Sociedad Española de Reumatología

GuipClinGot
Sociedad Española de Reumatología

CLINICAL PRACTICE GUIDELINES FOR MANAGEMENT OF GOUT

área científica MENARINI

www.formacionsanitaria.com

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TABLE OF CONTENTS

ABBREVIATIONS **8**

I. GENERAL DOCUMENT INFORMATION **10**

I.A. COOPERATING BODIES 10
I.A.1. GuipClinGot Group *10*
I.A.2. Coordinators *10*
I.A.3. Panelists *10*
I.A.4. Reviewers *13*
I.B. FUNDING 14
I.C. HOW TO USE THE CPG 15

II. METHODOLOGY **15**

II.A. PANELS INVOLVED IN THE DEVELOPMENT OF THE GUIDELINES 16
II.A.1. The panel of experts *16*
II.A.2. The panel of reviewers *17*
II.B. ESTABLISHMENT OF DEFINITIONS, SCOPE AND TASKS 17
II.C. PREPARING THE FIRST DRAFT 17
II.D. DEVELOPMENT OF SYSTEMATIC REVIEWS 17
II.E. DIFFUSION OF GUIPCLINGOT 21

III. PURPOSE, SCOPE AND USERS **21**

IV. CONCEPT AND DEFINITION **23**

IV.A. GOUT 23
IV.B. HYPERURICAEMIA 23
IV.C. PATHOGENIC CLASSIFICATION OF HYPERURICAEMIA AND GOUT 24

V. EPIDEMIOLOGY OF GOUT **26**

V.1. PREVALENCE AND INCIDENCE 26
V.2. IMPACT 26
V.3. RISK FACTORS 26
V.4. COMORBIDITIES 27

VI. DIAGNOSIS **27**

VI.A. CLINICAL DIAGNOSIS 27
VI.A.1. Gold standard *28*
VI.B. CLASSIFICATION CRITERIA 30
VI.C. IMAGING TECHNIQUES 33
VI.C.1. PLAIN X-RAYS 34
Joint space reduction: 0-4 ..... *37*
VI.C.2. Computed tomography and dual-energy computed tomography *37*
VI.C.3. Magnetic Resonance Imaging *38*
VI.C.4. Ultrasound *39*

VII. ASSESSMENT **44**

VII.A. GENERAL ASSESSMENT 44
VII.B. SPECIFIC ASSESSMENT 45

IDENTIFICATION SHEET: **47**

- **DATE OF BIRTH (AGE): _____** **47**

VII.C. LABORATORY TESTS 54
VII.C.1 . Episodes of acute inflammation *54*
VII.C.2. Intercritical period: first assessment after an acute episode *55*
VII.C.3. Intercritical Period: successive controls *58*

VIII. GOUT AND KIDNEY FAILURE 62

VIII.A. INTRODUCTION 62
VIII.B. TREATMENT OF ACUTE ATTACKS 64
VIII.B.1. Non-steroidal anti-inflammatories 64
VIII.B.2. Colchicine 64
VIII.B.3. Corticosteroids 65
VIII.B.4. Corticotropin (ACTH) 66
VIII.B.5. Interleukin-1 antagonists 66
VIII.C. PROPHYLAXIS FOR RECURRENCE OF ACUTE INFLAMMATION ATTACK 66
VIII.D. URATE-LOWERING MEASURES 68
VIII.E. DIET 68
VIII.F. URICOSURIC AGENTS 68
VIII.G. EXOGENOUS URICASES 70
VIII.H. ALLOPURINOL 70
VIII.I. FEBUXOSTAT 72
VIII.J. DIALYSIS 72
VIII.J.1. Fundamentals 73
VIII.J.2. Types 73
VIII.J.3. Incidence of gout in dialysis patients 74
VIII.J.4. Treatment of acute inflammation episodes 75
VIII.J.5. Prophylaxis of recurrent episodes of acute inflammation 76
VIII.J.6. Urate-lowering treatment 77
VIII.K. KIDNEY TRANSPLANT 78
VIII.K.1. Immunosuppressive drugs 79
VIII.K.2. Treatment of acute inflammation episodes 79
VIII.K.3. Prophylaxis of recurrent episodes of acute inflammation 80
VIII.K.4. Urate-lowering treatment 81

IX. SPECIAL CONSIDERATIONS 82

IX.A. THE NURSING PERSPECTIVE 82
IX.A.1. Patient education plan 83
IX.B. THE PATIENT'S PERSPECTIVE 86
IX.B.1. Recommendations for patients 86

X. MANAGEMENT IN PRIMARY CARE. REFERRAL CRITERIA 88

X.A. DIAGNOSIS IN PRIMARY CARE 88
X.B. GENERAL RECOMMENDATIONS IN PRIMARY CARE 90
X.B.1. Acute attack 90
IX.B.2. Evaluation and management of comorbidities 91
IX.B.3. Criteria for referral to specialized care 93

XI. TREATMENT 95

XI.A. NON-DRUG TREATMENT 95
XI.A.1. Diet 95
XI.A.2. Alcohol 97
XI.A.3. Obesity 97
XI.A.4. Exercise 97
XI.A.5. Smoking 98
XI.A.6. Education 98
XI.A.7. Dietary Supplements 98
XI.B. INDICATIONS OF DRUG TREATMENT 99
XI.C. DRUGS FOR GOUT: SUMMARY OF PRODUCT CHARACTERISTICS, INTERACTIONS AND ALLERGIES 100
XI.C.1. Summary of product characteristics and interactions 100
XI.C.2. Allergies 107
XI.D. URATE-LOWERING TREATMENT 109

XI.D.1. Allopurinol *110*
XI.D.2. Febuxostat *111*
XI.D.3. Benzbromarone *111*
XI.D.4. Indication of urate-lowering treatment and monitoring *112*
XI.E. PREVENTION OF ACUTE ATTACKS *114*
XI.F. TREATMENT OF ACUTE EPISODES 116
XI.F.1. NSAIDs *116*
XI.F.2. COXIB *117*
XI.F.3. Corticosteroids *118*
XI.F.4. ACTH *120*
XI.F.5. Colchicine *120*
XI.G. COMBINATION THERAPY 123
XI.G.1. Combination of enzyme inhibitors *123*
XI.G.2. Adding a uricosuric agent to a xanthine oxidase inhibitor *123*
XI.H. OFF-LABEL TREATMENTS OR TREATMENTS IN ADVANCED CLINICAL DEVELOPMENT 125
XI.H.1. Acute episodes of inflammation *125*
XI.H.2. Prevention of acute inflammation episodes *126*

XII. IMAGING TESTS FOR MONITORING TREATMENT RESPONSE 130

XII.A. IMAGING TESTS *130*
XII.B. ULTRASOUND *131*
XII.B.1. Assessment of therapeutic response *132*

REFERENCES 137

LIST OF TABLES

Table 1. Systematic reviews conducted. 18
Table 2. Levels of evidence of the Oxford Centre of Evidence-Based Medicine (2001)..... 19
Table 3. Pathogenic mechanisms of gout. 25
Table 4. Risk factors for gout. 27
Table 5. Misidentification of monosodium urate crystals (MSU). 31
Table 6. Classification Criteria. 32
Table 7. Diagnostic value of various tests (73). 33
Table 8. Diagnostic rule for primary care without joint fluid analysis. 33
Table 9. Utility and indications of imaging tests. 39
Table 10. Elementary ultrasonographic lesions in gout. 42
Table 11. Clinical history for patients with gout. 47
Table 12. Definitions of metabolic syndrome. 48
Table 13. Specific clinical assessment (acute episode). 49
Table 14. Specific clinical assessment (chronic episode). 50
Table 15. Domains to evaluate, instruments and properties. Acute episodes. 51
Table 16. Domains to assess, instruments and properties. Chronic manifestations. 52
Table 17. English Version of HAQ. 53
Table 18. Characteristics of various types of synovial fluid 55
Table 19. Laboratory tests in patients with gout. 59
Table 20. Proposals and strength of recommendation of clinical diagnosis. 89
Table 21. Clinical prediction scale for the diagnosis of acute gouty arthritis in PC. 89
Table 22. Using NSAIDs depending on cardiovascular and gastrointestinal risk. 91
Table 23. Proposals and strength of recommendation of clinical diagnosis. 94
Table 24. Clinical prediction scale for the diagnosis of acute gouty arthritis in PA. 94
Table 25. Gout related treatments approved in Spain and their characteristics (SPC)*.... 101
Table 26. Gout related treatments approved in Spain: interactions (according to the SmPC)*. 105
Table 27. Dose adjustment of allopurinol according to creatinine clearance (Hande). 108

LIST OF FIGURES

Figure 1. Sharp/van der Heijde Index: erosion assessment. 36
Figure 2. Joint space reduction. 37
Figure 3. Influence of diet on gout. 85

LIST OF IMAGES

Image 1. Aspiration of tophaceous material. 60
Image 2. MSU crystals under optical microscope with intense birefringence under polarizer. 61
Image 3. Urate crystals under optical microscope with polarizer and first-order red compensator. 61
Image 4. Simple anteroposterior x-ray of the hand. 133
Image 5. MRI of knee: Coronal sequence FSE-T2. 134
Image 6. MRI of knee. 135
Image 7. Synovitis. MRI T1 sequence with fat suppression after administration of IV gadolinium. 136

ABBREVIATIONS

Abbreviations	Definition
ACTH	Adrenocorticotropic hormone
AEMPS	Spanish Agency of Medicines and Medical Devices
AEPROSER	Spanish Association of Healthcare Professionals for the Study of Rheumatic Diseases of the SER
Bid	*bis in die* (twice daily)
CG	Cockcroft-Gault formula (creatinine clearance calculation)
CI	Confidence interval
CK	Creatine kinase
CKD	Chronic kidney disease
CPG	Clinical Practice Guidelines
CRP	C-reactive protein
CT	Clinical Trial
CT	Computed tomography
CV	*Curriculum Vitae*
DECT	Dual energy CT
DM	Diabetes mellitus
ECOSER	SER ultrasound working group
ESPOGUÍA	Spondylarthritis Clinical Practice Guidelines
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
EUMEUNET	Working group emerging EULAR network
FER	Spanish Rheumatology Foundation
FEUA	Fractional excretion of uric acid
GAQv2.0-GI	Specific Questionnaire for Assessment of Gout
GEACSER	Working Group SER crystal arthritis
GFR	Glomerular filtration rate
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
GRESSER	Spondylitis Study Group
GUIPCAR	Clinical Practice Guidelines for Rheumatoid Arthritis
HDL	High density lipoprotein
HRUS	High resolution ultrasound
HT	Hypertension
IM	Intramuscular
IMR	Internal Medical Resident
IV	Intravenous
MDD	Minimum detectable difference
MDRD	Modification of Diet in Renal Disease (estimated glomerular filtration rate)

mg/dL	milligram / deciliter
MRI	Magnetic resonance imaging
MSU	Monosodium urate
mSv	millisievert
MTP	Metatarsophalangeal
NNH	Number needed to harm
NNT	Number needed to treat
NSAID	Non-steroidal anti-inflammatory drugs
OMERACT	Outcome Measures in Rheumatology
OR	Odds ratio
PC	Primary Care
PCP	Primary Care Physician
PEP	Patient education programme
PET	Positron emission tomography
PNP	Purine nucleoside phosphorylase
PPI	Proton pump inhibitors
qd	*quaque die* (once per day)
RA	Rheumatoid Arthritis
RR	Relative risk
RU	SER Research Unit
s.c.	Subcutaneous
SD	Standard deviation
SEMFYC	Spanish Society of Family and Community Medicine
SER	Spanish Rheumatology Society
SF	Synovial fluid
SoMaMFyC	Madrid Society of Family and Community Medicine
SOR	Strength of recomendation
SPA	Spondylarthritis
SR	Systematic Review
TSH	Thyrotropin or thyroid stimulating hormone
uC	Uric acid clearance
UNIPAR	Renal Patient Registry of the Basque Autonomous Community
VAS	Visual Analogue Scale
vs.	*versus*
XO	Xanthine oxidase

I. GENERAL DOCUMENT INFORMATION

I.A. COOPERATING BODIES

The Spanish Society of Rheumatology (SER) is a nonprofit organization that acts as a sponsor of these clinical practice guidelines (CPG), having previously established the need for its development. In addition, the SER has also participated in the selection of the initial group of researchers, developing the work schedule, and drafting the contract with the funding source in terms appropriate to ensure the independence of its contents.

The Research Unit (RU) of the SER is responsible for the pre-selection of panelists, the development of methodology, the coordination of meetings, the issuing of the CPG, and conducting reviews of the evidence.

Menarini is the funding source of this CPG and is responsible, together with the SER, for the logistical coordination and timely performance of prescribed tasks.

I.A.1. GuipClinGot Group

The guidelines have been produced by GuipClinGot, a multidisciplinary group of health professionals, which is presented below along with a brief summary of the Curriculum Vitae (CV) of each of its members. All participants have made an explicit statement of their potential conflicts of interest.

I.A.2. Coordinators

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I.B. FUNDING

This CPG, sponsored by the SER, was funded by Menarini laboratories. The contract signed between the Spanish Rheumatology Foundation (FER), the RU staff employment agency and coordinator of RU payments to panelists and reviewers as the sole intermediary, and the pharmaceutical company, provided the total independence of the participants regarding the funding source. Under this contract, and even being responsible for funding the project, the pharmaceutical company has had no ability to influence the content of the guidelines, even assuming that the evidence contradicted the indication of any of its products.

I.C. HOW TO USE THE CPG

This CPG is organized into chapters. Each of them refers to different sections of the management of the disease: rationale and introduction, methodology, concept and definition, epidemiology, diagnosis, evaluation, gout and kidney failure, special situations, management in primary care (PC), treatment, etc.

Each chapter in turn contains one or more recommendations (highlighted in purple and bold), along with their respective rationale or explanation. The recommendations made in a clear and practical manner, are accompanied in addition by the level of evidence, strength of recommendation and level of mean agreement (in brackets). A certain flexibility was sought in drafting the chapters, a necessary feature for the CPG to be applicable to a reality characterized by varying circumstances (availability of certain technologies, training, patient preferences, etc.), which could affect clinical decision-making. The consequence is that, at times, it is left to the user to choose between various possibilities that are equal in the panel's judgment.

Both the documentation referred to in these guidelines, as well as the sources of evidence supporting various recommendations, can be useful to the physician for making decisions about assessment, monitoring or treatment of patients. Access to this information may be made from the index link, the electronic version of the guidelines and reference links located in the text.

Finally, there is a "Quick Guide" containing recommendations in abbreviated form that is available in paper format.

II. METHODOLOGY

CPGs are systematically developed recommendations to help the health professional and the patient to make decisions about the most appropriate care, and to select the diagnostic or therapeutic options best suited to addressing a health problem or a specific clinical condition. It aims to provide explicit recommendations and to be easily understandable for users, with the intention of influencing professional practice.

In the context of CPG, barriers are defined as those factors that prevent or hinder the implementation of change in professional practice, which in the case of CPG results in lack of adherence to their recommendations (2, 3). In order to overcome barriers, recommendations must have a high degree of evidence, be compatible with existing recommendations, facilitate decision-making and not require the learning or use of new skills.

The methodology used is suitable for the development of training recommendations and includes expert nominal groups, Delphi surveys and systematic reviews of the literature. During the development of the guidelines quality criteria of the AGREE instrument have been taken into account (4).

II.A. PANELS INVOLVED IN THE DEVELOPMENT OF THE GUIDELINES

II.A.1. The panel of experts

To form the expert panel an invitation was extended to all members of the GEACSER group. The aim of this group, consisting of rheumatologists particularly interested in the subject, is to promote the development of projects about crystal arthritis. In addition to accepting the invitation to participate, we used the following criteria for selecting panelists:

- *Multidisciplinary*. The panel should include the views of different groups of professionals and specialties involved in the management of gout. Therefore, in addition to rheumatologists, collaboration was requested from other experts whose opinion could contribute to improving care for the disease or the methodology of developing recommendations. In this case we had a radiologist, a nephrologist, a primary care physician (PCP), a nurse and a patient.
- *Expert knowledge*. Panel members should know in depth the subject of the CPG. The career of the experts, evaluated in terms of their *Curriculum Vitae*, should ensure respect of their opinions by the scientific community.
- *Geographic diversity,* with reasonable representation of the different regions of our country.
- *Diversity of care*. The recommendations should have meaning and application at both the inpatient and outpatient level.
- *Academic diversity*. Similarly, the CPG must represent both the point of view of schools or potential research centres, as well as that of professionals working in facilities without academic development.
- *Representative regarding gender*, with a balance of men and women on the panel.

The **tasks to be performed** by the panelists were:

a. Defining the content, scope and objectives of the guidelines.
b. Development of the recommendations.
c. Writing definitions.
d. Review and synthesis of the scientific evidence.
e. Addressing unforeseen issues that may arise during development of the CPG.

Besides ensuring their availability during the development of the project and its CV, all the panelists were asked to submit a declaration of conflicts of interest.

II.A.2. The panel of reviewers

Systematic reviews were conducted by members of the SER Evidence-based Rheumatology group. This group consists of rheumatologists trained and experienced in systematic reviews, whose main interest is the dissemination of these tools among the group of Spanish rheumatologists. Currently the group consists of 25 reviewers who follow the methodology proposed by the Cochrane Collaboration.

The reviewers were paid according to the reviews completed.

II.B. ESTABLISHMENT OF DEFINITIONS, SCOPE AND TASKS

Once the panelists were selected and they agreed to participate in the project, a meeting of the nominal group took place. The meeting included a theoretical presentation of the working methodology of the CPG, and the floor was opened for discussion to define the scope, objectives and users of the guidelines. The chapters to be written were agreed upon, those responsible for each chapter were appointed, questions were raised regarding systematic review and a calendar of deadlines and deliveries was set.

II.C. PREPARING THE FIRST DRAFT

After the meeting of the nominal group, panelists began writing their chapters and the corresponding recommendations, taking into account that the aim of these was to provide practical and specific advice on the different topics of these guidelines. In addition, it was explicitly requested that they be written based on the risk/benefit balance for the patient, regardless of the associated costs. Therefore, the recommendations should be developed according to the most appropriate action for the patient, maintaining the objective of improving quality of care.

II.D. DEVELOPMENT OF SYSTEMATIC REVIEWS

The authors conducted systematic reviews of the questions agreed upon with the experts, following standard methodology.

A documentation specialist (MPR) and a coordinator (EL) reviewed all the search strategies so that the terms used for the selection of the population, intervention and outcomes would be homogeneous among the different reviews to be performed, and facilitate the documents selected for review. The literature search was conducted in November 2011 in the following databases: MEDLINE, Embase, and Cochrane Central.

Table 1 shows the type and question of the reviews conducted.

Table 1. Systematic reviews conducted.

Type	Question
Diagnosis	Value of musculoskeletal ultrasound and magnetic resonance imaging for the diagnosis of gout
Prognosis	Value of musculoskeletal ultrasound and MRI to monitor response to treatment of gout
Diagnosis	Diagnostic value of renal function tests in chronic kidney failure
Efficacy	Efficacy of non-pharmacological treatment
Efficacy	Efficacy and safety of combination therapy
Safety	Safety of allopurinol (hypersensitivity, Stevens-Johnson syndrome)
Efficacy	Efficacy and safety of corticosteroids versus NSAIDs

Abbreviations: NSAID = Non-steroidal anti-inflammatory drug.

All reviews were adapted to a consensus editing format to facilitate subsequent interpretation. Once made, the reviews were submitted to the panel of experts for evaluation and assessment of the degree of evidence.

Parallel to the development of systematic reviews, experts were asked to draft recommendations for the chapter. These recommendations were compiled into a working document for all panel members to issue an opinion or clarify specific aspects.

Finally, experts and reviewers convened to pool the results of the reviews and associated recommendations.

For grading the level of evidence, the levels of the Oxford Centre of Evidence-Based Medicine(5) were used. This classification allows calculating the strength of the recommendations and evaluating the quality of evidence based on the best design to answer the question (Table 2).

Table 2. Levels of evidence of the Oxford Centre of Evidence-Based Medicine (2001).

GR	LE	Efficacy and safety	Efficacy and safety of drug (same class)	Prognosis	Diagnosis	Differential diagnosis, prevalence
A	1a	SR CT (homogeneity*)	SR CT "head-to-head" (homogeneity*)	SR beginning cohorts (homogeneity *) CDR † validated in different populations	Level 1 diagnostic SR studies (homogeneity*); CDR of 1b multicentre studies	SR prospective cohorts (homogeneity*)
	1b	Individual CT (with strict CI)	"Head-to-head" CT with important clinical outcomes	Individual beginning cohorts with >80% follow-up; CDR† validated in 1 population	Validation cohort study** with good reference standards †††; CDR† validated in one centre	Prospective cohorts study with good follow-up ****
	1c	"All or nothing" CT§		"All or nothing" case series	Absolute SpPins and SnNouts ††	"All or nothing" case series
B	2a	SR(homogeneity*) cohort studies	CT "head-to-head" CT with surrogate validated outcomes	SR (homogeneity*) retrospective cohorts or control groups in CT	Level 2 SR (homogeneity*) diagnostic studies	SR(homogeneity*) 2b and better studies
	2b	Individual study cohorts (or low-quality CT; e.g., <80% follow-up)	CT different drugs vs. placebo in similar or different patients with clinically important or validated surrogate outcomes	Retrospective cohort study or tracking placebos in CT; CRD referral† or validated in half sample only §§§	Exploratory cohort study ** with good reference standards ††††; CRD override or validated in half sample only §§§ or databases	Retrospective cohort study or with short follow-up
	2c	"Outcomes" research; ecological studies		"Outcomes" research		Ecological research
	3a	SR case-control studies (homogeneity *)	CT subgroup analyses of different drugs vs. placebo in similar or different patients with important clinical outcomes or validated surrogate		SR studies≥ 3b (homogeneity *)	SR studies≥ 3b (homogeneity *)
	3b	Individual case-control study	Different drugs vs. placebo CT in similar or different patients with unvalidated surrogate outcomes		Non-consecutive study or not consistently applied reference standards	Non-consecutive cohort study or very limited population
C	4	Case series (and cohort studies, case-control or low quality §§	Observational studies and administrative databases with clinically important outcomes	Case series studies of low quality prognosis ***	Case-control study or bad reference standard or not independent	Case series or does not conform to reference standards

D	5	Expert opinion without explicit critical appraisal or based on physiology, basic science or principles	Expert opinion without explicit critical appraisal or based on physiology, basic science or principles or non-randomized studies with unvalidated surrogate outcomes	Expert opinion without explicit critical appraisal or based on physiology, basic science or principles	Expert opinion without explicit critical appraisal or based on physiology, basic science or principles	Expert opinion without explicit critical appraisal or based on physiology, basic science or principles

Abbreviations: GR = grade/strength of the recommendation; LE = level of evidence; SR = systematic review; CT = clinical trial; CDR = clinical decision rule.

Notes: A negative sign "-" must be added to warn of the level that fails in the intended response because of: 1) a single study with wide confidence intervals, or 2) a systematic review with heterogeneity issues. In these cases the evidence is not conclusive, so it can only lead to grade D recommendations.

* By homogeneity we understand the absence of controversy or statistical or design heterogeneity. There may be revisions with statistical heterogeneity but which are not relevant from a clinical standpoint.

† Clinical Decision Rule: These are algorithms or scoring systems to estimate a prognosis or create a diagnostic classification.

‡ See first indication above about how to understand, evaluate and use trials or other studies with wide confidence intervals.

§ They are met when all patients died before receiving the treatment, but now some survive with it; or when some patients died before treatment, but none died with it.

§§ By poor quality cohort we understand those that do not have a good definition of comparison groups or measurements are not performed in a blinded or objective manner or have incomplete or too short follow-up or do not take into account important confounders. By case studies and poor quality controls we mean those which are either not well defined comparison groups or measurements that are not completely blind and made of the same and objective way, or do not take into account important confounders.

§§§ A "Split-sample validation" involves dividing the sample randomly into two parts, one in which the referral is made and another in which it is validated.

† † An "Absolute SpPin" is a diagnostic finding whose specificity is so high that a Positive result "rules-in" (i.e., confirming the diagnosis). An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a result Negative "rules-out" (i.e., excludes the diagnosis).

‡‡ Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.

††† "Good" reference standards are independent of the evidence and applied blindly or objectively to all patients. "Bad or poor" reference standards are not applied blindly or objectively, but are also independent of the evidence. Using an independent reference standard (the test is included or affects the reference) means that this is a level 4 study.

†††† Best value treatments are equally good but cheaper, or even better but at a similar or lower economic cost. Worst value treatments are equally good but at higher cost, or worse but at a similar or higher economic cost.

** Validation studies assess the validity of a specific diagnostic test, based on prior evidence. Exploratory studies collect information and analyze it to find factors with "significant" association.

*** By poor quality prognosis cohort study we understand a study in which the sample is biased in favour of patients who have had the outcome, or in which it is observed in less than 80% of the patients, or measured in a non-objective way or without correction for confounding variables.

**** Follow-up can be considered to be suitable where higher than 80%, with sufficient time to display alternative diagnoses (i.e., 1-6 months in acute or 1-5 years in chronic cases).

Another objective of this meeting was to quantify the level of agreement and consensus among experts. For this evaluation we used the Delphi method (two rounds) through anonymous online surveys as well as a physical meeting.

The CPG was assessed by two external reviewers, a rheumatologist expert in this clinical area (FPR) and a methodologist who was expert at conducting clinical practice guidelines (MJGY).

II.E. DIFFUSION OF GuipClinGot

Once the final text of the CPG was written, it was decided to publish it in PDF and HTML format on the website of the SER. Also, there was a quick guide (with the most relevant information, from the practical point of view for the physician) with the recommendations in both PDF and paper format as well as tables and/or images that can be useful. In order to get the CPG to the greatest number of Spanish rheumatologists, an e-mail was sent to all members of the SER with a direct link to the CPG. Inclusion of GuipClinGot in GuíaSalud, the CGP portal of the Quality Department of the Ministry of Health was requested and it was presented to the Spanish rheumatologists at the 2012 National Congress.

At least two articles were written for the *Reumatología Clínica* journal, one about the final recommendations and the other about the methodology used.

For international distribution, the guidelines will be translated into English in order to include it in the *National Guideline Clearinghouse*.

Finally, GuipClinGot will be updated approximately every 4 years, depending on the existence of new relevant information. The update will be complete, partial or with no modifications according to the importance of the new data available.

III. PURPOSE, SCOPE AND USERS

The aim of this CPG is to reduce variability in the treatment of gout, and try to improve quality of care by providing the physicians treating these patients with practical recommendations adapted to their setting and based on the best evidence available to advance comprehensive management of this pathology.

To date, CPGs have been developed in Spain to improve the quality of care in other musculoskeletal disorders such as rheumatoid arthritis (RA) and spondyloarthritis (SpA), but not for gout. Given its high prevalence and impact, as well as the large amount of resources and actors involved in the management of patients with gout, it was necessary to draft a CPG for this disease.

At the first meeting of the panel (September 2011) the scope of these guidelines was established:

1. In terms of the disease(s) addressed by GuipClinGot, it was decided that a single CPG should be drafted about gout in general. The considerations that were taken into account to make more inclusive guidelines (gout and related situations) were:

a) It is more practical for the rheumatologist to confront gout and related situations, with all that is involved in diagnosis, prognosis, treatment and monitoring, than in various interrelated processes.

b) There are no CPGs about gout in general.

c) The effort required is appropriate at this time but it is unclear whether the collaboration of various specialists to write other CPGs could take place later.

2. GuipClinGot includes a general introduction and sections on gout and related pathologies.

Regarding the users to whom GuipClinGot is directed, there was consensus that these should be CPG for rheumatologists, although with enough information from other bordering specialties to make it useful for both referral and interpretation of complications of the disease, follow-up or treatment. Therefore, apart from rheumatologists, it was decided to include as panelists and authors representatives of the following specialties: Family Medicine, Nephrology and Radiology, who were proposed in the initial meeting. Ultimately, there was also consensus on the participation of at least one nurse and one patient.

IV. CONCEPT AND DEFINITION

IV.A. GOUT

Gout is a disease caused by the deposition of monosodium urate (MSU) crystals in joints and peri-articular and subcutaneous areas. Like any deposition disease, it is a chronic process by definition, although the clinical manifestations may not be present or may occur only intermittently during the initial phases. The typical clinical manifestations are recurrent episodes of acute arthritis (episode of acute inflammation), which are separated by intercritical periods of varying duration. In addition to the joints, episodes of acute inflammation often also affect surface bursae – such as the olecranon or pre-patellar – and more infrequently deeper bursae or tendons.

The deposition of MSU crystals is conditioned by the existence of sustained hyperuricaemia. Without adequate urate-lowering treatment, the frequency of episodes of arthritis and the number of affected joints increase (6). Symptoms can continue even during the intercritical periods and inflammation may become persistent (chronic inflammatory manifestations of gout). There may be no correlation between the amount of deposition of crystals and intensity of symptoms. Patients with gout may develop long-term accumulations of MSU crystals called tophi. These accumulations can be located anywhere, but predominately in peri-articular and subcutaneous tissue; some characteristic areas are the olecranon, the Achilles tendon or the auricular helix. Their formation in the joints can cause functional limitation even in the absence of apparent inflammation.

IV.B. HYPERURICAEMIA

Hyperuricaemia is a necessary condition, although not sufficient by itself, for the onset of gout. There are different definitions of hyperuricaemia. In these guidelines it is defined as the presence of plasma urate above 7 mg/dL since, under physiological conditions, the saturation threshold is 6.8 mg/dL.

Some authors recommend using different cut-off points for both sexes based on the distribution of serum uric acid levels in the general population, since they tend to be lower in women, especially premenopausal women (7). However, these epidemiological cut-off points lack pathogenic significance in terms of MSU crystal formation.

On the other hand, asymptomatic hyperuricaemia is defined as the presence of elevated serum urate concentrations in the absence of clinical signs of joint inflammation. However, the results of studies using ultrasound and fluid aspiration have shown that the deposition of MSU crystals may appear even before clinical manifestations (8, 9). Therefore, in the presence of deposits shown by any technique with sufficient specificity, a diagnosis of gout must be considered in what might be called the pre-clinical phase. Despite not having developed clinical episodes of acute inflammation, these patients may have subclinical inflammation detectable by ultrasound (10).

IV.C. PATHOGENIC CLASSIFICATION OF HYPERURICAEMIA AND GOUT

Hyperuricaemia is caused by an imbalance between the production and the elimination of uric acid. This compound is the final product of the purine catabolism pathway. In contrast to most mammals, humans do not have uricase, which prevents the degradation of uric acid to allantoin, a molecule more water soluble and easy to eliminate, so most uric acid is eliminated by the kidneys. Within the kidney, uric acid undergoes marked reabsorption in the proximal tubule, excreting less than 10% of the filtrate in the glomeruli. The most frequent pathogenic mechanism of gout is decreased renal excretion of uric acid (Table 3). The results of some studies suggest that mutations in different tubular transporters (especially in GLUT9 and URAT1) could explain the variations found in some patients with gout (11).

Although in most patients no cause of the disease is detected (idiopathic gout), numerous drugs and comorbidities may cause uric acid abnormalities and trigger the disease process (secondary gout). Enzyme deficiencies are extremely rare and generate early gout with added systemic manifestations. Detection of reversible causes – such as drugs – is of particular relevance since it may modify patient management.

Table 3. Pathogenic mechanisms of gout.

