Naval Medical Center Portsmouth
Rheumatology Referral Guidelines

Diagnosis:	**Gout**

Clinic Name	Rheumatology
Clinic Phone Number	757-953-2160 or 2161
On Call Numbers	Duty Pager: 757-860-5702

1. Indications for Specialty Care:

- **Specifically refer for gout if:**
  - Uncertain of diagnosis or concern for an inflammatory arthritis (see inflammatory arthritis guidelines)
  - Urgent evaluation for monoarthritis (see below)
  - Difficult to control despite therapy and/or polyarticular gout
  - Prior allopurinol hypersensitivity
  - Patients on immunosuppressant medications as well as kidney transplant patients
  - Multiple co-morbidities such as severe heart failure

- Urgent evaluation for monoarthritis (one swollen joint). **Consideration needs to be first for an orthopedic evaluation if septic arthritis is in the differential diagnosis**. If other inflammatory arthritides such as crystalline arthritis (gout) needs to be considered then this should be arranged by a phone call to the duty Rheumatologist. Please see other causes of an acute red, hot and swollen joint below:
  - Crystalline arthritis: Pseudogout (CPPD)
  - Septic arthritis (can co-exist with gout < 2%)
  - Spondyloarthritis, Rheumatoid arthritis (or any connective tissue disease)
  - Trauma
  - Cellulitis
  - Palindromic Rheumatism

- **Gout can be managed by primary care without question.** However, due diligence is needed and these patients need routine follow-up and lab evaluation. There is a need to try and prove that the patient has gout. If patient does have gout then treat-to-target with a goal serum uric acid of less than 6.0 if on chronic urate lowering therapy. When patients are at goal this minimizes significant economic and clinical morbidity.

2. Quality Consult Criteria

When referring a patient, please include as much of the following information as possible (OK to cut and paste this into consult request)

1. Provisional diagnosis
2. Duration of Problem
3. Prior treatments
4. Current treatments/medications
5. Diagnostic studies obtained (imaging, labs, other tests, etc.)
6. Primary reason for consult
7. Use of referral guidelines

3. Diagnosis Definitions

- **Gout is a disease characterized by elevated serum urate concentration, with recurrent attacks of acute arthritis associated with monosodium urate crystals (MSU) in synovial fluid, but may also include tophi (typically painless nodular deposits of MSU crystals in and around tissues and around the joints) as well as interstitial renal disease and uric acid nephrolithiasis.**

- Symptoms occur when the excess uric acid, the result of inefficient excretion more commonly than overproduction, is deposited in restricted joint spaces.

- Gout arthritis is the most common cause of inflammatory arthritis in men over age 40 and it should not occur in premenopausal women. Gout does occur in post-menopausal women.

- **Gout Co-morbid Conditions:** Metabolic syndrome: obesity, diabetes, hyperlipidemia, hypertension, renal insufficiency, CHF, coronary artery disease. Gout is a primary risk factor for CAD and MI.

- The joints of the lower limbs are typically involved more often than upper limbs. **The first metatarsophalangeal (MTP) joint of the great toe is involved in > 50% of initial attacks and over time is affected in > 90% (this is termed podagral).** In order of frequency after the MTP joints are the instep, ankle, heel, knee, wrist, fingers and elbow.

- Gout and tophi have a predilection for cooler, acral sites, where the solubility of MSU crystals maybe diminished as a result of cooler temperatures. In addition, joints that have undergone degenerative changes provide a nidus that facilitates crystal formation.

4. Initial Diagnosis and Management

- The diagnosis is made by history and physical examination. **It is always important to aspirate an acutely inflamed joint and send the synovial fluid off for cell count, crystal examination, gram stain and culture.**

- There are four stages of gout:
  - **Asymptomatic Hyperuricemia**: Elevated serum uric acid level without gouty arthritis, tophi or uric acid nephrolithiasis. Up to 15% of these patients will eventually develop gout. In those who develop gout, most patients will have had 20 years of asymptomatic hyperuricemia before their first gout attack.
  - **Acute Gouty Arthritis**: A single joint is involved in 85% - 90% of patients (1st MTP in the foot is the most common initial joint involved and it is also called podagra), whereas up to 15% will have polyarticular involvement with their first attack. Attacks begin abruptly and reach maximum intensity within hours. The onset of attacks often occur during the night or early morning when the joint is the coolest. The affected joint becomes exquisitely painful, warm, red and swollen. A low grade fever may be present. The periarticular erythema and swelling may progress to resemble a noninfectious cellulitis termed “gouty cellulitis.” Early attacks often spontaneously resolve over 3-10 days. Desquamation of the skin overlying the affected joint can

occur with resolution of the inflammation.

