5-16-2022

# Urate-Lowering Therapy for Patients with Gout on Hemodialysis

Reem Alkilany
*Case Western Reserve University*

Douglas Einstadter
*Case Western Reserve University*, douglas.einstadter@case.edu

Maria Antonelli
*Case Western Reserve University*, maria.antonelli@case.edu

Author(s) ORCID Identifier: Reem Alkilany



Recommended Citation
Alkilany R, Einstadter D, Antonelli M. Urate-lowering therapy for patients with gout on hemodialysis. *Int J Rheum Dis.* 2022;25:769–774. doi: 10.1111/1756-185X.14334

Received: 10 March 2022 | Revised: 19 April 2022 | Accepted: 29 April 2022

DOI: 10.1111/1756-185X.14334

International Journal of Rheumatic Diseases WILEY

ORIGINAL ARTICLE

# Urate-lowering therapy for patients with gout on hemodialysis

Reem Alkilany[1] | Douglas Einstadter[2] | Maria Antonelli[1]

[1]Department of Medicine, Division of Rheumatology, MetroHealth Medical Center/Case Western Reserve University, Cleveland, Ohio, USA

[2]Center for Health Care Research and Policy, and Department of Internal Medicine, MetroHealth Medical Center/Case Western Reserve University, Cleveland, Ohio, USA

**Correspondence**
Reem Alkilany, Department of Medicine, Division of Rheumatology, MetroHealth Medical Center/Case Western Reserve University, 2500 MetroHealth Dr, Cleveland, OH 44109, Haman building, 5th floor, USA.
Email: r_alkilany@hotmail.com

## Abstract

**Objective:** Gout is the most common form of inflammatory arthritis and is caused by deposition of monosodium urate crystals resulting from a high burden of uric acid (UA). High UA burden also has been associated with increased morbidity and mortality in the general population and progression to chronic kidney disease. In persons with gout and end-stage renal disease (ESRD), prior studies suggest that UA levels decrease after initiation of hemodialysis (HD). We evaluated UA level and the use of urate-lowering therapies (ULTs) in patients with gout and ESRD on HD.

**Methods:** We performed a retrospective review of patients with gout and ESRD seen at a large urban public hospital (The MetroHealth System). We extracted data from the medical record (Epic) for patients diagnosed with gout and ESRD on HD. The main outcomes were the UA level and the use of ULTs before and after HD initiation.

**Results:** We identified 131 patients with gout on HD. Of these, 21 patients had crystal proven gout diagnosis, 10 of whom had data on UA level pre-HD and post-HD and were included in the analysis. For the total sample (N = 21), the mean age was 65 years, 7 were female and 20 were African American. Mean pre-HD and post-HD UA levels were 8.4 and 3.98 mg/dL respectively. Twenty-one patients were receiving ULT pre-HD, 11 discontinued post-HD.

**Conclusion:** Among patients with gout and ESRD, we observed a decrease in UA level associated with initiation of HD. For this group, discontinuation of ULTs may be appropriate.

KEYWORDS
end-stage renal disease on hemodialysis, gout arthritis, urate-lowering therapy

## 1 | INTRODUCTION

Gout is an inflammatory arthritis provoked by monosodium urate crystals (MSU) in joints and surrounding soft tissue.[1] It is associated with high serum uric acid (UA), defined as a level greater than 6.8 or 7.0 mg/dL.[2] In the USA, the prevalence of gout is estimated at 3.9% of adults (~8.3 million people) making it one of the most common inflammatory rheumatic diseases of adulthood.[2]

High serum UA levels have been linked to the development of new-onset chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the general population.[3] In patients on hemodialysis (HD) some studies have shown that increased serum UA levels are predictive of cardiovascular disease.[4,5] However, other studies have demonstrated that hyperuricemia in patients on HD has cardioprotective and mortality protective effects.[3,6] This is possibly due to the higher oxidative stress in ESRD patients compared to those with

