Universidade do Estado do Rio de Janeiro
Centro Biomédico
Faculdade de Ciências Médicas

Ana Beatriz Vargas dos Santos

Avaliação do manejo da gota, com foco especial no contexto da doença renal crônica

Rio de Janeiro
2018

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Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-Graduação em Ciências Médicas, da Universidade do Estado do Rio de Janeiro.

Orientador: Prof. Dr. Geraldo da Rocha Castelar Pinheiro

Coorientadora: Prof.ª Dra. Tuhina Neogi

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Rio de Janeiro
2018

DEDICATÓRIA

Às pessoas com gota

AGRADECIMENTOS

A Deus, por tudo.

À minha mãe e à minha irmã, meu porto-seguro, pelo amor e apoio incondicionais.

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RESUMO

SANTOS, Ana Beatriz Vargas dos. *Avaliação do manejo da gota, com foco especial no contexto da doença renal crônica.* 2018. 172 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2018.

A gota é uma das artropatias inflamatórias mais prevalentes entre adultos – menos frequente apenas do que a osteoartrite e a doença por depósito de cristais de pirofosfato de cálcio. Caracteriza-se por crises recorrentes de artrite aguda muito dolorosa e pode cursar com depósitos macroscópicos de ácido úrico (tofos). Apesar de ter sido descrita há mais de 4000 anos, ter etiologia definida, diagnóstico relativamente fácil e tratamento disponível, a gota continua sendo tratada de forma inadequada e está associada a alta morbimortalidade e a comprometimento da qualidade de vida. Esta tese teve como objetivo geral investigar o manejo da gota, com ênfase no contexto da doença renal crônica. Os objetivos específicos foram: (i) descrever e analisar as práticas atuais do manejo da gota entre reumatologistas brasileiros (estudo 1); (ii) revisar o manejo da gota e da hiperuricemia no contexto da doença renal crônica (estudo 2), (iii) revisar a relação da hiperuricemia e da terapia hipouricemiante com desfechos renais (estudo 2), e (iv) avaliar o efeito do alopurinol sobre a função renal de indivíduos com gota (estudo 3). O estudo 1 foi um inquérito sobre o tratamento da gota em uma amostra aleatória de 309 reumatologistas no Brasil. O estudo 2 foi uma revisão narrativa sobre o manejo da gota no contexto da doença renal crônica e sobre os efeitos da hiperuricemia e da terapia hipouricemiante sobre a função renal. No estudo 3, investigamos uma coorte de 9520 adultos residentes no Reino Unido com diagnóstico recente de gota, estratificada por tempo, pareada por escore de propensão. Avaliamos os efeitos do uso incidente de alopurinol ≥300 mg/dia sobre a função renal de pacientes sem doença renal crônica. O estudo 1 revelou conhecimento insatisfatório dos reumatologistas brasileiros, sobremodo o não reconhecimento do tofo gotoso como indicação da terapia hipouricemiante, a suspensão da terapia hipouricemiante durante uma crise aguda de gota, a prescrição inicial do alopurinol em doses altas e o não reconhecimento de que a terapia hipouricemiante deve ser mantida por tempo indeterminado. No estudo 2, sintetizamos as recomendações mais atuais sobre o manejo da terapia hipouricemiante, da profilaxia anti-inflamatória e do tratamento das crises agudas de gota. Mostramos, ainda, os efeitos deletérios da hiperuricemia e os potenciais benefícios da terapia hipouricemiante sobre a função renal. Os resultados dos trabalhos incluídos nesta revisão variaram de um efeito protetor dos hipouricemiantes à não identificação de uma associação significativa, sem nenhum artigo apontando efeito deletério da terapia hipouricemiante sobre os rins. Identificamos uma heterogeneidade grande nos critérios de inclusão dos participantes, com poucos estudos avaliando exclusivamente pacientes com gota, e alguns problemas metodológicos que poderiam gerar vieses nos achados. No estudo 3 identificamos um efeito nefroprotetor do alopurinol, com uma redução de 13% no risco de desenvolver doença renal crônica estágio ≥3. Diante do desconhecimento sobre o manejo da gota, sobretudo em pacientes com comprometimento da função renal, e das evidências sobre os benefícios amplos da terapia hipouricemiante, é de grande importância que programas de educação continuada no manejo da gota sejam propostos para garantir que os pacientes recebam um tratamento mais abrangente e adequado.

Palavras-chave: Gota. Doença renal crônica. Conhecimento. Tratamento. Alopurinol. Terapia hipouricemiante. Terapia uricorredutora.

ABSTRACT

SANTOS, Ana Beatriz Vargas dos *Evaluation of gout management, with a special focus on the context of chronic kidney disease.* 2018. 172 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2018.

Gout is one of the most prevalent inflammatory arthritis among adults – less common than osteoarthritis and calcium pyrophosphate deposition disease only. It is characterized by recurrent flares of very painful acute arthritis and may present macroscopic deposits of uric acid (tophi). Although it was first described over 4,000 years ago, has defined etiology, relatively easy diagnosis and available treatment, gout is still inadequately treated and it is associated with high morbimortality and negative effect on quality of life. This thesis aimed to investigate the management of gout, stressing the context of chronic kidney disease. Specific objectives were: (i) to describe and analyze current practices of gout management among Brazilian rheumatologists (study 1); (ii) to review the management of gout and hyperuricemia in the context of chronic kidney disease (study 2), (iii) to review the relation between hyperuricemia and urate-lowering therapy and renal outcomes (study 2), and (iv) to evaluate the effect of allopurinol on kidney function of individuals with gout (study 3). Study 1 was a survey on the treatment of gout in a random sample of 309 Brazilian rheumatologists. Study 2 was a narrative review on the management of gout in the context of chronic kidney disease and the effects of hyperuricemia and urate-lowering therapy on kidney function. In study 3, we investigated a cohort of 9520 adults residents in the United Kingdom with recently-diagnosed gout, stratified by time, matched by propensity score. We evaluated the effects of the incident use of ≥300 mg/day of allopurinol on the kidney function of patients without chronic kidney disease. Study 1 revealed that the Brazilian rheumatologists had unsatisfactory knowledge, especially the non-recognition of gouty tophi as an indication for urate-lowering therapy, the withdrawal of the urate-lowering therapy during a gout flare, the initial prescription of allopurinol in high doses and the non-recognition that urate-lowering therapy should be maintained indefinitely. In study 2, we synthesized the most updated recommendations on the management of urate-lowering therapy, anti-inflammatory prophylaxis and the treatment of gout flares. We also showed the deleterious effects of hyperuricemia and the potential benefits of urate-lowering therapy on kidney function. The results of the papers included in this review varied from a protective effect of the urate-lowering therapy to the non-identification of a significant association, with no article pointing out deleterious effect of the urate-lowering therapy on the kidneys. We identified large heterogeneity in the inclusion criteria of the participants, with few papers evaluating gout patients exclusively, and some methodological issues that could lead to biased findings. In Study 3 we identified a renoprotective effect of allopurinol, with a 13% reduction in the risk of developing chronic kidney disease stage ≥3. Considering the lack of knowledge about gout management, especially in patients with compromised kidney function, and in light of the body of evidence of the broad benefits of urate-lowering therapy, it is of great importance that continuing education programs about gout management are proposed to guarantee that patients receive a more adequate and complete treatment.

Keywords: Gout. Chronic kidney disease. Knowledge. Treatment. Allopurinol. Urate-lowering therapy.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS E SIGLAS

ACR	*American College of Rheumatology*
ACTH	*Adrenocorticotropic hormone = corticotropin*
AHS	*Allopurinol hypersensitivity syndrome*
AINEs	Anti-inflamatórios não esteroides
BMI	*Body mass index*
BSR	*Brazilian Society of Rheumatology*
CHF	*Congestive heart failure*
CI	*Confidence interval*
CKD	*Chronic kidney disease*
ClCr	*Clearance* de creatinina
CL_{cr}	*Creatinine clearance*
CME	*Continuous medical education*
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
CrCl	*Creatinine Clearance*
DRC	Doença renal crônica
DRESS	*Drug reaction with eosinophilia and systemic symptoms*
DSc	*Doctor of Science*
eGFR	*Estimated glomerular filtration rate*
EMA	*European Medicines Agency*
ESRD	*End-stage renal disease*
EUA	Estados Unidos da América
Eular	*European League Against Rheumatism*
EXCEL	*Febuxostat/Allopurinol Comparative Extension Long-Term study*
FDA	*US Food and Drug Administration*
FOCUS	*Febuxostat Open-label Clinical Trial of Urate-lowering Efficacy and Safety study*
FRCPC	*Fellow of the Royal College of Physicians of Canada*
GFR	*Glomerular filtration rate*
GLUT 9	*Glucose transporter 9*
GP	*General Practitioner*

HD	*Hemodialysis*
HLA	Antígeno leucocitário humano, do inglês *human leukocyte antigen*
HR	*Hazards ratio*
IA	*Intra-articular, intraarticular*
IC	Intervalo de confiança
IgA	*Immunoglobulin A*
IL-1b	*Interleukin 1b*
IM	*Intramuscular*
IMC	Índice de massa corporal
IU	*International units*
IV	*Intravenous*
JAMA	*Journal of the American Medical Association*
MA	*Massachusetts*
MD	*Doctor of Medicine*
MDRD	*Modification of Diet in Renal Disease*
MPH	*Master of Public Health*
MSU	*Monosodium urate*
N/A	*Not available*
NC	*North Carolina*
NLRP3	*NLR Family, Pyrin Domain-Containing 3*
NSAID	*Nonsteroidal anti-inflammatory drug*
OAT	*Organic anion transporter*
OR	*Odds ratio*
PCPs	*Primary care physicians*
PD	*Peritoneal dialysis*
PEPI	*Programs for Epidemiologists*
PhD	*Doctor of Philosophy*
PO	*Per os = oral*
PS	*Propensity score*
Pts	*Patients*
PUMC	*Peking Union Medical College*
RCT	*Randomized controlled trial*
RRT	*Renal replacement therapy*

SBR-2013	Congresso Brasileiro de Reumatologia de 2013
SC	*Subcutaneous*
SD	*Standard deviation*
SMD	*Standardized Mean Difference*
SUA	*Serum uric acid*
TFG	Taxa de filtração glomerular
TFP	*Task force panel*
THIN	*The Health Improvement Network*
THU	Terapia hipouricemiante
TX	Texas
UERJ	Universidade do Estado do Rio de Janeiro
UK	*United Kingdom*
ULT	*Urate-lowering therapy*
URAT1	*Urate transporter 1*
US	*United States*
USA	*United States of America*
USD	*US Dollar*
vs.	*Versus*
WSP	*Whole source population*
XOI	*Xanthine oxidase inhibitor*

LISTA DE SÍMBOLOS

%	Porcentagem
≥	Maior que ou igual a
>	Maior que
≤	Menor que ou igual a
<	Menor que
±	Mais ou menos
=	Igual a
+	Mais
~	Aproximadamente

SUMÁRIO

INTRODUÇÃO

Gota é a terceira artropatia inflamatória mais prevalente entre adultos, acometendo 3,9% da população adulta nos Estados Unidos e 1,4% no Reino Unido e na Alemanha.(1, 2) É uma das doenças há mais tempo caracterizadas, com descrições datadas mais de 2000 anos antes de Cristo.(3) Diferente da maioria das doenças reumáticas, a gota tem seu fator etiológico identificado (hiperuricemia) e o tratamento adequado pode levar o paciente a um estado equivalente à cura.(4) Apesar de tudo isso, a gota permanece sendo subtratada, frequentemente menosprezada como uma doença autoinfligida causada por um estilo de vida indisciplinado de excessos alimentares e de consumo excessivo de bebidas alcoólicas – uma impressão comum entre os médicos e a população geral.(5-7) O cenário terapêutico da gota no Brasil é desconhecido devido à paucidade de dados brasileiros disponíveis sobre a doença, mas provavelmente compartilha muitas das características identificadas em outros países, com dificuldades adicionais impostas pelo contexto socioeconômico e situação precária da saúde pública.

Além de conceitos terapêuticos inadequados e do preconceito supracitados, o manejo da gota enfrenta o desafio da frequente presença de comorbidades, como hipertensão arterial sistêmica, doença arterial coronariana, dislipidemia, *diabetes mellitus* e, especialmente, doença renal crônica (DRC).(8) Esta última associação tem peculiaridades importantes, tanto fisiopatológicas quanto terapêuticas. Como cerca de dois terços da eliminação do urato ocorrem por via renal, a disfunção renal comumente resulta em acúmulo de urato.(9) Por outro lado, a hiperuricemia tem consequências danosas aos rins, através do aumento do estresse oxidativo, do estímulo do sistema renina angiotensina aldosterona, indução de hipertensão glomerular e sistêmica, culminando em vasculopatia e em inflamação e fibrose tubulointersticial.(10) Quanto ao tratamento, a presença da DRC limita as opções terapêuticas da gota: os uricosúricos tornam-se menos eficazes no tratamento hipouricemiante; enquanto na abordagem das crises agudas de gota, os anti-inflamatórios não esteroides (AINEs) devem ser evitados e as doses da colchicina limitadas.(11) Um outro aspecto é a frequente redução da dose ou até suspensão do alopurinol quando um paciente com gota começa a apresentar redução da função renal, pelo receio do desenvolvimento da síndrome de hipersensibilidade ao alopurinol e de que o medicamento seja nefrotóxico.(12) Apesar de frequente, esta prática não apresenta respaldo na literatura.

Com base no exposto acima, esta tese teve como objetivos: (i) avaliar o padrão do tratamento da gota no Brasil, (ii) revisar o manejo da gota no contexto da DRC e (iii) avaliar o efeito do alopurinol sobre a função renal em pacientes com função renal normal ou quase normal, visto que o receio da nefrotoxicidade é uma das justificativas para seu uso limitado. A tese foi organizada em formato de artigos, apresentados na íntegra na seção de resultados, com detalhamento de seus desenhos e métodos na seção 3.

1 **REVISÃO DE LITERATURA**

1.1 **Gota**

A gota é a terceira artropatia inflamatória mais comum, com prevalências variando de 0,1% até 10% da população geral adulta.(13) Nos Estados Unidos, estima-se que a doença afete 3,9% dos adultos;(1) já entre os homens da tribo Maori, na Nova Zelândia, a prevalência alcança 18%.(14) O fator etiológico da gota é a hiperuricemia, definida bioquimicamente como níveis séricos de ácido úrico ≥6,8 mg/dL, considerado o ponto de saturação do urato em condições fisiológicas.(15) Uricemia persistentemente acima deste nível leva à cristalização e subsequente deposição do ácido úrico sob a forma de urato monossódico virtualmente em qualquer tecido do organismo, mas principalmente nas articulações e no tecido subcutâneo. No entanto, a hiperuricemia isolada não é suficiente para o desenvolvimento da gota, visto que a maioria dos indivíduos hiperuricêmicos não desenvolve a doença. O mesmo estudo com adultos americanos que identificou a prevalência de gota em 3,9% registrou a prevalência de hiperuricemia em torno de 21%.(1)

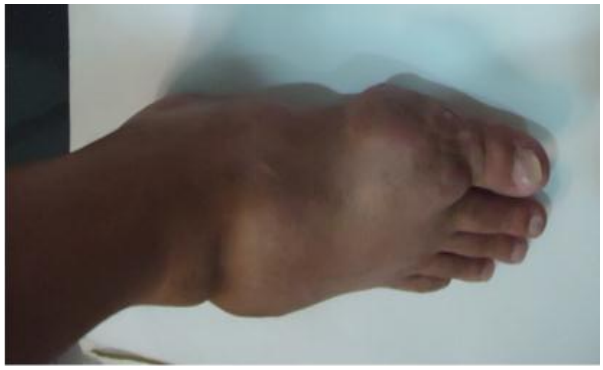
O ácido úrico é um ácido fraco, encontrado predominantemente sob a forma de ânion urato no soro humano em condições fisiológicas e sob a forma de ácido úrico, menos solúvel, na urina com pH em torno de 5 ou 6.(16) É um componente do metabolismo das purinas, que é convertido em alantoína pela enzima uricase em muitos animais. A alantoína é mais solúvel e mais facilmente excretada do que o ácido úrico. Como a uricase está ausente nos humanos, o ácido úrico se mantém como produto final desse metabolismo.(16) A maior parte do ácido úrico produzido diariamente advém do nosso metabolismo, sendo uma parte menor ingerida na dieta. Cerca de dois terços de sua eliminação ocorrem por via renal, enquanto aproximadamente um terço ocorre por via intestinal. A principal causa da hiperuricemia é a redução da excreção renal de ácido úrico, com apenas cerca de 10% dos pacientes com gota apresentando hiperprodução de urato.(16)

1.1.1 Quadro clínico

A gota manifesta-se clinicamente por crises recorrentes de artrite aguda, tradicionalmente caracterizadas por dor intensa, eritema, edema e grande limitação funcional.(17) Nas fases iniciais da doença, as primeiras crises costumam acometer uma única articulação, durar 7 a 14 dias se não tratadas e resolverem-se espontaneamente. Com a evolução da doença, as crises agudas passam a ser mais frequentes, com maior duração, mais resistentes ao tratamento anti-inflamatório e acometem mais articulações simultaneamente, até o estágio de artropatia crônica, em que os períodos intercríticos deixam de ser assintomáticos. As articulações dos membros inferiores, em especial a primeira metatarsofalangeana, são mais comumente acometidas, principalmente no início da doença, mas a gota pode afetar qualquer articulação, inclusive no esqueleto axial. Além de artrite, a gota pode causar bursite ou tendinite.

Outra manifestação importante é o tofo gotoso, depósito macroscópico de urato que pode ocorrer virtualmente em qualquer tecido do organismo (Figura 1). Estudos mais antigos relatam um intervalo comum de aproximadamente 10-12 anos para o desenvolvimento de tofo.(18, 19) No entanto, existem casos bem documentados de tofo como primeira manifestação da gota, além de pacientes clinicamente considerados não-tofáceos em que são identificados tofos aos exames de imagem.(18, 19)

Figura 1 - Foto do pé de um paciente com gota tofácea



Legenda: Foto do pé de um paciente com gota tofácea, com tofos volumosos principalmente no mediopé.
Fonte: A autora, 2011.

A gota acomete cerca de três vezes mais homens do que mulheres, com esta diferença sendo reduzida progressivamente após a menopausa devido à perda do efeito uricosúrico do estrogênio. Mulheres com frequência apresentam formas menos típicas da doença, como o

acometimento de articulações dos membros superiores mesmo nas primeiras crises agudas de artrite.

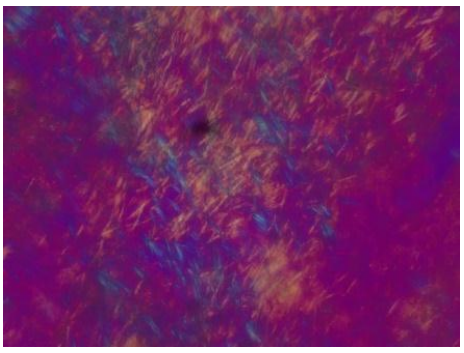
A gota frequentemente se associa a comorbidades, especialmente cardiovasculares (principalmente hipertensão arterial sistêmica e doença arterial coronariana), metabólicas (obesidade, dislipidemia e *diabetes mellitus*) e renais (DRC e nefrolitíase).(8) A presença de comorbidades aumenta significativamente com o tempo de doença, com um estudo revelando que antes da primeira crise de gota apenas 10% dos pacientes tinham o diagnóstico de pelo menos uma doença associada – esta proporção chegava a 93% após 13,7 anos de doença.(20)

1.1.2 Diagnóstico padrão-ouro e exames de imagem

O método diagnóstico padrão-ouro é a identificação de cristais de urato monossódico no líquido sinovial de uma articulação ou bursa ou no material aspirado de um depósito sugestivo de tofo (Figura 2). No entanto, frequentemente a gota é diagnosticada com base nos aspectos clínicos, laboratoriais e de exames de imagem.

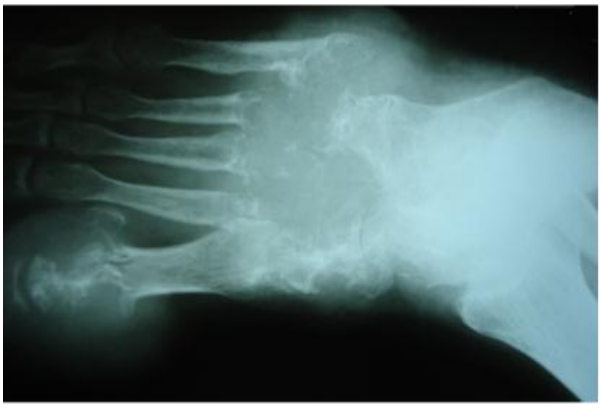
Os achados característicos nos exames de imagem incluem: erosão em saca-bocado com margem óssea sobrejacente (Figura 3), identificada à radiografia; sinal do duplo contorno (Figura 4) e depósitos tofáceos à ultrassonografia; e depósitos de urato monossódico identificados à tomografia computadorizada de dupla energia (Figura 5).(21, 22)

Figura 2 - Cristais de urato monossódico de material tofáceo avaliado sob microscopia com luz polarizada compensada



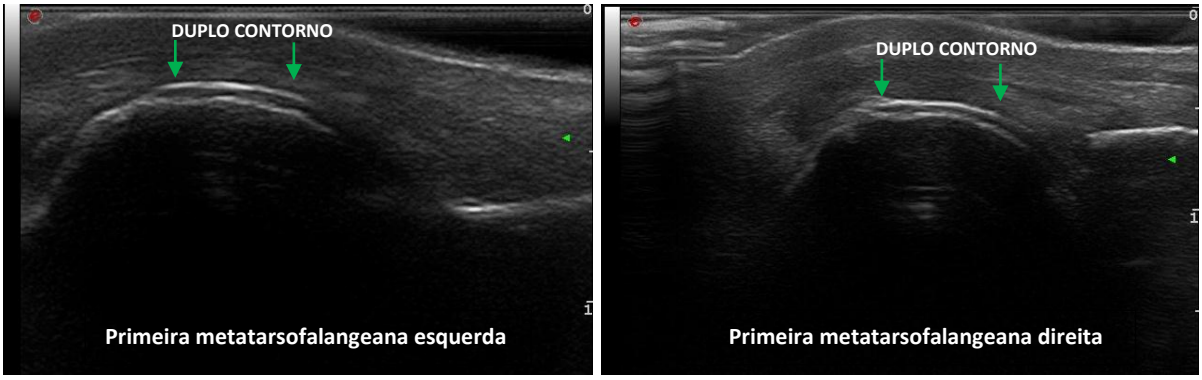
Fonte: A autora, 2015.

Figura 3 - Radiografia do pé de um paciente com gota tofácea



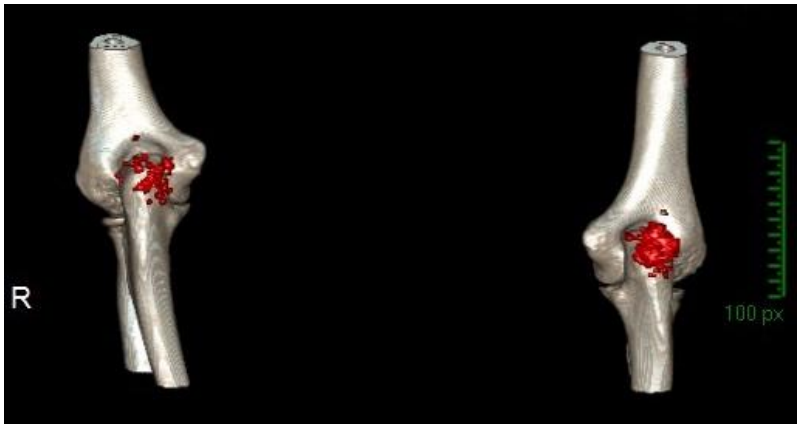
Legenda: Radiografia em incidência oblíqua do pé de um paciente com gota tofácea revelando significativa destruição óssea do mediopé pela massa tofácea e erosões ósseas grandes com margem óssea sobrejacente correspondendo ao aspecto em saca-bocado.
Fonte: A autora, 2011.

Figura 4 - Ultrassonografia articular em paciente com gota



Legenda: Imagem de ultrassonografia de um paciente com gota revelando o sinal do duplo contorno na primeira metatarsofalangeana bilateral – sinal indicativo de depósitos de cristais de urato monossódico na superfície da cartilagem hialina dessas articulações.
Fonte: Dr. Andrei de Oliveira Rosas, exame realizado no ambulatório de Reumatologia da UERJ.

Figura 5 - Tomografia computadorizada de dupla energia em paciente com gota



Legenda: Imagem de tomografia computadorizada de dupla energia mostrando em vermelho os depósitos de urato monossódico nos cotovelos de um paciente com gota tofácea.
Fonte: Dra. Silvana Machado Mendonça, exame realizado na clínica de diagnóstico por imagem CDPI.

1.1.3 Manejo terapêutico

O manejo da gota segue os mesmos quatro princípios, independentemente da presença de DRC: (i) redução da uricemia, (ii) profilaxia anti-inflamatória, especialmente ao iniciar terapia hipouricemiante (THU), (iii) tratamento anti-inflamatório das crises agudas de gota, e (iv) otimização da dieta e fatores de estilo de vida quando apropriado. A uricemia alvo para todos os pacientes é <6 mg/dL.(23) Para pacientes com tofo (ou persistência de sinais e sintomas apesar de uricemia <6 mg/dL), um alvo inferior deve ser considerado (<5 mg/dL).(23) Os medicamentos disponíveis para o tratamento da gota estão listados no Quadro 1.

Quadro 1 - Medicamentos para gota

Medicamentos para gota	**Disponibilidade no Brasil**
Terapia hipouricemiante	
Inibidores da xantina oxidase	
Alopurinol	Sim
Febuxostato	Não
Uricosúricos	
Benzbromarona	Sim
Lesinurade	Não
Probenecida	Não
Sulfinpirazona	Não
Uricase recombinante	
Pegloticase	Não
Rasburicase	Sim, mas sem aprovação para gota
Profilaxia anti-inflamatória	
Colchicina	Sim
Anti-inflamatórios não esteroides	Sim
Glicocorticoides	Sim
Canaquinumabe	Sim, mas sem aprovação para gota
Rilonacepte	Não
Terapia anti-inflamatória	
Colchicina	Sim
Anti-inflamatórios não esteroides	Sim
Glicocorticoides	Sim
Corticotrofina	Sim, mas sem aprovação como medicamento
Canaquinumabe	Sim, mas sem aprovação para gota
Anakinra	Não

Fonte: A autora, 2018.

1.2 **Doença renal crônica no contexto da gota**

A associação de DRC e gota é bastante frequente. Enquanto na população geral sem gota a prevalência de DRC estágio ≥3 (ou seja, taxa de filtração glomerular (TFG) <60 mL/min/1,73 m^2) é de 5%, entre os pacientes com gota esta prevalência é de 19,9%.(8) Sob a perspectiva nefrológica, a prevalência de gota padronizada por idade aumenta com o declínio da função renal: enquanto apenas 2,9% dos adultos com TFG ≥90 mL/min têm gota, esta prevalência chega a 24% daqueles com TFG <60 mL/min.(24)

A presença de disfunção renal num paciente com gota impõe limitações ao tratamento uricorredutor e anti-inflamatório. Os uricosúricos tornam-se menos eficazes com a redução da TFG, estando a benzbromarona contraindicada em TFG <20 mL/min(25) e o lesinurade contraindicado em TFG <45 mL/min(26). Os inibidores da xantina oxidase podem ser usados em estágios mais avançados da DRC, mas existem menos estudos nessa população, com menos dados de segurança disponíveis. A profilaxia e o tratamento das crises agudas de gota ficam ainda mais limitados do que a THU, devido às restrições ou contraindicações ao uso de colchicina e AINEs no contexto da DRC. Os glicocorticoides passam a ser os agentes anti-inflamatórios preferenciais nos estágios mais avançados de disfunção renal, mas este uso também deve ser cauteloso devido à frequente doença cardiovascular associada tanto à DRC quanto à gota.(17)

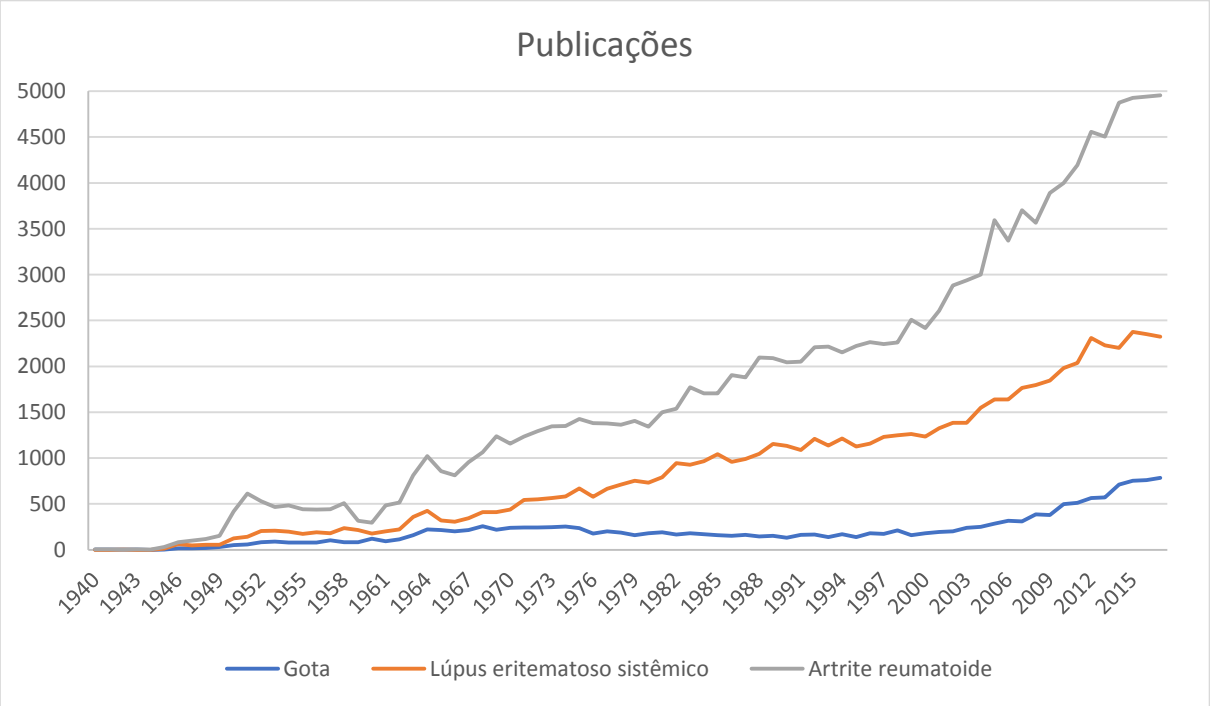
Quanto ao diagnóstico, a presença de DRC torna a identificação dos cristais de urato monossódico ainda mais essencial, visto que neste contexto tornam-se mais frequentes tanto a doença por depósito de cristais de pirofosfato de cálcio (outro tipo de artrite microcristalina)(27) quanto manifestações menos típicas da gota.

1.3 **Conhecimento sobre a doença**

O conhecimento sobre gota cresceu exponencialmente nos últimos anos, com aumento significativo das publicações depois de décadas de pouco interesse científico sobre ela (Gráfico 1). Todos os aspectos da doença têm sido estudados, desde genética e fisiopatologia da crise aguda de gota até ensaios clínicos com novos medicamentos. Infelizmente, estes avanços parecem ainda não terem se traduzido em benefício claro aos pacientes e conceitos

importantes para o entendimento da gota ainda não foram adequadamente disseminados ao público.(6, 28-31) Muitas recomendações foram publicadas,(23, 32-38) novos medicamentos foram lançados e o uso de medicamentos tradicionais foi revisitado, com mudanças claras na forma de prescrevê-los. No entanto, estudos continuam ressaltando o manejo inadequado da gota,(39-46) identificando o desconhecimento médico como uma das principais causas.(6, 47-50)

Gráfico 1 - Comparação do número de publicações indexadas ao PubMed no período de 1940 a 2017 sobre gota e outras duas doenças reumáticas



Legenda: Gráfico mostrando o crescimento do número de publicações sobre gota nas duas últimas décadas – crescimento tardio e ainda discreto quando comparado ao ocorrido para artrite reumatoide e lúpus eritematoso sistêmico, doenças menos prevalentes do que a gota.
Fonte: A autora, 2018; dados extraídos do endereço eletrônico: http://www.ncbi.nlm.nih.gov/pubmed.

Existe um problema específico em relação ao conhecimento sobre o alopurinol que impacta intensa e negativamente o manejo dos pacientes com gota, especialmente em países em que este é o único medicamento hipouricemiante disponível ou verdadeiramente acessível aos pacientes. Trata-se de um receio exagerado quanto à potencial toxicidade pelo alopurinol. Este receio tem alguns fundamentos. Existe uma reação adversa grave ao medicamento chamada síndrome de hipersensibilidade ao alopurinol. Esta síndrome caracteriza-se por erupção cutânea, eosinofilia, leucocitose, febre, hepatite e disfunção renal progressiva, e apresenta alta letalidade. Apesar de muito temida, no entanto, sua ocorrência é rara, com risco

maior em pacientes com DRC. Na década de 1980, foi publicado um artigo intitulado pelo autor (e não por uma sociedade médica específica) como “diretrizes” descrevendo uma tabela com ajuste de dose do alopurinol de acordo com a TFG.(51) No entanto, é importante ressaltar que esta recomendação nunca foi testada e tampouco houve comprovação de que seu uso reduz o risco da síndrome de hipersensibilidade ao alopurinol. Ademais, atualmente já existe bastante evidência científica esclarecendo seus fatores de risco, como a presença do HLA-B*5801 (especialmente entre chineses, tailandeses e coreanos), dose inicial alta do alopurinol (recomenda-se iniciar com ≤100 mg/dia) e a presença de DRC.(52, 53) Existe, também, evidência crescente de que o alopurinol pode ser gradativamente aumentado além da dose prevista pela tabela de correção pela TFG, mesmo em pacientes com DRC.(54, 55) Apesar de todos os avanços e novas evidências nesta área, recentemente foi publicado um estudo utilizando um sistema automático de correção de prescrições com base na creatinina sérica em que o alopurinol foi utilizado como exemplo.(12) Esta publicação gerou indignação imediata entre os especialistas em gota, sendo considerada um retrocesso científico.(56)

1.4 **Magnitude do problema**

Além de ser uma doença prevalente e comumente associada a outras enfermidades, a gota também está significativamente associada a comprometimento da qualidade de vida, prejuízo à capacidade laboral e aumento da mortalidade.

