A SURVEY ON THE DIAGNOSIS AND MANAGEMENT OF GOUT AMONG GENERAL PRACTITIONERS

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ABSTRACT

Objective: To determine the knowledge and practices of general practitioners in the diagnosis and management of gout and compare to clinical guidelines and quality of care indicators to ascertain shortcomings in care.

Methods: An email-based questionnaire survey of South African general practitioners relating a clinical case vignette of an acute inflammatory arthritis; specifically, gouty arthritis; with respect to diagnosis, management of acute gout, prophylaxis, indications and dosage of urate lowering therapy allopurinol, dietary modification and co-morbidity screening.

Results: Of the 2891 email invitations, 221 questionnaire surveys were included in the study (7.6%). There was near equal representation of general practitioners in solo (54.3%) and group practice (45.7%). The majority of general practitioners (94.6%) participating in the survey appropriately diagnosed gouty arthritis. The evaluation of gout with arthrocentesis was however, considered by only 4.1% participants and 12.7% co-prescribed prophylaxis when initiating urate lowering therapy. Urate lowering therapy was always initiated in gout patients by 14.9% of participating general practitioners and by 31.2% in those patients presenting with tophi and other characteristic features. In patients presenting with more than 2 attacks a year, 70% would initiate ULT. Titration of urate lowering therapy with serum urate levels were performed by 29% of participants. Gout was disagreed upon as a risk factor for ischaemic heart disease by 26.2% of participants. General practitioners who consulted 5 or more gout patients in a month were more likely to attempt joint aspiration (p=0.004), prescribe prophylaxis (p=0.025) and to have updated their knowledge in gout management in the last 2 years (p=0.003).

Conclusion: In this study, gout management, particularly chronic management is poorly implemented and is currently of a suboptimal standard compared to guideline recommendations and quality of care indicators. Gout management in South Africa needs to be addressed as it remains a curable inflammatory arthritis despite its increased prevalence around the world.

TABLE OF CONTENTS

CHAPTER 1 : BACKGROUND LITERATURE REVIEW 1

1.1. History 1

1.2. Definition of gout 1

1.3. Epidemiology 2

1.3.1. Risk factors 2

1.3.1.1. Genetic 2

1.3.1.2. Environmental factors 3

1.4. Aetiopathogenesis 4

1.4.1. Uric Acid Metabolism 4

1.4.2. Hyperuricaemia 7

1.4.2.1. Overproduction 7

1.4.2.2. Underexcretion 7

1.5. Clinical features 10

1.5.1. Stage 1 - Asymptomatic hyperuricaemia 11

1.5.2. Stage 2 - Acute gouty arthritis 11

1.5.3. Stage 3 - Intercritical gout 12

1.5.4. Stage 4 - Chronic tophaceous gout 12

1.5.5. Stage 5 - Uric acid urolithiasis and urate nephropathy 12

1.6. Diagnosis 13

1.7. Management 13

1.7.1. Acute management 14

1.7.1.1. Pharmacological 14

1.7.1.2. Non-Pharmacological 14

1.7.2. Chronic Management 15

1.7.2.1. Pharmacological 15

1.7.2.2. Non-Pharmacological 16

1.8. Prognosis 17

1.8.1. Disability 18

1.8.2. Co-morbidities 18

1.9. Challenges in management of gout 19

1.9.1. Allopurinol intolerance 19

1.9.2. Health practitioner knowledge and practice 20

1.10. Studies done previously 22

1.11. Aim and Objectives 36

1.11.1. Aim 36

1.11.2. Objectives 36

CHAPTER 2 : SUBJECTS AND METHODS 37

2.1. Study design 37

2.2. Subjects and Methods 37

2.3. Statistical Analysis 38

CHAPTER 3 : RESULTS 39

CHAPTER 4 : DISCUSSION 48

4.1. Strengths and limitations 54

CHAPTER 5 : CONCLUSIONS AND RECOMMENDATIONS 55

REFERENCES 57

APPENDIX A 60

APPENDIX B 61

APPENDIX C 66

APPENDIX D 67

APPENDIX E 70

LIST OF FIGURES

Figure 1.1 Urate production pathways implicated in the pathogenesis of gout. *(Choi et al., 2005)* 5

Figure 1.2 Uric acid excretion. *(Rees et al., 2014)* 6

Figure 1.3 Renal excretion of urate. *(Ragab et al., 2017)* 8

Figure 1.4 Cellular membrane transporters in the kidney. *(Keenan, 2016)*..... 9

Figure 3.1 Outline of email survey invitations and outcome of responses. 39

LIST OF TABLES

Table 1.1 Summary of previous studies 23

Table 3.1 Demographics and gout experience of General Practitioners 40

Table 3.2 Diagnosis and acute management of gout 42

Table 3.3 Chronic management of gout 43

Table 3.4 Lifestyle modification advice and co-morbidities 44

Table 3.5 Comparison of General Practitioners in solo practice versus group practice 45

Table 3.6 Comparison of responses by General Practitioners under 40 years versus General Practitioners over 40 years 45

Table 3.7 Comparison of less than 5 gout patients seen per month versus 5 or more gout patients seen by General Practitioners in a month 46

Table 3.8 Comparison of less than 2 acute gout patients seen per month versus 2 or more gout patients seen by General Practitioners in a month 47

LIST OF ABBREVIATIONS

Adenosine triphosphate	**ATP**
Adenosine triphosphate - binding cassette sub-family G member	**ABCG2**
Allopurinol Hypersensitivity Syndrome	**AHS**
American College of Rheumatology	**ACR**
British Society for Rheumatology	**BSR**
Computed tomography	**CT**
European League Against Rheumatism	**EULAR**
General practitioners	**GPs**
Glucose transporter 9	**GLUT9**
Health-related quality of life	**HRQoL**
Hydrochlorothiazide	**HCTZ**
Intramuscular	**IM**
Monosodium urate	**MSU**
Non-steroidal anti-inflammatory drugs	**NSAIDs**
Organic anion transporter 4	**OAT 4**
Proton pump inhibitor	**PPI**
Rheumatoid arthritis	**RA**
Serum urate	**SUA**
Solute carrier family 2 (facilitated glucose transporter) member 9	**SLC2A9**
Solute carrier family 22 (organic anion/cation transporter) members 12	**SLC22A12**
Uric acid transporter	**URAT1**

CHAPTER 1 : BACKGROUND LITERATURE REVIEW

1.1. History

Gout is a disease of antiquity, first described in the third millennium BC (2640 BC) in Egypt, as 'podagra' and referred to as the 'unwalkable disease' by Hippocrates in the fifth century BC. ***(Nuki and Simkin, 2006)*** It was termed the 'Disease of Kings' in ancient times as it was known then to be associated with an affluent lifestyle with the consumption of rich foods and excessive alcohol intake. The word gout was first used by the Dominican monk Randolphus of Bocking in the twelfth century AD, to describe podagra and comes from the Latin word 'gutta' meaning 'drop'. This originates from the medieval idea that every person's body contained four humours that were in balance to maintain good health and gout occurred when there was a desynchronization. Hippocrates' observation that gout tends to occur in post-pubertal males and post-menopausal women still holds true today; two thousand five hundred years later but despite possessing this ancient knowledge, the burden of this disease remains a challenge. ***(Nuki and Simkin, 2006)***

1.2. Definition of gout

Gout is a clinical syndrome that is a systemic crystal deposition disease predominantly affecting peripheral joints and the surrounding tissues as well as distant sites such as the renal system and urinary tract. ***(Benn et al., 2018, Ragab et al., 2017)*** It involves monosodium urate (MSU) crystal formation and deposition in soft tissues and synovial joints when the serum concentration of urate exceeds the critical saturation point of >0.36mmol/l, causing an inflammatory arthritis among other clinical features. ***(Neogi et al., 2015 , Richette et al., 2015)***

1.3. Epidemiology

Widely regarded as the 'rich man's disease', gout is the most common inflammatory arthritis in men and has now exceeded the prevalence of rheumatoid arthritis (RA) in older women. ***(Doherty et al., 2012)*** The resurgence of the disease in the last twenty years has been observed in several western countries affecting 0.9- 2.5% of adults. ***(Neogi et al., 2015, Richette et al., 2017)*** In the United Kingdom gout affects 1.4% of adults and in Germany over 1%. ***(Spencer et al., 2012)*** The prevalence is even higher in the United States, affecting 3.9% of the American population (8.3 million adults), with the highest documented prevalence of about 6% in the New Zealand Maoris. ***(Jackson et al., 2014, Richette et al., 2017)***

Males are 2-6 times more likely to suffer from gout than females. ***(Ragab et al., 2017)*** In recent years the affliction of gout has travelled east, with a prevalence of around 1% of the Chinese adults but not uniformly over Asia as a decrease in prevalence was reported in Taiwan. ***(Benn et al., 2018, Li et al., 2013)*** The number of individuals afflicted with gout was also shown to increase with age with 7% of males over sixty-five years, 9-10% of males over eighty years and 3-6% of females over eighty years being affected. ***(Doherty et al., 2012, Ragab et al., 2017)***

1.3.1. Risk factors

1.3.1.1. Genetic

It was found that hyperuricaemia and gout from the effects of genetic polymorphisms in Europeans were of comparable extent when compared to other ethnicities. ***(Benn et al., 2018)*** The heritability of serum urate (SUA) has been estimated to be 42-73% while the

heritability of renal urate clearance 60% and that of fractional excretion of urate at 87%. ***(Benn et al., 2018)***

Family studies have also shown a correlation between siblings, parents and offspring and SUA levels but this likely due to multiple genetic factors. ***(Benn et al., 2018)***

Lesch-Nyhan syndrome is an X-linked recessive, inborn error of uric acid metabolism with a deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase that has varying degrees of severity. Besides early onset gout and uric acid nephrolithiasis, there are severe neurological deficits. ***(Ragab et al., 2017)***

Another X-linked, enzymatic disease phosphoribosyl pyrophosphate synthetase presents in two clinical forms with again neurological deficits in the severe form and in the mild form with gout and uric acid renal calculi. ***(Ragab et al., 2017)***

1.3.1.2. Environmental factors

The increased prevalence of gout is being driven by a number of factors such as longevity, increased cardiovascular risk, metabolic syndrome, chronic renal insufficiency and certain treatments for these conditions (diuretics, low dose aspirin, cytotoxics, pyrazinamide etc.) and substituting treatments with alternatives where possible is indicated. ***(Doherty et al., 2012, Stamp and Chapman, 2013)***

High alcohol and meat intake; particularly high purine containing beer, spirits and meats such as beef, seafood and pork, drive up the high incidence of gout. ***(Ragab et al., 2017)***

Purine rich food derived from vegetable origin does not carry any risk to developing hyperuricaemia. Other modifiable dietary lifestyle risk factors have also been identified such as sugar sweetened-drinks, high content fructose foods, and orange and apple juices. ***(Ragab***

et al., 2017, Richette et al., 2017) Weight reduction and good hydration were also shown to be beneficial in reducing the SUA levels. ***(Jeyaruban et al., 2015, Ragab et al., 2017)***

1.4. Aetiopathogenesis

1.4.1. Uric Acid Metabolism

Uric acid is a product of purine metabolism (Fig. 1.1). Except in some high order primates and humans, it is degraded into allantoin and excreted as the final step in most mammals.***(Benn et al., 2018)*** Uricase, an enzyme required for the oxidative degradation of uric acid to the more soluble compound, allantoin is absent in humans. Hence, humans are the only mammals that develop gout spontaneously. ***(Choi et al., 2005)*** Uric acid exists as a urate anion (98-99%), its ionised form in the physiological pH and is thought to confer a survival advantage in humans and some primates because of its anti-oxidant property. ***(Benn et al., 2018, Choi et al., 2005)***

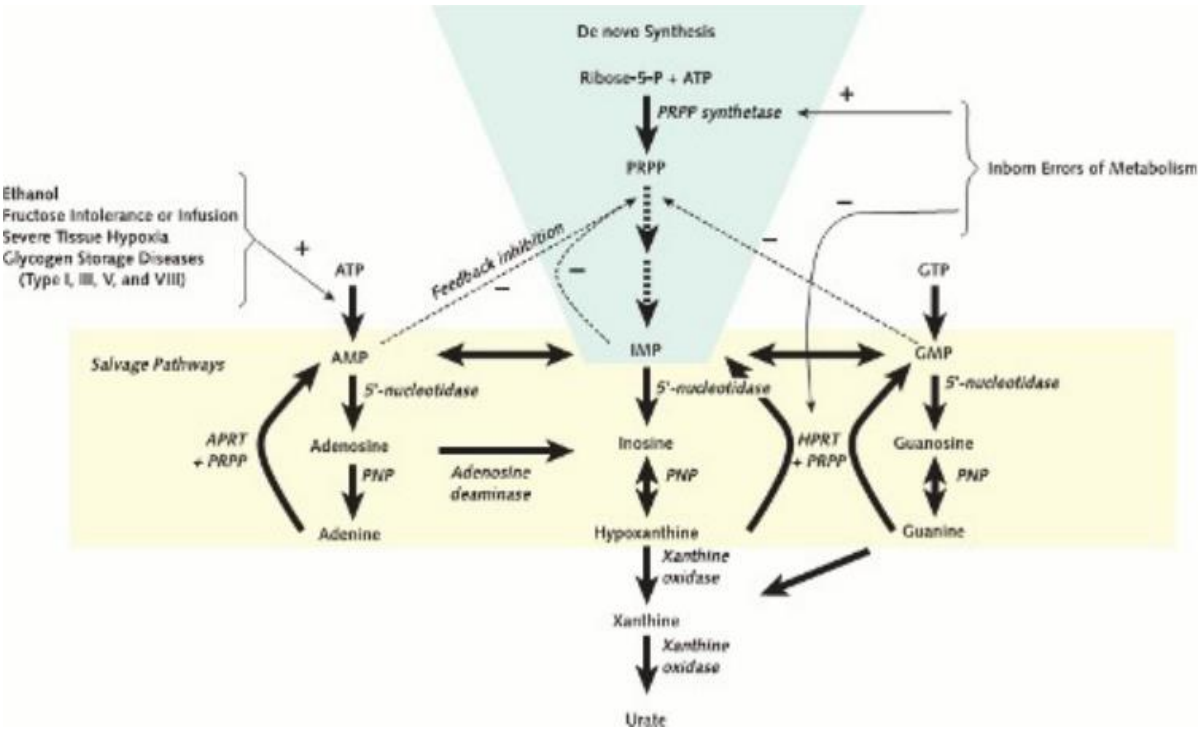

Figure 1.1 Urate production pathways implicated in the pathogenesis of gout. ***(Choi et al., 2005)***

Urate balance depends on exogenous purine intake (approximately 300mg) from dietary sources, endogenous urate synthesis (approximately 300-400mg) and its excretion via the gastrointestinal system and the majority, via the renal system (Fig 1.2). ***(Benn et al., 2018, Choi et al., 2005, Ragab et al., 2017)*** SUA levels are low in children but increase to normal levels in puberty. Levels are particularly higher in men than women except during post menopause where the levels are the same. ***(Ragab et al., 2017)***