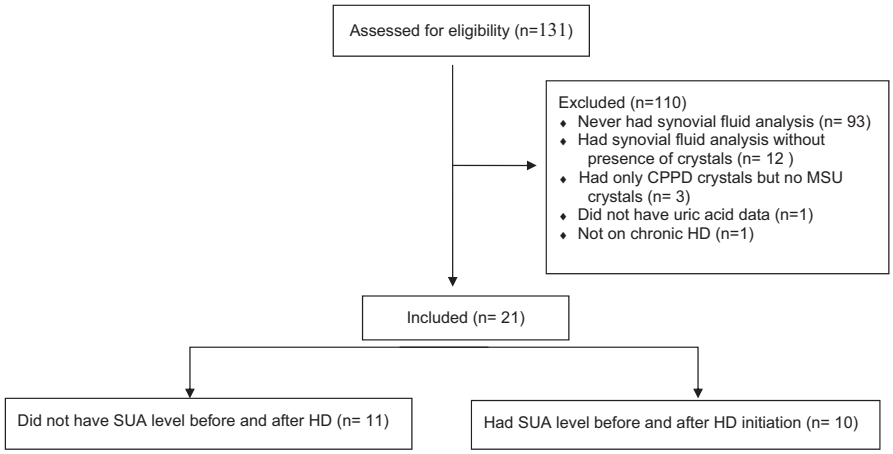


**FIGURE 1** Consolidated Standards of Reporting Trials flow diagram. CPPD, calcium pyrophosphate crystals; HD, hemodialysis; MSU, monosodium urate crystals; SUA, serum uric acid

preserved renal function and the antioxidant effect of UA which is responsible for more than half of the antioxidant capacity of blood.[3]

According to the American College of Rheumatology (ACR) 2020 gout management guidelines, pharmacologic urate-lowering therapy (ULT) is recommended for patients with CKD stages 2-5, or ESRD with prior gout attacks and current hyperuricemia.[2] A treat-to-target approach is recommended by the European League Against Rheumatism (EULAR) with the goal to maintain serum UA levels at <6 mg/dL (360 μmol/L) and <5 mg/dL (300 μmol/L) in those with severe gout.[7] The EULAR recommendation includes both patients with preserved renal function as well as those with ESRD.

Studies have shown that in patients with ESRD, hemodialysis reduces gout attacks[4,8] and significantly reduces uric acid levels by almost 60% without additional ULT.[4,9] Studies also suggest that the duration of HD enhances the serum UA lowering effect. These data suggest that serum UA levels trend lower with increased time on HD. Therefore, we decided to investigate UA levels in patients with ESRD on HD and to evaluate whether patients on HD continue to require ULT.

## 2 | MATERIALS AND METHODS

### 2.1 | Inclusion and exclusion criteria

We performed an observational, retrospective cohort study at a large urban public hospital system. We obtained MetroHealth Medical Center institutional review board (IRB) approval (IRB20-00014).

Searching the Epic electronic medical record we identified all patients with an office visit between 1 January, 2018 and 1 January, 2020 who had a diagnosis of ESRD on HD (International Classification of Diseases 10 [ICD 10] codes N18.6, Z99.2) and gout (ICD10 codes M10-M10.09, M1A-M1A.9XX1, M10.9) on their problem list. We then manually reviewed the charts of all identified patients to verify the diagnoses and to identify those with a serum UA level recorded between 2000 and 2020. The initial search yielded 131 patients. We excluded patients without documented synovial fluid analysis or synovial fluid analysis without documented MSU crystals present. We also excluded patients who received HD for a short period for a specific indication and patients undergoing peritoneal dialysis. After exclusion of patients with missing data, the final sample consisted of 21 patients with ESRD on HD and at least 1 analysis of synovial fluid demonstrating presence of MSU crystals.

### 2.2 | Patient and public involvement

No patients were involved.

### 2.3 | Data collection

We collected baseline demographic and clinical data, including age, gender, race/ethnicity, HD start date, up to 4 serum UA levels, synovial fluid analyses for presence or absence of MSU crystals or other crystals, presence or absence of tophi, presence or absence of rheumatoid arthritis on the problem list, and any results for anti-cyclic citrullinated peptide (CCP) antibodies and rheumatoid factor (RF). We also identified all prescriptions for allopurinol, colchicine, pegloticase, and febuxostat.