Múltiplos estudos têm demonstrado intenso comprometimento à qualidade de vida nos indivíduos com gota por diversas causas. Dentre elas estão dor intensa, limitações funcionais, comorbidades e uso dos medicamentos. Citadas ainda estão o temor de uma crise aguda de gota, limitações econômicas advindas das limitações laborais, desinformação (com frequentes informações erradas e outras conflitantes entre o público leigo ou não especialista e os médicos mais atualizados) e frequentes sentimentos negativos de vergonha e desesperança, com intenso sofrimento individual e familiar.(7, 57) Nas fases mais avançadas da doença, o isolamento social também é frequente e pode ocorrer, entre outras razões, pela dor, pelas limitações funcionais, pelo temor de uma crise aguda de gota ou por vergonha do prejuízo estético advindo dos tofos gotosos e das deformidades articulares. O preconceito associado à doença, caricaturando libações alimentares e alcoólicas, e o repetido discurso de doença autoinfligida fazem com que muitos pacientes, especialmente mulheres, sintam vergonha do

diagnóstico e procurem menos a atenção médica, além de prejudicarem marcadamente a relação médico-paciente para aqueles que buscam o atendimento.(5, 7, 29)

O aumento da mortalidade, principalmente por doença cardiovascular, já foi demonstrado em inúmeros estudos, porém ainda sem total esclarecimento se esta relação é causal ou uma associação pelas comorbidades e fatores de risco compartilhados.(58-70) Recentemente, um estudo chamou a atenção para a persistência deste incremento da mortalidade pela gota ao longo dos últimos 16 anos. Neste mesmo período, no entanto, houve redução da mortalidade na população geral, incluindo mortes atribuídas a doenças cardiovasculares, e redução significativa da mortalidade associada à artrite reumatoide.(61, 71, 72)

A gota é uma doença com graves consequências para seus portadores. Embora disponha de tratamento eficaz, ainda persistem visões ou mesmo crenças distintas sobre como tratá-la, sobretudo na vigência de doença renal. Nesse cenário, é fundamental que se avaliem essas visões e suas bases científicas, assim como se investiguem os efeitos do tratamento sobre a função renal dos pacientes.

2 **OBJETIVOS**

2.1 **Objetivo geral**

Investigar o manejo da gota, com ênfase na relação com doença renal crônica.

2.2 **Objetivos específicos**

Descrever e analisar as práticas atuais do manejo da gota entre reumatologistas brasileiros (estudo 1).

Revisar o manejo da gota e da hiperuricemia no contexto da doença renal crônica (estudo 2).

Revisar a relação da hiperuricemia e dos medicamentos uricorredutores com desfechos renais (estudo 2).

Avaliar o efeito do alopurinol sobre a função renal de indivíduos com gota (estudo 3).

3 **MATERIAIS E MÉTODOS**

3.1 **Estudo 1**

3.1.1 Desenho do estudo e população

O estudo 1 foi um estudo transversal realizado em 2013-2014, na forma de inquérito aplicado a uma amostra aleatória de reumatologistas associados à Sociedade Brasileira de Reumatologia. Escolhemos avaliar os reumatologistas por estes serem considerados os especialistas em gota.

3.1.2 Amostra

Inicialmente, obtivemos a lista de sócios da Sociedade Brasileira de Reumatologia, excluímos os sócios inativos e os sócios residentes, resultando em 1436 reumatologistas, distribuídos de forma heterogênea entre as macrorregiões do Brasil, como mostra a tabela 1.

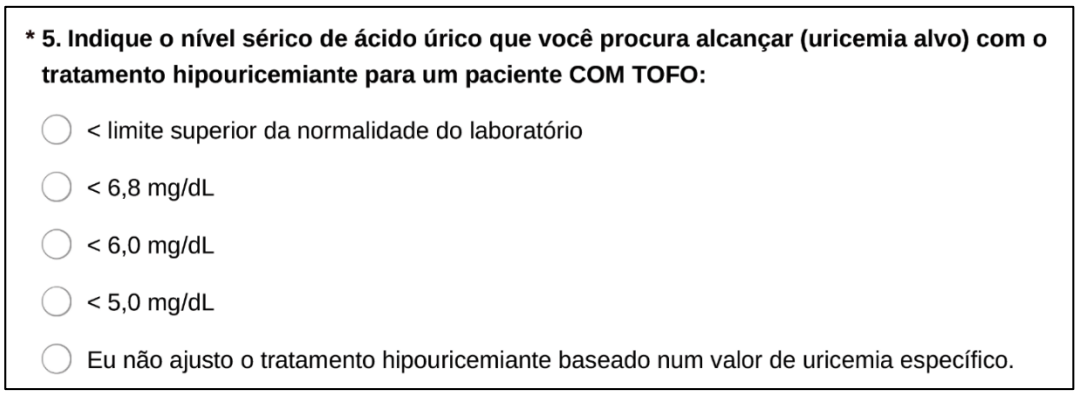
Tabela 1 - Distribuição dos reumatologistas associados à Sociedade Brasileira de Reumatologia por macrorregião do Brasil em 2013

Macrorregiões	**Reumatologistas associados à Sociedade Brasileira de Reumatologia**
Norte	50
Nordeste	236
Centro-Oeste	122
Sudeste	793
Sul	235
Total	**1436**

Fonte: Sociedade Brasileira de Reumatologia, 2013.

O tamanho amostral foi calculado objetivando um nível de confiança de 95% e um erro amostral de ±5%, considerando uma proporção estimada de 50% de respostas corretas para a principal pergunta do questionário, sobre uricemia alvo (Figura 6).

Figura 6 - Principal pergunta do questionário



Legenda: As opções de respostas "<6,0 mg/dL" e "<5,0 mg/dL" eram consideradas concordantes com as recomendações vigentes ("corretas"), enquanto as demais opções eram consideradas discordantes.
Fonte: A autora, 2013.

Essa pergunta foi escolhida por representar um dos principais avanços no tratamento da gota nos últimos anos. No entanto, por se tratar de uma recomendação recente à época do estudo, acreditamos que muitos reumatologistas no Brasil ainda a desconhecessem. Para o cálculo do tamanho amostral, consideramos apenas duas categorias de resposta para esta pergunta: (i) de acordo com as diretrizes de gota do Colégio Americano de Reumatologia de 2012,(23) para as opções "< 6,0 mg/dL" e "< 5,0 mg/dL", e (ii) discordante das diretrizes vigentes, para as demais opções.

Usando o programa PEPI (*Programs for Epidemiologists*, versão 11.39), o tamanho amostral necessário foi calculado como 304 indivíduos. Considerando uma possível falha em contactar 30% da amostra, 395 sócios foram selecionados de forma aleatória simples, utilizando a ferramenta eletrônica "*True Random Number Generator*", disponível no endereço eletrônico www.random.org.

A seleção da amostra manteve a proporcionalidade da distribuição dos reumatologistas pelas macrorregiões do Brasil encontrada na população fonte (Tabela 2).

Tabela 2 - Distribuição dos reumatologistas associados à SBR por macrorregião e sua distribuição proporcional na amostra teoricamente necessária e na amostra recrutada

Regiões do Brasil	**Reumatologistas associados à SBR**	**Estratificação por regiões da amostra necessária**	**Estratificação por regiões da amostra recrutada**
Norte	50	11	14
Nordeste	236	50	65
Centro-Oeste	122	26	34
Sudeste	793	168	218
Sul	235	50	64
Total	**1436**	**304**	**395**

Legenda: SBR – Sociedade Brasileira de Reumatologia.
Fonte: A autora, 2013.

3.1.3 Coleta de dados

Dados sobre as práticas terapêuticas na gota foram coletados utilizando um questionário eletrônico, cujo endereço virtual para acesso foi enviado por correio eletrônico. A pesquisa ficou disponível de 18 de dezembro de 2013 a 25 de março de 2014. Durante esse período, até quatro convites foram enviados por e-mail e até três tentativas de contato telefônico foram feitas para cada participante em potencial. A versão impressa do questionário eletrônico encontra-se no Apêndice A.

3.1.3.1 Instrumento

Entre julho e agosto de 2013, revisamos os inquéritos sobre tratamento de gota realizados previamente(73-91) e desenvolvemos a primeira versão do questionário utilizado neste projeto (Apêndice B), procurando enfatizar as medidas terapêuticas farmacológicas revisadas e modificadas na última década. Esta primeira versão ainda era impressa e contemplava aspectos de diagnóstico e tratamento da gota, em 15 perguntas distribuídas em duas páginas. Médicos com interesse especial em gota (reumatologistas, clínicos gerais e nefrologistas) da Universidade do Estado do Rio de Janeiro (UERJ) e um epidemiologista da Fundação Oswaldo Cruz analisaram o questionário opinando sobre as perguntas a serem melhoradas.

Após os ajustes recomendados foi realizado um teste piloto em 29/08/2013, no qual foi aplicada a primeira versão do questionário, ainda impresso, a 17 pessoas, incluindo sete

reumatologistas com título de especialista em reumatologia, quatro estudantes do quinto e sexto anos de medicina e seis residentes do primeiro e do segundo ano de reumatologia da UERJ. Essa primeira avaliação prática visava identificar o tempo de resposta e a compreensibilidade das questões e conhecer as opiniões dos respondedores sobre o instrumento. Todas as questões foram discutidas entre todos os presentes e todas as possíveis interpretações anotadas. As questões que geraram interpretações semelhantes por mais de 85% dos respondedores foram consideradas compreensíveis. Subsequentemente, discutimos as mudanças necessárias a cada questão para que todos tivessem interpretação semelhante e da forma mais clara possível. Os resultados parciais estão no Quadro 2.

Quadro 2 - Resultados parciais da avaliação prática da 1ª versão impressa do questionário

Respondedores	Total = 13 médicos • Especialistas = 7 • Residentes de reumatologia = 6
Tempo de resposta	Especialistas: • Mínimo = 6 minutos • Máximo = 17 minutos • Médio = 10 minutos e 15 segundos Residentes de reumatologia: • Mínimo = 9 minutos • Máximo = 19 minutos • Médio = 13 minutos e 40 segundos
Compreensibilidade	Satisfatória = 87% das questões Inadequada = questões 1 e 15
Conclusão pelo grupo	A apresentação visual do questionário, com tabelas e lacunas, requisitando respostas aparentemente objetivas, favoreceu a disposição dos participantes a responderem o questionário, apesar da sua extensão por 2 páginas completas. Algumas perguntas precisam ser reformuladas para minimizar as dúvidas e as possibilidades de erro de interpretação.

Legenda: Quatro estudantes de medicina também participaram desta avaliação do instrumento comentando sobre a compreensibilidade das questões, mas não completaram o questionário por julgarem não saber o suficiente sobre gota.

Fonte: A autora, 2013.

A partir desta avaliação e análise das críticas e sugestões recebidas, o questionário foi aprimorado. Foram incluídas algumas questões sobre tratamento e excluídas as duas únicas questões sobre diagnóstico. Como a aplicação da pesquisa ocorreria próxima ao Congresso Brasileiro de Reumatologia de 2013 (SBR-2013), evento com três atividades sobre gota (duas conferências e uma mesa redonda), incluímos outras duas perguntas no questionário: comparecimento ao SBR-2013 e comparecimento a alguma atividade sobre gota durante o evento. Posteriormente, especialistas em pedagogia revisaram o questionário visando reduzir a chance de acertos ao acaso.

Para aumentar sua aceitação, reconhecemos que o instrumento, além de claro e organizado, não deveria ser extenso, e as questões deveriam ser predominantemente objetivas, com o mínimo de respostas livres. Assim, revisamos mais uma vez o instrumento, convertendo perguntas abertas em questões de múltipla-escolha, reduzimos o número de assertivas e reordenamos alguns itens, criando blocos de questões organizadas por tema, resultando num aspecto visual mais agradável.

Para tornar o questionário mais prático e aumentar a chance de respostas, decidimos transformar o instrumento em um questionário eletrônico, o qual desenvolvemos usando a ferramenta de pesquisa online SurveyMonkey (SurveyMonkey, Palo Alto, Califórnia, EUA - www.surveymonkey.com). Esta ferramenta nos permitiu organizar o questionário em múltiplas páginas sequenciais e bloquear a mudança das respostas após a submissão de uma página, evitando que o participante inferisse a resposta esperada com base nas questões seguintes. O uso do SurveyMonkey também nos permitiu aplicar lógica de ramificação, recurso que define a pergunta subsequente com base na resposta à pergunta atual. Por exemplo: na pergunta 5, citada acima (Figura 6), se o respondedor escolhesse a assertiva “Eu não ajusto o tratamento hipouricemiante baseado num valor de uricemia específico.”, não lhe seriam apresentadas as questões seguintes sobre uricemia alvo. Da mesma forma, só veria a questão “Você assistiu alguma atividade sobre gota?” quem tivesse respondido sim à pergunta “Você participou do Congresso Brasileiro de Reumatologia de 2013 (SBR-2013)?”. Este sistema de lógica de ramificação, além de evitar a possibilidade de respostas por inferência baseada no restante do questionário, também evita perguntas desnecessárias para alguns participantes, reduzindo o tamanho do instrumento e o tempo de resposta. O questionário eletrônico foi testado e ajustado algumas vezes, até chegarmos à versão final, que pode ser acessada pelo endereço https://pt.surveymonkey.com/r/tratamento-gota-doutorado.

Na primeira página desta versão final do questionário eletrônico, havia um texto de abertura informando que o inquérito estava sendo realizado em nome da Comissão de Gota da

Sociedade Brasileira de Reumatologia, assegurando o caráter científico e oficial, societário, desta pesquisa.

3.1.3.2 Divulgação da pesquisa

Utilizamos o SBR-2013 para ampla divulgação da pesquisa através de *slide* projetado nos intervalos das aulas (Figura 7), exposição de cartazes (Figura 8) nos quatro pontos de maior circulação do congresso e abordagem interpessoal, explicando sobre a pesquisa e estimulando a participação para o caso de receberem o convite.

Figura 7 - *Slide* exibido nos intervalos das aulas do Congresso Brasileiro de Reumatologia de 2013

Fonte: A autora, 2013.

Figura 8 - Cartaz exposto nos quatro pontos de maior circulação de pessoas durante o Congresso Brasileiro de Reumatologia de 2013

Fonte: A autora, 2013.

3.1.4 Variáveis

A pesquisa incluiu perguntas sobre o tratamento da crise aguda de gota, a THU e a profilaxia anti-inflamatória, além de perguntas sobre dados demográficos, treinamento/experiência em reumatologia, número de pacientes com gota vistos mensalmente e cenário da prática clínica (privado *versus* acadêmico *versus* ambos).

O primeiro conjunto de perguntas foi sobre o medicamento preferencial para tratar uma crise aguda de gota em oito cenários diferentes e as respostas incluíram colchicina (dose alta, dose baixa), AINEs, corticosteroides (oral, intramuscular, intra-articular), ou combinações de dois desses medicamentos. Esses cenários incluíam diferentes combinações de três características: o número de articulações afetadas (mono *versus* poliarticular), duração da crise aguda de gota no momento em que o tratamento seria iniciado (<36 horas *versus* >36 horas) e a presença de DRC (paciente saudável *versus* paciente com ClCr menor que 60 mL/min).

O conjunto de perguntas seguinte investigou o manejo da THU durante uma crise aguda de gota (manutenção da dose, modificação da dose ou descontinuação da THU);

profilaxia anti-inflamatória para prevenir crises de gota ao se iniciar THU (medicamento preferencial e tempo de manutenção da profilaxia); indicações, dose inicial e duração da THU após atingir a uricemia desejada; nível de uricemia alvo; e frequência da avaliação laboratorial (até atingir uricemia alvo e depois disso). Probenecida, sulfinpirazona, febuxostato e pegloticase não foram incluídos na pesquisa porque não estão disponíveis para tratamento da gota no Brasil.

3.1.5 Análise estatística

Proporções e seus intervalos de confiança de 95% (IC 95%) foram estimados para todas as variáveis nominais, e a significância estatística das diferenças entre respondentes e não respondentes foi avaliada pelo teste qui-quadrado. As médias e os respectivos desvios-padrão foram calculados para variáveis contínuas e as diferenças entre os grupos tiveram sua significância avaliada pelo teste t de Student.

Avaliamos a concordância das práticas relatadas pelo reumatologista com as diretrizes de gota do Colégio Americano de Reumatologia, de 2012. Para isto, selecionamos cinco itens considerados especialmente importantes para esta pesquisa, fossem por representar um conceito novo, como a uricemia alvo, fossem por representar um conceito antigo frequentemente ignorado na prática clínica, como a necessidade de se manter durante a crise aguda de gota a THU que já esteja em uso. As recomendações, as perguntas selecionadas do questionário e as respectivas respostas consideradas concordantes com as recomendações estão explicitadas no Quadro 3.

Em seguida, avaliamos os potenciais preditores de concordância com essas diretrizes,(23, 36) definindo as respostas concordantes expostas no Quadro 3 como as variáveis dependentes. As variáveis independentes foram sexo, idade, tempo de graduação em medicina, anos de prática de reumatologia, região geográfica, atividade acadêmica, residência em reumatologia, comparecimento ao SBR-2013, comparecimento a alguma atividade sobre gota no SBR-2013 e número médio de pacientes com gota atendidos por mês.

O processo de modelagem foi realizado em três fases. Inicialmente, modelos de regressão logística univariados foram ajustados para as dez variáveis independentes. Em seguida, aqueles com valores de $p \leq 0{,}20$ foram selecionados para análise multivariada subsequente(92) e, por fim, aqueles com p-valor $\leq 0{,}10$ foram mantidos no modelo final.

Todos os valores de p foram bicaudais. Valores de p ≤0,05 e entre 0,06 e 0,10 foram considerados estatisticamente significantes e de significância limítrofe, respectivamente. O software Stata (versão 12.0, College Station, TX, EUA) foi utilizado para todas as análises estatísticas.

3.1.6 Aspectos éticos

Este projeto recebeu aprovação do Comitê de Ética em Pesquisa do Hospital Universitário Pedro Ernesto – UERJ (Plataforma Brasil, CAAE 20338513.2.0000.5259 – Anexo A). O mesmo Comitê de Ética dispensou a exigência de obtermos dos participantes um termo de consentimento assinado. Por se tratar de um questionário autoaplicado a médicos, capazes de julgar as vantagens e desvantagens de sua participação, a submissão do questionário preenchido foi considerada como consentimento para participar.

Todos os dados foram analisados anonimamente e em conjunto.

Quadro 3 - Avaliação de concordância das respostas dos participantes com as Diretrizes para Manejo da Gota do Colégio Americano de Reumatologia de 2012(23, 36)

Diretrizes de gota do Colégio Americano de Reumatologia de 2012*(23, 36)	**Perguntas do questionário do estudo**	**Respostas consideradas concordantes**
(1) "Para países onde comprimidos de colchicina de 1,0 mg ou 0,5 mg em vez de 0,6 mg estão disponíveis, o painel de força-tarefa recomenda, caso apropriado, 1,0 mg de colchicina como dose de ataque, seguido de 0,5 mg 1 hora mais tarde. e, então, seguida, conforme necessário, após 12 horas, por colchicina continuada (até 0,5 mg 3 vezes ao dia) até resolução da crise aguda de gota";	**Questão 1:** Para tratamento da crise, num paciente SEM COMORBIDADES, qual seria a sua primeira escolha? **Questão 2:** Para tratamento da crise, num paciente COM CLEARANCE DE CREATININA ≤60 ML/MIN, qual seria a sua primeira escolha?	(1) **Não** seleção da assertiva "Colchicina 0,5 mg/hora até resolução do quadro ou efeito colateral"
(2) "A colchicina foi recomendada como uma opção apropriada para crise aguda de gota se iniciada dentro de 36 horas após o início dos sintomas"	**Questão 1:** Para tratamento da crise, num paciente SEM COMORBIDADES, qual seria a sua primeira escolha? - Início há MAIS de 36 horas **Questão 2:** Para tratamento da crise, num paciente COM CLEARANCE DE CREATININA ≤60 ML/MIN, qual seria a sua primeira escolha? - Início há MAIS de 36 horas	(2) **Não** seleção de ambas as assertivas "Colchicina 0,5 mg/hora até resolução do quadro ou efeito colateral" e "Colchicina até 2 mg/dia"
(3) "A terapia hipouricemiante farmacológica em curso não deve ser interrompida durante uma crise aguda de gota"	**Questão 3:** Na crise aguda de gota, num paciente em uso de medicação hipouricemiante (p. ex. alopurinol), você:	(3) "mantém a dose do hipouricemiante"
(4) "A meta mínima de urato sérico é <6 mg/dL. Reduzir a uricemia abaixo de 5 mg/dL pode ser necessário para melhorar os sinais e sintomas de gota."	**Questão 5:** Indique o nível sérico de ácido úrico que você procura alcançar (uricemia alvo) com o tratamento hipouricemiante para um paciente COM TOFO:	(4) "<6,0 mg/dL" ou "<5,0 mg/dL"
	Questão 6: Indique o nível sérico de ácido úrico que você procura alcançar (uricemia alvo) com o tratamento hipouricemiante para um paciente SEM TOFO:	(5) "<6,0 mg/dL" ou "<5,0 mg/dL"
(5) Alopurinol - "A dose inicial não deve ser superior a 100 mg/dia para nenhum paciente, e deve-se começar com 50 mg/dia na doença renal crônica estágio 4 ou pior".	**Questão 11:** Ao prescrever alopurinol, em geral, com que dose você inicia o tratamento? - Paciente com função renal normal	(6) "50 mg/dia" ou "100 mg/dia"
	Questão 11: Ao prescrever alopurinol, em geral, com que dose você inicia o tratamento? - Paciente com ClCr ≤60 mL/min	(7) "50 mg/dia" ou "100 mg/dia"

Legenda: Cinco itens das diretrizes de gota do Colégio Americano de Reumatologia de 2012, perguntas do questionário que avaliaram esses itens e respectivas respostas consideradas concordantes com as diretrizes. *Tradução livre pela autora.

Fonte: A autora, 2013.

3.2 **Estudo 2**

3.2.1 Desenho do estudo

O estudo 2 foi uma revisão narrativa da literatura sobre o manejo da gota e da hiperuricemia na presença de DRC e sobre os efeitos da hiperuricemia e da THU sobre a função renal.

3.2.2 Fonte de dados

Utilizamos o Medline como a base de dados inicial, revisando também a lista de referências dos artigos selecionados.

Os termos de busca foram:

a) *gout, gouty, gout arthritis, hyperuricemia, urate, uric acid*;
b) *chronic kidney disease, kidney transplant, renal transplant, dialysis, hemodialysis, peritoneal dialysis, kidney dysfunction, renal failure, renal insufficiency*;
c) *allopurinol, febuxostat, lesinurad, benzbromarone, probenecid, sulfimpyrazone, pegloticase*;
d) *colchicine, nonsteroidal anti-inflammatory drugs, NSAIDs, steroids, glucocorticoids, ACTH, corticotropin, adrenocorticotropin, interleukin-1 inhibitor, canakinumab, anakinra, rilonacept*.

Adicionalmente, revisamos as páginas eletrônicas das agências oficiais responsáveis pelo controle e supervisão de medicamentos dos Estados Unidos (*US Food and Drug Administration* – FDA), Europa (*European Medicines Agency* – EMA) e Canadá (*Health Canada*) referentes aos medicamentos de interesse: alopurinol, febuxostato, lesinurade, benzbromarona, probenecida, sulfinpirazona, pegloticase, colchicina, AINEs, glicocorticoides, corticotropina e inibidores da interleucina 1.

A busca bibliográfica ocorreu de dezembro de 2015 a agosto de 2016.

3.2.3 Critérios de inclusão e exclusão

Os critérios de inclusão foram:

a) ambos os sexos, idade ≥18 anos; e
    a. terapia farmacológica uricorredutora na função renal normal; ou
    b. terapia farmacológica uricorredutora em todos os estágios de DRC, incluindo as terapias de substituição renal (transplante renal, hemodiálise e diálise peritoneal); ou
    c. terapia farmacológica da crise aguda de gota na função renal normal; ou
    d. terapia farmacológica da crise aguda de gota em todos os estágios de DRC, incluindo as terapias de substituição renal (transplante renal, hemodiálise e diálise peritoneal); ou
    e. profilaxia anti-inflamatória na função renal normal; ou
    f. profilaxia anti-inflamatória em todos os estágios de DRC, incluindo as terapias de substituição renal (transplante renal, hemodiálise e diálise peritoneal); ou
b) estudos animais e em humanos sobre a relação da hiperuricemia com desfechos renais; ou
c) estudos animais e em humanos sobre a relação da THU com desfechos renais.

3.2.4 Síntese dos artigos revisados e estruturação do artigo

Realizamos a síntese dos artigos revisados, estruturando o texto em duas partes principais: manejo da gota e da hiperuricemia na presença de DRC e efeitos da hiperuricemia e da THU sobre a função renal. Para adequação ao periódico em que foi publicado, criamos um caso clínico fictício para introduzir o tema e concluir o artigo.

3.2.5 Aspectos éticos

Não houve necessidade de avaliação deste estudo pelo Conselho de Revisão Institucional do Campus Médico da Universidade de Boston, bastando para o periódico em que foi publicado a declaração de ausência de conflitos de interesse por ambas as autoras.

3.3 **Estudo 3**

3.3.1 Desenho do estudo e população

O estudo 3 foi um estudo de coorte em uma população de adultos com gota atendidos pelo sistema de saúde do Reino Unido.

3.3.2 Fonte de dados

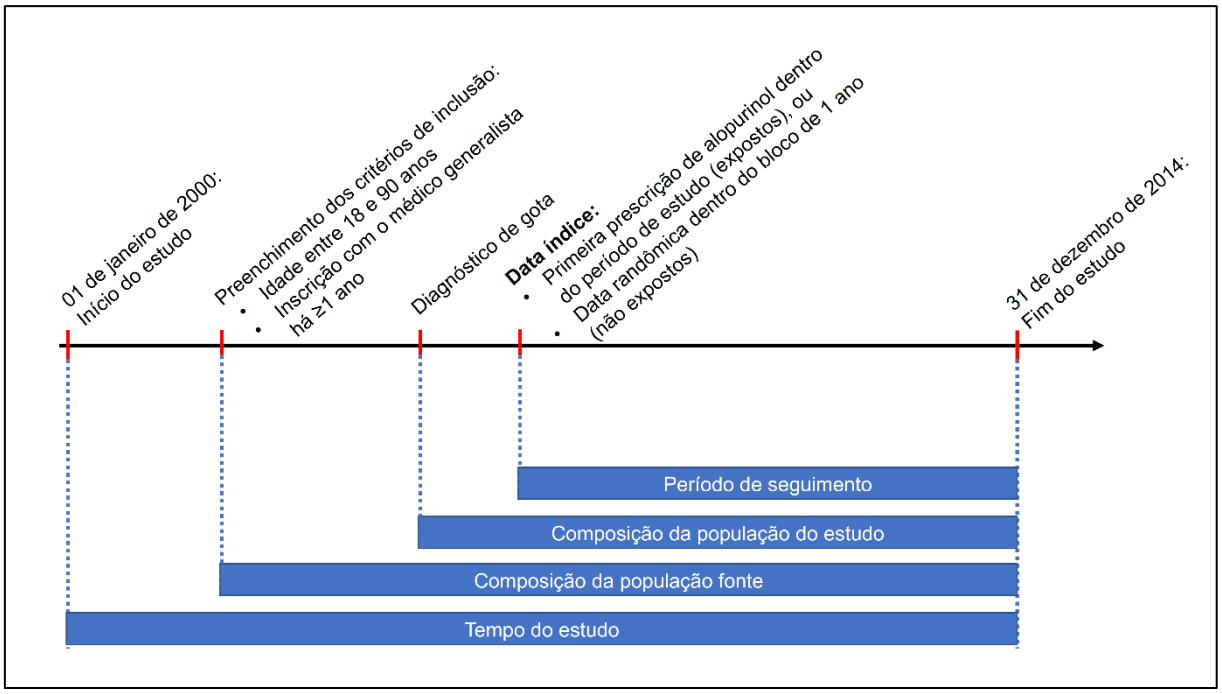
A base de dados *The Health Improvement Network* (*THIN*) contém informações anônimas, incluindo dados demográficos, diagnósticos, prescrições, resultados de exames laboratoriais, internações hospitalares, consultas e encaminhamentos, coletados sistematicamente durante os cuidados de rotina pelos médicos generalistas participantes em todo o Reino Unido. Mais de 11 milhões de pacientes foram registrados no *THIN* e mais de 3 milhões estão atualmente matriculados ativamente. Os diagnósticos são registrados como códigos alfanuméricos chamados códigos Read.(93) As prescrições são registradas usando os códigos Multilex emitidos pelo *First Databank*.(94) O *THIN* foi validado para uso em pesquisa farmacoepidemiológica.(95)

3.3.3 Participantes

Foram incluídos indivíduos com idade entre 18 e <90 anos com gota incidente (recém-diagnosticada) entre 1º de janeiro de 2000 e 31 de dezembro de 2014, que haviam sido inscritos para acompanhamento com seu médico generalista pelo menos um ano antes do diagnóstico de gota. Este diagnóstico foi baseado no primeiro registro de um código diagnóstico de gota.

Os critérios de exclusão apresentados a seguir tiveram como referência os diferentes momentos representados na Figura 9.

Figura 9 - Momentos de um indivíduo fictício durante o estudo



Fonte: A autora, 2018.

Os critérios de exclusão foram:

a) Diagnóstico de DRC estágio ≥3 antes do diagnóstico de gota, sendo DRC definida como TFG <60 mL/min em pelo menos duas ocasiões com mais de 90 dias de intervalo em um ano, sem TFG interveniente ≥75 mL/min, ou pelo menos um código diagnóstico para DRC estágio 4, DRC estágio 5, hemodiálise, diálise peritoneal ou transplante renal;

b) Uso de THU (alopurinol, febuxostato, probenecida ou sulfinpirazona) no ano anterior ao diagnóstico da gota. Benzbromarona não foi incluída por não ter seu uso liberado no Reino Unido;
c) Uma das seguintes condições durante os 12 meses anteriores à data índice: (i) uso de THU diferente de alopurinol; (ii) câncer ativo diferente de cânceres *in situ*, carcinoma de células escamosas de pele ou carcinoma basocelular de pele; e (iii) nenhum contato com o sistema de saúde (ou seja, nenhuma consulta com o médico generalista, nenhum teste laboratorial e nenhuma prescrição);
d) Uma das seguintes condições a qualquer momento antes da data índice: (i) transplante de órgão sólido exceto rim ou transplante de medula óssea; (ii) doença renal primária (incluindo doença renal policística) ou vasculite sistêmica que afete os rins; (iii) cirrose; e (iv) mieloma múltiplo ou carcinoma renal;
e) Ocorrência do diagnóstico de gota no último dia do estudo (já que nenhum acompanhamento seria possível);
f) Ausência de dados sobre o índice de massa corporal (IMC) a qualquer momento antes da data índice;
g) Ausência de dados sobre nível sérico de urato no período de seis meses antes do diagnóstico de gota até 30 dias após a data índice.

3.3.4 Variáveis

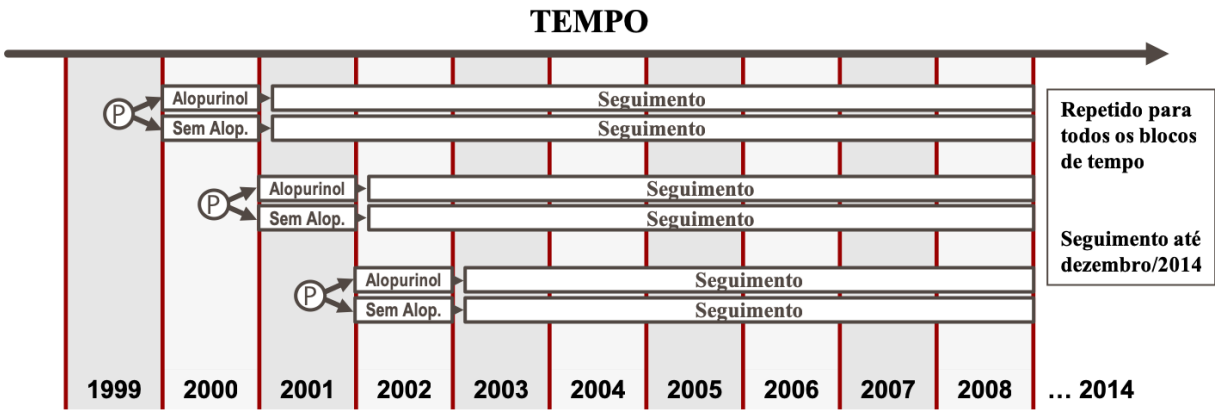
3.3.4.1 Exposição

A exposição foi definida como uso incidente de alopurinol, com base na primeira prescrição deste medicamento. Para nossa análise primária, os iniciadores de alopurinol estavam restritos àqueles que receberam uma dose inicial ≥300 mg/dia. Apesar de reconhecermos que esta não é a dose inicial recomendada atualmente, escolhemos esta dose porque avaliamos dados de 2000 a 2014. As diretrizes para tratamento da gota do Colégio Americano de Reumatologia foram publicadas no final de 2012, o que significa que as mudanças na prática não teriam sido percebidas de forma significativa no período de tempo do nosso estudo. A maioria das doses iniciais de alopurinol tem sido, historicamente, 300

mg/dia, e a maioria dos pacientes, historicamente, não tem sua dose de alopurinol ajustada. Assim, para avaliar os efeitos de uma dose "eficaz" de alopurinol nesta amostra, optamos por nos concentrar na dose inicial de pelo menos 300 mg/dia para identificar os efeitos biologicamente relevantes do alopurinol – ainda que menos de 50% dos pacientes com gota atinjam o alvo terapêutico com esta dose.(96, 97)

Criamos blocos de tempo acumulado na coorte, de um ano, dentro dos quais identificamos os iniciadores de alopurinol e os não usuários de alopurinol, considerando possíveis tendências seculares (Figura 10). A data índice foi definida como a data da primeira prescrição de alopurinol para os expostos e uma data aleatoriamente atribuída no bloco de um ano para cada indivíduo não exposto pareado.