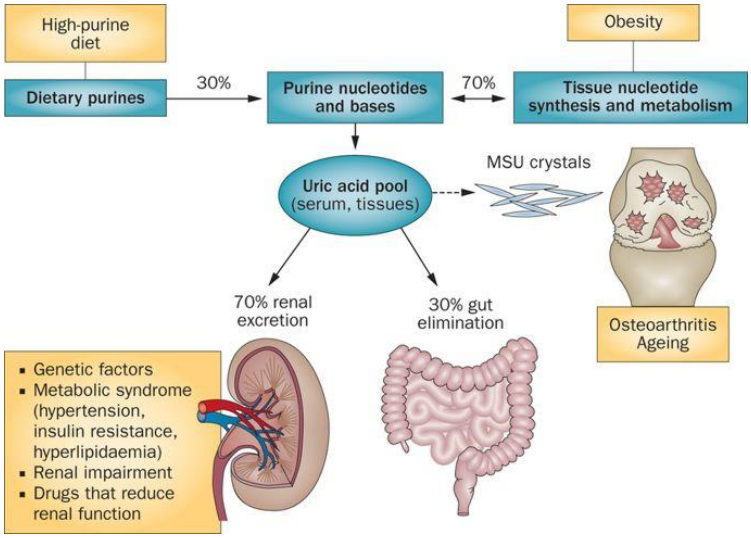

Figure 1.2 Uric acid excretion. ***(Rees et al., 2014)***

The relationship between a purine rich diet and SUA is more complex as certain diets containing sweetened soft drinks or beer have a greater impact on SUA levels independent to just their purine content. ***(Benn et al., 2018)*** An example is the upregulation of the fructokinase enzyme expression in response to generation of uric acid from fructose containing sweetened drinks. ***(Benn et al., 2018)***

Sustained hyperuricaemia is required as a prerequisite for gout to manifest. In the vast majority of patients it is due to renal underexcretion of urate as opposed to the overproduction of urate, but commonly is the result of the cumulative effect of both processes. ***(Ragab et al., 2017)*** Importantly, hyperuricaemia does not equate or progress to gout in all individuals and other factors such as genetic predisposition and co-morbidities cause gout to manifest. ***(Ragab et al., 2017)***

Currently the prediction of which patients will progress to gout is difficult and at this time there is no global consensus on treatment of asymptomatic hyperuricaemia, which remains an active field of research. ***(Benn et al., 2018, Ragab et al., 2017)***

1.4.2. **Hyperuricaemia**

Hyperuricaemia is defined as a SUA level above (404umol/l). ***(Benn et al., 2018)***

1.4.2.1. **Overproduction**

Overproduction of endogenous urate causing hyperuricaemia is by 2 mechanisms:-

1. Genetic disorders where the purine salvage pathways (Fig 1.1) are deficient as in the case of Lesch-Nyhan syndrome as mentioned above.
2. More commonly conditions that lead to accelerated cellular turnover such as malignancies, and haematological conditions result in overproduction of urate. ***(Ragab et al., 2017)*** This effect is compounded by cytotoxic drugs used to treat these conditions with increased cell lysis. This phenomenon is commonly referred to as tumour lysis syndrome.

   Dietary intake causing overproduction of urate exogenously is another factor and is discussed above.

1.4.2.2. **Underexcretion**

Hyperuricaemia is the result of underexcretion in ninety percent of cases. The fractional excretion of urate is reduced in gout patients to 3-5% compared to 6-8% in normal individuals and this represents a major contributor to hyperuricemia. ***(Benn et al., 2018)***

Urate excretion in the kidneys is divided into 4 phases. The first 2 phases involve the passage of the glomerular filtrate from the Bowman's capsule followed by reabsorption of the majority of urate from the filtrate in the proximal tubule. ***(Ragab et al., 2017)***The last 2 phases occurs when some of the reabsorbed urate is excreted into the proximal tubule with another resorption phase occurring further. ***(Ragab et al., 2017)*** From the high fraction of

renal excreted urate, approximately 91-95% of filtered urate is reabsorbed at the proximal tubules delivering urate back into the serum. ***(Benn et al., 2018)*** Ultimately 3-10% of the filtered urate is discharged in the urine. ***(Benn et al., 2018)*** Uric acid crystals are not soluble and require cell membrane transporters to be absorbed and secreted. ***(Ragab et al., 2017)***

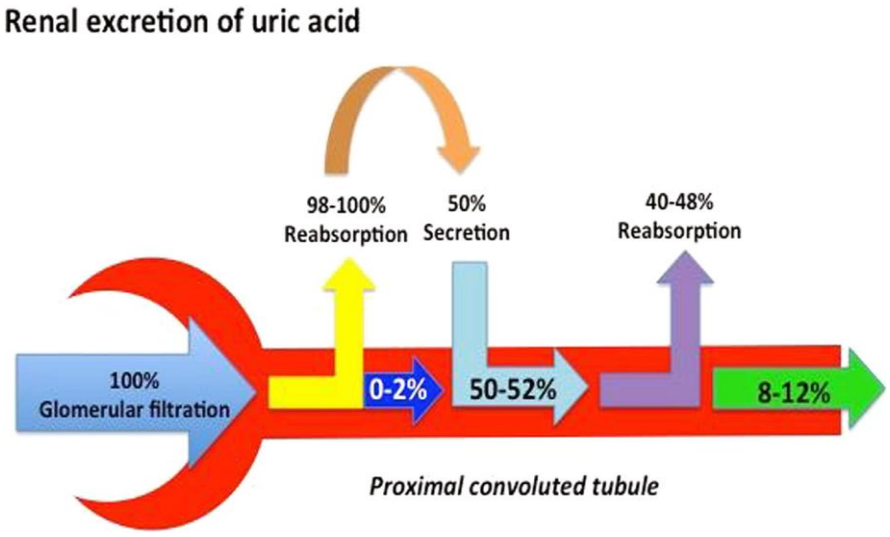

Figure 1.3 Renal excretion of urate. ***(Ragab et al., 2017)***

More common genetic abnormalities result in reduced renal and gastrointestinal cellular secretory transporters which, in turn, increase SUA levels by failing to excrete urate appropriately.

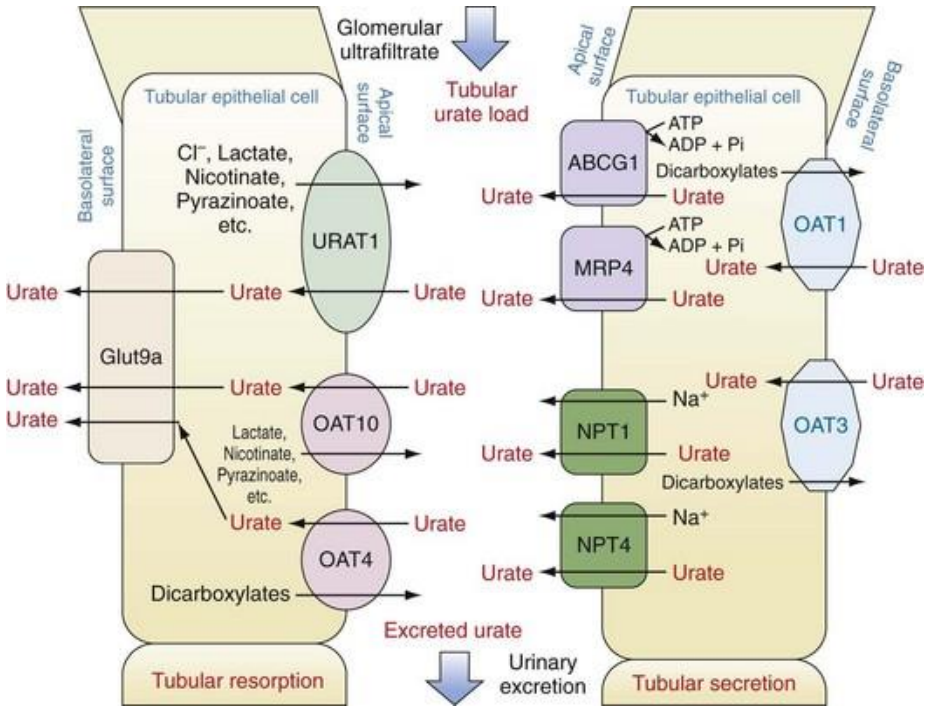

Figure 1.4 Cellular membrane transporters in the kidney. ***(Keenan, 2016)***

As shown in Fig 1.4, uric acid transporter (URAT1) has been identified as the main urate transporter found on the apical membrane border of the proximal tubule cells of the kidney. As well as urate it transports other organic anions such as salicylate and lactate to name a few. ***(Benn et al., 2018)*** The transport of urate from the glomerular filtrate is an active transport process. Polymorphisms of URAT1 genes, solute carrier family 22(organic anion/cation transporter) member 12 (SLC22A12) and solute carrier family 2, facilitated glucose transporter member 9 (SLC2A9), result in decreased excretion of urate overall in the urine and through reuptake predispose to hyperuricaemia. URAT1 is a drug target with a number of primary and secondary uricosurics utilising the cell membrane transporter to increase fractional excretion of urate. ***(Benn et al., 2018)***

Other transporters can also be affected causing underexcretion of urate such as glucose transporter 9 (GLUT9), which is a voltage dependent urate uniporter and also involved in hexose transport. Variants of this cell membrane transporter are associated with hyperuricaemia leading to gout and a homozygous mutation presents with hyperuricosuria which would predispose individuals to nephrolithiasis. ***(Benn et al., 2018)***

Organic anion transporter 4 (OAT 4) has been associated with gout due to inefficient renal secretion of urate. ***(Benn et al., 2018)***

Adenosine triphosphate-binding cassette sub-family G member aka breast cancer resistance protein (ABCG2) is present in both renal and gastrointestinal systems and is an adenosine triphosphate (ATP-driven) efflux pump transporting uric acid. It was found that dysfunction of this transporter is a major factor in human hyperuricaemia. ***(Benn et al., 2018, Ragab et al., 2017)*** Reduced renal excretion of urate from genetic abnormalities such as an uromodulin mutation that regulates water permeability at the thick ascending limb of the loop of Henle, ultimately causes an increase of SUA levels by not allowing adequate excretion of urate. ***(Ragab et al., 2017)***

There are in fact numerous other transporters beyond the scope of this study that cause susceptibility to hyperuricaemia and gout from genetic variations and functional impairments.

1.5. Clinical features

Gout is clinically categorised into 5 stages:

1.5.1. Stage 1 - Asymptomatic hyperuricaemia

Gout begins with a period of asymptomatic hyperuricaemia which as the SUA levels increases, the risk of precipitation to form MSU crystals escalates. Initially deposition of these MSU crystals occurs in peripheral joints and soft tissues such as bursae and tendon sheaths silently as well as parenchymal organs such as the kidneys. ***(Doherty et al., 2012)*** Usually patients have no symptoms or signs and are discovered on routine laboratory results of SUA level over 400umol/l. ***(Ragab et al., 2017)***

1.5.2. Stage 2 - Acute gouty arthritis

Above a critical saturation point of crystal formation, a self-limiting acute inflammatory response occurs which manifests as an acute gouty attack when crystals enter the joint space invoking this most painful synovitis. ***(Doherty et al., 2012)*** The fundamental features of this synovitis include swelling, extreme tenderness, erythema, heat and functional loss. A typical gout patient presents with a peripheral inflammatory monoarthritis or oligoarthritis of rapid onset, mostly rousing the patient from sleep and is still the classic presentation after two thousand five hundred years. ***(Nuki and Simkin, 2006, Underwood, 2006)*** The peripheral joints are the usual targets of an acute gout attack such as the first proximal metatarso-phalangeal joint (podagra), other metatarsal and tarsal joints, the ankle, knee, elbow, wrist and small joints of the hand. ***(Ragab et al., 2017)***

The reason for peripheral joint predisposition is due to the crystal formation of excess serum MSU reaching the critical point of saturation at cooler areas of the body. ***(Underwood, 2006)*** Typically acute gouty attack occurs within a twenty four hour period of a heavily inflamed and extremely painful mono or oligoarthritis and resolves within a 7-10 day period

without treatment. ***(Benn et al., 2018)*** Constitutional symptoms such as fever and malaise may be present.

1.5.3. Stage 3 - Intercritical gout

This is the period between acute attacks of gout where the patient is asymptomic for months possibly years. The intercritical gout period shortens with each acute attack in cases where the hyperuricaemia is not controlled which eventually may result in the next stage. ***(Ragab et al., 2017)***

1.5.4. Stage 4 - Chronic tophaceous gout

Chronic tophaceous gout becomes apparent after many years of inadequate control of hyperuricaemia resulting in MSU crystal deposition in joints and soft tissues, manifesting as palpable subcutaneous tophaceous deposits or bony erosions. ***(Benn et al., 2018, Ragab et al., 2017)*** These tophi are typically found on the helix of the earlobe, olecranon process of the elbow, hands and Achilles tendon. Tophi discharge appears as white chalky material at sites of breaks in the skin. ***(Ragab et al., 2017)***

1.5.5. Stage 5 - Uric acid urolithiasis and urate nephropathy

Up to twenty percent of patients with gout develop uric acid urolithiasis and they contribute 5-16.5% of all kidney stones. ***(Benn et al., 2018)*** This may be due to urate crystals initiating calcium oxalate precipitation. Alkalinisation of urine usually decreases the possibility of developing uric acid stones which requires acidic urine to aid stone formation. ***(Benn et al., 2018)*** Increased SUA levels are also associated with an increased risk for acute kidney injury. ***(Benn et al., 2018)*** Chronic interstitial nephropathy in gout is where MSU crystals have been deposited in the kidney at the site of the renal medulla causing ongoing chronic

inflammation and decreasing renal function. With ULT and dissolution of the crystals, renal function may improve. ***(Benn et al., 2018)***

1.6. Diagnosis

The gold standard in the diagnosis of gout is the detection of MSU crystals under polarised light microscopy in a synovial fluid or tophus aspirate. ***(Ragab et al., 2017)*** The crystals are negatively birefringent where in one plane they appear yellow and in the ninety degrees plane appear blue. SUA are not useful in the diagnosis of acute gout, as they may be normal in a third of patients with acute gout, although the hyperuricaemia will be evident at some point after an acute attack.

Urinary uric acid levels of more than 800mg/24hours may allow interpretation of the aetiology of hyperuricaemia in gout patients. ***(Ragab et al., 2017)***

Imaging is helpful although plain radiography is unlikely to show the typical changes of periarticular erosions and bone cysts, features typical of established disease. More recently ultrasonagraphy has been used to detect early changes. The double contour sign is a useful sign. Rarely is Computed Tomography necessary to detect tophi in joints and bones. ***(Ragab et al., 2017)***

CT has the same drawbacks as conventional radiography in early gout but has high resolution and contrast in chronic gout. Its main functionality comes in assessing disease activity and response to treatment but together with magnetic resonance imaging, its cost is nearly prohibitive. ***(Ragab et al., 2017)***

1.7. Management

The management of gout is in two stages. Firstly, the management of acute gouty arthritis followed by therapies to manage the underlying hyperuricaemia.

1.7.1. Acute management

Acute management includes pharmacological and non-pharmacological measures.

1.7.1.1. Pharmacological

High dose, non-steroidal anti-inflammatory drugs (NSAIDs) and lower dose colchicine have been recommended as first line treatment options of gout. ***(Ragab et al., 2017, Richette et al., 2017)*** The European League Against Rheumatism (EULAR) guidelines do not make a differentiation of the mode of delivery of NSAIDs (oral or intramuscular) and make mention of proton pump inhibitors (PPI) when appropriate for gastrointestinal ulcer protection.

Commencement of colchicine twelve hours within an acute gout attack and at a lower dose was found to be effective compared to the previous higher doses with markedly reduced side effects.