- **Intercritical Gout**: This is the asymptomatic intervals between acute attacks of gout. Over 60% of patients will have a second attack within 1-2 years, whereas 5% to 10% may never have another attack ever.
- **Chronic Tophaceous Gout**: The development of subcutaneous, synovial or subchondral bone deposits of MSU crystals. Chronic gout is also characterized by permanent joint damage and typically is polyarticular.

Diagnosing Gout:

- **Try to make a crystal proven diagnosis and get X-rays.**
  - Reasons**:**
    - Hyperuricemia is found in gout and it is a risk factor, but it alone does not equal gout. Most hyperuicemics do not have gout.
    - A third of acute gout flares will have a normal serum uric acid and a third of polyarticular gout patients have a + Rheumatoid Factor (RF). Clinical presentation is not 100% specific for gout.
    - Chronic urate lowering therapy is lifelong and thus once it is started the patient is committed to lifelong therapy. Allopurinol hypersensitivity can be deadly.

  - Arthrocentesis:
    - Fresh synovial fluid or a tophus aspirate must be evaluated for the presence of MSU crystals. Aspiration during an acute attack has the highest yield, but synovial fluid from the knee during an intercritical period can also be diagnostic.
    - The intra or extracellular crystals are needle shaped and negatively birefringent (ye**ll**ow when para**ll**el) to the axis of a red compensator and blue when perpendicular).
    - The synovial fluid is inflammatory (typically 20,000 to 100,000 leukocytes) with a predominance of neutrophils.

  - Imaging:
    - Plain X-rays:
      - Soft tissue swelling around affected joint can be seen in acute attacks of gout.
      - In chronic gout, tophi and bony erosions can be seen and can often be diagnostic. Articular tophi produce irregular soft-tissue densities that are occasionally are calcified.
      - Bony erosions in gout appear “punched out” with sclerotic margins and overhanging edges, sometimes termed rat bite erosions. Joint space is typically preserved until late in the disease and juxta-articular osteopenia is absent.
    - Musculoskeletal Ultrasound:
      - Gout can show up as a superficial, hyperechoic band (deposition of urate crystals) on the surface of articular cartilage (“double contour sign”).
    - Dual Energy CT:
      - Two X-ray tubes with different voltages are aligned at 90 degrees to one another. This allows identification of urate crystal deposits because the chemical composition of uric acid causes lower attenuation of X-ray photons tracking through it in comparison to bone calcium.
      - The urate deposits can be easily separated from surround tissues with a high degree of sensitivity and specificity, which aids in the diagnosis of difficult cases.

5. Ongoing Management and Objectives

Primary treatment goal is to alleviate pain and improve quality of life. Please see acute and chronic gout therapies below.

1. Acute Gout Therapy:

Treatment Options	Drugs	Dosage	Common adverse effects	Considerations
NSAIDS (1st line)	All NSAIDS are effective Indomethacin (Drug of choice)	Oral 50 mg four times per day for 24-48hrs, then 50 mg three times per day; taper then discontinue after attack subsides. Or 75 mg twice a day	Headache, GI (pain, dyspepsia, heartburn, nausea).	Caution required for patients with PUD, active bleeding, anticoagulation or antiplatelet therapy, renal dysfunction, CKD, HTN, fluid retention, CHF or hepatic disease
Anti-gout agent	Colchicine	1.2 mg loading dose and 0.6 mg 1 hour later then 0.6 mg after 12hrs as needed, 1-2 times daily until symptoms resolve	GI (cramping, abdominal pain, nausea, vomiting and diarrhea)	Most effective within the 1st 36hrs of an attack Caution required for patients with renal dysfunction, CKD or hepatic disease** Avoid use with concomitant P450 3A4 and P-glycoprotein inhibitors*
Intra-articular steroids	Triamcinolone or methylprednisolone	40 mg for large joints, 10-20 mg for smaller joints and bursae	Post-injection flare, skin hypopigmentation, bleeding, pain, tendon rupture	Useful in the treatment of 1-2 involved joints or bursae. Effective within the first 24hrs of an attack in 90% of patients. Good choice in CKD patients
Systemic Corticosteroids	Prednisone Triamcinolone acetonide	0.5 mg/kg per day for 5-10 days or for 2-5 days then taper for 7-10 days. *Prednisone 40 mg po x 3 days the decrease by 5 mg every day until off (use 5 mg tablets so 8 tablets daily for 3 days then decrease by one tablet until off, dispense #60) 60 mg IM, can repeat once	GI (abdominal distension, ulcers, HTN, headache, insomnia)	Caution required for patients with DM, fluid retention (CHF), ongoing infection or increased infection risk, or PUD Rebound arthropathy may occur Good option in patients with CKD IA, IV and IM administration possible for patients who are NPO
Hormone (stimulates corticosteroid production)	Adrenocorticotrophic hormone (ACTH)	25-40 IU subcutaneously every 12 as needed (1-3 doses typical	Musculoskeletal, endocrine, metabolic, GI, cardiovascular, nervous system, dermatological effects, hypersensitivity reactions	Option for patients who are NPO Less effective in patients on long term oral corticosteroids therapy Short duration of action Much more costly than alternative therapies

*P450 3A4 and P-glycoprotein inhibitors including cyclosporine, clarithromycin, erythromycin, ketoconazole, itraconazole, disulfiram, HIV protease inhibitors, diltiazem, verapamil and grapefruit juice.