Figura 10 - Desenho do estudo: blocos de tempo acumulado na coorte, de um ano, com pareamento 1:1 baseado nos escores de propensão



Legenda: P – par (indivíduos pareados).
Fonte: A autora, 2018.

3.3.4.2 Desfecho

O desfecho foi definido como: (i) TFG <60 mL/min em pelo menos duas ocasiões com mais de 90 dias de intervalo dentro de um ano sem TFG interveniente ≥75 mL/min; (ii) hemodiálise ou diálise peritoneal; ou (iii) transplante renal. Para definição da data do desfecho pelo primeiro critério (baseado em dois valores de TFG), consideramos como tendo ocorrido na data do primeiro valor de TFG baixo. A segunda TFG de qualificação pode ocorrer após o término do acompanhamento do estudo (por exemplo, após o 90º aniversário ou após 31 de

dezembro de 2014). A TFG foi calculada usando a fórmula MDRD (do inglês, *Modification of Diet in Renal Disease*).(98) A análise dos valores da creatinina sérica para o cálculo da TFG em *THIN* foi previamente validada.(99)

3.3.4.3 Covariáveis

As covariáveis analisadas estão descritas no Quadro 4.

Indivíduos com valores ausentes para creatinina sérica e sem o código diagnóstico para DRC estágio 2 foram considerados como tendo função renal normal, sendo classificados como TFG ≥90 mL/min ou DRC estágio 1 com base nos dados de prevalência de DRC estágio ≥3 em pacientes com gota em torno de 20%, sendo essa prevalência menor nos primeiros anos da doença.(8, 20)

Quadro 4 - Covariáveis analisadas

Categorias	**Covariáveis**	**Tipo de variável**	**Período de avaliação**
Dados demográficos	Sexo	Categórica: • Feminino • Masculino	A qualquer momento
	Idade	Contínua	À data índice
	Índice de massa corporal	Contínua	Mais recente antes da data índice
	Número de visitas ao médico generalista	Contínuas	Nos 12 meses antes da data índice
	Hospitalização nos 12 meses antes da data índice		
Comorbidades	• Doença cardiovascular • *Diabetes mellitus* • Insuficiência cardíaca • Hipertensão arterial sistêmica	Categóricas: • Sim • Não	A qualquer momento anterior à data índice
Uso de medicamentos	• Inibidores da enzima conversora de angiotensina • Aspirina em dose baixa para prevenção de doenças cardiovasculares • Colchicina • Diuréticos (de alça, tiazídicos ou similares a tiazida) • Insulina • Outros medicamentos para *diabetes mellitus* • Losartana • Outros bloqueadores dos receptores da angiotensina II • Anti-inflamatórios não esteroides	Categóricas: • Sim • Não	Nos 12 meses antes da data índice
Dados laboratoriais	Urato sérico basal	Contínua	De seis meses antes do diagnóstico de gota até 30 dias após a data índice
	Albuminúria basal	Categórica: • Normal: <30 mg/g • Microalbuminúria: 30 – 300 mg/g • Macroalbuminúria: >300 mg/g	Nos cinco anos anteriores à data índice
Outros	Duração da gota	Contínua	À data índice
	Função renal basal (baseada em códigos diagnósticos ou dados laboratoriais)	Categórica: • DRC 1 ou TFG ≥90 mL/min • DRC 2 ou TFG 60 a <90 mL/min	Nos cinco anos anteriores à data índice

Legenda: DRC 1 – doença renal crônica estágio 1; DRC 2 – doença renal crônica estágio 2; TFG – taxa de filtração glomerular.
Fonte: A autora, 2018.

3.3.5 Análises estatísticas

Pareamos usuários incidentes de alopurinol com não usuários de alopurinol na proporção de 1:1 usando escores de propensão para minimizar os efeitos de confundimento por indicação. Para calcular os escores de propensão foi utilizada a regressão logística com o uso incidente de alopurinol como variável dependente e potenciais confundidores que refletem as indicações para o uso de alopurinol e/ou risco de desenvolver DRC (listadas no Quadro 4) como variáveis independentes.

O tempo de seguimento iniciou a partir da data índice e continuou até a ocorrência do desfecho, morte, desligamento da clínica do médico generalista, data da última coleta de dados pelo médico generalista, aniversário de 90 anos ou final do estudo (31 de dezembro de 2014).

A associação do uso incidente de alopurinol ≥300 mg/dia com DRC estágio ≥3 entre os indivíduos com gota incidente foi avaliada usando modelos de riscos proporcionais de Cox, estratificados por blocos de um ano acumulados na coorte, com um segundo modelo adicionalmente ajustado para as covariáveis incluídas no escore de propensão.

A análise primária utilizou uma abordagem de intenção de tratar. Também comparamos a incidência cumulativa de DRC em ambos os grupos usando curvas de Kaplan-Meier para avaliar a possibilidade de depleção de suscetíveis. Para avaliar o impacto do risco concorrente de morte em nossos resultados primários, utilizamos a abordagem de Fine e Gray e a abordagem de risco específico por causa.

Devido ao grande número de dados faltantes sobre o IMC e urato sérico, respectivamente 11,6% e 36,6% dos 72.597 indivíduos potencialmente elegíveis após a criação dos blocos, realizamos imputação múltipla de dados. Primeiro, com os blocos de um ano já definidos, imputamos cinco vezes o conjunto de dados para atribuir valores aos dados faltantes de IMC e de urato sérico. Em seguida, para cada um desses cinco bancos imputados, foram calculados os escores de propensão e formados os pares com bases nesses escores. Em cada um dos bancos, foi estimada a razão de riscos (*hazards ratio*) com os respectivos ICs 95%; realizamos um segundo modelo, ajustando adicionalmente para as covariáveis incluídas no escore de propensão. Por fim, calculamos a média das cinco razões de risco com respectivo IC para cada modelo.

O equilíbrio das covariáveis no conjunto de dados pareados pelo escore de propensão foi avaliado usando a diferença de média padronizada (*standardized mean difference* – SMD),

avaliada através da *macro* %pmdiag do programa estatístico SAS versão 9.3 (SAS Institute, Cary, NC). Quanto mais próxima de zero for a diferença de média padronizada, melhor é o equilíbrio da covariável.

Para garantir que os métodos usados em nossa análise principal foram apropriados, avaliamos se o pressuposto de riscos proporcionais de Cox foi respeitado, ou seja, se a magnitude do efeito de uma determinada covariável não mudou com o tempo. Para avaliar se houve alguma violação da premissa de riscos proporcionais, realizamos três verificações. Primeiro, incluímos um termo de interação (log de tempo x exposição) no modelo de regressão de Cox. Em segundo lugar, utilizamos o comando "ASSESS PH".(100) Por fim, criamos um gráfico Log-Negative Log. Adicionalmente, avaliamos os resíduos de Schoenfeld por inspeção visual.

Realizamos, também, algumas análises de sensibilidade. Primeiramente, censuramos os usuários incidentes de alopurinol ≥300 mg/dia quando os mesmos paravam de usar o alopurinol ou reduziam a dose para <300 mg/dia e os não-usuários quando estes começavam a usar alopurinol. Em seguida, realizamos novas análises incluindo todos os iniciadores de alopurinol, independentemente da dose inicial. Por fim, repetimos as análises limitando os usuários incidentes de alopurinol àqueles prescritos uma dose inicial <300 mg/dia.

Todas as análises foram realizadas usando SAS 9.3 (SAS Institute, Cary, NC). Os valores de p foram bilaterais e considerados significativos se <0,05.

3.3.6 Aspectos éticos

O Conselho de Revisão Institucional do Campus Médico da Universidade de Boston e o Comitê de Revisão do *THIN* aprovaram o estudo.

4 **RESULTADOS**

4.1 **Estudo 1**

Este artigo foi publicado na revista Plos One em 14 de agosto de 2015. Referência: Adherence to the 2012 American College of Rheumatology (ACR) Guidelines for Management of Gout: A Survey of Brazilian Rheumatologists. Vargas-Santos AB, Castelar-Pinheiro G da R, Coutinho ES, Schumacher HR Jr, Singh JA, Schlesinger N. PLoS One. 2015 Aug 14;10(8):e0135805. doi: 10.1371/journal.pone.0135805. eCollection 2015.(101)

4.1.1 Artigo 1

Adherence to the 2012 American College of Rheumatology (ACR) Guidelines for Management of Gout: A Survey of Brazilian Rheumatologists

Ana Beatriz Vargas-Santos, Geraldo da Rocha Castelar-Pinheiro, Evandro Silva Freire Coutinho, H. Ralph Schumacher, Jr., Jasvinder A. Singh, Naomi Schlesinger

ABSTRACT

Objective: To describe the current pharmacological approach to gout treatment reported by rheumatologists in Brazil. **Methods:** We performed a cross-sectional survey study using an online questionnaire e-mailed to 395 rheumatologists, randomly selected, from among the members of the Brazilian Society of Rheumatology. **Results:** Three hundred and nine rheumatologists (78.2%) responded to the survey. For acute gout attacks, combination therapy (NSAIDs or steroid + colchicine) was often used, even in monoarticular involvement, and colchicine was commonly started as monotherapy after 36 hours or more from onset of attack. During an acute attack, urate-lowering therapy (ULT) was withdrawn by approximately a third of rheumatologists. Anti-inflammatory prophylaxis (98% colchicine) was initiated when ULT was started in most cases (92.4%), but its duration was varied. Most (70%) respondents considered the target serum uric acid level to be less than 6 mg/dL. Approximately 50% of rheumatologists reported starting allopurinol at doses of 100 mg daily or less and 42%

reported the initial dose to be 300 mg daily in patients with normal renal function. ULT was maintained indefinitely in 76% of gout patients with tophi whereas in gout patients without tophi its use was kept indefinitely in 39.6%. **Conclusion:** This is the first study evaluating gout treatment in a representative, random sample of Brazilian rheumatologists describing common treatment practices among these specialists. We identified several gaps in reported gout management, mainly concerning the use of colchicine and ULT and the duration of anti-inflammatory prophylaxis and ULT. Since rheumatologists are considered as opinion leaders in this disease, a program for improving quality of care for gout patients should focus on increasing their knowledge in this common disease.

INTRODUCTION

Gout is the most common inflammatory arthritis and one of the oldest known arthritides. Its prevalence has increased for the last few decades.[1-4] It is one of the few rheumatic diseases where etiology, pathophysiology, diagnosis and treatment are well established. Despite the existence of this knowledge, gout is often poorly managed.[5-11]

This paradox has been investigated. Some potential explanations were: 1) doctors' misconception that gout is a well-known and perhaps "unimportant disease", so there is no need for regular scientific updating and 2) patients' lack of information about their disease and its management which may partially explain their poor adherence to treatment.[12-15] On the other hand, some changes in the last decade may have impacted the current scenario. There is a growing interest in gout as documented by the increasing number of publications in this field, including the launch of new drugs for the treatment of gout and studies related to increasing gout prevalence and the poor quality of care of gout patients.[1-13,16,17] There is a need to translate this knowledge into better practice. Several national and international organizations compiled the available evidence into management guidelines and recommendations since 2006.[18-25] A major challenge to these guidelines relates to their effective adoption by the practicing health care providers. Adherence to guidelines needs to be assessed in order to improve the quality of care provided to gout patients.

Many studies have evaluated doctors' reports of their approaches to treating patients with gout (S1 Table).[26-44] With few exceptions, response rates in these studies have varied from 21% to 58%, thus, limiting their generalizability. Evidence-based guidelines for treatment of gout were published by the American College of Rheumatology (ACR) in 2012.[22,23] Adherence to these guidelines has already been evaluated,[45] but, to our knowledge, ours is the first survey to do it in a representative national sample of rheumatologists. The

objectives of our study were to evaluate the current pharmacological treatment of gout as reported by rheumatologists in Brazil, and to assess where gaps in recommended care exist, so that future continued medical education programs can target these gaps and address them in a comprehensive fashion.

MATERIALS AND METHODS

Study design and population

A cross-sectional study was undertaken in a population of practicing rheumatologists, members of the Brazilian Society of Rheumatology (BSR).

Sample design

A simple random sample was obtained from a list of 1436 practicing rheumatologists provided by the BSR, which was made available to us for this study. The sample was stratified proportionally to the number of rheumatologists in each Brazilian geographic region to prevent the absence of rheumatologists from areas with a small number of specialists. The sample size was calculated according to the following parameters: a confidence level of 95% and an error of 5%, considering an expected proportion of correct answers of 50% for the most important question in the authors' opinion (target serum uric acid [SUA] level). Using PEPI (Programs for Epidemiologists, version 11.39), the sample size was calculated as 304 individuals. Considering a possible failure to contact 20–30% of the sample, 395 members were randomly selected using the online tool "True Random Number Generator" available in www.random.org. The study was approved by the Ethics Committee of Hospital Universitário Pedro Ernesto. The Ethics Committee waived the requirement to obtain a signed consent form. The submission of the completed questionnaire was deemed to constitute consent to participate. All data were analyzed anonymously.

Data collection

A self-administered questionnaire was developed using the online survey tool SurveyMonkey (SurveyMonkey, Palo Alto, California, USA– www.surveymonkey.com). The survey was available from December 18, 2013 to March 25, 2014. During that period, up to four invitations were sent via e-mail and up to three telephone calls were made for each potential participant. The questionnaire is attached as a supplement (S1 File).

Domains assessed

The survey included questions regarding the treatment of acute attack as well as treatment with the urate-lowering therapy (ULT) and prophylaxis. It also included questions about demographics and training/experience in rheumatology, number of gout patients seen monthly and practice setting (private versus [vs.] academic vs. both). The first set of questions was regarding the preferred drug to treat an acute gout attack in eight different scenarios and responses included colchicine (high dose, low dose), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids (oral, intramuscular, intraarticular), or combinations of two of these drugs. These scenarios included different combinations of three features: the number of affected joints (mono vs. polyarticular), duration of the acute attack at the time the treatment was to be started (<36 hours vs. >36 hours), and the presence of chronic kidney disease (CKD) (healthy patient vs. patient with a creatinine clearance [CrCl] less than 60 mL/min).

The next set of questions queried the management of the ULT during an acute gout attack (continuation, discontinuation, dose modification); anti-inflammatory prophylaxis to prevent gout attacks during ULT initiation (colchicine vs. NSAIDs; duration); indications, starting dose and duration of ULT after achieving the target SUA level (discontinuation, 1–6 months, 7–11 months, 1–3 years, ≥4 years, until tophi resolution, indefinite); target SUA level (<6 vs. <5 vs. <6.8 mg/dL vs. <upper limit of normal vs. no consideration for SUA level), and frequency of laboratory evaluation (until the target SUA achieved and after that; every 1–3 months, every 4–6 months, every 7–9 months, every 10–12 months). Probenecid, febuxostat and pegloticase were not included in the survey because they are not available in Brazil.

Outcome: Concordance with 2012 ACR gout guidelines

We assessed the concordance of rheumatologist-reported practices with the following 2012 ACR gout guidelines: 1) “For countries where 1.0 mg or 0.5 mg rather than 0.6 mg tablets of colchicine are available, the task force panel (TFP) recommended, as appropriate, 1.0 mg colchicine as the loading dose, followed by 0.5 mg 1 hour later, and then followed, as needed, after 12 hours, by continued colchicine (up to 0.5 mg 3 times daily) until the acute attack resolves”; 2) “Colchicine was recommended as an appropriate option for acute gout if started within 36 hours of symptom onset”; 3) “Ongoing pharmacologic ULT should not be interrupted during an acute gout attack”; 4) “The minimum serum urate target is <6 mg/dL. Serum urate lowering below 5 mg/dL may be needed to improve gout signs and symptoms”; 5) Allopurinol–“Starting dosage should be no greater than 100 mg/day for any patient, and start at 50 mg/day in stage 4 or worse CKD”.

The specific outcomes assessed related to the management of acute gout and ULT were: 1) no prescription of high dose colchicine, i.e., 0.5 mg/hour until symptom resolution or side effect, to treat acute gout; 2) no prescription of colchicine as monotherapy to treat acute attacks lasting more than 36 hours; 3) maintenance of ULT dose during acute gout attack; 4) target SUA level <6 or <5 mg/dL for patients with tophi and for patients with no tophi; 5) initial dose of allopurinol of 50 mg/day or 100 mg/day for patients with normal renal function and for patients with a CrCl ≤60 mL/min.

Statistical analysis

We calculated proportions and their 95% confidence intervals (95% CIs) for categorical variables and means and standard deviations for continuous variables. The statistical significance of the differences between respondents and non-respondents was assessed by chi-squared test or Student's t-test, as appropriate.

Proportions of rheumatologists' responses on managing acute gout and ULT management in acute and chronic gout were compared. We evaluated the potential predictors of concordance of rheumatologist's practice with the ACR guidelines. Seven dependent variables mentioned above were assessed. Firstly, univariate logistic regression models were fitted for the following ten independent variables related to the rheumatologist: gender, age, time since medical school graduation, years of practicing rheumatology, geographic region, academic activity, residency in rheumatology, attending the 2013 BSR Meeting, attending any conference on gout in the 2013 BSR Meeting and average number of patients with gout seen in one month. Variables with p-values ≤0.20 were selected for subsequent multivariate analysis[46] and those with p-value ≤0.10 were kept in the final model.

All p-values were two-sided. P-values ≤0.05 and between 0.06 and 0.10 were considered statistically significant and of borderline significance, respectively. Stata software (version 12.0, College Station, TX, USA) was used for all statistical analysis.

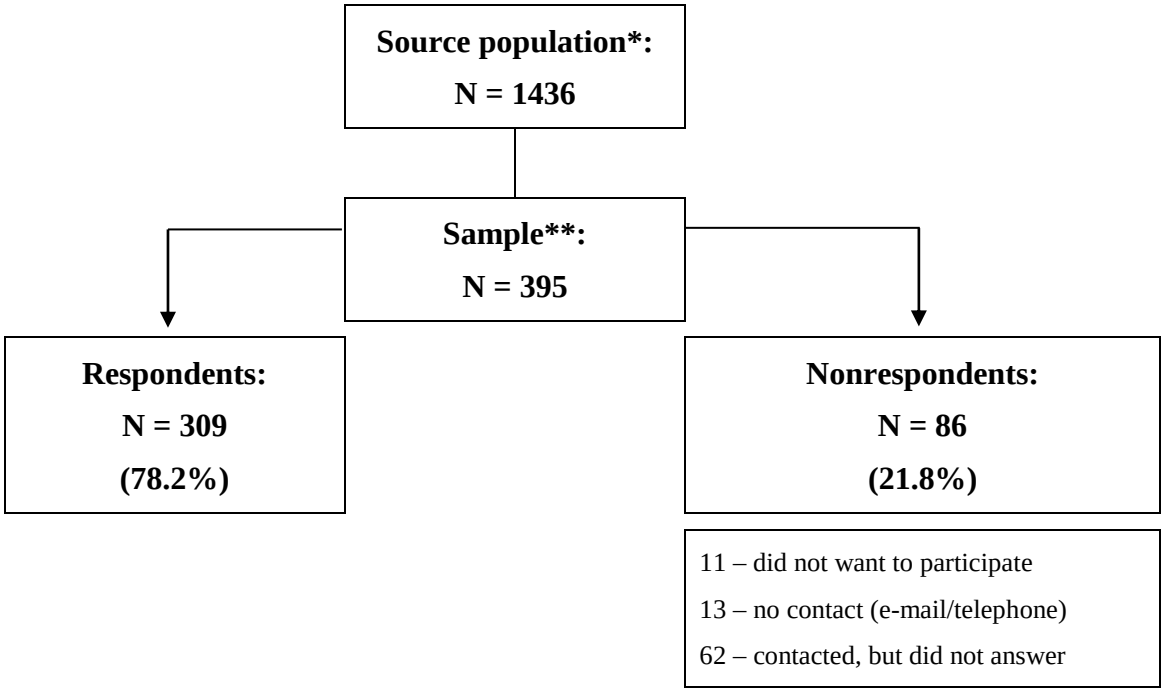
RESULTS

Of the original sample of 395 rheumatologists, 309 (78.2%) responded to the survey. Fig 1 shows the flow diagram of participants' selection.

Demographic and other characteristics of the sample are presented in Table 1. The mean age of the participants was 46.1 years (range: 29–88 years, median 44 years), 58% were women, and approximately 2/3rd had >10 years of experience in rheumatology and provided

care to ≤10 gout patients per month. Fifty three percent were only in private practice and 87% were board certified by the BSR.

Figure 1 - Flow diagram of participants' selection



* Practicing rheumatologists, members of the Brazilian Society of Rheumatology;
** Random sample, stratified proportionally to the number of rheumatologists in each Brazilian geographic region.

Compared to survey responders, nonresponders were older (51.6 vs. 46.1 years, p <0.001), more likely to be men (53 vs. 42%, p = 0.08), fewer were board certified rheumatologists (71 vs. 87%, p = 0.001) and fewer attended the 2013 BSR Meeting (47 vs. 64%, p = 0.003).

Acute gout treatment

A combination of an NSAID plus colchicine was the preferred treatment option for an acute gout attack in an otherwise healthy patient, ranging from 38.5% (polyarticular, >36 hours) to 51.5% (polyarticular, <36 hours), while the combination of a corticosteroid with colchicine was the most common choice for patients with CKD, from 27.5% (monoarticular, <36 hours) to 47.6% (polyarticular, >36 hours) (Table 2).

Table 1 - Description of the study sample and comparison between respondents and nonrespondents

Feature	Respondents	Nonrespondents	P value
Age*	**[N = 309]**	**[N = 78]****	
	46.1 years (±12.0)	51.6 years (±12.5)	<0.001
Female gender***	**[N = 309]**	**[N = 86]**	
	58.3 (52.7–63.8)	46.5 (35.8–57.3)	0.08
Time practicing rheumatology***	**[N = 302]**	**N/A**	
0–10 years	37.4 (31.9–42.9)	N/A	
11–20 years	22.5 (17.8–27.3)	N/A	
21–30 years	22.2 (17.5–26.9)	N/A	
≥31 years	17.9 (13.5–22.2)	N/A	
Gout patients seen monthly***	**[N = 302]**	**N/A**	
0–5 patients	33.1 (27.8–38.5)	N/A	
6–10 patients	35.8 (30.3–41.2)	N/A	
11–20 patients	20.9 (16.3–25.5)	N/A	
≥21 patients	10.3 (6.8–13.7)	N/A	
Type of practice***	**[N = 302]**	**N/A**	
Academic	1.3 (0.0–2.6)	N/A	
Private	53.3 (47.7–59.0)	N/A	
Combined	45.4 (39.7–51.0)	N/A	
Board certified (BSR)***	**[N = 309]**	**[N = 86]**	
Yes	86.7 (82.9–90.5)	70.9 (61.1–80.7)	0.001
2013 BSR Meeting***	**[N = 309]**	**[N = 86]**	
Yes	64.1 (58.7–69.5)	46.5 (35.8–57.3)	0.003

* Mean (standard deviation)
** 8 missing data
*** Proportion (95% confident interval)
N/A: not available; BSR: Brazilian Society of Rheumatology.

More than 90% of respondents reported to always or almost always prescribe a prophylactic treatment when initiating ULT (Table 3), in concordance with the ACR guidelines.

Analyzing the eight possible scenarios (Table 2) simultaneously, we identified that a significant proportion of rheumatologists indicated, once at least, the use of treatment modalities that are recommended not to be used as per the ACR guidelines: the use of high dose colchicine by 10% (95% CI, 6.7–13.4), and starting colchicine monotherapy more than 36 hours after the onset of the attack by 20.1% (95% CI, 15.6–24.6). During an acute attack, 31.4% of respondents withdrew ULT. There was great variation in the duration of anti-inflammatory prophylaxis as reported by the respondents: less than one month by 16.9% and

5.1% and indefinitely by 9.8% and 34.6% of respondents for patients without and with tophi, respectively (Table 3).

Table 2 - Acute gout management: first choice drug(s) to treat an acute gouty attack in different scenarios (N = 309)

Gout attack	**Monoarticular**				**Polyarticular**			
Symptoms' onset	**<36 hours**		**>36 hours**		**<36 hours**		**>36 hours**	
Health status	**Healthy***	**CKD****	**Healthy**	**CKD**	**Healthy**	**CKD**	**Healthy**	**CKD**
Scenario	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Medication	**% (CI 95%)**	**% (CI 95%)**	**% (CI 95%)**	**% (CI 95%)**	**% (CI 95%)**	**% (CI 95%)**	**% (CI 95%)**	**% (CI 95%)**
High colchicine***	5.2 (2.7 - 7.7)	2.9 (1.0 - 4.8)	1.6 (0.2 - 3.0)	2.3 (0.6 - 3.9)	2.3 (0.6 - 3.9)	1.9 (0.4 - 3.5)	0.0	1.3 (0.0 - 2.6)
Low colchicine****	16.5 (12.3 - 20.7)	23.0 (18.3 - 27.7)	6.8 (4.0 - 9.6)	12.3 (8.6 - 16.0)	3.2 (1.3 - 5.2)	8.7 (5.6 - 11.9)	3.2 (1.3 - 5.2)	6.5 (3.7 - 9.2)
NSAID	22.3 (17.7 - 27.0)	1.0 (0.0 - 2.1)	22.3 (17.7 - 27.0)	1.9 (0.4 - 3.5)	15.5 (11.5 - 19.6)	1.0 (0.0 - 2.1)	13.9 (10.0 - 17.8)	1.0 (0.0 - 2.1)
PO steroid	0.3 (0.0 - 1.0)	15.9 (11.8 - 20.0)	0.6 (0.0 - 1.5)	18.8 (14.4 - 23.1)	2.3 (0.6 - 3.9)	25.2 (20.4 - 30.1)	2.9 (1.0 - 4.8)	25.9 (21.0 - 30.8)
IM steroid	1.0 (0.0 - 2.1)	7.8 (4.8 - 10.8)	1.9 (0.4 - 3.5)	8.1 (5.0 - 11.1)	3.6 (1.5 - 5.6)	14.6 (10.6 - 18.5)	3.6 (1.5 - 5.6)	14.2 (10.3 - 18.2)
IA steroid	2.3 (0.6 - 3.9)	18.1 (13.8 - 22.4)	3.9 (1.7 - 6.0)	17.5 (13.2 - 21.7)	0.0	0.3 (0.0 - 1.0)	0.0	1.0 (0.0 - 2.1)
NSAID + colchicine	46.3 (40.7 - 51.9)	2.6 (0.8 - 4.4)	46.9 (41.3 - 52.5)	2.3 (0.66 - 3.9)	51.5 (45.9 - 57.1)	1.0 (0.0 - 2.1)	38.5 (33.1 - 44.0)	1.0 (0.0 - 2.1)
NSAID + steroid (PO/IM/IA)	1.9 (0.4 - 3.5)	1.3 (0.0 - 2.6)	6.8 (4.0 - 9.6)	1.3 (0.0 - 2.6)	6.8 (4.0 - 9.6)	1.6 (0.2 - 3.0)	14.2 (10.3 - 18.2)	1.6 (0.2 - 3.0)
Steroid (PO/IM/IA) + colchicine	4.2 (2.0 - 6.5)	27.5 (22.5 - 32.5)	9.1 (5.8 - 12.3)	35.6 (30.2 - 41.0)	14.9 (10.9 - 18.9)	45.6 (40.0 - 51.2)	23.6 (18.9 - 28.4)	47.6 (42.0 - 53.2)

* Healthy besides gout.
** Chronic kidney disease, defined here as creatinine clearance ≤60 mL/min.
*** Colchicine 0.5 mg/hour until symptom resolution or side effect.
**** Colchicine ≤2 mg/day.
CI: confidence interval; NSAID: nonsteroidal anti-inflammatory drug; PO: *per os*; IM: intramuscular; IA: intra-articular.

Table 3 - Management of urate-lowering therapy (ULT) during an acute gouty attack and anti-inflammatory prophylaxis of gout attacks

Questions and respective options	Proportion (95% CI)
During an acute gouty attack in a patient using ULT, you:	**[N = 309]**
Increase the ULT dose	0.3 (0.0 – 1.0)
Keep the ULT dose*	67.0 (61.7 – 72.3)
Reduce the ULT dose	1.3 (0.0 – 2.6)
Withdraw the ULT	31.4 (26.2 – 36.6)
How often do you give prophylactic treatment to prevent acute gouty attacks when initiating ULT?	**[N = 302]**
Always*	64.9 (59.5 – 70.3)
Almost always*	27.5 (22.4 – 32.5)
Sometimes	3.6 (1.5 – 5.8)
Almost never	1.7 (0.2 – 3.1)
Never**	2.3 (0.6 – 4.0)
How long do you keep prophylaxis for patients WITHOUT tophi?	**[N = 295]**
<1 month	16.9 (12.6 – 21.3)
1-6 months	42.4 (36.7 – 48.0)
7-12 months	10.8 (7.3 – 14.4)
Until they reach the target serum uric acid level	20.0 (15.4 – 24.6)
Indefinitely	9.8 (6.4 – 13.2)
How long do you keep prophylaxis for patients WITH tophi?	**[N = 295]**
<1 month	5.1 (2.6 – 7.6)
1-6 months	23.4 (18.5 – 28.2)
7-12 months	15.6 (11.4 – 19.8)
Until they reach the target serum uric acid level	13.9 (9.9 – 17.9)
Until resolution of tophi	7.5 (4.4 – 10.5)
Indefinitely	34.6 (29.1 – 40.0)
Do you prefer colchicine or NSAID for chronic prophylaxis of acute gouty attacks?	**[N = 295]**
Colchicine	97.6 (95.9 – 99.4)
NSAID	2.4 (0.6 – 4.1)

* Answers in agreement with the 2012 ACR gout guidelines.
** Participants who answered not to prescribe anti-inflammatory prophylaxis when initiating ULT were excluded from the other questions concerning this topic.
CI: confidence interval; NSAID: nonsteroidal anti-inflammatory drug.

Table 4 shows the final multivariate models evaluating predisposing factors to answers about acute gout in concordance to the ACR guidelines. Considering that ORs lower than 1 represent a reduced chance of concordance with the ACR guidelines, the geographical regions showed a heterogeneous pattern of agreement for the three therapeutic approaches evaluated. Older professionals and those without academic practice were less likely to choose the recommended procedure in two out of the three provided situations. Finally, male rheumatologists had a 70% less chance of not prescribing high dose colchicine for acute gout.

Table 4 - Multivariate-adjusted predictors of concordance between reported acute gout management and the 2012 ACR gout guidelines

Outcomes [Pseudo R2]	**OR (CI 95%)**	**P**
No prescription of high dose colchicine* for acute gout [0.1084]		
a) Gender (ref.: female)		
Male	0.30 (0.13 – 0.68)	**0.004**
b) Activity (ref.: academic, with or without private)		
Private only	0.32 (0.14 – 0.77)	**0.011**
c) Geographic region of Brazil (ref.: South)		
Midwest	0.75 (0.14 – 4.14)	0.740
North	0.79 (0.07 – 8.79)	0.850
Northeast	0.29 (0.07 – 1.16)	0.080
Southeast	0.81 (0.22 – 3.05)	0.761
No prescription of colchicine as monotherapy for acute gouty attack lasting >36 hours [0.0548]		
a) Age (continuous variables in years)	0.97 (0.94 – 0.99)	**0.004**
b) Geographic region of Brazil (ref.: Northeast)		
Midwest	0.15 (0.04 – 0.55)	**0.005**
North	0.45 (0.07 – 2.86)	0.400
South	0.32 (0.09 – 1.14)	0.080
Southeast	0.27 (0.09 – 0.82)	**0.020**
To keep ULT dose during an acute gouty attack [0.1496]		
a) Age (continuous variables in years)	0.92 (0.90 – 0.95)	**<0.001**
b) Activity (ref.: academic, with or without private)		
Private only	0.62 (0.36 – 1.07)	0.088
c) Geographic region of Brazil (ref.: South)		
Midwest	0.24 (0.08 – 0.73)	**0.012**
North	0.28 (0.07 – 1.20)	0.086
Northeast	0.55 (0.20 – 1.51)	0.243
Southeast	0.51 (0.22 – 1.20)	0.121

* Colchicine 0.5 mg/hour until symptom resolution or side effect.
ACR: American College of Rheumatology; OR: odds ratio; CI: confidence interval; ULT: urate-lowering therapy. OR lower than 1 represents a reduced chance of concordance with the 2012 ACR gout guidelines.

Urate-lowering therapy

Table 5 summarizes the questions regarding ULT.