The last of the first line pharmacological treatment option endorsed by the EULAR 2016 guidelines is the prescription of a short course (7 days) of high dose corticosteroids (prednisolone) with their efficacy comparable to NSAIDs. ***(Ragab et al., 2017, Richette et al., 2017)***

As a second line option in patients with contraindications to the above agents the EULAR guidelines recommend biological agents such as interleukin-1 blocker (canakinumab) where infection would not prohibit its use and it is registered for the treatment of acute gout. ***(Ragab et al., 2017, Richette et al., 2017)***

1.7.1.2. Non-Pharmacological

Local treatment with ice, rest and elevation of the affected joint are the only recommended advices. ***(Hui et al., 2017)***

1.7.2. Chronic Management

The objective of the chronic management of gout is to reduce SUA to within the normal range and by doing so reduce the risk of acute gouty attacks and tophaceous gout. This is achieved by pharmacological and non-pharmacological interventions.

1.7.2.1. Pharmacological

For the most part allopurinol is the drug of choice to lower SUA levels. Allopurinol is a xanthine oxidase inhibitor, introduced in the 1960s; is inexpensive and readily accessible to general practitioners. ***(Benn et al., 2018, Ragab et al., 2017, Underwood, 2006)***

It is specifically a purine inhibitor and its active metabolite is oxypurinol. Not only does oxypurinol block the xanthine oxidase enzyme, it also inhibits further purine synthesis and has a long half-life requiring only daily dosing of allopurinol. ***(Ragab et al., 2017)***

As the initiation of ULT may lead to recurrent attacks of gout due to crystal mobilisation, prophylaxis with either low-dose colchicine or NSAIDs should be prescribed for a period of six months towards but this period might be extended in patients with chronic tophaceous gout. ***(Richette et al., 2017)***

Allopurinol is usually started in a low dose of 100mg daily with the dose increased every to two to four weeks and titrated based on SUA levels. Only about a quarter of patients achieve the target SUA level of 0.36mmol/l and the dose needs to be escalated to a maximum of 800-900 mg daily. ***(Benn et al., 2018, Ragab et al., 2017, Richette et al., 2017)***

Conversely the drug is to be used with extreme caution in the elderly and patients with renal dysfunction. In these cases it is recommended that the starting dose be 50mg daily. The

major drawback of allopurinol is the potential for life threatening skin adverse effects like toxic epidermal necrolysis and Stevens-Johnson syndrome.

In view of the potentially serious toxicity of allopurinol, a non-purine xanthine oxidase inhibitor, febuxostat, has been developed in the last decade. This drug is more potent than allopurinol but is considered a second-line therapy in patients who are intolerant to allopurinol. The drug is not available in South Africa. ***(Ragab et al., 2017, Richette et al., 2017)***

Uricosurics lower SUA levels by increasing urinary excretion of uric acid. Due to the risk of renal calculi these agents are seldom used as monotherapy and in most cases are combined with xanthine oxidase inhibitors like allopurinol. Drugs in this category include sulphinpyrazone, probenecid, lesinurad and benzbromarone. ***(Benn et al., 2018)*** Other drugs reported with uricosuric effects are the angiotensin receptor blocker losartan, statins such as atorvastatin and other lipid lowering agents like fenofibrate. These drugs are not sufficient in their own right to control the hyperuricaemia but are particularly useful in patients with comorbidities like hypertension and dyslipidaemia.

Lastly, pegloticase, a PEGylated recombinant uricase, is used in the treatment of refractory gout not responding to oral agents. It is administered intravenously in two weekly cycles and significantly reduces SUA levels but currently is not available in South Africa. ***(Benn et al., 2018, Ragab et al., 2017)***

1.7.2.2. **Non-Pharmacological**

Non-pharmacological interventions play a very important role in the control of hyperuricaemia and reduction of recurrent attacks of gout. These measures include changes

in diet and avoidance of medications that are known to increase SUA levels and patient education.

1) Dietary measures that are important include overall reduction in calorie intake, minimising intake of animal proteins that have high purine content, such as red meat and seafood, alcoholic beverages with high guanosine content and drinks with high fructose content as mentioned above in 1.3.1.2.

   By contrast, cherries and cherry juice has been shown to reduce the frequency of gouty attacks. Low fat milk and products was also shown to have a uricosuric effect. ***(Richette et al., 2017)***

2) Drugs that are known to increase SUA levels include diuretics, aspirin, antituberculous agents such as pyrazinamide and cyclosporine. ***(Doherty et al., 2012)***

3) Patient education is crucial with regards to achieving the target SUA and reducing the burden and damage of gout.

1.8. Prognosis

Without treatment, some 60% of patients with acute gout would experience at least one attack within a year. ***(Eggebeen, 2007)*** With each subsequent attack the likelihood of joint destruction increases with deformities and deposition of tophi. ***(Richette and Bardin, 2010)*** If left untreated for five years, 30% of patients develop tophi. ***(Richette and Bardin, 2010)*** On the other hand tight control of SUA levels using a combined approach of lifestyle modification and ULT in most instances will effectively ‘cure’ gout.

1.8.1. **Disability**

Gout is an eminently treatable and curable disease. However if inadequately treated repeated attacks of acute gout and subsequent joint damage affects productivity in the workplace, social interactions and overall health-related quality of life (HRQoL). Studies show besides the worsening risk of morbidity and mortality, there is also a significant decrease in HRQoL with the average patient suffering decreased mental and physical wellbeing. ***(Khanna et al., 2012b)*** Patients with chronic tophaceous gout and frequent flares have a worse HRQoL while patients with tophi reported greater work impairment than those without. ***(Khanna et al., 2012b)*** More frequent flares and severity of gout were associated with more usage of healthcare.

1.8.2. **Co-morbidities**

Gout is often associated with lifestyle related co-morbidities such as hypertension, cardiovascular disease, chronic kidney disease and metabolic syndrome in general. ***(Benn et al., 2018, Ragab et al., 2017, Richette et al., 2017)*** Nearly 40% of patients with gout have hypertension and the hyperuricaemia plays a pathogenic role in hypertension as well as the medications used for treatment. Studies reveal reducing hyperuricaemia improves hypertension control. ***(Benn et al., 2018)***

Gout and hyperuricaemia have been found to be independent risk factors in cardiovascular disease. ***(Choi and Curhan, 2007, Krishnan et al., 2006, Stamp and Chapman, 2013)*** Low grade inflammation occurs with high SUA levels and there is endothelial dysfunction. ***(Benn et al., 2018)*** Studies are still ongoing to determine if ULT is warranted in patients with hyperuricaemia and cardiovascular disease. ***(Benn et al., 2018)***

Renal disease has both cause and effect in the pathogenesis of gout. ***(Richette et al., 2017, Stamp and Chapman, 2013)*** Renal dysfunction increases SUA levels which predispose patients to gout. ***(Stamp and Chapman, 2013)*** Untreated gout leads to eventual urate nephropathy and nephrolithiasis. ***(Richette et al., 2017)*** Renal underexcretion of urate, as discussed above, is the most common mechanism of hyperuricaemia in patients with gout.

Diabetes Mellitus type 2 was shown to be an independent risk factor in the development of hyperuricaemia in population based studies. ***(Benn et al., 2018)*** Insulin treatment increases renal reabsorption of uric acid and the increase adenosine that results from failure of oxidative phosphorylation feeds into uric acid production worsening hyperuricaemia. ***(Choi et al., 2005, Ragab et al., 2017)***

Obesity was shown to increase SUA and weight loss reduces levels. ***(Choi et al., 2005, Richette et al., 2017)*** Dyslipidaemia is frequently seen in patients with gout and as mentioned above some of the lipid-lowering agents have uricosuric effects on SUA. ***(Richette et al., 2017, Stamp and Chapman, 2013)***

1.9. Challenges in management of gout

Although gout is potentially curable there are many challenges in the management of chronic gout related to the chronic intermittent nature of the illness and not infrequent side effects of ULT like allopurinol and lack of proficiency amongst general practitioners (GPs).

1.9.1. Allopurinol intolerance

One of the major drawbacks of allopurinol is the high risk of potentially fatal adverse effects due to a number of reasons. A reason for the dismal prescription rates of allopurinol is the fear of allopurinol hypersensitivity. ***(Roddy et al., 2007)*** Allopurinol should be started at low

dose even in normal renal function patients as high doses may predispose susceptible patients to serious cutaneous reactions and to those with renal impairment, more so. ***(Richette et al., 2017)*** Up to one out of five patients have intolerability to allopurinol and may develop a potentially rare fatal reaction however this seems less likely in the primary care. ***(Roddy et al., 2007, Underwood, 2006)*** Around 2% to 4% of cutaneous reactions were reported by allopurinol initiators from maculo-popular rash to Stevens-Johnson syndrome. ***(Ragab et al., 2017)***

Allopurinol Hypersentivity Syndrome (AHS) is characterised by a rash, eosinophilia, fever, hepatitis and renal failure. Its incidence is estimated at 0.1% of allopurinol users. Renal impairment, diuretic use and allopurinol initiation are risk factors for AHS. A genetic association (HLADR B*5801) has also been found to AHS and affects the Asian population so much so that in Taiwan, it is recommended to be screened prior to allopurinol initiation and the ACR recommends screening patients of Han, Korean and Thai ancestry. ***(Ragab et al., 2017, Stamp and Chapman, 2013)*** The responsible allele in the Caucasian population is low so the risk of developing a reaction is correspondingly low.

1.9.2. Health practitioner knowledge and practice

Several studies in recent times reflect inadequate knowledge and gout management among health practitioners as one of the main factors leading to poor outcomes. In spite of several simple and practical guidelines on the management of gout, the utilisation by GPs is poor, leading them to be unable to offer best practice medicine, often relying on self-directed learning and assuming patients know extensively about the disease. ***(Jeyaruban et al., 2015, Li et al., 2013, Spencer et al., 2012)*** Gout compared to other musculoskeletal conditions is

not given high priority in undergraduate medical programmes and because of a perceived lack of interest and activity in the literature and guidelines is not viewed as a serious condition. ***(Doherty et al., 2012, Terrill and Riordan, 2018)***

Gout is mostly treated by GPs as opposed to rheumatologists and although updated clinical guidelines exist they are mostly published in rheumatology journals rather than being made accessible to primary care providers and therefore a reason for poor practices. ***(Mikuls et al., 2005, Richette et al., 2017, Singh et al., 2010)***

Reasons for inadequate control of gout are multifactorial including clinicians' lack of insight, favouring short term pain relief over long term ULT, incorrect dosing, non-prescription of prophylaxis when initiating ULT and lack of monitoring. ***(Roddy et al., 2007, Singh et al., 2010, Spencer et al., 2012)*** Other issues on patient treatment failure are non-adherence to ULT, the experience of avoidable side effects, lack of education on gout triggers, reluctance to modify lifestyle and the worsening of symptoms despite availability of effective treatments. ***(Harrold et al., 2010, Roddy et al., 2007, Spencer et al., 2012)***

Another concern is the lack of knowledge of quality of care indicators among primary care providers and end point targets for treatment. There is also little or no lifestyle advice given which hinders chronic care and treatment to patients despite there being new therapeutic guidelines such as American College of Rheumatology 2012 Guidelines (ACR) and the more recent EULAR 2016 gout management guidelines. ***(Spencer et al., 2012)***

A wide chasm often exists that separates what practitioners intend to convey and what patients' understand.

1.10. **Studies done previously**

Similar studies have been undertaken in countries around the world to attempt to understand the deficiencies in the management gout. Since the vast majority of gout patients are treated in primary healthcare, it was only natural that most studies and surveys were performed on primary healthcare practitioners, rheumatologists, the primary healthcare population and patients with gout.

A number of key aspects were focussed upon by these studies such as initiation of ULT and monitoring of SUA levels, lifestyle modification, acute management of gout, prophylaxis prescription and the period prescribed for, diagnostic techniques and considerations, etc. Table 1.1 is a summary off recent studies that looked at the management of gout by primary care practitioners.

Table 1.1 Summary of previous studies

Author	Country (year)	Participants/database (sample size)	Key research questions	Key findings
(Mikuls et al.)	UK (2005)	UK General Practice Research Database (n = 63105)	Adherence to: Quality indicator 1: Incorrect dosing of allopurinol in renal failure Quality indicator 2: Inadequate dose adjustment with concomitant allopurinol and azathioprine or 6-mercaptopurine Quality indicator 3: Treatment of asymptomatic hyperuricaemia	Hypertension as a co-morbidity was found in 25% of gout patients and cardiovascular disease in 26% respectively. Practice deviation to the quality indicators ranged from 25% to 57%. **Quality Indicator 1**: Incorrect dosing of allopurinol in renal failure at 25.95%. **Quality Indicator 2**: Inadequate dose adjustment with concomitant allopurinol and azathioprine or 6-mercaptopurine at 25%. **Quality Indicator 3**: Treatment of asymptomatic hyperuricaemia 56.69%.
(Mikuls et al.)	USA (2006)	MEDMARX database (national internet-accessible error reporting program) (n = 700)	Medication errors	39% of facilities participating in MEDMARX program had medication errors related to gout treatment reported. Reported errors were predominantly from inpatient hospital setting and related to allopurinol (n=524), colchicine (n=315), probenecid (50) and sulfinpyrazone (n=2). Allopurinol and colchicine errors were attributable to physician prescribing (23% to 39%). Physician prescribing practices are a potential target for quality improvement in gout care.
(Roddy et al.)	UK (2007)	Postal questionnaire to patients registered with 2 general practices with possible gout to come for clinical assessment (n = 4249)	To assess concordance of chronic gout management with EULAR 2006 gout recommendations **Proposition 2:** patient education and appropriate lifestyle advice regarding weight loss if obese, diet and reduced alcohol (especially beer) are core aspects of management. **Proposition 7**: ULT is indicated	88.41% with clinical confirmation of gout (145/175) subjects received lifestyle modification advice and written educational material concerning gout. 30% of subjects (44/145) that were seen previously by doctors and clinically assessed as gout were taking allopurinol. 10 patients had clinically evident tophi with only 2 on allopurinol currently and 4 patients taking allopurinol in the past. Chronic arthropathy and radiographic changes were not assessed. Patients on allopurinol had less attacks of acute gout in the last 12 months compared to non-users. (32% vs 57%).

			in patients with recurrent acute attacks, arthropathy, tophi or radiographic changes of gout. **Proposition 8**: the therapeutic goal of ULT is to promote crystal dissolution and prevent crystal formation; this is achieved by maintaining the SUA below saturation point for MSU (≤360umol/l) **Proposition 9**: allopurinol is an appropriate long-term ULT; it should be started at a low dose (eg. 100g daily) and increased by 100mg every 2-4 weeks if required. The dose must be adjusted in patients with renal impairment; if allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent or allopurinol desensitisation. (the latter only in a case of a mild rash) **Proposition 12**: when gout is associated with diuretic therapy, stop the diuretic if possible, for hypertension and hyperlipidaemia consider use of losartan and fenofibrate, respectively (both have modest uricosuric effects)	31/44 (70%) patients were taking allopurinol at doses of 300mg daily. 5/44 (11%) were taking 100mg daily and 4/44 (10%) were taking a dose above 300mg. 25 patients were on a diuretic during the first attack of gout or prior. The diuretic had not been stopped in 64% of these patients (16). Even among allopurinol users disease control is suboptimal. 23% of allopurinol users did not attain SUA levels of <360umol/l. None of the 65 patients that used allopurinol had a severe hypersensitivity reaction. The treatment of gout in a primary care-based population appears suboptimal and poorly concordant with the recent EULAR recommendations for the management of gout reflecting on primary care practitioners.