Type	Pathogenic mechanism	Cause
Primary gout	Increased production of uric acid (5-10%)	
	Reduced renal excretion of uric acid (90-95%)	
Secondary gout	Increased production of uric acid	• Diet rich in purines • Increased ATP catabolism (i.e. ethanol, intense exercise, tissue ischaemia, glycogen storage) • Psoriasis • Paget's bone disease • Haematologic and neoplastic diseases with increased cell turnover • Cytotoxic chemotherapy (including tumour lysis syndrome) • Genetic defects in the purines pathway (over-expression of phosphoribosylpyrophosphate synthetase, deficiency of hypoxanthine-guanine phosphoribosyltransferase - Lesch-Nyhan and Kelley-Seegmiller syndrome) • Deficit of glucose-6-phosphate dehydrogenase (glycogenosis type I)
	Reduced renal excretion of uric acid	• Chronic kidney disease • Extracellular volume depletion, dehydration • Acidosis • Drugs (e.g. thiazides, loop diuretics, salicylates at low doses, niacin, pyrazinamide, cyclosporine) • Lead poisoning (saturnine gout) • Analgesic nephropathy • Polycystic kidney disease • Medullary cystic kidney disease • Other family interstitial nephropathy • Endocrinopathies (hyperparathyroidism, hypothyroidism)

V. EPIDEMIOLOGY OF GOUT

V.1. PREVALENCE AND INCIDENCE

The prevalence of gout ranges from 0.03% (Nigeria, men) to 15% (Taiwan, aborigines), with an average value of 1-2% in Western countries (12). Its incidence is estimated at about 1 or 2 per 1,000 (13, 14). In any case, it is important to note that in studies on the epidemiology of gout diagnostic criteria are not applied, but in most cases the estimates are based on a diagnosis self-referred by the subjects or from existing data in administrative databases – and can vary from a diagnosis to a prescription for allopurinol, or a high uric acid value according to different cut-off points, which generally show low concordance with diagnostic criteria (15).

The epidemiology of gout is closely related to that of hyperuricaemia, the main risk factor. Hyperuricaemia prevalence is about 10%; about 10% of patients with hyperuricaemia develop gout and between 80 and 90% of patients with gout have hyperuricaemia (12).

Some authors claim that there is an increase in the incidence of gout, although the validity of the studies on which they are based is low (16, 17). However, given the strong association of this disease with risk factors related to lifestyle and age, it is logical to think that prevalence may be increasing (18).

V.2. IMPACT

The burden of chronic gout disease is significant, both socially and economically. Patients with attacks of gout or chronic gout have low scores on quality of life questionnaires related to health, mainly in the areas of pain, activity limitation and disability (19-25). The results of some studies comparing costs among patients with gout and controls show a difference of $134 per month ($p < 0.001$) and more than $8,000 over a period of 5 years (26). Costs incurred by patients with gout are primarily related to hospitalization, probably due to associated comorbidities. In refractory gout, incremental health costs can be up to $10,000 per year, of which 40% is directly related to gout (27). Moreover, gout negatively affects labour productivity, especially in urate-lowering treatment-refractory patients (25).

V.3. RISK FACTORS

Gout is four to six times more common in men than women. The onset of the disease is typically during middle age, it is uncommon before age 30, and its incidence increases with age (12,14, 28-31). Women rarely have gouty arthritis attacks before menopause. The prototype of the patient suffering from a first episode of gout is a male between 40 and 50 years old, usually overweight or obese, fond of good food and regular alcohol consumption.

Table 4 shows the elements that have been considered as potential risk factors or indicators of the need for protection against gout. It is important to note that even in cases with a more

clear relation, the odds ratio (OR) does not reach the value of 3 or is only seen in the highest exposure quintiles, not having ruled out any possible indirect associations due to unmeasured variables.

Table 4. Risk factors for gout.

High risk	Uncertain risk	Possible protective factor
Diets rich in animal purines (32)	Diets rich in plant purine (32)	Dairy (32)
Alcohol (14, 33-37)	Powdered milk	Cherries (38)
Diuretics (14, 39, 40)	1q21 region of chromosome 1 (41)	Vitamin C (42)
Cyclosporine in transplantation (43-47)	1q21 region of chromosome 1 (41)	Coffee, including decaf (48, 49)
SLC2A9 gene (encodes glucose and fructose transporter GLUT9)(50).	Thymine-adenine repeat polymorphism of the oestrogen receptor gene located at chromosome 6q25.1 (51)	SLC22A12 (encodes URAT1, a renal tubular transporter of uric acid) (52, 53)

V.4. COMORBIDITIES

The magnitude of the relationship between chronic kidney failure and gout has been estimated at an odds ratio of 2.48, with a 95% confidence interval (CI) of 2.19 to 2.81 (14). Metabolic syndrome, and its components (hyperglycaemia/diabetes, abdominal obesity, hypertriglyceridaemia, low HDL cholesterol, high blood pressure (hypertension) and risk of atherosclerotic events), is independently associated with hyperuricaemia and gout (54-56). The results of a study of the temporal relationship between gout and metabolic syndrome showed that the first attack may precede the diagnosis of metabolic disorders and associated diseases in up to 90% of cases (55). Gout is more common in obese individuals (57-59), and up to 54% of patients with gout are obese (55). Several studies have evaluated the association between hypertension and hyperuricaemia, which revealed that half of untreated hypertensive patients have hyperuricaemia (13, 58-62). Similarly, numerous studies also support the association between cardiovascular disease and gout, including mortality (63-69). Moreover, up to 15% of patients with gout will develop diabetes and up to 37% hyperglycaemia at some time in their lives (55). Finally, hypertriglyceridaemia occurs in up to 63% of patients with gout and HDL levels are below the normal range in 17% of patients.

VI. DIAGNOSIS

VI.A. CLINICAL DIAGNOSIS

It has been more than three centuries since the first description of MSU crystals in material from a tophus (70), and more than 50 years since its identification in synovial fluid and pathogenic involvement in gout (71). Despite the time elapsed and the relative ease of accurate diagnosis of this disease (72, 73), the reality in routine clinical practice, both in

primary and in specialized care, is that the diagnosis is mainly based on mere clinical impression or classification criteria (74-77). In a representative sample of Spanish Rheumatology departments, 74% of diagnoses of gout were made based on clinical impression or criteria (75).

VI.A.1. Gold standard

Recommendation 1: The definitive diagnosis of gout is based on the identification of MSU crystals in synovial fluid or tophaceous material (LE 2b; GR B; DA 100%).

Identifying MSU crystals in a sample of synovial fluid (SF) or an aspirate of a tophus allows irrefutable diagnosis of gout (73, 78). Visualization of crystals must be done using an optical microscope fitted with polarized light and first order red compensator (gold standard)(73,79,80).

Recommendation 2: In intercritical periods, it is possible to obtain synovial fluid so as to establish the diagnosis of gout (LE 2b; GR B; DA 100%).

Obtaining synovial fluid or tophaceous materials and studying them to detect crystals are simple and rapid techniques (72, 79). In general, once the sample is obtained a few drops are placed on a slide; the amount used is minimal to avoid dispersion of the liquid to the margins when placing the coverslip (79). The excess fluid causes the sample to exceed the limits of the coverslip, staining the work area and making visualization difficult due to the movement of the cells. The slide and coverslip must be clean because dust particles can be very birefringent and confusing for inexperienced observers (81). Microscopic examination requires no sample preparation but should be done as soon as possible after collection. Otherwise the edges of the coverslip are sealed with clear nail polish to prevent the sample from drying out and it may be used for later analysis (79). Another option is to freeze the sample at 4 ° C, preferably in an EDTA tube; this procedure has shown adequate detection of intracellular crystals after 72 hours of storage (82).

The objective of the synovial fluid study is to determine the presence or absence of MSU crystals. To detect and identify crystals the search should start at 100x or 200x magnification, and if in doubt it can reach 400x; searches with higher increases are of little use. Urate crystals have a variable morphology, often acicular, with high birefringence, negative elongation (81) and a length of between 3 and 40 microns (83), although those from tophi may be higher. Although the gold standard is an optical microscope with polarized filters with first order red compensator, analysis with a microscope with ordinary light can detect MSU crystals and their differentiation from calcium pyrophosphate crystals due to their morphology, enabling a possible provisional diagnosis (84). Polarizing filters make it possible to assess the presence and intensity of the birefringence; all MSU crystals exhibit strong birefringence, while only one in five calcium pyrophosphates shows this feature and it is always weak. The first-order red compensator allows to classify the type of birefringence (positive or negative) according to the colour of the glass and its relation to the axis of the compensator (85).

Sometimes, especially after arthrocenthesis of asymptomatic small joints, the amount of fluid aspirated is minimal. However, before disposing of the syringe after an apparently unsuccessful puncture, it is important to press the plunger hard against the slide repeatedly as this may facilitate the release of very small crystal samples or fluid retained within the needle. Aspiration of a few drops of alcohol before pressing the syringe plunger against the slide also may be useful for extracting small quantities of sample.

In patients with gouty arthritis MSU crystals can be found in joints with current or previous inflammatory signs. According to the results of various studies, the sensitivity varies between 85% and 95% in swollen joints (71, 80, 83) and between 52 and 100% in asymptomatic joints with a history of inflammation (71, 80, 86 - 92). Also, sometimes MSU crystals can be found in joints that have never been swollen (sensitivity between 22% and 66%) (86,89, 91). The probability of identifying MSU crystals decreases as time from the latest episode of arthritis, duration of urate-lowering treatment and effectiveness in reducing uric acid levels increase (90, 91).

Although it is an uncommon situation, an initial study of synovial fluid without finding MSU crystals does not definitively exclude the diagnosis of gout, as they can be found in a subsequent study (93, 94). The main sources of error in the identification of these crystals are described in Table 5 (81, 94).

Several studies have evaluated the reliability of the laboratory in the identification of crystals in synovial fluid and in general the results were very poor in laboratories performing the procedure on a regular basis (95-98). However, it is important to maintain some caution in interpreting these data due to the lack of information on key factors such as the training and experience of the observers, the technique used and the type of microscope used. It has also been found that training the observers significantly increases consistency of the procedure. The results of a study published in 2005 showed that the sensitivity and specificity of MSU crystal identification in 64 SF samples analyzed by three people with no previous experience was over 95% after a short training period (99). Therefore, these results underscore the importance of training healthcare professionals responsible for synovial fluid analysis.

Recommendation 3: In cases of arthritis of unknown origin gout should be included in the differential diagnosis (LE 5; GR D; DA 92%).

Recommendation 4: The presence of MSU crystals does not rule out the presence of concomitant infection (LE 3a; GR C; DA 92%).

The presence of MSU crystals in synovial fluid does not rule out other coexisting pathologies. Although uncommon, sometimes MSU crystals and calcium pyrophosphate can be identified in the same joint. This consideration should be particularly important in cases of suspected septic arthritis, raised especially given the presence of other risk factors, atypical clinical forms, different from previous gout attacks or in the case of elderly patients (81, 100, 101). Septic arthritis can occur within joints affected by gout, in which case MSU crystals will be detected in the SF, so if no culture is performed, infection may go unnoticed.

Recommendation 5: "Symptomatology" and serum uric acid levels do neither confirm nor rule out the diagnosis of gout (LE 5; GR D; DA 77%).

VI.B. CLASSIFICATION CRITERIA

Three classical classification criteria for gout were published over thirty years ago (Table 6) (102, 103); also, there are two recent proposals for diagnostic rules (104, 105). Despite the time elapsed since their publication, so far no proper validation study has been performed of the classical criteria. In this sense, demonstrated validity rates do not exceed 70% and 77% for sensitivity and positive predictive value, respectively, in a population with monoarthritis treated at a Rheumatology department (106).

The **ACR criteria**, published in 1977 (103) and defined at the time as preliminary classification criteria, are the most used (107). For the development of these criteria gout patients were used as cases while controls were patients with "pseudogout", rheumatoid arthritis or septic arthritis, in both situations diagnosed by a rheumatologist. No diagnoses were agreed upon, and the available data on the study population are scarce. The results of a subsequent study have shown that these criteria have limited validity in patients with monoarthritis and suspicion of gout, according to the family physician, with sensitivity values of 80%, specificity of 64%, positive predictive value of 80% and negative value of 65% (108).

In addition to the ACR criteria, **EULAR recommendations** are available for the diagnosis of gout (73) based on scientific evidence and expert opinion (Table 7). However, one of the weaknesses of these recommendations is that an important part of the studies used a clinical diagnosis as gold standard.

Recently ACR criteria and the EULAR recommendations have been combined for identifying shared items and formulate a new proposal of diagnostic criteria (105) (Table 6). The diagnostic value of this new approach has been tested in a Mexican population in which patients with gout, confirmed by the identification of crystals, were compared with patients diagnosed with rheumatoid arthritis (RA), osteoarthritis or spondyloarthropathies (109). The presence of 4 or more of the proposed new criteria achieved sensitivity and specificity of 97.3% and 95.6% respectively, with a positive likelihood ratio of 22.1. Although initially the results seem extraordinary, it is important to emphasize the high risk of selection bias in this study, since the gouty population consists of severe cases, both based on the country of origin and because of being patients referred to a tertiary hospital, and controls are patients with different well-established rheumatic diseases. For these reasons, before recommending its wide use validation studies are necessary in a broad range of population types.

Moreover, in primary care (PC) a rule has been developed for the classification of episodes of acute arthritis without requiring an analysis of synovial fluid (104). This diagnostic model was derived from the data of 382 patients presenting to PC with monoarthritis, mostly in the first metatarsophalangeal joint. It includes 7 clinical and laboratory variables weighted with a maximum score of 13 (Table 8). The authors suggest two cutoff points: scores ≤4 make the diagnosis of gout very unlikely while a score ≥8 represents a probable diagnosis of gout. Intermediate scores are considered indefinite. The ability of these criteria to rule out gout is very good (for scores ≤4, the negative likelihood ratio is 0.01), but its diagnostic value is low, with a positive likelihood scores ≥ 2.66 for scores ≥8, slightly better than the individual clinical

criteria incorporated. Besides its applicability in clinical presentations other than the studied one, such as polyarthritis, arthritis in Emergency Departments, etc. is not known.

Hyperuricaemia is defined as the elevation of plasma urate concentration above its solubility limit under physiological conditions. This value is 6.8 mg/dL (110). Long-term hyperuricaemia is a necessary factor for the occurrence of gout and has traditionally been used for diagnosis. However, hyperuricaemia is a common metabolic disorder, especially in males above 40 years, and only a minority of patients with hyperuricaemia, especially those with moderate urate levels (7 to 8.9 mg/dL), will develop an episode of acute gout in 5 years (111). Therefore, although it is a necessary condition, long-term hyperuricaemia is not sufficient to establish a diagnosis of gout. Furthermore, normal levels of plasma urate do not rule out the presence of gout, especially if the measurement was made during an arthritis attack , because in these situations serum uric acid can drop to normal levels or occasionally even to hypouricaemic levels (112 - 115).

The pattern of rapid-onset acute monoarthritis, with erythema located in the lower limb joints is very suggestive of crystalline arthritis (although not specific to gout). In case of recurrent gout with hyperuricaemia, a clinical diagnosis can be reasonably accurate (73), but never definitive. In most atypical presentations like polyarticular or oligoarticular, there is greater likelihood of erroneous diagnosis (77, 116). Like hyperuricaemia, a clinically compatible symptomatology does not guarantee definitive diagnosis of gout.

It has been suggested that topical application of ice on the inflamed joint can help differentiate gouty arthritis from other arthropathies (117). However, this is based on the results of a single retrospective study conducted with few patients with joint pain with or without swelling, thus the risk of bias is high.

Table 5. Misidentification of monosodium urate crystals (MSU).

Absence of identification of MSU crystals in patients with high clinical suspicion of gout
• Not gout
• The fluid is extracted from a synovial sac adjoining or near where the crystals are (effusion by sympathy)
• There are only ultramicroscopic crystals
• Deposition of crystals in small spheres (118)
• Delayed visualization of the sample (crystal dissolution)
• Human error (most likely with the lack of experience of the observer)
Suspected MSU crystal-induced arthritis actually due to other causes
• The presence in the synovial fluid or in the coverslip or slides of other elements with negative birefringent that confuse the observer (cholesterol crystals, corticosteroid crystals, cartilage fragments or dust particles)
• There are crystals but arthritis is due to another cause (e.g., septic arthritis)

Table 6. Classification Criteria.

Type of criteria	Number necessary	Definition
Primary Gout	Any of the 3 following	A. MSU crystals in synovial fluid B. Tophus with urate crystals (shown chemically or with polarized light microscopy) C. Presence of at least 6 clinical, laboratory or radiological criteria: • More than an acute attack • Inflammation developed in a day • Attack of monoarticular arthritis • Pain or swelling of the 1st MTP • Acute unilateral tarsal arthritis • Suspected tophus • Hyperuricaemia • Swelling of one joint (Rx) • Subchondral cyst (Rx) • Negative culture of joint fluid during an acute attack
Rome	At least 2 of the 4 following	A. Urate levels >7 mg/dL in men or >6 mg/dL in women B. Tophus C. MSU crystals present in synovial fluid or tissue D. History of pain and inflammation attacks with remission in 1-2 weeks
New York	MSU crystals in SF or at least 2 of the following:	A. History of at least two attacks of pain and inflammation with remission in 1-2 weeks B. History or observation of gout C. Presence of tophi D. Good response to colchicine: reduction of majority of inflammatory signs in the first 24 h of treatment
Clinical diagnosis	At least 4 of the following:	A. More than one attack of acute arthritis B. Mono- or oligoarticular attack C. Rapid progression of pain and swelling in 24 h D. Podagra E. Erythema F. Unilateral tarsitis G. Likely tophus H. Hyperuricaemia (>7 mg/dL in men or >6 mg/dL in women)

Abbreviations: MSU = monosodium urate, MTP = metatarsophalangeal joint, RX = plain radiography, SF = synovial fluid, h = hours, mg = milligram, dL = deciliter.

Table 7. Diagnostic value of various tests (73).

Diagnostic test	Comparison pattern	Sensitivity	Specificity	Positive LR
Painful, swollen joint, sudden onset and limited to the two weeks prior	Clinical gout	0.98 (0.95-1.02)	0.23 (0.1-0.35)	1.27 (1.08-1.5)
Erythema	Clinical gout	0.92 (0.88-0.96)	0.62 (0.58-0.66)	2.44 (2.19-2.73)
Podagra	Clinical gout	0.96 (0.91-1.01)	0.97 (0.96-0.98)	30.64 (20.51-45.77)
Definitive tophus	Clinical gout	0.30 (0.24-0.36)	0.99 (0.99-1.00)	39.95 (21.06-75.79)
Probable tophus	Clinical gout	0.20 (0.13-0.27)	1.00 (0.99-1.00)	33.99 (10.71-107.85)
Crystals in episode of acute inflammation	Clinical gout	0.84 (0.77-0.92)	1.00 (0.99-1.00)	566.6 (35.5-9053.5)
Intercritical gout crystals	Crystals	0.70 (0.50-0.87)	0.95 (0.83-1.08)	15.13 (0.99-229.95)

Abbreviations: LR = Likelihood Ratio.

Table 8. Diagnostic rule for primary care without joint fluid analysis.

	Score
1. Male sex	2.0
2. Gout attack (self-declared)	2.0
3. Involvement of first metatarsophalangeal joint	0.5
4. Maximum swelling in one day	1.0
5. Erythema on the joint	2.5
6. Comorbidity: hypertension or cardiovascular disease *	1.5
7. Plasma urate concentration of >5.88 mg/dL	3.5
	Maximum 13
≤4: Gout is unlikely **≥8: Gout is likely**	

* Cardiovascular disease: angina, myocardial infarction, heart failure, stroke, transient ischaemic attack or peripheral vascular disease.
Abbreviations: mg = milligram, dL = deciliter.

VI.C. IMAGING TECHNIQUES

The use of imaging techniques may include plain radiography, high-resolution ultrasound (HRUS), computed tomography (CT), dual energy computed tomography (dual-energy CT), and magnetic resonance imaging (MRI). For now, only measurement of tophi by ultrasound and MRI comply with (119, 120) the OMERACT filter in order to be considered outcome measures for urate-lowering treatment.

There are no studies on the sensitivity to the change of tophi measurement with CT, PET or radiography during urate-lowering treatment, although dual-energy CT initially seems to be a highly reproducible technique. Finally, the diagnostic utility of positron emission tomography (PET) has not yet been assessed in patients with gout.

VI.C.1. Plain x-rays

Recommendation 6: It is not recommended to perform plain radiography, CT or MRI for the diagnosis of gout (LE 2b; GR B; DA 77%).

Plain x-rays have a limited role in the early phases of the disease. In fact, overall, only 45% of patients with gout have radiographic findings that usually appear in advanced stages (121). During acute episodes of inflammation the only finding, although nonspecific, is an increased volume and density of the periarticular soft tissue reflecting secondary inflammatory changes in the deposition of crystals or in the synovial membrane of the articular cartilage surface, that disappear after resolution of the acute attack.

During the chronic phase of the disease, crystal deposits increase nodular density of periarticular soft tissue and underlying bone erosions, typically on the edge of the small joints of the hands and feet, especially the first metatarsophalangeal joint. These tophi are not detectable by radiography until they reach a size of 5-10 mm. The results of a cross-sectional study on 78 first toe metatarsophalangeal joints showed that the performance of plain radiography for detecting erosions was lower than that of ultrasound (22 joints versus 52) (122). Intratophus calcifications are rare and, if present, they are usually located peripherally (120). In patients not receiving urate-lowering treatment there was an estimated cumulative prevalence of intraosseous tophi on plain radiography 40%, 55% and 70% at 5, 10 and 15 years of follow up, respectively (123).

Oblique projections facilitate the detection of erosions. Bone erosions are usually ovoid in shape, with cystic appearance and marginal sclerosis usually being oriented along the longitudinal axis of the bone. Another typical characteristic is the presence of pendant or overhanging edges, and the absence of associated periarticular osteopenia (122). In terms of location, erosions may be intra-articular, para-articular or located at a considerable distance from the joint. Intra-articular erosions usually start in the articular margin and move towards the centre; conversely, para-articular erosions tend to be eccentric and located below tophi (120).

A feature that differentiates it from RA is that bone density and joint space tend to be preserved until late stages of the disease, in which erosions can cause extensive joint destruction (120).

Occasionally proliferative club-shaped bone changes of the metatarsals, metacarpals and phalanges, growth of the ulnar styloid process, and diaphyseal periosteal reaction and thickening can be observed (125).

Plain x-ray also detects intraosseous, punctate or circular calcifications, often located in the subligamental or subchondral region, which requires differential diagnosis with enchondroma or bone infarcts. Sometimes intraosseous tophi can be seen, as lytic areas with generally well defined edge (126) and chondrocalcinosis, present in 5% of patients with gout.

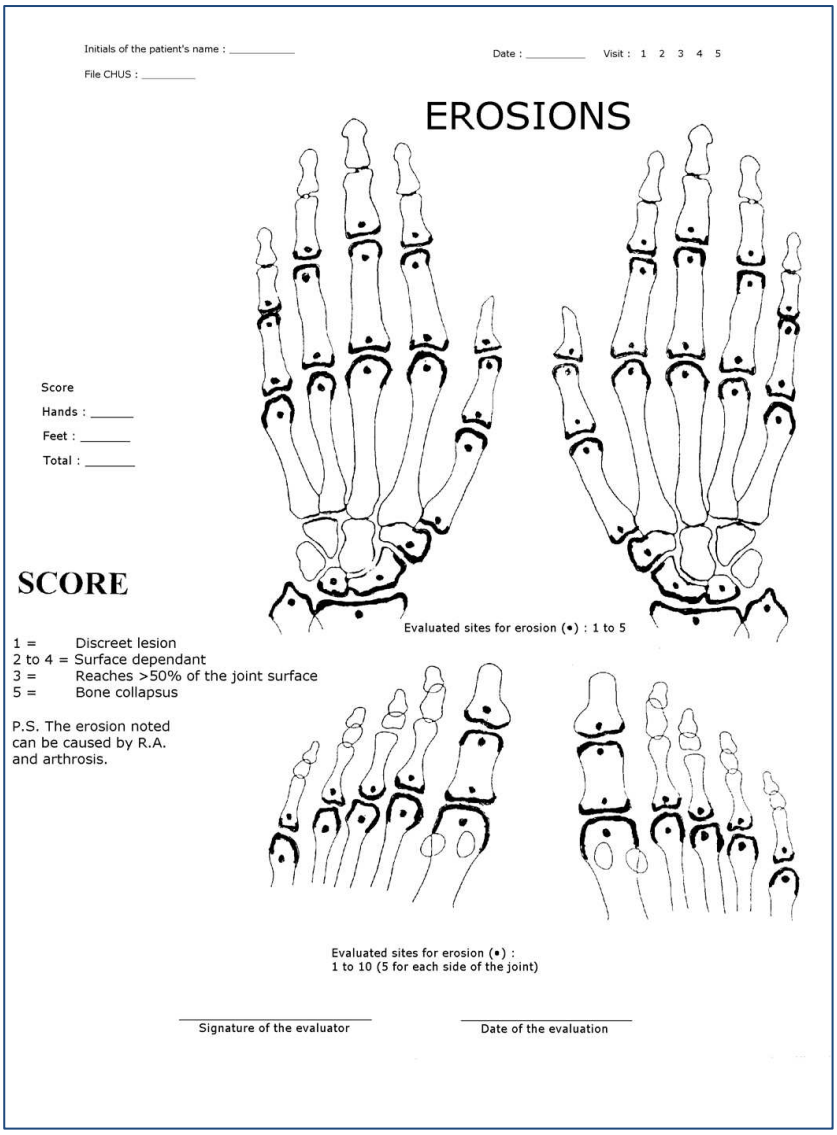
Radiographic involvement level can be studied using a modified version of the Sharp / van der Heijde index, which assesses the presence of bone erosions and joint space narrowing in the same joints as in RA and also the distal interphalangeal joints (127). It has been shown that this

index is reproducible and capable of discriminating between early and late stages of the disease, also showing a high correlation with functional capacity (127).

In RA erosions are assessed in 32 joints of the hands and 12 of the feet. In the case of gout 42 joints of the hands and 22 of the feet are examined. Erosions are evaluated on a scale of 0 to 5 points for each joint of the hands and of 0 to 10 for the feet. Therefore, the total score of erosions (sum of all joints) can reach a maximum value of 280 in RA and 430 in gout (Table 9).

Relative to the decrease in joint space, 30 joints of the hands and 12 of the feet are assessed in the case of RA and the same, plus the distal interphalangeal, in the case of gout (40 for hands and 22 for feet). The rating scale for each joint goes from 0 to 4. Accordingly, a maximum score of 168 can be achieved for RA and 248 for gout.

Figure 1. Sharp/van der Heijde Index: erosion assessment.



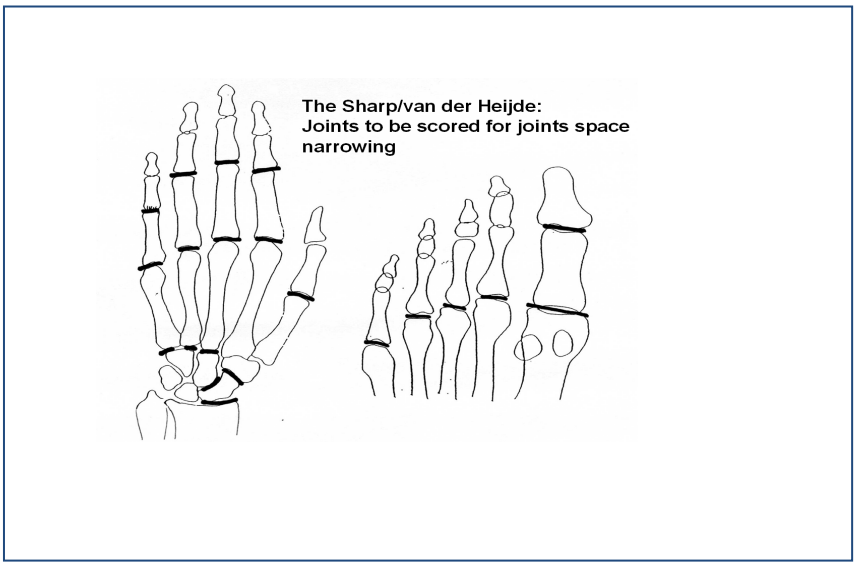
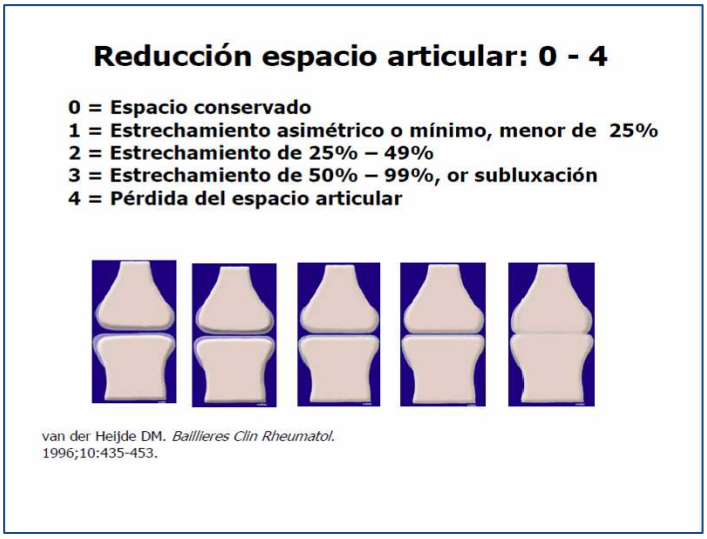


Figure 2. Joint space reduction.



Joint space reduction: 0-4

0 = Conserved space
1 = Asymmetrical or minimal narrowing, less than 25%
2 = Narrowing of 25% - 49%
3 = Narrowing of 50% - 99%, or subluxation
4 = Loss of joint space

VI.C.2. Computed tomography and dual-energy computed tomography

Recommendation 6: It is not recommended to perform plain radiography, CT or MRI for the diagnosis of gout (LE 2b; GR B; DA 77%).

See **RS1.**

The CT allows excellent visualization of tophi. MSU crystals have a density of 150-200 Hounsfield units, which can be useful for the differential diagnosis with other subcutaneous nodules (125).

The ability of these techniques to detect erosion is higher than resonance and plain radiography and it constitutes the best method of assessing bone lesions. It has been shown that there is a high correlation between the presence of erosions and tophi. In fact, intraosseous tophi are found in up to 81.8% of joints with small bone erosions and 100% of those larger than 7.5 mm (125, 128).

Moreover, the CT is also useful for directing aspiration, detecting complications of the disease, or identifying tophi in deep locations inaccessible by other methods (129). A scoring system was developed for bone lesions by CT (130), but it has yet to be validated.

Dual energy CT is being used with high levels of sensitivity, reproducibility and diagnostic accuracy. This type of CT uses two X-ray tubes operating simultaneously, although with different kilovoltage (80 and 140 kVp). The method is based on the different behaviour of

matter in terms of various parameters such as energy load and composition, which facilitates the differential diagnosis of urate deposits in the soft tissues and other types of deposits (calcium, dystrophic) (131-133). Post-processing allows 3D volumetric reconstruction of tophi and colour-coded sequential images according to the components of nodules (134).

One of the limitations of CT is patient exposure to ionizing radiation. In this regard, studies are underway at doses below 1 mSv, i.e. below the maximum allowable dose for the general population exposure to natural radiation (132).

VI.C.3. Magnetic Resonance Imaging

Recommendation 6: It is not recommended to perform plain radiography, CT or MRI for the diagnosis of gout (LE 2b; GR B; DA 77%).

See **RS1.**

Although the findings are not entirely specific, MRI can assess the presence of bone erosions and joint deposits. Furthermore, performing MRI after gadolinium IV infusion facilitates the study of inflammatory changes of the synovial membrane and detection of associated structural lesions, such as meniscal or ligament pathology, which can raise confusion in case of chronic symptoms associated with urate deposit.

MRI is especially useful in patients with isolated tophi without joint disease, allowing differential diagnosis with neoplastic processes, pigmented villonodular synovitis, and granulomatous diseases such as fungal infections or tuberculosis, or tophi with significant inflammatory reaction that may mimic septic arthritis or osteomyelitis (135).