The main study outcome was serum UA levels before and after initiation of HD and the use of ULT. The secondary outcome was racial and demographic disparities in our sample.

### 2.4 | Statistical analysis

This was a retrospective observational study. We report patient characteristics and outcomes as counts (%) for categorical variables and means (SD) for continuous variables. We calculated the mean UA level and 95% CI using a single-sample *t* test. We compared the serum UA level pre- and post-initiation of HD using a paired *t* test. We report the results as the mean difference with 95% CI.

## 3 | RESULTS

The initial search yielded 131 patients. After individually reviewing each chart to confirm the HD status and gout diagnosis

**TABLE 1** Detailed data for the total sample

| ID | Age | Gender | Race | HD | PD | NOE | MSU | CPPD | TOPHI | UACID | Losartan | Statin | RA | RF | CCP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 72.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 4.70 | 0 | 0 | 0 | 0 | 0 |
| 2 | 68.00 | Female | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 9.0 | 0 | 1 | 0 | 0 | 0 |
| 3 | 87.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 7.3 | 0 | 0 | 0 | 0 | 0 |
| 4 | 72.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 1 | 1.6 | 0 | 1 | 0 | 0 | 0 |
| 5 | 48.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 9.9 | 0 | 0 | 0 | 0 | 0 |
| 6 | 47.00 | Female | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 3.1 | 0 | 1 | 0 | 0 | 0 |
| 7 | 43.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 11.1 | 0 | 0 | 0 | 0 | 0 |
| 8 | 83.00 | Female | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 3.5 | 0 | 0 | 0 | 0 | 0 |
| 9 | 63.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 5.2 | 0 | 0 | 0 | 0 | 0 |
| 10 | 60.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 7.4 | 0 | 0 | 0 | 0 | 0 |
| 11 | 70.00 | Female | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 3.1 | 0 | 0 | 0 | 0 | 0 |
| 12 | 58.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 7.9 | 0 | 0 | 0 | 0 | 0 |
| 13 | 71.00 | Female | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 10.7 | 0 | 0 | 0 | 0 | 0 |
| 14 | 67.00 | Male | White | 1 | 0 | 0 | 1 | 0 | 0 | 4.3 | 0 | 1 | 0 | 0 | 0 |
| 15 | 84.00 | Female | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 5.9 | 0 | 0 | 0 | 0 | 0 |
| 16 | 78.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 1 | 0 | 5.8 | 0 | 1 | 0 | 0 | 0 |
| 17 | 45.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 4.4 | 0 | 1 | 0 | 0 | 0 |
| 18 | 53.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 6.6 | 0 | 0 | 0 | 0 | 0 |
| 19 | 69.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 8.6 | 0 | 0 | 0 | 0 | 0 |

(Continues)

TABLE 1 (Continued)

| ID | Age | Gender | Race | HD | PD | NOE | MSU | CPPD | TOPHI | UACID | Losartan | Statin | RA | RF | CCP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | 75.00 | Female | Black/African American | 1 | 0 | 0 | 1 | 0 | 1 | 3.3 | 0 | 0 | 1 | 1 | 0 |
| 21 | 44.00 | Male | Black/African American | 1 | 0 | 0 | 1 | 0 | 0 | 3.7 | 0 | 0 | 0 | 0 | 0 |
| Total | n/a | n/a | n/a | 21 | 0 | 0 | 21 | 1 | 2 | | 0 | 5 | 1 | 1 | 0 |
| Mean | 64.62 | | | | | | | | | | | | | | |

*Note*: General data for the total sample as explained in the text.

Abbreviations: CCP, anti-cyclic citrullinated peptide antibody; CPPD, calcium pyrophosphate crystals; HD, hemodialysis; MSU, monosodium urate crystals; NOE, not otherwise specified; PD, peritoneal dialysis; RA, rheumatoid arthritis; RF, rheumatoid factor; UACID, most recent uric acid level.