Author	Country (year)	Participants/database (sample size)	Key research questions	Key findings
(Annemans et al.)	Germany/ UK (2008)	Analysis of IMS Disease Analyzer (a longitudinal database) Patients with gout from Germany n = 34797 Patients from Germany included in the study n = 4006 Patients with gout from the UK n = 34071 Patients from the UK included in the study n = 7443	Analysis of IMS Disease Analyzer (a longitudinal database) with anonymised patient records maintained by 650 general practitioners in the UK and 400 general practitioners and internists in Germany for a study on gout management and co-morbidities.	Prevalence of gout in Germany and the United Kingdom was reported as 1.4%. In Germany, the most common co-morbidity was reported as diabetes in 25.9% of the population with gout while in the United Kingdom it was obesity, affecting 27.7%. Hypertension was common in both populations affecting 18.5% of the Germans and 17.5% of British patients with gout. Heart failure and myocardial infarction were reported in 10.8% and 5.8% of Germans with gout respectively and 7.1% of heart failure and 7.4% of myocardial infarction in British patients. In Germany and the UK 84.5% and 63% of gout patients respectively, received treatment. Allopurinol was prescribed to 93% Germans and 89% of UK patients with gout. Colchicine was prescribed in 15% of German patients and 16% of UK patients. 80.3% of patients in Germany received NSAID prophylaxis while in the UK, 89.4% of patients received NSAIDs. Allopurinol average daily dosage reflected 65.7% prescribing >200mg but ≤300mg in Germans and 63.3% in UK patients. Doses of >300mg were prescribed in 3.4% of German patients and 2.1% of patients in the UK. Average daily doses in the range of 50–100 mg were prescribed in 22.4% of those in Germany and 21% of patients in the UK. SUA levels were tested in 9% of Germans and 14% of UK patients. The amount of patients from both countries who had annual SUA tests was less than 1%. Gout flares were experienced by 41% of Germans and 72% of UK patients. The frequency of gout flares was positively correlated with the level of SUA.
(Owens et al.)	Ireland (2008)	20 point questionnaire General Practitioners n = 170	Assessing management of gout to EULAR 2006 guidelines	91% of GPs do not refer patients with gout. 89% diagnose gout with clinical acumen alone. 3% use arthrocentesis for synovial fluid evaluation.

				77% used SUA levels as a diagnostic tool. 66% started patients on ULT. 32% monitored SUA levels in patients on ULT. 86% routinely screened for co-morbidities.
(Yeap et al.)	Malaysia (2009)	Questionnaires total for doctors n = 128 Non- Rheumatologists n = 61 General Practitioners n = 67	Ascertain management of gout in Malaysia.	82% of doctors used clinical acumen. 73.4% of doctors used tophi as a marker for gout. 23.4% of doctors used nephrolithiasis as a marker for gout. 79.7% of doctors used SUA levels as a diagnostic tool. 41.4% of doctors would use arthrocentesis for gout diagnosis. 28.1% of doctors used radiographs as a diagnostic tool. 10.2% of doctors would use allopurinol to treat acute gout while 68% would use NSAIDs and 66.4% would use colchicine. Corticosteroids were not favoured by greater than 90% in all delivery modalities. 50% of participants would stop allopurinol in patients experiencing acute gout attacks. Allopurinol would be started 2 weeks after acute attack in 87.5% and continued lifelong by 54.7% of doctors. Alcohol cessation was advocated by 58.6% of participants. 15% of doctors would treat asymptomatic hyperuricaemia. Diagnosis of gout and Allopurinol use not consistent with current guidelines.

Author	Country (year)	Participants/database (sample size)	Key research questions	Key findings
(Roddy et al.)	UK (2010)	Analysis of 2 interlinked regional primary care databases. Consultations in Primary Care Archive during 2001 to 2004. Gout consultations n = 673	Assessment of gout diagnosis and management	583 patients (87%) had consulted for acute gout. 90 consults (13%) were not for acute gout. 68% (61/90) consults were for long term management and 24% (22/90) showed signs of improvement after attacks. Hypertension as a co-morbidity was found in (178/673) 26% of patients. Cardiovascular risk factors were found in (208/673) 31% of gout patients. In the 583 patients with acute gout, 68% were prescribed traditional NSAIDs and 15% colchicine. Antibiotics were prescribed in 5% of the patients. No intraarticular steroids were prescribed. The most frequently prescribed NSAIDs were diclofenac (41%), indomethacin (32%), naproxen (14%) and ibuprofen (11%). 7% were not prescribed any agent. Gastroprotective agents were co-prescribed in (67/395) 17% of patients on NSAIDs. Out of the 86 patients on colchicine, 0.5mg four times a day was prescribed in 57 patients (66%). Of the 673 patients consulting for gout, 157 patients (23%) were prescribed ULT. Of the patients on ULT, 98% (154/157) was on allopurinol. ULT was prescribed for 18% (119/673) of patients who consulted for acute gout within 12 months of the first gout attack. 23 patients of the 119 (19%) were started on allopurinol during the acute attack. Suboptimal care for acute gout in primary care.

Author	Country (year)	Participants/database (sample size)	Key research questions	Key findings
(Primatesta et al.)	USA (2011)	PharMetrics Patient-Centric Database Gout Patients included in the study n = 177637	Analysis of patients 20-89 years from the US with at least 2 diagnosis of gout claims between 1 Jan 1996 to Dec 2008	Hypertension was found in 36.1% and ischaemic heart disease in 10.2% of patients with co-morbidities. 1.2% of patients were hospitalised within the 12 months after the index presentation. 31.8% had their index visit at a primary care physician office while 2.7% were diagnosed by rheumatology. Emergency visit was 5.9%. Traditional NSAIDs were used by 38.7%, corticosteroids 21% and colchicine 16.7% in acute gout. Allopurinol was prescribed in 31.8%. 39% of patients did not receive any treatment during 1 year of gout diagnosis. During gout flares treated within 7 days, 67% of the patients received traditional NSAIDs while 39.8% received colchicine. Corticosteroids were prescribed to 26.7% patients. Allopurinol was prescribed to 29.9% of patients during the 7 days post gout flare.
(Fara et al.)	Argentina (2012)	Multiple choice questionnaire General Practitioners n = 86 Internal Medicine specialists n = 52 Rheumatologists n = 33	Evaluation of current treatment of gout in Buenos Aires	Gout was commonly seen by 51.5% of rheumatologists compared to 8.1% of GPs.11.5% of internal medicine specialists consulted gout patients. 51.5% of rheumatologists diagnosed gout on uric acid crystal identification, 28.8% of internal medicine and 26.7% of GPs. Tophi were observed by 60.6% of rheumatologists, 30.8% of internal medicine and 30.2% of GPs. Rheumatology and internal medicine prescribe colchicine in 75.8%, 80.8% respectively with 7.7% of GPs doing the same. Rheumatologists measure BMI less often than internal medicine specialists with 66.7% and 92.3% and waist circumference with 45.5% and 75% respectively.

Author	Country (year)	Participants/database (sample size)	Key research questions	Key findings
(Cottrell et al.)	UK (2013)	An electronic database of a North Staffordshire primary care medical practice Gout diagnosis n = 305	Audit criteria were developed from the EULAR and BSR/BHPR guidelines.	Among 305 gout patients, 74% had a recorded SUA level. 34% of patients had used ULT.25% of patients were currently taking ULT. Of those taking ULT, 99% were on allopurinol and 1% on probenecid. 20% of patients were started on allopurinol on the day they were diagnosed with gout. Starting doses of allopurinol were 100mg in 62%, 200mg in 6% and 300mg in 32%. 22% of the 305 patients had SUA levels done. Of the 76 patients currently taking allopurinol, 34% had SUA levels in the last year and 38% had a level ≤360umol/l. 304 patients with gout had a recorded BMI. Diet was discussed in 14%, fluid intake in 14% and alcohol intake 6%. 24% of patients with gout received a prescription for diuretics. (30/56) 54% were receiving lipid lowering therapy.
(Harrold et al.)	USA (2013)	Questionnaire Primary care physicians n = 838 Internal Medicine Physicians n = 387 Family Medicine Practitioners n = 444	Assessment of acute, intercritical and tophaceous gout treatment using European and American recommendations and guidelines	Greater than 80% of primary care physicians referred less than 10% of gout patients for rheumatology management. 9.6% of family medicine practitioners were aware of gout guidelines. 11.8% of internal medicine physicians were aware. 84% of primary care physicians would not aspirate an acute inflamed joint in a patient with renal dysfunction and 86.6% would order a SUA level. Colchicine was suggested by 58.8% of primary care physicians in acute management of renal patients with gout with 55.6% of family medicine practitioners recommending the same. NSAIDs were suggested by 50.5% of primary care physicians overall with 58.8% of all family medicine practitioners in acute management of renal patients with gout. Corticosteroids were suggested by 45% overall and by 40% of all family medicine practitioners in acute management of renal patients with gout.

				ULT was suggested by 15.4% overall and by 15% of all family medicine practitioners. 52.9 % of family medicine practitioners counselled patients appropriately to decrease pork, beef and organ meats. Use of NSAIDs for long term management of gout were recommended by 16.5% overall with 19.1% of all family medicine practitioners despite being used on renal patients with gout. Provision of prophylaxis when initiating ULT in patients with tophaceous gout was provided by 29.5% overall with 23.6% of family medicine practitioners in agreement. Findings are consistent with other studies, that acute and chronic gout are sub optimally managed by primary care doctors.

Author	Country (year)	Participants/database (sample size)	Key research questions	Key findings
(Li et al.)	China (2013)	10 point questionnaire Questionnaire total for Doctors n = 184 Rheumatologists n = 33 Non- Rheumatologists n = 151 Questionnaire total for Gout Patients n = 149	To investigate disease related knowledge of gout patients and doctors and identify targets for education	The pre requisite for gout as an overabundance of SUA was known by 98.7% of non-rheumatologists while MSU crystals in the joint space acute causing acute gout by 94% of non-rheumatologists. In the treatment of acute gout, allopurinol was prescribed by 9.3% by non-rheumatologists. In the treatment of chronic gout, 76% of non-rheumatologists started allopurinol while 7.3% and 16% started NSAIDs and colchicine respectively, to reduce SUA levels. 55.6% of non-rheumatologists knew the optimum SUA level target and 43.6% knew that ULT was life-long. 24% of non-rheumatologists stated they would stop allopurinol if a patient had an acute attack while on ULT and 12.5% of rheumatologists agreed with this assertion. 90.1% of non-rheumatologists believed hypertension was common in patients with gout. Further education should focus on non-rheumatologists and patients in the areas of ULT, duration of treatment, SUA level, and prophylaxis.
(Pascart and Flipo)	France (2013)	Questionnaire Total Doctors n = 977 Rheumatologists n =98 General Practitioners n = 879	To assess common practice on the issue of gout	90.2% of GPs found hyperuricaemia useful for the diagnosis of gout while 47.6% found synovial fluid MSU identification necessary for gout diagnosis. 94.8% of doctors prescribed prophylaxis for 63 days against acute gout attacks. 14.1% of doctors would assess for metabolic syndrome. 7.2% of GPs would assess patients' alcohol consumption. Consistency with international guidelines but management of gout needs to improve in France.

Author	Country (year)	Participants/database (sample size)	Key research questions	Key findings
(Ozturk et al.)	Turkey (2016)	Detailed Clinical and Laboratory Evaluation at a Rheumatology Clinic confirming gout diagnosis with questionnaire Gout Patients n = 319 Primary Care Practitioners n = 53 Orthopaedics n = 101 Physical Therapy and Rehabilitation n = 29 Internal Medicine n = 70 Rheumatology n = 49 Other n = 17	Questionnaire on first admission of gout, speciality of doctor admitting and gout management prescribed	56.9% of patients had hypertension as co-morbid disease. Out of 313 patients admitted, 6.1% had joint aspiration performed during the acute attack. There was no statistical significance between the different specialities. 12.8% of patients overall were referred to another centre without any treatment including analgesia. Out of primary care, 28.8% were referred. Referral rates was significant for primary care vs all other specialities ($p<0.05$). NSAIDs were the preferred first line agent in acute attacks of gout with 60.06% of all patients being prescribed as monotherapy or in combination. There was no statistical difference in prescribing practices between other subspecialties and primary care except physical therapy ($p<0.05$). NSAID prescriptions did not differ in co-morbid patients. 58.15% of all patients were treated with colchicine for acute gout. Primary care prescribed colchicine less than other subspecialties except orthopaedics were there was no difference ($p<0.05$). 7.99% of patients were treated with corticosteroids with none from primary care. 11.9% of all patients were treated with allopurinol during an acute attack in combination with other treatment. 5.8% of patients from primary care with 20.9% from internal medicine and 27.1% from rheumatology. 7.5 % of patients from primary care received allopurinol. 34.5% of patients from orthopaedics were started on allopurinol. Diet and lifestyle modification was recommended to 90.6% of patients. 9.4% of patients from primary care were prescribed modifications and 19.8% by orthopaedics. Colchicine was prescribed in long term management of gout significantly more than allopurinol ($p<0.001$). 30.2% of primary care patients were treated with colchicine only as long term management. Acute and chronic gout care suboptimal in Turkey and urgent educational interventions are needed for both primary care practitioners and other specialities.

Author	Country (year)	Participants/database (sample size)	Key research questions	Key findings
(Spaetgens et al.)	Netherlands (2016)	Mixed Methods Study (GRAMMS) General Practitioners n = 32	Questionnaires on gout knowledge and 9 item Brief Illness Perceptions Structured interviews with general practitioners in the context of gout daily practice	**Open ended answer analysis** 15.6% had recently updated their knowledge on gout within 1 year. The cause of gout was correctly identified in 96.9% of GPs as an overabundance of uric acid and the cause of acute gouty attacks by 93.8% as crystals. 87.5% of GPs chose ULT allopurinol for lowering SUA levels. 12.5% of GPs knew the target SUA level. 75% of GPs chose losing weight as a non-pharmacological means of lowering SUA level in the multiple choice question. 62.5% of GPS answered lifelong as the duration of the ULT. 71.9% recommended daily colchicine as prophylaxis. 50% knew that hypertension was commonly associated with gout. **Interview analysis** 31.2% of GPs believed SUA levels were necessary to diagnose gout while 31.2% believed SUA levels were not necessary for a diagnosis 18.8% stated starting ULT when tophi are found. 37.5% of GPs stated not prescribing ULT lifelong. 28% of GPs did not prescribe prophylaxis. Of the 72% that do prescribe prophylaxis, none do so for more than 2 months. 81.2% looked at SUA levels. 18.8% only do so if patients continue having attacks. 53.1% based effectiveness of ULT on clinical features such as absence of gout attacks. 12.5% gave dietary advice and 21.9% claimed adjustment of diet not effective.

Author	Country (year)	Participants/database (sample size)	Key research questions	Key findings
(Terrill and Riordan) .	Australia (2017)	Questionnaires given to doctors that belong to the Illawarra Network General Practitioners n = 45 Medical Officers n = 42	Assessment of management of gout	65.1% of respondents altogether felt their knowledge of gout to be adequate 59.1% of GPs answered that joint aspiration was the best test to diagnose gout while 85.7% of medical officers felt the same. 36.4% of GPs felt clinical suspicion was better. In the use of colchicine for acute gout management, 59.1% would give 1mg colchicine, 0.5mg an hour later followed by 0.5mg twice daily compared to 9.5% of medical officers. A further 20.5% of GPs would use 1mg twice daily. After an acute attack of gout, ULT would be started 14 days later by 47.7% of GPs compared to 69% of medical officers. GPs were more likely to start prescribing ULT within 7 days compared to medical officers, 52.3% to 31% respectively. 45.3% of all respondents would dose ULT to treat to target while 46.5% would dose to creatinine clearance. Prophylaxis would be started by 81.8% of respondents but continued only by 17.4% for 3 to 6 months. Poor adherence to recommended practice on colchicine and allopurinol.