Tophi are displayed as soft tissue masses, with a variable medium-low signal, heterogeneous on T2, and typically homogeneous and hypointense on T1 (136). Following IV administration of contrast medium enhancement can be displayed around the nodular image called crown due to increased vascularity associated with granulation tissue.

Tophi localization is variable, and intratendinous, intraligamentous, intrasynovial, intraosseous, or extraligamentous paraarticular tophi can be observed. Moreover, they generally tend to be deposited along fascial and compartmental planes and not radially (136).

As tophus volume increases calcifications and ossification appear which may cause tendon ruptures, nerve compression and myopathy secondary to denervation; all these entities can be diagnosed with MRI. This imaging technique also facilitates the differential diagnosis with other entities associated with hypointense paraarticular masses such as xantofibromas or benign fibroblastic tumours, which usually do not occur with surrounding oedema (135).

As in plain radiography and CT, in MRI erosions appear at paraarticular sites, underlying tophi. The image is characterized by sclerotic border, low intensity and overhanging osteophytes, and it may be accompanied by proximal bone oedema. MRI is very useful to assess the state of the synovium. Under normal conditions this structure is virtually unnoticeable with its thread-like enhancement. In cases of gouty synovitis a diffuse or focal thickening of the synovial is seen with a medium-low signal on T2 sequences, that allows differential diagnosis with other entities such as pigmented villonodular synovitis, amyloid or haemophilic arthropathy and

chronic synovitis such as RA. The contrast media produce an intense linear enhancement, nodular or mixed, of 2-3 mm thickness (137).

MRI has proven to meet the OMERACT filter as an outcome measure for urate-lowering treatment (138).

Table 9. Utility and indications of imaging tests.

Test	Acute phase	Chronic phase	OMERACT filter (120, 139)
Plain x-ray	• Little utility • Differential diagnosis with other processes (pyrophosphate arthritis)	• Detection of erosions • Compromise of joint space • Possible tophi detection	NO
Conventional CT	• Little utility • Differential diagnosis with other processes	• Detection of erosions • Assessment of joint space • Detection of tophi and quantification of their volume	NO
Dual-energy CT	• MSU composition of paraarticular masses that support the diagnosis	• Same advantages as the conventional CT • Monitor urate-lowering treatment by volumetric measurement of tophi	NO
MRI	• Differential diagnosis with other processes	• Detection of tophi, erosions and involvement of other joint structures • Assessment of synovial membrane and inflammation • Monitoring response to urate-lowering treatment	YES

Abbreviations: CT = computed tomography, MRI = magnetic resonance imaging.

VI.C.4. Ultrasound

Recommendation 6: It is not recommended to perform plain radiography, CT or MRI for the diagnosis of gout (LE 2b; GR B; DA 77%).

Recommendation 7: Ultrasound assists in the diagnosis of gout; crystal visualization is what establishes the definitive diagnosis (LE 4; GR C; DA 75%).

Recommendation 8: Ultrasound-guided puncture facilitates obtaining fluid or other samples for the diagnosis of gout (LE 4; GR C; DA 100%).

See **RS1.**

In recent years there has been significant progress in the knowledge and application of ultrasound to the study of rheumatic diseases. This imaging technique has many advantages, among which are the absence of radiation, its low cost compared with MRI and CT, appropriate reproducibility data, good patient acceptance, high resolution, the possibility of exploration in real time and its effectiveness as a diagnostic method. In the case of gout, in

addition to allowing visualization of normal and pathological anatomical structures, ultrasound provides information on the vascular flow of the scanned tissues.

Despite not being included in the recommendations published to date for the diagnosis of gout (73), ultrasound is an ideal procedure to detect crystal material in soft tissue. Due to their physical properties, MSU crystals deposited in joints reflect ultrasound waves more intensely than the tissue in which they are located, allowing easy viewing and making this procedure an accurate detection technique. It also improves the efficiency of US-guided arthrocentesis by facilitating the selection of synovial fluid extraction zones for the identification of crystals. For all these reasons, professionals who work with ultrasound propose its use for the diagnosis of gout.

VI.C.4.1. Why is ultrasound necessary in the diagnosis of gout?

Due to its recent introduction as a diagnostic method for gout, there has not yet been sufficient diffusion of the advantages of ultrasound or a generalization of its use in this disease, there being widespread ignorance among clinicians about its potential. Consequently, perhaps the first thing to ask is if ultrasound is necessary for the diagnosis of gout.

According to EULAR recommendations, the diagnosis of gout should be based primarily on the appearance of MSU crystals in synovial fluid or tophi (73). However, the reality of clinical practice is far from this recommendation. The results of GEMA (75), a study on the variation in the diagnosis and treatment of gout in our country, revealed that only 25.7% of the 804 patients studied had been diagnosed by demonstration of uric acid crystals, having observed similar findings in other studies (140). In most cases, the diagnosis of gout is based on the Wallace criteria published in 1977, without prior testing of their validity. The results of subsequent validation studies have shown rates that are far from excellence (sensitivity 65-68%, specificity 78-88%, 32% false negatives and 22% false positives) (141), and undertake to subscribe EULAR recommendations for the definitive diagnosis by demonstration of crystals. These data demand an explanation of the possible reasons for not using crystal visualization as a basis for diagnosis of gout.

The identification of MSU crystals has proven to be a sensitive and specific test for the diagnosis of gout, but its detection is conditioned by the presentation of the disease as acute arthritis or asymptomatic phase. In the case of acute arthritis, microscopic examination of synovial fluid had a sensitivity of 84% with a specificity of 100%, while in the intercritical period joints aspirate showed low sensitivity to 70%, maintaining a 95% specificity (73). In patients with asymptomatic hyperuricaemia the possibility of crystal detection is much smaller, appearing in only one in 19 cases (91). Moreover, the identification of crystals has a moderate - good interobserver reliability (kappa values between 0.35 and 0.63), which does not meet the standards of excellence desirable for such cases (73). All these data justify the use of clinical criteria in routine practice.

The evidence discussed suggests the need to modify the diagnostic strategy for gout from two perspectives: a) emphasis on the dissemination and implementation of clinical practice guidelines, and b) the search for new diagnostic approaches with appropriate validity parameters.

The availability of new diagnostic methods of a non-invasive nature often enjoys very good acceptance by clinicians and patients. In this sense, ultrasound can easily identify a series of

elementary lesions (122, 126, 142-146) (Table 6) which, even without being pathognomonic, can help define the existence of this disease with high post-test probability, or efficiently guide the diagnostic puncture.

VI.C.4.2. Validity of elementary ultrasound lesions in the diagnosis of gout

Each disease has specific sonographic findings. The combination of certain elementary lesions in certain locations helps us to establish the diagnosis of patients. In recent years there have been various studies to identify these elementary lesions and analyze their validity rates (122, 143-146). The results of these studies, although still not widely used and appreciated by the medical community, allow us to establish a new approach for the diagnosis of gout with appropriate parameters of accuracy and validity.

Various elementary ultrasound lesions have been associated with the diagnosis of gout. Probably the most useful and specific is the **"double contour sign."** This sign is produced by hyperechoic reinforcement of hyaline cartilage surface due to the reflection of ultrasound by impinging on MSU crystal deposits, a physical phenomenon which causes urate deposits to be seen as an increase in the cartilage interface surface to a thickness similar to the subchondral bone. Several studies have examined the validity of the double contour sign (122,144,146,147). Grassi et al. examined a group of 60 patients (34 with disease due to calcium pyrophosphate crystals and 26 with gout) with diagnosis confirmed by analysis of synovial fluid. Ultrasound examination showed that the double contour sign appeared only in patients with gout, while those with calcium pyrophosphate crystal deposition disease had hyperechogenic aggregates in the middle layer of the cartilage parallel to the cortical bone in the form of a thin irregular or dotted line (143). So chondrocalcinosis ultrasound images are clearly different from those of gout.

The second most useful sign or elemental lesion in the ultrasound diagnosis of gout are **hyperechoic areas** located in different locations, such as synovial joints, tendon sheaths, tendons or other soft tissues, having a sensitivity of 79% and a specificity of 95% (145). The dotted lines and hyperechoic aggregates in these same tissues have a sensitivity of 80% and specificity of 75%. The presence of hyperechoic areas or hyperechoic aggregates give ultrasound a high sensitivity of 96%, although the specificity drops slightly to 73% (145).

Ultrasound imaging of **erosions**, another gout characteristic, corresponds to a discontinuity of the cortical bone that appears in two perpendicular planes. Ultrasound has been shown to be three times more sensitive than radiography to detect erosion of less than 2 mm ($p < 0.001$) (122). In a study comparing the performance of ultrasound and conventional x-ray for the diagnosis of gout sensitivity and specificity rates of 31% (32/102 patients) and 93% (55/59 patients), were obtained for plain x-ray, compared to 96% (98/102) and 73% (43/59) respectively for ultrasound (145). The authors concluded that ultrasound is a much more sensitive technique than plain x-ray but less specific.

The presence of hyperechoic dots in the synovial fluid is a characteristic finding of microcrystal deposition diseases, both gout and chondrocalcinosis, but may appear in other processes such as osteoarthritis or RA. This fact enhances the diagnostic sensitivity but lacks specificity (145) (11).

Another proven benefit of ultrasound is the identification and measurement of tophi. In a study on characterization of tophi using different imaging techniques it was observed that ultrasound allowed visualising the presence of at least 1 tophus in joints where MRI revealed only images of suggestive nodules. In addition, aspiration of nodules showed the presence of MSU crystals in 83% of those identified as tophi by ultrasound (119).

Doppler ultrasound can also detect increased vascular flow in the synovium, tendon and inflammation tophi associated, so it is a useful procedure for diagnosing active, symptomatic or subclinical synovitis or tenosynovitis. The evidence shows that the Doppler signal is able to distinguish between inflamed and non-inflamed synovium both in asymptomatic patients with gout (10, 148), and in patients with hyperuricaemia.

Table 10. Elementary ultrasonographic lesions in gout.

Elementary ultrasonographic lesions in gout
Soft tissue oedema
Double contour sign
Hyperechoic areas with or without posterior shadowing
Hyperechoic aggregates
Cortical bone erosions
Dotted images in synovial fluid
Synovitis: Doppler signal

The utility of ultrasound for **guided aspiration** and subsequent identification of MSU crystals improves the diagnostic yield of this procedure. With the ultrasound study the most suitable locations for synovial fluid or tophus aspiration can be selected, allowing subsequent microscopic identification of crystals. This selection is not based solely on the presence of synovial fluid, but also on the extent of the deposits. In patients with asymptomatic hyperuricaemia the use of ultrasound for these purposes has increased the percentage of crystal identification to 34.6% (9/26) of patients with hyperuricaemia (148).

Although few reliability studies have been conducted, data available to date show good or excellent results. In the measurement of tophi intraclass correlation coefficient values greater than 0.90 were obtained for intraobserver assessments, and between 0.71 and 0.83 for interobserver reproducibility (147). Interobserver concordance studies have shown (kappa) values of 0.76 for elementary soft tissue lesions, 0.87 for detection of erosions (122), and 0.68 for the double contour sign in the knee (147). Moreover, in a recent analysis of five readers good or excellent interreader reliability data were obtained for detecting erosions, double contour, hyperechoic areas and Doppler signal, although these results do not only depend on each of the scanned lesions, but also on various joints studied, achieving superior results in knees and first metacarpophalangeal joints (144).

In terms of feasibility, only a few studies have been performed so far, although the use of an index based solely on the examination of four joints and two elementary lesions has been proposed, having shown good rates of face and content validity for the diagnosis of gout, and allowing examination of a patient in just six minutes (144).

In summary, ultrasound is a recently introduced imaging technique for the diagnosis of gout. A series of elementary ultrasonographic lesions were described with a sensitivity and specificity that allows their use in the clinical setting, although specificity is obviously lower than the gold

standard (crystal identification). Similarly, the reliability data are adequate or even superior to those reported for the identification of uric acid crystals in optical microscopy. Moreover, ultrasound improves the accuracy of guided puncture, thus increasing the diagnostic yield of synovial fluid or tophaceous material aspiration for the subsequent identification of crystals in the microscopic study. Finally, feasibility data are still limited, although published studies appear promising.

VII. ASSESSMENT

The history and examination of the patient with gout should help identify the status and severity of the disease and its impact on quality of life. It should also establish the extent of damage, and the associated comorbidity risk (73, 149). This will enable accurate treatment decisions, both short and long term, to achieve treatment goals: dissolve tophi, prevent acute episodes of inflammation, prevent tissue damage and achieve cure of the disease (149, 150). Table 11 presents a format for specific clinical history for the patient with MSU crystals disease.

Recommendation 9: In all patients with gout both the aetiology and the mechanism inducing hyperuricaemia must be assessed (LE 5; GR D; DA 92%).

VII.A. GENERAL ASSESSMENT

Recommendation 10: In the first assessment of a patient with gout a complete history should be taken, along with a complete general and musculoskeletal physical examination. (LE 5; GR D; DA 100%).

In the first assessment a **complete medical history** is taken, which includes, among other data, information on smoking habit, preferably pack-years, and alcohol consumption; date of menopause in women, and lifestyle habits, mainly related to physical exercise and diet. All these factors are important because they add comorbidity to the disease and are subject to change. It should be noted that smoking is not associated with the presence of gout, but it is associated with alcohol consumption and the increased cardiovascular risk observed in these patients (149-151).

Recommendation 11: Special attention should be paid to cardiovascular risk factors, using any of the available risk estimation tools (LE 5; GR D; DA 92%).

In addition, **cardiovascular risk comorbidities** are also recorded, including the presence of the various components of metabolic syndrome and renal function (149-152). It is essential to study cardiovascular risk since it worsens the prognosis of gout (153). This measurement can be made with any of the available assessment tools; the SCORE index (154) is one of the best suited to the Mediterranean lifestyle and is validated in a Spanish population with rheumatic disease (155). Any specific tool with which the physician is familiar can be used, however, such as the Framingham risk tables (156). The SCORE index can be calculated from the values of systolic blood pressure, total cholesterol, age, gender, and smoking habit (157), although there are also easy to use automatic calculators that incorporate additional information such as height, presence of diabetes and history of cardiovascular events (158). Similarly, and for the

same reasons, it is essential to study the presence of metabolic syndrome. There are numerous definitions of metabolic syndrome, but the most widely used are those of the World Health Organization (159) and the American Heart Association (160) (Table 12). Decreased **renal function** is another of the comorbidities to consider; it is the subject of a specific chapter in these guidelines. The identification and treatment of comorbidities and risk factors is part of the required assessment and comprehensive management of patients with gout. Finally, given that many treatments can be associated with hyperuricaemia, it is important to collect information on all drugs the patient takes and that may require dose adjustment.

Recommendation 12: The panel recommends to evaluate in patients with gout the magnitude of the attack and severity of the disease (LE 5; GR D; DA 92%).

Having identified the clinical stage of the disease, it is essential to carry out a specific assessment. For acute episodes, assessment should include pain, joint involvement (number and degree of tender and swollen joints), perceived health status, according to both the patient and the physician, and the degree of disability (Table 13). In chronic forms it is necessary to determine serum urate levels, the frequency and intensity of attacks, presence of tophi, pain, quality of life, functional capacity, joint involvement (number and size of tender and swollen joints), and the overall assessment of the patient's health status (Table 14). In the opinion of the expert panel this evaluation, designed by OMERACT to monitor patients participating in clinical trials, can be used in routine clinical practice considering that the domains studied are defined therapeutic goals.

VII.B. SPECIFIC ASSESSMENT

Recommendation 13: Specific assessment of patients with gout includes serum urate level, the frequency and intensity of attacks (number and size of tender and swollen joints), the presence of tophi, pain, quality of life, functional capacity, and overall assessment of health status (LE 5; GR D; DA 92%).

Having identified the patient's general characteristics, it is important to carry out a specific study of disease due to MSU crystals. Since 2002 the OMERACT group has worked on defining the areas of health to assess and designing measurement instruments. According to this group, the domains to be studied in patients with acute and chronic manifestations of gout must be five and seven, respectively (Tables 15 and 16). In addition, various specific measurement instruments have been designed and there are others under development (161, 162). These instruments, developed for monitoring patients in controlled clinical trials, meet the OMERACT filter of validity, sensitivity to change and reproducibility (163), and may be useful for patient-specific assessment in clinical practice. However, their limitations include the lack of tools for the assessment of some health domains (under development), and the lack of definition of criteria for adequate response to treatment.

The five domains that can be evaluated in the ***acute episode*** are pain and joint swelling, overall health status, response to therapy and physical function (164). **Pain** should be assessed by visual analogue scale (VAS) of 100 mm or Likert scale of 11 points. For **joint swelling** a 4-point

Likert scale is used, which can also allow to assess pain to joint tenderness. In addition, the homunculi of 66 swollen joints and 68 tender joints routinely used in the evaluation of patients with other rheumatic inflammatory pathologies can be used. Assessment of **overall health** status and **response to treatment** is conducted by both the patient and the physician, using a 5-point Likert scale. Finally, the HAQ (165) is used to evaluate **functional capacity**. Inflammation markers proposed by consensus are the erythrocyte sedimentation rate (ESR) in mm/h, and the C-reactive protein (CRP) in mg/dL, although there is no agreement on what is the best time for its determination. Finally, a consensus has not been reached on how to measure work disability in cases where it constitutes an important outcome, although the expert panel recommends the WAPAI instrument adapted for gout (166). Table 15 presents the clinimetric characteristics of different measuring instruments that have been evaluated to date.

In patients with ***chronic manifestations*** the first domain to consider is **serum urate levels**. The therapeutic response criterion is the long-term maintenance of serum uric acid <6.0 mg/dL, which will result in the resolution of tophi and acute attacks. Despite serum uric acid levels being a surrogate variable of the magnitude of the disease, its periodic determination is recommended due to its adequate clinimetric properties, low cost and ease of measurement. Although some experts support the repeated assessment of serum uric acid levels and use their long-term average value, the reality is that there is no consensus on what should be the appropriate frequency of measurements (161-164, 167).

The second domain is the **acute attack**, for which there is a measuring instrument, under development and not yet validated, which is based on three items: a) identification of the patient's recurrence, b) the presence of joint pain at rest and c) counting of swollen joints and increase in temperature (168).

The third domain is the **presence and magnitude of tophi**. Its measurement can be made with clinical or imaging methods. Among the first to be included are the Vernier gauge and tape measure. Although both methods show adequate validity and reproducibility in the hands of an expert, proper use requires time and skill, which has led OMERACT experts not to consider this domain as relevant. Measurement with imaging techniques (ultrasound, CT or MRI) is also adequate, although not recommended for use in clinical practice due to the need of equipment and trained personnel (125, 164).

The fourth area to assess is **quality of life**, an area particularly important both from the patient's and the physician's perspective. As happens in other rheumatic diseases, assessment of the quality of life in patients with gout is made with a generic and a specific instrument; the most commonly used are the SF-36, which has demonstrated its utility and sensitivity to change, and the specific gout assessing questionnaire (GAQv2.0-GI) (169). Both indices have been used in clinical trials, but there is little experience of their use in clinical practice. Functional capacity can be assessed with the HAQ, while pain and inflammation can be studied using previously discussed procedures for acute episodes. Furthermore, it is suggested to use the homunculus of 66/68 swollen and tender joints or Ritchie 44-joint count of swollen and tender joints (164). Tables 13 and 14 show data collection forms, with specific tools for acute episodes and chronic manifestations of the disease, taking into account OMERACT recommendations and adapting them to clinical practice.

Table 11. Clinical history for patients with gout.

IDENTIFICATION SHEET: • Date of birth (age): _____ • Gender: Male € Female € • Education: None € Primary € Secondary € Higher € • Profession: _____	FAMILY HISTORY: • History of gout in family: Yes € No € • Relationship: Parents € Siblings € Children €
PERSONAL NON-PATHOLOGICAL HISTORY • Smoking: Never smoked € Current smoker € Ex-smoker (>1 year) • Date began smoking:_____ • Date quit smoking:_____ • Years smoking:_____ • Number of cigarettes daily:_____ • Number of packs per year • Physical activity: Yes € No € • Type of exercise:_____	• Current alcoholism: Yes € No€ • Type of drink: • Frequency of consumption: • Amount consumed: • Date of menopause (women):_____ • High protein diet: Yes € No € • Type of proteins:_____
COMORBIDITY: • Hyperuricaemia: Yes € No € Date:_____ • Hypercholesterolaemia: Yes € No € Date:_____ • Hypertriglyceridaemia: Yes € No € Date:_____ • Hyperglycaemia : Yes € No € Date:_____ • Diabetes Mellitus (DM) non insulin dependent: Yes € No € Date:_____ • Kidney failure: Yes € No € Date:_____ • High blood pressure: Yes € No € Date:_____ • Cardiac failure: Yes € No € Date:_____ • Obesity: Yes € No € Date:_____ • Cutaneous psoriasis: Yes € No € Date:_____ • Normal renal function: Yes € No € • History of kidney-urethral calculi: Yes € No €	Treatment for comorbidities: Drug_____dose_____Date_____. Drug_____dose_____Date_____. Drug_____dose_____Date_____. Drug_____dose_____Date_____. Drug_____dose_____Date_____. Drug_____dose_____Date_____.
CARDIOVASCULAR RISK • SCORE points:	http://riskscore.lshtm.ac.uk/calculator.html
Metabolic syndrome: Yes € No €	
History of gout • Date of first acute attack: _____ • Number of attacks in past year:_____ • Date of last acute attack:_____ • Presence of tophi: Yes € No € • Type of joint involvement: Polyarticular: Yes € No € Oligoarticular: Yes € No € Monoarticular: Yes € No €	Treatment prior to acute attack Drug_____dose_____ Date_____. Drug_____dose_____ Date_____. Drug_____dose_____ Date_____. Drug_____dose_____Date_____. Drug_____dose_____Date_____. Drug_____dose_____Date_____.
Physical examination • Weight (Kg):_____ Height (m):_____ BMI:_____. • Truncal obesity: Yes € No €	Systolic BP:_____ Diastolic BP:_____
ADD SPECIFIC ASSESSMENT OF PATIENT ACCORDING TO TYPE OF MANIFESTATION (ACUTE OR CHRONIC)	
Concomitant treatment of hyperuricaemia and acute attack prevention :	Drug_____dose_____Date_____. Drug_____dose_____Date_____. Drug_____dose_____Date_____.
Consider changes in the drugs that increase serum uric acid levels	Diuretics, any type: Yes € No € Thiazide-type diuretics: Yes € No € Cyclosporin-A: Yes € No € Tacrolimus: Yes € No €
DEFINE THERAPEUTIC OBJECTIVES AND TIME FRAME TO ACHIEVE THEM	

Abbreviations: kg = kilogram; m = metres; BMI = body mass index; BP = blood pressure.

Table 12. Definitions of metabolic syndrome.

Definition of the World Health Organization
1. Insulin resistance • Presence of NIDDM • Elevated fasting blood glucose: ≥110 mg/dL • Altered glucose tolerance curve
2. Blood pressure (≥140/90 mmHg or pharmacological treatment)
3. Dyslipidaemia • Plasma triglycerides ≥150 mg/dL • HDL cholesterol ≤35 mg/dL in men and ≤40 mg/dL in women
4. Obesity • Body mass index ≥30 and/or • Waist/hip circumference ≥0.9 in men and ≥0.85 in women
5. Urinary albumin ≥20 mg/min 6. Albumin/creatine ratio ≥30 mg/g
Criterion: insulin resistance plus at least two of the other criteria
Definition of the American Heart Association
1. Hyperglycaemia: fasting glucose ≥100 mg/dL
2. Blood pressure: BP ≥130/85 mmHg
3. Dyslipidaemia • Plasma triglycerides ≥150 mg/dL • HDL cholesterol <40 mg/dL in men and <50 mg/dL in women
4. Truncal obesity • Waist circumference ≥102 cm in men and ≥88 cm in women
Criterion: presence of at least 3 of the above

Abbreviations: NIDDM = non insulin dependent diabetes mellitus; mg = milligram; dL = decilitre; mmHg = millimetres of mercury; min = minutes; g = mgrm; cm = centimetre.

Table 13. Specific clinical assessment (acute episode).

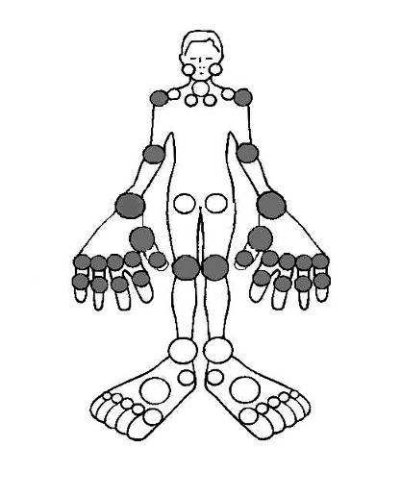
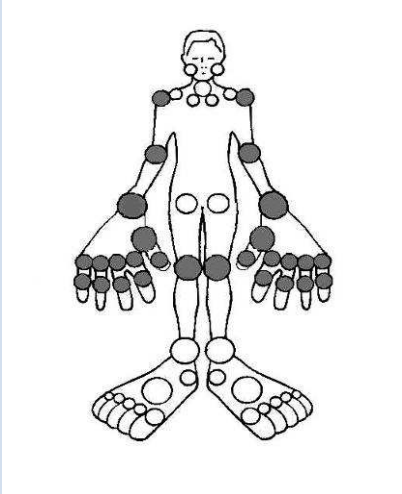
1. PAIN How much joint pain do you have today?	
2. No. of SWOLLEN JOINTS (68 joints)  Assessment of joint swelling by physician. None €, Mild €, Moderate €, Severe €	3. No. of TENDER JOINTS  Assessment of joint pain by physician. No pain €, Mild €, Moderate €, Severe €
4. PATIENT SELF-ASSESSMENT OF HEALTH STATUS How is the gout today? (mark the best option): Very good €, Good €, Normal €, Bad €, Very Bad €	
5. ASSESSMENT OF HEALTH STATUS BY PHYSICIAN How is the patient today?: Very Well €, Well €, Normal €, Poor €, Very Poor €	
6. PATIENT'S RESPONSE TO TREATMENT How do you consider response to treatment?: Very good €, Good €, Normal €, Poor €Very poor €	
7. HAQ	
8. Acute phase reactants	ESR, CRP
9. Work disability	WAPAI

Table 14. Specific clinical assessment (chronic episode).

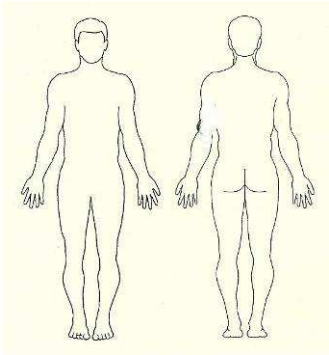
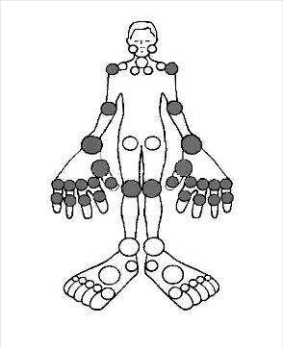
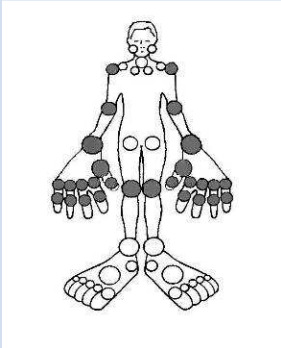
Serum uric acid levels: _____ mg/dL	
Number of gout attacks in the last year: _____	
Presence of tophi 	Identify a target lesion to measure The largest or the most symptomatic may be chosen Count the number of tophi:_____
No. of SWOLLEN JOINTS (68 joints)  Assessment of joint swelling by physician. No €; Mild €; Moderate €; Severe €	**No. of TENDER JOINTS (66 joints)**  Assessment of joint pain by physician. No pain €; Mild €; Moderate €; Severe €
FUNCTIONAL CAPACITY: HAQ	
Quality of Life: • Generic: SF-36 • Specific: GAQv2.0-Gout Impact	
PAIN How much joint pain do you have today? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ o ☐ None Very much	
PATIENT SELF-ASSESSMENT OF HEALTH STATUS How is the gout today? (mark the best option): Very good €, Good €, Normal €, Bad €, Very Bad €	
ASSESSMENT OF HEALTH STATUS BY PHYSICIAN How is the patient today?: Very Well €, Well €, Normal €, Poor €, Very Poor €	
Acute phase reactants	ESR, CRP.
Work disability	WAPAI

Table 15. Domains to evaluate, instruments and properties. Acute episodes.

Domain	Instrument	Clinimetric Properties				
		Feasibility	Face validity	Construct validity	Content	Reproducibility
Pain	5-point Likert scale: • 0 absence • 5 unbearable pain VAS of 100 mm	√ √	√ √	√ NA	√ NA	NA NA
Joint swelling	4-point Likert scale	√	√	NA	NA	NA
Joint pain	4-point Likert scale	NA	NA	NA	NA	NA
Response to treatment (patient)	5-point Likert scale	√	√	Si	√	NA
Response to treatment (physician)	5-point Likert scale	√	√	No	√	NA
Functional capacity	HAQ	√	NA	NA	NA	NA

Abbreviations: NA = not assessed; mm = millimetre; HAQ = health assessment questionnaire.

Table 16. Domains to assess, instruments and properties. Chronic manifestations.

Domain	Instrument	Clinimetric Properties				
		Feasibility	Face validity	Construct validity	Content	Reproducibility
Serum urate	Trinder Method	√	√	NA	NA	√
Attack	In preparation					
Tophus	• Physical measurement • Calibrator • Tape • Imaging methods • US • CT • MRI	√ √ No No No	√ √ √ √ √	√ √ √ ?	√ √ √ √	√ √ √ √
Quality of life • **Generic** • **Specific** **Functional capacity**	 SF-36 GAQv2.0-GI HAQ	 √ √ √	 √ √ √	 √ √ √	 √ √ √	 √ √ √
Pain	5-point Likert: • 0 absence • 5 unbearable pain VAS of 100 mm	NA NA	NA NA	NA NA	NA NA	NA NA
Assessment of disease status (patient)	5-point Likert scale	NA	NA	NA	NA	NA
Work disability	None					
Joint Swelling/Pain	None Possible: • Count of 66 or 44 swollen joints • Count of 68 or 44 tender joints					

Abbreviations: NA = not assessed; US = ultrasound; CT = computed tomography; MRI = magnetic resonance imaging; mm = millimetre; HAQ = health assessment questionnaire; VAS= visual analogue scale.

Table 17. English Version of HAQ.