(defined by the presence of UA crystals in synovial fluid analysis), 22 patients were on HD and had a synovial fluid analysis demonstrating UA crystals. One patient had both MSU and calcium pyrophosphate crystals and 1 patient did not have any documented UA level. After exclusion of patients with missing data, the final sample consisted of 21 patients with ESRD on HD and at least 1 analysis of synovial fluid demonstrating presence of MSU crystals (Figure 1).

For the total of 21 patients, the mean age was 65 years, 7 were female, 14 were male, 20 African American and 1 White. Two patients had tophi documented on physical exam, 1 had rheumatoid arthritis with elevated RF. Allopurinol was prescribed to 19 patients pre-HD and was continued in 7/19 patients after they started HD; allopurinol was discontinued before HD initiation in 3/19 patients, within 1 year from HD initiation in 7/19 patients, and within 10 years from HD initiation in 2/19 patients. One patient was on febuxostat and one was on pegloticase, both were discontinued after initiation of HD. No one was on losartan and only 5/21 patients were placed on statin (Table 1).

From the total sample, 10 patients had an available serum UA level measured before and after initiation of HD; 8 were within 1 year of HD initiation, 1 within 3 years and 1 within 4 years of HD initiation (Table 2). Among those 10 patients, the mean age was 64 (SD 15), 4 were female and all were African American. The mean UA level before initiating HD was 8.43 mg/dL (95% CI 6.6-10.2) and the median was 8.2. The mean post-HD UA level was 3.98 mg/dL (95% CI 2.94-5.02) and median of 3.60 after HD was started (Table 1). Our analysis showed a statistically significant and clinically meaningful difference in UA before and after HD initiation, the mean UA difference (post-HD – pre-HD) was −4.45 mg/dL, (95% CI −6.49 to −2.41), $P = .008$.

## 4 | DISCUSSION

Hyperuricemia has been associated with adverse cardiovascular outcomes and increased morbidity and mortality in the general population.[10] However, in patients on HD, data on the effect of hyperuricemia have been controversial.[11] In patients on chronic HD, some studies including large retrospective studies have not shown an association between high serum UA level and cardiovascular mortality. Some have even shown an increased risk of all-cause mortality and cardiovascular mortality with lower serum UA and lower risk with elevated serum UA levels.[6,12-14] A 2-year prospective observational study of 261 hemodialysis patients from Tel Aviv University showed that lower serum UA is an independent risk factor for all-cause and cardiovascular mortality as well as future cardiovascular disease; for each 1 mg/dL increase in baseline serum UA, the hazard ratio of all-cause and cardiovascular death was 0.55 (95% CI 0.43-0.72 and 0.43-0.72 respectively).[17] Recently, Zawada et al showed a U-shaped pattern between serum UA and all-cause mortality with lowest risk at serum UA levels of 6.5 mg/dL (387 μmol/L).[15] In the chronic HD patient population, there is a paradoxical epidemiology

**TABLE 2** UA levels before and after HD initiation

| ID | Age | Gender | Race | Tophi | UA post-HD | UA pre-HD |
|---|---|---|---|---|---|---|
| 1 | 72 | Male | Black/African American | 0 | 4.7 | 9.5 |
| 2 | 72 | Male | Black/African American | 1 | 1.6 | 11 |
| 3 | 47 | Female | Black/African American | 0 | 3.1 | 8.5 |
| 4 | 83 | Female | Black/African American | 0 | 3.5 | 4.4 |
| 5 | 70 | Female | Black/African American | 0 | 3.1 | 6.7 |
| 6 | 78 | Male | Black/African American | 0 | 5.8 | 9.1 |
| 7 | 45 | Male | Black/African American | 0 | 4.4 | 13.2 |
| 8 | 53 | Male | Black/African American | 0 | 6.6 | 7.9 |
| 9 | 75 | Female | Black/African American | 1 | 3.3 | 7.9 |
| 10 | 44 | Male | Black/African American | 0 | 3.7 | 6.1 |
| Median | | | | | 3.60 | 8.2 |
| Mean | 64 | | | | 3.98 | 8.43 |
| SD | 15 | | | | | |
| 95% CI | | | | | 2.94-5.02 | 6.6-10.2 |

*Note:* Data for uric acid level before and after HD initiation.