Table 5 - Urate-lowering therapy (ULT) (continues)

Questions and respective options	Proportion (95% CI)
When would you initiate ULT? Check all that apply.	**[N = 308]**
After their first gouty attack	45.8 (40.2–51.4)
After two or more gouty attacks a year*	64.0 (58.6–69.4)
When a patient has tophi*	46.8 (41.1–52.4)
When a gout patient has CKD*	24.7 (19.8–29.5)
None of the above	3.6 (1.5–5.7)
Choose the SUA level you consider the goal for ULT for a patient WITH TOPHI:**	**[N = 308]**
<5.0 mg/dL*	38.0 (32.5–43.4)
<6.0 mg/dL*	40.9 (35.4–46.4)
<6.8 mg/dL	5.5 (3.0–8.1)
<upper limit provided by the lab	7.8 (4.8–10.8)
I don't adjust the ULT based on a specific level of serum uric acid.	7.8 (4.8–10.8)
Choose the SUA level you consider the goal for ULT for a patient WITHOUT TOPHI:	**[N = 283]**
<5.0 mg/dL*	15.5 (11.3–19.8)
<6.0 mg/dL*	54.4 (48.6–60.3)
<6.8 mg/dL	18.4 (13.8–22.9)
<upper limit provided by the lab	9.5 (6.1–13.0)
I don't adjust the ULT based on a specific level of serum uric acid.	2.1 (0.4–3.8)
If you were to initiate ULT in a patient, would you wait for the resolution of the acute gouty attack?	**[N = 302]**
Yes	96.7 (94.7–98.7)
How long after resolution of the acute gouty attack would you wait to initiate ULT?***	**[N = 292]**
1–3 weeks	76.7 (71.8–81.6)
4–6 weeks	21.6 (16.8–26.3)
7–9 weeks	0.7 (0.0–1.6)
10–12 weeks	1.0 (0.0–2.2)
In general, when you initiate allopurinol, what is the initial dose you prescribe for a patient with normal renal function?	**[N = 302]**
50 mg/day*	2.3 (0.6–4.0)
100 mg/day*	49.0 (43.3–54.7)
200 mg/day	6.0 (3.3–8.6)
300 mg/day	42.7 (37.1–48.3)
In general, when you initiate allopurinol, what is the initial dose you prescribe for a patient with CrCl ≤60 mL/min?	**[N = 299]**
50 mg/day*	28.4 (23.3–33.6)
100 mg/day*	62.5 (57.0–68.1)
200 mg/day	5.0 (2.5–7.5)
300 mg/day	4.0 (1.8–6.3)

Table 5 - Urate-lowering therapy (ULT) (continuation)

Questions and respective options	Proportion (95% CI)
Do you prescribe benzbromarone for patients with CrCl >60 mL/min?	**[N = 302]**
Always	7.9 (4.9–11.0)
Almost always	16.6 (12.3–20.8)
Sometimes	47.0 (41.4–52.7)
Almost never	14.2 (10.3–18.2)
Never	14.2 (10.3–18.2)
Do you prescribe benzbromarone for patients with CrCl between 30 and 60 mL/min?	**[N = 302]**
Always	3.3 (1.3–5.3)
Almost always	7.6 (4.6–10.6)
Sometimes	22.2 (17.5–26.9)
Almost never	35.4 (30.0–40.9)
Never	31.5 (26.2–36.7)
Do you prescribe benzbromarone for patients with CrCl <30 ml/min?	**[N = 302]**
Always	2.0 (0.4–3.6)
Almost always	2.6 (0.8–4.5)
Sometimes	9.3 (6.0–12.6)
Almost never	15.6 (11.5–19.7)
Never	70.5 (65.4–75.7)
Do you prescribe benzbromarone for patients with current renal underexcretion of uric acid and a history of kidney stones in the past?	**[N = 302]**
Always	3.6 (1.5–5.8)
Almost always	5.0 (2.5–7.4)
Sometimes	12.9 (9.1–16.7)
Almost never	20.9 (16.3–25.5)
Never	57.6 (52.0–63.2)
Do you prescribe benzbromarone for patients also using allopurinol?	**[N = 302]**
Always	1.7 (0.2–3.1)
Almost always	6.3 (3.5–9.0)
Sometimes	42.1 (36.5–47.7)
Almost never	21.5 (16.9–26.2)
Never	28.5 (23.4–33.6)
For how long after achieving the target SUA level do you prescribe ULT for a patient with gout WITHOUT tophi?	**[N = 283]**
Withdraw the medication	2.1 (0.4–3.8)
Maintain for 1–6 months	21.6 (16.7–26.4)
Maintain for 7–11 months	11.7 (7.9–15.4)
Maintain for 1–3 years	17.3 (12.9–21.7)
Maintain for 4 or more years	7.8 (4.6–10.9)
Maintain indefinitely*	39.6 (33.8–45.3)

Table 5 - Urate-lowering therapy (ULT) (conclusion)

Questions and respective options	Proportion (95% CI)
For how long after achieving the target SUA level do you prescribe ULT for a patient with gout WITH tophi?	**[N = 283]**
Withdraw the medication	1.4 (0.0–2.8)
Maintain for 1–6 months	2.8 (0.9–4.8)
Maintain for 7–11 months	4.2 (1.9–6.6)
Maintain for 1–3 years	6.4 (3.5–9.2)
Maintain for 4 or more years	3.2 (1.1–5.2)
Maintain until tophi resolution	5.7 (2.9–8.4)
Maintain indefinitely*	76.3 (71.3–81.3)
How often do you check your patients SUA levels BEFORE achieving uric-acid levels goals?	**[N = 283]**
Every 1–3 months*	80.6 (75.9–85.2)
Every 4–6 months	19.1 (14.5–23.7)
Every 7–9 months	0.4 (0.3–1.0)
Every 10–12 months	0.0 (-)
How often do you check your patients SUA levels AFTER achieving uric-acid levels goals?	**[N = 283]**
Every 1–3 months	5.7 (2.9–8.4)
Every 4–6 months*	71.4 (66.1–76.7)
Every 7–9 months	13.1 (9.1–17.0)
Every 10–12 months	9.9 (6.4–13.4)

* Answers in agreement with the 2012 American College of Rheumatology gout guidelines.
** Participants who reported not to adjust ULT for patients with tophaceous gout based on the SUA level were excluded from other questions that were based on the concept of a target SUA level.
*** This question was offered only to those who answered that they would wait for the resolution of the acute gouty attack to initiate ULT.
CI: confidence interval; CKD: chronic kidney disease; SUA: serum uric acid; CrCl: creatinine clearance.

For patients with and without tophi, 80% and 70%, respectively, of respondents reported considering a SUA level lower than 6 mg/dL as a target for ULT. Approximately 80% of respondents reported checking SUA every one to three months before the laboratory goal is achieved, and around 70% reported to verify it every four to six months after achieving the target. These answers are concordant with the ACR guidelines.

Over 42% of rheumatologists start allopurinol at doses of 300 mg daily for patients with normal renal function, which is in disagreement with the ACR guidelines. ULT was reported to be maintained indefinitely for patients without identified tophi only by 39.6% of respondents, whereas about one third reported maintaining ULT for less than one year after achieving the target SUA level.

Multivariate final models evaluating predisposing factors to answers about ULT in concordance to ACR guidelines are shown in Table 6. For two out of four questions, rheumatologists who had not attended a Rheumatology residency program were less likely to be in agreement to the ACR guidelines. Older physicians, those with more than 10 years of practicing rheumatology or time since graduation from medical school showed a reduced chance of concordance to the guidelines in at least one question. Chance of agreement was reduced for all regions compared to the South, but the difference failed to show statistical significance, except for the Midwest region for which the p-value reached a borderline level. Finally, not attending the 2013 BSR Meeting or any gout conference in that Meeting was associated with a reduced chance of being adherent to ACR recommendations.

Table 6 - Multivariate-adjusted predictors of concordance between reported urate-lowering therapy management and the 2012 ACR gout guidelines

Outcomes [Pseudo R2]	**OR (CI 95%)**	**P**
Target serum uric acid level (<5 or <6 mg/dL) for patients with tophi [0.0713]		
a) Age (continuous variable in years)	0.97 (0.95 – 0.99)	**0.015**
b) Residency in rheumatology (ref.: yes)	0.56 (0.30 – 1.03)	0.062
c) Attendance at the 2013 BSR Meeting (ref.: yes)	0.45 (0.25 – 0.80)	**0.007**
Target serum uric acid level (<5 or <6 mg/dL) for patients without tophi [0.0376]		
a) Time practicing Rheumatology (ref.: 0 – 10 years)		
11 – 20 years	0.44 (0.22 – 0.86)	**0.018**
21 – 30 years	0.58 (0.28 – 1.20)	0.142
≥31 years	0.45 (0.21 – 0.98)	**0.043**
b) Attendance at any gout lecture at the 2013 BSR Meeting (ref.: yes)	0.46 (0.25 – 0.84)	**0.011**
Initial dose of allopurinol (50 or 100 mg/day) for patients with normal renal function [-]		
None	-	-
Initial dose of allopurinol (50 or 100 mg/day) for patients with CrCl ≤60 mL/min [0.0920]		
a) Time since Medical School graduation (ref.: 0 – 10 years)		
11 – 20 years	0.32 (0.06 – 1.67)	0.178
21 – 30 years	0.22 (0.04 – 1.14)	0.072
≥31 years	0.25 (0.05 – 1.26)	0.093
b) Geographic region of Brazil (ref.: South)		
Midwest	0.11 (0.01 – 1.10)	0.060
North	0.13 (0.01 – 1.66)	0.117
Northeast	0.21 (0.02 – 1.88)	0.161
Southeast	0.23 (0.03 – 1.81)	0.162
c) Residency in rheumatology (ref.: yes)	0.36 (0.15 – 0.85)	**0.019**

ACR: American College of Rheumatology; OR: odds ratio; CI: confidence interval; BSR: Brazilian Society of Rheumatology; CrCl: creatinine clearance. OR lower than 1 represents a reduced chance of concordance with the 2012 ACR gout guidelines.

DISCUSSION

This is the first representative national physician survey assessing adherence to the 2012 ACR gout guidelines. We used a random sample of Brazilian rheumatologists to perform this survey and had a 78% response rate. We noted discordance between practice and the ACR gout guidelines related to the use of colchicine in the treatment of an acute gout attack, ULT discontinuation during an acute gout attack, duration of anti-inflammatory prophylaxis, initial high-dose and duration of ULT. We found practice was concordant with ACR gout guidelines with regards to the treatment of acute gout attack, prescription of anti-inflammatory prophylaxis when initiating ULT, SUA monitoring and target SUA achievement. Several findings merit further discussion.

We observed problems in acute gout management that reflected discordance between guidelines and practice. First, practitioners reported the use of colchicine in patients with acute gout >36 hours duration, which is not recommended by the guidelines. This is based on pharmacokinetics and clinical observations that colchicine should preferably be started early in an acute attack and for this clinical scenario, other treatment options, such as corticosteroids and NSAIDs are more suitable.[23] Another observation was the use of high-dose colchicine of >2 mg/day. This is again a safety issue, given that a recent randomized trial showed equal efficacy with <2 mg/day compared to >2 mg/day dose and higher toxicity with the higher dose.[47] We recognize that the rates of discordance were low, but it is possible that many other rheumatologists consider these therapeutic approaches in their daily practice, since the question was restricted to the first choice treatment in predetermined situations. Both prescriptions represent a higher risk to benefit for colchicine and given a clear guidance from the ACR guidelines, we think this needs to be corrected.

We observed a discordance in the management of anti-inflammatory prophylaxis between the ACR guidelines and physician practice, with some reporting continuing prophylaxis indefinitely after initiating ULT while others prescribed anti-inflammatory prophylaxis for <1 month. Thus, the duration of anti-inflammatory prophylaxis was either too long or too short for some gout patients starting ULT. A short duration of prophylaxis may lead to frequent gout flares during ULT dose adjustment and an indefinite duration, without a clear indication, put the patient on an unfavorable risk-benefit balance.[48] This identifies another area where physician education might help to improve practice.

Withdrawing ULT during an acute gout attack was reported by a higher than expected proportion of respondents, which is in disagreement with the current guidelines. Stopping

ULT during an acute attack may lead to persistence or a more difficult to control gout attack.[14]

The maintenance of ULT indefinitely was only reported as advocated by 76.3% and 39.6% of respondents for patients with and without tophi, respectively, contrary to the ACR guidelines recommendation of continuing indefinitely all measures needed to maintain SUA lower than 6 mg/dL.

Only half of respondents reported starting allopurinol at doses of 100 mg daily or less for patients with normal renal function, as recommended by the ACR guidelines, while 42.7% reported to prescribe an initial dose of 300 mg daily. The prescription of 300 mg/day starting dose of allopurinol is inconsistent with the current guidelines, and this higher dose has associated potential higher risk of allopurinol hypersensitivity reaction as well as more gout flares.[14,49]

Based on the results of the multivariate analysis, we conclude that the recent changes in gout management may not have been communicated effectively to a significant proportion of rheumatologists; rheumatologists who were older, those in practice for a longer time duration and those working exclusively in private practice had higher rates of discordance with the gout guidelines.

We observed several practice patterns for gout management that are concordant with ACR guidelines. It was reassuring to observe that anti-inflammatory prophylaxis was commonly instituted when initiating ULT (92.4%), with a percentage very similar to results from previous studies: 90% (US, 2006)[37] and 95% (France, 2013)[27]. We noted that a high percentage of rheumatologists aimed at a SUA target of lower than 6 mg/dL or 5 mg/dL in non-tophaceous and tophaceous gout, respectively. We considered both answers as concordant with ACR guidelines that recommend a SUA target of <6 mg/dL, but suggest reducing it below 5 mg/dL in some cases, including in the presence of tophus. Our findings are consistent with an earlier survey of US rheumatologists where 84% of respondents reported to aim for a SUA level lower than 6 mg/dL, but the question did not discriminate between patients with or without tophi, and the response rate was lower than to our survey.[37] Most respondents reported checking SUA every one to three months before achieving the SUA target and every four to six months after the target has been achieved. The ACR guidelines recommend monitoring of SUA every 2 to 5 weeks during ULT titration, and every 6 months once the SUA target is achieved, a measure believed to enhance patient compliance.

In our survey, in an otherwise healthy patient, corticosteroids (monotherapy or in combination with colchicine) were prescribed for acute gout by 7.8% respondents for

monoarticular attack with <36 hours duration and by 30.1% for polyarticular attack with >36 hours duration. On the other hand, 90% of rheumatologists appropriately used corticosteroids in a polyarticular attack lasting more than 36 hours, in a patient with CKD. This higher utilization of corticosteroids in the presence of CKD likely indicates the appropriate avoidance of NSAIDs and possibly colchicine, due to known adverse events associated with their use in these populations.[50,51] The low rate of intraarticular corticosteroid injections for monoarticular attacks was surprising, but has been observed in other survey studies.[31,34]

It is important to highlight study limitations. Non-response should be taken into account while interpreting findings, especially considering that more responders were board-certified and attended the 2013 BSR Meeting compared with non-responders, suggesting that results from this survey are likely to overestimate general rheumatologists' behavior. However, our response rate for a physician survey is two to three times greater than that of previous surveys[26-44] and well in excess of what is reported for physician surveys in general. Due to study design and limited resources, we did not audit patient charts for physicians responding to the survey, and therefore we were unable to confirm whether the practice reported by the physician is actually truly reflective of management of their gout patients. We believe that physicians reported their real practice, not what they considered as the expected or "correct" answer, as instructed explicitly in our survey. We do not think that these findings can be generalized to general medicine practice in Brazil or to other country settings. Such studies, in the future, will allow a better understanding of current gout management and how this can be improved. We recognize that rheumatologists are not the primary providers of gout care; however, they are believed to be the key opinion leaders in this topic. The main strength of our nationwide study is the representativeness of our sample, which was randomly selected, a high participation rate (typically unusual for physician surveys) and comprehensive assessment of key ACR gout guidelines domains.

We have identified several areas that should be the focus of continued education on gout treatment for the Brazilian rheumatologists, based on this survey assessing the adherence to 2012 ACR guidelines for the management of gout.[22,23] These include: 1) not to start colchicine as monotherapy when an attack has lasted longer than 36 hours; 2) avoidance of high-dose colchicine; 3) maintenance of a stable dose of ULT during acute attacks; 4) duration of anti-inflammatory prophylaxis for at least six months; 5) duration of ULT; and 6) the need to initiate allopurinol in low doses.

CONCLUSION

In conclusion, in this representative study of Brazilian rheumatologists, we found that several practice patterns were concordant with the 2012 ACR gout guidelines, but also that an opportunity exists to improve gout management in several areas. Several physician characteristics were associated with discordance with the ACR guidelines. Based on these data, we are developing a physician education program to fill these knowledge gaps and improve practice. Our aim is to improve the management of gout patients in Brazil using this program.

ACKNOWLEDGMENTS

We are grateful to the Brazilian Society of Rheumatology for providing us with the data we needed, to the Gout Committee members for their support and to the rheumatologists whose participation made this survey possible.

SUPPORTING INFORMATION

S1 Table - Similar surveys

S1 File - Questionnaire used in the survey

S1 Table - Similar surveys (continues)

Place, year of publication	Source population	Selected for contact	Responses	Overall response rate
Austria, 2014[26]	Members of the Austrian Society of Rheumatology	WSP (574)	127	22.1%
French Polynesia, 2014[27]	Rheumatologists and GPs from the French Polynesia	N/A	49	N/A
USA, 2013[28]	Primary Care Practitioners from the American Medical Association	Random nationwide sample of 2200 PCPs	838	40.1%*
France, 2013[29]	Rheumatologists and GPs from the France	N/A	977	N/A
Argentina, 2012[30]	Rheumatologists, internists and GPs from Buenos Aires city	Professionals from different scenarios**	171	≤20%***
Malaysia, 2009[31]	Doctors attending rheumatology post-graduate courses	Doctors attending courses in 2005 where the authors were invited speakers	145	54.5%
USA, 2008[32]	Primary Care Practitioners from the USA	PCPs attending a series of 25 accredited educational meetings from April through September 2006	688	N/A
Dutch, 2008[33]	Dutch rheumatologists and those in training, members of the Dutch Society of Rheumatology	WSP (252)	122	50.4%
Ireland, 2008[34]	GPs in the North Dublin GP Partnership	WSP (170)	80	47.0%
Eular, 2007[35]	Delegates attending the Eular Meeting – 2006	Delegates visiting the commercial stands	741	6.7%****
China, 2006[36]	Internists from PUMC Hospital, Beijing	Physicians attending medical and rheumatology grand rounds (121)	93	76.9%

S1 Table - Similar surveys (conclusion)

USA, 2006[37]	Rheumatologists from the USA	The first 2500 American rheumatologists listed alphabetically in the 2004-2005 ACR directory with fax numbers	518	20.7%
China, 2006[38]	Physicians from China	121 internists from PUMC Hospital,[36] and 75 physicians attending a national CME workshop of rheumatology	100	51.0%
Mexico, 2003[39]	Rheumatologists, internists, orthopedic surgeons and GPs from Mexico City	All rheumatologists (133) and internists (423); and a random sample of orthopedic surgeons (640) and GPs (640)	212	11.5%
France, 1996[40]	French rheumatologists	2520 French rheumatologists	750	29.8%
Brazil, 1994[41]	Rheumatologists and GPs from the city of São Paulo	All rheumatologists (252) and a random sample of GPs (500)	421	56.0%
New Zealand, 1991[42]	Rheumatologists and GPs from New Zealand	All rheumatologists (27) and a 10% random sample of GPs (207)	189	80.8%
Australia, 1989[43]	Rheumatologists and GPs from New South Wales and Queensland	All rheumatologists (85) and a random sample of GPs (430)	326	63.3%
Canada, 1988[44]	Rheumatologists and GPs from the Province of Ontario	All rheumatologists (87) and a random sample of GPs (200)	189	65.8%

* After excluding physicians who reported not caring for gout patients (n=51) or those not contacted due to incorrect addresses (n=61).
** Professionals assisting to different scientific events related to rheumatology, physicians working in several emergency rooms and medical clinics, and members of the Rheumatology department of the Hospital JM Ramos Mejia.
*** Believed by the authors to be ≤20%.
**** Percentage of attendees at the Eular Meeting 2006.
WSP: whole source population; GPs: general practitioners; N/A: not available; PCPs: primary care physicians; PUMC Hospital: Peking Union Medical College Hospital; Eular: European League Against Rheumatism; ACR: American College of Rheumatology; CME: continuous medical education.

S1 File - Questionnaire used in the survey (continues)

Survey of Gout Treatment in Brazil

THE GOUT COMMITTEE OF THE BRAZILIAN SOCIETY OF RHEUMATOLOGY NEEDS YOUR ASSISTANCE!

Dear colleagues,

We are conducting a survey on gout treatment practices by Brazilian Rheumatologists.

Responses should reflect clinical practice, with no concern for right or wrong.

The data will be evaluated without any identification of responders.

It will take less than 10 minutes!
Join!
Thank you!

Gout Committee

Sociedade Brasileira de Reumatologia
Comissão de Gota

S1 File - Questionnaire used in the survey (continuation)

Survey of Gout Treatment in Brazil

About the pharmacological approach of acute gouty attack

1. What is your first choice for an acute gouty attack in an OTHERWISE HEALTHY PATIENT?

	colchicine 0.5 mg/hour until symptom resolution or side effect	colchicine ≤ 2 mg/day	Nonsteroidal anti-inflammatory drug (NSAID)	PO steroid	IM steroid	Intra-articular steroid	NSAID + colchicine	NSAID + steroid (PO/IM/IA)	Steroid (PO/IM/IA) + colchicine
Monoarticular involvement, onset < 36 hours	◯	◯	◯	◯	◯	◯	◯	◯	◯
Monoarticular involvement, onset > 36 hours	◯	◯	◯	◯	◯	◯	◯	◯	◯
Polyarticular involvement, onset < 36 hours	◯	◯	◯	◯	◯	◯	◯	◯	◯
Polyarticular involvement, onset > 36 hours	◯	◯	◯	◯	◯	◯	◯	◯	◯

2. What is your first choice for an acute gouty attack in a patient with CREATININE CLEARANCE (CrCl) ≤ 60 ML/MIN?

	colchicine 0.5 mg/hour until symptom resolution or side effect	colchicine ≤ 2 mg/day	Nonsteroidal anti-inflammatory drug (NSAID)	PO steroid	IM steroid	Intra-articular steroid	NSAID + colchicine	NSAID + steroid (PO/IM/IA)	Steroid (PO/IM/IA) + colchicine
Monoarticular involvement, onset < 36 hours	◯	◯	◯	◯	◯	◯	◯	◯	◯
Monoarticular involvement, onset > 36 hours	◯	◯	◯	◯	◯	◯	◯	◯	◯
Polyarticular involvement, onset < 36 hours	◯	◯	◯	◯	◯	◯	◯	◯	◯
Polyarticular involvement, onset > 36 hours	◯	◯	◯	◯	◯	◯	◯	◯	◯

3. During an acute gouty attack in a patient using urate-lowering therapy (ULT) (eg. allopurinol), you:

- ◯ Increase the dose of the ULT
- ◯ Keep the dose of the ULT
- ◯ Reduce the dose of the ULT
- ◯ Withdraw the ULT

S1 File - Questionnaire used in the survey (continuation)

Survey of Gout Treatment in Brazil

About urate-lowering therapy (ULT)

4. When would you initiate ULT? Check all that apply.

- ☐ After their first gouty attack.
- ☐ After two or more gouty attacks a year.
- ☐ When a patient with gout has tophi.
- ☐ When a patient with gout has chronic kidney disease.
- ☐ None of the above.

5. Choose the serum uric acid (SUA) level you consider the goal for ULT for a patient WITH TOPHI:

◯ < upper limit of normal ◯ < 6.8 mg/dl ◯ < 6.0 mg/dl ◯ < 5.0 mg/dl ◯ I do not titrate ULT based on the SUA level

Questions 6 to 10 are only offered to those who did not answer "I do not titrate ULT based on the SUA level" in the question 5.

6. Choose the SUA level you consider the goal for ULT for a patient WITHOUT TOPHI:

◯ < upper limit of normal ◯ < 6.8 mg/dl ◯ < 6.0 mg/dl ◯ < 5.0 mg/dl ◯ I do not titrate ULT based on the SUA level

7. How often do your patients reach this target with current treatments?

◯ Always ◯ Almost always ◯ Sometimes ◯ Almost never ◯ Never

8. For how long after achieving the target SUA level do you prescribe ULT for a patient with gout WITHOUT tophi?

◯ Withdraw the medication
◯ Maintain for 1 - 6 months
◯ Maintain for 7 - 11 months
◯ Maintain for 1 - 3 years
◯ Maintain for 4 or more years
◯ Maintain indefinitely

Page 3

S1 File - Questionnaire used in the survey (continuation)

Survey of Gout Treatment in Brazil

About urate-lowering therapy (ULT)

9. For how long after achieving the target SUA level do you prescribe ULT for a patient with gout WITH tophi?

- ◯ Withdraw the medication
- ◯ Maintain for 1 - 6 months
- ◯ Maintain for 7 - 11 months
- ◯ Maintain for 1 - 3 years
- ◯ Maintain for 4 or more years
- ◯ Maintain until tophi resolution
- ◯ Maintain indefinitely

10. How often do you check your patients SUA levels?

	1-3 months	4-6 months	7-9 months	10-12 months	I do not check it.
Before achieving the target SUA level:	◯	◯	◯	◯	◯
After achieving the target SUA level:	◯	◯	◯	◯	◯

11. How many of your patients have ever presented an allergic reaction to allopurinol under your care?

	0	1 - 5	6 - 10	11 - 15	> 15
Mild reaction	◯	◯	◯	◯	◯
Severe reaction	◯	◯	◯	◯	◯

12. In general, when you initiate allopurinol, what is the initial dose you prescribe?

	50 mg/day	100 mg/day	200 mg/day	300 mg/day
For a patient with normal renal function	◯	◯	◯	◯
For a patient with CrCl ≤ 60 ml/min	◯	◯	◯	◯

13. What is the maximum dose of allopurinol most frequently prescribed by you?

	≤ 300 mg/day	350 - 450 mg/day	500 - 600 mg/day	650 - 750 mg/day	800 - 900 mg/day
For a patient with normal renal function	◯	◯	◯	◯	◯
For a patient with CrCl ≤ 60ml/min	◯	◯	◯	◯	◯

S1 File - Questionnaire used in the survey (continuation)

Survey of Gout Treatment in Brazil

About urate-lowering therapy (ULT)

14. Do you prescribe BENZBROMARONE?

	always	almost always	sometimes	almost never	never
For patients with CrCl > 60 ml/min	◯	◯	◯	◯	◯
For patients with CrCl between 30 and 60 ml/min	◯	◯	◯	◯	◯
For patients with CrCl < 30 ml/min	◯	◯	◯	◯	◯
For patients with current renal underexcretion of uric acid and a history of kidney stones in the past	◯	◯	◯	◯	◯
For patients also using ALLOPURINOL	◯	◯	◯	◯	◯

15. If you were to initiate ULT in a patient, would you wait for the resolution of the acute gouty attack?

◯ Yes

◯ No

16. How long after resolution of the acute gouty attack would you wait to initiate ULT?

◯ 1 - 3 weeks

◯ 4 - 6 weeks

◯ 7 - 9 weeks

◯ 10 - 12 weeks

This question is offered only to those who answered "YES" to the question 15.

S1 File - Questionnaire used in the survey (continuation)

Survey of Gout Treatment in Brazil

About prophylaxis of acute gouty attacks

17. How often do you give prophylatic treatment to prevent acute gouty attacks when initiating ULT?

◯ Always ◯ Almost always ◯ Sometimes ◯ Almost never ◯ Never

The following questions in this page are not offered to those who answered "NEVER" to the question 17.

18. How long do you keep prophylaxis for patients WITHOUT tophi?

◯ < 1 month
◯ 1 - 6 months
◯ 7 - 12 months
◯ Until they reach the target SUA level
◯ Indefinitely

19. How long do you keep prophylaxis for patients WITH tophi?

◯ < 1 month
◯ 1 - 6 months
◯ 7 - 12 months
◯ Until they reach the target SUA level
◯ Until resolution of tophi
◯ Indefinitely

20. Do you prefer colchicine or NSAID for chronic prophylaxis of acute gouty attacks?

◯ Colchicine
◯ NSAID

S1 File - Questionnaire used in the survey (continuation)

Survey of Gout Treatment in Brazil

About you

21. Gender:

- ◯ Female
- ◯ Male

22. About you

	Age	Time since Medical School graduation	Time practicing Rheumatology
In years			

23. State in which you practice:

State	

24. On average, number of gout patients you see monthly:

Patients with gout/month	

25. Type of practice

◯ Private ◯ Academic ◯ Combined

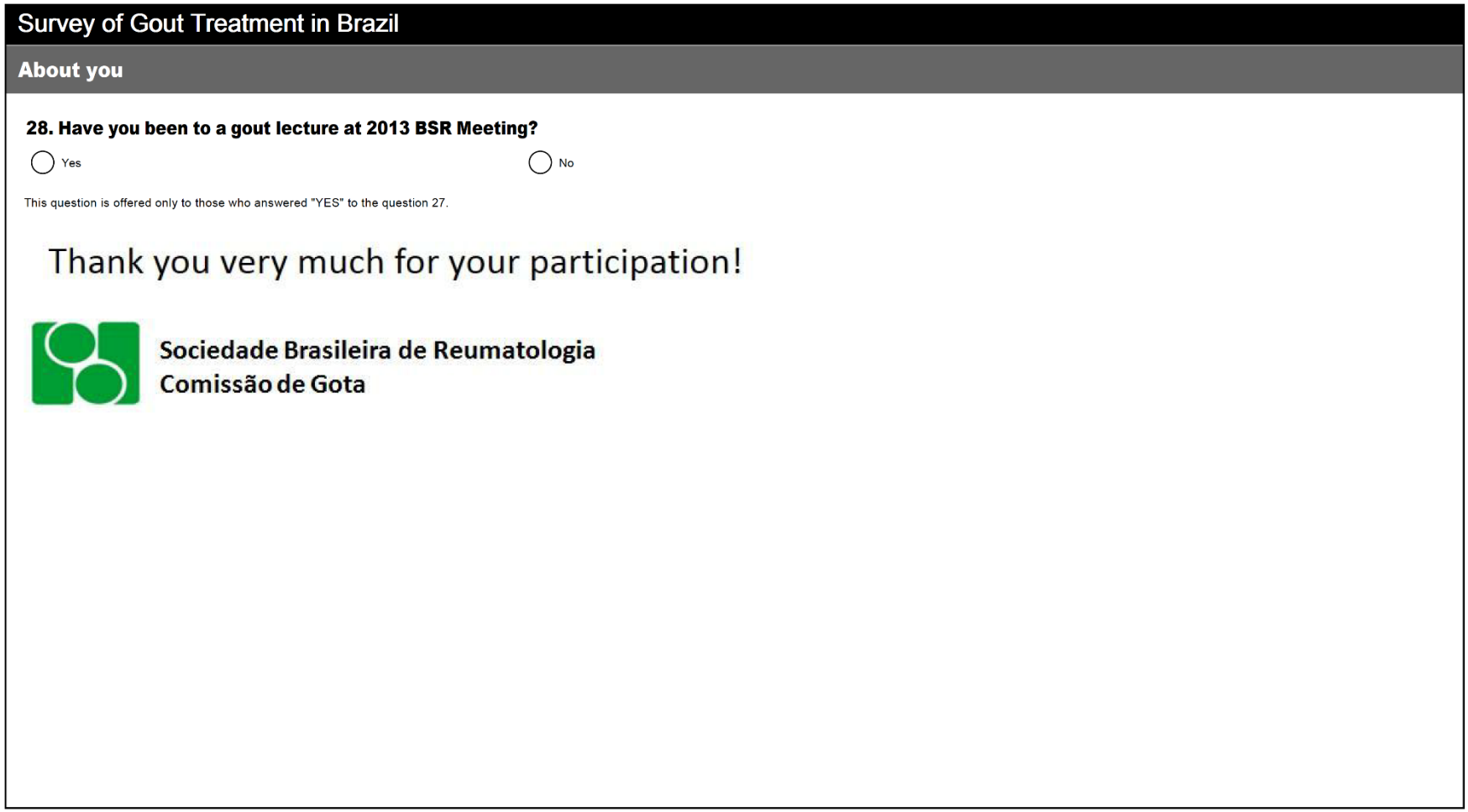
26. Residency or specialization in Rheumatology?

◯ No ◯ Residency ◯ Specialization

27. Did you attend the Brazilian Society of Rheumatology Meeting in 2013 (2013 BSR Meeting)?

◯ Yes ◯ No

S1 File - Questionnaire used in the survey (conclusion)



Survey of Gout Treatment in Brazil

About you

28. Have you been to a gout lecture at 2013 BSR Meeting?

◯ Yes ◯ No

This question is offered only to those who answered "YES" to the question 27.

Thank you very much for your participation!

Sociedade Brasileira de Reumatologia
Comissão de Gota

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4.2 **Estudo 2**

Este estudo foi conduzido sob a orientação da Professora e Co-orientadora Tuhina Neogi e o respectivo artigo foi publicado na American Journal of Kidney Disease em 26 de abril de 2017. Referência: Management of Gout and Hyperuricemia in CKD. Vargas-Santos AB, Neogi T. Am J Kidney Dis. 2017 Sep;70(3):422-439. doi: 10.1053/j.ajkd.2017.01.055. Epub 2017 Apr 26.(102)

4.2.1 Artigo 2

Management of Gout and Hyperuricemia in CKD

Ana Beatriz Vargas-Santos and Tuhina Neogi

ABSTRACT

Hyperuricemia and gout, the clinical manifestation of monosodium urate crystal deposition, are common in patients with chronic kidney disease (CKD). Although the presence of CKD poses additional challenges in gout management, effective urate lowering is possible for most patients with CKD. Initial doses of urate-lowering therapy are lower than in the non-CKD population, whereas incremental dose escalation is guided by regular monitoring of serum urate levels to reach the target level of <6 mg/dL (or <5 mg/dL for patients with tophi). Management of gout flares with presently available agents can be more challenging due to potential nephrotoxicity and/or contraindications in the setting of other common comorbid conditions. At present, asymptomatic hyperuricemia is not an indication for urate-lowering therapy, though emerging data may support a potential renoprotective effect.