	During the past week, have you been able to...	Without any difficulty	With some difficulty	With much difficulty	Unable to do
Dressing and grooming	1) Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
	2) Shampoo your hair?	☐	☐	☐	☐
Arising	3) Stand up from an armless chair?	☐	☐	☐	☐
	4) Get in and out of bed?	☐	☐	☐	☐
Eating	5) Cut up your own meat?	☐	☐	☐	☐
	6) Open a new carton of milk?	☐	☐	☐	☐
	7) Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Walking	8) Walk outdoors on flat ground?	☐	☐	☐	☐
	9) Climb up five steps?	☐	☐	☐	☐
Hygiene	10) Wash and dry your entire body?	☐	☐	☐	☐
	11) Get on and off the toilet?	☐	☐	☐	☐
	12) Take a bath?	☐	☐	☐	☐
Reach	13) Reach and get down a 5 lb object (e.g. a bag of sugar) from just above your head?	☐	☐	☐	☐
	14) Bend down to pick up clothing off the floor?	☐	☐	☐	☐
Grip	15) Open car doors?	☐	☐	☐	☐
	16) Open jars which have been previously opened?	☐	☐	☐	☐
	17) Turn taps on and off?	☐	☐	☐	☐
Activities	18) Run errands and shop?	☐	☐	☐	☐
	19) Get in and out of a car?	☐	☐	☐	☐
	20) Do chores such as vacuuming, housework or light gardening?	☐	☐	☐	☐
	Check any activities for which you usually need help from another person: ☐.....Dressing/grooming ☐.....Walking, strolling ☐....Opening and closing things (Grip) ☐.....Arising ☐ .....Personal hygiene ☐....Errands and household chores ☐.....Eating ☐.....Reaching				
	Check any of these **utensils** that you use regularly: ☐.....Wide handle cutlery ☐.....Opener for previously opened jars ☐.....Cane, crutches, walker or wheelchair ☐.....Special bath seats or bar ☐.....High seat for toilet				

0	0.000
1	0.125
2	0.250
3	0.375
4	0.500
5	0.625
6	0.750
7	0.875
8	1.000
9	1.125
10	1.250
11	1.375
12	1.500
13	1.625
14	1.750
15	1.875
16	2.000
17	2.125
18	2.250
19	2.375
20	2.500

VII.C. LABORATORY TESTS

The utility of laboratory tests in gout varies depending on the different stages of the disease. In recurrent episodes of acute inflammation, analytical measurements allow diagnosis of the process and its comorbidities, whereas in intercritical periods and periods of chronic disease they facilitate diagnostic evaluation and proper monitoring.

VII.C.1 . Episodes of acute inflammation

During the **first episode of acute inflammation** laboratory tests should include two major aspects:

VII.C.1.1. Demonstration of MSU crystals in synovial fluid

Synovial fluid study is the first step for the accurate diagnosis of an episode of acute inflammation. In general, synovial fluid aspiration from the joint or affected bursa is a simple procedure, even in small joints such as the MTP (80). In addition, it allows the study of the material from a nodule suspected of being a tophus.

In acute gouty arthritis macroscopic appearance of the synovial fluid is inflammatory, with a yellow opalescent or white chalky colour if tophaceous material is aspirated (Image 1). For direct smears a drop is placed on a slide with a coverslip and viewed immediately with a polarized light microscope with first order red compensator in search of microcrystals, which will allow differential diagnosis with other microcrystalline arthritis, such as that produced by pyrophosphates.

MSU crystals are needle-shaped. They exhibit intense refringence (very bright with the polarizer) (Image 2) and negative elongation (yellow in parallel alignment to the axis of the compensator and blue in perpendicular alignment) (71) (Image 3). Demonstration of MSU crystals constitutes a definitive diagnosis of gout and should be performed, whenever possible, before any arthritis of unknown origin (73).

Septic arthritis is the first differential diagnosis of acute gouty inflammation. Therefore, the synovial fluid should be sent to the laboratory for microbiological analysis and cell count, as both processes can occur simultaneously (101, 103).

Cell counts are typically high, with a number of neutrophils that can range from 2,000 to 50,000 per microliter. The highest counts should lead to suspicion of infection, although there is not always a relationship between neutrophil count and infectious processes. Similarly, differential diagnosis can be considered with other pathologies such as crystal arthritis, reactive arthritis, and even rheumatoid arthritis (170) (Table 18).

Table 18. Characteristics of various types of synovial fluid

Characteristic	Normal	Non-inflammatory	Inflammatory	Purulent	Haemorrhagic
Colour	Clear	Yellow	Opalescent yellow	Yellow or green	Red
Leukocytes/mm3	<200	200 - 2000	2,000-50,000	>50,000	Same as in blood
Protein (g/dL)	1 - 2	1 - 3	3 - 5	3 - 5	Same as in blood
Glucose (mg/dL)	Same as blood	Same as blood	25% < than in blood	< to 75% of level in blood	Same as in blood

Abbreviations: mm = millimetres; g = gram; mg = milligram; dL = decilitre.

VII.C.1.2. Analysis of blood and urine

During the acute episode CBC and biochemical profile must be performed urgently, including measurement of glucose, urea, creatinine, GOT (glutamic oxaloacetic transaminase), GPT (glutamic pyruvic transaminase), ions and CRP. Furthermore, a must be conducted.

The results of these tests can be useful to rule out other causes of acute arthritis or highlight important comorbidities for the therapeutic management of acute episodes, such as diabetes, kidney failure, liver disease or blood disease.

The amount of serum uric acid during the acute episode deserves special mention. In this phase of the disease, the serum concentration of uric acid decreases in up to 40% of patients due to increased renal urate clearance (115). Therefore, uric acid levels can be elevated (which would support the diagnosis), but also normal, in which case the measurement must be repeated after at least two or three weeks.

In **recurrent episodes of acute inflammation** in patients already diagnosed new analysis is not required, unless a complication is suspected or there is poor outcome of arthritis despite adequate treatment.

VII.C.2. Intercritical period: first assessment after an acute episode

Recommendation 14: Once the acute episode is overcome the patient with gout should be studied by blood and urine analysis for determination of the following parameters: complete blood count, blood chemistry panel, liver and kidney functions, acute phase reactants and study of urinary uric acid clearance (LE 5; GR D; DA 100%).

Once the first episode has been resolved, or after an acute attack in undiagnosed patients, the patient will be seen after at least three weeks to assess hyperuricaemia and conduct a full study to characterize the disease and identify its causes. This study will include the following tests:

1. CBC: the objective is to verify the normality of cell lines for future treatments and exclude haematologic and lymphoproliferative pathologies as a cause of disease.
2. C-Reactive Protein (CRP, preferably high sensitivity): control of possible residual or active inflammatory activity.
3. Blood chemistry: determining glucose, urea, ions, lipid profiles, hepatic and renal function.
    - Liver panel: it will reveal the liver function and highlight the frequent association with non-alcoholic fatty liver (171), alcoholism and possible drug toxicity.
    - Lipid profile: more than 60% of patients with gout have associated hyperlipidaemia (172, 173), which may require the use of drugs of combined action, such as fenofibrate, which in addition to being lipid-lowering is uricosuric (73).
    - Glucose and study of type II DM if applicable: it has been shown that patients with gout have a 15%prevalence of type II DM (173), with a relative risk (RR) of 1.70 (95% CI: 1. 38; 2.11) concerning hyperuricaemia (172).
    - Renal function: Renal function is decreased in 30-40% of gouty patients (75, 174). Renal impairment is due to different mechanisms. On the one hand, chronic kidney disease (CKD) is a cause of hyperuricaemia, particularly in patients with comorbid chronic hypertension or DM; on the other hand, gout can also cause renal calculi and interstitial deposition in up to 40% of patients (175).
    - Glomerular filtration rate (GFR): the two most frequently used formulas are the Cockcroft-Gault (CG) to estimate creatinine clearance and the MDRD (Modification of Diet in Renal Disease) or CKD-EPI equation for estimating glomerular filtration rate (176).
4. Elemental analysis of urine sediment: pH study (lithiasis risk factor), density and abnormal findings. Urine sediment: presence of oxalate and/or crystals.
5. Serum uric acid assessment: this is the major risk factor for the development of the disease (73) and the most important biomarker as a diagnosis outcome measure (163), since uric acid levels are directly related to the incidence of gouty arthritis and its decrease with disease control.
6. Renal urate excretion study: the leading cause of hyperuricaemia in primary and secondary gout is decreased renal excretion of uric acid (177, 178). The parameters to assess renal excretion are:
    - 24-hour uricosuria: it has been the most common form of evaluating this function, although it has some limitations because it does not provide information on the renal management of urate and its value depends on the level of serum uric acid.
    - Urine uric acid/creatinine ratio: this is an index of renal excretion. Values greater than 0.7 mg in the presence of normal renal function may be indicative of endogenous overproduction.
    - Uric acid clearance (UaC): it evaluates the renal excretion of uric acid and is especially useful in patients with decreased glomerular filtration rate (CKD, grade 3-5). It allows assessment of the baseline risk of urolithiasis in patients susceptible to treatment with uricosurics. Since the clearance does not change during treatment with xanthine oxidase (XO) inhibitors, the measurement can be made during follow-up in patients treated with these drugs (177).
    - UaC: urine volume x (Urine uric acid/ serum uric acid) (volume * Uua/Pua/1400)

- Fractional excretion of uric acid (Feua) assesses renal excretion in patients with normal renal function

$$Feua = (Uur \times CRP)/(Ucr \times Pur) \times 100$$

Uua = urinary concentration of uric acid
Pcr = plasma concentration of creatinine
Ucr = urinary concentration of creatinine
Pua = plasma concentration of uric acid

- Simkin index: expresses urate excretion (mg) per deciliter of glomerular filtration

$$SI = (Uua \times Pcr)/Ucr$$

This index has the advantage that it can be done with voided urine. However, it also has some drawbacks: since the formula includes the Ucr/Pcr ratio, in patients with CKD the numerator increases and the denominator decreases, resulting in a higher final score and a possible false positive of normal excretion. The overall correction with clearance is not adequate, unless it is stratified by level of kidney function (177).

Knowledge of the cause of hyperuricaemia can guide, at least in theory, the choice of agents that decrease synthesis (allopurinol, febuxostat, uricase) and drugs that increase excretion (benzbromarone). Restriction on the use of benzbromarone by the AEMPS (179) limits the establishment of pathophysiological treatment and unifies initial therapy of all gouty patients with allopurinol or febuxostat, leaving the use of benzbromarone only for cases with failure of other available urate-lowering drugs licensed for this indication.

7. Microcrystals study: If the patient has not been diagnosed in the acute episode through identification of urate crystals, aspiration of synovial fluid should be attempted during the intercritical phase. Aspiration is performed in the most frequently affected joint (first MTP, knee, etc.). The presence of intraarticular crystals has been shown in asymptomatic joints, especially in patients not treated with urate-lowering drugs (80, 90). In this regard, the EULAR group set as a recommendation conducting intercritical arthrocenthesis whenever possible (73).

Furthermore, MSU crystals can also be seen in the material extracted from puncturing a tophus. One way to increase the likelihood of viewing these crystals is to dilute the synovial fluid with a few drops of ethanol aspirated into the extraction syringe (ethanol or methanol as fixatives do not dissolve urate crystals, unlike formaldehyde).

Ultrasound, if available, can help us identify urate deposits and perform a US-guided puncture (143).

If diagnosis is not possible in the intercritical phase the patient should be invited to make contact during the next episode of acute arthritis.

VII.C.3. Intercritical Period: successive controls

VII.C.3.1. Patients treated with drugs reducing uric acid synthesis

Recommendation 15: Once urate-lowering treatment has been initiated, laboratory tests should be performed to verify the achievement of the therapeutic goal (serum uric acid levels <6 mg/dL), and to monitor possible comorbidities and drug toxicity (LE 5; GR D; DA 100%).

In patients treated with drugs that reduce the synthesis of uric acid (allopurinol and febuxostat) an analytical control must be performed at 4-8 weeks of initiation of treatment to assess the level of serum uric acid and possible toxicity. Such monitoring shall include: complete blood count, blood chemistry and urine CRP (to estimate the level of inflammation) and TSH if treatment started is febuxostat.

The second control will take place within three months of the first. In principle, this time is usually sufficient to achieve the therapeutic goal of reaching a blood urate concentration of <6 mg/dL and <5 mg/dL in patients with severe gout. In cases which do not reach this result a treatment adjustment should be considered. The analytical control is similar to that described for six weeks with therapeutic adjustment every three months to reach the desired serum uric acid level.

Having achieved the therapeutic goal controls shall be conducted every 6 months or at least once a year, depending on the patient's urate load. When the patient has reached a steady state in the absence of acute episodes and disappearance of tophi, controls may become annual.

VII.C.3.2. Patients treated with uricosurics

Within two weeks of starting treatment with benzbromarone a study of liver function should be carried out and subsequently full analytical control with measurement of GFR and fractional excretion of uric acid (FEUA) to evaluate safety and efficacy. The periodicity of subsequent checks, every six weeks to three months, will vary depending on the response to treatment and will always follow the recommendations of the SMPC, indicating controls every 2 weeks or according to clinical unit protocol (180, 181).

VII.C.3.3. Patients treated with uricase

In patients treated with uricases (rasburicase or pegloticase) due to lack of sufficient response or intolerance to other urate-lowering drugs, it is recommended to determine the activity of glucose-6-phosphate dehydrogenase and catalase before starting the administration of the compound.

Table 19. Laboratory tests in patients with gout.

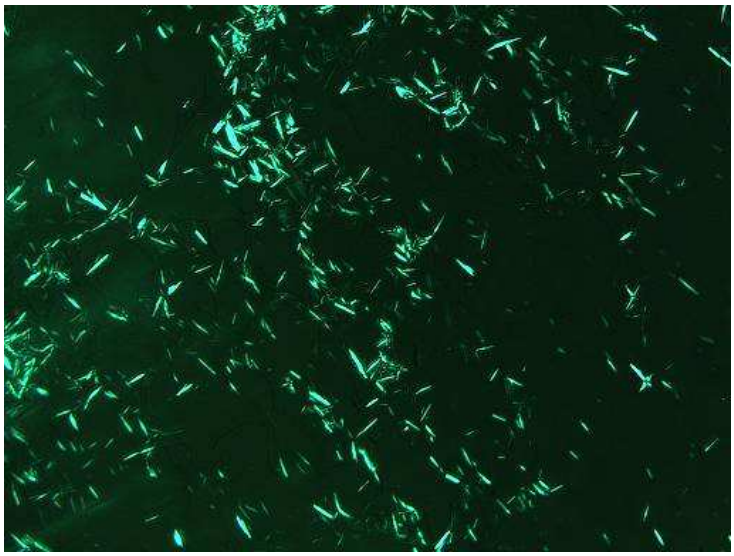
	ASSESSMENTS	MICROCRYSTALS DIAGNOSTIC STUDY	BLOOD AND URINE STUDIES
Acute episode	First	• Arthrocentesis • Count • Culture • Microcrystals study	• CBC • CRP • Elemental biochemistry • Urine (elemental/sediment)
Acute episode	Successive	Synovial fluid study if there is diagnostic uncertainty	Study only required if there is diagnostic uncertainty
Asymptomatic post-episode period or permanent activity	At 4-6 weeks after the acute episode: assessment of urate management and the presence of comorbidities	In undiagnosed cases trying to prove the presence of MSU crystals in asymptomatic joints or tophi.	• Blood glucose • Lipid profile, liver and renal functions • CBC, LDH • ESR and CRP • Uricosuria (24 h) • GFR and uric acid
	Between 6 and 12 weeks after initiation of urate-lowering treatment: Serum uric acid control and drug toxicity	In undiagnosed cases trying to prove the presence of MSU crystals in asymptomatic joints or tophi	• CBC • Lipid profile, liver and renal functions (if applicable) • CRP
	At 3 months: serum uric acid control and toxicity		• CBC • Lipid profile, liver and renal functions (if applicable) • CRP
Serum uric acid >6 mg/dL, tophus and/or inflammatory activity	Quarterly control of serum uric acid and inflammatory activity. Adjust treatment if with uricosurics		• Blood glucose • CBC • Lipid profile, liver and renal functions (if applicable) • ESR, CRP • Uricosuria (24 h) • GFR and uric acid • Fractional excretion of undissociated uric acid in urine
Serum uric acid <6 mg/dL. Absence of arthritis and tophus	Control every six months to three years and annually thereafter		• Blood glucose • CBC • Lipid profile, liver and renal functions (if applicable) • ESR, CRP • Uricosuria (24 H) • GFR and uric acid

Abbreviations: CRP = C-reactive protein; MSU = Monosodium urate; ESR = erythrocyte sedimentation rate; mg = milligram; dL= decilitre; h= hours; GFR = glomulerar filtration rate.

Image 1. Aspiration of tophaceous material.

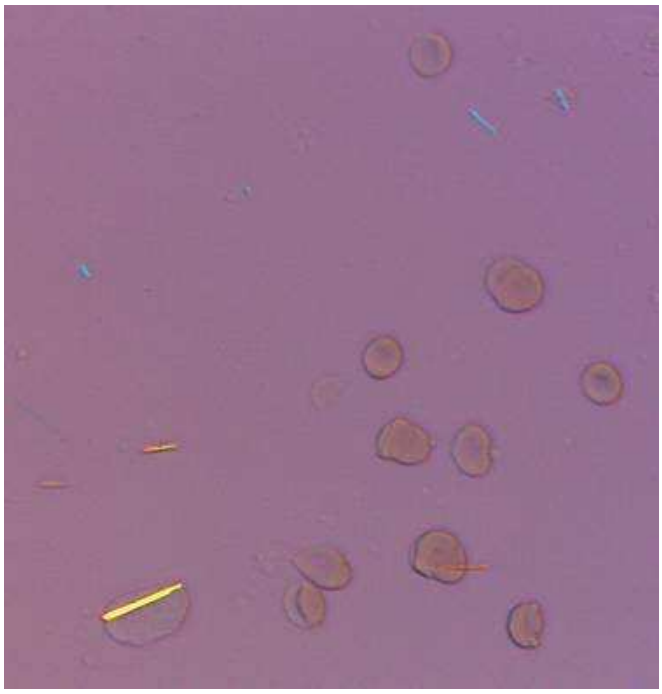
Courtesy of Dr. Mercedes Jiménez Palop

Image 2. MSU crystals under optical microscope with intense birefringence under polarizer.



Courtesy of Dr. Mercedes Jiménez Palop

Image 3. Urate crystals under optical microscope with polarizer and first-order red compensator.



Courtesy of Dr. Mercedes Jiménez Palop

VIII. GOUT AND KIDNEY FAILURE

VIII.A. INTRODUCTION

Among the diseases associated with gout, kidney failure is the most important and most influences treatment, since 40-50% of gout patients have some degree of renal dysfunction. Virtually none of the first-line drugs for treatment of gout is free of contraindications or significant limitations for use in patients with kidney failure. Therefore, this group of patients requires a particularly careful reading of the available evidence in order to achieve an appropriate balance between the benefits and risks of treatment.

The link between gout and kidney function is very close including, among others, renal urate transport as the main determinant of uric acid clearance and the mutually causal relationship between gout and chronic kidney failure. The identification of membrane transporters with marked specificity for urate in the renal proximal tubule has improved the understanding of the mechanisms of renal excretion of this anion, and lays the foundation for possible therapeutic targets for gout that are still under study. Moreover, the relationship between gout and chronic kidney disease (CKD) has persisted throughout history; before the introduction of urate-lowering therapy a high proportion of patients with gout had chronic kidney failure, and conversely, a high percentage of patients with kidney failure had gout. However, the idea that gout is in itself a major cause of kidney failure has been losing credibility over time, since there is a significant association between gout, hyperuricaemia and various cardiovascular, and therefore renal, risk factors. In fact, in the U.S. registry it is considered that under advanced chronic kidney disease, the prevalence of gouty nephropathy is only 0.02% (182), and is currently thought that gout is a rare cause of advanced CKD in need of kidney replacement therapy (183).

Despite the fact that the capacity of hyperuricaemia and gout to produce, by themselves, a significant deterioration of renal function is subject to dispute, there is no doubt about the reverse situation, i.e., that kidney failure itself favours the development of both hyperuricaemia and gout (178, 184). Between 30% and 60% of gout patients have some degree of renal dysfunction defined by a glomerular filtration rate less than 90 mL/min/1.73 m^2, calculated with the Cockcroft-Gault equation corrected for ideal body weight (185). In the U.S. the prevalence of CKD in patients with gout rises to almost 40% (174).

Among the many pathologies associated with gout (hypertension, heart failure, coronary heart disease, insulin resistance, etc.), kidney failure is the most important and most influences treatment, so it receives particular attention in these guidelines. The degree to which kidney disease affects the management of gout is easily noticeable when analysing the options available to reach intended therapeutic targets that include the following:

1) Resolving acute attacks as quickly and safely as possible
2) Prevent recurrence of attacks
3) Prevent or reverse MSU deposits

Achieving these objectives is more difficult in patients with CKD because of the potential complications of many of the medications indicated for gout (186). For example, NSAID use is

contraindicated in the control of acute attacks and preventing their recurrence because they increase the risk of acute and chronic kidney damage. Colchicine is limited (and even contraindicated in patients with advanced CKD) to avoid potential adverse effects on the muscular or nervous system. The use of urate-lowering therapy for preventing deposition of MSU may limit both treatment with uricosurics due to their theoretical lithiasis promoting effect or toxicity, as well as uricostatics such as allopurinol whose recommended doses in patients with CKD impede reaching target uric acid levels. New and effective therapeutic alternatives such as febuxostat also have limitations in patients with CKD grades 4 and 5, since at present they are not recommended for use in patients with GFR less than 30 mL/min or kidney transplant recipients, due to the lack of clinical trials in this population.

These limitations do not represent exceptional situations in clinical practice. However, the number of CKD patients in clinical trials is significantly lower than the patients with gout and normal kidney function. Therefore, it is quite common to have to base treatment decisions on data from studies conducted with small numbers of patients or with a short-term follow-up.

The above comments highlight the importance of carefully analysing both the benefits and risks of treatments. The benefits are based on the potential progression of this entity to severe forms (182), which can be associated with multiple cardiovascular complications such as heart disease and stroke (187, 188); can significantly increase the prevalence of urolithiasis (189), and can seriously affect the quality of life of patients with uncontrolled gout (22, 190). On the other hand, the failure of the treatment of gout entails high healthcare costs (149, 152, 191). Regarding the risks, it is important to note that 35-50% of an unselected population of patients with gout had major contraindications for treatment with NSAIDs, colchicine, corticosteroids or probenecid according to FDA criteria (192). Therefore, the challenge posed by the presence of CKD in patients with gout is to assume that the achievement of therapeutic goals proposed for patients with normal renal function involves higher risk as a cost. This necessitates a particularly close and critical reading of the literature on the subject, because when there are a number of therapeutic alternatives it is easier to accept a contraindication, even when it is relative, than when there are various options.

This chapter will attempt to summarize data from the current literature on how the presence of kidney disease determines the treatment recommended by physicians. The narrative will attempt at all times to avoid repeating generalities regarding the treatment of gout that are addressed in other chapters of these guidelines, although sometimes the justification for a recommendation requires recalling its theoretical basis.

VIII.B. TREATMENT OF ACUTE ATTACKS

Corticosteroids are the drugs of choice for acute episodes in patients with renal dysfunction. When their use is discouraged (e.g. diabetic patients), low-dose colchicine is recommended and treatment should start as soon as possible. Unlike what happens in patients with normal kidney function, the use of NSAIDs should be avoided.

In general, the success of the therapy in these situations is more dependent on the promptness of beginning treatment than the drug used. In patients with normal kidney function the drugs of choice are NSAIDs, colchicine, corticosteroids and corticotropin (ACTH or Cortrosyn).

VIII.B.1. Non-steroidal anti-inflammatories

At high doses these drugs have shown efficacy in the treatment of acute episodes of gout, both traditional such as cyclooxygenase 2 selective inhibitors and, secondarily, prostaglandin inhibitors.

Renal prostaglandin production is scarce in healthy euvolemic subjects, so the haemodynamic effect of these drugs is not relevant and there is no toxicity at this level (193). However, the secretion of prostaglandin, prostacyclin and thromboxane A2 is very important for maintaining renal haemodynamics in low perfusion. Therefore, the inhibition of prostaglandin synthesis in pathological situations such as CKD, congestive heart failure, cirrhosis, advanced age, volume depletion or diuretic treatment (194), causes reduced renal vasoconstriction and blood flow (195). This in turn can cause proteinuria, salt and water retention, hypertension, hyperkalaemia (196), and even acute tubular necrosis, acute interstitial nephritis (197-199), and chronic kidney damage (200-202). In patients with CKD there is no safe dose defined, so NSAIDs should be avoided even in short cycles. In any case, if their use is considered unavoidable, they should be used for the shortest time possible and renal function should be monitored closely.

VIII.B.2. Colchicine

Recommendation 16: In patients with CKD, the use of oral colchicine can be assessed to reduce the severity of an acute attack, following SmPC specifications (LE 1b, GR A, DA 92%).

Although its efficacy and safety have not been compared in the treatment of acute episodes in relation to NSAIDs, oral colchicine is effective in reducing the signs and symptoms of an acute attack (201).

Intravenous administration has been associated with potential fatal complications (203). Following oral administration it is rapidly absorbed and metabolized in the liver by cytochrome P450 3A4 (CYP3A4) and it is also a substrate for P-glycoprotein or multidrug transporter 1. It is

excreted via biliary and renal excretion, with approximately 20% of the compound excreted by the kidney, so that its clearance is significantly decreased in the presence of chronic kidney disease. In a study of a single oral dose of 1 mg of colchicine in familial Mediterranean fever patients, there was a 4-fold increase in the half-life of the drug in patients with advanced kidney failure (204). This can cause intracellular accumulation and toxicity (205) which in turn can appear as vacuolar myopathy, axonal neuropathy or neutropenia (206).

Gastrointestinal toxicity and difficulty of management in CKD patients confine its use mostly to acute attacks in these patients. However, before completely ruling out its use, we should carefully consider two fundamental aspects: the dose used and interactions with other drugs.

Regarding the dose, a recent study showed that administration of low doses (1 or 2 mg followed by 0.6 mg in 1 hour) in the first 12 hours of onset of symptoms was as effective as higher doses despite displaying a frequency of adverse effects similar to placebo and significantly lower than in the high dose group (207).

Furthermore, it should be noted that acute toxicity of colchicine occurs mainly in patients with simultaneous administration of cytochrome P450 (CYP3A4) and P-glycoprotein (P-gp), in particular macrolides, cyclosporine, statins and calcium channel blockers (verapamil and diltiazem) (208, 209). In fact, the toxicity of colchicine is probably more related to concomitant medication than to the drug itself (210). Still, we must keep in mind that statin therapy is currently recommended for all patients with CKD because of their tendency to accelerated atherogenesis (211), which increases the risk of rhabdomyolysis in this group if colchicine is used concomitantly.

Recommendation 17: In patients with CKD, consider discontinuing statins while using colchicine (LE 3a; GR B; DA 70%).

VIII.B.3. Corticosteroids

Corticosteroids are especially recommended in cases where NSAIDs and colchicine are contraindicated, a situation common in patients with CKD (149, 152); therefore they should be considered the first choice of treatment for acute episodes in this group of patients.

Nevertheless, it should be noted that the current most common aetiology of kidney disease in patients in renal replacement therapy, both prevalent and incidental, is diabetes mellitus. In some countries, diabetes is responsible for about half of the incidental cases of kidney disease (212). In this group high-dose corticosteroids are contraindicated (213).

Recommendation 18: In cases of CKD and diabetes, a therapeutic option for the treatment of acute gout may be colchicine rather than NSAIDs or corticosteroids (LE 3a; GR B; DA 75%).

VIII.B.4. Corticotropin (ACTH)

Recommendation 19: In case of CKD, note that corticotropin has similar indications and efficacy to corticosteroids in the treatment of acute gout attacks (LE 1b; GR A; DA 82%).

Corticotropin has some indications and similar efficacy to corticosteroids in the treatment of episodes of acute inflammation (214-216).

VIII.B.5. Interleukin-1 antagonists

They can be very effective in patients with contraindications to the other options (CKD, diabetes and liver disease) (218, 219).

VIII.C. PROPHYLAXIS FOR RECURRENCE OF ACUTE INFLAMMATION ATTACK

Patients with CKD should avoid using NSAIDs and consider colchicine, a compound with a potentially superior safety profile than currently assigned, provided that the dose is adjusted and simultaneous use of potentially myotoxic drugs is avoided.

Recommendation 20: In patients with CKD and gout NSAIDs are not recommended for the prevention of new attacks (LE 3a; GR B; DA 92%).

In patients with CKD and gout NSAIDs are not recommended for the prevention of new attacks.

The recommendation not to use NSAIDs in patients with renal dysfunction, regardless of the duration of treatment, and insufficient effectiveness of corticosteroids for the prophylaxis of attacks (e.g. observed in transplant patients, in whom their use as low-dose immunosuppressants does not seem to prevent them) very significantly limits the options available for the prophylaxis of acute attacks in these patients; therefore the role of colchicine merits special attention.

Recommendation 21: In patients with CKD and gout the use of colchicine for prophylaxis of new attacks can be assessed using the Summary of Product Characteristics (LE 2b; GR B; DA 92%).

Low-dose colchicine markedly reduces seizure frequency when associated with urate-lowering therapy. However, the use of this compound in patients with renal dysfunction must incorporate certain precautions. In this regard, it is recommended to reduce the dose to 0.5 mg/day with creatinine clearance 35-50 mL/min and 0.5 mg every 2-3 days when kidney function is less than 35 mL/min (220). In addition, since dialysis does not allow clearing the drug, it is recommended to avoid the use of colchicine in patients undergoing this procedure,

since the risk of toxicity may be high (178). In fact, in Spain the colchicine SmPC expressly contraindicates its prescription in patients with GFR less than 30 mL/min (221).

Although these recommendations seem reasonable, the reality is that they are unsupported by long-term safety and efficacy studies and strict compliance would, in clinical practice, leave patients with CKD, i.e., almost half of all patients with gout (174), no therapeutic options for prophylaxis of acute episodes. The results of studies using "adjusted" doses in a significant number of patients suggest that the drug's safety allows its use in this group of patients.

The use of colchicine as maintenance therapy in 50 patients with CKD and creatinine values above 1.5 mg/dL (mean 3.2) and glomerular filtration rate of 35 mL/min only produced one case of toxicity (2.5%) in the form of myotoxicity [creatine kinase (CK) 3,809 U/L], which reversed upon discontinuation of the drug (222).

A recent compilation of phase III trials assessing the effectiveness of urate-lowering treatment with febuxostat found that 59% of the total 4,101 patients enrolled had a GFR of less than 90 mL/min. Sixty-eight percent of patients received prophylaxis with colchicine (0.6 mg/day) and the rest with an NSAID (usually naproxen, 250 mg twice a day). Prophylaxis was maintained for 8 weeks in about half of cases, and for 6 months in the other half (223-225). The difference in the occurrence of diarrhoea among those using colchicine or other prophylaxis was only 1.8% (of 4,101 patients) in all three studies. In the group with preventive maintenance treatment for 6 months (2,269 patients), the frequency of diarrhoea was lower among those who received colchicine than in patients treated with NSAIDs, although the differences did not reach statistical significance. Overall, prophylaxis tolerance was good (226).

These data suggest that colchicine tolerability is reasonable at the indicated doses in patients with CKD, at least in grades 1, 2 and 3. Nevertheless, it is prudent to monitor possible side effects by controlling CK, transaminases and blood count. As already mentioned, the frequent use of statins in these patients determines the use of the compound due to the increased risk of rhabdomyolysis (211), so suspension of the use of statins is recommended during the use of colchicine.

VIII.D. URATE-LOWERING MEASURES

Allopurinol, even at doses higher than historically recommended, benzbromarone and febuxostat are safe and effective alternatives for urate-lowering treatment of patients with CKD.

Recently published recommendations advise urate-lowering therapy in patients with gout who have more than one acute episode per year, arthropathy, tophi, uric acid lithiasis, or need for diuretic therapy, since they are the groups most at risk of further attacks (227 - 231). However, despite the fact that the guidelines of the British Society for Rheumatology and the American College of Rheumatology consider kidney failure as reason enough to start such therapy in patients with gout (152), this assumption was not considered in the EULAR recommendations (149).

The results of some studies have suggested that the reduction of uric acid by urate-lowering treatment slows progression of kidney disease, but they failed to exclude the effect of other factors such as diet (protein intake), controlling blood pressure or other therapeutic measures (232-236).

VIII.E. DIET

Although there is some controversy, numerous publications suggest that moderate protein restriction slows the progression of kidney disease (237-241), so it is a measure recommended by current guidelines (242). In patients with CKD and gout consumption of white fish and low-fat white meats as source of protein can be especially advisable, with the dual aim of slowing the deterioration of kidney function and decreasing serum uric acid levels.