Author	Country (year)	Participants/database (sample size)	Key research questions	Key findings
(Terrill and Riordan)	Australia (2018)	Surveys were sent to the 11/15 hospital networks during the 2016 orientation week Medical graduates n = 164	Assessment of knowledge and beliefs of gout, management and adequacy of university teaching	81.1% stated gout was a serious condition. 54.9% stated reading gout management guidelines. 51.2% felt that they were taught adequately on acute gout management while 37.2% thought they were adequately taught on chronic gout management. 19.5% (32/164) believed ULT should be withheld if already on ULT during an acute attack. 7.3% believed the dose of ULT should be increased. 3.1% (5/162) believed methotrexate and corticosteroids would allow for a quicker recovery during an acute attack. 7.4% believed starting allopurinol with NSAIDs would hasten recovery. The recommended colchicine dose for acute gout attacks by EULAR 2016 gout guidelines was considered by 28% (39/139) of medical graduates. 7.9% would prescribe 0.5mg three times a day while 14.4% would prescribe every 6hrs. 44..4% (72/162) stated starting allopurinol at least 14 days after an acute attack while 8% would start during an attack. 56.2% would dose allopurinol based on renal function while 19.1% stated using SUA levels. 23.5% (38/162) stated titrating allopurinol to SUA levels monthly while 25.3% would assess 6 monthly and titrate to renal function. 18.5% would assess 6monthly and titrate to SUA levels. 56.8% (92/162) were aware of prophylaxis being recommended when ULT is initiated. Prophylaxis options of colchicine and NSAIDs were selected by 46.7% (42/90) and corticosteroids and NSAIDs by 20%. 28.4% (25/88) would continue prophylaxis till the SUA level is within target range or for at least 3 to 6 months. 15.9% would stop prophylaxis after a week. 35% (56/160) were aware of other ULT agents such as febuxostat or benzbromarone. New graduates knowledge of gout management is inadequate.

The fact remains that the management of gout is suboptimal around the world. ***(Jeyaruban et al., 2015, Richette et al., 2017)*** Effective treatment is dependent on both the patient and the prescribing health practitioner.

There are no studies currently in South Africa that examines the knowledge and management of gout by GPs or a comparison of outcomes to treatment guidelines.

In light of this, we plan to investigate and report on the knowledge and practices of GPs in South Africa and compare with other studies any significant differences in treatment practice of gout.

1.11. **Aim and Objectives**

1.11.1. **Aim**

The aim of the study was to investigate the level of clinical expertise in the diagnosis and management of gout by GPs in South Africa.

1.11.2. **Objectives**

1) To determine the knowledge and practices of GPs in the diagnosis and management of acute gout and long term prevention and management of chronic gout in relation to current international quality indicators and clinical practice guidelines.
2) To compare differences in practice between subgroups by age of GPs, type of practice and amount of gout patients seen per month

CHAPTER 2 : SUBJECTS AND METHODS

2.1. Study design

A cross sectional, electronic survey of GPs in private practice.

2.2. Subjects and Methods

General Practitioners practising in two provinces in the Republic of South Africa viz. Gauteng and Kwa-Zulu Natal were invited by email to participate in an electronic survey. Email addresses were accessed from databases, Medpages™ and Upper South Coast Independent Practitioners Association. The invitations were sent over a three month period with the aim of achieving at least 200 completed questionnaires in 2016 with a single reminder one month following the initial email invitation. Medpages™ is a medical communications company that specialises in advertising on behalf of healthcare professionals, hospital groups and health insurance companies with a large database of GPs' contact details. For the purposes of the study and cost constraints, only 2000 email invitations were sent using this service. The balance of the invitations was sent using the Upper South Coast Independent Practitioners Association database. In total 2891 email invitations were sent to GPs.

The email questionnaire was designed using eSurv™. eSurv™ is a free survey tool for creating online surveys, forms, polls and questionnaires. The questionnaire was designed with certain questions having multiple answers and unless the initial sets of questions were answered, the questionnaire would not progress. We also sought not to make the questionnaire overbearing and to keep the completion time under 10 minutes. The questionnaire was piloted and edited amongst local medical practitioners before finalisation

and mass email circulation. Response to the email by clicking on the link was taken as consent to participate after reading the participant letter (Appendix A). Briefly the questionnaire (Appendix B) included 19 questions without demographics, a clinical vignette as a trigger and covered questions on diagnosis, investigations and management of gout. Incomplete questionnaires were excluded. Completed questionnaires were uploaded anonymously onto a database on the eSurv™ website upon the questionnaire being submitted upon completion, where it was analysed and that data exported to Microsoft Excel and Medcalc™ ,analysed and presented in Microsoft Word™. The study was approved by the University of the Witwatersrand Human Research Ethics Committee. (Appendix C)

2.3. Statistical Analysis

Responses to questions are presented as percentages. To compare responses between subgroups, the chi square test was applied. A p-values <0.05 were deemed to be significant. Significant results were presented as odds ratio with 95% confidence interval.

CHAPTER 3 : RESULTS

A total of 2891 invitations were emailed (Fig 3.1). Responses were received from 227 (7.85%) GPs. Six responses were excluded from the final analysis because they were deemed to have been inadequately completed. Hence, total responses that were included for analysis were 221 (7.64%).

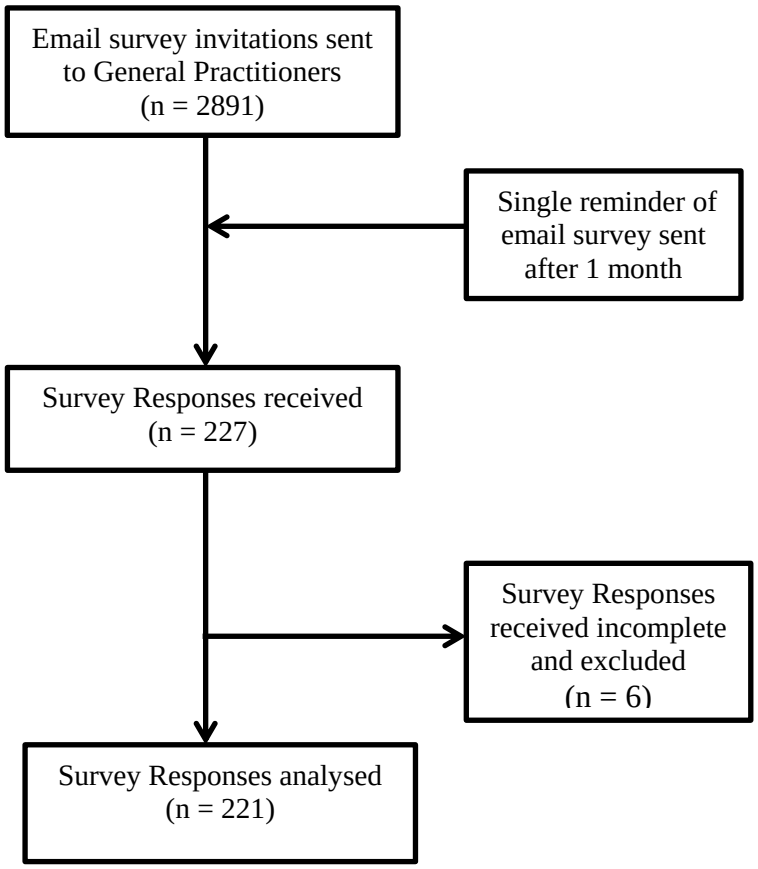

Figure 3.1 Outline of email survey invitations and outcome of responses.

Table 3.1 summarises the demographics, type of practice, clinical experience and gout management updates of the participants. The majority of the participants responded were in the age group of <40 years (29.9%), were males (51.6%) and in solo practice (54.3%). In terms of clinical experience, most participants had seen 2 or more cases per month of acute gout (71.5%) but just over 50% consulted 5 or more gout cases per month. With respect to updating of gout knowledge only 54.3% had done so in the last 2 years with a near equal split between conference attendance, general articles on gout and gout clinical guidelines.

Table 3.1 Demographics and gout experience of General Practitioners

Question no.	Question/Variable	Response	n (%)
Demographics: Question 1	Age band	Age <30 <40 <50 <60 >60	 18 (8.1) 66 (29.9) 62 (28.0) 43 (19.5) 32 (14.5)
Demographics: Question 2	Gender	Men Women	114 (51.6) 107 (48.4)
Demographics: Question 3	Type of practice	Solo Group	120 (54.3) 101 (45.7)
Question 8	How many acute gout patients are seen in a month?	<2 2 to 3 >3	63 (28.5) 78 (35.3) 80 (36.2)
Question 7	How many gout patients are seen in a month?	<5 5 to 10 >10	103 (46.6) 99 (44.8) 19 (8.6)
Question 18	Have you updated your knowledge on gout in the last 2 years?	Yes No	120 (54.3) 101 (45.7)
Question 19	*If yes, how did you update yourself?	Conference Guideline Article	32 (26.7) 46 (38.3) 42 (35.0)

*n=120

The responses to the clinical vignette revealed 94.6% of participants considered gout as part of the differential diagnosis (Table 3.2). Only 19.5% considered septic arthritis as a differential diagnosis while 40.5% considered osteoarthritis, a non-inflammatory arthritis. Most participants based their confirmatory diagnosis on clinical examination and laboratory

blood tests. A quarter of participants relied solely on their clinical acumen while joint aspiration was considered by only 2.3% of participants to establish a diagnosis in acute inflammatory arthritis. Specifically, in cases of suspected gout, joint aspiration would never be performed by 71% of participants.

In the acute management of an acutely inflamed joint, more than half of the respondents favoured diclofenac as the NSAID of choice. However, in a suspected case of acute gout the drug of choice was colchicine by over a quarter of respondents followed by intramuscular (IM) NSAIDs (21.3%). Non-steroidal anti-inflammatory drugs either alone or in combination were prescribed by 69.7% of participants while corticosteroids either alone or in combination were prescribed by 15.4% of participants as a first line treatment option for acute gout.

Table 3.2 Diagnosis and acute management of gout

Question no.	Variable/Question	Response	n (%)
*Question 1	What are the 2 most likely causes of arthritis in this patient?	Rheumatoid arthritis	1 (0.5)
		Rheumatoid arthritis and Gouty arthritis	32 (14.5)
		Rheumatoid arthritis and Osteoarthritis	6 (2.7)
		Rheumatoid arthritis in differential diagnosis	39 (17.6)
		Osteoarthritis	3 (1.4)
		Osteoarthritis and Gouty arthritis	80 (36.0)
		Osteoarthritis and Septic arthritis	1 (0.5)
		Osteoarthritis in differential diagnosis	90 (40.7)
		Gouty arthritis	56 (25.3)
		Gouty arthritis and Septic arthritis	41 (18.6)
		Gouty arthritis in differential diagnosis	209 (94.6)
		Septic arthritis	1 (0.5)
		Septic arthritis in differential diagnosis	43 (19.5)
Question 2	How do you generally make/confirm the diagnosis?	Clinical exam and Blood tests eg.(CRP,RF,ESR,UA)	142 (64.3)
		Clinical exam and Joint aspiration	5 (2.3)
		Clinical exam and Radiographs	18 (8.1)
		Clinical exam only	56 (25.3)
Question 5	How often do you perform joint aspiration in a patient suspected to have gout?	Always	9 (4.1)
		Never	157 (71.0)
		Sometimes	55 (24.9)
Question 3	Which NSAIDs do you prefer prescribing in the treatment of an acute swollen joint?	Indomethacin	19 (8.6)
		Diclofenac	117 (53.0)
		Ibuprofen	27 (12.2)
		Cataflam	58 (26.2)
*Question 4	In the patient above in whom a diagnosis of gout is made, what is your anti-inflammatory of choice?	Oral NSAIDs	22 (10.0)
		Oral NSAIDs, oral steroids	2 (0.9)
		Oral NSAIDs, oral colchicine	14 (6.3)
		Oral NSAIDs, IM NSAIDs	11 (5.0)
		Oral NSAIDs, oral steroids, IM NSAIDs	2 (0.9)
		Oral NSAIDs, oral steroids, oral colchicine	1 (0.4)
		Oral NSAIDs, oral colchicine, IM NSAIDs	10 (4.5)
		Oral NSAIDs with combination therapy	69 (31.2)
		IM NSAIDs	47 (21.3)
		IM NSAIDs, oral steroids	5 (2.3)
		IM NSAIDs, oral colchicine	25 (11.3)
		IM NSAIDs, oral steroids, oral colchicine	8 (3.6)
		IM NSAIDs with combination therapy	115 (52.0)
		Oral steroids	5 (2.3)
		Oral steroids, oral colchicine	4 (1.8)
		Oral steroids with combination therapy	34 (15.4)
		Oral colchicine	58 (26.2)
		Oral colchicine with combination therapy	127 (57.5)
		All	7 (3.2)
Question 4	In the patient above in whom a diagnosis of gout is made, what is your anti-inflammatory of choice?	NSAIDs prescribed for acute gout	
		Yes	154 (69.7)
		No	67 (30.3)

*Participants could choose more than 1 option

In the chronic management of gout (Table 3.3), 14.9% of participants would always start ULT. After the first attack of gout, 25.8% of participants would start ULT while 70.1% would start ULT after 2 attacks. However, 31.2% of participant GPs would only start ULT for tophaceous gout. Majority of participants titrate allopurinol using clinical response while 14.9% never do.

The most commonly prescribed dose of allopurinol by participants (80.1%) was 300mg. Prophylaxis was always prescribed by a minority of participants at 12.7% with a further 17.6% never prescribing.

Table 3.3 Chronic management of gout

Question no.	Variable/Question	Response	n (%)
Question 12	How often do you treat gout with a ULT like allopurinol?	Never Sometimes Almost always Always	7 (3.2) 66 (29.9) 115 (52.0) 33 (14.9)
*Question 11	When do you consider using ULT like allopurinol in a patient with gout?	≥2 attacks in a year, ≥2 attacks in a year, 1st attack ≥2 attacks in a year, tophi ≥2 attacks in a year, kidney stones ≥2 attacks in a year, 1st attack, tophi ≥2 attacks in a year, tophi, kidney stones ≥2 attacks in a year, in all combinations 1st attack of gout 1st attack of gout, tophi 1st attack of gout, tophi and kidney stones After first attack of gout in all combinations Kidney stones Kidney stones, tophi History of kidney stones in all combinations Tophi Presence of tophi in all combinations All options	91 (41.2) 1 (0.4) 25 (11.0) 8 (3.6) 2 (0.9) 28 (12.7) 155 (70.1) 49 (22.0) 1 (0.4) 3 (1.4) 57 (25.8) 3 (1.4) 3 (1.4) 45 (20.4) 7 (3.2) 69 (31.2) 1 (0.4)
Question 14	Do you titrate the dose of allopurinol on the basis of?	Serum uric acid level Never Clinical response	64 (29.0) 33 (14.9) 124 (56.1)
Question 13	What dose of allopurinol do you most commonly prescribe?	100mg 300mg >300mg	42 (19.0) 177 (80.1) 2 (0.9)
Question 10	How often do you co-prescribe colchicine or a NSAID when initiating ULT like allopurinol?	Always Almost always Occasionally Never	28 (12.7) 80 (36.2) 74 (33.5) 39 (17.6)

*Participants could choose more than 1 option

Dietary advice was always considered by 91.8% of participants with 90% focussing on alcohol, weight and redmeat reduction (Table 3.4). As part of lifestyle modification, drugs taken concomitantly with gout were assessed and 81.9% chose to stop or change HCTZ with an alternative

Just over 25.8% of participants have >50% of their gout patients with hypertension. Just over a quarter of participants disagreed about gout being a risk factor for ischaemic heart disease.