INDEX WORDS: Hyperuricemia; gout; chronic kidney disease; urate-lowering therapy; allopurinol; febuxostat; uricosurics; uricase; colchicine; nonsteroidal anti-inflammatory drugs; glucocorticoids; management; review; renal failure; hemodialysis; kidney transplant; chronic gout; acute gout; gout flare; therapy; treatment.

CASE PRESENTATION

A 58-year-old man with long-standing nontophaceous gout presents to the emergency department with incapacitating pain due to arthritis in the left knee and right first metatarsophalangeal joint. He has chronic kidney disease (CKD), currently stage 3b (estimated glomerular filtration rate [eGFR] of 32 mL/min). His most recent serum urate level is 7.9 mg/dL. He is currently taking allopurinol, 100 mg/d, a dose that was based on his creatinine clearance (CL_{cr}). He also has hypertension, dyslipidemia, and congestive heart failure (CHF). He avoids nonsteroidal anti-inflammatory drugs (NSAIDs) and limits his colchicine prophylactic dose to 1 tablet every other day due to his kidney disease. He has also been told by his cardiologist to avoid prednisone due to possible fluid overload with resultant decompensation of his CHF. This is his third visit to the emergency department within the last year due to gout-related pain.

INTRODUCTION

Gout, the clinical manifestation of crystalline monosodium urate (MSU) deposition, is the most common inflammatory arthritis in adults, especially in men, with increasing prevalence worldwide, ranging from 0.1% to 10% and estimated to be 3.9% in the United States.[1,2] Hyperuricemia, which is biochemically defined as serum urate level ≥6.8 mg/dL based on the limit of urate solubility, is even more common. Using population-level sex-specific serum urate distributions to define hyperuricemia, a US study reported a prevalence of 21.2% among men (serum urate >7.0 mg/dL) and 21.6% among women (serum urate >5.7 mg/dL).[2]

Because two-thirds of human urate excretion occurs through the kidneys, with the remaining one-third occurring through the gastrointestinal tract, decreased kidney function is associated with hyperuricemia. However, several large epidemiologic studies and small trials suggest that hyperuricemia may potentially be associated with the development and progression of hypertension and CKD.[3] Regardless of which is cause or consequence, the association of CKD with gout and hyperuricemia is common.[4,5] Approximately 20% of adults

with gout have CKD stage ≥3 compared with 5% of individuals without gout; 15% of adults with hyperuricemia have CKD stage ≥3 compared with 3% of individuals without hyperuricemia.[6] The age-standardized prevalence of gout and hyperuricemia increases as kidney function declines, with 24% of adults with eGFRs <60 mL/min having gout compared with 2.9% of adults with eGFRs ≥90 mL/min.[5]

Clinicians therefore are frequently confronted with managing gout in the setting of kidney disease. The management of gout flares can be challenging because of cautions or contraindications in those with diminished kidney function, as well as other common comorbid conditions that occur frequently in CKD. Among adults with CKD stage 3, a total of 87.8% have hypertension, 16.9% have diabetes, 22.9% have ischemic heart disease, and 3.5% have CHF.[7] Similarly, patients with gout, irrespective of kidney disease, have high prevalences of these conditions.[6] These comorbid conditions affect therapeutic decision making, particularly for gout flare management, because the agents available have precautions and/or contraindications in these settings. However, there is often unnecessary excessive concern regarding urate-lowering therapy (ULT) in the context of CKD, frequently leading to inadequate management of gout.

CLINICAL CONTEXT

The most typical presentation of gout is the acute onset of a monoarthritis, generally affecting the lower limbs (classically the first metatarsophalangeal joint), lasting 7 to 14 days without therapy, followed by an asymptomatic period of varying duration.[8] Without treatment, flares tend to recur progressively more frequently, last for longer periods, and can become more resistant to treatment for some. In later stages, a chronic inflammatory arthritis can occur with persistent symptoms; often tophi develop with longer duration of disease, although occasionally tophi can be the initial clinical manifestation of gout.[9] In women, the first presentation of gout generally occurs after menopause because of the uricosuric effects of estrogen.[10] Although mono- or oligoarthritis of a lower limb is a common gout flare presentation, other patterns are not infrequent, such as upper-limb involvement and polyarticular flares.[11] Patients with CKD are anecdotally thought to have more variable presentations of their gout flares, including a higher frequency of polyarticular flares. These presentations are also more common among women and elderly individuals and often are associated with diuretic use and CKD.[12-14] Thus, clinicians must remember to consider gout flare in their differential diagnosis of acute joint symptoms in a patient with kidney disease, even if the pattern of joint involvement is not “classic.”

The diagnosis of gout is confirmed by the identification of MSU crystals under polarizing microscopy in synovial fluid aspirated from a joint or bursa or in material aspirated from a tophus. This gold-standard confirmation is especially important for patients with CKD, for whom the prevalence of other conditions that mimic gout is also common, such as calcium pyrophosphate deposition disease (formerly known as "pseudogout" and now labeled acute calcium pyrophosphate crystal arthritis), for which the diagnosis is also confirmed by synovial fluid analysis.[15]

In the absence of a crystal-proven diagnosis, other elements of the history and physical examination can be helpful in supporting a diagnosis of gout. Although not intended for use in making diagnoses, the 2015 American College of Rheumatology (ACR)–European League Against Rheumatism classification criteria for gout highlight some of the key factors to consider when evaluating an individual for the possibility of gout.[16,17] Classification criteria are intended for use in research to identify individuals for enrollment into clinical studies and therefore do not necessarily cover the full spectrum of the disease.

MANAGEMENT OF GOUT IN CKD

The management of gout follows the same 4 principles regardless of the presence of CKD: (1) lower serum urate level (ie, manage the hyperuricemia), (2) provide prophylaxis while initiating ULT, (3) treat gout flares, and (4) optimize dietary and lifestyle factors as appropriate. Over a prolonged period with adequate management of hyperuricemia, defined as maintenance of serum urate level <6 mg/ dL or <5 mg/dL for those with tophaceous gout, gout flares will diminish in frequency and severity, with eventual cessation of flares, and tophi can be prevented and/or resolve.

Management of Hyperuricemia

Hyperuricemia is a necessary, though not sufficient, cause of gout because there are many more individuals with hyperuricemia than with clinically evident gout. Nonetheless, the mainstay and primary focus of gout therapy is to lower elevated serum urate levels to achieve the clinical outcomes that matter to patients: cessation and prevention of flares, resolution and prevention of tophi, and control of inflammatory arthritis for those with chronic gouty arthritis.

In 2012, the ACR published guidelines for the management of gout.[18,19] New in these guidelines was the recommendation to initiate ULT with the first gout flare in patients with CKD stage ≥2.[18] The rationale for this new ULT indication is that these patients often have

limited options for gout flare management. By initiating ULT earlier, the aim is to avoid the need to treat subsequent gout flares with potentially nephrotoxic or contraindicated agents. For patients with normal eGFRs, indications for ULT continue to include recurrent gout flares (≥2 per year), tophi, and nephrolithiasis. In addition, imaging evidence of tophi is a new indication for ULT.

In line with other treatment guidelines, the ACR guidelines noted insufficient evidence to address the management of asymptomatic hyperuricemia.[18,20-22] As reviewed next, there are emerging data regarding the potential benefit of ULT in CKD beyond the context of gout that points to the need for large trials to definitively address this issue.

Nonpharmacologic approaches can be recommended to all patients with gout as adjunctive measures. These include weight loss and avoiding excess intake of purine-rich foods, alcoholic beverages, and fructose-rich beverages. Total prohibition of purine intake is not recommended because the impact on serum urate levels is limited (reduction of ~1 mg/dL) and this represents a great burden for the patient; thus, lifestyle approaches should be considered adjunctive and should not replace pharmacologic treatment.[23] Further, because the primary determinant of hyperuricemia in most patients is related to kidney clearance of uric acid, either reflecting inherited kidney transport factors and/or low eGFR, blaming the patient for their gout is counterproductive and contributes to poor management of gout because patients are reluctant to discuss their condition with health care providers.[24,25]

Pharmacologic therapy for lowering serum urate levels includes uricosuric agents that address the most common cause of hyperuricemia, kidney urate underexcretion, xanthine oxidase inhibitors (XOIs) that prevent purine metabolites from being converted to urate, and uricase therapy that oxidizes urate through an enzymatic reaction that is no longer present in humans to the highly soluble end product, allantoin (Table 1[18,26-35]). At lower GFRs, uricosuric agents may not be efficacious; accordingly, agents with other mechanisms of action need to be used. Although dialysis in principle is uricosuric and is often accompanied by a reduction in gout flares despite persistent hyperuricemia, dialysis patients may still require ULT to achieve the serum urate target level and tophus resolution.[36,37] There are other mechanisms also being targeted, though none are advanced enough in their development for approval or clinical use.

Table 1 - Urate-Lowering Agents With Recommendations for Urate-Lowering Management in Patients With Normal and Reduced Kidney Function

Urate-Lowering Agents	Doses	Recommendations for CKD 3-5	Recommendations for CKD 5D (dialysis)
		XOIs[a]	
Allopurinol	Starting: 50-100 mg/d; maximal approved: 800 mg/d (900 mg/d in the UK)	CL_{cr} ≥30 mL/min: start with ≤100 mg/d[18] CL_{cr} <30 mL/min: start with 50 mg/d[18]	Intermittent HD: should be administered postdialysis,[26,27] start with 100 mg alternate days postdialysis Daily HD: additional 50% of dose may be required postdialysis Daily PD: start with 50 mg/d All types of RRT: uptitrate dose with 50-mg increments every 2-5 wk, measure serum urate predialysis
Febuxostat	Starting: 40 mg/d; maximal approved: 80 mg/d (120 mg/d in Europe)	Insufficient data for CL_{cr} <30 mL/min	Despite some successful reports of dialysis patients using febuxostat up to 80 mg/d, this agent is not FDA approved for use in dialysis due to a lack of trials in this population[28-32]
		Uricosuric Agents[b]	
Benzbromarone[c]	Starting: 25-50 mg/d; maximal approved: 200 mg/d	Contraindicated if CL_{cr} <20 mL/min	Contraindicated
Lesinurad[d]	Starting: 200 mg/d together with XOI; maximal approved: 200 mg/d	Contraindicated if CL_{cr} <45 mL/min	Contraindicated
Probenecid	Starting: 250 mg twice daily; maximal approved: 2,000 mg/d	Not effective if CL_{cr} ≤30 mL/min	Contraindicated
Sulfinpyrazone[c]	Starting: 50 mg twice daily; maximal approved: 800 mg/d	Not effective if CL_{cr} ≤30 mL/min	Contraindicated
		Recombinant Uricase	
Pegloticase	Starting: 8 mg IV every 2 wk; maximal approved: 8 mg IV every 2 wk	No dose adjustment needed	No dose adjustment needed[33]

Note: Additional considerations: losartan may be the antihypertensive drug of choice for patients with hyperuricemia and/or gout based on its uricosuric effect. Sevelamer may be the phosphate binder of choice for patients with advanced CKD and gout, based on its urate-lowering effect.[34,35]

Abbreviations: CKD, chronic kidney disease; CL_{cr}, creatinine clearance; FDA, US Food and Drug Administration; HD, hemodialysis; IV, intravenous; PD, peritoneal dialysis; RRT, renal replacement therapy; UK, United Kingdom; XOI, xanthine oxidase inhibitor.

[a]Titrate dose every 2 to 5 weeks to reach the serum urate target; for allopurinol, this uptitration can occur beyond the CL_{cr}-based dose.

[b]Titrate dose every 2 to 5 weeks to reach the serum urate target.

[c]Not available in the United States.

[d]Approved for use only in combination with an XOI.

Regardless of which ULT is chosen, general principles include initiation of therapy concomitantly with prophylaxis, use of a low starting dose followed by regular monitoring of serum urate levels with ongoing dose titration until the target is achieved, ULT should not be withdrawn or have its dose changed during gout flares, and serum urate should continue to be monitored with additional dose adjustments as needed (Box 1). Optimally, ULT should be initiated when the patient is free of a gout flare, although the 2012 ACR gout treatment guidelines propose that ULT could be started during a gout flare as long as effective anti-inflammatory therapy has been established. However, this approach has not been fully tested for potential negative consequences, such as prolonging a flare, and can add to a patient's confusion about which medication is being used for which purpose.[38,39]

Box 1 - General Approach to Managing Hyperuricemia in Gout Patients

Initiate anti-inflammatory prophylaxis concomitantly with or before starting urate-lowering therapy
Start urate-lowering therapy at a low dose and titrate dose to serum urate target
Check serum urate regularly
Aim for a serum urate target level <6 mg/dL for most patients; consider <5 mg/dL for some, such as those with tophi
Maintain anti-inflammatory prophylaxis for at least 6 mo, continuing until after both serum urate target achievement and resolution of clinical manifestations (last flare, tophus resorption)

Xanthine Oxidase Inhibitors

Xanthine oxidase converts purine metabolites to urate. Thus, XOIs decrease urate production from endogenous and dietary purine sources and are considered first-line therapy, though uricosurics are an acceptable alternate first-line option.[18]

Allopurinol. Allopurinol, a purine-base analogue available since the 1960s, is the most widely used ULT. Although it is effective, its appropriate use has been hampered by certain misconceptions. This is largely due to the decades-old proposed allopurinol dose adjustment according to CL_{cr} to levels that should theoretically achieve the same serum level of oxypurinol, the active metabolite, as a 300-mg dose of allopurinol would achieve in a patient with normal kidney function.[40] This algorithm was developed to theoretically mitigate against the risk for allopurinol hypersensitivity syndrome (AHS), which manifests as rash,

eosinophilia, leukocytosis, fever, hepatitis, and progressive kidney failure, with high mortality rates.[40] However, this strategy has never been proved to lower this risk in patients who tolerate low starting doses of allopurinol.[26] Further, with this dosing strategy, <50% of patients achieve the target serum urate level.[18,41-44] Notably, the peak dose of allopurinol does not appear to be associated with AHS in patients with CKD; rather the risk for AHS is primarily related to the initial dose of allopurinol and whether the patient is a carrier of the variant HLA-B*5801 allele, and the risk is highest in the first 6 months of use.[45-51]

The allopurinol dose can be safely increased beyond the CL_{cr}-based dose in patients with kidney disease; allopurinol can be used in patients receiving hemodialysis or peritoneal dialysis who still require ULT, as detailed in Table 1.[45,52-55] For all patients initiating allopurinol therapy, the starting dose should be low, specifically 50 mg/d for patients with CKD stage 4 or 5, and not >100 mg/d in all others.[18] Initiating ULT at a low dose aims to reduce the risk for gout flare and for AHS or other allergic reactions. The daily dose should then be uptitrated by 50 to 100 mg every 2 to 5 weeks as needed to achieve the serum urate target level.[18]

Febuxostat. Febuxostat is a non–purine-selective XOI that was approved by the US Food and Drug Administration (FDA) in 2009. Trials assessing febuxostat's efficacy compared it to a fixed dose of allopurinol of 300 mg/d, or 200 mg/d in those with some degree of kidney disease.[56-59] Because this allopurinol dose is not sufficient to adequately achieve the serum urate target level for a majority of patients, it is not clear from these trials how superior febuxostat is in comparison to appropriately titrated allopurinol; a randomized controlled trial is currently underway to assess this. Febuxostat can be used in patients with eGFRs ≥30 mL/min without dose adjustment. However, data for the efficacy and safety of febuxostat in CKD stages ≥3, including kidney replacement therapy, are limited. In the CONFIRMS trial, which randomly assigned 2,269 participants, only 18% had an estimated CL_{cr} <60 mL/min, whereas one of the largest trials of XOIs to date in people with CKD stages 3 and 4 randomly assigned only 96 participants.[59,60] Most other trials included only patients with CKD stage 2 or better. There are only some case reports, small clinical trials, and observational studies on the use of febuxostat in patients on dialysis therapy and/or with a kidney transplant.[28-32,61,62]

Regarding side effects, the frequency of mild skin reactions was similar to those in allopurinol treatment arms in these trials, at about 2% to 5%.[56,57,59] Some severe cases of adverse cutaneous reactions have been reported, including drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis, particularly in patients with a history of cutaneous adverse reactions to allopurinol

and patients with CKD, leading to a warning by the European Medicines Agency and Health Canada regarding this issue.[63-67] No association between HLA-B*5801 allele status and these reactions has been reported to date. There was a potential cardiovascular safety signal in the initial febuxostat trials program, with additional trials required prior to approval.[68] In the postmarketing period, there have been some reported cases of heart failure leading Health Canada to request that the manufacturer include a warning for the risk of heart failure in patients with cardiovascular disease and/or other risk factors in the Canadian label.[69] Studies comparing the safety of febuxostat and allopurinol are currently underway.[70,71]

The cost-effectiveness of febuxostat has been evaluated in comparison to allopurinol. However, interpretation of these studies is challenging because some were sponsored by the manufacturer of febuxostat and most used suboptimal doses of allopurinol as the comparator arm.[72-75] The ACR guidelines do not distinguish between the 2 XOIs because cost was not considered; allopurinol may therefore be a reasonable initial option for most patients.[76]

Uricosurics

Uricosuric agents act through transporter proteins involved in kidney urate reabsorption and/or secretion, such as the urate transporter 1 (URAT1), glucose transporter 9 (GLUT9), organic anion transporter 1 (OAT1), OAT3, OAT4, and OAT10.

Uricosurics are underused, particularly in the United States. This is partly related to the need for multiple tablets and twice-daily dosing of probenecid, which until recently was the only uricosuric agent available in the United States. Lesinurad, a uricosuric URAT1 and OAT4 inhibitor approved by the FDA in 2015, must be coprescribed with an XOI because in randomized trials, lesinurad monotherapy was associated with acute kidney failure more commonly than the comparator arms. Thus, an indication for monotherapy was not pursued. Creatinine level increases noted during these trials were generally reversible. Benzbromarone is a more potent uricosuric drug, but it is not approved by the FDA in the United States and is unavailable in some European countries due to concerns regarding hepatotoxicity.[77]

Uricosurics must be avoided in patients with prior nephrolithiasis and are contraindicated in the presence of uricosuria greater than 700 to 800 mg/24 h. Patients using a uricosuric agent must ensure adequate fluid intake due to the risk for nephrolithiasis. Because uricosurics lose efficacy as kidney function declines, probenecid is not recommended for those with a CL_{cr} <30 mL/min, and lesinurad is not recommended for those with a CL_{cr} <45 mL/min.

Although not developed as drugs that reduce urate levels, 2 commonly used drugs have uricosuric properties: losartan and fenofibrate. Losartan, an angiotensin receptor blocker, is commonly used in all stages of CKD. The safety of fenofibrate is uncertain in advanced kidney disease, particularly in combination with statins due to increased risk for rhabdomyolysis.

Uricase

Pegloticase is a pegylated recombinant porcine uricase, the enzyme responsible for converting urate to allantoin, which is more soluble than urate and therefore more easily eliminated. Its approved use is for gout that is refractory to oral ULT. Pegloticase is administered intravenously every 2 weeks, with the current label supporting 6 months of therapy, though longer term therapy has been successfully reported. Following completion of that regimen, patients are transitioned back to oral ULT. Because pegloticase is derived from porcine uricase and is pegylated, there is a risk for immunogenicity, with infusion reactions and anaphylaxis. The reported rate of hypersensitivity reactions was 26% and 44% for infusions every 2 weeks and monthly, respectively, in a 6-month study and 44% in an open-label extension study (18% were severe reactions).[78,79] Anaphylaxis occurred in ~5% of participants in the pivotal trials that led to approval.[78] Hypersensitivity reactions are highly correlated with increasing serum urate levels; thus, serum urate must be assessed prior to each infusion and therapy must be discontinued if serum urate level is >6 mg/dL on 2 successive occasions. Pegloticase, which is administered with 250 mL of normal saline solution, can be used in advanced CKD, including in dialysis patients, without dose adjustment.[33] Reports of heart failure associated with pegloticase have prompted a label warning, advising exercising caution in patients who have CHF and monitoring patients closely following infusion.

Anti-inflammatory Prophylaxis of Gout Flares

Colchicine and NSAIDs are considered first-line drugs for prophylaxis of gout flares, and less preferably, low-dose glucocorticoids may also be considered when colchicine and NSAIDs are contraindicated (Table 2[80]).[19] Current guidelines recommend prescribing prophylaxis for all patients initiating ULT and maintaining prophylaxis for as long as there is evidence of ongoing gout disease activity (ie, flare or tophus) and/or the serum urate target level has not been achieved. In particular, prophylaxis should be continued for the greater of at least 6 months, 3 months beyond reaching the serum urate target level for those without

tophi, or 6 months beyond reaching the serum urate target level for those in whom previously detected tophi have resolved.[19]

Table 2 - Suggested Anti-inflammatory Prophylaxis Regimens to Prevent Gout Flares

	Normal kidney function	**CKD 3-5**	**CKD 5D (dialysis)**
Colchicine	Up to 0.6 mg every 12 hours; once daily may be sufficient	CrCl ≥30 mL/min: dosage adjustment not required CrCl <30 mL/min: initial dose: 0.3 mg/day; caution if up-titrated; monitor closely for adverse effects	Not removed by dialysis; increased risk of myo/neurotoxicity; FDA label: 0.3 mg twice a week with close monitoring[80]
NSAID	Low-dose, e. g. naproxen 250 mg every 12 hours; lowest necessary dose	Avoid	May be considered

Note: Glucocorticoids may be considered when colchicine and NSAIDs are contraindicated, not tolerated, or not efficacious; low-dose (≤10 mg/d) prednisone or prednisolone; use lowest necessary dose.
Abbreviations: CKD, chronic kidney disease; CL_{cr}, creatinine clearance; FDA, US Food and Drug Administration; NSAID, nonsteroidal anti-inflammatory drug.

Management of Gout Flares

Gout flares, which are intensely painful episodes of self-limited arthritis, are usually the first clinical manifestation of gout. They are by far the most important manifestation of the disease for patients and are the primary burden of this disease. Gout flares occur when MSU crystals activate the NLRP3 inflammasome, often in conjunction with a second signal such as certain free fatty acids, leading to elaboration of interleukin 1b (IL-1b) release.[81] The presence of MSU crystals alone is insufficient to cause gout flares because they can be detected in the synovial fluid of asymptomatic joints. Several factors have been identified that increase the risk for gout flares, including dietary factors (eg, animal-derived purines and alcohol), hospitalizations (especially in the setting of surgery), and diuretics, among others. It is also well-recognized that initiation of ULT leads to an increase in gout flares in the short term. It is generally thought that fluctuations in serum urate levels contribute to gout flares. Patients should be counseled regarding avoidance of pertinent dietary and lifestyle triggers.[19,82] Such a preventive strategy may be particularly important for patients with CKD, who often have fewer therapeutic options for adequately treating gout flares.

Treatment options for gout flares in the United States include colchicine, NSAIDs, glucocorticoids (oral, intra-articular, intramuscular, and intravenous), and subcutaneous or intramuscular corticotropin, though there is limited evidence for this latter option. IL-1

antagonism with canakinumab is an approach approved by the European Medicines Agency for the management of gout flares, but not yet approved in the United States.[83-85] Anakinra is occasionally used off label in the United States in patients for whom the other therapies cannot be used. Regardless of which therapeutic approach is used, the earlier the treatment is started, the faster the flare is brought under control. Local ice therapy can be used adjunctively.[86] A "medications-in-the-pocket" strategy should be encouraged for patients who understand their disease well to start treatment at the first signs of a flare; often immediate initiation of gout flare therapy can abort the attack entirely. General principles to consider for gout flare management are highlighted in Box 2, and specific considerations for patients with CKD are reviewed in Table 3 for each drug.

Box 2 - General Principles for Gout Flare Management

Treatment options
- Colchicine
- Nonsteroidal anti-inflammatory drugs
- Glucocorticoids (PO, IA, IM, IV)
- ACTH (SC, IM)
- Interleukin 1 inhibitors (off-label in the US)
- Ice

Time to start
- Immediately: "medications-in-the-pocket." Note: colchicine is less effective if started >24 h after a flare has started

Dose
- High dose, then taper

Duration
- 7-14 d (until flare resolves; otherwise a rebound flare can occur)

Urate-lowering therapy
- No interruption

Abbreviations: ACTH, corticotropin; IA, intra-articular; IM, intramuscular; IV, intravenous; PO, oral; SC, subcutaneous.

Colchicine

Colchicine is most effective for managing gout flares when started within the first 36 hours based on its mechanism of action, pharmacokinetics, and clinical data.[87] The recommended regimen for individuals with normal kidney function is 1.2 mg at the first sign of a gout flare, followed by 0.6 mg 1 hour later based on fairly recent clinical trial data demonstrating similar efficacy and lower side effects with this strategy compared to a higher dose strategy.[19,88] Although colchicine was used off label for decades to manage gout flares,

this more recent trial led to FDA approval of Colcrys (Takeda Pharmaceuticals U.S.A., Inc.) for this new indication, with a resultant marked increase in price and difficulty obtaining generic colchicine.[89] After this initial therapy, colchicine treatment should be continued once or twice daily until resolution of the flare, or other gout flare therapy should be used.

Table 3 - Suggested Treatment for a Gout Flare in Patients With Normal and Decreased Kidney Function

	Normal Kidney Function	**CKD 3-5**	**CKD 5D (dialysis)**
Colchicine	1.2 mg at the first sign of a gout flare followed by 0.6 mg 1 h later; then, 0.6 mg every 12 h or followed by other gout flare therapy	Not recommended in patients already receiving colchicine for prophylaxis CL_{cr} ≥30 mL/min: dosage adjustment not required CL_{cr} <30 mL/min: consider dosage reduction; treatment course should not be repeated more frequently than every 14 d per FDA label	0.6 mg as a single dose; FDA-approved label states that treatment course should not be repeated more frequently than every 14 d; not removed by dialysis
NSAID	Any NSAID in its full daily dose	CL_{cr} 30-59 mL/min: avoid or use with caution depending on the kidney disease CL_{cr} <30 mL/min: relatively contraindicated	May be used
Glucocorticoid	0.5 mg/kg/d, followed by progressive weaning; eg, start prednisone at 30 mg/d, then reduce by 5 mg every 2 d	Dosage adjustment for CKD not required	Dosage adjustment for CKD not required
ACTH	SC or IM; treatment option for patients with restrictions to oral drugs; initial dose of 25-40 IU; doses repeated as clinically indicated	Dosage adjustment for CKD not required	Dosage adjustment for CKD not required
Interleukin-1 inhibitors	Off-label use of anakinra to treat gout flares in patients with multiple comorbid conditions and contraindications to the mentioned options has become more frequent in the US; canakinumab is approved for gout flare management by the EMA; dose: anakinra 100 mg/d SC; canakinumab 150 mg SC single dose, to be repeated no sooner than at least 12 wk in patients who respond and require retreatment	CL_{cr} <30 mL/min: for anakinra, mean plasma clearance of anakinra declined by 70-75%; consider dose reduction, as 100 mg every other day; for canakinumab, no dose reduction is needed, though clinical experience is limited	For anakinra: <2.5% of administered dose is removed by hemodialysis or continuous ambulatory peritoneal dialysis; consider dose reduction, as 100 mg every other day; for canakinumab, no dose reduction is needed, though clinical experience is limited

Abbreviations: ACTH, corticotropin; CKD, chronic kidney disease; CL_{cr}, creatinine clearance; EMA, European Medicines Agency; FDA, US Food and Drug Administration; NSAID, nonsteroidal anti-inflammatory drug; SC, subcutaneous.

For patients with CKD, colchicine must be used at lower doses with a number of caveats. Specifically, with CL_{cr} ≥30 mL/min, dose adjustment is not required. Per the FDA-approved package insert, for CL_{cr} <30 mL/min, dose reduction is not required, but a treatment course should not be repeated within a 2-week period. For patients treated with hemodialysis, the FDA insert states that only a single 0.6-mg dose should be used, and also not repeated within a 2-week period; the same approach should be used for peritoneal dialysis patients. Importantly, if colchicine is already used for prophylaxis, it should not be used to treat a gout flare in patients with CKD. The risk for neuromyotoxicity increases with declining kidney function and with concomitant use of many medications, including cyclosporine and lipid-lowering medications such as statins and fibrates (Box 3[90-92]).

Nonsteroidal Anti-inflammatory Drugs

There are no data to suggest that one NSAID is more efficacious than another. NSAIDs generally are avoided in individuals with CKD, particularly those with advanced CKD not receiving dialysis. Clinicians may consider avoidance of NSAIDs in patients with concomitant diabetes mellitus even in the absence of obvious CKD given the high risk for kidney disease in such patients. Frequent use of NSAIDs for gout flare management can contribute to kidney disease. Cardiovascular risk and gastrointestinal bleeding risk need to be considered when NSAIDs are used, as for a nondialysis population.

Glucocorticoids

When considering kidney safety, glucocorticoids may be the safest option for patients with CKD, remaining highly effective regardless of flare duration. A common regimen is to start with 0.5 mg/kg of body weight per day for the first few days, followed by progressive tapering.[9,19] Intra-articular glucocorticoid injection is preferable when only 1 or 2 joints are affected. Due to cross-reactivity with the mineralocorticoid receptor, there may be an increased risk for heart failure with many glucocorticoids, likely due to increased renal sodium avidity. Accordingly, for patients with concomitant CHF, dexamethasone may be the preferred formulation if the intra-articular route is not possible because it is considered to have the least mineralocorticoid potency.

Box 3 - Colchicine Toxicity Manifestations and Risk Factors

Toxicity Manifestations

- Neuromuscular toxicity: may manifest mildly as a tingling sensation or subjective weakness or severely as overt peripheral neuropathy with axonal degeneration and rhabdomyolysis; common manifestations: proximal muscle weakness, elevated serum creatine kinase, neuropathy and/or myopathy on electromyography
- Blood dyscrasias: myelosuppression, aplastic anemia
- Gastrointestinal manifestations: anorexia, nausea, vomiting, bloating, diarrhea
- Pharyngeal pain
- Death

Risk Factors

- Decreased kidney function
- Hepatic dysfunction
- Elderly patients
- Statins[a]
- Fibrates
- High dose
- Concomitant use of P-glycoprotein or CYP3A4 inhibitors,[b] such as:
  - Clarithromycin
  - Cyclosporine
  - Tacrolimus
  - Certain antifungals
  - Certain calcium channel blockers (verapamil, diltiazem)
  - Grapefruit juice

Special Alert

Concomitant use of colchicine with P-glycoprotein or CYP3A4 inhibitors, especially clarithromycin, is contraindicated in patients with chronic kidney disease as it can result in death[90]

[a]Increased risk for myopathy is thought to be due to pharmacodynamic factors and/or competition for CYP450 or P-glycoprotein and possible effects of impaired statin elimination via CYP450 and/or drug transporter (eg, P-glycoprotein inhibition).[91] There is increased risk for myopathy/rhabdomyolysis with atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin.[92]

[b]Colchicine metabolism is performed by these systems, with colchicine being considered a major substrate of CYP3A4.

Corticotropin (ACTH)

Parenteral corticotropin (subcutaneous or intramuscular) is considered an appropriate alternative to treat gout flares in patients who have restrictions to oral drugs, with no recommendation of dose adjustment in CKD, though its use lacks the support of rigorous clinical trial data.[19]

It is not uncommon for a patient with severe CKD to have limited improvement of his or her gout flare with the recommended lower colchicine doses. Because NSAIDs are contraindicated, that leaves glucocorticoids as the primary option, though off-label use of the IL-1 antagonist anakinra is used in some patients, particularly when glucocorticoids also cannot be used.

Additional special considerations for the management of gout in kidney transplant recipients are shown in Box 4.

Box 4 - Additional Special Considerations for the Management of Gout in Kidney Transplant Recipients

Immunosuppressant Drugs

- Use of xanthine oxidase inhibitors (allopurinol, febuxostat) is contraindicated with concomitant purine analogues, such as azathioprine and mercaptopurine, because this combination can result in higher and potentially toxic plasma concentrations of these drugs, leading to bone marrow suppression
- Preferably avoid the hyperuricemic effects of cyclosporine
- As such, mycophenolate mofetil should generally be the preferred immunosuppressant for gout patients with a kidney transplant

Urate-Lowering Therapy

- All available urate-lowering drugs may be considered, according to current level of kidney function

Anti-Inflammatory Prophylaxis and/or Treatment of a Gout Flare

- NSAIDs should be used with caution and close monitoring of kidney function, considering their effects on kidney hemodynamics
- Colchicine should be avoided in combination with cyclosporine and tacrolimus due to an increased risk for colchicine myotoxicity

Note: There are limited data regarding gout management in kidney transplant recipients.
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

THE RELATION OF URIC ACID AND ULT TO KIDNEY OUTCOMES

CKD leads to hyperuricemia due to decreased urinary uric acid excretion. Hyperuricemia also may induce decreased kidney function and contribute to CKD progression through a number of potential mechanisms. It is possible that controlling hyperuricemia, especially if achieved early, may reduce kidney disease risk.

Mechanisms of Hyperuricemia-Induced Kidney Damage

Hyperuricemia may cause endothelial dysfunction, reflecting the effects of a reduction of nitric oxide bioavailability, the stimulation of oxidative stress, and activation of the renin-angiotensin system.[3,93-95] Oxidative stress can stimulate smooth muscle cell proliferation of the afferent arterioles, thereby decreasing kidney perfusion. How much of these vascular effects are due to urate itself versus xanthine oxidase remains controversial.[93] Nonetheless, hyperuricemia induced in a rat model results in systemic hypertension, primary kidney arteriolopathy, and glomerular hypertension and hypertrophy, with resultant kidney hypoperfusion and eventual tubulointerstitial inflammation and fibrosis (Box 5).[96-100] When

hyperuricemia was prevented or corrected to normouricemia early in the course of disease with allopurinol, febuxostat, or benziodarone (a uricosuric), these manifestations were prevented.[96-101] In another rat model, allopurinol and benzbromarone limited the kidney damage caused by cyclosporine.[102] The effects of uricosurics (benziodarone and benzbromarone) in these experiments support the direct effects of urate rather than these effects being simply due to xanthine oxidase.