2. Prophylaxis: Medications used when starting chronic urate lowering therapy (ULT) to help prevent against flares when initiating chronic ULT and when making adjustments in the chronic ult.

- Anti-inflammatory medicines (can be used alone or in combination). Please consider co-morbid conditions and if appropriate for use. For example, colchicine can be used with Indocin. Start 5-7 days prior to initiation of chronic ULT.
    - **Colchicine: This is the prophylaxis agent of choice. Dose medication based on GFR.**
        - GFR > 60: colchicine 0.6 mg po bid (and if they can tolerate loose stools)
        - GFR 30-60: colchicine 0.6 mg po daily
        - GFR < 30: colchicine 0.6 mg every other day or 0.3 mg every day
        - When using colchicine chronically follow CBC and CK to screen for bone marrow suppression and reversible painful axonal neuromyopathy (elevated CK, proximal muscle weakness, peripheral neuropathy). These side effects more commonly occur in patients with renal insufficiency and also in patients also on cyclosporine.

- NSAIDs:
  - Use full anti-inflammatory dose
- Prednisone: Use lowest dose effective
  - Can be used < 10 mg/day when patients have contraindications to NSAIDs or colchicine

- Never use alone chronically without a urate lowering drug. Otherwise, urate continues to deposit in the joints, kidneys, and tissues. Eventually this causes end organ damage.
- Continue prophylaxis agents until:
  - 3-6 months after serum uric acid (sUA) goal of less than 6.0.
    - 3 months in patients at goal sUA without tophi
    - 6 months in patients at goal sUA with one or more tophi.

3. Urate Lowering Therapy Without Medications:

- **Low purine diet**: Avoid high purine meats; this can lower serum UA (sUA) by 0.5 mg/dl to 1 mg/dl. Dairy products are protective. Try and get daily protein in the form of non-fat or low-fat dairy products. Abstain from beer or alcoholic spirits. Wine in moderation (two 4-5 oz. servings per day) is not associated with gout. Stay hydrated.
- **Maintain normal body weight:** 15lb weight loss lowers sUA by 1.0-2.0 mg/dl.
- **Vitamin C**: 500-1000 mg per day. Lowers sUA by 0.5 mg /dl.
- **Other:**
  - Control HTN (alone this can decrease sUA levels) and avoid diuretics which can cause hyperuricemia unless clinically indicated for CHF, edema, etc.

4. Indications For Chronic Urate Lowering Therapy (ULT):

- Radiographic erosions
- More than 2-3 acute attacks within 1 to 2 years
- Renal stones (urate or calcium)
- Tophaceous gout
- Established gout with chronic kidney disease stage 2 or worse
- MSU proven gout, evidence on dual energy CT (NMCP rheumatology)

5. Chronic ULT:

- **Goal = sUA < 6.0**:
  - In order to deplete body stores of excess urate. Prevents disease progression. Can reverse soft tissue and joint damage. Urate lowering therapy is usually lifelong because you can't eliminate the primary cause of gout in most patients.
- **Body fluids are saturated with UA when sUA is > 6.8 mg/dl**:
  - UA precipitates in the tissues of the body and crystal deposition occurs.
- **When to start a ULT**:
  - Never stop or start a urate lowering therapy during an acute attack. It can worsen the gout flare and when restarting the medication it can cause a gout flare. Fluctuations in sUA worsen attacks in intensity, duration and number of joints involved.
  - Resolve the acute attack first. Continue prophylaxis drug. Begin therapy 5-7days up to 2 weeks after acute attack resolves. If on chronic ULT do not stop and continue even during an acute flare.
  - Asymptomatic hyperuricemia with no prior history of gouty arthritis, tophaceous deposits or nephrolithiasis should only be treated in situations in which there may be acute overproduction (chemotherapy, radiation) of uric acid as in the acute tumor lysis syndrome.
    - Some recommend treatment if urinary uric acid excretion is > 1100 mg/d because of 50% nephrolithiasis.
    - Otherwise, there are currently no widely accepted indications for treatment of asymptomatic hyperuricemia other than non-pharmacologic interventions (weight loss, dietary modification, and decrease alcohol intake).