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Table 3.4 Lifestyle modification advice and co-morbidities

Question no.	Variable/Question	Response	n (%)
Question 15	How often do you give patients with gout dietary advice?	Always Sometimes Never	203 (91.8) 17 (7.7) 1 (0.5)
*Question 16	What aspects of dietary advice do you focus on?	Alcohol reduction Alcohol and redmeat reduction Alcohol and weight reduction Weight reduction Redmeat reduction All of the above	3 (1.4) 14 (6.2) 1 (0.5) 1 (0.5) 3 (1.4) 199 (90.0)
*Question 9	Which medication would you consider stopping or changing if possible in this patient presenting with acute gout?	Simvastatin Simvastatin and HCTZ Simvastatin in all combinations HCTZ HCTZ and Enalapril HCTZ in all combinations Enalapril Enalapril in all combinations All of the above	10 (4.5) 7 (3.2) 31 (14.0) 181 (81.9) 7 (3.2) 209 (94.6) 2 (0.9) 23 (10.4) 14 (6.3)
Question 6	In the patients with gout in your practice, what proportion has concomitant hypertension?	<10% 10% to 50% >50% >90%	26 (11.8) 134 (60.6) 57 (25.8) 4 (1.8)
Question 17	Do you believe that gout is a risk factor for ischaemic heart disease?	Strongly agree Agree Disagree	40 (18.1) 123 (55.7) 58 (26.2)

*Participants could choose more than 1 option

Subgroup analysis of the data was done to compare responses by type of practice (solo vs group), age of practitioners (under 40 years vs over 40 years) and by number of gout patients seen per month. Only significant findings were represented in the following tables:

Table 3.5 Comparison of General Practitioners in solo practice versus group practice

Variable	Total (n=221)	Solo Practice (n=120)	Group Practice (n=101)	Odds Ratio (95% CI)	P-value
Male Female	114 (51.6) 107 (48.4)	73 (60.8) 47 (39.2)	41 (40.6) 60 (59.4)	2.27 (1.32 - 3.90)	0.003
Start Allopurinol after 2 gout attacks Yes No	 155 (70.1) 66 (29.9)	 77 (64.2) 43 (35.8)	 78 (77.2) 23 (22.8)	0.53 (0.29 - 0.96)	0.035
Gout risk factor in Ischaemic Heart Disease Agree Disagree	 163 (73.7) 58 (26.2)	 98 (81.7) 22 (18.3)	 65 (64.4) 36 (35.6)	2.47 (1.33 – 4.57)	0.004

Male participant GPs were more likely to be in solo practice compared to female GPs. Allopurinol was started after 2 attacks, a quality of care indicator in ACR 2004 ***(Mikuls et al., 2004)***, more often by GPs in group practice. GPs in solo practice were more in agreement that gout is a risk factor for ischaemic heart disease.

Table 3.6 Comparison of responses by General Practitioners under 40 years versus General Practitioners over 40 years

Variable	Total (n=221)	Age <40 (n=84)	Age >40 (n=137)	Odds Ratio (95% CI)	P-value
Solo Practice Group Practice	120 (54.3) 101 (45.7)	34 (40.5) 50 (59.5)	86 (62.8) 51 (37.2)	0.40 (0.23 - 0.70)	0.001
Male Female	114 (51.6) 107 (48.4)	27 (32.1) 57 (67.9)	87 (63.5) 50 (36.5)	0.27 (0.15 - 0.48)	<0.0001
Acute Gout <2 ≥2	 63 (28.5) 158 (71.5)	 33 (39.3) 51 (60.7)	 30 (21.9) 107 (78.1)	2.31 (1.27 - 4.19)	0.006
Allopurinol doses prescribed 100mg ≥300mg	 42 (19.0) 179 (81.0)	 26 (31.0) 58 (69.0)	 16 (11.7) 121 (88.3)	2.39 (1.69 - 6.81)	0.0004
Updated Knowledge in the last 2 years on gout management Yes No	 120 (54.3) 101 (45.7)	 31 (36.9) 53 (63.1)	 89 (65.0) 48 (35.0)	0.32 (0.18 - 0.56)	0.0001

Participant GPs over 40 years old are more likely to be in solo practice compared to under 40 year old GPs and male in the survey. Participants over 40 years were also more likely to have

updated their knowledge on gout management in the last 2 years. GPs under 40 years performed better treating patients with acute gout and prescribing guideline recommended dose of allopurinol.

Table 3.7 Comparison of less than 5 gout patients seen per month versus 5 or more gout patients seen by General Practitioners in a month

Variable	Total (n=221)	Gout patients seen <5 in a month (n=103)	Gout patients seen ≥5 in a month (n=118)	Odds Ratio (95% CI)	P-value
Age				1.84 (1.06 - 3.18)	0.03
<40 General Practitioners	84 (38.0)	47 (45.6)	37 (31.4)		
>40 General Practitioners	137 (62.0)	56 (54.4)	81 (68.6)		
Corticosteroids prescribed for acute gout				0.36 (0.16 - 0.80)	0.011
Yes	34 (15.4)	9 (8.7)	25 (21.2)		
No	187 (84.6)	94 (91.3)	93 (78.8)		
Joint Aspiration				0.41 (0.22 - 0.75)	0.004
Almost Always	64 (29.0)	20 (19.4)	44 (37.3)		
Never	157 (71.0)	83 (80.6)	74 (62.7)		
Acute Gout				7.62 (3.81 -15.25)	<0.0001
<2	63 (28.5)	50 (48.5)	13 (11.0)		
≥2	158 (71.5)	53 (51.5)	105 (89.0)		
Allopurinol doses prescribed				2.77 (1.37 - 5.62)	0.004
100mg	42 (19.0)	28 (27.2)	14 (11.9)		
>300mg	179 (81.0)	75 (72.8)	104 (88.1)		
Prophylaxis with colchicine or NSAIDs when prescribing ULT				0.54 (0.32 - 0.93)	0.025
Almost Always	108 (48.9)	42 (40.8)	66 (55.9)		
Occasionally	113 (51.1)	61 (59.2)	52 (44.1)		
Updated Knowledge in the last 2 years on gout management				0.44 (0.27 - 0.76)	0.003
Yes	120 (54.3)	45 (43.7)	75 (63.6)		
No	101 (45.7)	58 (56.3)	43 (36.4)		

Under 40 year old participant GPs were more likely to consult less than 5 patients with gout a month compared to over 40 year old GPs. General practitioners who consulted less than 5 patients a month performed better in assessing an inflamed joint and dosing allopurinol according to guideline recommendations on initiation but saw less than 2 acute gout patients per month. General Practitioners who consulted more than 5 gout patients a month were more

likely to prescribe corticosteroids for the treatment of acute gout, perform joint aspiration and prescribe prophylaxis when initiating ULT. These GPs were also more likely to have updated their knowledge on gout management in the last 2 years.

Table 3.8 Comparison of less than 2 acute gout patients seen per month versus 2 or more gout patients seen by General Practitioners in a month

Variable	Total (n=221)	Acute Gout patients seen ≤2 in a month (n=63)	Acute Gout patients seen ≥2 in a month (n=158)	Odds Ratio (CI 95%)	P-value
NSAIDs prescribed for acute gout				0.5 (0.27 - 0.92)	0.026
Yes	154 (69.7)	37 (58.7)	117 (74.1)		
No	67 (30.3)	26 (41.3)	41 (25.9)		
Allopurinol doses prescribed				2.23 (1.11 - 4.5)	0.022
100mg	42 (19.0)	18 (28.6)	24 (15.2)		
≥300mg	179 (81.0)	45 (71.4)	134 (84.8)		
Updated Knowledge in the last 2 years on gout management				0.4 (0.22 - 0.72)	0.002
Yes	120 (54.3)	24 (38.1)	96 (60.8)		
No	101 (45.7)	39 (61.9)	62 (39.2)		

Participant GPs who consulted 2 or more patients with acute gout in a month were more likely to prescribe NSAIDs and also to have updated their knowledge on gout management in the last 2 years. General Practitioners who consulted less than 2 patients for acute gout in a month were more consistent in prescribing allopurinol at the recommended initiating dose.

CHAPTER 4 : DISCUSSION

This electronic survey is the first study that has explored the clinical expertise and practices in the diagnosis and management of gout amongst GPs in South Africa. The study showed the majority of GPs in the survey (94.6%), performed well in diagnosing gout as well as in dispensing lifestyle modification advice. However, when assessing other areas of management in relation to published quality indicators for gout (APPENDIX D), the participating GPs performed suboptimal.

With the increased prevalence of gout reported around the world, one of the many concerns noted was the misdiagnosis and or delayed diagnosis of gout in the primary care population. ***(Harrold et al., 2013, Kuo et al., 2015, Richette et al., 2017)***

General practitioners (86%) are confident in the management of gout when compared to other musculoskeletal conditions. ***(Mikuls et al., 2005)*** and are reasonably accurate to specialists in diagnosing gout clinically. ***(Roddy et al., 2007)*** Our study demonstrated in a practical scenario compared to a straightforward question on diagnostic confidence that 94.6% of GPs surveyed identified gout as part of their differential diagnosis.

Interestingly, septic arthritis was selected by 19.5% of respondents in their differential diagnoses. This is a cause for concern as septic arthritis should always be considered a differential diagnosis especially if considering an acute inflamed joint and should be actively excluded. It was noted that gouty arthritis and septic arthritis together as differentials received 18.6% of consideration among general practitioners which we considered the most correct choice.

In the survey, GPs (64%) use biochemical tests such as inflammatory markers and SUA levels to confirm the diagnosis. In other studies, large majorities of respondents used SUA to diagnose gout. ***(Harrold et al., 2013, Owens et al., 2008, Pascart and Flipo, 2013,***

Spaetgens et al., 2016, Yeap et al., 2009) This practice however is fraught with problems of non-specificity with regards to confirming a diagnosis and may lead to the currently non-recommended treatment of asymptomatic hyperuricaemia.

Joint aspiration has a multi-faceted role of being a gold standard for the diagnosis of gout by the identification of MSU crystals by polarising microscopy which has 100% sensitivity as well as excluding a diagnosis of septic arthritis with reasonable certainty. ***(Neogi et al., 2015, Underwood, 2006)*** In a study, 84% of primary care practitioners would not aspirate an acutely inflamed joint. ***(Underwood, 2006)*** In other health professional studies, 11%, 3% and 6.1% would perform joint aspiration respectively which indicates that this reluctance is a common finding. ***(Owens et al., 2008, Ozturk et al., 2016, Underwood, 2006)***

In our study when assessing an acute arthritis, joint aspiration was the least utilised test with only 2.3% of GPs prepared to perform diagnostic arthrocentesis in an inflamed joint. When joint aspiration for gout was specifically assessed, the majority of GPs in the study (71%) would never perform joint aspiration to confirm or establish a diagnosis.

However, as gout is mostly treated by GPs due to effective treatment being available in the acute setting for pain relief, the use of joint aspiration to detect MSU crystals becomes less viable in clinical practice. ***(Doherty et al., 2012)*** This is likely due to time constraints in busy practice, reduced confidence in the skill of joint aspiration, hesitancy in aspirating as an invasive procedure as well as the resources to make a timeous diagnosis. It is also likely that most patients diagnosed present with classical signs and symptoms where tests to verify the diagnosis are regarded as unnecessary and are treated with an almost ‘syndromic’ approach.

More than a quarter (26%) of respondents used clinical acumen alone to diagnose patients in comparison to other studies reflecting a much higher proportion of respondents. ***(Owens et al., 2008, Yeap et al., 2009)*** With regard to the gout classification, clinical acumen may be used to diagnose gout but only prove successful in the most classical of case

presentations. Secondary and other unusual presentations of gout maybe misdiagnosed or missed. ***(Neogi et al., 2015)***

Non-steroidal anti-inflammatory drugs are a mainstay of treatment for inflammatory arthritis like gout and are recommended where there are no contraindications. ***(Richette et al., 2017, van Durme et al., 2014)*** Almost 52% of GPs considered IM NSAIDs as an acceptable treatment option for acute gout and surprisingly 21.3% of GPs stated that IM NSAIDs would also be their sole option. There is no disparagement for IM NSAIDs use in the treatment of acute gout; however efficacy might be questioned in terms of duration of action and period of treatment. ***(Richette et al., 2017)***

Oral NSAIDs as a sole option accounted for nearly 10% of responses with an unexpectedly low 31.2% across all responses as a treatment option despite the wide use of 'gout packs' (combinations of NSAIDs, corticosteroids and possibly colchicine).

Respondents to the study (53%) preferred using diclofenac sodium as the NSAID of choice to treat an acute inflamed joint similarly to ***(Roddy et al., 2010).*** With the scenario in mind, the majority of GPs (94.6%) considered gout as a diagnosis but only 9% prescribed indomethacin as their NSAID of choice in comparison to a study in the United Kingdom where indomethacin was the favoured NSAID. ***(Underwood, 2006)*** Indomethacin has uricosuric properties compared to other NSAIDs such as naproxen and diclofenac. ***(Stamp and Chapman, 2013)***

A large minority of respondents (26.2%) prescribed oral colchicine as monotherapy to treat acute gout in comparison to a study in Turkey where 58.15% of GPs used colchicine as monotherapy. ***(Ozturk et al., 2016)*** In various studies, colchicine prescriptions varied from 15% to 45% in the treatment of acute gout. ***(Jeyaruban et al., 2015)***

Oral corticosteroid use may also cause severe adverse effects at high doses taken over long periods of time, however in the treatment of acute gout is recommended for only a short

duration at moderate doses and with a more favourable side effect profile. Comparison of oral steroids and NSAIDs found equal effectiveness in the treatment of gout. ***(Richette et al., 2017***) In this study, oral corticosteroids was underutilised with 15.4% of surveyed GPs prescribing to treat acute gout. General practitioners who consulted more gout patients per month were more likely to prescribe corticosteroids on subgroup analysis.