Box 5 - Mechanisms by Which Hyperuricemia May Contribute to Kidney Damage

Reduced nitric oxide bioavailability
Stimulation of oxidative stress
Activation of the renin-angiotensin system
Systemic and glomerular hypertension
Kidney vasculopathy
Tubulointerstitial inflammation and fibrosis

Hyperuricemia and Kidney End Points in Observational Studies

Though many observational studies have identified associations between hyperuricemia and CKD onset or progression, multiple others have not.[103-126] In a Japanese study of 48,177 patients, serum urate level ≥6 mg/dL was an independent predictor of end-stage kidney disease in women,[104] and an increase in serum urate levels over 10 years was an independent risk factor for eGFR decline.[115] Similarly, higher baseline serum urate level was also associated with kidney function decline in 16,186 patients with hyperuricemia enrolled in the Kaiser Permanente Southern California Health Plan.[116] Complementing these findings, hyperuricemia in healthy individuals without decreased kidney function at baseline in 3 large cohorts was associated with higher risk for developing kidney disease.[107,108] However, several observational studies have failed to identify a significant relation of serum urate level to CKD.[121-126] For example, in the Modification of Diet in Renal Disease Study, which followed up 840 individuals with eGFRs between 13 and 55 mL/min for up to 3.5 years, baseline serum urate level was not associated with CKD progression.[121] The Cardiovascular Health Study, a prospective community-based cohort of 4,610 individuals followed up for a mean of 6.6 years, found no association between hyperuricemia and incident CKD, although there was a modest association with CKD progression.[106]

Cohort Studies of ULT and Kidney Disease

Several observational studies have evaluated the effect of ULT on kidney function in participants with normal kidney function and patients with varying degrees of CKD and varying causes of decreased kidney function (Table 4[127-133]). Although some are promising, definitive conclusions cannot be drawn from these observational studies of hyperuricemia and/or ULT on kidney effects, reflecting potential residual confounding and other biases, including publication bias. Well-conducted clinical trials are needed for more valid insights to be drawn.

Randomized Trial Data of Kidney Effects of ULT

Only a few randomized clinical trials (Table 5[134-150]) have assessed the effect of ULT, primarily allopurinol, on kidney outcomes. The febuxostat development program offered opportunity to gain insights into the effects of ULT on kidney function in the context of blinded randomized trials. However, although many trials were large, the numbers with CKD were small, patients with advanced kidney disease (eGFR <30 mL/min/1.73 m^2) were excluded, and kidney end points were not specifically reported as part of the main randomized controlled trial publications, but rather as part of open-label extension studies that have the inherent validity issues of observational cohort studies.

In summary, interpretation of the evidence to date regarding the role of urate in kidney disease and the potential renoprotective effect of urate level lowering is hampered by lack of high-level evidence. Studies to date have largely evaluated allopurinol and febuxostat, which are both XOIs. Thus, whether beneficial effects on kidney disease noted in some observational studies are truly related to urate lowering versus inhibition of xanthine oxidase cannot be discerned. Evaluation of the effects of a uricosuric agent in the context of kidney end points would provide further insights as to whether uric acid level lowering itself versus xanthine oxidase inhibition is the mechanism by which there appears to be promising renoprotective effects. Nonetheless, at the present time, treatment guidelines do not recommend treating asymptomatic hyperuricemia. Sufficiently powered, well-conducted, double-blinded, placebo-controlled, randomized trials are needed to provide definitive direction into this important matter.

Table 4 - Observational Studies of Urate-Lowering Therapy in Gout and Nongout Conditions, With Reported Results on Kidney Function (continues)

Study	Study Design	Setting & Participants	Exposure	Results
Whelton et al[127] (2011)	FOCUS: open-label extension study	24 centers in US; 116 hyperuricemic gout pts with CL_{cr} >50-79 mL/min at baseline	Febuxostat 40, 80, or 120 mg/d	Effects of serum urate reduction were associated with maintenance or improvement in eGFR over 5-y follow-up
Pai et al[128] (2013)	Cohort study	Outpt nephrology department at Nizam's Institute of Medical Sciences, Hyderabad, India; 183 pts with hyperuricemia, with eGFR <90 mL/min (mean baseline eGFR, 35.4 mL/min in the exposed and 38.9 mL/min in the nonexposed)	Allopurinol 100 mg/d vs usual treatment	eGFR remained stable in pts treated with allopurinol while control group presented significant decline in kidney function, resulting in a significant difference between groups at 1 and 2 y of follow-up
Whelton et al[129] (2013)	Report of kidney outcomes from the EXCEL study	174 centers in US and Canada; 551 pts with gout and serum creatinine ≤1.5 mg/dL[56] or ≤2.0 mg/dL[57]	Only febuxostat, at any dose[a]	Greater reductions in serum urate were associated with less decline in eGFR
Levy et al[116] (2014)	Cohort study	Kaiser Permanente Southern California Health Plan, US; 16,186 pts with hyperuricemia and CKD ≤3b	ULT (allopurinol, febuxostat, probenecid)	Pts who achieved serum urate <6 mg/dL on ULT had 37% lower risk for kidney disease progression
Shibagaki et al[130] (2014)	Observational study	University hospitals, Japan; 70 pts with serum urate ≥8 mg/dL and eGFR ≤45 mL/min	Febuxostat 10-60 mg/d, adjusted to target serum urate ≤6.0 mg/dL	Pts with CKD 3b presented 7.4% increase in eGFR from baseline, while those with CKD 4 and 5 showed decreased eGFR at 24 wk; serum urate at wk 24 and relative and absolute reduction in serum urate were identified as independent variables for increase in eGFR in multivariate analysis
Kim et al[131] (2015)	Cohort study	Dongguk University Ilsan Hospital (tertiary hospital), Goyang, Korea; 158 pts with asymptomatic hyperuricemic and CKD 3	ULT (allopurinol, febuxostat, benzbromarone)	Individuals on ULT had significantly less kidney disease progression, and those who achieved the target serum urate with ULT dose adjustment had better kidney outcomes compared with those maintained on initial dose

Table 4 - Observational Studies of Urate-Lowering Therapy in Gout and Nongout Conditions, With Reported Results on Kidney Function (conclusion)

Study	Study Design	Setting & Participants	Exposure	Results
Singh & Yu[132] (2016)	Cohort study	Medicare claims data from 2006-2012 (5% random sample), US; 30,022 allopurinol treatment episodes with no diagnostic code for kidney failure in previous 183 d	Allopurinol dose and duration	Higher allopurinol dose was independently protective against incident kidney failure in elderly allopurinol users; longer allopurinol use may be associated with decreased risk for incident kidney failure
Ma et al[133] (2016)	Cohort study	Zhongshan Hospital (tertiary hospital), Shanghai, China; 106 primary gout pts with eGFR >60 mL/min and 51 healthy controls	ULT (allopurinol 300 mg/d, febuxostat 40 or 80 mg/d, benzbromarone 50 mg/d) used by 88 gout pts	CL_{cr} showed significant increase in xanthine oxidase inhibitor group at 6 mo of treatment

Abbreviations: CKD, chronic kidney disease; CLcr, creatinine clearance; eGFR, estimated glomerular filtration rate; EXCEL, Febuxostat/Allopurinol Comparative Extension Long-Term study; FOCUS, Febuxostat Open-label Clinical Trial of Urate-lowering Efficacy and Safety study; pts, patients; ULT, urate-lowering therapy.
[a]In the EXCEL study, 1,086 individuals from 2 prior phase 3 trials[56,57] were enrolled and randomly assigned to either allopurinol, 100 to 300 mg; febuxostat, 80 mg; or febuxostat, 120 mg, and were permitted to switch among these 3 arms during the first 6 months to achieve and maintain the serum urate target.[58]

Table 5 - Intervention Studies of Urate-Lowering Therapy in Gout and Nongout Conditions, With Reported Results on Kidney Function (continues)

Trial	Study Design	Participants	Intervention	Results
Gibson et al[134] (1982)	Randomized trial	59 pts with gout and normal kidney function	Allopurinol 200 mg/d + colchicine 0.5 mg twice a day vs colchicine 0.5 mg twice a day	Allopurinol-treated patients did not present change in kidney function, while those receiving only colchicine had a significant decrease in eGFR at 2 y of follow-up
Dahlöf et al[135] (2002)	Double-blind randomized trial	9,193 pts aged 55-80 y with essential hypertension and left ventricular hypertrophy	Losartan vs atenolol for at least 4 y	There was no significant difference in serum creatinine between groups at the end of the trial, although the increase in serum urate was lower in the losartan group
Siu et al[136] (2006)	Randomized trial	54 pts with CKD (proteinuria >0.5 g/24 h and/or serum creatinine >1.35 mg/dL) of varying causes and asymptomatic hyperuricemia	Allopurinol (100-300 mg/d) vs conventional therapy	While serum urate levels were significantly reduced in the treatment arm, there was only a nonsignificant trend toward lower serum creatinine in the allopurinol group at 12 mo; nonetheless, the combined end points of significant deterioration in kidney function and dialysis dependence occurred in 16% in the allopurinol group compared to 46% in the control group ($P = 0.02$), suggesting a renoprotective role for allopurinol
Momeni et al[137] (2010)	Double blind placebo-controlled randomized trial	40 pts with type 2 diabetes mellitus and diabetic nephropathy (proteinuria ≥500 mg/24 h and serum creatinine <3 mg/dL)	Allopurinol 100 mg/d vs placebo	At 4 mo, allopurinol-treated patients showed significantly lower 24-h urine protein compared to control group, while serum creatinine remained stable in both groups
Kanbay et al[138] (2011)	Randomized study	105 participants with normal kidney function: 72 with hyperuricemia + 33 normouricemic controls	Allopurinol 300 mg/d (in hyperuricemic) vs no treatment (hyperuricemic pts and normouricemic controls)	Allopurinol use was associated with significant increase in eGFR at 4 mo in comparison to baseline, while hyper- and normouricemic controls had no significant change in the same period
Kao et al[139] (2011)	Double-blind placebo-controlled randomized trial	67 pts with CKD 3 and left ventricular hypertrophy	Allopurinol 300 mg/d vs placebo	eGFR remained stable in both groups, with no significant difference in change in eGFR between groups at 9 mo

Table 5 - Intervention Studies of Urate-Lowering Therapy in Gout and Nongout Conditions, With Reported Results on Kidney Function (continuation)

Trial	Study Design	Participants	Intervention	Results
Shi et al[140] (2012)	Open-label controlled randomized trial	40 pts with IgA nephropathy, with proteinuria 0.15-2.0 g/24 h, albumin >3.5 g/dL, creatinine <3 mg/dL, and serum urate >6 mg/dL in women and >7 mg/dL in men	Allopurinol 100-300 mg/d vs usual care	At 6 mo, there was no significant difference in eGFR or change in eGFR between groups
Goicoechea et al[141] (2010) and Goicoechea et al[142] (2015)	Open-label randomized trial	113 pts with eGFR <60 mL/min	Allopurinol 100 mg/d (n = 57) vs continuation of usual therapy (n = 56)	After 2 y, the allopurinol arm had significantly reduced serum urate, indicating adherence to therapy, with 47% lower risk for kidney disease progression compared to control group; of original 113 pts, 107 were followed up again 5 y later, during which time 12 of 56 allopurinol users stopped treatment and 10 of 51 controls started allopurinol; while results were consistent with the original report, these data must be interpreted with caution given the post hoc nature, small sample size, and nonrandomized (observational) nature of the data
Kim et al[143] (2014)	Post hoc analysis of data derived from a phase 3, double-blind, randomized trial	Pts with gout and creatinine ≤1.5 mg/dL	Febuxostat (40, 80, or 120 mg/d) vs allopurinol (300 mg/d) vs placebo	At 4 wk, pts on ULT presented significant decrease in serum creatinine compared to control group; in adjusted model, serum urate changes were significantly correlated with changes in serum creatinine
Liu et al[144] (2015)	Open-label randomized trial	176 pts with type 2 diabetes mellitus, normoalbuminuria, and asymptomatic hyperuricemia with normal baseline kidney function (mean eGFR 90 mL/min)	Allopurinol dose-adjusted according to serum urate vs conventional therapy	After 3 y of follow-up, the allopurinol-treated group had significantly lower urinary albumin excretion rate and serum creatinine, along with significantly higher eGFR in comparison to the group under conventional therapy

Table 5 - Intervention Studies of Urate-Lowering Therapy in Gout and Nongout Conditions, With Reported Results on Kidney Function (continuation)

Trial	Study Design	Participants	Intervention	Results
Sircar et al[145] (2015)	Double-blind placebo-controlled randomized trial	108 pts with CKD 3 and 4 with asymptomatic hyperuricemia	Febuxostat 40 mg/d vs placebo	Patients on febuxostat experienced less eGFR decline than placebo group at 6 mo
Tanaka et al[146] (2015)	Open-label RCT	45 pts with CKD 3 and asymptomatic hyperuricemia (22 on allopurinol 50-100 mg/d)	Febuxostat 10-40 mg/d, adjusted with serum urate target of <6 mg/dL vs conventional therapy; pts on allopurinol at baseline could either continue allopurinol or switch to febuxostat	There was no significant difference in eGFR between febuxostat and control groups at 12 wk
Sezai et el[147] (2015)	Single-blind RCT	109 pts with eGFR ≤60 mL/min and serum urate ≥8 mg/dL, not on ULT, undergoing cardiac surgery	Febuxostat up to 60 mg/d (up to 40 mg/d if eGFR ≤30 mL/min) vs allopurinol up to 300 mg/d (up to 200 mg/d if eGFR ≤30 mL/min); doses adjusted to target serum urate ≤6.0 mg/dL	There was no significant difference in eGFR between treatment groups at 1, 3, or 6 mo despite significantly lower serum urate in the febuxostat group at these times
Saag et al[60] (2016)	Placebo-controlled blinded pilot randomized trial	96 gout pts with moderate to severe kidney impairment (eGFR 15-50 mL/min/1.73 m^2)	Febuxostat vs placebo	Primary end point: change in serum creatinine from baseline to mo 12; no significant differences in serum creatinine or eGFR between febuxostat arms vs placebo at 6 or 12 mo of follow-up
Bose et al[148] (2014)	Systematic review and meta-analysis of 5 RCTs evaluating eGFR[134,138-141] and 3 RCTs evaluating change in serum creatinine[136,137,149]	Varying clinical conditions and kidney function stages	Allopurinol vs placebo or conventional treatment	Change in serum creatinine from baseline favored allopurinol compared with control arms, although change in eGFR was not significantly different between groups; allopurinol may slow CKD progression, but adequately powered randomized trials are necessary to provide a more definitive conclusion

Table 5 - Intervention Studies of Urate-Lowering Therapy in Gout and Nongout Conditions, With Reported Results on Kidney Function (conclusion)

Trial	Study Design	Participants	Intervention	Results
Kanji et al[150] (2015)	Systematic review and meta-analysis of 5 RCTs[136,137,139-141]	Varying clinical conditions in patients with CKD 3-5	Allopurinol vs placebo or conventional treatment	There was a small but significant improvement in eGFR favoring allopurinol, though when limited to 3 RCTs in which eGFR was not calculated by the metaanalysis' authors from serum creatinine data, this finding was no longer significant; this meta-analysis highlights the paucity of large well-conducted RCTs of allopurinol's effects on kidney end points

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; RCT, randomized controlled trial; ULT, urate-lowering therapy.

CASE REVIEW

For this patient, the first goal is to treat the current gout flare. Given his kidney disease and CHF, the optimal treatment would be intra-articular injection of the left knee and right first metatarsophalangeal joint. In lieu of that, a course of dexamethasone can be considered for its lower mineralocorticoid potency to minimize the risk for CHF exacerbation. Colchicine should be avoided because he already uses it for prophylaxis. Colchicine, 0.6 mg, every other day was continued for prophylaxis, and the allopurinol dose was kept stable until 2 weeks after the end of this gout flare, at which point the allopurinol dose was increased to 200 mg daily and further uptitrated based on regular monitoring of serum urate levels. He was also counseled regarding adjunctive lifestyle factors. At a dose of 450 mg/d, serum urate level was 5.6 mg/dL. Having achieved the target level of <6 mg/dL (because he has no tophi), he was maintained on this dose. After 6 months of serum urate levels remaining at <6 mg/dL, colchicine treatment was discontinued. After a year of therapy, he did not experience further gout flares.

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4.3 **Estudo 3**

Este artigo foi aceito para publicação pelo JAMA Internal Medicine em 15 de julho de 2018 (Anexo B). Referência: Risk of chronic kidney disease with allopurinol use in gout. Vargas-Santos AB, Peloquin C, Zhang Y, Neogi T.

4.3.1 Artigo 3

Risk of Developing Chronic Kidney Disease with Allopurinol Use in Gout

Ana Beatriz Vargas-Santos, Christine E Peloquin, Yuqing Zhang, Tuhina Neogi

KEY POINTS

Question: What is the relation of allopurinol use in patients with gout to the risk of developing chronic kidney disease stage ≥3?

Findings: In this population-based cohort study, the use of allopurinol in patients with gout did not increase the risk of kidney function decline, and in fact, was significantly associated with a 13% lower risk at doses ≥300 mg/day.

Meaning: Since allopurinol does not appear to be associated with kidney function decline, clinicians should consider other potential contributors when faced with kidney function decline in patients with gout.

ABSTRACT

Importance: Clinicians are often cautious about use of allopurinol in patients with gout when renal function declines. **Objective:** To assess the relation of allopurinol use in gout to the risk of developing chronic kidney disease stage ≥3. **Design:** Time-stratified propensity-score matched, population-based, prospective cohort study of individuals with newly diagnosed gout who initiated allopurinol ≥300 mg/day compared with those who did not initiate allopurinol, analyzed using Cox proportional hazards regression. **Setting:** The Health Improvement Network (THIN), a United Kingdom general practitioner electronic health records database. **Participants:** Among adults aged 18-89 years with newly diagnosed gout, we propensity-score matched 4,760 initiators of allopurinol ≥300 mg/day to the same number

of non-initiators of allopurinol, excluding those with chronic kidney disease stage ≥3 or urate-lowering therapy use before their gout diagnosis. **Exposure:** Allopurinol initiation at a dose of ≥300 mg/day. **Main outcome and measure:** Development of chronic kidney disease stage ≥3. **Results:** Of the 4,760 allopurinol initiators and same number of non-initiators, 579 and 623, respectively, developed chronic kidney disease stage ≥3, with a mean follow-up time of 5 and 4 years, mean age of 57 years, and mean body mass index of 30kg/m² for both groups. Use of allopurinol at ≥300 mg/day was associated with lower risk of developing chronic kidney disease stage ≥3 compared with non-users, with a hazards ratio of 0.87 (95% confidence interval 0.77–0.97). Allopurinol initiation at <300 mg/day was not associated with renal function decline (hazards ratio 1.00, 95% confidence interval 0.91–1.09). **Conclusions and Relevance:** In this large cohort, allopurinol initiation at ≥300 mg daily was associated with a lower risk of renal function deterioration. Since allopurinol does not appear to be associated with renal function decline, clinicians should consider evaluating other potential causes when patients with gout experience renal function decline.

INTRODUCTION

Gout is the most common inflammatory arthritis, affecting 3.9% Americans,[1] yet only one-third of patients with gout receive urate-lowering therapy (ULT),[2,3] leading to disease progression. This suboptimal management of gout is compounded by the frequently occurring comorbidity of chronic kidney disease (CKD) stage ≥3 which occurs in 20% of patients with gout, compared with 5% of those without gout,[4] making management of gout flares more challenging, and often limiting use of uricosuric agents.[5]

Allopurinol is the most widely used ULT. Unfortunately, clinicians are often cautious about using allopurinol in CKD, largely stemming from concerns about allopurinol hypersensitivity syndrome (AHS). This has led to widespread empiric use of the Hande criteria,[6] which guides renal-dosing of allopurinol, though there are no data demonstrating reduction in AHS risk with this approach.[7] Instead, renal-dosing of allopurinol compounds the poor management of gout,[8] and adds to the perception that allopurinol may be detrimental for renal function. In contrast, recent studies provide support for starting allopurinol at a low dose with gradual dose escalation to serum urate target with close monitoring, even among patients with renal insufficiency, without increased risk of AHS.[9-11] Further, there is emerging evidence that ULT may be beneficial for kidney dysfunction.[12-21] Thus, there are no clear data to suggest that allopurinol is detrimental to renal function in patients with gout. Despite this, clinicians commonly hold or lower the dose of allopurinol or even discontinue allopurinol

entirely when a patient with gout exhibits kidney function decline,[22] leading to worse gout outcomes.

Although CKD is common in gout, the majority of people with gout have normal kidney function, particularly early in the course of disease, yet there are limited data regarding renal effects of allopurinol among those with gout and normal kidney function.[23-25] Importantly, there is no evidence that allopurinol is nephrotoxic. We, therefore, aimed to assess the relation of allopurinol initiation to the risk of developing CKD stage ≥3 among people with newly diagnosed gout.

PATIENTS AND METHODS

Study design

We conducted a time-stratified propensity score-matched cohort study in The Health Improvement Network (THIN), which is a general practitioner (GP) electronic medical records database representative of the UK general population.

Data source

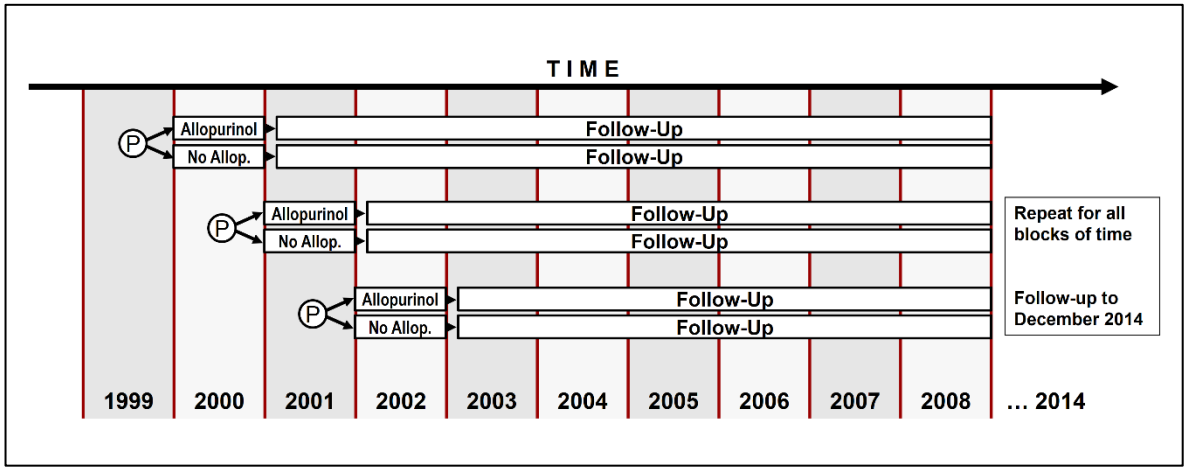
THIN contains anonymized data including demographics, diagnoses, prescriptions, laboratory test results, hospital admissions, consultations, and referrals, systematically collected by participating GPs throughout the UK. Over 11 million patients have been registered in THIN and over 3 million are currently actively enrolled. Diagnoses are recorded as Read codes.[26] Prescriptions are recorded using the Multilex codes issued by First Databank.[27] THIN has been validated for use in pharmacoepidemiological research.[28]

Participants

We included subjects aged 18 to <90 years with incident (newly diagnosed) gout between January 1st, 2000 and December 31st, 2014, who had been enrolled with their GP for at least one year prior to the gout diagnosis. The diagnosis of gout was based on the first instance of a gout Read code. We excluded individuals with CKD stage ≥3 prior to gout diagnosis (defined as either glomerular filtration rate (GFR) <60 mL/min on at least two occasions more than 90 days apart within one year with no intervening GFR ≥75 mL/min or at least one Read code for CKD stage 4, CKD stage 5, hemodialysis, peritoneal dialysis or kidney transplant) and subjects with ULT use (allopurinol, febuxostat, probenecid, or sulfinpyrazone) within the year prior to gout diagnosis. From this sample, we identified incident allopurinol users based on the first instance of allopurinol prescription at any time

after the gout diagnosis. For our primary analysis, allopurinol initiators were restricted to those who were prescribed a dose of ≥300 mg/day, because this dose is considered to be required for most patients. We created one-year cohort accrual blocks to account for secular trends (Figure 1). The index date was defined as the date of first allopurinol prescription for the exposed and a randomly assigned date within the one-year accrual block for each matched unexposed subject. We matched allopurinol initiators to allopurinol non-users 1:1 using propensity scores to minimize confounding by indication. To calculate the propensity scores, we used logistic regression with incident allopurinol use as the dependent variable and potential confounders that reflect indications for allopurinol use and/or risk of developing CKD (listed below) as the independent variables.

Figure 1 - Study design: one-year cohort accrual blocks, with 1:1 propensity-scores matching



Legend: P – pair (matched pair).

Prior to propensity-score matching, we excluded subjects with the following within one year prior to the index date: 1) use of ULT other than allopurinol; 2) active cancer other than "in situ" cancers, squamous skin cancer, or basal skin cancer; and 3) no contact with the health care system (i.e., no appointment with the GP, no laboratory test and no prescription). At any time prior to the index date, the following were additional exclusions: 1) other organ or bone marrow transplant; 2) primary kidney disease (including polycystic kidney disease) or systemic vasculitis that affects the kidneys; 3) cirrhosis; and 4) multiple myeloma or renal carcinoma. Additionally, we excluded subjects whose gout diagnosis occurred on the last day of the study, and individuals lacking data on body mass index (BMI) at any time before the index date or serum urate in the period from six months prior to the gout diagnosis through 30 days after the index date.

Outcome definition

The outcome was defined as either 1) GFR <60 mL/min on at least two occasions more than 90 days apart within one year with no intervening GFR ≥75 mL/min; 2) hemodialysis or peritoneal dialysis; or 3) kidney transplant.

Fulfillment of the outcome definition based on two GFR values was considered to have occurred on the date of the first low GFR value. The second qualifying GFR could occur after study follow-up end (e.g. after the 90th birthday or after December 31st, 2014). GFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[29] Analysis of serum creatinine values for computation of GFR in THIN has been previously validated.[30]

Covariates

Covariates included in the propensity score were 1) gout duration (time between gout diagnosis and index date); 2) baseline serum urate, assessed from six months prior to gout diagnosis through 30 days after the index date; 3) baseline kidney function (GFR 60 to <90 mL/min classified as CKD stage 2 vs. GFR ≥90 mL/min classified as CKD stage 1); 4) baseline albuminuria status (normal: <3 mg/mmol; microalbuminuria: 3-30 mg/mmol; macroalbuminuria: >30 mg/mmol) within five years prior to the index date; 5) age at the index date; 6) gender; 7) most recent BMI prior to the index date; 8) comorbidities assessed any time prior to the index date (cardiovascular disease, diabetes mellitus, heart failure, hypertension); 9) hospitalization within one year prior to the index date; 10) number of visits to the GP within one year prior to the index date; 11) medication use within one year prior to the index date (angiotensin-converting-enzyme inhibitors, low-dose aspirin for cardiovascular disease prevention, colchicine, diuretics (loop, thiazides or thiazide-like), insulin, non-insulin diabetes drugs, losartan, non-losartan angiotensin II receptor blockers, non-steroidal anti-inflammatory drugs (NSAIDs)).

Subjects with missing values for serum creatinine and no Read code for CKD stage 2 were considered to have normal kidney function, thus classified as CKD stage 1 in the propensity score, based on the data that CKD ≥3 prevalence among gout patients is 19.9%, and is lower in the first years of the disease.[4,31]

Statistical analysis

Follow-up time started from the index date and continued until the outcome occurred, death, transfer out of the GP practice, date of last data collection by the GP, when a subject turned 90 years old, or end of the study (December 31st, 2014).

The relation of incident allopurinol use of ≥300 mg daily to CKD stage ≥3 among subjects with incident gout was assessed using Cox proportional hazards models using an intention-to-treat approach, stratified by one-year cohort accrual blocks. In a second model, we additionally adjusted for the covariates included in the propensity score. The assessment of covariate balance, evaluation of the proportionality assumption, and multiple imputation of missing data were performed (Supplementary material). Because subjects could stop using allopurinol or have the dose reduced and non-users could start using the medication, we performed a sensitivity analysis censoring subjects at exposure status change. Additional sensitivity analyses included all allopurinol initiators, regardless of initial dose, and restricting to those prescribed a dose <300 mg/day. We compared the cumulative incidence of CKD in both groups using Kaplan-Meier curves to assess for the possibility of depletion of susceptibles. To assess the impact of the competing risk of death, we utilized the Fine and Grey and cause-specific hazard approaches.

All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). P-values were two-sided and considered significant if <0.05. The Institutional Review Board at Boston University Medical Campus and THIN Review Committee approved the study.

RESULTS

Cohort selection

The source population comprised 6,919,613 subjects, among which we identified 105,151 with newly diagnosed gout; 22,096 subjects were excluded for meeting the outcome definition before the gout diagnosis, and 3,531 and 15 subjects were excluded due to using allopurinol and other ULT within one year prior to the gout diagnosis, respectively. After applying the additional exclusion criteria and then creating the one-year cohort accrual blocks, 43,764 subjects remained eligible (Figure 2). A total of 17,558 allopurinol initiators were identified, of whom 12,176 were excluded because their initial daily dose was <300 mg, leaving 5,382 allopurinol initiators using a dose of ≥300 mg/day. Of these, 4,760 were propensity-score matched to an equal number of non-users. Comparison of characteristics of those who were excluded versus included (eTable 1) indicated no substantial differences between the two groups, except for a slightly higher prevalence of CKD stage 2, hypertension,

certain medication use, and GP visits among the matched subjects, suggesting that those excluded may have been slightly healthier.

Patient Characteristics

Covariates were well balanced (eMethods 2) between the allopurinol initiators and non-users, with a mean age of 57 years, mean BMI of 30 kg/m^2 and mean GFR was 77 mL/min among both groups; as expected, the majority were male (Table 1). Overall, 71% of exposed and unexposed had CKD stage 2 or eGFR 60-89 mL/min, with the remaining 29% having CKD stage 1 or eGFR ≥90 mL/min (Table 1). The use of medications was also similar among allopurinol initiators and non-users, with 31% using diuretics and 73% using NSAIDs (Table 1). Among those initiating allopurinol at a dose of ≥300 mg/day, 94.5% were prescribed a dose of 300 mg/day. The mean duration of allopurinol use was 2.3 years. Additional post-baseline characteristics are provided in eTable 2.