Abbreviations: CI, confidence Interval; HD, hemodialysis; UA, uric acid.

phenomenon where lower blood pressure, lower body mass index and lower serum low-density lipoprotein are correlated with unfavorable outcome, this suggests that there probably are other non-traditional cardiovascular risk factors and outcomes in this patient population.[11,18]

Gout is experienced in almost 20% of patients with CKD stage 3, compared to 5% of those with normal kidney function.[16] In a large analysis of 601 patients from 5 outpatient dialysis centers in Germany, investigators noted that the incidence of gout flares in patients on HD was only 3.6%, and hyperuricemia increased the risk by 17%.[11] However, another study by Yeo et al evaluated 216 patients on dialysis (HD and peritoneal dialysis), almost 25% of whom experienced gout, suggesting that HD alone is insufficient to achieve target UA mandating ULT and treat-to-target approach in this patient population.[16] Our results suggest that initiation of HD is associated with a decrease in UA levels in ESRD patients. Compared to current guideline recommendations to continue ULT, our results found that over 50% of patients on allopurinol at the start of HD had the medication stopped after they started HD. Patients on other ULT (eg, febuxostat or pegloticase) also had their medication stopped after initiation of HD.

We found poor monitoring of gout in our study patients, specifically a lack of serum UA monitoring after initiation of HD and continuation of the same dose of allopurinol contrary to recommended dosage post-HD.[10,19] In addition, we noticed that the diagnosis of gout often occurred without evidence of synovial fluid analysis. It is possible that gout flares continued despite a lower serum UA level post-dialysis. However, as we did not collect data on the frequency or severity of gout flares, we are not able to assess this hypothesis. Furthermore, some studies suggest that hyperuricemia has a cardioprotective effect in patients on HD, contrary to the general population, raising some concerns that very low UA levels may be harmful.[3,17]

One notable finding was the African American predominance in our sample (95%). While this may be unique to the patient population at our institution, other studies have suggested that African Americans tend to have higher prevalence of gout (5% compared to 4% Caucasians).[11,20] Future studies are necessary to confirm our results at other institutions.

Our study has some limitations that should be recognized. Our data come from a single site, which may affect generalizability. The sample size is small, and not all subjects had pre- and post-HD serum UA levels available. We did not collect information on gout symptoms, and we are not able to comment on the effect of serum UA levels or urate-lowering treatment on symptom burden. Our inclusion criteria may have missed some eligible subjects and we did not include patients with ESRD on peritoneal dialysis.

## 5 | CONCLUSION

Despite the study limitations, our data suggest that the management of gout in patients with ESRD and on dialysis requires further study. There is a need for improved monitoring of UA levels and assessment of the need for ULT among patients with gout and ESRD on hemodialysis. Because HD-treated patients often have multiple comorbidities, ULT contributes to polypharmacy and may influence drug interactions. Also, it highlights racial disparities with markedly increased gout risk in African American patients on HD. Further research on this topic may help to inform updated guidelines specifically for ULT in patients on dialysis. Improved collaboration between primary care providers, rheumatologists and nephrologists can help to ensure proper monitoring of these patients and to weigh the risk and benefits of continued ULT based on the serum UA level.

### AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript.

### ACKNOWLEDGEMENTS

We would like to acknowledge Dr Stanley Ballou, MD and Dr Nora Singer, MD for their valuable input and support.

### CONFLICT OF INTEREST

No conflict of interest.

### ETHICS APPROVAL

MetroHealth Medical Center IRB approval IRB20-00014.