6. Chronic ULT Therapies:

Type of agent	Drug	Dosing	Considerations
Xanthine Oxidase inhibitors (1st line)	Allopurinol	Initiate 100 mg daily; titrate upward every 2-4 weeks to reach target serum UA; maximum dose: 900 mg/dl.	Requires renal dosing: Initiate at 50 mg/day for patients with CKD (stage 4 or worse); Rash (2%) usually mild but includes TEN, vasculitis and potentially fatal hypersensitivity syndrome (testing recommended for high risk groups)*; bone marrow suppression and hepatitis are rare SE Increases levels of azathioprine (Imuran) and 6-MP and dose needs to be decreased by half
	Febuxostat (Uloric)	Initiate at 40 mg/day; titrate to maximum dose of 80 mg/day after 2-4 weeks if sUA is not at goal	May cause liver enzyme elevation, arthralgia, or rash Liver tests needed in patients who develop fatigue, anorexia, RUQ abdominal discomfort, dark urine, jaundice Black box warning for MI, CVA
Uricosuric agent	Probenecid	250 mg twice daily for 1 week, then 500 mg twice daily; titrate in 500 mg increments every 4 weeks until target sUA level is reached; maximum dose is 2-3 g/day	Avoid in patients with history of urolithiasis and those with GFR < 50 ml/min
	Losartan (Cozaar)	No FDA approved dosing	Useful in patients with HTN Decreases sUA by 20-30%; Raises urine pH therefore preventing UA kidney stones (specific for Losartan)
	Fenofibrate (Tricor)	No FDA approved dosing	Useful in patients with dyslipidemia Decreases sUA by 20-30%; occurs only with Tricor; effects are additive with Losartan
	Vitamin C	500-1000 mg daily	Decreases sUA by 0.5 mg/dl
Urate Oxidase Enzyme	Pegloticase* (Krystexxa)	8 mg IV q 2 weeks	IV infusion over ≥ 120 min Severe infusion/allergic reactions possible May exacerbate CHF

*Koreans with CKD (stage 3 or worse) and all Han Chinese and Thai Patients. Associated with HLA-B*5801.

The 15 Secrets of Gout Management:

1. **Prove the patient has gout**. Therapy is life long and all medications carry risks and side effects. Strive for a crystal proven diagnosis.
2. Don't use prophylactic medications (colchicine, NSAIDs, prednisone) without also using urate lowering therapy.
3. **Colchicine is the prophylactic medication of choice** but remember to discontinue it 3-6 months after target sUA goal has been met. It can cause neuromyopathy in patients with renal insufficiency and chronic long term use and has several drug interactions which should be noted.
4. **Continue prophylactic medication for 3-6 months after target sUA is achieved**.
5. Don't start a urate lowering therapy (allopurinol, febuxostat, and probenecid) without using a prophylactic medication beforehand and concomitantly.
6. **Urate lowering therapy is analogous to using DMARDs in rheumatoid arthritis**. It prevents significant morbidity and disability.
7. **Allopurinol is still the drug of choice for chronic urate lowering therapy**. Do not forget it can cause a rash and hypersensitivity reaction. If patient develops a rash, stop the medication and have the patient restart medication when rash has resolved at the dose where they had no rash. If this at 100 mg consider change to another agent.
8. Be proactive and check sUA levels in addition to CBC and LFTs every 2-4 weeks and adjust urate lowering therapy to goal. Patients will get better faster. They should not have gout flares if sUA is at goal.
9. You can combine allopurinol or febuxostat with probenecid to achieve goal sUA.
10. **Goal sUA goal is < 6.0 and for tophaceous gout < 5.0.**
11. **Never start or stop urate lowering medications during a gout flare**. It will worsen the gout flare and possibly cause a gout flare when medication restarted.
12. Treat all patients with lifestyle changes (diet, weight loss, hydration, **Vitamin C**).
13. **Avoid diuretics if possible in patients with gout for control of HTN.**
14. Use Losartan (Cozaar) or calcium channel block (CCB) for HTN control and Fenofibrate (TriCor) for hyperlidemia in gout patients.
15. Educate patient about the importance of knowing their disease process and why it is important to treat gout.

6. Criteria for Return to Primary Care

- Diagnosis of gout is established and the patient is low risk and without significant co-morbid conditions.

Date Adopted or Last Reviewed:	01 Feb 2018	By	CDR Shauna O'Sullivan LCDR Jeffrey Eickhoff LCDR Terrence Kilfoil LCDR Jason Weiner
Referral Guidelines require review every three years.			

7. Resources/References

- American College of Rheumatology: https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Gout
- American College of Rheumatology Guidelines for Management of Gout: https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Gout
- Arthritis Foundation: https://www.arthritis.org/about-arthritis/types/gout/articles/gout-treatments-guidelines.php
- Neogi T, et al. 2015 Gout Classification Criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis and Rheumatology 2015; 67(10): 2557-2568.