Figure 2 - Flow diagram of study participants

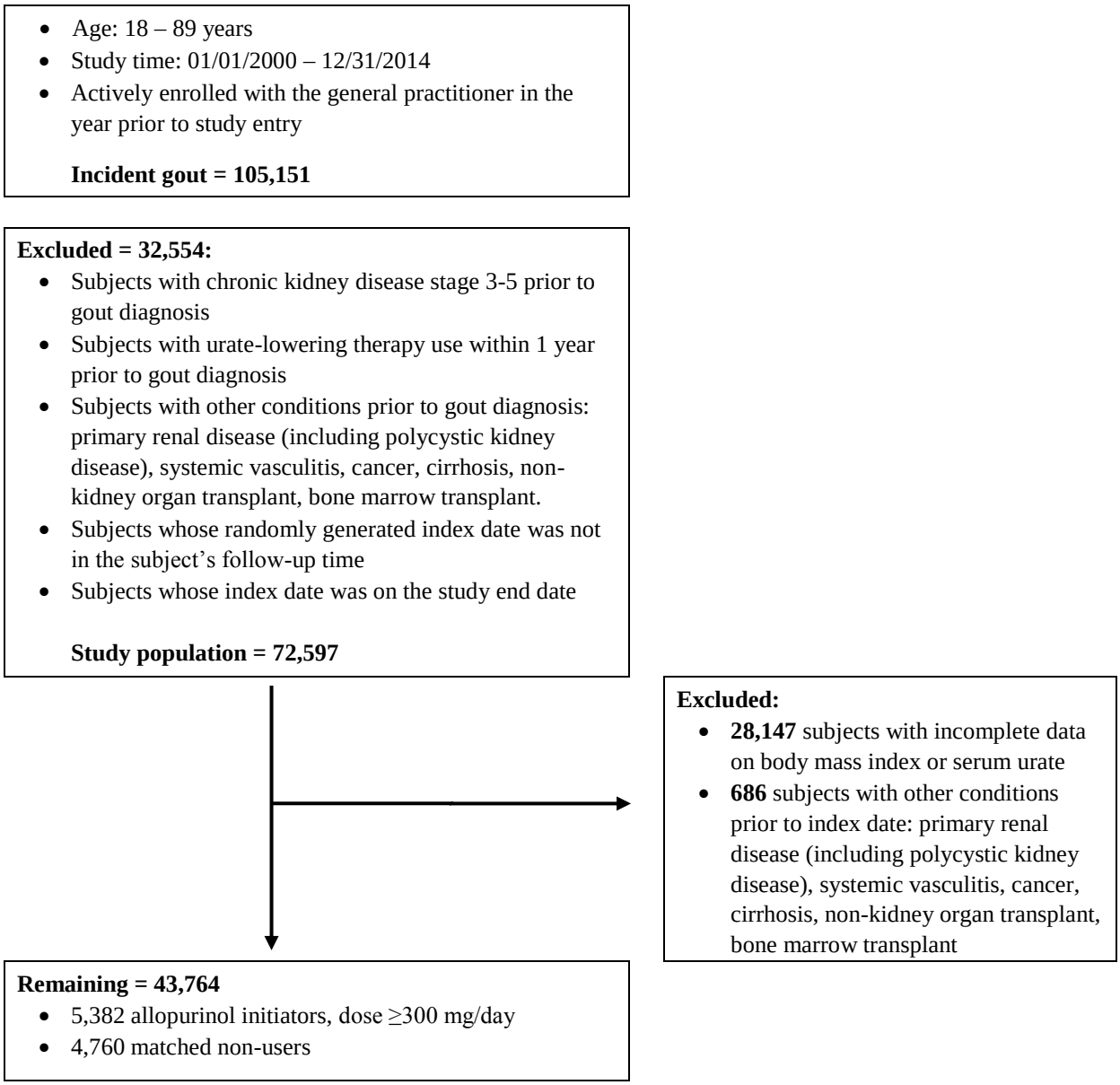


Table 1 - Baseline characteristics of participants

	Allopurinol initiators ≥300 mg/day n = 4,760	Non-initiators n = 4,760
Demographics		
Age, years, mean (SD)	57.4 (13.3)	57.4 (13.9)
Male, n (%)	3,975 (83.5)	3,971 (83.4)
Body mass index, kg/m^2, mean (SD)	30.0 (5.4)	30.1 (5.5)
Gout duration, years, mean (SD)	1.2 (2.1)	1.2 (1.6)
Hospitalization in year prior to index date, n (%)	516 (10.8)	510 (10.7)
Visits to the general practitioners in year prior to index date, n (%)		
0	269 (5.7)	283 (5.9)
1	474 (10.0)	494 (10.4)
2	636 (13.4)	638 (13.4)
3	601 (12.6)	558 (11.7)
4	547 (11.5)	559 (11.7)
5	442 (9.3)	430 (9.0)
6-7	675 (14.2)	667 (14.0)
8-10	536 (11.3)	532 (11.2)
≥11	580 (12.2)	599 (12.6)
Mean initiating allopurinol daily dose, n (%)		
300 mg	4,500 (94.5)	
400-500 mg	176 (3.7)	
600 mg	80 (1.7)	
>600 mg	4 (0.1)	
Comorbid conditions, n (%)		
Chronic kidney disease stage 2 or eGFR 60-89 mL/min per 1.73 m^2	3,354 (70.5)	3,370 (70.8)
Hypertension	2,223 (46.7)	2,243 (47.1)
Diabetes mellitus	396 (8.3)	384 (8.1)
Cardiovascular disease	538 (11.3)	553 (11.6)
Heart failure	187 (3.9)	183 (3.8)
Concomitant medication use, n (%)		
Diuretics (loop, thiazide, thiazide-like)	1,472 (30.9)	1,488 (31.3)
Angiotensin-converting-enzyme inhibitor	1,246 (26.2)	1,264 (26.6)
Losartan	93 (2.0)	101 (2.1)
Other angiotensin II receptor blockers	359 (7.5)	367 (7.7)
Colchicine	791 (16.6)	810 (17.0)
Nonsteroidal anti-inflammatory drugs	3,461 (72.7)	3,499 (73.5)
Low dose aspirin	819 (17.2)	825 (17.3)
Insulin	33 (0.7)	28 (0.6)
Other drugs for diabetes mellitus	227 (4.8)	217 (4.6)
Laboratory data		
Serum urate level, mg/dL, mean (SD)	8.2 (1.4)	8.2 (1.4)
eGFR, mL/min, mean (SD)	77.0 (17.6)	77.0 (17.5)
Albuminuria, n (%)		
Missing	4,367 (91.7)	4,365 (91.7)
Normal (<3 mg/mmol)	276 (5.8)	287 (6.0)
Moderately increased (3-30 mg/mmol)	98 (2.1)	83 (1.7)
Severely increased (>30 mg/mmol)	19 (0.4)	25 (0.5)

SD: standard deviation.

Risk of chronic kidney disease related to allopurinol use

Of the 4,760 subjects in each group, 579 allopurinol initiators and 623 non-users developed CKD stage ≥3 during a mean follow-up time of 5 and 4 years, respectively (Table 2). The propensity score-matched hazards ratio (HR) was 0.87 (95% confidence interval (CI) 0.77–0.97). When additionally adjusted for the propensity score covariates, the effect estimate remained virtually unchanged (HR 0.88 (95% CI 0.79–0.99)). Allopurinol initiators had lower cumulative incidence of CKD stage ≥3 during the entire follow-up time compared with non-users (Figure 3).

Table 2 - Risk of developing CKD ≥3 among subjects with incident gout and incident allopurinol use of at least 300 mg/day

Main results	**Incident allopurinol user (n = 4,760)**	**Non-allopurinol user (n = 4,760)**
Incident CKD stage ≥3, n (%)	579 (12.2)	623 (13.1)
Death, n (%)	254 (5.3)	240 (5.0)
Mean follow-up time, years	4.9	4.5
Crude incidence rate (CKD stage ≥3) per 1000 person-years	24.9	29.4
Propensity score-matched hazards ratio (95% CI)	0.87 (0.77–0.97)	
Adjusted* hazards ratio (95% CI)	0.88 (0.79–0.99)	

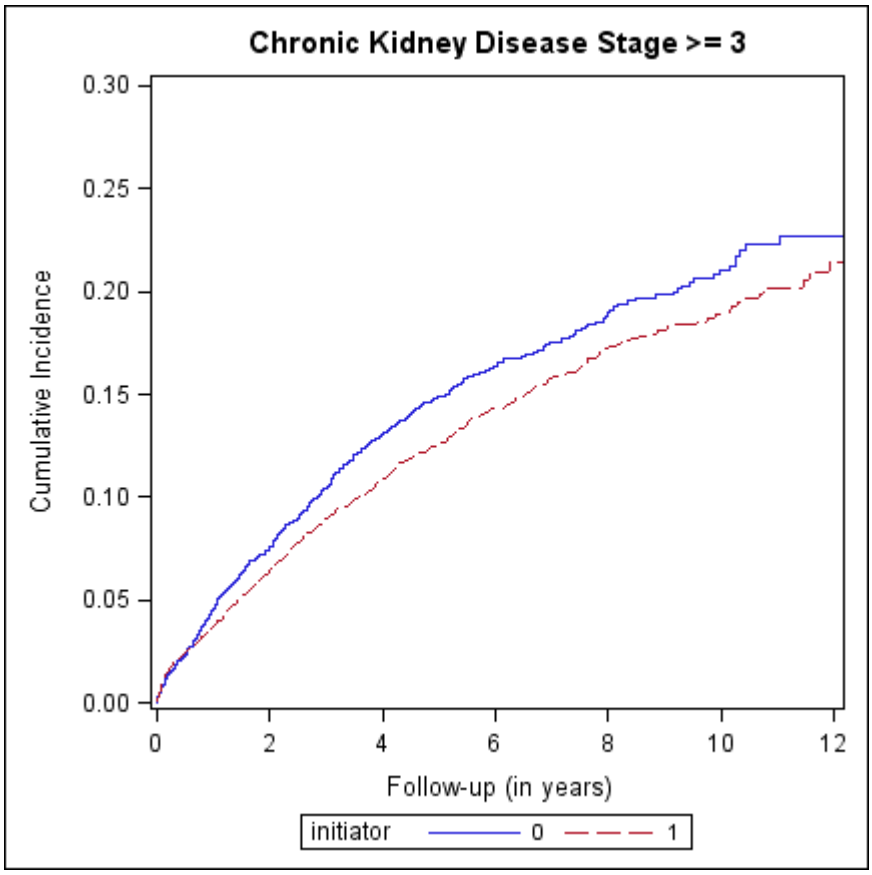
* Variables included in the propensity-score model and included in the adjusted hazards ratio model: 1) gout duration; 2) baseline serum urate; 3) baseline kidney function and albuminuria;4) general (age, gender, body mass index); 5) comorbidities (cardiovascular disease, diabetes mellitus, heart failure, hypertension); 6) hospitalization; 7) number of visits to the general practitioner; 8) medication use (angiotensin-converting-enzyme inhibitor, aspirin, colchicine, diuretics, insulin, other drugs for diabetes mellitus, losartan, other angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs).
CKD: chronic kidney disease; CI: confidence interval.

Six allopurinol initiators and 4 non-users progressed to dialysis or kidney transplant, with 7 of them having met the GFR definition prior to dialysis/transplant. Allopurinol initiators visited their GP more often than non-users (mean number of visits: 20.5 ± 23.2 versus 18.3 ± 22.4, respectively) and had their GFR assessed more frequently (mean GFR assessments: 4.7 ± 5.6 versus 4.0 ± 5.3, respectively) during the follow-up period.

Censoring allopurinol initiators when they stopped using allopurinol or reduced the dose and non-users when they started using allopurinol resulted in similar findings, with an adjusted propensity score-matched HR of 0.83 (95% CI 0.72–0.95). For the sample as a whole, regardless of allopurinol dose at initiation, the propensity score-matched HR was 1.00 (95% CI 0.93–1.08). When restricting to allopurinol initiators who were prescribed a dose of

<300 mg/day, no effect was found, with an adjusted HR of 1.02 (95% CI 0.93–1.12). Imputation of missing data resulted in similar findings (HR 0.92 (95% CI 0.84–1.00)).

Figure 3 - Risk of chronic kidney disease stage ≥3 by allopurinol initiation ≥300 mg/day versus non-initiators: Kaplan-Meier Curve



The Fine and Grey and the cause-specific hazard competing risk of death regression models yielded effect estimates virtually identical to our primary results, with a HR of 0.87 (95% CI 0.78–0.98) and 0.87 (95% CI 0.78–0.97), respectively.

DISCUSSION

This study is one of few that have evaluated the relation of allopurinol to renal function among patients with gout and normal or near-normal kidney function at baseline. Allopurinol use, initiated at a dose of ≥300 mg/day, was associated with a 13% reduction in the risk of developing CKD stage ≥3. In contrast, initiation of allopurinol at a dose of <300 mg/day had no association with developing CKD stage ≥3, consistent with current thinking that most patients need doses higher than 300 mg/day to achieve clinically meaningful

outcomes.[8,32-36] Nonetheless, at minimum, allopurinol does not appear to have a detrimental effect on renal function in individuals with gout.

Most studies to date evaluating the effects of urate-lowering on renal function have been conducted in non-gout populations with varying degrees of baseline kidney function, often CKD stage 3.[12-17,19,37-46] The majority of these studies have demonstrated either a beneficial or no significant association with renal function. Importantly, no study has identified a harmful association with allopurinol. Nonetheless, because people with gout have intrinsic differences compared with those with asymptomatic hyperuricemia, including higher mortality, more comorbidities and more NSAID use, these studies' results are not directly applicable to gout patients.

In one of the first intervention studies evaluating renal function effects of urate-lowering in 59 patients with gout whose initial mean GFR was 94 ± 24 mL/min randomized to allopurinol and colchicine or to colchicine alone, there was a significant difference in kidney function favoring allopurinol over a two-year period.[23] In a prospective observational study, xanthine oxidase inhibitor use over 6 months in patients with gout and normal kidney function was associated with a significant increase in GFR compared with healthy subjects.[24] In another study of 179 subjects with gout whose mean baseline GFR was ~70 mL/min, high dose febuxostat (120 mg/day) was associated with significant improvement in GFR compared with placebo over a 4-week period, while lower doses and allopurinol 300 mg/day was not, and increases in GFR were significantly associated with reductions in serum urate.[25] In an administrative database, gout control related to allopurinol adherence was associated with significantly decreased risk of ESRD in a sample with hypertension.[47]

The decline of kidney function in gout patients is multifactorial. Beyond the natural decline that occurs with aging, there are the postulated deleterious effects of hyperuricemia, the frequent use of NSAIDs, highly prevalent comorbidities, such as hypertension and diabetes mellitus, and common use of other medications, such as diuretics.[4,48] The potential beneficial effect of allopurinol may occur through serum urate reduction and reduction of oxidative stress through xanthine oxidase inhibition itself.[49] As well, patients who achieve the serum urate target experience reduction in flares, making renally-harmful NSAID use less frequent. Of note, achievement of target serum urate in gout management often requires doses higher than 300 mg, in line with our findings.

We recognize some limitations of our study. First, as with any observational study, there is potential for residual confounding despite our use of propensity score matching. However, for unmeasured confounding to change our results such that allopurinol's true effect

is harmful would be unlikely (E-value 2.84).[50] Second, there is potential misclassification of allopurinol status since allopurinol use was based on prescription data, without ability to evaluate adherence in these data. Third, consistent with the known suboptimal management and monitoring of gout therapy, only few subjects had subsequent measurements of serum urate after treatment initiation, limiting our ability to evaluate the effect of serum urate on GFR. Nonetheless, our research question was specifically about the effects of allopurinol on renal function, regardless of mechanism. Fourth, there was possible detection or surveillance bias unfavorable to allopurinol because patients on allopurinol visited their GP more frequently, had their GFR assessed more often, and had slightly longer follow-up. Thus, allopurinol users could be more readily diagnosed with CKD simply on the basis of having laboratory tests assessed more frequently and over a longer period, making our findings conservative.

We also recognize that our primary focus on those that initiated allopurinol at ≥300 mg/day is not the current recommended starting dose of allopurinol (100 mg/day or 50 mg/day for CKD stage 4 or worse) with monitored dose escalation until serum urate target is achieved to reduce risk of AHS.[51] Because our study spanned the years 2000-2014, prior to more recent treatment guidelines, when allopurinol dosing had traditionally been started at 300 mg/day without dose escalation, we opted to study what would be more likely to be biologically relevant, in line with the literature indicating that doses <300 mg/day typically do not enable patients to achieve their target serum urate.[36] Nonetheless, our study findings suggest that starting at recommended lower doses with monitored dose escalation should not negatively impact renal function.

Our study also has a number of strengths. The large population-based sample offered an opportunity to detect even small detrimental effects if there were any to be noted. The new-user design, as standard in pharmacoepidemiological studies, with the additional restriction to newly diagnosed gout to ensure that allopurinol use was truly incident, and the use of propensity scores to account for confounding by indication were important strategies to minimizing bias.

CONCLUSIONS

In summary, in this large newly diagnosed gout cohort with normal/near-normal kidney function, the initiation of allopurinol ≥300 mg/day was associated with lower risk of developing CKD stage ≥3. These findings in the context of the existing body of literature, including the recent demonstration of safe allopurinol dose-escalation in patients with gout

and CKD,[11] indicate that allopurinol should not adversely affect renal function in patients with gout. Since allopurinol does not appear to be associated with renal function decline, clinicians should consider evaluating other factors when faced with renal function decline in their patients with gout rather than lowering the dose of or discontinuing allopurinol, a strategy that has contributed to the ongoing suboptimal management of gout.

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Conflicts of interests: Ana Beatriz Vargas-Santos has received speaking fee (USD <1,000.00) and supporting for international medical events from Grünenthal. Christine Peloquin, Yuqing Zhang and Tuhina Neogi have no relevant conflicts of interest.

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Author Contributions: Dr. Neogi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Dr. Vargas-Santos and Dr. Neogi.

Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, or material support: Dr. Peloquin, Dr. Yuqing and Dr. Neogi.

ONLINE-ONLY SUPPLEMENT

Methods Supplement: Bias Analysis

eMethods 1: Missing data

Due to a high number of missing data on body mass index (BMI) and serum urate, respectively 11.6% and 36.6% of the 72,597 potentially eligible subjects after the blocking process, we performed multiple imputation. First, we imputed the high-dose allopurinol blocked dataset five times to impute missing BMI and serum urate values. Then, we created five propensity score- (PS)-matched datasets from the five imputed blocked datasets. For each of them, we calculated PS-matched hazards ratio (HR) with respective 95% confidence intervals (CI) and performed a second model additionally adjusting for the covariates included in the PS. Lastly, we calculated the mean HR and CI bounds from all five HR to create one summary HR for each model. The results from this multiple imputation analysis reinforced our primary findings, with a PS-matched HR of 0.89 (95% CI 0.82–0.97, p=0.007) and further adjusted for the PS variables, the HR was 0.92 (95% CI 0.84–1.00, p=0.05).

eMethods 2: Covariate balance

Covariate balance in the PS-matched dataset was assessed using the standardized mean difference (SMD), evaluated through SAS Macro %pmdiag. The closer the SMD is to 0, the better is the covariate balance. All SMD were lower than 0.1, ranging from <0.01 to 0.03, confirming a very good balance overall.

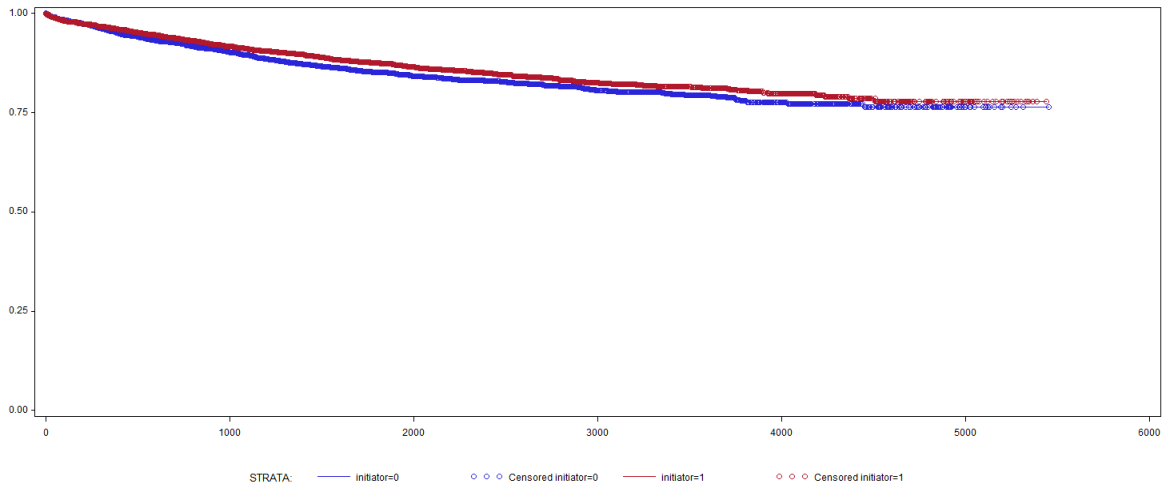
	SMD prior to PS-matching	**SMD post PS-matching**
Age	0.34	0
Female	0.20	0
Body mass index	0.21	0.01
Gout duration	0.97	0.02
Hospitalization in year prior to index date	0.05	0
Visits to the general practitioners in year prior to index date	0.06	0.01
Baseline CKD stage 2 or eGFR 60-89 mL/min per 1.73m^2	0	0.01
Hypertension	0.04	0.01
Diabetes mellitus	0.10	0.01
Cardiovascular disease	0.01	0.01
Heart failure	0.07	0
Diuretics (loop, thiazide, thiazide-like)	0.24	0.01
Angiotensin-converting-enzyme inhibitor	0.01	0.01
Losartan	0.09	0.01
Other angiotensin II receptor blockers	0.03	0.01
Colchicine	0.32	0.01
Nonsteroidal anti-inflammatory drugs	0.64	0.02
Low dose aspirin	0.05	0
Insulin	0.02	0.01
Other drugs for diabetes mellitus	0.10	0.01
Serum urate level	0.93	0.03
Albuminuria	0.07	0

SMD: standardized mean difference; PS: propensity-score; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

eMethods 3: Evaluation of the proportionality assumption

To ensure that the methods used for our main analysis were appropriate, we assessed whether the major assumption of the Cox proportional hazards model was respected, which is that the effect of a given covariate does not change over time. To assess if there was any violation of the proportional hazards assumption, we performed three checks. First, we included an interaction term (log of time x initiator) in the proportional hazards regression model, obtaining a p-value of 0.7406, therefore rejecting the violation hypothesis. Second, we included an "ASSESS PH" statement in the regression model,(32) and no violation was identified, with p=0.3680. Lastly, we created a Log-Negative Log plot, which showed both lines converging at the beginning of follow-up and persisting as roughly parallel lines throughout the graphic, confirming that the hazards were proportional over time (e**Figure**). Evaluation of the Schoenfeld residuals by visual inspection also indicated compatibility with proportional hazards assumption.

eFigure - Log-Negative Log plot



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Supplementary tables

eTable 1 - Comparison of characteristics of excluded versus included subjects

Subjects	Excluded n = 41,009	Eligible n = 31,588	Matched n = 9,520
Demographics			
Age, years, mean (SD)	58.6 (14.8)	59.2 (13.6)	57.4 (13.6)
Male, n (%)	33,196 (80.9)	24,673 (78.1)	7,946 (83.5)
Body mass index missing, n (%)	8,440 (20.6)	0 (0.0)	0 (0.0)
Body mass index, kg/m^2, mean (SD)	29.2 (5.4)	29.2 (5.3)	30.0 (5.5)
Gout duration, years, mean (SD)	0.4 (0.4)	1.1 (1.7)	1.2 (1.9)
Hospitalization in year prior to index date, n (%)	4,335 (10.6)	3,343 (10.6)	1,026 (10.8)
Visits to the GP in year prior to index date, n (%)			
0	3,473 (8.5)	1,433 (4.5)	552 (5.8)
1	6,106 (14.9)	2,960 (9.4)	968 (10.2)
2	6,148 (15.0)	4,026 (12.7)	1,274 (13.4)
3	5,190 (12.7)	4,078 (12.9)	1,159 (12.2)
4	4,327 (10.6)	3,693 (11.7)	1,106 (11.6)
5	3,334 (8.1)	3,063 (9.7)	872 (9.2)
6-7	4,773 (11.6)	4,638 (14.7)	1,342 (14.1)
8-10	3,903 (9.5)	3,690 (11.7)	1,068 (11.2)
≥11	3,755 (9.2)	4,007 (12.7)	1,179 (12.4)
Comorbid conditions, n (%)			
CKD stage 2 or eGFR 60-89 mL/min per 1.73m^2	22,345 (54.5)	21,826 (69.1)	6,724 (70.6)
Hypertension	16,308 (39.8)	14,206 (45.0)	4,466 (46.9)
Diabetes mellitus	2,958 (7.2)	2,749 (8.7)	780 (8.2)
Cardiovascular disease	4,986 (12.2)	3,388 (10.7)	1,091 (11.5)
Heart failure	1,895 (4.6)	979 (3.1)	370 (3.9)
Concomitant medication use, n (%)			
Diuretics (loop, thiazide, thiazide-like)	11,523 (28.1)	8,676 (27.5)	2,960 (31.1)
Angiotensin-converting-enzyme inhibitor	9,294 (22.7)	7,733 (24.5)	2,510 (26.4)
Losartan	761 (1.9)	769 (2.4)	194 (2.0)
Other angiotensin II receptor blockers	2,224 (5.4)	1,980 (6.3)	726 (7.6)
Colchicine	5,952 (14.5)	4,351 (13.8)	1,601 (16.8)
Nonsteroidal anti-inflammatory drugs	27,652 (67.4)	21,084 (66.7)	6,960 (73.1)
Low dose aspirin	7,317 (17.8)	5,582 (17.7)	1,644 (17.3)
Insulin	317 (0.8)	259 (0.8)	61 (0.6)
Other drugs for diabetes mellitus	1,790 (4.4)	1,677 (5.3)	444 (4.7)
Laboratory data			
Serum urate level missing, n (%)	26,572 (64.8)	0 (0.0)	0 (0.0)
Serum urate level, mg/dL, mean (SD)	8.2 (1.5)	7.3 (1.6)	8.2 (1.4)
Albuminuria, n (%)			
Missing	37,905 (92.4)	28,464 (90.1)	8,732 (91.7)
Normal (<3 mg/mmol)	2,193 (5.3)	2,227 (7.1)	563 (5.9)
Moderately increased (3-30 mg/mmol)	769 (1.9)	788 (2.5)	181 (1.9)
Severely increased (>30 mg/mmol)	142 (0.3)	109 (0.3)	44 (0.5)

SD: Standard deviation; GP: general practitioner; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

eTable 2 - Post-baseline characteristics of allopurinol initiators at ≥300 mg/day versus non-initiators

	n (%)
Allopurinol initiators:	
Decreased dose then stopped allopurinol	296 (6.2)
Stable dose then stopped allopurinol	2,471 (51.9)
Increased dose then stopped allopurinol	73 (1.5)
Remained on allopurinol at a decreased dose	95 (2)
Remained on allopurinol at the same dose	1,757 (36.9)
Remained on allopurinol at an increased dose	68 (1.4)
Allopurinol use duration:	
<6 months	1,990 (41.8)
6 months - <1 year	536 (11.3)
1 - <2 years	592 (12.4)
2 - <4 years	618 (13.0)
≥4 years	1,024 (21.5)
Use of nonsteroidal anti-inflammatory drugs	3,589 (75.4)
Use of colchicine	1,166 (24.5)
Allopurinol hypersensitivity syndrome	6 (0.13)
Non-initiator (comparator) group:	
Started allopurinol	396 (8.3)
Use of nonsteroidal anti-inflammatory drugs	3,002 (63.1)
Use of colchicine	707 (14.9)
Allopurinol hypersensitivity syndrome	2 (0.04)

eTable 3 - Sensitivity analysis: Baseline characteristics of allopurinol initiators at <300 mg/day versus non-initiators

	Allopurinol initiators at <300 mg/day n = 10,179	Non-initiators n = 10,179
Demographics		
Age, years, mean (SD)	58.6 (13.4)	58.4 (13.9)
Male, n (%)	8,429 (82.8)	8,431 (82.8)
Body mass index, kg/m^2, mean (SD)	30.0 (5.4)	30.0 (5.4)
Gout duration, years, mean (SD)	1.5 (2.5)	1.4 (1.8)
Hospitalization in year prior to index date, n (%)	1,319 (13.0)	1,330 (13.1)
Visits to the general practitioners in year prior to index date, n (%)		
0	451 (4.4)	428 (4.2)
1	910 (8.9)	872 (8.6)
2	1,235 (12.1)	1,288 (12.7)
3	1,256 (12.3)	1,313 (12.9)
4	1,122 (11.0)	1,103 (10.8)
5	981 (9.6)	975 (9.6)
6-7	1,465 (14.4)	1,438 (14.1)
8-10	1,337 (13.1)	1,328 (13.0)
≥11	1,422 (14.0)	1,434 (14.1)
Comorbid conditions, n (%)		
Chronic kidney disease stage 2 or eGFR 60-89 mL/min per 1.73m^2	7,137 (70.1)	7,181 (70.5)
Hypertension	4,781 (47.0)	4,786 (47.0)
Diabetes mellitus	912 (9.0)	873 (8.6)
Cardiovascular disease	1,280 (12.6)	1,283 (12.6)
Heart failure	443 (4.4)	438 (4.3)
Concomitant medication use, n (%)		
Diuretics (loop, thiazide, thiazide-like)	3,011 (29.6)	2,968 (29.2)
Angiotensin-converting-enzyme inhibitor	2,825 (27.8)	2,821 (27.7)
Losartan	228 (2.2)	222 (2.2)
Other angiotensin II receptor blockers	757 (7.4)	718 (7.1)
Colchicine	2,397 (23.5)	2,279 (22.4)
Nonsteroidal anti-inflammatory drugs	7,129 (70.0)	7,299 (71.7)
Low dose aspirin	1,891 (18.6)	1,877 (18.4)
Insulin	74 (0.7)	67 (0.7)
Other drugs for diabetes mellitus	541 (5.3)	516 (5.1)
Laboratory data		
Serum urate level, mg/dL, mean (SD)	8.2 (1.3)	8.2 (1.3)
Albuminuria, n (%)		
Missing	8,963 (88.1)	9,007 (88.5)
Normal (<3 mg/mmol)	864 (8.5)	812 (8.0)
Moderately increased (3-30 mg/mmol)	304 (3.0)	309 (3.0)
Severely increased (>30 mg/mmol)	48 (0.5)	51 (0.5)

SD: standard deviation; eGFR: estimated glomerular filtration rate.

eTable 4 - Sensitivity analysis: Risk of developing CKD ≥3 among subjects with incident gout and incident allopurinol use of <300 mg/day

Main results	**Incident allopurinol user (n = 10,179)**	**Non-allopurinol user (n = 10,179)**
Incident CKD stage ≥3, n (%)	986 (9.7)	970 (9.5)
Death, n (%)	404 (4)	454 (4.5)
Mean follow-up time, years	3.6	3.5
Crude incidence rate (CKD stage ≥3) per 1000 person-years	26.7	27.1
Propensity score-matched hazards ratio (95% CI)	1.00 (0.91–1.09)	
Adjusted* hazards ratio (95% CI)	1.02 (0.93–1.12)	

* Variables included in the propensity-score model and included in the adjusted hazards ratio model: 1) gout duration; 2) baseline serum urate; 3) baseline kidney function and albuminuria;4) general (age, gender, body mass index); 5) comorbidities (cardiovascular disease, diabetes mellitus, heart failure, hypertension); 6) hospitalization; 7) number of visits to the general practitioner; 8) medication use (angiotensin-converting-enzyme inhibitor, aspirin, colchicine, diuretics, insulin, other drugs for diabetes mellitus, losartan, other angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs).
CKD: chronic kidney disease; CI: confidence interval.

eTable 5 - Comparisons of baseline characteristics of participants for allopurinol initiators at ≥300 mg/day versus <300 mg/day

	Allopurinol initiators at <300 mg/day n = 10,179	Allopurinol initiators at ≥300 mg/day n = 4,760
Demographics		
Age, years, mean (SD)	58.6 (13.4)	57.4 (13.3)
Male, n (%)	8,429 (82.8)	3,975 (83.5)
Body mass index, kg/m^2, mean (SD)	30.0 (5.4)	30.0 (5.4)
Gout duration, years, mean (SD)	1.5 (2.5)	1.2 (2.1)
Hospitalization in year prior to index date, n (%)	1,319 (13.0)	516 (10.8)
Visits to the general practitioners in year prior to index date, n (%)		
0	451 (4.4)	269 (5.7)
1	910 (8.9)	474 (10.0)
2	1,235 (12.1)	636 (13.4)
3	1,256 (12.3)	601 (12.6)
4	1,122 (11.0)	547 (11.5)
5	981 (9.6)	442 (9.3)
6-7	1,465 (14.4)	675 (14.2)
8-10	1,337 (13.1)	536 (11.3)
≥11	1,422 (14.0)	580 (12.2)
Comorbid conditions, n (%)		
Chronic kidney disease stage 2 or eGFR 60-89 mL/min per 1.73 m^2	7,137 (70.1)	3,354 (70.5)
Hypertension	4,781 (47.0)	2,223 (46.7)
Diabetes mellitus	912 (9.0)	396 (8.3)
Cardiovascular disease	1,280 (12.6)	538 (11.3)
Heart failure	443 (4.4)	187 (3.9)
Concomitant medication use, n (%)		
Diuretics (loop, thiazide, thiazide-like)	3,011 (29.6)	1,472 (30.9)
Angiotensin-converting-enzyme inhibitor	2,825 (27.8)	1,246 (26.2)
Losartan	228 (2.2)	93 (2.0)
Other angiotensin II receptor blockers	757 (7.4)	359 (7.5)
Colchicine	2,397 (23.5)	791 (16.6)
Nonsteroidal anti-inflammatory drugs	7,129 (70.0)	3,461 (72.7)
Low dose aspirin	1,891 (18.6)	819 (17.2)
Insulin	74 (0.7)	33 (0.7)
Other drugs for diabetes mellitus	541 (5.3)	227 (4.8)
Laboratory data		
Serum urate level, mg/dL, mean (SD)	8.2 (1.3)	8.2 (1.4)
Albuminuria, n (%)		
Missing	8,963 (88.1)	4,367 (91.7)
Normal (<3 mg/mmol)	864 (8.5)	276 (5.8)
Moderately increased (3-30 mg/mmol)	304 (3.0)	98 (2.1)
Severely increased (>30 mg/mmol)	48 (0.5)	19 (0.4)

SD: standard deviation; eGFR: estimated glomerular filtration rate.

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CONSIDERAÇÕES FINAIS

Esta tese traz informações novas sobre o conhecimento da gota pelos reumatologistas no Brasil, revisa o manejo da gota no contexto da DRC e soma à literatura mais uma evidência do potencial nefroprotetor do alopurinol.

Escolhemos avaliar os reumatologistas quanto ao conhecimento sobre manejo da gota porque – apesar de tratarem apenas um pequeno percentual dos pacientes com gota – estes são os formadores de opinião neste tópico. Julgávamos, no entanto, que este conhecimento fosse insatisfatório à semelhança do que ocorre em outros países, o que acabou por se confirmar nos dados apresentados do estudo 1 desta tese. Entre diversos aspectos, chamaram a atenção o não reconhecimento do tofo gotoso como indicação da THU, a suspensão da THU durante uma crise aguda de gota, a prescrição inicial do alopurinol em doses altas e o não reconhecimento de que a THU deve ser mantida por tempo indeterminado. Cabe ainda salientar que, embora a maioria dos reumatologistas reconheça o conceito de uricemia alvo, os valores recomendados precisam ser mais amplamente difundidos. É possível que o não investimento dos reumatologistas em atualizar os seus conhecimentos sobre a gota venha do fato de que esta seja considerada, no senso comum, uma doença simples, antiga e fácil de tratar. Os resultados do estudo 1 substanciaram o objetivo da Comissão de Artrites Microcristalinas da Sociedade Brasileira de Reumatologia de difundir mais o conhecimento sobre a gota, especialmente os conceitos modificados nas últimas décadas. Desde 2013, as atividades sobre gota nos congressos e jornadas da Sociedade Brasileira e das sociedades regionais de reumatologia vêm crescendo significativamente em número e em público. Será interessante repetir este estudo num futuro próximo.

Ainda com o objetivo de tornar o conhecimento mais acessível e difundido, realizamos uma revisão narrativa sobre o manejo adequado da gota no contexto da DRC. Privilegiamos a apresentação das recomendações sob forma de tabelas e quadros com intuito de facilitar a consulta por parte dos médicos. Nesta revisão, mostramos os efeitos deletérios da hiperuricemia e os potenciais benefícios da THU sobre a função renal. Os resultados desses trabalhos variaram de um efeito protetor dos hipouricemiantes à não identificação de uma associação significativa, sem identificar artigos apontando efeito deletério da THU sobre os rins.