VIII.F. URICOSURIC AGENTS

Although the main indication of XO inhibitors is hyperuricaemia secondary to urate overproduction, the reality is that these drugs are used in the majority of patients (243, 244), without taking into account that the source of hyperuricaemia in 90% of cases of gout is decreased renal excretion of uric acid (less than 800 mg/day, with clearance of less than 6 mL/min), which in theory would make uricosuric agents the basis of urate-lowering treatment.

Within this group of drugs, the indication of probenecid and sulfinpyrazone (not marketed in Spain) is limited to patients with normal kidney function, because both their effectiveness and that of losartan is low in patients with CKD (149). Losartan is commonly used in the treatment of hypertension without any reported increased risk of nephrolithiasis. Its uricosuric effect is relatively modest and transient, reaching a plateau at doses of 50 mg/day, although its role in the treatment of gout has not been studied (245).

Recommendation 22: In patients with mild/moderate CKD and gout the uricosuric drug of choice is benzbromarone at doses of 50-200 mg/day (LE 1b, GR A, DA 91%).

In patients with mild/moderate CKD the uricosuric drug of choice is benzbromarone at doses of 50-200 mg/day (152). This compound is well tolerated and its efficacy is superior to that of allopurinol, both in patients with normal renal function (246, 247) and patients with CKD (180, 248-251). Although benzbromarone can reduce the effectiveness of allopurinol in increasing the clearance of oxypurinol, the association of both compounds is superior to the isolated administration of the former (252, 253). This is because the urate-lowering effect of benzbromarone is more potent than its oxypurinol clearance action (180, 254, 255).

The possibility of severe hepatotoxicity, though its occurrence is rare, has limited its use (256). However, in a retrospective series of 200 patients treated for 5 years with benzbromarone at doses of 75-100 mg/dL there was no significant hepatotoxicity, so that some authors have questioned the potential likelihood of this compound to produce the serious hepatotoxicity symptoms described (257).

The use of uricosurics has also been limited by the possible occurrence of urolithiasis. The urinary changes that promote nephrolithiasis due to uric acid are hyperuricosuria, low urinary pH and decreased urine volume (258). Although the risk of nephrolithiasis increases considerably when uric acid excretion exceeds 1,000 mg/day (231), the main determinant of its solubility is urinary pH. The pH of plasma (7.40) allows most plasma uric acid to be dissociated in the form of urate; however, the pH of urine (5 to 5.5) causes only 50% of uric acid to be dissociated as highly soluble monovalent urate, whereas the remaining undissociated 50% has a much lower solubility and is the main component of uric acid calculi. It has been described that with normal urine pH 5.35, the saturation limit of uric acid in urine is 20 mg/dL (10 mg/dL undissociated uric acid); with pH 6.0 (slightly less acidic) the solubility limit increases to 100 mg/dL (1 g per litre of urine excreted), and it exceeds 1,200 mg/L with pH 6.5 (258, 259).

Uric acid lithiasis is primarily related to acidification deficits and the subsequent tendency to maintain a urine pH below 5.8 in contrast to the changes that take place in normal conditions throughout the day and that make urinary pH often exceed 6.0 (259-261). Accordingly, while ensuring sufficient hydration to produce around 2 litres of urine per day, to prevent lithiasis it is essential to alkalize the urine using potassium citrate (1 mEq/kg body weight) or sodium bicarbonate (6 - 12 g/day) up to a pH of 6-6.5 (259).

Recommendation 23: In patients with CKD administering potassium citrate (30-80 mEq/day) helps keep urinary pH above 6 and dissolve renal calculi formed by uric acid (LE 3a; GR B, DA 70%).

Administration of potassium citrate (30-80 mEq/day) helps keep urinary pH above 6 and dissolve renal calculi formed by uric acid (262). However, in patients with uric acid excretion deficit primary alterations in urinary pH have not been described (as has been stated, the main risk factor for lithiasis due to uric acid), so that the doses described for urinary alkalinisation drugs cannot be extrapolated to this patient group.

In a study conducted on 216 patients with 784 person-years of exposure it was observed that the basal clearance of uric acid can be useful in selecting patients eligible for uricosuric

treatment, whereas the undissociated urinary uric acid can be used to evaluate the risk of lithiasis during follow-up. Moreover, increased risk of lithiasis was not demonstrated in patients treated with benzbromarone who maintained a concentration of undissociated uric acid <20 mg/dL (181).

Therefore, hypoexcretor patients (uric acid clearance <6 mL/min) may benefit from treatment with uricosurics as long as hydration and adequate urine pH are maintained. During follow-up a concentration of undissociated uric acid <20 mg/dL (181) must be maintained, calculated based on a nomogram that uses urinary pH and the total concentration of 24-hour urinary uric acid (263).

VIII.G. EXOGENOUS URICASES

In patients with CKD there has been only one study, of rasburicase administration to 10 subjects, whose results have not been established, nor have efficacy and long-term safety (263). Pegloticase (pegylated uricase) has not been formally evaluated in patients with CKD, although some of the patients (30%) in Phase III trials showed CKD defined as GFR <60 mL/min.

VIII.H. ALLOPURINOL

Allopurinol is the most frequently prescribed urate-lowering drug, regardless of the aetiology of hyperuricaemia (243, 244). The intact molecule is metabolized in the liver and has a half-life of 1-3 hours, but the XO converts into oxypurinol, the active metabolite of urinary excretion, whose half-life is 12-17 hours, thus the compound can be administered once daily.

Recommendation 24: In patients with CKD it is recommended to adjust the dose of allopurinol according to the SmPC (LE 5; GR D; DA 77%).

The effectiveness of allopurinol in the treatment of gout is dose dependent, increasing to 800-900 mg/day (264, 265). The maximum dose approved by the FDA is 800 mg/day (266), and the guidelines of the British Society of Rheumatology place the recommended dose limit of 900 mg/dL (152), although these recommendations are based more on studies of efficacy rather than safety.

The limiting factor in the use of allopurinol is its potential toxicity, which can exhibit different patterns of severity. In most cases toxicity is limited to mild and reversible skin rash whose frequency ranges from 0.8% (267) to 2% of patients (268). However, in 0.4% of cases there may appear a symptom called allopurinol hypersensitivity syndrome that occurs, on average, at 3 weeks of starting treatment and is accompanied by high mortality (25%) (269).

It has been suggested that the adverse effects of allopurinol would be more frequent in patients with decreased GFR, since the lower subsequent elimination of oxypurinol means greater exposure to the drug (270) and also the incidence of hypersensitivity syndrome is 2-3 times higher in patients with CKD (271).

Greater frequency of this condition in patients with kidney failure has led to the recommendation for dose reduction in these cases according to the guidelines published by

Handel in 1984, which is based on the proportionality between the reduction of oxypurinol clearance and glomerular filtration rate (272). According to these guidelines, the recommended dose for subjects with GFR of 100 mL/min should not exceed 300 mg/day. To assess the impact of these recommendations it suffices to say that the majority of patients treated with allopurinol received doses less than or equal to 300 mg/day (244, 273), despite the fact that this does not achieve the objective of lowering urate blood levels below 6 mg/dL in over 50% of patients (180, 224). A recent retrospective study conducted on 3,122 patients with gout treated with allopurinol in primary care found that achieving urate concentration below 6 mg/dL was only achieved in 25.6% of patients without CKD and in 22.2% of those with CKD (174).

Therefore, once again, the potential toxicity of a drug of great importance in the treatment of gout largely limits its use or its efficacy, especially in patients with kidney disease. However, is it justified in this case to maintain a degree of caution that influences the results in this way? Some arguments seem to run counter to the supposed linear association between acute toxicity of allopurinol and kidney function.

Most severe hypersensitivity reactions appear shortly after starting treatment and are not clearly associated with blood levels of the drug (274). Moreover, the correlation between plasma levels of oxypurinol and allopurinol and GFR is less than expected, plasma urate levels being practically nil (275). In fact, intervention studies with dose adjustment according to renal function have failed to demonstrate a decrease in the number of serious reactions. By contrast, other retrospective studies have shown that drug dosage according to GFR does not reduce the incidence of hypersensitivity to allopurinol, or there is no correlation between the frequency of hypersensitivity reactions and dosage given, also giving this dosage a very low success rate (assessed by decrease of urate levels below 6 mg/dL). In general, however, the main limitation of these studies is the sample's small number of patients (276, 277). Increasing doses of allopurinol above the afore-mentioned recommendations has been observed to be effective and safe even in patients with CKD (278). The incidence of adverse effects is similar in patients with average GFR of 54 mL/min and doses of approximately 300 mg/day, not adjusted to Hande recommendations (dosage 60% higher than that proposed by Hande), as well as in those whose treatment is adjusted to these recommendations, suggesting that allopurinol maintains a high safety profile and efficacy at doses significantly higher than those recommended (279).

In a recent trial allopurinol (300 mg/day) was administered to 36 patients, of whom 8 had GFR 50-80 mL/min, for 4 months. In 17 cases it was not possible to reduce serum uric acid to 5 mg/dL, so the dose was increased to 600 mg/day. There were no serious reactions and there were only 2 skin reactions during treatment with 300 mg/day. Moreover, in 13 of the 17 patients treated with 600 mg/day urate levels were safely reduced to values of <5 mg/dL (250). These results suggest that the safety and efficacy of allopurinol is greater than described, and that the overestimation of its potential toxicity favours the poor outcome, indicating the need for further studies to clarify the safe dosage of this compound.

Currently, the British Society for Rheumatology allows increasing the dose to 900 mg daily, although with adjustment for renal function (152), whereas EULAR recommends progressively increasing dosage until reaching the target serum uric acid levels proposed for patients with normal renal function (149).

For the moment, the suitable dosage in patients with CKD has not been established. What is unquestioned is that the dose recommended by the Summary of Product Characteristics for severe cases (up to 900 mg/day in patients with normal renal function) is almost three times

higher than that recommended by Hande, and that its use may be accompanied by a marked increase in the effectiveness of the drug in all ranges of renal function, although there are no data supporting its safety (250).

VIII.I. FEBUXOSTAT

This is a non-purine based XO inhibitor that, unlike allopurinol, is metabolized by the liver mainly as inactive metabolites and is partially excreted in faeces, which makes it a drug of particular interest in patients with CKD (280).

The results of three large clinical trials in patients with various degrees of renal function have shown that febuxostat is significantly superior to allopurinol in terms of achieving the target serum uric acid levels for all degrees of renal function (from GFR >30 mL/min, i.e. from normal renal function, to CKD grades 1-3), although allopurinol was only used at maximum doses of 300 mg/day in patients with normal renal function, and 100-200 mg in patients with mild to moderate CKD. The drop-out rate due to appearance of rash or biochemical changes associated with liver dysfunction was similar between patients receiving febuxostat and those treated with allopurinol, with no significant differences observed in terms of adverse effects (223-225). One of these trials compared the efficacy of febuxostat to allopurinol in various degrees of CKD (1, 2 or 3).

Recommendation 25: Patients with CKD should be evaluated for the use of febuxostat, since it has been shown to be superior to allopurinol in all strata of mild-moderate CKD, even at doses of 40 mg/day, with a similar frequency of adverse effects (LE 1b, GR A; DA 80%).

Febuxostat was superior to allopurinol in all strata of CKD included (mild to moderate) with similar frequency of adverse effects (281).

Patients with mild to moderate CKD can start with a dose of 80 mg/day, although the above studies suggest that 40 mg/day may be sufficient (in the European Union the 40 mg dose has not been tested). The efficacy and safety of febuxostat has not been compared with high-dose allopurinol that achieved the highest success rates of over 80% (278), nor has its use been studied in patients with CKD grades 4-5, i.e. GFR of less than 30 mL/min. On the other hand, it is unknown whether patients with hypersensitivity to allopurinol can be safely treated with febuxostat, since this has been an exclusion criterion in the studies published to date.

According to some authors, in patients with stage 3 CKD it is reasonable to use steroids as a treatment for acute episodes, in progressive doses of allopurinol up to 800 mg/day as urate-lowering therapy, and colchicine to prevent attacks, reserving the use of febuxostat for cases of intolerance or failure to achieve established serum uric acid targets (186).

VIII.J. DIALYSIS

Dialysis treatment is based on the transfer of solutes from blood to dialysate, which affects the urate concentration and the drugs used in the treatment of gout such as colchicine and allopurinol. The use of high permeability dialysis membranes facilitates the use of these

compounds in dialysis patients, once the dose is adjusted, so that treatment of gout is based on the same principles as in CKD patients not requiring dialysis. On the other hand, dialysis also treats urate considerably improving serum uric acid control with respect to patients with CKD who are on stages 4-5 of predialysis. Febuxostat has not yet been tested in dialysis patients.

No specific studies have been conducted on gout-afflicted patients with grade 5 CKD requiring dialysis, thus the recommendations in this group are based on extrapolations from descriptions of earlier stages of CKD, experience with the use of the recommended drugs, and a reasonable analysis of the pharmacokinetics and pharmacodynamics of common medications for the treatment of gout in this group. In any event, nephrologists appear to have less difficulty than the guidelines describe with the use of these compounds (282).

In fact, it is possible that excessive caution (understood by many as contraindication) has led to under-utilization of some drugs, such as allopurinol or colchicine, compared to other major contraindications, such as NSAIDs and corticosteroids (192).

VIII.J.1. Fundamentals

Understanding the basic mechanisms of dialysis is essential to interpret their influence on the diagnostic and therapeutic approach to many diseases, including gout.

Dialysis is a blood purification treatment consisting of exposing the blood to an artificial liquid (saline solution with calcium, bicarbonate, chloride and glucose,) free of the solutes it seeks to purify (such as potassium, phosphorus, uric acid, creatinine, urea, etc.), to generate a concentration gradient which facilitates the diffusion of solute from the plasma to the dialysis liquid or vice versa. In most cases, the solute concentration is lower in the dialysis liquid than in plasma, producing diffusion from the plasma to the liquid.

The usual indication for dialysis is very advanced CKD (glomerular filtration rate less than 10 mL/min/1.73 m^2), in which the main objective is the purification of solutes that cannot be excreted by the kidneys and that generate excessive, life-threatening concentrations. The substances to be excreted can be endogenous (minerals, hydrogenated products of metabolism, etc..) or exogenous (drugs). In cases of advanced CKD and gout the urate would belong to the first group of solutes and the drugs used in the treatment of gout, such as colchicine or allopurinol, would belong to the second. The degree of purification achieved by dialysis depends on the physicochemical characteristics of each molecule. In general, lower molecular weight of the solute facilitates removal by dialysis. Therefore, it should be noted that patients with gout and dialysis are those who show a lesser degree of renal clearance (CKD grade 5) of both urate and drugs used in the treatment of gout, although they may have some level of extra-renal clearance, which does not appear with lower levels of CKD.

VIII.J.2. Types

The following describes, in broad terms, the two types of dialysis: haemodialysis and peritoneal dialysis.

Haemodialysis involves letting the blood circulate through an extracorporeal circuit in which it interacts with the dialysate (free of solutes that are to be eliminated) through an artificial filter (dialyzer) to achieve the desired solute clearance. Several weekly sessions are held (usually three) of 3-4 hours in duration. Lowering the concentration of solutes in the plasma causes, secondarily, the solutes to pass from the interstitial space into the plasma to balance concentrations. Due to the large capacity of haemodialysis for purifying low molecular weight solutes (less than 1,000 daltons; that of the urate is 168), the elimination rate from plasma to the dialysis fluid is much higher than the passage of solutes from the interstitial space to the plasma, so that the blood concentration of these solutes is usually high (higher than normal) just before haemodialysis, and low (even below normal values) immediately thereafter; it then begins increasing in the following days as the intravascular space refills with these solutes until the next session. Uric acid, due to its low molecular weight, is no exception. Its blood levels reach the valley immediately post-dialysis and gradually increase until the start of the next dialysis.

By contrast, peritoneal dialysis uses the anatomo-functional structure of the peritoneum; the peritoneal cavity has a monolayer of mesothelial cells that is continuous with an interstice in which blood flows through inside capillaries. Peritoneal dialysis is based on the introduction and maintenance of the dialysis fluid in the peritoneal cavity through a catheter. During the dwell time of the liquid in this cavity solutes accumulated as a result of kidney failure pass from the blood flowing through the capillaries to the peritoneal dialysis fluid by virtue of a concentration gradient generated between them. In this type of dialysis it is the peritoneal membrane itself, i.e., the interstitial tissue that runs from the capillary wall to the mesothelial layer lining the peritoneal cavity, which acts as a filter. With the passage of hours spent in the cavity dialysis fluid becomes saturated with solutes (potassium, phosphorus, uric acid, creatinine, urea), thus reducing the concentration gradient compared to plasma and excretion capacity is gradually lost. So dialysis fluid must be replaced (removed from the peritoneal cavity and replaced with new fluid) several times a day (3-4 changes with average stays of 6-8 hours in day mode, and 5-6 changes with stays of 1-2 hours at night). In peritoneal dialysis the passage of solutes from blood to liquid is much slower and gradual than in haemodialysis, but this difference is compensated by its continuous nature (at all hours of day and night and every day), compared to the brief and intermittent nature of haemodialysis. The slower rate in the passage of solutes from blood to dialysate results in reverse diffusion from the interstitial space into the plasma to balance concentrations occurring at the same rate, so that with peritoneal dialysis there are no peak and valley blood levels, unlike in haemodialysis.

VIII.J.3. Incidence of gout in dialysis patients

There is some controversy about the incidence of gout in patients undergoing dialysis treatment. Data from a U.S. registry with information on over 250,000 dialysis patients showed an incidence of gout of 5.4% per year, 11.5% at 3 years and 15.4% at 5 years, values higher than previously reported and which could be overestimated by failing to register any gout episodes before the start of dialysis treatment (182). However, the few existing studies on this topic have published very low figures for the incidence of gout in dialysis patients and certainly lower than those obtained in cases of CKD in pre-dialysis or kidney transplant.

During acute episodes of gout monocytes secrete pro-inflammatory cytokines such as interleukins (IL) IL-1 and TNF-α; however, in the advanced stage of CKD immunosuppression of monocytes diminishes their ability to synthesize IL-1β, IL-6, and TNF-α in response to

monosodium urate. This alteration may be responsible, at least partially, for the lower incidence of gout in these patients. In addition to decreased secretion of these cytokines, it is possible that the clearance of inflammatory mediators may increase due to the technique of dialysis itself (255, 283-285).

Another possible explanation for the decline in the incidence of gout in dialysis patients would be uric acid clearance by dialysis, which will be discussed later.

VIII.J.4. Treatment of acute inflammation episodes

VIII.J.4.1. Non-steroidal anti-inflammatories

The rationale for not using nephrotoxic drugs in patients with CKD is to prevent further deterioration of kidney function and thus delay the need for dialysis. One might think, therefore, that once kidney function is lost and chronic treatment with dialysis is required for patient survival, it no longer makes sense to avoid nephrotoxic medications. However, even in patients on dialysis, residual kidney function is a major contributor to total clearance of solutes accumulated in renal failure (total elimination is the sum of dialysis and residual kidney function), so it is very important to maintain the residual function to reduce morbidity, mortality and the impact of dialysis on quality of life. The smaller the residual renal function the higher dose of dialysis is required, resulting in longer duration or frequency of sessions in patients on haemodialysis and in greater number of daily exchanges of dialysis fluid in patients using peritoneal dialysis. Therefore, the use of NSAIDs should be avoided in patients on dialysis (286).

VIII.J.4.2. Colchicine

It is widely known that there is a need to maintain a high level of caution in using this drug in patients with CKD, both in acute episodes and in prophylaxis, because of reduced clearance. However, this precaution seems to make sense more in cases of prolonged use than in acute episodes, as long as treatment cycles are not repeated early (287, 288). In patients with normal renal function the treatment of acute episodes is performed with three tablets of 0.5 or 0.6 mg, after which more colchicine should not be administered for at least 3 days (when it can be considered a new cycle) because of intraleukocytic accumulation. By contrast, in patients with GFR <30 mL/min (CKD grades 4-5) and no other therapeutic options, the interval between acute treatment cycles should be extended to two weeks (208, 289), with close monitoring of CK, GPT and blood count to detect possible toxicity in muscle, liver, or bone marrow (290). However, the SPC approved by the FDA is less restrictive than that of the AEMPS, which is the source of these suggestions.

Although there is no description of the interval between doses for patients on dialysis, it is logical that it would be still higher or even avoid the repetition of cycles of colchicine for acute episodes, since dialysis does not clear this molecule and thus increases the risk of toxicity (178). Indeed, conventional haemodialysis is inefficient in clearing colchicine due to its high protein binding and tissue availability (291). In fact, the guidelines of prescription drugs on kidney failure indicate that colchicine is not dialyzable (287, 292). However, it was recently reported that high-permeability haemodialysis membranes clear such important quantities of colchicine that even higher doses may be required in patients with indications such as Familial

Mediterranean Fever (293). That is, the use of existing dialysis membranes not only eliminates the risk of toxicity due to insufficient clearance and subsequent accumulation of the drug, but on the contrary, the clearance power can necessitate increasing the dose. The use of these membranes is increasingly common (in many units they exceed the conventional membrane), which may allow safe use of colchicine.

Recommendation 26: The use of high permeability haemodialysis membranes with high clearance power could allow safe use of colchicine in patients with CKD, but we must remember that in Spain this indication is not reflected in its SPC (LE 3a; GR B; DA 78%).

In any case, we must remember that the use of colchicine is contraindicated in the Spanish SmPC if the glomerular filtration rate is below 30 mL/min.

VIII.J.4.3. Corticosteroids

As already mentioned, the use of corticosteroids is recommended, especially when NSAIDs and colchicine are contraindicated or inadvisable, a situation that occurs with CKD patients (149, 152) and those on dialysis, which is why these drugs should be considered the first choice of treatment in acute episodes for this group of patients, provided no diabetes coexists.

VIII.J.4.4. Corticotropin (ACTH)

Its indications and effectiveness in the treatment of episodes of acute joint inflammation due to gout are similar to those of corticosteroids (214-216). In Spain tetracosactide, an analogue of ACTH, is available.

VIII.J.4.5. Anti-interleukin-1 agents

These drugs are efficacious and could be effective in patients with contraindications for other therapeutic options (CKD, diabetes and liver disease). Dosing regimens specifically designed for patients with CKD are unknown.

VIII.J.5. Prophylaxis of recurrent episodes of acute inflammation

According to current recommendations, prophylaxis of acute episodes in patients on dialysis is an almost impossible goal, at least in a safe and efficient manner. In addition to the low efficacy of corticosteroids and the recommendation to avoid NSAIDs it must be noted that colchicine clearance is significantly decreased in the presence of CKD, which is why its use has come to be avoided in patients on dialysis, on the premise of the theoretically limited clearance of this molecule during the dialysis procedure (287, 291, 292).

However, as already stated, the use of high permeability membranes for haemodialysis provides degrees of drug clearance that appear to allow its use, at least at the doses indicated

(and even higher in some pathologies such as Familial Mediterranean Fever), which significantly reduces the risk of toxicity (287, 291-293).

Recommendation 27: In haemodialysis patients who require prophylaxis of acute episodes it would be advisable to use high permeability membranes and to prescribe a dose of 0.5-0.6 mg of colchicine after dialysis, but it must be noted that this is not approved in the current SMPC (LE 4; GR C; DA 78%).

Therefore, in haemodialysis patients requiring prophylaxis of acute episodes it would be advisable to use high permeability membranes and to prescribe a dose of 0.5-0.6 mg after dialysis based on the assumption that the drug is cleared more than previously thought. However, in Spain, the SmPC for colchicine includes contraindications in patients with GFR <30 mL/min.

VIII.J.6. Urate-lowering treatment

VIII.J.6.1. Urate clearance by dialysis

In quantitative terms, most authors define patients as hypoexcretors if they excrete less than 600-800 mg of uric acid daily. While in most cases of gout renal excretion of uric acid is reduced at baseline, in those with progressive kidney failure elimination decreases as kidney disease progresses. However, when a patient with stage 5 CKD starts dialysis treatment, both peritoneal and haemodialysis, the amount of uric acid eliminated daily from the body increases significantly.

Conventional haemodialysis reportedly clears amounts of urate that allow reducing deposits (294). Although the vast majority of haemodialysis patients are treated for three weekly sessions of 180-240 minutes (up to 2,000-3,000 mg of uric acid eliminated per week, equivalent to an average of 300-400 mg/day), the frequency and duration of the sessions, and therefore the total amount of uric acid cleared, is potentially variable.

Recommendation 28: The low-medium intensity doses of peritoneal dialysis (3-4 daily peritoneal fluid stays) allow extraction of 500 mg of uric acid daily (LE 3b; GR B; DA 78%).

Similarly, peritoneal dialysis can be applied with varying intensity. Treatment guidelines for low-medium intensity (3-4 daily peritoneal fluid stays) allow extraction of 500 mg of uric acid daily (295-298).

VIII.J.6.2. Sevelamer

On the other hand, late-stage CKD is associated with increased serum phosphate levels, which is a therapeutic priority due to the potential impact on morbidity and survival. Sevelamer, an intestinal phosphate binder used in the treatment of hyperphosphataemia associated with

advanced CKD, appears to reduce serum uric acid. In a recent study of haemodialysis patients with serum urate levels greater than 8 mg/dL, there were decreases in excess of 2.5 mg/dL (299). However, its value in the treatment of gout or cardiovascular prevention in these patients is still undefined.

Recommendation 29: Sevelamer, an intestinal phosphate binder used in the treatment of hyperphosphataemia associated with advanced CKD, can reduce serum uric acid levels (LE 2a; GR B; DA 78%).

VIII.J.6.3. Allopurinol

In haemodialysis patients, interdialysis clearance of oxypurinol is minimal, but during a 4-hour haemodialysis its plasma concentration decreases to around 40%, so that the half-life during haemodialysis is lower than in persons with normal renal function. Therefore, allopurinol should be administered after the dialysis session (300).

Recommendation 30: Allopurinol should be administered after haemodialysis (LE 2a; GR B; DA 88%).

VIII.J.6.4. Other drugs

Logically, in dialysis patients uricosuric treatment is meaningless because of the decreased response to any drug that acts through urinary excretion of a substance. Furthermore, there is no experience in the use of febuxostat or exogenous uricases in these patients.

VIII.K. KIDNEY TRANSPLANT

The incidence of gout is elevated in this group due, firstly, to the baseline CKD and the risk factors associated with hyperuricaemia and, secondly, to the fact that many of the immunosuppressants used in the treatment are metabolized by P450 cytochrome, which complicates the use of colchicine. In these patients uricosurics have been tested with good results, although not febuxostat.

According to the results of various studies, the incidence of gout in kidney transplant recipients ranges between 1.7 and 35%, with an even greater variability for hyperuricaemia (5-84%). Despite its high prevalence in transplant patients, the incidence is much lower in those receiving calcineurin inhibitor-free immunosupressants (301), and its natural history differs from that seen in the general population, as the development of tophi and gouty arthritis attacks is much faster, after a period of hyperuricaemia in the transplant population. In addition, attacks usually affect less "typical" joints (302). These characteristics are the result of the combination of various degrees of kidney failure and the use of diuretics and calcineurin inhibitors as part of immunosuppressive therapy (303-306).

VIII.K.1. Immunosuppressive drugs

According to the literature, cyclosporine is the immunosuppressant with the greatest risk of causing hyperuricaemia. This compound produces renal vasoconstriction, with subsequent decline in glomerular filtration rate, and altered tubular transport of uric acid. The vasoconstrictor effect may be enhanced by interaction with NSAIDs (307). In Western countries tacrolimus, also belonging to the calcineurin group of immunosuppressants, has almost completely replaced cyclosporine (308). There is no consensus about the risk of hyperuricaemia with tacrolimus compared to cyclosporine; some studies show the risk to be similar (309, 310), while others showed a decrease of hyperuricaemia with the use of tacrolimus (303, 311). Because tacrolimus has a similar effect to that of cyclosporine on renal circulation, it can be expected to also present similar interaction with NSAIDs.

Recommendation 31: In kidney transplant patients, tacrolimus, due to having a mechanism of action similar to cyclosporine, in theory could lead to interaction with NSAIDs (LE 2b; GR B; DA 100%).

Within another family of immunosuppressants, mTOR (mammalian target of rapamicyn) inhibitors such as sirolimus induce hyperuricaemia much less frequently than cyclosporine (19% versus 52%, after 3 months of treatment) (312).

Azathioprine is metabolized by XO which, in turn, is inhibited by allopurinol and febuxostat. Simultaneous administration of both compounds slows azathioprine metabolism and increases the risk of bone marrow toxicity, so that their association is contraindicated.

Recommendation 32: In renal transplant patients, concomitant administration of azathioprine and allopurinol reduces the metabolism of azathioprine and increases the risk of bone marrow toxicity, so their association is contraindicated (LE 2b; GR B; DA 90%).

However, in Western countries azathioprine is generally not used as an immunosuppressant in transplanted patients (308), having been replaced by mycophenolate, which does not present interactions with allopurinol, allowing their simultaneous use.

VIII.K.2. Treatment of acute inflammation episodes

Treatment of acute episodes in transplant patients is subject to the same considerations as in non-transplant patients with CKD, because both groups share similar situations such as CKD, hypertension, use of diuretics, etc. Therefore, steroids are preferable to colchicine and NSAIDs should be avoided.

Colchicine indication is lower in the subgroup of patients treated with calcineurin inhibitors (cyclosporine and tacrolimus) than in non-transplant patients. This assertion is based on the

greater toxicity of colchicine in patients taking P450 cytochrome (CYP3A4) and P-glycoprotein (P-gp) inhibitors (208, 209). Most transplant patients receive corticosteroids and calcineurin inhibitors as immunosuppressive treatment and many of them also take lipid-lowering statins, which besides enhancing myotoxicity, inhibit or are metabolized through these cytochromes. Moreover, cyclosporine may alter renal and hepatic clearance of colchicine (313, 314). If it is necessary to use colchicine, results of a cyclosporine-colchicine interaction study recommend reducing the dose of the latter to 1/3 in acute episodes and 1/4 in prophylaxis, given the potent inhibition that the former exerts on P-glycoprotein (315).

Recommendation 33: If it is necessary to use colchicine in patients with kidney transplant and cyclosporine A, it is recommended to reduce the dose of colchicine to one-third in acute episodes and to one-fourth in prophylaxis (LE 2b; GR B; DA 77%).

Although interaction with tacrolimus has not been studied it is recommended to use the association with colchicine similarly, since tacrolimus also is a potent inhibitor of P-glycoprotein (316).

Meanwhile, corticosteroids seem to give good results in the treatment of acute attacks, but only a small study has been conducted (13 patients) (317).

Recommendation 34: In kidney transplant patients corticosteroids may be a therapeutic option in the treatment of acute attacks (LE 3b; GR B; DA 90%).

The mechanism of action of corticoprin also makes it a possible therapeutic alternative, although currently we have no specific studies in transplant patients.

Recommendation 35: In patients with kidney transplant, corticotropin is a potential therapeutic alternative for the treatment of acute attacks (LE 4; GR C; DA 70%).

VIII.K.3. Prophylaxis of recurrent episodes of acute inflammation

As in the treatment of acute inflammation episodes (see above), the prophylaxis of recurrent episodes should not include the use of NSAIDs and also avoid, as much as possible, the use of colchicine, or use it with extreme caution. Therefore, this is the group of kidney patients who pose more problems for the prophylaxis of acute attacks (evidence level IV, strength of recommendation C).

VIII.K.4. Urate-lowering treatment

Although evidence is not available, patients with transplants appear to have a tendency to experience repeat attacks of gout, therefore some authors recommend starting urate-lowering treatment after the first episode. Allopurinol as well as uricosuric agents have proven effective and reasonably safe in managing hyperuricaemia in transplant patients, with an advantage for the latter. Benziodarone at doses of over 75 mg has proven more effective than allopurinol in post-transplant hyperuricaemia control (318). Benzbromarone has also shown great efficacy in transplant patients, even those treated with cyclosporine (319, 320).

