH, temperature and hydration status of the body, and only occurs in a small minority of people with hyperuricemia. It is the deposition of the MSU crystals that gives the clinical signs and symptoms of gout. These crystals can deposit in joints, soft tissues and solid

organs such as the kidneys leading to the corresponding clinical manifestations of arthritis, tophi formation and renal abnormalities.

An acute gouty attack occurs with rapid onset when the MSU crystals deposit within a joint. The crystal deposition initiates the inflammation cascade resulting in localized and systemic symptoms. An acute attack can be quite debilitating. The affected joints are usually extremely painful, swollen and erythematous. Some have described the pain of an acute gouty attack as some of the worst pain one can experience. Patients may also present with fever, bursitis and cellulitis. Symptoms usually peak within 24-48 hours after onset. Between acute attacks, patients usually have long asymptomatic periods. With disease progression, acute attacks may become more frequent and other manifestations of chronic hyperuricemia may become evident. These include the formation of soft tissue masses, or tophi, and kidney stones, nephropathy and possible renal failure resulting from urate crystal deposition in the kidneys.

Treatment of gout can be divided into acute and chronic management. Treatment of acute gouty attacks is aimed at reducing the inflammatory reaction of the body to the MSU crystal deposition. NSAID's such as ibuprofen, naproxen and indomethacin are often used as first line therapy. Additionally, systemic and local corticosteroids have been successfully employed in the treatment of acute gout, as has ACTH albeit less commonly. An important point to make is that the use of intra-articular steroids can be extremely beneficial in the treatment of a monoarticular attack of gout. It can deliver effective medicine while avoiding the side effects of systemic steroids; it also allows for the completion of a diagnostic arthrocentesis. Finally, colchicine has also been used for acute attacks of gout, particularly in those patients with contraindications to use of the other listed options. Chronic management of gout is first aimed at the modification of those modifiable risk factors that may be present. Patients should be instructed to avoid food and drink high in purine content. In particular, purine-rich meats and seafood, as well as beer and hard liquor should be avoided. Of note, purine-rich vegetables and wine

appear to have much less of an effect on the development of gouty attacks. Patients should also be encouraged to decrease their weight when appropriate as this can significantly reduce the risk for gout. Finally, the patient's medication history should be reviewed and the use of low-dose aspirin and diuretics should be minimized as these can cause hyperuricemia. In patients with 2 or more acute attacks per year, treatment with allopurinol, a urate lowering agent, should be considered. In patients with fewer occurrences, lifestyle modification and education alone can suffice.

AEROMEDICAL CONCERNS:

Acute attacks of gout can be extremely debilitating. The pain and inflammation involved can severely limit one's ability to function. The acute symptoms can limit ability to carry out flight duties because of the distraction from the pain and the systemic symptoms such as fever. Even when the acute pain is controlled, joint symptoms can limit the airman's ability to properly evacuate an aircraft when needed. As a result, flight duties should be restricted during an acute gouty attack until resolution of symptoms has occurred. When symptoms are resolved, without medications or on medications that are aeromedically acceptable such as ibuprofen and naproxen, the airman can be returned to flight duties. If more than 2 acute attacks occur annually, the airman should be considered for initiation of allopurinol therapy. Concerns regarding chronic effects of gout include renal abnormalities and restricted mobility secondary to the presence of gouty tophi.

MEDICAL WORKUP:

Diagnosis of gout can be made using the classification criteria put forth by the American College of Rheumatology. An arthrocentesis which shows monosodium urate crystals in joint fluid or the presence of tophi confirmed with examination are in and of

themselves diagnostic of gout (American College of Rheumatology). There are, however, ways a clinician can diagnose gout without direct examination of monosodium urate crystals from a patient. The presence of six out of twelve other findings is also qualifying for a diagnosis of gout. These criteria include findings such as hyperuricemia, redness observed over the affected joints and unilateral first metatarsophalangeal joint involvement. The one diagnosis that must be ruled out during an acute gouty attack is that of septic arthritis. Other diseases which cause monoarticular and oligoarticular arthritis, such as pseudogout and reactive arthritis, must also be considered.

Initial evaluation of gout in an aviator should not differ from the non-aviator. Work-up should include a thorough history and exam, focusing specifically on the presence of any modifiable risk factors for the development of gout. These include the airman being overweight, dietary habits, alcohol use and medication use. These should be addressed and the airman counseled accordingly. Laboratory examination should include a serum uric acid during an asymptomatic period as well as a urinalysis to search for evidence of any renal abnormality.

If the airman experiences less than 2 attacks per year or is well controlled on allopurinol and there is no evidence of chronic renal damage, the airman should be granted waiver for flight duties. The airman should continue to be followed for further developments of or worsening of this disease.

Follow up evaluations should include an annual serum uric acid level, basic metabolic panel, and a urinalysis.

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VITA

Mark L. Jacques, M.D. was born June 1, 1973 in Staten Island, New York. He is the son of Richard and Lorraine Jacques of Troy, New York. His high school education was completed in 1991 at La Salle Institute in Troy, New York. He then received a Bachelor of Science, summa cum laude, from Rensselaer Polytechnic Institute, in Troy, New York in 1995. Dr. Jacques then attended the State University of New York at Stony Brook School of Medicine, where he completed his Doctor of Medicine in 1999. He completed a residency in pediatrics at Winthrop University Hospital in Mineola, New York where he served as Chief Resident. He was certified by the American Board of Pediatrics in October 2004. Dr. Jacques joined the United States Army in July 2004, assuming the position of Flight Surgeon. He has since been stationed with 3-4 Assault Helicopter Battalion, 4th Infantry Division, serving at Fort Hood Texas and has deployed to Iraq for 12 months in support of Operation Iraqi Freedom. This capstone is the culmination of the completion of a Master of Public Health. Major Jacques currently remains on active duty with United States Army.

Permanent address: 111 Elmgrove Avenue, Troy, New York 12180

This capstone was typed by the author.