A revisão supracitada identificou uma grande heterogeneidade nos critérios de inclusão dos participantes, assim como alguns problemas metodológicos capazes de introduzir

vieses nos resultados descritos. Diante desta constatação, realizamos um estudo populacional com cerca de 10.000 participantes (estudo 3). Nossos resultados mostraram um efeito nefroprotetor do alopurinol na dose ≥300 mg/dia entre pacientes com função renal normal ou quase normal ao início do seguimento. Atualmente, estamos trabalhando em um estudo semelhante a este, avaliando pacientes com DRC estágios 3 e 4 à inclusão.

Diante das importantes lacunas no conhecimento sobre o manejo da gota, sobretudo em pacientes com comprometimento da função renal, e das recentes evidências sobre os benefícios amplos da THU, é de grande importância que programas de educação continuada abordem os conceitos atuais do manejo da gota para garantir a esses pacientes um tratamento mais adequado.

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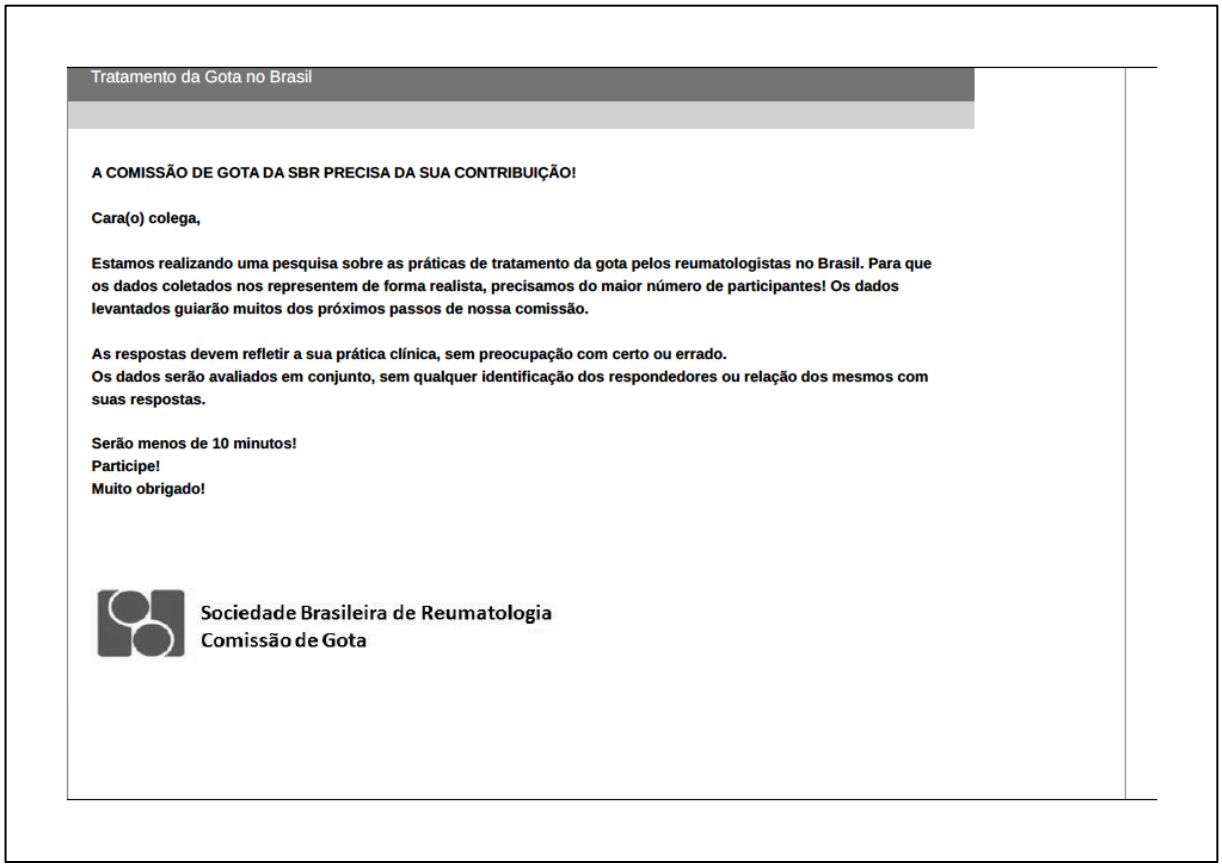
APÊNDICE A - Versão impressa do questionário eletrônico utilizado no estudo 1 (accessível em: https://pt.surveymonkey.com/r/tratamento-gota-doutorado)



Tratamento da Gota no Brasil

A COMISSÃO DE GOTA DA SBR PRECISA DA SUA CONTRIBUIÇÃO!

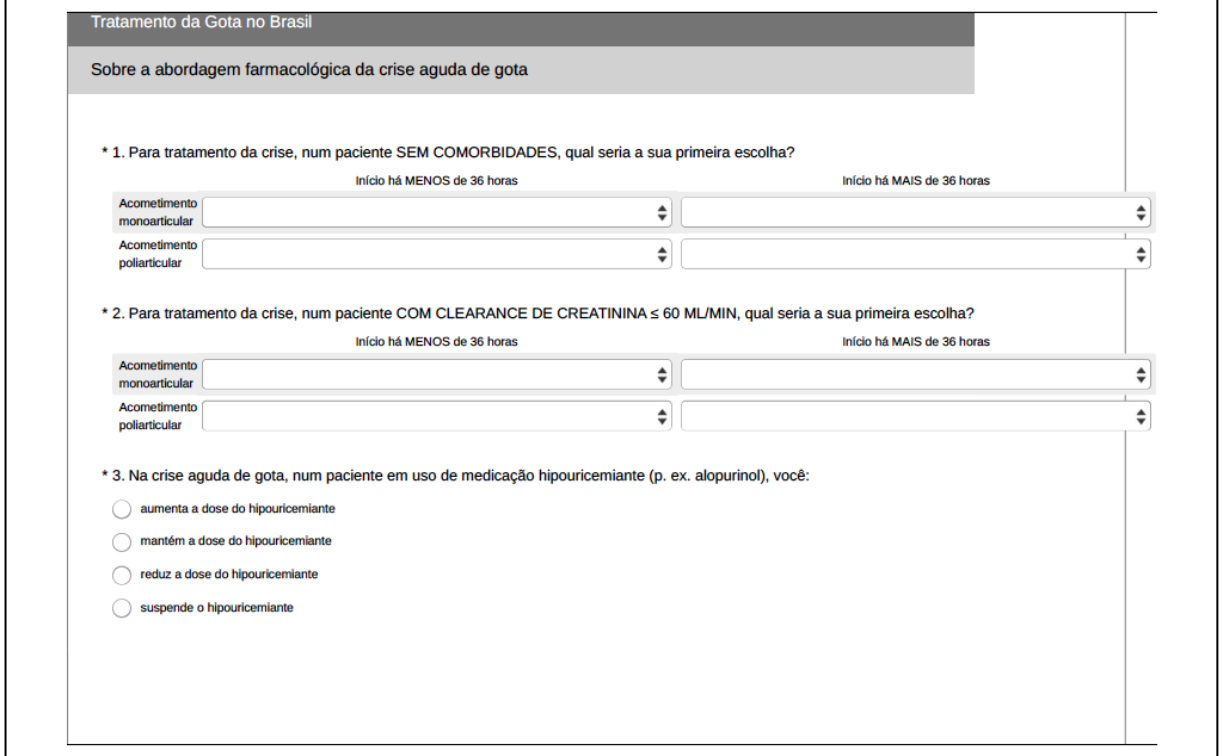
Cara(o) colega,

Estamos realizando uma pesquisa sobre as práticas de tratamento da gota pelos reumatologistas no Brasil. Para que os dados coletados nos representem de forma realista, precisamos do maior número de participantes! Os dados levantados guiarão muitos dos próximos passos de nossa comissão.

As respostas devem refletir a sua prática clínica, sem preocupação com certo ou errado.
Os dados serão avaliados em conjunto, sem qualquer identificação dos respondedores ou relação dos mesmos com suas respostas.

Serão menos de 10 minutos!
Participe!
Muito obrigado!

Sociedade Brasileira de Reumatologia
Comissão de Gota



Tratamento da Gota no Brasil

Sobre a abordagem farmacológica da crise aguda de gota

* 1. Para tratamento da crise, num paciente SEM COMORBIDADES, qual seria a sua primeira escolha?

	Início há MENOS de 36 horas	Início há MAIS de 36 horas
Acometimento monoarticular		
Acometimento poliarticular		

* 2. Para tratamento da crise, num paciente COM CLEARANCE DE CREATININA ≤ 60 ML/MIN, qual seria a sua primeira escolha?

	Início há MENOS de 36 horas	Início há MAIS de 36 horas
Acometimento monoarticular		
Acometimento poliarticular		

* 3. Na crise aguda de gota, num paciente em uso de medicação hipouricemiante (p. ex. alopurinol), você:

- ◯ aumenta a dose do hipouricemiante
- ◯ mantém a dose do hipouricemiante
- ◯ reduz a dose do hipouricemiante
- ◯ suspende o hipouricemiante

Tratamento da Gota no Brasil

Sobre o tratamento hipouricemiante

* 4. Quando você prescreve uma medicação hipouricemiante? Marque todas as opções que se apliquem:

- [ ] Após a 1ª crise de gota.
- [ ] Após 2 ou mais crises de gota em 1 ano.
- [ ] Quando um paciente com gota apresenta tofo.
- [ ] Quando um paciente com gota tem insuficiência renal crônica.
- [ ] Nenhuma das opções acima.

* 5. Indique o nível sérico de ácido úrico que você procura alcançar (uricemia alvo) com o tratamento hipouricemiante para um paciente COM TOFO:

- ◯ < limite superior da normalidade do laboratório
- ◯ < 6,8 mg/dL
- ◯ < 6,0 mg/dL
- ◯ < 5,0 mg/dL
- ◯ Eu não ajusto o tratamento hipouricemiante baseado num valor de uricemia específico.

Tratamento da Gota no Brasil

Sobre o tratamento hipouricemiante

* 6. Indique o nível sérico de ácido úrico que você procura alcançar (uricemia alvo) com o tratamento hipouricemiante para um paciente SEM TOFO:

- ◯ < limite superior da normalidade do laboratório
- ◯ < 6,8 mg/dL
- ◯ < 6,0 mg/dL
- ◯ < 5,0 mg/dL
- ◯ Eu não ajusto o tratamento hipouricemiante baseado num valor de uricemia específico.

* 7. Com que frequência seus pacientes conseguem alcançar a uricemia alvo com os tratamentos atuais?

◯ Sempre ◯ Quase sempre ◯ Às vezes ◯ Quase nunca ◯ Nunca

* 8. APÓS ALCANÇAR A URICEMIA ALVO, idealmente, por quanto tempo você prescreve uma medicação hipouricemiante?

	SEM tofo	COM tofo
Para um paciente com gota		

* 9. Com que frequência você verifica a uricemia de seus pacientes?

	A cada
Até alcançarem a uricemia alvo:	
Após alcançarem a uricemia alvo:	

Tratamento da Gota no Brasil

Sobre o tratamento hipouricemiante

* 10. Quantos dos seus pacientes já apresentaram reação alérgica ao alopurinol durante o seu acompanhamento?

Reação leve	
Reação grave	

* 11. Ao prescrever alopurinol, em geral, com que dose você inicia o tratamento?

Paciente com função renal normal	
Paciente com ClCr ≤ 60 mL/min	

* 12. Qual a dose máxima de alopurinol mais frequentemente prescrita por você?

Paciente com função renal normal	
Paciente com ClCr ≤ 60 mL/min	

* 13. Você prescreve BENZBROMARONA?

	Sempre	Quase sempre	Às vezes	Quase nunca	Nunca
Para pacientes com ClCr > 60 mL/min	○	○	○	○	○
Para pacientes com ClCr entre 30 e 60 mL/min	○	○	○	○	○
Para pacientes com ClCr < 30 mL/min	○	○	○	○	○
Para pacientes hipoexcretores com história de litíase renal no passado	○	○	○	○	○
Para pacientes em uso de ALOPURINOL	○	○	○	○	○

* 14. Para iniciar um agente hipouricemiante, você geralmente espera a resolução da crise aguda?

○ Sim

○ Não

Tratamento da Gota no Brasil

Sobre o tratamento hipouricemiante

* 15. Quanto tempo após a resolução da crise aguda de gota você espera?

- 1-3 semanas
- 4-6 semanas
- 7-9 semanas
- 10-12 semanas

Tratamento da Gota no Brasil

Sobre profilaxia da crise aguda de gota

* 16. Com que frequência você prescreve profilaxia para prevenir crises agudas de gota ao iniciar uma medicação hipouricemiante?

Sempre Quase sempre Às vezes Quase nunca Nunca

Tratamento da Gota no Brasil

Sobre a profilaxia da crise aguda de gota

* 17. Por quanto tempo você mantém a profilaxia?

	SEM tofo	COM tofo
Pacientes		

* 18. Que medicamento você prefere para profilaxia crônica de crise aguda de gota?

- ◯ Colchicina
- ◯ AINE

Tratamento da Gota no Brasil

Dados pessoais

* 19. Sexo:

- ◯ Feminino
- ◯ Masculino

* 20. Sobre você

	Idade	Tempo de formado	Tempo de atuação em reumatologia
Em anos			

* 21. Estado no qual trabalha:

Estado	

* 22. Em média, quantos pacientes com gota você atende por mês?

Pacientes com gota/mês	

* 23. Como caracteriza-se sua atividade na reumatologia?

- ◯ Assistencial
- ◯ Acadêmica
- ◯ Ambas

* 24. Tem residência ou especialização em reumatologia?

- ◯ Não
- ◯ Residência
- ◯ Especialização

* 25. Você participou do Congresso Brasileiro de Reumatologia de 2013 (SBR-2013)?

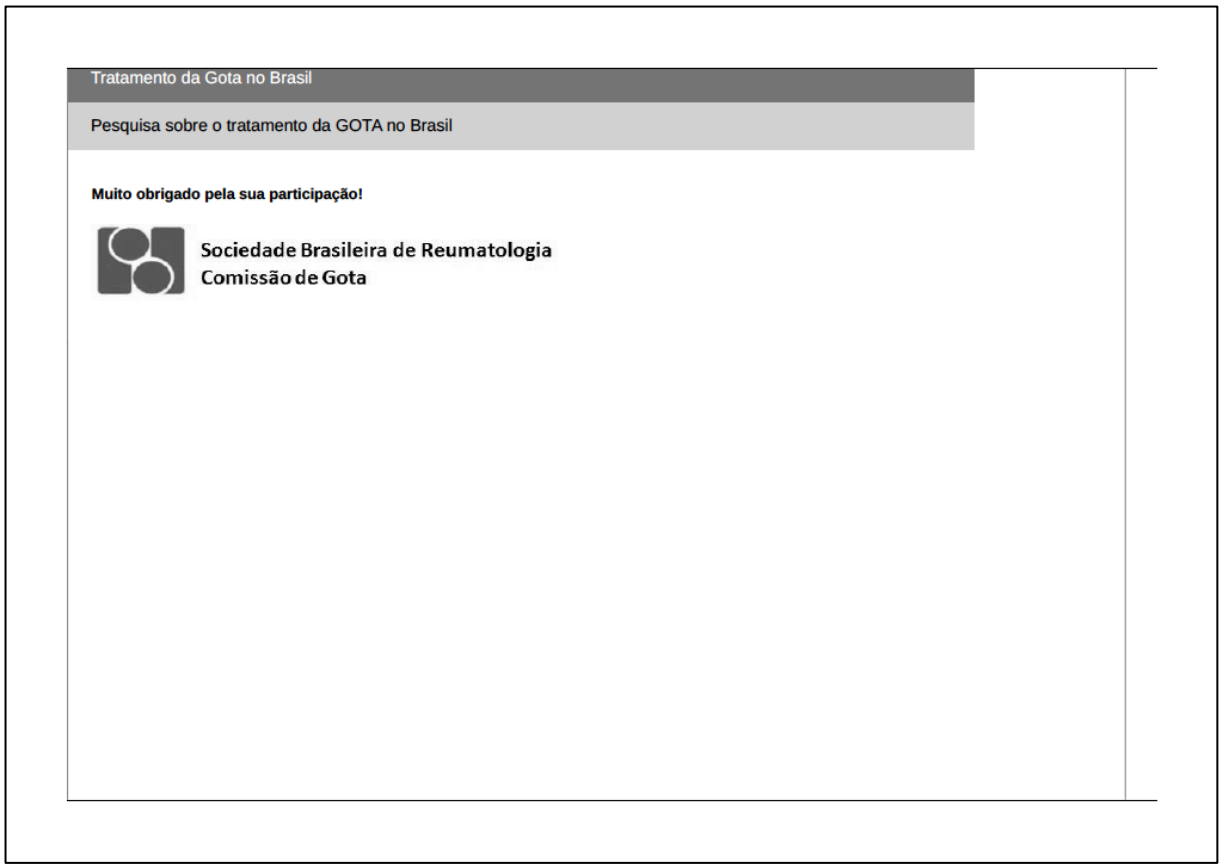
- ◯ Sim
- ◯ Não

Tratamento da Gota no Brasil

Dados pessoais

* 26. Você assistiu alguma atividade sobre gota?

- ◯ Sim
- ◯ Não


Tratamento da Gota no Brasil
Pesquisa sobre o tratamento da GOTA no Brasil
Muito obrigado pela sua participação!
Sociedade Brasileira de Reumatologia
Comissão de Gota

APÊNDICE B - Primeira versão do questionário do estudo 1

Pesquisa sobre tratamento da gota no Brasil

Por favor, escreva a percentagem do tempo numa escala de 0 – 100% (0% = nunca, 100% = sempre).

1) Com que frequência você:

a) examina o líquido sinovial em um paciente com suspeita de gota aguda sem identificação prévia de cristais?_____%

b) solicita a uricosúria de 24 horas em um paciente diagnosticado com gota?_____%

2) Qual é a sua medicação de escolha para uma crise aguda de gota nas seguintes situações? Circule todas as opções que se apliquem:

Paciente sem comorbidades	**Paciente com insuficiência renal crônica estágio 3** [*clearance* de creatinina (ClCr) entre 30 e 60 ml/min]
a) Colchicina 0,5mg/hora até resolução ou efeito colateral	a) Colchicina 0,5mg/hora até resolução ou efeito colateral
b) Colchicina em dose baixa (até 2mg/dia)	b) Colchicina em dose baixa (até 2mg/dia)
c) AINE não seletivo	c) AINE não seletivo
d) AINE seletivo COX2	d) AINE seletivo COX2
e) AINE não-seletivo + colchicina	e) AINE não-seletivo + colchicina
f) AINE seletivo COX2 + colchicina	f) AINE seletivo COX2 + colchicina
g) Corticoide VO – medicamento/dose:_____	g) Corticoide VO – medicamento/dose:_____
h) Corticoide intra-articular: ( )triancinolona ( )metilprednisolona ( )outro: _____	h) Corticoide intra-articular: ( )triancinolona ( )metilprednisolona ( )outro:_____
i) Colchicina + corticoide: ( )VO ( )IM ( )intra-articular	i) Colchicina + corticoide: ( )VO ( )IM ( )intra-articular
j) Corticoide IM: ( )betametasona ( )metilprednisolona ( ) outro:_____	j) Corticoide IM: ( )betametasona ( )metilprednisolona ( )outro:_____
k) Outro (especifique): _____	k) Outro (especifique): _____

3) Com que frequência você prescreve uma medicação hipouricemiante para os seus pacientes com gota? _____ %

4) Quando você prescreve uma medicação hipouricemiante? Circule todas as opções que se apliquem:

a) Quando um paciente tem hiperuricemia assintomática.	f) Quando o paciente tem tofo.
b) Após sua 1ª crise de gota.	g) Apenas quando um paciente tem uricemia acima de um nível específico (especifique o nível: _____mg/dl).
c) Após sua 2ª crise de gota.	
d) Após 2 crises de gota em 1 ano.	h) Quando há história atual ou passada de litíase renal.
e) Após ≥ 3 crises de gota em 1 ano.	i) Outro (especifique): _____

5) **Ao iniciar uma medicação hipouricemiante**, como se distribui a sua escolha entre alopurinol e benzbromarona?

Condição do paciente:	Alopurinol (%)	Benzbromarona (%)
• função renal normal		
• ClCr entre 30 e 60 ml/min		
• ClCr < 30ml/min		
• História atual ou passada de litíase renal		

6) Você limita a dose do alopurinol segundo o ClCr do paciente? ( )Sim ( )Não

7) Se você pretende iniciar um agente hipouricemiante para um paciente,

a. Você espera a resolução da crise aguda? ( ) Sim ( ) Não ( ) Às vezes

b. Em caso afirmativo, quanto tempo após a resolução da crise aguda de gota você esperaria para iniciar o tratamento? _____ horas ou _____ dias ou _____ meses

8) Com que frequência você prescreve **profilaxia** para prevenir crises agudas de gota ao iniciar uma medicação hipouricemiante? _____ %

a) Você prefere colchicina ou AINE? ( ) colchicina ( ) AINE

b) Por quanto tempo?

Paciente sem tofo: ___semanas ___meses ( )indefinidamente ( )até uricemia alvo

Paciente com tofo: ___semanas ___meses ( )indefinidamente ( )até uricemia alvo ( )até resolução do(s) tofo(s)

9) Você inicia **profilaxia** crônica após uma crise aguda de gota em pacientes que não estejam começando uso de uma medicação hipouricemiante? ( )Sim ( )Não

Em caso afirmativo,

a) você prefere colchicina ou AINE? ( ) colchicina ( ) AINE

b) por quanto tempo? ___semanas ___meses ( )indefinidamente

10) Na sua experiência, com que frequência você vê uma crise aguda de gota ocorrer ao iniciar uma medicação hipouricemiante? Com profilaxia: _____% e sem profilaxia _____%.(0% = nunca, 100% = sempre)

11) Por quanto tempo você prescreve uma medicação hipouricemiante? Por favor, escolha a(s) opção(ões) que melhor se aplique(m) a você.

Paciente sem tofo: ___anos ( )indefinidamente ( )até uricemia alvo

Paciente com tofo: ___anos ( )indefinidamente ( )até uricemia alvo ( )até resolução do(s) tofo(s)

12) Qual a uricemia alvo para o tratamento hipouricemiante?

Paciente sem tofo: _____ mg/dl Paciente com tofo: _____ mg/dl

13) Que percentagem dos seus pacientes consegue alcançar esta meta com os tratamentos atuais? Por favor, escreva a percentagem de pacientes numa escala de 0 - 100%. _____ %.

14) Com que frequência você checa o nível de ácido úrico?

Até alcançar a uricemia alvo: a cada _____ mês/meses. **Após alcançar a uricemia alvo**: a cada _____ mês/meses.

15) Quanto à orientação dietética, você (circule todas as opções que se apliquem):

1. restringe ( ) proíbe ( ) a ingestão de alimentos ricos em purina de origem animal (carne, miúdos e frutos do mar)
2. restringe ( ) proíbe ( ) a ingestão de alimentos ricos em purina de origem vegetal (feijão, soja, legumes, etc.)
3. restringe ( ) proíbe ( ) a ingestão de bebidas alcoólicas
4. enfatiza a importância dos aspectos nutricionais relacionadas com eventuais comorbidades?
5. estimula a ingestão de laticínios?
6. estimula a ingestão de vitamina C?
7. Outro (especifique): _____

Tempo de formado: _____ anos

Tempo de atuação em reumatologia: _____

Residência/especialização em reumatologia: ( )sim ( )não

Quantos pacientes com gota você atende por mês: _____

Atividade: assistencial / acadêmica / combinada

Estado no qual você trabalha: _____

Muito obrigado pela atenção!

ANEXO A - Comprovante de aprovação do estudo 1 pelo Comitê de Ética em Pesquisa do Hospital Universitário Pedro Ernesto/UERJ

HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO/ UNIVERSIDADE DO ESTADO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação do padrão de tratamento da artrite gotosa entre os reumatologistas no Brasil

Pesquisador: Ana Beatriz Vargas dos Santos
Área Temática:
Versão: 1
CAAE: 20338513.2.0000.5259
Instituição Proponente: Hospital Universitário Pedro Ernesto/UERJ
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 419.650
Data da Relatoria: 09/10/2013

Apresentação do Projeto:
O conhecimento sobre a gota apresentou um grande avanço na última década, com descobertas nas mais diferentes áreas. Ocorreram algumas mudanças de paradigmas, especialmente sobre a orientação dietética e o tratamento dos pacientes acometidos. Na literatura brasileira, artigos sobre gota são escassos e não sabemos como é a prática atual dos reumatologistas nesse campo. Este projeto baseia-se na aplicação de um questionário sobre as práticas reumatológicas atuais no tratamento e acompanhamento dos pacientes com gota no Brasil.

Objetivo da Pesquisa:
Objetivo Primário: Avaliar, entre os reumatologistas no Brasil, as práticas atuais no tratamento da gota.
Objetivo Secundário: Identificar os pontos críticos que devem ser abordados na divulgação dos novos conhecimentos sobre a gota entre os reumatologistas no Brasil.

Avaliação dos Riscos e Benefícios:
Riscos: Não haverá riscos para os médicos que responderem o questionário nem ocorrerá nenhuma forma de identificação dos mesmos. Os dados obtidos serão trabalhados em conjunto, e não de forma individual.
Benefícios: O levantamento de dados sobre as práticas atuais dos reumatologistas no tratamento

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Bairro: Vila Isabel **CEP:** 20.551-030
UF: RJ **Município:** RIO DE JANEIRO
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HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO/ UNIVERSIDADE DO ESTADO

Continuação do Parecer: 419.650

da gota no Brasil pode apontar os principais pontos a serem abordados na divulgação do conhecimento sobre a doença permitindo um melhor manejo desses pacientes.

Comentários e Considerações sobre a Pesquisa:

Elaboração de um questionário que avalie as principais variáveis no tratamento do paciente com gota no Brasil. Serão levados em conta aspectos relacionados às características da nossa população e aos hábitos dos médicos brasileiros, e as novas recomendações internacionais de tratamento desta enfermidade. Após a análise crítica deste instrumento pelos integrantes da Comissão de Artrites Microcristalinas da Sociedade Brasileira de Reumatologia (SBR), o mesmo será aplicado aos reumatologistas que participarão do XXX Congresso Brasileiro de Reumatologia - SBR 2013.

Considerações sobre os Termos de apresentação obrigatória:

o pesquisador solicita a ausência do TCLE ne pesquisa.

Justificativa: Trata-se de uma pesquisa com os médicos presentes no XXX Congresso Brasileiro de Reumatologia - SBR 2013 que se disponham a responder um questionário sobre suas práticas no tratamento da gota. Nenhum sujeito será identificado e todos os dados serão abordados em conjunto.

Recomendações:

Conclusões ou Pendências e Lista de Inadequações:

Prezado pesquisador, solicitamos que seja refeito a Justificativa de ausência do TCLE por conter informações equivocadas. EStá se solicitando não aplica-lo, porém no mesmo documento é citado que vai aplicar um TCLE junto com o questionario.

Situação do Parecer:

Pendente

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

O CEP/HUPE não comunica o pesquisador sobre o resultado da análise do projeto, ficando a cargo do pesquisador a responsabilidade da obtenção das avaliações. Caso o projeto esteja Pendente, o pesquisador deverá responder (em até 60 dias) as pendências, a contar da data do Parecer Consubstanciado. Os pesquisadores que não atenderem os prazos estabelecidos terão seus projetos arquivados, devendo ser submetidos novamente para avaliação.

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HOSPITAL UNIVERSITÁRIO
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Continuação do Parecer: 419.650

RIO DE JANEIRO, 09 de Outubro de 2013

Assinador por:
WILLE OIGMAN
(Coordenador)

Endereço: Avenida 28 de Setembro 77 - Térreo
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HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO/ UNIVERSIDADE DO ESTADO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação do padrão de tratamento da artrite gotosa entre os reumatologistas no Brasil

Pesquisador: Ana Beatriz Vargas dos Santos
Área Temática:
Versão: 2
CAAE: 20338513.2.0000.5259
Instituição Proponente: Hospital Universitário Pedro Ernesto/UERJ
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 431.785
Data da Relatoria: 22/10/2013

Apresentação do Projeto:
O conhecimento sobre a gota apresentou um grande avanço na última década, com descobertas nas mais diferentes áreas. Ocorreram algumas mudanças de paradigmas, especialmente sobre a orientação dietética e o tratamento dos pacientes acometidos. Na literatura brasileira, artigos sobre gota são escassos e não sabemos como é a prática atual dos reumatologistas nesse campo. Este projeto baseia-se na aplicação de um questionário sobre as práticas reumatológicas atuais no tratamento e acompanhamento dos pacientes com gota no Brasil.

Objetivo da Pesquisa:
Objetivo Primário: Avaliar, entre os reumatologistas no Brasil, as práticas atuais no tratamento da gota. Objetivo Secundário: Identificar os pontos críticos que devem ser abordados na divulgação dos novos conhecimentos sobre a gota entre os reumatologistas no Brasil.

Avaliação dos Riscos e Benefícios:
Riscos: Não haverá riscos para os médicos que responderem o questionário nem ocorrerá nenhuma forma de identificação dos mesmos. Os dados obtidos serão trabalhados em conjunto, e não de forma individual. Benefícios: O levantamento de dados sobre as práticas atuais dos reumatologistas no tratamento da gota no Brasil pode apontar os principais pontos a serem abordados na divulgação do conhecimento sobre a doença permitindo um melhor manejo desses

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HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO/ UNIVERSIDADE DO ESTADO

Continuação do Parecer: 431.785

pacientes.

Comentários e Considerações sobre a Pesquisa:

Elaboração de um questionário que avalie as principais variáveis no tratamento do paciente com gota no Brasil. Serão levados em conta aspectos relacionados às características da nossa população e aos hábitos dos médicos brasileiros, e as novas recomendações internacionais de tratamento desta enfermidade. Após a análise crítica deste instrumento pelos integrantes da Comissão de Artrites Microcristalinas da Sociedade Brasileira de Reumatologia (SBR), o mesmo será aplicado aos reumatologistas que participarão do XXX Congresso Brasileiro de Reumatologia - SBR 2013.

Considerações sobre os Termos de apresentação obrigatória:

o pesquisador solicita a ausência do TCLE ne pesquisa. Justificativa: Trata-se de uma pesquisa com os médicos presentes no XXX Congresso Brasileiro de Reumatologia - SBR 2013 que se disponham a responder um questionário sobre suas práticas no tratamento da gota. Nenhum sujeito será identificado e todos os dados serão abordados em conjunto.

Recomendações:

Conclusões ou Pendências e Lista de Inadequações:

A pesquisadora atendeu a solicitação do parecer anterior. projeto aprovado.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

1. Comunicar toda e qualquer alteração do projeto e termo de consentimento livre e esclarecido. Nestas circunstâncias a inclusão de pacientes deve ser temporariamente interrompida até a resposta do Comitê, após análise das mudanças propostas. 2. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes. 3. O Comitê de Ética solicita a V. Sª., que ao término da pesquisa encaminhe a esta comissão um sumário dos resultados do projeto.

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Continuação do Parecer: 431.785

RIO DE JANEIRO, 22 de Outubro de 2013

Assinador por:
WILLE OIGMAN
(Coordenador)

Endereço: Avenida 28 de Setembro 77 - Térreo
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HOSPITAL UNIVERSITÁRIO
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PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação do padrão de tratamento da artrite gotosa entre os reumatologistas no Brasil

Pesquisador: Ana Beatriz Vargas dos Santos
Área Temática:
Versão: 3
CAAE: 20338513.2.0000.5259
Instituição Proponente: Hospital Universitário Pedro Ernesto/UERJ
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 500.040
Data da Relatoria: 13/12/2013

Apresentação do Projeto:
=Emenda para alteração de informações do Protocolo

Objetivo da Pesquisa:
=Emenda para alteração de informações do Protocolo

Avaliação dos Riscos e Benefícios:
=Emenda para alteração de informações do Protocolo

Comentários e Considerações sobre a Pesquisa:
A pesquisadora solicita para avaliação as seguintes modificações ao projeto:
mudança do questionário impresso para o questionário online e avaliação de uma amostra aleatória ao invés de uma amostra de conveniência.

Considerações sobre os Termos de apresentação obrigatória:
Sem alterações na documentação.

Recomendações:

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HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO/ UNIVERSIDADE DO ESTADO

Continuação do Parecer: 500.040

Conclusões ou Pendências e Lista de Inadequações:

após análise, o CEP/HUPE aprovou as mudanças sobre o projeto relatadas pela pesquisadora.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

1. Comunicar toda e qualquer alteração do projeto e termo de consentimento livre e esclarecido. Nestas circunstâncias a inclusão de pacientes deve ser temporariamente interrompida até a resposta do Comitê, após análise das mudanças propostas. 2. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes. 3. O Comitê de Ética solicita a V. Sª., que ao término da pesquisa encaminhe a esta comissão um sumário dos resultados do projeto.

RIO DE JANEIRO, 18 de Dezembro de 2013

Assinador por:
ANTONIO FELIPE SANJULIANI
(Coordenador)

Endereço: Avenida 28 de Setembro 77 - Térreo
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ANEXO B - Comprovante de aceite do artigo 3

From: <jamainternalmed@msubmit.net>
Date: July 15, 2018 at 21:09:38 EDT
To: <tneogi@bu.edu>
Subject: IMD18-0981R1 Decision Letter
Reply-To: <jamainternalmed@jamanetwork.org>

July 15, 2018

Dr Tuhina Neogi
Boston University School of Medicine
Clinical Epidemiology Research & Training Unit
650 Albany St.
Suite X-200
Boston, MA 02118

RE: Risk of Developing Chronic Kidney Disease with Allopurinol Use in Gout

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