Recommendation 36: Benzbromarone has shown great effectiveness in kidney transplant patients, even those treated with cyclosporine A (LE 2a; GR B; DA 90%).

Uric acid lithiasis is very rare, in contrast to the high incidence of hyperuricaemia and gout in kidney transplant recipients treated with cyclosporine (46). Finally, there has been no evaluation of febuxostat or rasburicase in transplant patients; in these patients amlodipine increases uric acid clearance (321, 322), although its role in the management of gout has not been defined.

IX. SPECIAL CONSIDERATIONS

IX.A. THE NURSING PERSPECTIVE

The existence of a clear relationship between diet, lifestyle and the appearance of hyperuricaemia and gout has been known for a long time. Therefore, and as happens with other metabolic diseases, promoting healthy lifestyles becomes of paramount importance in these patients (323), especially when taking into account that such measures are safe and low-cost. Non-pharmacological options can be therapeutic measures on their own or in conjunction with drug therapy to achieve better control of the disease (149, 324).

Patient education programs (PEP) are a set of structured activities aimed at increasing the knowledge level of patients about a specific disease and changing health-related behaviours. Such a program is considered effective only if it is able to produce changes towards the adoption of healthy lifestyles. We must not forget that patients with gout are people with a particular personal, family, and work life. Therefore, a comprehensive or holistic assessment of the patient is necessary to achieve specific therapeutic goals, previously agreed upon with the patient, and to allow for proper design of educational interventions.

Recommendation 37: The Rheumatology nurse can provide the patient with a gout-specific education program, defined as a set of structured activities aimed at increasing the level of knowledge about the experience of being a patient with gout and promoting healthy lifestyles (LE 5; GR D; DA 93%).

Despite recognizing the proven benefits of these interventions, experience confirms the difficulties of influencing a patient to adopt healthy lifestyles. Increasing the level of patient knowledge regarding their disease is not difficult, however, modification of negative or unhealthy behaviour is a much more complicated process. Therefore, one of the fundamental objectives of a PEP is to increase self-efficacy, defined as the confidence one has in achieving a certain goal (325); patients with high levels of self-efficacy believe they can make positive changes in health. Another basic factor for behaviour change, and self-efficacy, is motivation. Some authors have reported various strategies to increase our ability to motivate patients (326, 327).

While scientific evidence is scarce, there is a widespread perception that health education for patients with gout should address improving outcomes both directly, in terms of improving self-efficacy perceived by the patient, and indirectly, by increasing adherence to treatment and improving adoption of healthy habits (149).

Since for a significant proportion of patients hyperuricaemia is part of a concomitant metabolic syndrome, the presence of gout should alert clinicians to the association of modifiable comorbidity factors (323), the detection and treatment of which are an essential part of therapeutic management.

IX.A.1. Patient education plan

Recommendation 38: The education program for patients with gout (individual or group) will address the following key issues: therapeutic target, diet and alcohol consumption, pain management, cardiovascular risk management, weight control, exercise, and information about the treatments prescribed in order to improve adherence and patient safety (LE 5; GR D; DA 86%).

The application of general recommendations related to a healthy diet, overweight reduction, restriction of purine-rich foods and refined sugars and reducing alcohol consumption (328, 329), may decrease the serum uric acid and thus the risk of gout attacks. Such lifestyle changes can also have a beneficial effect in other associated pathologies, such as hyperlipidaemia, hypertension, atherosclerosis, and insulin resistance (1, 149, 324, 330, 331).

In addition to these general recommendations, below are the key issues to be included in the PEP:

Pain management: Advise the patient of the need for analgesic treatment on the prescribed schedule, and avoid self-prescription. In addition, applying cold to painful joints may be useful.

Diet: The most effective type of diet for managing patients with gout has yet to be established (331) attributable, at least in part, to the fact that strict restriction of purines in the diet only achieves moderate decreases (between 15 - 20%) in serum uric acid levels (Image 4).

Moreover, it is important to mention that diets based on consuming foods low in purines usually have some drawbacks, mainly related to their high content of saturated fat and refined carbohydrates. However, diets aimed at reducing insulin resistance decrease plasma urate levels while improving insulin sensitivity, which improves plasma levels of glucose, insulin and triglycerides. This would, in turn, reduce the incidence of cardiovascular diseases.

Although there is no clear consensus on the most effective type of diet, there are general dietary recommendations for the management of patients with gout for use primarily in nursing care. These recommendations include:

- Avoid excessive consumption (more than two times per week) of red meat, viscera and animal proteins that provide elements for purine synthesis and saturated fats and decrease renal excretion of uric acid. Alcoholic drinks *per se* induce hyperuricaemia and reduce uric acid excretion while increasing its production (36), especially beer (with or without alcohol), due to its high content of guanosine, a purine (36, 332). Glucose uptake and other simple carbohydrates do not increase plasma levels of urate, contrary to what occurs with fructose. In fact, consumption of fructose-sweetened beverages and/or soft-drinks is associated with an increased risk of gout in both sexes (333). Finally, prolonged periods of fasting should be avoided, since they increase catabolic hyperuricaemia.
- Advise patients to consume 3-5 meals a day (330). Some foods are especially recommended. For example, "light" soft-drinks (not associated with increased risk of gout); whole-grain foods improve insulin sensitivity. Vegetable protein, such as nuts, oats, legumes, beans, lentils and vegetables (1) are not associated with increased risk of gout, *even those with high purine content* (spinach, asparagus, mushrooms, leeks, cauliflower, radishes) (324). Vegetable oils and oily fish are recommended for their

omega-3 acid content (330). Coffee consumption is associated with lower levels of uric acid than tea (334). Milk and dairy products (skim) as well as eggs are protein foods that are poor in purines; wine in moderate amounts (1 drink per day in women, 1-2 drinks per day for men) is not associated with an increase in serum uric acid (332), while vitamin C supplements (500 mg/day minimum) are uricosuric.

Cardiovascular risk: Some evidence supports the relationship between hyperuricaemia, atherosclerosis and coronary heart disease, possibly because of the association between hyperuricaemia and endothelial dysfunction (54, 335-337). Therefore, cardiovascular risk assessment and monitoring of classical risk factors are indispensible in the management of patients with hyperuricaemia and gout. Of course, smoking is a modifiable risk factor that must be addressed in the interview with patients (149).

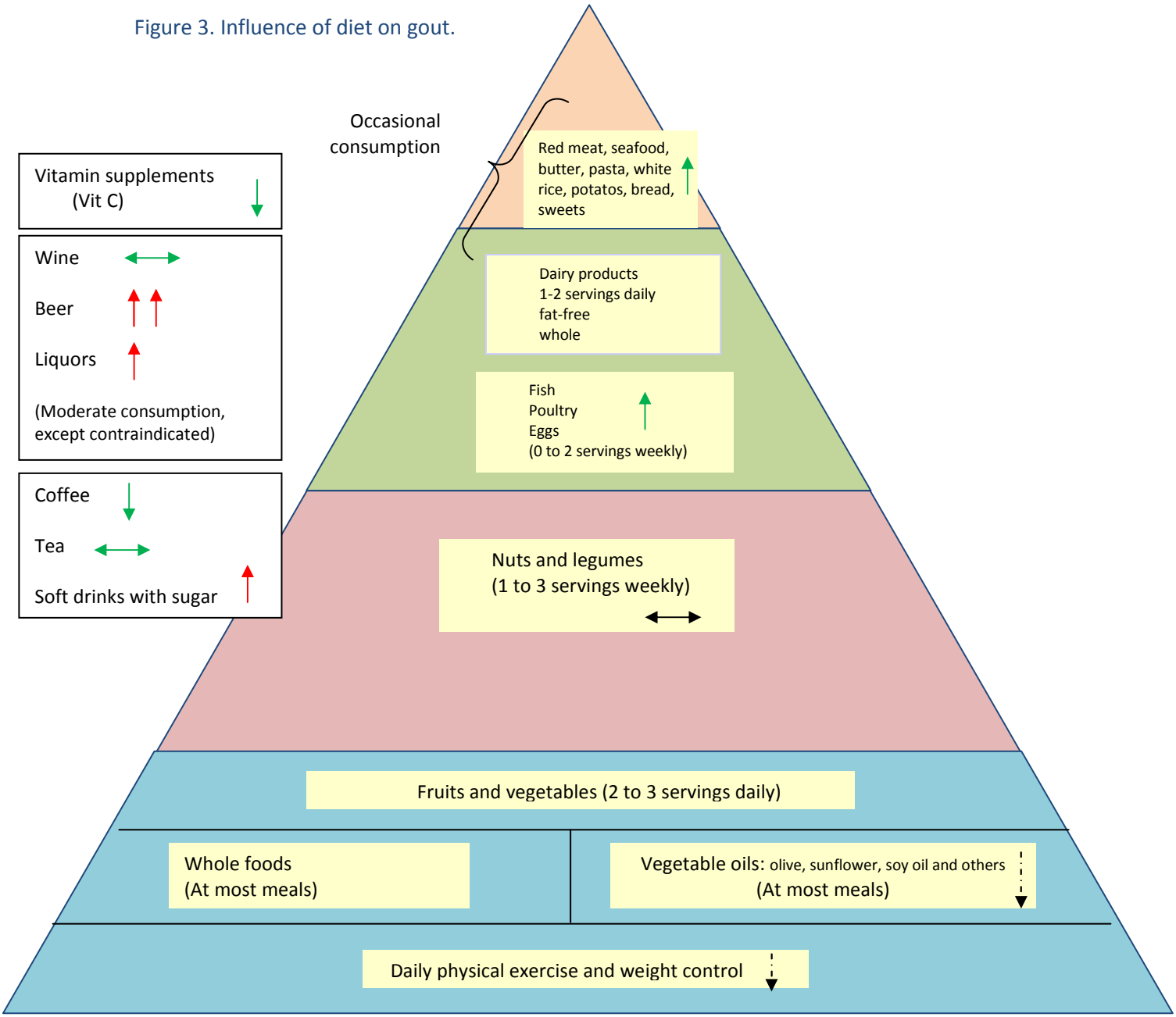
Weight control: Recommending a weight-reduction diet is particularly important for obese patients with gout, due to frequent coexistence of metabolic syndrome and other associated diseases. Weight gain and additional volume of adipose tissue are reportedly predictors of gout in men, due to both an increased production and decreased renal excretion of urate, while weight loss is a protective factor (338). The results of some epidemiological studies suggest that calorie restriction and weight loss are accompanied by a decrease in plasma urate levels due to increased excretion and decreased synthesis of uric acid (172, 339).

Physical exercise. Engaging in regular exercise is a healthy habit that should be encouraged in all patients with hyperuricaemia and gout (324).

Adherence to treatment: All drugs can cause side effects. Nursing staff needs to know drug interactions as well as possible interactions and changes in the toxicity profile of the drugs when administered in combination. Therefore, besides close monitoring of treatment, sufficient individualized information should be provided on the possible toxicity resulting from the use of these drugs in order to keep the patient from abandoning treatment. Similarly, a mechanism should be provided for immediate contact between nursing staff and patient (e.g., telephone) to quickly and effectively resolve any doubts related to treatment.

This will encourage proper compliance and avoid "on demand" visits due to lack of adherence to prescribed patient treatment plans.

Figure 3. Influence of diet on gout.



Adapted from Choi HK et al., 2005 (1). *The up arrows indicate increased risk of gout, the down arrows decreased risk, and the horizontal arrows indicate no effect on risk. The dashed line indicates potential effect but without clear evidence about the development of gout.*

IX.B. THE PATIENT'S PERSPECTIVE

The diagnosis of gout does not have to produce negative feelings. It is a frequent pathology and not self-inflicted. At the time of diagnosis the patient needs adequate information because, in general, the PC doctor communicates suspicion that the condition is present and provides quick and immediate solutions, but without the possibility of devoting sufficient time to full explanations.

Although the PCP is responsible for monitoring the patient's pathological processes, the reality is that he/she can only answer immediate and generic questions about most of them, which is especially true in the case of gout. Therefore, the relationship with the specialist becomes very important because this professional is the one who can provide sufficient information about the disease, the frequency of attacks and how to recognise them, as well as the suitability of different treatments, their side effects and possible alternatives.

Knowing that gout is caused by the deposition of uric acid crystals, mainly related to dietary habits or the use of medications such as diuretics, facilitates a proper coping process. It offers patients and specialists the possibility of trying to find a balance between the patient's dietary habits and the drugs used to manage other pathologies, in addition to finding the treatment that works best for the patient and can decrease the likelihood of attack. It is therefore imperative for the patient to trust the specialist responsible for their treatment and follow his/her instructions.

IX.B.1. Recommendations for patients

1. The establishment of a relationship of mutual trust between doctor and patient is essential for both to know exactly what is occurring in the process, facilitate understanding of its production mechanisms and create a climate of relative safety to ensure adherence to treatment. Faith in the professional is key to trusting in his/her ability to manage the disease and achieve therapeutic results.
2. Maintaining a generally positive attitude towards life and the disease is also important, both for the patient (because it allows proper coping), and the doctor (because it facilitates the relationship with the patient and the establishment of an individualized and correct treatment plan).
3. It is essential to identify the process, not only because of the disease itself, but because attitude and accommodation to it can vary greatly among patients. Not everyone is able to cope with certain life experiences with the necessary maturity and calm.
4. In order to use the correct drugs for each case and decrease the risk of associated side effects it is very important to carefully ask about all medications taken by the patient and the magnitude of his/her attacks.
5. The challenge for the physician, as a professional, is to know each patient's process, their peculiarities and their needs. However, the patient best knows his/her clinical situation

and, sometimes, their judgment must prevail over that of the doctor, especially in the case of the PCP. "Nobody knows better than the patient when to go to the ER".

6. The PCP is responsible for the overall follow-up of the patient, while the specialist is the one who must deal with the acute and specific problems.
7. The current availability of electronic medical records allows fluid and on-going communication between the different levels of care, which provides a more streamlined care process, especially in terms of results. In addition, the computerization of medical records and laboratory tests allows immediate access to any professional and therefore significantly improves the quality of care. Finally, it is important to have reports written legibly, preferably printed.

There is widespread demand among patients for their increased participation in decision-making based on the availability of more information. It is a controversial issue as the doctor may think that the opinion that should prevail is his/hers, since it is based on scientific or technical aspects. It is very difficult to find a compromise. The doctor can react poorly if patients require certain actions based on information obtained on the Internet or other means, which cannot be scientifically proven. The patient may suggest options and rely on medical judgment. It is essential, therefore, to create a climate of mutual trust that allows a clear and deliberate explanation on the mechanisms involved in the pathogenesis of the condition and drug actions, so that the patient can make the right decision on his/her disease and its treatment.

The patient believes in the beneficial effect of diet, although experience tells him that attacks always follow dietary changes. In any case, the relationship with the diet should be relative and flexible, as extreme behaviours are never good. It is important to know the foods and regimens that can increase uric acid and use "some care" but not live obsessively. The ideal situation is to find a middle ground.

He is aware of his/her limitations but they not make him/her suffer. He/she has already had to live with it. One accepts and adapts. And he/she will find other satisfactions in life, hobbies, friends, family, etc.

X. MANAGEMENT IN PRIMARY CARE. REFERRAL CRITERIA

X.A. DIAGNOSIS IN PRIMARY CARE

Recommendation 39: Although the gold standard for the diagnosis of gout is the visualization of crystals, in patients with typical symptoms such as intermittent arthritis with complete resolution at the first MTP joint (podagra) in the presence of prior hyperuricaemia, clinical diagnosis may be a reasonable alternative for the PC doctor up to definitive diagnosis (LE 5; GR D; DA 91%).

Clinical manifestations of gout may be heterogeneous, but generally we can distinguish four characteristic phases: urate deposit without clinical manifestations, breakthrough episodes of acute inflammation with full resolution, asymptomatic periods between attacks and chronic gout.

The gold standard in the diagnosis of gout is the identification of urate crystals in synovial fluid or tophus aspirates using polarized light microscopy (73, 152). However, most PCPs lack the experience to perform arthrocentesis and have neither referral laboratories nor adequate equipment. Therefore, at this level of care only a probable diagnosis of gout can be reached based on clinical history, physical examination, laboratory tests and imaging tests that are usually reduced to a single radiographic study. In most patients a reasonable presumptive diagnosis is possible, based on the presence of multiple typical clinical features (340, 341) that can be observed by performing a careful personal and family medical history and a thorough physical examination. These typical characteristics include the following:

- Acute monoarthritis with intense pain and redness (up to 80% of initial episodes of gout are monoarticular)
- Preferred location in the lower extremities, especially first MTP
- Background inflammatory episodes in lower limb joints
- Complete resolution of the acute episode in a period varying from a few days to two weeks
- Presence of lesions suggestive of tophi
- Family history of gout and use of drugs that increase urate levels
- Presence of comorbidity and gout risk factors such as obesity, hypertension, metabolic syndrome, hypertriglyceridaemia and diabetes.

Table 20 presents the proposals and strength of recommendation (SOR) of clinical diagnosis established by experts.

Furthermore, a clinical prediction scale was developed to aid diagnosis of acute gouty arthritis without arthrocentesis in PC (108); it is available online (*UMC gout calculator*). The scale combines data from the clinical history and physical examination with serum urate levels

(Table 21). Clinical diagnosis by family physicians is moderately valid. The use of the proposed scale discretely increases the probability of a correct diagnosis, but its main use is to help exclude the condition (NPV 87%). A score below 4 indicates an extremely low probability that the condition is due to gout. The main limitation of this study is that it was conducted in patients with monoarthritis (57% in the 1st MTP and 85% in lower limb joints) 89% of whom were patients with erythema. Therefore, these data apply to patients with typical clinical forms, in whom diagnosis is substantially in accordance with the gold standard, but which cannot be extrapolated to other forms of presentation.

Table 20. Proposals and strength of recommendation of clinical diagnosis.

Proposal	SOR (95% CI) VAS 100	A-B%
Gout attacks with rapid development of severe pain, swelling and tenderness in at least 6-12 hours, particularly erythema, are highly suggestive of crystal deposition disease, although not specifically gout.	88 (80-96)	93
In typical presentations of gout (such as recurrent gout with hyperuricaemia) clinical diagnosis alone is sufficiently accurate, but cannot be considered definitive without identification of crystals.	95 (91-98)	100
Identifying MSU crystals in synovial fluid or in aspirated tophi allows a definitive diagnosis of gout.	96 (93-100)	100
Microscopic examination for MSU crystals in all synovial fluid samples obtained from undiagnosed inflamed joints is recommended.	90 (83-97)	87
The identification of MSU crystals in asymptomatic joints may allow definitive diagnosis in intercritical periods.	84 (78-91)	93
Gout and septic arthritis may coexist. In suspected cases of septic arthritis Gram stain and culture of synovial fluid must be done, even if MSU crystals have already been identified.	93 (87-99)	93
Although hyperuricaemia is the most important risk factor for gout, elevated plasma levels of urate do not confirm or rule out the disease. Many patients develop hyperuricaemia but not gout, while, on the contrary, during acute attacks urate levels may be normal.	95 (92-99)	93
Renal excretion of uric acid should be determined in selected gout patients, especially those with a family history of early onset of gout, acute episodes in individuals under 25 years, or renal calculi.	72 (62-81)	60
Although x-rays may be useful for differential diagnosis and may show typical features of chronic gout, they are not suitable for diagnostic confirmation.	86 (79-94)	93
Assessment of risk factors for gout and comorbidities is essential, especially for those related to metabolic syndrome (obesity, hyperglycaemia, hyperlipidaemia, and hypertension)	93 (88-98)	100

A-B%: Percentage of the strength of recommendation, based on the EULAR ordinal scale (A = fully recommended, B = strongly recommended, C = moderately recommended, D = weakly recommended, E = not recommended)
Abbreviations: CI = confidence interval; MSU = monosodium urate; SOR = strength of recommendation, VAS = visual analogue scale (0-100 mm, 0 = not recommended, 100 = fully recommended).

Table 21. Clinical prediction scale for the diagnosis of acute gouty arthritis in PC.

Criterion	Score
Male sex	2.0
Previous episodes of arthritis	2.0
Symptom onset within 1 day	0.5
Joint hyperaemia	1.0
First MTP joint involvement	2.5
HBP or cardiovascular disease	1.5
Uric acid >5.88 mg/dL	3.5

Interpretation: The probability of gout is 2.8% for scores ≤4; 27% for scores>4 and <8, and 80.4% for scores ≥8. **Abbreviations**: MTP = metatarsophalangeal, mg = milligram, dL = deciliter, HBP = high blood pressure.

X.B. GENERAL RECOMMENDATIONS IN PRIMARY CARE

Hyperuricaemia and gout are often associated with hypertension, obesity, diabetes, hyperlipidaemia, atherosclerosis, and alcohol intake. Certain nutritional strategies and changes in lifestyle can have a beneficial role in both hyperuricaemia and in associated processes. Communication and closer contact between patients and primary care physicians may increase compliance with these measures.

The patients should be instructed about their disease, triggering factors and long-term consequences as well as about control and management of cardiovascular risk factors, with emphasis on the importance of hypertension.

A meta-analysis of 13 trials evaluated the effect of vitamin C on serum uric acid. Overall, the methodological quality of the trials analysed was low, especially in terms of design, showing a significant heterogeneity (inconclusive result), and maximum impact on serum uric acid levels (upper limit of confidence interval 95%) of 0.6 mg/dL (5).

Recommendation 40: Patient education and changes in lifestyle, especially with regard to weight loss, diet, and reduced alcohol consumption, are fundamental aspects of patient management in which the primary care physicians can have a leading role (LE 2a; GR B; DA 100%).

X.B.1. Acute attack

See **Chapter XI** for more information.

In the therapeutic management of acute episodes by PC, since NSAID prescribing is very common, special attention should be paid to prior assessment of comorbidities, cardiovascular risk, and risk of gastrointestinal bleeding before starting treatment, since all of these conditions may limit some of the options available. Recently, a multidisciplinary group published a consensus document on the use of NSAIDs (342) in terms of cardiovascular risk and gastrointestinal bleeding in the patient. In addition, a tool is available on the Internet that offers various treatment alternatives (*http://www.e-hims.com/Sensar/*).

Table 22. Using NSAIDs depending on cardiovascular and gastrointestinal risk

Gastrointestinal Risk[1]	Cardiovascular Risk[2]	
Low ↓ High	Low	High
	• Non-selective NSAIDs[3]	• Naproxen + PPI
	• Cox-2[4] Inhibitors • Non-selective NSAIDs[1] + PPI	• Naproxen + PPI
	• Ibuprofen/Diclofenac + PPI • Celecoxib + PPI	• Avoid use of NSAIDs to the extent possible • When necessary: o Diclofenac/naproxen + PPI o Cox-2[4] Inhibitors + PPI

[1]The high gastrointestinal risk is related to the number of gastrointestinal risk factors present (previous episodes, age ≥65 years, continued use of NSAIDs, concomitant use of aspirin/anticoagulants/corticosteroids).
[2] Cardiovascular risk: 10-year risk of fatal cardiovascular event (low <10%, high ≥10%)
[3] Ibuprofen/diclofenac/naproxen
[4] Celecoxib, etoricoxib

Recommendation 41: The choice of treatment will give special consideration to comorbidities and possible interactions with drugs used to treat them. During acute episodes of inflammation urate-lowering drugs should not be prescribed, suspended or changed in dose (LE 5; GR D; DA 100%).

- Clinical response depends on the time it takes to start treatment; the best response comes with early treatment.
- In acute attacks, intra-articular injection of corticosteroids is rarely applicable in PC.
- In patients with episodes of acute inflammation urate-lowering therapy should not be discontinued if they were already taking it before the attack. Urate-lowering therapy should not be started during an acute gout attack.
- With regard to prophylaxis of acute episodes of gout, the same indications as in specialized care are recommended (see **Chapter XI**).
- The same indications for urate-lowering treatment as those used in specialized care are recommended (see **Chapter XI**).

IX.B.2. Evaluation and management of comorbidities

See **Chapter VII** for more information.

The initial patient assessment should identify potential comorbidities using a checklist containing the following processes: obesity, metabolic syndrome, diabetes mellitus, hypertension, chronic kidney disease and its stages, alcohol abuse, congestive heart failure, cerebrovascular disease, high cholesterol, heart disease, high or low gastrointestinal bleeding, organ transplantation and drug-to-drug interactions.

Comorbidity may affect the course of treatment of gout and the frequency of occurrence of acute attacks (343). Hyperuricaemia may be an indicator of renal vascular damage in essential

hypertension. Moreover, many authors consider it as a potential cardiovascular risk factor (69).

Recommendation 42: Primary care should play a role in the assessment and management of comorbidities present in patients with gout (LE 5; GR D; DA 100%).

Salicylates exert a paradoxical effect on the renal management of uric acid; at low doses they reduce renal clearance of urate, inducing hyperuricaemia; high doses increase uricosuria because of their uricosuric effect. In any case, the use of antiplatelet therapy does not depend on the possibility of inducing hyperuricaemia and gout but on different cardiovascular risk factors. The impact of antiplatelet therapy on urate levels is small.

Recommendation 43: In primary care patients with gout and indication of cardiovascular events prevention administration of low-dose aspirin should not be suspended (LE 5; GR D; DA 100%).

Hypertension is a pathological process usually controlled by the PCP. The use of diuretics is associated with the occurrence of hyperuricaemia and gout (338, 344). The effect of thiazide and loop diuretics on renal management of uric acid varies depending on the dosages used. At high doses administered intravenously, these compounds reduce proximal reabsorption of urate, thus producing a uricosuric effect. However, at the low doses commonly used orally they increase tubular reabsorption of uric acid, resulting in a net retention effect. Accordingly, and as far as possible, patients with gout and hypertension should avoid the use of thiazide and loop diuretics, employing as antihypertensives angiotensin receptor antagonists (especially losartan for its uricosuric effect) (345) or calcium channel blockers that also have uricosuric effects (346).

Recommendation 44: Primary care patients with gout and hypertension should be assessed for suspension of thiazide and loop diuretics and initiation of treatment with angiotensin receptor antagonists (especially losartan) or calcium channel blockers (LE 5, GR D, DA 100%).

Similarly, hypercholesterolaemia is a common disorder in patients with gout. Among the statins, atorvastatin is the only one showing a modest uricosuric effect (347).

The existence of hyperuricaemia and gout with diabetes or insulin resistance appears to be explained by a sodium reabsorption-mediated decreased renal excretion of uric acid in the proximal tubule and hyperinsulinaemia. The results of various studies have shown an association between the components of metabolic syndrome and plasma urate levels (348). Finally, some authors have also managed to demonstrate a relationship between hyperuricaemia and metabolic syndrome mediated by fructose, a sugar widely used in bakery products and soft drinks (349, 350).

IX.B.3. Criteria for referral to specialized care

Rheumatic diseases are one of the most frequent reasons for consultation (10-40%) in PC. In the case of gout, the role of the PCP should focus on establishing the suspected diagnosis and instituting appropriate treatment for hyperuricaemia and acute attacks. Although there is good correlation between clinical suspicion and definitive diagnosis by visualization of uric acid crystals, the family physician should consider referring the patient to Rheumatology in the following situations:

1. Diagnostic confirmation in atypical cases or cases with inadequate treatment response
2. Complex differential diagnosis
3. Polyarticular or tophaceous gout
4. Gout in a patient with clinically significant chronic kidney disease or solid organ transplant
5. Assessing specific therapeutic alternatives that are not accessible from PC: hospital medicines and special situations (see corresponding chapter)
6. Unfavourable course of the disease with lack of response to symptomatic or urate-lowering treatment
7. Need for additional examinations such as colour Doppler, high-resolution MRI or dual-energy CT for the assessment and monitoring of complex cases.

Table 23. Proposals and strength of recommendation of clinical diagnosis.

Proposal	SOR (95% CI) VAS 100	A-B%
In gout attacks the rapid development of significant pain, swelling and sensitivity that is reached in less than 6-12 hours, especially if erythema is also present, is highly suggestive of crystals deposition disease, though not specifically gout.	88 (80-96)	93
In typical gout presentations (e.g. recurring podagra with hyperuricaemia) clinical diagnosis alone is fairly accurate, though not definitive, unless there is confirmation of visualization of crystals.	95 (91-98)	100
Demonstration of MSU crystals in synovial fluid or aspirated tophi allows a definitive diagnosis of gout.	96 (93-100)	100
In all synovial fluid samples obtained from inflamed joints without aetiologic diagnosis visualization of MSU crystals is recommended.	90 (83-97)	87
Identification of MSU crystals from asymptomatic joints may allow definite diagnosis in intercritical periods	84 (78-91)	93
Gout and septic arthritis may coexist, so when it is suspected a Gram stain and culture of synovial fluid should be performed, even if MSU crystals are identified.	93 (87-99)	93
Despite being the most important risk factor for gout, elevated serum uric acid does not confirm or rule out gout. Many patients with hyperuricaemia do not develop gout, while during acute attacks serum uric acid levels may be normal.	95 (92-99)	93
Renal excretion of uric acid should be determined in selected patients with gout, especially those with a family history of early onset of the disease, episodes under 25 years, or patients with renal calculi.	72 (62-81)	60
Although x-rays may be useful for differential diagnosis and may show typical features of chronic gout, they are not useful to confirm the diagnosis of acute gout.	86 (79-94)	93
Risk factors of gout and comorbidities should be assessed, including typical features of metabolic syndrome (obesity, hyperglycaemia, hyperlipidaemia, and hypertension)	93 (88-98)	100

A-B%: Percentage of the strength of recommendation, based on the EULAR ordinal scale (A = fully recommended, B = strongly recommended, C = moderately recommended, D = weakly recommended, E = not recommended).
Abbreviations: CI = confidence interval; MSU = monosodium urate; SOR = strength of recommendation, VAS = visual analogue scale (0-100 mm, 0 = not recommended, 100: strongly recommended).

Table 24. Clinical prediction scale for the diagnosis of acute gouty arthritis in PA.

Criterion	Score
Male sex	2.0
Previous episodes of arthritis	2.0
Symptom onset within 1 day	0.5
Joint hyperaemia	1.0
First MTP joint involvement	2.5
HBP or cardiovascular disease	1.5
Uric acid >5.88 mg/dL	3.5

Interpretation: The probability of gout is 2.8% for scores ≤4; 27% for scores >4 and <8, and 80.4% for scores ≥8.
Abbreviations: PC = primary care MTP = metatarsophalangeal, HBP = high blood pressure, mg = milligram, dL = deciliter.

XI. TREATMENT

Recommendation 45: Lifestyle changes should be suggested if drug treatment is prescribed to reduce serum uric acid levels after diagnosis of gout, but taking into account patient characteristics and comorbidities (LE 5; GR D; DA 92%).

When a patient is diagnosed with gout, a number of dietary and hygiene measures must be established that will be described in this chapter. And it is important to note that although these fail to achieve the therapeutic goal and it is decided to prescribe a urate-lowering treatment, these should still be followed.

XI.A. NON-DRUG TREATMENT

In gout non-pharmacological therapeutic measures are as important as drug therapy (149). In fact, there is evidence that the implementation of these measures improves the prognosis of the disease (351). Non-pharmacological treatment should be individualized according to the patient's lifestyle, associated comorbidity, use of other medications, disease status and therapeutic goals established a priori (150). Besides discussing with the patient the treatment plan to encourage their active involvement, compliance level will be assessed periodically and the necessary modifications and adjustments will be made for proper monitoring and the necessary adaptations to the changing characteristics of the disease (116, 149, 351).