With regards to prophylaxis it was noted in the study that 18% of respondents did not prescribe any prophylactic agent when starting ULT and that a small minority of GPs (12.7%) would always prescribe prophylaxis. This is in comparison to an American study where only 23.6% family practitioners provided prophylaxis and a Brazilian study on rheumatologists had 65% always prescribing prophylaxis. ***(Harrold et al., 2013, Vargas-Santos et al., 2015)*** There has always been apprehension to the prescription and the duration of prophylaxis possibly due to inadequate training and information at undergraduate level where gout is not a priority. ***(Roddy et al., 2007)***

Allopurinol is the first line ULT due to its safety, inexpensive cost, ease of dosing and tolerability. ***(Richette et al., 2017, Stamp and Chapman, 2013)*** In our study only 14.9% of GPs always considered ULT prescription with 52% reporting almost always prescribing. The under-prescription of ULT is also evident in other studies despite being the key to curing gout. Primary care practitioners reported 23% to 25% of their patients with gout were on ULT. ***(Jeyaruban et al., 2015)*** In a UK study approximately 25% of patients received ULT within 1 year from diagnosis and only 33% of prevalent patients received ULT at all. ***(Kuo et al., 2015)*** Another study from the UK showed that only 30% of eligible patients were on ULT. ***(Roddy et al., 2007)*** In an American study, less than 20% of primary care practitioners prescribed optimal treatment which involved ULT and prophylaxis in the intercritical period and even with patients with tophaceous gout. ***(Harrold et al., 2013)***

A common underlying concern noted is the reluctance by GPs to initiate ULT and the awareness of when to commence. ***(Jeyaruban et al., 2015, Kuo et al., 2015)*** As per previous ACR 2012 guideline recommendations, majority (70%) of GPs decided to initiate ULT after 2 or more attacks of gout per year. ***(Khanna et al., 2012a)*** Nearly a quarter of GPs would initiate ULT at the first onset of proven gout reflecting the recommendation of starting ULT during an acute attack provided anti-inflammatory treatment was adequate by the ACR 2012 guideline. ***(Khanna et al., 2012a)***

However, only 31.2% would consider initiating ULT in patients with tophaceous gout alone or with other characteristics which is an ACR 2018 quality of care indicator (APPENDIX D) ***(FitzGerald et al., 2018)***

The 2016 EULAR guidelines recommend beginning a discussion and implementation of ULT after the first attack of proven gout. ***(Richette et al., 2017)*** Urate lowering therapy initiation is the goal of chronic gout treatment as established above. The EULAR 2016 guidelines recommend ULT should be initiated at low dose and titrated upwards to avoid precipitating acute flares of gout and hypersensitivity reactions which will improve adherence in the long term. The guidelines also recommend in all patients regardless of normal kidney function, allopurinol be prescribed at low dose starting at 100mg and increased at 2 weekly or monthly increments. ***(Richette et al., 2017)*** An overwhelming majority (80%) of general practitioners chose to initiate ULT at the familiar fixed dose of 300mg allopurinol. A minority (19%) prescribed 100mg when initiating ULT which is an ACR 2018 quality of care indicator with 1% starting at a dose above 300mg. ***(FitzGerald et al., 2018)***

Serum urate levels maintained at levels less than 360umol/l is the recommended level at which dissolution of uric acid crystals occur and saturation of uric acid in joints and soft tissues are prevented. ***(Roddy et al., 2007)*** Less than a third of GPs (29%) used SUA levels to guide their prescription of ULT and treat to target. The majority (56%) stated using clinical

response to titrate ULT which is not a recommended practice. Throughout numerous studies it was noted that patients on ULT did not have their SUA levels checked and by extrapolation, GPs are not ordering them. ***(Jeyaruban et al., 2015)*** This result reflects most study findings that even if ULT is prescribed, its effects on SUA are not monitored which hamper treating to target. ***(Doherty et al., 2012)***

As diuretics, particularly loop and thiazides are a predisposing agent to acute attacks of gout, 95% of GPs chose to stop or replace HCTZ among other decisions of treatment, which is in line with current 2016 EULAR guideline recommendations and an ACR 2018 quality of care indicator. ***(FitzGerald et al., 2018, Richette et al., 2017)*** Comparing this result to other studies with greater than 30% of patients remained on diuretics; GPs surveyed in this practical scenario performed well in their decision to stop or prescribe alternatives. ***(Jeyaruban et al., 2015)***

Hypertension as a co-morbidity in patients with gout was chosen to be evaluated in our survey due to its common presence in other studies as well as certain medication classes may precipitate acute gout. In the study, 28% of GPs had greater than 50% of patients with gout had concomitant hypertension. In various studies the population group reflected diverse results with approximately 40% of patients with gout also afflicted with concomitant hypertension. ***(Mikuls et al., 2005, Stamp and Chapman, 2013)*** Further studies that were undertaken in the USA reported hypertension present in 78% and 74% of their sample population. ***(Harrold et al., 2012, Richette et al., 2015)***

Gout has been recognised as an independent risk factor in hypertension, chronic kidney disease and cardiovascular disease and conversely chronic kidney disease a risk factor for gout. ***(Richette et al., 2015)***

Another co-morbidity evaluated in the survey was cardiovascular disease screening with an unambiguous question; specifically whether gout was considered a risk factor in

ischaemic heart disease. The results show 26% of respondents disagreed completely with the assertion that gout is a risk factor for ischaemic heart disease despite being mentioned in the ACR, BSR and EULAR guidelines as an independent risk factor. ***(Hui et al., 2017, Khanna et al., 2012a, Richette et al., 2017)***

The majority (54%) of GPs in the South African setting did not update their knowledge on gout in the last 2 years. This may partially explain the poor results found in this study.

The 46% that stated to have updated their knowledge were further questioned as to what platform they used. The majority (38%) used a guideline with another 35% did so using an article. The last 27% attended a conference on gout management. It is apparent that multiple avenues of dissemination need to be pursued for gout management updates and guidelines to reach GPs.

4.1. **Strengths and limitations**

This electronic survey is the first to evaluate gout diagnosis and management amongst GPs in South Africa. Gauteng and KwaZulu-Natal provinces were chosen due to their high quantity of GPs in practice.

The study also endeavoured to assess multiple aspects of gout management in an efficient manner to gain an overall understanding as per the objectives and to also be comparable to similar studies from around the world.

Another weakness of the study is the lack of demographic data on GPs. In order to keep the survey within a short time frame and not discourage potential respondents, it was decided to limit demographic data.

The survey was on clinical decision making and not necessarily what GPs actually do in practice however, it was assumed that the answers would be consistent with best medical practice.

CHAPTER 5
CONCLUSIONS AND RECOMMENDATIONS

Gout management was found to be suboptimal in most areas of concern, mirroring numerous studies around the world. Unfortunately gout is looked upon as a disease of excess that is self-inflicted, treated only as an acute symptomatic disease.

Despite gout being a rheumatological disease with various manifestations and phases; some of which are destructive and debilitating the longer left inadequately treated; numerous studies as well as our own demonstrate the suboptimal care rendered.

Firstly, gout needs a change a paradigm shift to be acknowledged as a chronic long term disease and not just acute gouty attacks that recur and treated symptomatically. This needs to be made clear to all levels of clinicians and the general public. Gout needs a higher priority in rheumatology teaching at the undergraduate level as the disease is exceedingly common, treated almost exclusively by primary healthcare and is a ‘curable’ inflammatory arthritis. With this mind-set change other aspects of management will not be so easily neglected.

Secondly, gout treatment should be looked upon as target based not symptom based in reference to SUA used to titrate ULT just as dyslipidaemia is treated and titrated with statins. Clinicians do not inform patients about the long term treatment of gout with ULT do not prescribe prophylaxis on initiation of ULT and do not monitor ULT using recommended options. Only this will ensure a sufficient decrease in SUA levels below saturation preventing acute flares and chronic destructive arthropathy; the end result that is seen so often seen at hospital level. Patient education and reinforcement of adherence should be regarded as mandatory here lest the patient experience rebound attacks after deliberately discontinuing or inadequately adhering to treatment. It was often found that GPs did not have adequate time to

motivate and educate patients nor the inclination to do so because of patient volume and lack of financial incentive. It is also recommended to have education drives on gout awareness such as for diabetes and hypertension.

Thirdly, guidelines produced for gout must be GP centred, disseminated with their needs in mind and with their input, and have indications for referral of patients for specialist care including those with refractory gout, renal impairment and multiple co-morbidities. With this in mind an easy to follow proforma may be developed covering the necessary steps to be addressed such as discussing curable nature of gout, discussing the need for long term ULT, lifestyle modification targets and attempts by the patient, SUA results and renal function documented, ULT doses and etc. This would ensure that the patient encounter is as fruitful as can be in the short consultation time.

REFERENCES

Annemans, L., Spaepen, E., Gaskin, M., et al. (2008) Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. *Ann Rheum Dis,* 67**,** 960-6.

Benn, C. L., Dua, P., Gurrell, R., et al. (2018) Physiology of Hyperuricemia and Urate-Lowering Treatments. *Frontiers in Medicine,* 5.

Choi, H. K. & Curhan, G. (2007) Independent impact of gout on mortality and risk for coronary heart disease. *Circulation,* 116**,** 894-900.

Choi, H. K., Mount, D. B. & Reginato, A. M. (2005) Pathogenesis of gout. *Ann Intern Med,* 143**,** 499-516.

Cottrell, E., Crabtree, V., Edwards, J. J. & Roddy, E. (2013) Improvement in the management of gout is vital and overdue: an audit from a UK primary care medical practice. *BMC Fam Pract,* 14**,** 170.

Doherty, M., Jansen, T. L., Nuki, G., et al. (2012) Gout: why is this curable disease so seldom cured? *Ann Rheum Dis,* 71**,** 1765-70.

Eggebeen, A. T. (2007) Gout: an update. *Am Fam Physician,* 76**,** 801-8.

Fara, N., Vazquez Mellado, J., Sequeira, G. & Kerzberg, E. (2012) A survey on the current evaluation and treatment of gout in Buenos Aires, Argentina. *Reumatol Clin,* 8**,** 306-9.

Fitzgerald, J. D., Mikuls, T. R., Neogi, T., et al. (2018) Development of the American College of Rheumatology Electronic Clinical Quality Measures for Gout. *Arthritis Care Res (Hoboken),* 70**,** 659-71.

Harrold, L. R., Mazor, K. M., Negron, A., et al. (2013) Primary care providers' knowledge, beliefs and treatment practices for gout: results of a physician questionnaire. *Rheumatology (Oxford),* 52**,** 1623-9.

Harrold, L. R., Mazor, K. M., Peterson, D., et al. (2012) Patients' knowledge and beliefs concerning gout and its treatment: a population based study. *BMC Musculoskelet Disord,* 13**,** 180.

Harrold, L. R., Mazor, K. M., Velten, S., Ockene, I. S. & Yood, R. A. (2010) Patients and providers view gout differently: a qualitative study. *Chronic Illn,* 6**,** 263-71.

Hui, M., Carr, A., Cameron, S., et al. (2017) The British Society for Rheumatology Guideline for the Management of Gout. *Rheumatology (Oxford),* 56**,** 1246.

Jackson, G., Dalbeth, N., Te Karu, L., et al. (2014) Variation in gout care in Aotearoa New Zealand: a national analysis of quality markers. *N Z Med J,* 127**,** 37-47.

Jeyaruban, A., Larkins, S. & Soden, M. (2015) Management of gout in general practice--a systematic review. *Clin Rheumatol,* 34**,** 9-16.

Keenan, R. T. N. J., Pillinger M.H. (2016) Etiology and Pathogenesis of Hyperuricemia and Gout.

Khanna, D., Fitzgerald, J. D., Khanna, P. P., et al. (2012a) 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken),* 64**,** 1431-46.

Khanna, P. P., Nuki, G., Bardin, T., et al. (2012b) Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use: Results from a cross-sectional survey. *Health Qual Life Outcomes,* 10**,** 117.

Krishnan, E., Baker, J. F., Furst, D. E. & Schumacher, H. R. (2006) Gout and the risk of acute myocardial infarction. *Arthritis Rheum,* 54**,** 2688-96.

Kuo, C. F., Grainge, M. J., Mallen, C., Zhang, W. & Doherty, M. (2015) Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis,* 74**,** 661-7.
Li, Q. H., Dai, L., Li, Z. X., et al. (2013) Questionnaire survey evaluating disease-related knowledge for 149 primary gout patients and 184 doctors in South China. *Clin Rheumatol,* 32**,** 1633-40.
Mikuls, T. R., Curtis, J. R., Allison, J. J., Hicks, R. W. & Saag, K. G. (2006) Medication errors with the use of allopurinol and colchicine: a retrospective study of a national, anonymous Internet-accessible error reporting system. *J Rheumatol,* 33**,** 562-6.
Mikuls, T. R., Farrar, J. T., Bilker, W. B., Fernandes, S. & Saag, K. G. (2005) Suboptimal physician adherence to quality indicators for the management of gout and asymptomatic hyperuricaemia: results from the UK General Practice Research Database (GPRD). *Rheumatology (Oxford),* 44**,** 1038-42.
Mikuls, T. R., Maclean, C. H., Olivieri, J., et al. (2004) Quality of care indicators for gout management. *Arthritis Rheum,* 50**,** 937-43.
Neogi, T., Jansen, T. L., Dalbeth, N., et al. (2015) 2015 Gout Classification Criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheumatol,* 67**,** 2557-68.
Nuki, G. & Simkin, P. A. (2006) A concise history of gout and hyperuricemia and their treatment. *Arthritis Res Ther,* 8 Suppl 1**,** S1.
Owens, D., Whelan, B. & Mccarthy, G. (2008) A survey of the management of gout in primary care. *Ir Med J,* 101**,** 147-9.
Ozturk, M. A., Mercan, R., Gok, K., et al. (2016) The management of gout in different clinical specialties in Turkey: a patient-based survey. *Clin Rheumatol,* 35**,** 3019-24.
Pascart, T. & Flipo, R. M. (2013) Gout: from international guidelines to current practice. Results from a physician questionnaire. *Clin Rheumatol,* 32**,** 1693-4.
Primatesta, P., Plana, E. & Rothenbacher, D. (2011) Gout treatment and comorbidities: a retrospective cohort study in a large US managed care population. *BMC Musculoskelet Disord,* 12**,** 103.
Ragab, G., Elshahaly, M. & Bardin, T. (2017) Gout: An old disease in new perspective - A review. *J Adv Res,* 8**,** 495-511.
Rees, F., Hui, M. & Doherty, M. (2014) Optimizing current treatment of gout. *Nat Rev Rheumatol,* 10**,** 271-83.
Richette, P. & Bardin, T. (2010) Gout. *Lancet,* 375**,** 318-28.
Richette, P., Clerson, P., Perissin, L., Flipo, R. M. & Bardin, T. (2015) Revisiting comorbidities in gout: a cluster analysis. *Ann Rheum Dis,* 74**,** 142-7.
Richette, P., Doherty, M., Pascual, E., et al. (2017) 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis,* 76**,** 29-42.
Roddy, E., Mallen, C. D., Hider, S. L. & Jordan, K. P. (2010) Prescription and comorbidity screening following consultation for acute gout in primary care. *Rheumatology (Oxford),* 49**,** 105-11.
Roddy, E., Zhang, W. & Doherty, M. (2007) Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendations. *Ann Rheum Dis,* 66**,** 1311-5.
Singh, J. A., Alpert, M. D. & Kerr, G. (2010) A national survey of Veterans Affairs rheumatologists for relevance of quality of care indicators for gout management. *Arthritis Care Res (Hoboken),* 62**,** 1306-11.

Spaetgens, B., Pustjens, T., Scheepers, L., et al. (2016) Knowledge, illness perceptions and stated clinical practice behaviour in management of gout: a mixed methods study in general practice. *Clin Rheumatol,* 35**,** 2053-61.

Spencer, K., Carr, A. & Doherty, M. (2012) Patient and provider barriers to effective management of gout in general practice: a qualitative study. *Ann Rheum Dis,* 71**,** 1490-5.

Stamp, L. K. & Chapman, P. T. (2013) Gout and its comorbidities: implications for therapy. *Rheumatology (Oxford),* 52**,** 34-44.

Terrill, M. & Riordan, J. (2017) A survey of the assessment and management of gout in general practitioners and medical officers within the Illawarra Network, Australia. *Int J Rheum Dis,* 20**,** 990-5.

Terrill, M. & Riordan, J. (2018) A survey on the beliefs and knowledge of gout management in new medical graduates - New South Wales, Australia. *Int J Rheum Dis,* 21**,** 517-22.

Underwood, M. (2006) Diagnosis and management of gout. *Bmj,* 332**,** 1315-9.

Van Durme, C. M., Wechalekar, M. D., Buchbinder, R., et al. (2014) Non-steroidal anti-inflammatory drugs for acute gout. *Cochrane Database Syst Rev***,** CD010120.

Vargas-Santos, A. B., Castelar-Pinheiro Gda, R., Coutinho, E. S., et al. (2015) Adherence to the 2012 American College of Rheumatology (ACR) Guidelines for Management of Gout: A Survey of Brazilian Rheumatologists. *PLoS One,* 10**,** e0135805.