### ORCID

*Reem Alkilany* https://orcid.org/0000-0001-5589-9760

### REFERENCES

1. Martillo MA, Nazzal L, Crittendon DB. The crystallization of monosodium urate. *Curr Rheumatol Rep*. 2014;16(2):400.
2. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American college of rheumatology guideline for the management of gout. *Arthritis Care Res (Hoboken)*. 2020;72(6):744-760. doi:10.1002/acr.24180
3. Bae E, Cho HJ, Shin N, et al. Lower serum uric acid level predicts mortality in dialysis patients [published correction appears in Medicine (Baltimore). 2016 Aug 07;95(31):e5074]. *Medicine (Baltimore)*. 2016;95(24):e3701.
4. Doualla M, Nkeck JR, Halle MP, et al. Assessment of the efficacy of hemodialysis on uric acid clearance in a sub-Saharan African population at the end stage kidney disease. *BMC Nephrol*. 2020;21:378.
5. Dousdampanis P, Trigka K, Musso CG, et al. Hyperuricemia and chronic kidney disease: an enigma yet to be solved. *Ren Fail*. 2014;36(9):1351-1359.
6. Li M, Ye ZC, Li CM, et al. Low serum uric acid levels increase the risk of all-cause death and cardiovascular death in hemodialysis patients. *Ren Fail*. 2020;42(1):315-322.
7. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017;76:29-42.
8. Eleftheriadis T, Golphinopoulos S, Pissas G, Stefanidis I. Asymptomatic hyperuricemia and chronic kidney disease: Narrative review of a treatment controversial. *J Adv Res*. 2017;8(5):555-560.
9. Alaraj M, AlTamimi N, Rayyan W, et al. Role of age and uric acid levels on dialysis efficacy among end stage renal disease patients in Saudi Arabia. *J Res Med Dent Sci*. 2017;4(2):92-96.
10. Singh JA. Gout and comorbidity: a nominal group study of people with gout. *Arthritis Res Ther*. 2017;19(1):204.
11. Rohn B, Jansing W, Seibert FS, et al. Association of hyperuricemia and serum uric acid lowering therapy with mortality in hemodialysis patients. *Ren Fail*. 2020;42(1):1067-1075.
12. Latif W, Karaboyas A, Tong L, et al. Uric acid levels and all-cause and cardiovascular mortality in the hemodialysis population. *Clin J Am Soc Nephrol*. 2011;6(10):2470-2477.
13. Park C, Obi Y, Streja E, et al. Serum uric acid, protein intake and mortality in hemodialysis patients. *Nephrol Dial Transplant*. 2017;32(10):1750-1757.
14. Kim CS, Jin DC, Yun YC, Bae EH, Ma SK, Kim SW. Relationship between serum uric acid and mortality among hemodialysis patients: Retrospective analysis of Korean end-stage renal disease registry data. *Kidney Res Clin Pract*. 2017;36(4):368-376.
15. Zawada AM, Carrero JJ, Wolf M, et al. Serum uric acid and mortality risk among hemodialysis patients. *Kidney Int Rep*. 2020;5(8):1196-1206.
16. Yeo E, Palmer SC, Chapman PT, Frampton C, Stamp LK. Serum urate levels and therapy in adults treated with long-term dialysis: a retrospective cross-sectional study. *Intern Med J*. 2019;49(7):838-842.
17. Beberashvili I, Sinuani I, Azar A, et al. Serum uric acid as a clinically useful nutritional marker and predictor of outcome in maintenance hemodialysis patients. *Nutrition*. 2015;31(1):138-147.
18. Nurmohamed SA, Nubé MJ. Reverse epidemiology: paradoxical observations in haemodialysis patients. *Neth J Med*. 2005;63(10):376-381.
19. Vargas-Santos AB, Neogi T. Management of gout and hyperuricemia in CKD. *Am J Kidney Dis*. 2017;70(3):422-439.
20. Singh JA. The impact of gout on patient's lives: a study of African-American and Caucasian men and women with gout. *Arthritis Res Ther*. 2014;16(3):R132.

**How to cite this article:** Alkilany R, Einstadter D, Antonelli M. Urate-lowering therapy for patients with gout on hemodialysis. *Int J Rheum Dis*. 2022;25:769–774. doi:10.1111/1756-185X.14334