The prevalence of comorbidity associated with MSU crystals is high (43% obesity, 62% hypertension, 61% hyperlipidaemia) (75), underscoring the importance of the measures relating to appropriate diet, weight control, reducing the consumption of alcohol and tobacco, exercise and patient education (33, 75, 149, 351).

XI.A.1. Diet

The information available on the relationship between food and the occurrence of gout or increased serum urate is diverse and occasionally of questionable methodological quality. The lack of firm evidence, along with perceptions of the physician and patient, limits the possibility of precise recommendations (33, 149, 150, 351).

There is evidence that some foods increase the risk of gout and others reduce it. Diets low in purines have little effect on reducing serum urate, with decreases less than 1 mg/day (351), and entail dietary regimens that are difficult to comply with over the long-term, making it impossible to achieve a clinically significant reduction in serum uric acid with diet only (33, 149, 150, 351). However, foods that increase the risk of gout and/or serum urate levels should be avoided and patients should be encouraged to consume foods that decrease them.

Foods that consistently increase the risk of gout include: red meat (pork, beef or lamb), shellfish, fish and, in general, products with high animal protein content. Food, beverage, and dietary preparations rich in fructose also have been associated with increased risk of gout and insulin resistance (33, 149, 150, 339, 351, 352).

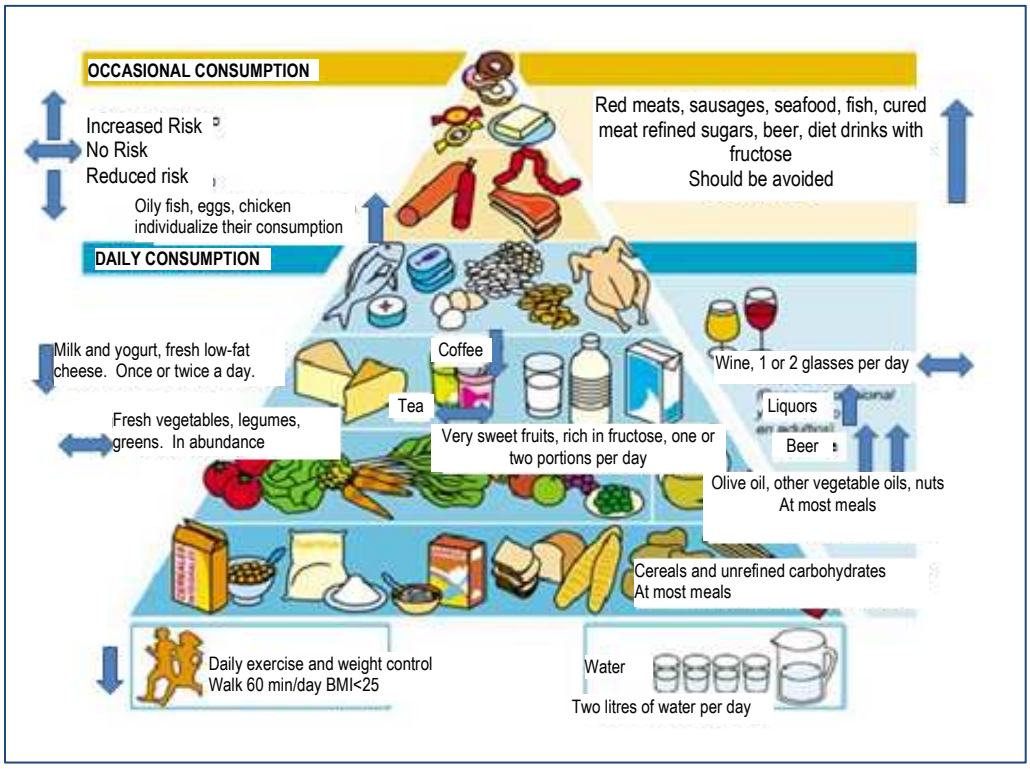
Among those that reduce the risk of gout and serum uric acid levels are milk, yogurt, and low-fat products. Coffee consumption and vegetable proteins (legumes and nuts) have also shown a protective effect (33, 75, 339, 352).

Neither increased risk of gout or hyperuricaemia was described in individuals with high intake of purine-rich foods of plant origin (peas, beans, green beans, lentils, spinach, mushrooms, oatmeal or cauliflower) (32, 150), which are recommended as part of a balanced diet. One drawback of oily fish, which is rich in omega-3 fatty acids with its beneficial effects for the management of comorbidity, is its high protein content. Therefore, the use of these foods should be individualized according to comorbidity and the eating habits of each patient.

In conclusion, the gout sufferer's diet should have a balance of protein, carbohydrates and lipids, with reduced intake of red meat, saturated fat and refined carbohydrates and adequate energy intake to maintain a stable weight. The Mediterranean diet has all these features so its recommendation must conform to the physician and patient perspectives (33, 75, 351, 353). Diets aimed at improving insulin resistance or metabolic syndrome are a good choice.

Image 4 shows the impact of diet on the risk of MSU crystal deposition disease of and its implications in the context of the food pyramid (351, 354, 355).

Image 4. Dietary recommendations tailored to Mediterranean diet.



XI.A.2. Alcohol

Alcohol consumption increases the risk of gout and serum urate, the increases paralleling the amount of alcohol consumed. Risk differences exist depending on the type of drink. In any case, excessive consumption of any alcohol must be avoided. Regarding differences in the type of drink it must be noted that beer is associated with increased risk of gout and elevated serum urate levels, while wine shows no increased risk after adjusting for other factors; liquors are somewhere in the middle. Although wine consumption is not recommended as part of non-pharmacological treatment of gout, it is clear that its intake in moderation – two drinks a day – is not contraindicated, and also has a proven beneficial effect on cardiovascular risk.

XI.A.3. Obesity

Cases of obesity require an adequate weight reduction program. Diet will be adjusted according to the degree of obesity and the patient's lifestyle. Evidence shows that weight reduction decreases the number of attacks and serum urate levels. Cases with morbid obesity and/or significant risk factors (cardiovascular and diabetes), will be referred to an expert for dietary control and short-term regular monitoring.

Generally, obese patients must meet the previously mentioned recommendations based on a low calorie diet that will facilitate gradual weight loss. Achieving and maintaining a body mass index <25 helps to achieve the therapeutic goal and has a beneficial impact on the disease and its associated comorbidities (355).

XI.A.4. Exercise

Evidence indicates that patients with MSU crystal deposition disease who exercise have fewer attacks (356). It remains to be determined whether physical activity *per se* has an impact on uric acid, although the results of observational studies show that healthy men and athletes who engage in more intense exercise have serum urate figures lower than those who have less physical activity (357). In addition, exercise helps to reduce weight and improves lipid profile, glycaemic control, blood pressure, and insulin resistance, producing a subsequent beneficial effect on cardiovascular risk, which is the basis of the pyramid of the Mediterranean lifestyle. The exercise recommended is the same as for patients with cardiovascular risk (351, 355).

XI.A.5. Smoking

Although tobacco has not been shown to affect gout, smoking cessation is advised due to increased cardiovascular risk and its association with alcohol consumption (149).

XI.A.6. Education

There is little evidence on the effect of informing and educating the gout-afflicted patient on improving compliance and achieving treatment goals (358, 359). However, most experts agree on the importance and necessity of educational measures in the treatment of the disease (149), although it is not clear how to bring them up with the patient, much less how to assess them.

The patient should be informed about the disease, the chances of cure, and treatment goals. The deleterious effect of comorbidity must be explained, both with regard to the disease and about associated fatal risks, highlighting the subsequent need to improve the situation. Information may be provided by various means (verbal, written, internet, new technologies, etc.), but always as part of a structured education program to be reinforced at every visit. In addition to the information, the patient should agree on short-term treatment goals (decreased alcohol consumption, replacement of beer with moderate amounts of wine), and long-term goals (reduction of tophi or lesser number of acute attacks).

XI.A.7. Dietary Supplements

The anti-inflammatory effect of omega-3 fatty acids in various chronic diseases and their beneficial effect on the lipid profile have led some authors to recommend their use as a dietary supplement, primarily in the form of eicosapentaenoic or docosahexaenoic acid and other derivatives from plant sources. Omega-3 fatty acids of vegetable origin have proven effective in experimental models in rats with induced gout. The results of some epidemiological studies show that adults who ingest 500-2000 mg/day of vitamin C have a lower risk of acute attacks of gout, and may also experience reduced cardiovascular risk. However, the design of these studies does not allow specifying causal relationships (33, 351).

There is no conclusive evidence on the beneficial effect of vegetable-based omega-3 fatty acids supplements or vitamin C in preventing acute attacks of gout or serum uric acid.

XI.B. INDICATIONS OF DRUG TREATMENT

Recommendation 46: The treatment goal is the dissolution of MSU crystals by reducing serum urate levels (LE 5; GR D; DA 100%).

The goal of treatment of gout is its "cure", based on the disappearance of inflammation through the dissolution of MSU crystals in joint fluid and tissues, and the prevention and treatment of breakthrough acute inflammation episodes. Dissolution of urate crystals in tissues is achieved by reducing the plasma concentration below its saturation level, thanks to the use of dietary measures, and in most patients, specific pharmacological treatment .

There is no consensus on when drug treatment should begin. Some authors recommend starting urate-lowering therapy after the occurrence of a second gout attack, in the presence of tophi, or in severe or difficult to treat attacks (360), using only general measures after a first attack. This approach may be questionable for several reasons: first, there is a good correlation between the number of attacks and the magnitude of urate deposit, plus some patients may develop prominent tophi with no previous history of arthritis (361). Moreover, the increased cardiovascular risk associated with gout *per se* (171, 336), higher even in long-standing cases with extensive deposits (tophaceous gout) (153, 336), is probably mediated by persistent inflammation associated with the presence of crystals in tissues and in the synovial fluid. It has been suggested that the reduction of uric acid levels in cases of CKD can slow the progression of the disease (232), presumably by dissolution of urate crystals deposited in the renal interstitium, although the effect of other factors has not been excluded. These data suggest a potential benefit from urate-lowering treatment initiation after diagnosis of the disease, especially in the case of patients at risk of developing extensive deposits (i.e., very high hyperuricaemia, transplant).

The pharmaco-economic aspect can be useful for deciding when to start treatment, although there are few studies. The results of a cost-effectiveness study of allopurinol published in 1995 (362) showed that this compound is cost-effective if treatment is established from the second attack, but also possibly from first taking into account the gastrointestinal risks of NSAIDs. The main limitations of this study relate to its theoretical nature (hypothetical model), and the lack of inclusion of other potential benefits of early treatment onset and additional adverse effects of NSAIDs.

The reduction of serum urate is associated with disappearance of arthritis attacks, dissolution of MSU crystals in synovial fluid and tophi resolution, which results in the cure of the disease (363). During a prospective study (364) it was observed that patients with uric acid levels kept below 6.0 mg/dL, presented a lower rate of acute attacks, and had reduced presence of crystals in synovial fluid (44% vs. 88 %) than those who maintained high levels. These results have been confirmed in retrospective studies (365) and population based-studies (21, 27, 366). 2002, Perez-Ruiz et al. (367) demonstrated an inverse correlation between serum uric acid and the rate of reducing the size of tophi, so that the lower the serum uric acid levels, the greater the reduction rate. In this study tophi disappeared in all patients within 6-60 months after the initiation of urate-lowering treatment. Furthermore, serum urate fulfils the OMERACT validation criteria for soluble biomarkers (167).

Although there is agreement that serum uric acid reduction should be the therapeutic goal in gout, various published expert recommendations do not agree on the target concentration to be achieved. EULAR recommendations advise a level lower than 6.0 mg/dL, below the urate saturation limit (about 6.8 mg/dL), but point out that in situations of extensive deposits, lower concentrations can accelerate the process of tophi resolution (149). The guidelines of the British Society for Rheumatology recommend serum uric acid below the average level of the British population, which is approximately 5 mg/dL (152). Recently published recommendations by a panel of American experts (78) once again established a cut-off serum urate of <6.0 mg/dL as the level to be achieved, although the authors state that in cases of extensive deposits levels below 4 mg/dL are acceptable to accelerate dissolution of the crystals. Given the lack of consensus it is important to note that the rate of tophi resolution (367), and presumably also of the crystals is greater at lower serum uric acid levels (363), achieving a faster resolution of the attacks and of subclinical inflammation.

Recommendation 47: Serum uric acid must reach levels below 6.0 mg/dL, although lower concentrations can accelerate the cure of the disease (LE 1b; GR A; DA 100%).

XI.C. DRUGS FOR GOUT: SUMMARY OF PRODUCT CHARACTERISTICS, INTERACTIONS AND ALLERGIES

XI.C.1. Summary of product characteristics and interactions

Table 25. Gout related treatments approved in Spain and their characteristics (SPC)*.

ACTIVE INGREDIENT	STRUCTURE AND MECHANISM OF ACTION	DOSAGE AND ADMINISTRATION	INDICATIONS	CONTRAINDICATIONS	ADVERSE EFFECTS
ALLOPURINOL **Various** **100 mg tablet** **300 mg tablet**	UA reduction in plasma and urine by inhibiting XO	- **Dose:** 2 to 10 mg/kg/day or: o 100 to 200 mg daily in mild disorders o 300 to 600 mg daily in moderate disorders o 700 to 900 mg daily in serious disorders . - **Method**: oral - **Frequency:** once daily after meals. In case of intolerance, try to distribute the dose several times daily.	Treatment of major **clinical manifestations** of uric acid/urates deposit: - gouty arthritis - cutaneous tophi - kidney disease with deposition of crystals or calculi formation. Treatment of **renal calculi** of 2.8-dyhydroxyadenine associated with deficient activity of adenine phosphoribosyl transferase. Treatment of recurrent mixed **renal calculi of** calcium oxalate in the presence of hyperuricosuria, when other measures have failed.	Hypersensitivity to active ingredient or excipients. **Precaution with kidney disease**: Consider initiating treatment with a maximum dose of 100 mg/day and increase only if the serum and/or urinary urate response is not satisfactory. In severe kidney failure, it may be advisable to use less than 100 mg per day or using single doses of 100 mg at intervals greater than one day. o Regimens based on creatinine clearance are not recommended due to imprecise lower clearance values. Caution in patients treated with azathioprine or 6-mercaptopurine because of possible interaction with risk of severe bone marrow toxicity	- **Very common**: --- - **Common**: rash - **Uncommon**: o Hypersensitivity o Nausea-vomiting o Increased transaminases - **Rare**: o Steven-Johnson syndrome o Toxic epidermal necrolysis o Hepatitis
FEBUXOSTAT **Menarini** **80 mg tablet** **120 mg tablet**	UA reduction in plasma and urine by inhibiting XO	- **Dose:** 80 mg once a day, regardless of meals. - **Method:** oral. - If after at least 2-4 weeks of treatment serum UA is still >6 mg/dL, dosage of 120 mg can be considered once daily.	Treatment of **chronic hyperuricaemia** in situations where urate deposit already occurred (including a history or presence of tophi and/or gouty arthritis).	- Hypersensitivity to active ingredient or excipients. - Caution in patients with thyroid disorders - Not recommended for: o Patients treated with azathioprine or 6-mercaptopurine because of possible interaction with risk of severe bone marrow toxicity o Patients with advanced CKD due to lack of experience	- **VERY common**: --- - **Common**: o Acute gout attack o Headache o Diarrhoea, nausea o Increased transaminases o Rash - **Uncommon:** o Reduced appetite o Reduced libido

				o Patients with CHF or ischaemic heart disease	o Insomnia, dizziness, paresthaesia, somnolence o Altered taste o Hypoesthaesia o Atrial fibrillation, palpitations, ECG changes o Hypertension, blushing, flushing o Dyspnoea, upper respiratory tract infection o Abdominal pain, gastroesophageal reflux, vomiting, dry mouth, dyspepsia, constipation, loose stools, flatulence, gastrointestinal discomfort o Dermatitis, urticaria, pruritus o Arthralgia, myalgia, musculoskeletal pain, weakness and muscle spasm o Nephrolithiasis, haematuria, urinary frequency, kidney failure o Fatigue, oedema, pain/discomfort in the chest, hyperamylasaemia, thrombocytopenia, increased creatinine o Anaemia, uraemia, hyperlipidaemia, increased lactate dehydrogenase - **Rare:** o Pancytopenia o Weight gain/loss, increased appetite, anorexia o Hyperlipidaemia, nervousness, tinnitus o Pancreatitis, mouth ulcers o Alopecia, hyperhidrosis o Arthritis, joint and musculoskeletal stiffness o Urinary urgency, erectile dysfunction o Thirst, hyperglycaemia

					o Activated partial thromboplastin time prolonged o Increased ALP
BENZBROMARONE Prostrakan Pharmaceuticals 100 mg tablet	Reduction of serum UA by increasing its renal clearance (tubular reuptake inhibition) and intestinal excretion.	- **Dose**: 50-100 mg, that can be increased to 200 mg per day - **Method**: oral - **Frequency**: daily	**Lack of response or intolerance to allopurinol** in: - Severe gout (polyarticular or tophaceous), in which it is essential to control hyperuricaemia - - Hyperuricaemia in patients with renal failure with CrCl >20 mL/min - Hyperuricaemia in patients with kidney transplant Prescription limited to nephrologists and rheumatologists.	- Hypersensitivity, - Liver failure, hepatic porphyria, concomitant use of hepatotoxic drugs (especially for TB), - Hyperuraturia >700 mg/24 h, uric lithiasis, gout secondary to haemopathy	- **Hepatic:** Severe hepatotoxicity, cytolytic type, especially in first year of treatment. It is recommended that liver enzymes be monitored fortnightly during this period.**Renal**: renourethral colic - **Hipersensitivity** (raree) - **Digestive:** diarrhoea, nausea
COLCHICINE Seid 1 mg Colchicine ® granules	Anti-inflammatory effect, probably related to inhibition of leukocyte mobility, inhibiting phagocytosis of urate crystals and antimitotic activity (interruption of cell division in metaphase and anaphase).	**- Gout attack:** 1mg p.o. at the first sign of attack. If it persists, additional 1 mg at 1-2h. Maximum dose: 2 mg in the first 24 h, 6 mg in the first four days. If necessary because gout pains persist, the pattern described above could be repeated but only after at least 3 days without treatment ("washout period") o Dose should be reduced in patients with CKD with GFR 30-50 mL/min. o Should be monitored, especially in patients with liver failure and the dose reduced if required. **- Prevention of gout attack** with urate-lowering drugs and chronic gout treatment: 1 mg	- Treatment of **acute attacks** and **chronic gout** - **Prophylaxis** of acute attacks due to initiating treatment with uric acid mobilizers - **Periodic disease** (Familial Mediterranean Fever)	- Hypersensitivity - Pregnancy - Severe kidney disease and haemodialysis - Severe liver failure - Severe gastrointestinal disturbances, peptic ulcer - Cardiac disorders - Blood dyscrasias - 14 days after use of inhibitors of CYP3A4 and/or P-glycoprotein	- **Common:** Nausea, vomiting, abdominal pain - **Uncommon:** o Peripheral neuropathy, myopathy o Alopecia o Azoospermia o Agranulocytosis, thrombocytopenia and aplastic anaemia (long course)

		orally daily **- Familial Mediterranean Fever:** 1-2 mg per day			
COLCHICINE + DICYCLOVERINE Seid 0.5 + 5 mg Colchimax® tablets	Colchicine has anti-inflammatory effects, probably related to inhibition of leukocyte mobility, inhibiting phagocytosis of urate crystals and antimitotic activity (interruption of cell division in metaphase and anaphase). Dicycloverine is a muscarinic cholinergic antagonist. It acts by reducing smooth muscle spasms and various types of glandular secretion, by selective blockade of M1 acetylcholine receptors.	The same as for colchicine.	The same as for colchicine.	The same as for colchicine, plus: - Glaucoma - Closed angle glaucoma - Prostate adenoma - Gastrointestinal obstructive disease, ulcerative colitis, reflux esophagitis, pyloric stenosis, ileus - Myasthenia gravis - Obstruction or urinary retention, any uro-prostatic pathology	Those described for colchicine. Anticholinergic drug adverse reactions (not all of them recorded with dicycloverine) include: - Gastrointestinal effects such as dry mouth, nausea, vomiting and abdominal pain - Central nervous system such as drowsiness, weakness, headache - Ophthalmologic such as blurred vision, diplopia, mydriasis and increased eye pressure - Dermatological effects are skin rash and urticaria - Urinary retention - Tachycardia - Dyspnoea - Dyspnea

The data in this table are obtained from the summary of product characteristics of the Spanish Agency of Medicines and/or the European Medicines Agency, data available at June 30, 2012

†**Adverse** events: Very common (at least 1 in 10 patients), common (at least 1 in 100 patients), uncommon (at least 1 in 1000 and less than 1 in 100), rare (at least 1 in 10,000 and less than 1 in 1,000 patients). In the case of febuxostat safety data comes from phase III clinical trials.

Abbreviations: UA = uric acid, CrCl = creatinine clearance, ECG = electrocardiogram; kg = kilogram, mg = milligram, APL = alkaline phosphatase, CKD = chronic kidney disease, CHF = congestive heart failure. * Indicates trade name is because often the confusion among them is common, but the dose contained is different (1 mg versus 0.5 mg) and one of them is associated to dicycloverine (anticholinergic).

Table 26. Gout related treatments approved in Spain: interactions (according to the SmPC)*.

ACTIVE INGREDIENT	DRUG	TYPE OF INTERACTION	POSSIBLE CONSEQUENCES	RECOMMENDATIONS
ALLOPURINOL	AZATHIOPRINE - 6-MERCAPTOPURINE	Elimination metabolism inhibition of both drugs, by blocking xanthine oxidase.	Toxicity due to azathioprine and 6-mercaptopurine: pancytopenia	No concomitant use
	SALICYLATES	At high doses, increased renal clearance of oxypurinol (the active metabolite of allopurinol)	Reduced effectiveness of allopurinol	No recommendation has been established
	WARFARIN	Metabolic interaction with increased anticoagulant effect	Excessive anticoagulation, bleeding	Monitoring levels of anticoagulation
	CYCLOSPORINE	Increased plasma levels of cyclosporin by renal tubular level interaction	Cyclosporine toxicity	Monitoring blood levels of cyclosporine
FEBUXOSTAT Menarini	AZATHIOPRINE - 6-MERCAPTOPURINE	Inhibition of metabolism of elimination of both drugs, by blocking the XO (similar to allopurinol, although no specific studies exist with febuxostat]	Toxicity due to azathioprine and 6-mercaptopurine: pancytopenia	No concomitant use
	NSAIDs	Removing febuxostat elimination by competitive inhibition of glucuronidation.	No clinical consequences have been proven	No dose adjustment required
	Antacids (Hydroxides of Mg 2 + and Al 3+)	Reduced absorption of febuxostat	No clinical consequences have been proven	No dose adjustment required
BENZBROMARONE Prostrakan Pharmaceuticals	HEPATOTOXIC DRUGS, especially for TB		Risk of hepatotoxicity	Avoid concomitant use
	PYRAZINAMIDE	The former, more interference of the uricosuric activity by competition in the renal tubule	Possible reduction of efficiency	Avoid concomitant use
	SALICYLATES	Interference of the uricosuric activity by competition in the renal tubule	Possible reduction of efficiency	No recommendation has been established
	WARFARIN	Increased anticoagulant effect	Excessive anticoagulation, bleeding	Monitoring levels of anticoagulation
COLCHICINE Seid	ANTI-INFECTIVE DRUGS - Clarithromycin, erythromycin, telithromycin - Also itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir	Removal metabolism inhibition of colchicine (CYP3A4)	Colchicine toxicity increased	Increase precautions The FDA recommends therapeutic alternatives or reducing colchicine dosage in half.
	CYCLOSPORIN-A	Increased plasma levels of colchicine due to P-glycoprotein inhibition	Enhancement of neurotoxicity and myotoxicity	Increase precautions
	LIPID-LOWERING DRUGS (Statins and Fibrates)	Increased risk of myotoxicity	Myopathy, rhabdomyolysis	Increase precautions The FDA does not recommend monitoring muscle enzymes as they do not necessarily prevent severe myopathy.
COLCHICINE + DICYCLOVERINE Seid	ANTI-CHOLINERGICS tricyclic antidepressants, amantadine, class I antiarrhythmic agents (quinidine), antipsychotics (phenothiazines), benzodiazepines, MAO inhibitors, narcotic	Potentiation of anticholinergic effect of dicycloverine	Anticholinergic syndrome risk	Increase precautions

	analgesics (meperidine), nitrates and nitrites, antacids and sympathomimetic agents			

* The data in this table are obtained from the summary of product characteristics of the Spanish Agency of Medicines and/or the European Medicines Agency. FDA: Food and Drug Administration, to date June 30, 2012

XI.C.2. Allergies

Within the group of gout drugs, allopurinol is the compound that most frequently produces allergic reactions, complicating the management of gout because it is the most widely used urate-lowering treatment. It is estimated that approximately 2% of patients have a hypersensitivity reaction to this drug. Although most of them are mild exanthematous skin reactions, more severe forms have also been reported and even some with fatal outcome (368, 369). In fact, allopurinol has been pointed to as the leading cause of toxic epidermal necrolysis, or Lyell's syndrome, in Europe (370). Also, there have been reports of DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) associated with the use of allopurinol, and in addition to the rash fever, elevated acute phase reactants with eosinophilia, abnormal liver enzymes and renal function impairment. Toxic epidermal necrolysis as well as DRESS syndrome are within the spectrum of drug hypersensitivity reactions, mediated by a cellular immune response (type IV Gell-Coombs) (371, 372) causing high morbidity and mortality.

Allopurinol hypersensitivity seems to have an idiosyncratic origin, although some published studies have observed a relationship between renal function of patients and the incidence of these reactions, being more frequent in cases of poor renal function (272), which could be due to excessive drug dosage due to accumulation of its active metabolite, oxypurinol. This relationship formed the basis for recommending a dosage of allopurinol according to renal function as measured by creatinine clearance (Hande algorithm, Table 27). Other risk factors include female gender, use of diuretics and some HLA alleles present in certain Asian ethnic groups (373).

However, there are no definitive conclusions about this association. In a retrospective study conducted in Mexico (279) there was no difference in the incidence of allergic reactions to allopurinol in patients with renal function adjusted prescription and those treated in accordance with the Hande algorithm. The main limitation of the study is its small sample size (120 patients; only 5 had hypersensitivity reactions associated with allopurinol, 2 in the first group and 3 in the second). The results of subsequent studies have shown that higher doses than those recommended in the Hande algorithm are safe and can achieve the therapeutic goal of reducing uric acid more frequently (278). In fact, it seems that it is the starting dose of the drug (corrected for creatinine clearance), and not the maintenance dose, which is related to the occurrence of hypersensitivity reactions (374) (see Table 25: Indications).

In patients with a history of hypersensitivity reaction to allopurinol some authors recommend a desensitization pattern, starting with doses of 50 mcg and increasing, cautiously and gradually, every 3 days to reach 50-100 mg. This pattern has been effective and safe (375), although it is not without risks and is not recommended in patients with severe previous reactions. At present, given the existence of therapeutic alternatives to allopurinol, it seems more sensible to opt for a change of drug than to initiate desensitization therapy. Specifically, relative to febuxostat, Chohan (376) recently reported a series of 13 patients with a history of severe hypersensitivity to allopurinol treated with febuxostat; 12 of them tolerated the treatment, while the remaining patient, who had an exfoliative rash prior to allopurinol treatment, presented cutaneous leukocytoclastic vasculitis upon introduction of the new drug.

With respect to the rest of the urate-lowering drugs, allergic reactions have been reported with all of them (see Table 25: Indications). Regarding febuxostat, both controlled and post-marketing studies have detected cases of skin rash (defined as a common side effect that

occurs in 1:10-1:100 patients) and rarely Stevens-Johnson syndrome and anaphylactic reactions (defined as those that appear in 1:1,000 to 1:10,000 patients) (377).

Therefore, and in conclusion, it should be noted that, within this rarity, cases of hypersensitivity occur more frequently with allopurinol, presumably related to the starting dose of the drug and the patient's renal function. At its appearance switching to febuxostat or benzbromarone treatment is advisable, relegating desensitization therapy to exceptional situations.

Table 27. Dose adjustment of allopurinol according to creatinine clearance (Hande).

Creatinine clearance (mL/min)	Maintenance doses of allopurinol (mg)
0	100mg every 3 days
10	100mg every 2 days
20	100mg per day
40	150mg per day
60	200mg per day
80	250mg per day
100	300mg per day
120	350mg per day
140	400mg per day

Abbreviations: mL = millilitre; min = minute; mg = milligram.

XI.D. URATE-LOWERING TREATMENT

Recommendation 48: The urate-lowering drugs available (allopurinol, febuxostat and benzbromarone) have shown to be highly effective in achieving the therapeutic goal when prescribed in adequate doses (LE 1b, GR A, DA 100%).

Gout manifestations are due to the presence of urate crystals in tissues. Deposition of urate crystals is reversible since reduction of serum uric acid to levels below the saturation point of urate in plasma dissolves them (363). In the absence of urate crystals there is no gout and EULAR recommendations 2006 consider this disease "curable" (149). Thus, the main objective of the treatment of gout is to dissolve uric acid crystals, reducing serum uric acid to adequate levels persistently and long-term.

The initiation of urate-lowering treatment can be a trigger for gout attacks (224, 378). It is therefore recommended not to start any treatment of this type during an attack, but to wait until after its resolution. Moreover, the establishment of urate-lowering treatment must be accompanied by prophylaxis for prevention of breakthrough acute attacks (see section XI.E.), taking into account that if the expected decrease of uric acid is very sharp and rapid, the risk is especially high and can cause serious attacks and polyarticular presentation (226). In addition to prophylaxis, it is recommend to start urate-lowering treatment with a low-dose step-up protocol, until adequate control of plasma urate is achieved.

Recommendation 49: Urate-lowering treatment should be started from low doses, progressively stepping-up if necessary, until reaching effective doses to achieve a therapeutic serum uric acid level (LE 1b; GR A; DA 100%).

It is important to educate patients about the importance of compliance and the need to maintain long-term treatment to achieve the therapeutic goals set, since lack of compliance is a frequent cause of treatment failure (379, 380).

The prescription of urate-lowering drugs should be performed in appropriate doses for optimum control and adjusted to the therapeutic target (target serum uric acid), maintained regularly and long term. Proper patient education promotes proper compliance, since discontinuation is associated with recurrence of symptoms (381).

Recommendation 50: Currently it is not possible to recommend one urate-lowering drug over another (LE 5; GR D; DA 80%).

Drugs approved in Spain to reduce uric acid in patients with gout may have two different mechanisms of action. The first is XO enzyme inhibition, a route used by allopurinol and febuxostat. The second is to increase renal excretion of uric acid secondary to inhibition of urate in tubular transporters (the most important is URAT-1) responsible for the renal reabsorption of urate by URAT-1 increasing its elimination in the urine and consequently decreasing serum uric acid.

Recommendation 51: The selection of the urate-lowering drug will be based on data regarding efficacy, safety and experience of the prescribing physician, the patient's clinical profile – severity of illness and comorbidity – and indications, recommendations and restrictions described in each product's SmPC (LE 5; GR D; DA 91%).

XI.D.1. Allopurinol

For over half a century allopurinol has been the most widely used urate-lowering drug because of its availability. This compound is a prodrug that, when administered orally, exhibits adequate bioavailability and is rapidly metabolized to oxypurinol, the major active metabolite.

The approved doses on the SmPC in Spain allow prescription of 900 mg/day (382) in severe cases, although the prescribed dose is rarely higher than 300 mg/day in clinical practice (75). Serum uric acid reduction is proportional to the dose of allopurinol administered, so that the percentage of patients achieving the therapeutic goal of uric acid increases with the use of higher doses (250, 383). However, no studies have been conducted with an allopurinol dose above 600 mg/day; at this dose there is only one study whose main limitation is the small number of patients exposed, only 17 for two months, about 3 patient-years of exposure (250). There are no specific safety data from published prospective studies or trials with these doses (264, 384), which has led to a clear reservation regarding the use of these doses in practice (75).