Yeap, S. S., Goh, E. M. & Gun, S. C. (2009) A survey on the management of gout in Malaysia. *Int J Rheum Dis,* 12**,** 329-35.

APPENDIX A

PARTICIPANT APPROVAL LETTER

Participant information letter

Dear Colleague

My name is Anees Ahmed. I am a registrar in the Department of Internal Medicine at the Chris Hani Baragwanath Academic Hospital.

As part of my training at the University of the Witwatersrand, research needs to be conducted under supervision. I would like to invite you to participate in my research study, which is being conducted in the field of Rheumatology specifically on approach and management to an inflamed joint.

The study involves completing a short web-based questionnaire, which should take no more than ten minutes to complete. The study has been approved by the Postgraduate Committee of the University of the Witwatersrand. Your participation is voluntary and all responses will be uploaded anonymously to an electronic database hosted by eSurv™. Information you provide can therefore not be traced back to you and published results will have no identifying data. Participants will be sent the outcome of the study. The study may help identify areas in which the diagnosis and treatment of gout can be improved upon.

To participate, kindly click here. This will also imply consent to participate.

Should you have any further queries my contact details are 0723045300, gambit.ahmed@gmail.com and of my supervisor, Prof M. Tikly, tikly.mohammed @wits.ac.za.

Thank you for taking time to participate in the survey and your contribution will be much appreciated.

Yours sincerely

Dr A Ahmed

APPENDIX B

EMAIL SURVEY QUESTIONNAIRE

A. Study Questionnaire

A 45 year old male overweight dispatch clerk diagnosed with essential hypertension controlled on 2 agents (hydrochlorothiazide and enalapril) and dyslipidaemia on simvastatin therapy for 3 years presents to your practice with a 2 day history of swelling and tenderness of the right ankle and midfoot. On further enquiry he has had 3 episodes of pain for the last year. On examination it is warm to touch, swollen, inflamed and tender with no nidus of infection found to the particular limb.

Some questions may have more than one correct option

* 1. What are the 2 most likely causes of arthritis in this patient?

- ☐ Rheumatoid arthritis
- ☐ Osteoarthritis
- ☐ Gouty arthritis
- ☐ Septic arthritis

* 2. In your practice, how do you generally make/confirm the diagnosis?

- ○ Clinical presentation with blood tests eg. (CRP, RF, ESR, UA)
- ○ Clinical presentation with joint aspiration
- ○ Clinical presentation with xray
- ○ Clinical presentation

* 3. Which nsaid do you prefer prescribing in the treatment of an acute swollen tender joint?

- ○ Indomethacin
- ○ Diclofenac
- ○ Ibuprofen
- ○ Cataflam

---

* 4. In the patient above in whom a diagnosis of gout is made, what is your anti-inflammatory of choice?

- ☐ Prescribe oral nsaid eg. Indomethacin
- ☐ Administer IM nsaid such as Diclofenac
- ☐ Prescribe oral corticosteroids eg. Prednisone

- [ ] Prescribe oral colchicine

* 5. In a patient in whom you suspect gout, how often do you aspirate the joint for crystal analysis?

- ○ Always
- ○ Never
- ○ Sometimes

---

* 6. In the patients with gout in your practice, what proportion has concomitant hypertension?

- ○ Less than 10%
- ○ Between 10% - 50%
- ○ Greater than 50%
- ○ Greater than 90%

7. How many patients with gout do you treat in your practice in an average month?

- ○ <5
- ○ 5-10
- ○ >10

* 8. Of the patients presenting with gout, how many patients present with an acute attack of gout to your practice?

- ○ <2
- ○ 2-3
- ○ >3

---

* 9. Which medication would you consider stopping or changing if possible in this patient presenting with acute gout?

- [ ] Simvastatin
- [ ] Hydrochlorothiazide
- [ ] Enalapril
- [ ] All of the above

* 10. How often do you co-prescribe colchicine or a non-steroidal anti-inflammatory drug when initiating uric acid lowering therapy like allopurinol?

- ○ Never
- ○ Occasionally
- ○ Almost always

- Always

* 11. When do you consider using uric acid lowering drugs like allopurinol in a patient with gout?

- ≥2 attacks within a year
- After the first attack of gout
- Patient with history of kidney stones
- Presence of tophi

* 12. How often do you treat gout with a uric acid lowering drug like allopurinol?

- Never
- Sometimes
- Almost always
- Always

* 13. What dose of allopurinol do you most commonly prescribe?

- 100mg daily
- 300mg daily
- >300mg daily

---

* 14. Do you titrate the dose of allopurinol on the basis of?

- Serum uric acid level
- Never titrate drug dose
- Clinical response to drug

* 15. How often do you give patients with gout dietary advice?

- Always
- Sometimes
- Never

* 16. What aspects of dietary advice do you focus on?

- Alcohol reduction
- Weight reduction
- Red meat reduction
- All of the above

* 17. Do you believe that gout is a risk factor for ischaemic heart disease?

- Strongly agree

- Agree
- Disagree

* 18. Have you in the last 2 years updated your knowledge on the diagnosis and treatment of gout?

- Yes
- No

19. If yes, how did you update yourself?

- Attending a talk/conference
- Reading a guideline
- Reviewing an article

B. Demographics

1. How old are you?

- <30years
- <40years
- <50years
- <60years
- >60years

2. What is your gender?

- Male
- Female

3. Is your practice solo or group practice?

- solo
- group

4. Would you like to have feedback on the outcome of the study?

- Yes
- No

Thank you for your time and completing the survey.

APPENDIX C

ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Anees Ahmed

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150766

NAME: (Principal Investigator)	Dr Anees Ahmed
DEPARTMENT:	Internal Medicine Private Practices across Durban and Johannesburg
PROJECT TITLE:	A Survey on the Diagnosis and Management of Gout Among General Practitioners
DATE CONSIDERED:	31/07/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof M. Tikly
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	10/04/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX D

ACR Quality of care indicators for gout management

Quality Indicators	
Measure 1. Use of uric acid–lowering therapy	IF a gout patient is receiving an initial prescription for allopurinol *and* has significant renal impairment (defined as a serum creatinine level ≥2 mg/dl or measured/estimated creatinine clearance ≤50 ml/minute), THEN the initial daily allopurinol dose should be <300 mg per day, BECAUSE the risk of allopurinol-related toxicity is increased in the presence of significant renal impairment in gout patients given a daily allopurinol dose equal to or exceeding 300 mg.
Measure 2. Use of uric acid–lowering therapy	IF a gout patient is given a prescription for xanthine oxidase inhibitor in the setting of required therapy with *either* 1) azathioprine (Imuran) *or* 2) 6-MP, THEN the dose of azathioprine/6-MP should be reduced by a minimum of 50%, BECAUSE concurrent use of a xanthine oxidase inhibitor leads to a substantial increase in serum levels of azathioprine (and 6-MP) and increases the risk for severe drug-related myelosuppression.
Measure 3. Use of uric acid–lowering therapy	IF a patient with tophaceous gout is given an initial prescription for a urate-lowering medication (xanthine oxidase inhibitor, probenecid, or sulfinpyrazone) *and* lacks both 1) significant renal impairment (a serum creatinine level ≥2 mg/dl or measured/estimated creatinine clearance ≤50 ml/minute) and 2) peptic ulcer disease, THEN a prophylactic anti-inflammatory agent (colchicine or NSAID) should be given concomitantly, BECAUSE prophylactic anti-inflammatory therapy reduces the risk of rebound gout attacks, which frequently follow the initiation of urate-lowering therapy.
Measure 4. Use of uric acid–lowering therapy	IF a patient has asymptomatic hyperuricemia characterized by 1) no prior history of gouty arthritis or tophaceous deposits *and* 2) no prior history of nephrolithiasis or hyperuricosuria *and* 3) no ongoing treatment of malignancy, THEN urate-lowering therapies should *not* be initiated, BECAUSE there is currently no widely accepted indication for the treatment of asymptomatic hyperuricemia.
Measure 5. Use of uric acid–lowering therapy	IF a gout patient is started on urate-lowering therapy and has *either* 1) a history of nephrolithiasis *or* 2) significant renal insufficiency (serum creatinine level ≥2 mg/dl or measured/estimated creatinine clearance ≤50 ml/minute), THEN a xanthine oxidase inhibitor should be started as the initial urate-lowering medication rather than a uricosuric agent (probenecid or sulfinpyrazone), BECAUSE in contrast to xanthine oxidase inhibitors, uricosuric agents increase the renal excretion of urate, enhancing the risk of nephrolithiasis, and may have diminished efficacy in the context of significant renal insufficiency.
Measure 6. Use of uric acid–lowering therapy	IF a patient has hyperuricemia and gouty arthritis characterized by *any* of the following clinical characteristics, 1) tophaceous deposits, 2) gouty erosive changes on radiographs, or 3) gout attack frequency of ≥2 attacks per year, THEN the patient should be offered treatment with a urate-lowering drug, BECAUSE urate-lowering drugs have been well-tolerated and effective in decreasing the attack frequency and disease severity for those with severe gout.
Measure 7. Use of uric acid–lowering therapy	IF a gout patient is given a prescription for a xanthine oxidase inhibitor, THEN a serum urate level should be checked at *least once* during the first 6 months of continued use, BECAUSE periodic serum urate measurements are required for appropriate dose adjustments of xanthine oxidase inhibitors (escalations or reductions).
Measure 8. Behavioral modifications	IF a patient is diagnosed with gout and has *either* 1) obesity (defined as a body mass index ≥28 kg/m^2) or 2) frequent alcohol use (≥1 alcoholic beverage per day), THEN as part of their overall therapy, patients should be advised on the importance of weight loss *and/or* decreased alcohol use, BECAUSE weight loss and reduction of alcohol intake may be beneficial components of gout therapy

Measure 9. Use of anti-inflammatory agents	IF a patient has acute gouty arthritis and lacks *both* of the relative contraindications to gout treatment, 1) significant renal impairment (a serum creatinine level ≥2 mg/dl or measured/estimated creatinine clearance ≤50 ml/minute) and 2) peptic ulcer disease, THEN the patient should be treated with an anti-inflammatory agent to include one of the following: 1) NSAID, 2) ACTH or glucocorticoid (either systemic or intraarticular administration), *or* 3) colchicine, BECAUSE anti-inflammatory agents have been shown to be both effective and well-tolerated for the short-term treatment of acute gout. Patients with renal impairment and a history of peptic ulcer disease may be at a higher risk for gout medication toxicity.
Measure 10 Use of anti-inflammatory agents	IF a gout patient receives long-term prophylactic oral colchicine (defined as a minimum daily dose of 0.5 mg for a duration of 6 months or longer) and has significant renal insufficiency (a serum creatinine level ≥2 mg/dl or measured/estimated creatinine clearance ≤50 ml/minute), THEN a complete blood cell count *and* creatine kinase should be evaluated a minimum of one time for every 6 months of continued use, BECAUSE the risk of colchicine-related myopathy and myelosuppression appears to be substantially increased in the context of reduced renal function.

(Mikuls et al., 2004)

ACR Electronic Clinical Quality Measures for Gout

Quality Indicators	
Measure 1. Colchicine dosing	IF a patient receives colchicine for treatment of gout, THEN the dose of colchicine should not exceed 2.4 mg in any 24-hour period, BECAUSE higher doses of colchicine are associated with increased risk of adverse drug events and do not provide additional therapeutic benefit.
Measure 2. Indications for ULT	IF a patient with gout has sUA 6 mg/dl and has 1 of the following: tophus/tophi or 2 or more attacks per year, THEN ULT should be prescribed, BECAUSE such therapy will improve sUA levels, decrease the risk for recurrent attacks, and reduce tophus deposition
Measure 3. Uninterrupted ULT	IF a patient has gout and receives ULT, THEN ULT should be uninterrupted, BECAUSE interrupting ULT may cause or exacerbate gout flare.
Measure 4. sUA surveillance after start or change in ULT	IF a patient with gout starts on or changes ULT, THEN sUA should be measured within 6 months after dose change, BECAUSE sUA levels are necessary to optimize ULT management.
Measure 5. sUA surveillance for patients with active gout or tophi	IF a patient with gout has persistent tophus/tophi or 2 or more attacks per year, THEN sUA should be measured at least every 6 months, BECAUSE optimal sUA control is necessary to reduce gouty flares and decrease tophaceous deposits.
Measure 6. Optimize ULT	IF a patient with gout has persistent tophus/tophi or 2 or more attacks per year AND sUA is >6.8 mg/dl, THEN ULT management should be optimized, BECAUSE optimization of ULT management will improve sUA levels, decrease the risk for recurrent attacks, and reduce tophus deposition.
Measure 7. sUA surveillance for all patients on ULT	IF a patient with gout is receiving ULT, THEN sUA should be measured at least once every 12 months, BECAUSE sUA levels are necessary to optimize ULT management.
Measure 8. sUA target for all patients on ULT	IF a patient with gout has been treated with ULT for at least 12 months, THEN sUA should be <6.8 mg/dl, BECAUSE adequate control of sUA is needed to reduce acute gouty attacks and reduce tophus size.
Measure 7/8. Treat-to-target	IF a patient with gout has been treated with ULT for at least 12 months, THEN sUA should be checked at least once yearly AND be <6.8 mg/dl, BECAUSE adequate control of sUA is needed to reduce acute gouty attacks and reduce tophus size.

Measure 9. Allopurinol starting dose	IF a patient is newly started on allopurinol, THEN the starting dose should be <300 mg/day, BECAUSE this strategy may reduce risk of early gout flares and reduce the risk of hypersensitivity reactions. Stricter dose limitations required for patients with renal disease (as an example for patients with CKD ≥4 (GFR <30 ml/min), THEN, the starting dose of allopurinol should be ≤50 mg/day).
Measure 10. Gout flare prophylaxis	IF a patient with gout is initiated on ULT, THEN anti-inflammatory prophylaxis should be used concomitantly consisting of low-dose colchicine, NSAID, or glucocorticoid, BECAUSE concomitant use of prophylaxis reduces the risk of gout flares.

(FitzGerald et al., 2018)

APPENDIX E

TURNITIN Report

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"Comorbidity in Rheumatic Diseases", Springer Nature, 2017
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Roger Kornu, Kathryn H. Dao, Catalina Orozco, Rahul K. Patel. "Rheumatology", Elsevier BV, 2012
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Melanie Kolz. "Meta-Analysis of 28,141 Individuals Identifies Common Variants within Five New Loci That Influence Uric Acid Concentrations", PLoS Genetics, 06/05/2009
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Rodrigo Balbino Chaves Amorim, Ana Beatriz Vargas-Santos, Leticia Rocha Pereira, Evandro Silva Freire Coutinho, Geraldo da Rocha Castelar-Pinheiro. "Gout treatment: survey of Brazilian rheumatology residents", Clinical Rheumatology, 2017
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Harrold, L. R., K. M. Mazor, A. Negron, J. Ogarek, C. Firneno, and R. A. Yood. "Primary care providers' knowledge, beliefs and treatment practices for gout: results of a physician questionnaire", Rheumatology, 2013.
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Kuo, C.-F., M. J. Grainge, C. Mallen, W. Zhang, and M. Doherty. "Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study", Annals of the Rheumatic Diseases, 2014.
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Nicola Dalbeth, Thomas Bardin, Michael Doherty, Frédéric Lioté et al. "Discordant American College of Physicians and international rheumatology guidelines for gout

management: consensus statement of the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN)", Nature Reviews Rheumatology, 2017