An inverse relationship has been seen between levels of oxypurinol and creatinine clearance (385, 386), so it is necessary to correct the dose of allopurinol for renal function. This correction can be made based on creatinine clearance or glomerular filtration rate (270), starting with low doses and gradually stepping up to maximum dose of 400 to 600 mg/day per decilitre of glomerular filtration rate. Other more conservative and frequently used empirical dose correction regimens based on GFR (272) are associated with poorly controlled serum uric acid levels in most patients (276). A recent retrospective study shows that oxypurinol concentrations required for good control of uric acid are above those recommended as the maximum dose within the safety range indicated in the SmPC (387).

Allopurinol side effects are not uncommon and can be severe, including DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) (388, 389), toxic epidermal necrolysis, and Stevens-Johnson syndrome (370, 390). Allopurinol toxicity increases with certain HLA haplotypes uncommon in the Caucasian population (391), with the presence of kidney failure and with the use of high starting doses relative to the patient's glomerular filtration rate. Other common side effects include increased liver enzymes and the appearance of skin rash.

Allopurinol, like any XO inhibitor, interferes with the metabolism of azathioprine and 6-mercaptopurine, which facilitates the accumulation of these compounds and may result in toxicity, especially in bone marrow.

XI.D.2. Febuxostat

This is a selective inhibitor of both isoforms of XO, a drug for oral administration in a single daily dose metabolized in the liver. Its metabolites, mostly inactive, are excreted through the digestive tract and kidneys without significant alteration to its pharmacokinetics in situations of mild to moderate renal or hepatic impairment. The reduction of serum uric acid with doses approved in the European Union is linear and dose-dependent (392-394).

Febuxostat is approved in Spain and the European Union with a starting dose of 80 mg/day, which may increase to 120 mg/day after exposure to the starting dose for at least 2 weeks without achieving the target of serum uric acid <6 mg/dL.

Clinical trials involving patients with mean serum uric acid levels prior to treatment of around 10 mg/dL, have shown that administration of febuxostat at doses between 80 and 120 mg achieves the target of serum uric acid <6 mg/dL in 80% - 90% of patients (224, 225, 395), with serum uric acid control rates very superior to those obtained with allopurinol 300 mg/day. Moreover, its effectiveness is consistent over the long-term (233, 396) with no change in the safety profile.

Clinically significant adverse effects are rare with febuxostat, the most common being elevated liver enzymes. Febuxostat is not recommended in patients with ischaemic heart disease or congestive heart failure until there is more data on long-term cardiovascular safety from on-going trials, as well as in patients with stage 4 (GFR <30 mL/min) or stage 5 (GFR <10 mL/min, kidney transplant or dialysis) chronic kidney disease, due to lack of experience. It is contraindicated in patients receiving concomitant therapy with azathioprine or 6-mercaptopurine due to serious bone marrow toxicity risk. Special caution is required in patients with thyroid disease, although in clinical trials observed increase of TSH was similar in patients treated with allopurinol and febuxostat.

XI.D.3. Benzbromarone

Benzbromarone is a halogenated benzofuran that potently and selectively inhibits renal tubular transporter URAT-1, favouring the renal excretion of uric acid. This drug has high bioavailability after oral administration, is metabolized in the liver and excreted via the bile, so its pharmacokinetics are not significantly altered in patients with mild or moderate chronic kidney disease (stages 2 - 3). The effect of uricosurics depends on having sufficient filtered urate load to the glomerulus (sufficient glomerular filtration), but unlike sulfinpyrazone and probenecid, benzbromarone maintains efficiency even with low glomerular filtration stages (CRD 4).

The starting dose is typically 50 mg/day and can be increased to 200 mg/day as necessary. In a recent trial it was observed that 92% of gout-afflicted patients with normal renal function who were not reaching serum uric acid levels below 5 mg/dL with 300 mg/day of allopurinol, reached this therapeutic target (370, 389, 390) with 200 mg/day of benzbromarone, although there is no safety data beyond the two months' follow-up. Similarly, several studies and case

series show the efficacy of benzbromarone in patients with mild to moderate kidney disease, and kidney transplant patients treated with diuretics or cyclosporine (249, 318, 320).

In general, benzbromarone is well tolerated, although its prescription is limited in the European Union due to the infrequent occurrence of severe hepatic cytolysis. Therefore, its use in Spain is specifically limited to patients with polyarticular and tophaceous gout or allopurinol intolerance or inadequate control of serum uric acid. It is restricted to use in hospitals and by rheumatologist and nephrologists (179). Biweekly liver enzymes checks are recommended during the first year of treatment or according to hospital protocol (179).

As with all uricosurics, increased renal excretion of urate may lead to an increase in the risk of renal calculi, due to both uric acid and calcium oxalate. Therefore, its use is contraindicated in patients with hyperuricaemia due to hyperproduction (normal urate clearance) or a history of urolithiasis (179). The risk factors associated with renal lithiasis during uricosuric treatment are the existence of a history of urolithiasis, hyperproduction of urate (for contraindications, see the SmPC), and a high concentration of undissociated uric acid during follow-up. Therefore, uric acid concentration and pH must be monitored during clinical follow and if necessary fluid intake or urine alkalinization should be increased (181).

In patients with intolerance other uricosurics might be useful occasionally, such as probenecid and sulfinpyrazone, although these compounds are not marketed in Spain, so permission must be sought as foreign medication. These drugs are characterized by low long-term tolerability, inconvenient dosage due to the need for dosing two or three times a day, and poor efficacy in patients with chronic kidney disease stage 3 or less.

XI.D.4. Indication of urate-lowering treatment and monitoring

Recommendation 52: It is advisable to begin urate-lowering treatment in patients who have not achieved the therapeutic goal of uric acid (<6 mg/dL) with dietary health measures (LE 5, GR D, AA 85%).

As mentioned previously, once the disease is diagnosed, measures should be implemented to achieve the therapeutic goal, which is the "cure" of gout. This will be accomplished through the dissolution and disappearance of MSU deposits, which in turn is possible by reducing serum uric acid below 6 mg/dL. The first option is the introduction of dietary health measures (if applicable). When the therapeutic goals have been reached with these lifestyle modifications within 3-6 months, treatment should also be initiated with urate-lowering therapy. This does not exclude the fact that the patient has to follow the previously outlined non-pharmacological measures.

Recommendation 53: Treatment for the prevention of acute episodes of inflammation should always be prescribed unless contraindicated, at least during the first six months of urate-lowering treatment (LE 2b; GR B; DA 100%).

On the other hand, beginning urate-lowering treatment can trigger acute inflammation (397). Therefore, it is advisable not to begin treatment during an attack but to wait until it is resolved. In addition, when starting urate-lowering treatment it must be accompanied by treatment to prevent (prophylaxis) the occurrence of breakthrough acute episodes of inflammation because if the anticipated decline in serum uric acid levels is very sharp and

rapid, the risk of attack is especially high and the attack may be polyarticular and intense. Recommended prophylaxis is prescribing a urate-lowering treatment starting at low doses and then increasing them until adequate serum uric acid control is achieved.

Recommendation 54: Urate-lowering therapy should be maintained in the long term to achieve complete dissolution of the crystals and prevent recurrence of hyperuricaemia (LE 5; GR D; DA 100%).

Although a minimum of 6 months of drug treatment was indicated previously, each patient must be evaluated individually to confirm whether the therapeutic objective is reached; if it is not reached, drug therapy (if not contraindicated) should be maintained over the long-term until the therapeutic goal is reached.

In this regard, it is important to educate the patient about the need for long-term treatment to achieve therapeutic goals, since lack of compliance is a common cause of treatment failure (359).

Recommendation 55: There must be close monitoring both in terms of efficacy and safety when drugs are used for the treatment of gout (LE 5; GR D; DA 92%).

It is equally important to note that, as is done in other patients, the response to therapy should be monitored in terms of efficacy ("curing" gout) and safety (occurrence of adverse events).

Recommendation 56: Evaluation of response to urate-lowering treatment may be made based on a number of variables, including: frequency of acute attacks, serum uric acid levels, presence and number of MSU crystals in synovial fluid, and number and size of tophi (LE 5; GR D; DA 91%).

XI.E. PREVENTION OF ACUTE ATTACKS

Preventing acute attacks refers to the measures (pharmacological and non-pharmacological) necessary to prevent the occurrence of acute inflammation in all patients with gout.
It has been shown that patients who are not treated with urate-lowering drugs constantly have MSU crystals within previously inflamed joints (89, 90). These joints produce a continuous interaction between the crystals and the cells (398), with an increase in cellularity compared to asymptomatic joints without crystals, indicating the existence of a subclinical inflammation process (89). This inflammation is the basis of gout attacks. The mechanism of action of colchicine, a drug commonly used to prevent attacks, is precisely to reduce persistent subclinical inflammation (399), making the process more stable.

As long as the crystals remain inside the joint, gout attacks can occur at any time. Thus arises the need to implement preventive treatment in any patient with gout initiating a therapy aimed at reducing serum uric acid, especially in those beginning urate-lowering drug treatment, as they are *a priori* more likely to have acute attacks and even more so when the drug is more potent.

Colchicine, according to its SmPC, may be given in preventive doses of 0.5 to 1 mg/day. It has been estimated that at these doses it prevents attacks secondary to joint inflammation in at least 50% of patients with gout (400). However, there is no agreement on the duration of this treatment. The results of a 6-month study suggest that it should be maintained at least for that length of time (401). Note that in this study, half the patients had to reduce the dose to 0.6 mg/day due to intolerance. In this sense, the EMA and FDA recommended prophylaxis for 6 months based on the CONFIRMS trial with febuxostat (226).

Similarly, it is known that after the start of appropriate urate-lowering treatment crystals remain in the joint for a long time, during which attacks may occur. Specifically, this is up to 2.5 years, and less than 1.5 years in patients with long-standing non-tophaceous gout and not longer than 10 years, respectively, with serum uric acid reduced to about 4 mg/dL (363). The extension of the FOCUS study showed that at 12 months follow-up, without prophylaxis from the third month and with suitable serum uric acid control (≤6 mg/dL) only 5% of patients without tophi had acute attacks, compared to 30% of patients with tophi (233).

Furthermore, the reduction of uric acid to normal values reportedly reduces frequency of attacks (366, 402), probably due to the lower concentration of urate crystals in synovial fluid seen after serum uric acid normalization (363). These results raise the possibility of agreement between patient and clinician on earlier suspension of preventive treatment as long as patients assume and understand the persistent risk of suffering an attack. Finally, it should be remembered that after crystals gout is "cured" (73) and this is, in fact, the best prevention strategy.

In patients with intolerance to colchicine, lower doses can be used on alternate days (0.5 or 1 mg). It should be kept in mind that the recommended dose is 0.5 mg/day if there is intolerance or CKD with GFR <60 mL/min. Colchicine is contraindicated with GFR <30ml/min. It should be noted that in Spain a combination of colchicine 0.5 mg and dicyclomine 10 mg (anticholinergic substance) is marketed for patients with gastrointestinal intolerance to colchicine. Another alternative to colchicine is low doses of NSAIDs (e.g., 25 mg/day of

indomethacin or 250 - 500 mg/day for naproxen), although there is no critical assessment of this therapeutic alternative or a licensed indication in this direction by the AEMPS.

The best known triggers for attacks are decreasing serum uric acid secondary to effective urate-lowering treatment (for example after administration of uricase, uric acid dropping abruptly and significantly) (378, 403), and the coincidence of serious illness or surgery (404) – particularly sepsis (405) – that occur with a decrease in serum uric acid secondary to increased renal clearance of uric acid. Therefore, in these circumstances it is particularly necessary to perform proper prophylaxis of acute attacks.

Another special situation that has not been subjected to critical assessment is that of patients with long-standing gout, frequently tophaceous, who suffer repeated acute attacks or on-going inflammation despite the establishment of appropriate treatment for gout. This group presents special therapeutic difficulties because the occurrence of recurrent acute attacks despite adequate prophylaxis prevents administration of urate-lowering treatment. In these cases it may be necessary to perform a more intensive preventive treatment such as the administration of colchicine to the maximum tolerated daily dose. It should be reminded that in relation to the maximum tolerated dose, it may not have an approved indication in its SmPC.

Recommendation 57: The use of NSAIDs or corticosteroids to prevent acute episodes of inflammation in asymptomatic patients may be considered under conditions other than those approved by the AEMPS (LE 5; GR D; DA 73%).

XI.F. TREATMENT OF ACUTE EPISODES

Gout attacks are episodes of acute inflammation of articular or periarticular structures, usually of short duration and with monoarticular involvement, although they can also be oligo or polyarticular forms.

Without treatment, the natural course of these episodes can vary from hours to several weeks in which the patient has severe pain (406). Although resting the affected joint and the local application of cold may relieve symptoms (407), non-pharmacological measures are often insufficient (408) to quickly resolve the process.

The goal of treatment of the attacks is to get a quick resolution of inflammation with an adequate safety margin, as well as subsequent relief of pain and associated disability. Therefore, drugs should be used to reduce inflammation, relieve pain and reduce the duration of attacks considering that, according to some authors, clinical resolution will be faster the sooner treatment begins (152).

The available evidence on treatment of acute gout attacks is scarce and there are few placebo-controlled trials because regulatory agencies do not consider their use ethical. Most trials comparing active treatments have low methodological quality, are made with a small number of patients, and the diagnosis of gout is established according to different criteria not always including the identification of MSU crystals. An additional limitation is the use of various drugs in different doses and by different routes of administration, which makes indirect comparisons (in the absence of head-to-head studies) or meta-analysis of the results difficult.

XI.F.1. NSAIDs

Recommendation 58: NSAIDs are effective in acute gout attacks. Maximum dosage is recommended in the absence of contraindications and suspension as soon as the attack is resolved. Dose reduction can be assessed after the first 2-3 days of treatment if there is clinically significant improvement (LE 5; GR D; DA 83%).

XI.F.1.1. Efficacy

Different types of NSAIDs have been used in acute gout, providing a first-choice treatment in the absence of contraindications, although available evidence lacks the robustness that would be desirable for such a prevalent problem.

A systematic review (409) of the effectiveness of interventions for the treatment of acute gout or the prevention of recurrences identified 30 randomized clinical trials, of which 17 were discarded (1 for not providing data on pain evolution, 3 for inadequate randomisation and 13 for including unavailable drugs – phenylbutazone, rofecoxib, proquazone, carpofen, among others). Of the remaining, in addition to placebo-controlled tenoxicam study (410), there were nine comparison studies of generally low quality, except 2 of etoricoxib *vs.* indomethacin (411, 412) and 1 of ketorolac *vs.* indomethacin (413). The efficacy results between the drugs compared were similar in all studies, except one in which differences were detected at a single follow-up point (414), so probably these changes are not relevant from the clinical point of

view. In the authors' opinion the only solid conclusion to be drawn from the data is that the analgesic capacity of etoricoxib (120 mg daily) and indomethacin (150 mg daily) are equivalent.

The most important determinant of therapeutic success is not the NSAID to choose, but the early onset of treatment, which is associated with more rapid resolution of symptoms (152).

XI.F.1.2. Safety

A major limitation of NSAIDs is gastrointestinal toxicity. Therefore, before starting treatment an assessment should be performed of the baseline gastrointestinal risk for each patient, of the safety profile of the NSAID to be used, and the need to involve preventive treatment and use a COXIB (415). Concurrent use of other NSAIDs should be avoided and, where necessary, these compounds will be used for the shortest time possible. NSAIDs are contraindicated in patients with acute attacks of gout and ulcers or active gastrointestinal bleeding.

Regarding prevention of NSAID-induced ulcers (416) it is necessary to assess the use of misoprostol or proton pump inhibitors (PPI) for gastric ulcers and ranitidine in double doses or PPIs for duodenal ulcers, knowing that the latter are better tolerated.

Although the lower intestinal tract complications associated with NSAID use are often subclinical, they may cause serious injury including bleeding, strictures or perforations. Moreover, neither COXIBs nor other studied drugs have proven effective in the prevention or treatment of NSAID-induced enteropathy (417).

As is the case with gastrointestinal risk, before starting treatment with NSAIDs or COXIBs there must be assessment of cardiovascular risk (418). In high-risk cases it is preferable not to use NSAIDs/COXIBs or add antiplatelet agents, but the effectiveness of this measure is unknown in short-term treatments. In intermediate-risk patients low-dose NSAIDs may be prescribed for the shortest time possible, and in those with low risk general prescription rules are accepted. Still, the available evidence does not allow us to establish the safety of NSAIDs, either classic or COXIBs, regarding their cardiovascular risk profile, although it seems that naproxen might be the least harmful (419).

Despite the above, the potential cardiovascular risk of any of these compounds is not currently established in the case of gout, which in addition usually carries other risk factors or cardiovascular disease.

All these considerations must be taken into account when prescribing an NSAID/COXIB.

XI.F.2. COXIB

Recommendation 59: In acute gout attacks COXIBs can be considered an alternative to traditional NSAIDs in patients with high or medium gastrointestinal risk, administered with or without PPI, depending on the type of patient (LE 2a; GR B; DA 83%). (416)

The use of rofecoxib, lumiracoxib and etoricoxib in acute episodes of gout has been studied. The first two are not discussed in these guidelines because of their lack of availability (suspension of marketing). In clinical trials of etoricoxib at doses of 120 mg daily, with indomethacin 50 mg 3 times a day as an active comparator (411, 412), it was shown that

etoricoxib is comparable in efficacy to indomethacin and has a lower incidence of treatment-related adverse events (16.5% etoricoxib versus 37.2% indomethacin, p = 0.002) (411).

XI.F.3. Corticosteroids

Recommendation 60: In acute gout attacks corticosteroids are recommended for patients with contraindications to NSAIDs/COXIBs. They can be administered either by intraarticular injection in the case of monoarthritis, or systemically in cases with more extensive joint involvement (LE 2b; GR B; DA 100%).

XI.F.3.1. Intraarticular injections

Intraarticular injection of deposition dosage forms is a reasonable option in patients with monoarthritis. Although the evidence of benefit is limited to small open-label trials, results indicate that it is a safe and effective option. In a prospective study of patients with acute gout, confirmed by identification of MSU crystals, low dose injections of triamcinolone acetonide (10 mg) were performed in 20 joints of 19 patients with monoarthritis. Resolution of the attack was defined based on the fulfilment of the following assumptions: 1) pain reduction of at least 50% from baseline, 2) absence of signs of inflammation in the examination performed by the physician, and 3) a patient score of 4 = better to 5 = much better on a 1-5 Likert scale. In the first 24 hours the attack was resolved in 55% of patients, while at 48 hours the crisis had disappeared in 100% (420). The procedure was well tolerated, with no adverse effects or recurrences observed. One patient had a new attack at 3 months that was treated the same way. In view of these results it can be concluded that, even in small doses, intraarticular corticosteroids quickly resolve gout attacks without producing unwanted systemic effects.

Intraarticular infiltration should be performed after confirmation of the diagnosis, even in the same medical visit, and once the presence of infection is ruled out. It is generally recommended to use triamcinolone acetonide (40 mg for large joints such as knee and 10 mg for small joints) or betamethasone disodium phosphate (equivalent dose).

Due to the need for diagnostic arthrocentesis (MSU crystal identification) and the peculiarities of the procedure, the application of this treatment is reserved for rheumatologists or other trained and experienced practitioners.

XI.F.3.2. Systemic drugs

There have been various studies comparing corticosteroids and NSAIDs or ACTH. One of them evaluated intramuscular (IM) triamcinolone acetonide versus oral indomethacin in 27 men with gout confirmed by identification of crystals and an average number of affected joints >2 (419). Fourteen patients with contraindications to indomethacin received an injection of triamcinolone acetonide (60 mg), with the possibility of a second injection if there was less than 50% improvement in the first follow-up visit (3 cases), and 13 were treated with oral indomethacin, 50 mg three times daily, with possible dose reduction after an improvement of at least two days. Seven subjects were lost to follow-up. In the absence of differences between the two compounds, the authors concluded that the safety and efficacy of triamcinolone is similar to that of indomethacin, especially in patients with contraindications for the use of NSAIDs.

Another study compared the use of oral prednisone versus IM diclofenac combined in an initial single dose, with subsequent administration of oral indomethacin in 90 patients, of whom more than 90% had monoarthritis (421). A group of patients (n = 46) received an initial injection of diclofenac 75 mg plus indomethacin 50 mg IM 3 times/day for 2 days, followed by indomethacin 25 mg 3 times/day for 3 days. The other group (n = 44) received an initial injection with placebo and 30 mg of prednisone per day for five days. The main result, decrease [mean and standard deviation (SD)] in pain score by visual analogue scale (VAS) of 100 mm, was -1.7 (SD 1.6) for diclofenac/indomethacin versus -2.9 (SD -2.0) mm/day for prednisolone (mean difference 1.2 mm/day, 95% CI 0.4-2.0 mm/day, p = 0.0026). The frequency of adverse events was higher in patients treated with diclofenac/indomethacin than in those who received prednisolone (29 *vs.* 12 patients, p <0.05), with 5 cases of gastrointestinal bleeding among the former (11%) compared to none among the latter. In addition, it was necessary to discontinue treatment in 7 patients in the NSAID group due to the emergence of serious gastrointestinal adverse effects. The recurrence rate was similar in both groups. However, this study is not without limitations such as the performance of a purely clinical diagnosis, without identification of crystals, or the use of 2 different NSAIDs for the same episode.

Siegel et al. contrasted use of triamcinolone acetonide with ACTH, both intramuscularly in 31 men with gout confirmed by identification of MSU crystals and an average 2.5 affected joints (215). Sixteen patients received an initial injection of 60 mg of triamcinolone acetonide and 15 were treated with 40 IU of intramuscular ACTH, with the possibility of repeated dosing with less than 50% improvement in the follow-up visits. Two patients in the ACTH group did not achieve a 50% improvement after 3 doses, so they were treated with triamcinolone acetonide and were excluded from analysis. Efficacy was measured as number of days to resolution of 100% of symptoms, yielding an average of 8 days in both groups. No adverse reactions were observed, although the number of reinjections was 11 for the ACTH group and 5 for the triamcinolone acetonide group.

In a subsequent Cochrane review, which included the 3 studies mentioned (422), no clinically relevant differences were observed between steroids and comparators studied, nor were significant adverse effects attributable to corticosteroids. Therefore, the use of short-term corticosteroids appears safe, although the results of the review are inconclusive due to methodological limitations (study quality very low or moderate; not conducive to appropriate statistical analysis).

The same authors subsequently published a study with a suitable design that compared prednisolone and naproxen, both orally, in monoarticular gout (423). They conducted a randomized clinical trial on 120 patients with gout confirmed by identification of crystals (out of 381 with monoarthritis referred by Primary Care). Patients were randomized to receive prednisolone (35 mg once daily, n = 60) or naproxen (500 mg twice daily, n = 60) for 5 days, in a double-blind (patients and physicians) setting. The primary outcome was pain measured by 100 mm VAS, with a previously set equivalence margin of 10%. Per protocol and intention to treat analyses were performed. The reduction in pain score at 90h was 44.7 mm and 46.0 mm for prednisolone and naproxen, respectively (difference 1.3 mm, 95% CI -9.8 to 7.1), which suggests their equivalence. There were no differences between the groups in terms of presentation of adverse effects.

XI.F.4. ACTH

The efficacy data are limited and the doses used were very different. In a retrospective study of 38 patients with crystal arthritis (33 gout and 5 pseudogout) and contraindications or lack of response to NSAIDs, who received 40 or 80 units of intravenous ACTH three times a day, there was resolution of acute attacks in 97% of cases after 5.5 days of treatment. There were some side effects, although none of a serious nature and recurrence, so it may be necessary to repeat the treatment (214).

Siegel, in a study conducted with 40 units of ACTH, observed that the need for reinjection due to insufficient improvement was higher in the ACTH group than in the triamcinolone group (215).

The above data demonstrates that the use of ACTH appears to provide results inferior to corticosteroids and with a greater number of relapses. Therefore, it seems unnecessary to recommend its use given the availability of various corticosteroids. On the other hand, ACTH is not available in Spain, unlike tetracosactide, which has been approved for a clinical trial (ECTEFABE) for the treatment of acute episodes of inflammation of gout in patients with contraindications or unacceptable risk for prescription of colchicine and NSAIDs.

XI.F.5. Colchicine

Colchicine is a drug widely used to treat gout attacks in spite of the lack of available evidence; despite having proven effective symptomatically, its gastrointestinal toxicity is very common, especially in high-dose regimens. However, at low doses and at an early stage it can be effective (424).

Recommendation 61: The early use of low-dose colchicine is effective in controlling acute gout attacks and so it should be considered in these cases (LE 1b; GR A; DA 86%).

XI.F.5.1. High doses

Cochrane published a review (424) that included a placebo-controlled open trial (425), of moderate methodological quality, in which colchicine was administered at a loading dose of 1 mg, followed by 0.5 mg every two hours until there was a response or occurrence of toxicity (nausea, vomiting or diarrhoea) *vs.* placebo. The efficacy of colchicine was superior to placebo in improving pain (>50% reduction at 48 h: 73% *vs.* 36%, p<0.05), with a relative risk for 50% pain reduction of 2 (95% CI 1.09-3.68) and a NNT of 3. However, all patients treated with colchicine (n = 22) developed diarrhoea and vomiting after oral administration of a mean dose of 6.7 mg (median time 24 hours, range 12-36 hours). Moreover, most of the patients showed signs of toxicity prior to improvement, with an OR for gastrointestinal disorders (excluding nausea) in the colchicine group *vs.* placebo of 49.85 (95% CI 15.28-162.60) . The number needed to harm (NNH) was one.

XI.F.5.2. Low doses

In a randomized placebo-controlled study (207) the efficacy and safety of two regimens of colchicine was evaluated in a group of 184 patients with acute attacks of gout. Using a dose of 1.8 mg was compared to a starting dose of 1.8 mg followed by 0.6 mg once every hour to a cumulative maximum of 4.8 mg, with administration of the drug in the first 12 hours after onset of symptoms. The main outcome was the proportion of patients responding to treatment (pain assessment prior to treatment, within 12 hours after onset of gout attack, and pain reduction >50% in the first 24 hours of the first treatment dose). Both colchicine regimens were superior to placebo (proportion of responders in the high-dose, low-dose and placebo groups of 33%, 38% and 16%, p = 0.034 and p = 0.005, respectively), and in all assessments low doses showed efficacy similar to high doses. However, the frequency of gastrointestinal adverse events with high doses of colchicine was double compared to that observed with low doses. The overall rate of adverse events was 77%, 37% and 27% respectively in the high-dose, low-dose and placebo groups. Patients with low doses showed a safety profile similar to placebo. However, 77% of the high-dose group had diarrhoea (OR 21.3, 95% CI 8-57), which was severe in 19% of cases, while the proportion of patients with diarrhoea in the low-dose group was 23%, without any serious cases.

Thus, although early-onset oral colchicine is effective for the treatment of pain in the first 24 hours of an acute episode, the gastrointestinal toxicity of high doses substantially worsens its risk/benefit profile, which discourages the use of this traditional approach with high doses.

XI.F.5.3. Intravenous administration

The existence of alternative therapies and association with severe systemic reactions such as aplastic anaemia, hepatic necrosis, acute renal failure, disseminated intravascular coagulation, seizures and even death discourages the administration of intravenous colchicine (203, 426). Colchicine is not approved in Spain for intravenous administration.

On the other hand, we must take into account the many, and potentially frequent, colchicine drug interactions, especially with those drugs that interfere with the functions of the P-glycoprotein (P-gp) membrane transporter or the P450 system cytochrome component, CYP3A4. Concomitant use of colchicine is contraindicated with P-gp inhibitors (cyclosporine, tacrolimus, amiodarone, quinidine, azole antifungals, some calcium channel blockers, vinca alkaloids, erythromycin, etc.) or CYP3A4 inhibitors (protease inhibitors, macrolides, antifungals, etc.). Furthermore, caution should be exercised with the combination of colchicine and other less potent CYP3A4 inhibitors, such as statins and other lipid-lowering agents.

The Spanish Agency of Medicines and Medical Devices (AEMPS) recently reported serious cases of accidental overdose of colchicine and published the summary of product characteristics in January 2011 changing indications, contraindications, interactions and prescribing pattern of colchicine (221) (see SmPC).

XI.G. COMBINATION THERAPY

"Combination therapy" refers to joint use of various drugs authorized in Spain and the European Union for the treatment of hyperuricaemia in patients with gout: allopurinol and febuxostat, as XO inhibitors, and benzbromarone, probenecid and sulfinpyrazone as uricosurics. Furthermore, drug combinations may also include other compounds that have uricosuric effects that are not indicated for reducing serum uric acid in patients with gout, but are allowed for treatment of other frequently associated diseases, such as hypertriglyceridaemia (fenofibrate), hypercholesterolaemia (atorvastatin) or hypertension (losartan).

The goal of the combined treatment is two-fold: first, to achieve a level of uric acid that allows the dissolution of urate tissue deposits in patients who have not achieved this goal with monotherapy regimens (149); and second, to try to sharply reduce serum uric acid to facilitate more rapid dissolution of deposits in patients with severe gout (427).

XI.G.1. Combination of enzyme inhibitors

Recommendation 62: It is generally not advisable to combine two urate-lowering drugs with the same mechanism of action (LE 5; GR D; DA 100%).

There are no published data to support the efficacy and safety of the combination of XO inhibitors such as allopurinol and febuxostat, therefore they are not suitable for co-administration (78).

Recommendation 63: There are no robust studies on the safety or possible pharmacokinetic interactions of different combinations of urate-lowering drugs. Consequently, caution in prescribing and close monitoring of their safety are recommended (LE 4; GR C; DA 100%).

It has also been shown that the simultaneous use of inhibitors of various enzymes in the pathways of purine metabolism, such as allopurinol (XO) and Ulodesin (BCX4208, an inhibitor of purine nucleoside phosphorylase, PNP), have an additive effect in reducing serum uric acid levels (428).

XI.G.2. Adding a uricosuric agent to a xanthine oxidase inhibitor

No data are available on the combination of febuxostat with registered uricosuric drugs, although there have been reports of additive effects on reducing serum uric acid with no apparent pharmacokinetic interaction with lesinurad (RDEA594) in healthy volunteers and in patients with gout (429, 430). The addition to allopurinol treatment of various compounds with uricosuric effect is more effective in reducing serum uric acid than the use of either drug alone. In this respect results are only available from single and open-label studies. A sequential design trial showed that the reduction of uric acid (target <5 mg/dL) achieved with the

simultaneous use of probenecid, 500 mg bid, and allopurinol, 200 or 300 mg qd, was superior to that obtained with the use of allopurinol alone (247). Furthermore, a comparative study found that the decrease in uric acid and the reduction rate of tophi were higher with the combination of benzbromarone, 50 mg qd, and allopurinol, 300 mg qd, than with allopurinol alone (367). Finally, the results of a restrospective series of 8 patients showed a beneficial effect on the reduction of serum uric acid and tophi by adding 400 mg qd of sulfinpyrazone to allopurinol 800 mg qd (431).

In patients with stage 3 chronic kidney disease or lower probenecid and sulfinpyrazone lose effectiveness, thus their prescription is not advisable (432).

None of these studies included long-term follow-up, so the safety of these combinations could not be established. Although in 2004 the AEMPS withdrew fixed dose combinations of allopurinol and benzbromarone (433), this organization has taken no clear position on their use in non-fixed dose combinations, or concerning the need to request permission for off-label treatment.

Recommendation 64: The AEMPS withdrew the authorization of drugs with allopurinol-benzbromarone in a fixed dose combination for safety reasons. Therefore, if they are chosen, it is recommended to request authorization for their off-label prescription use (LE 4; GR C; DA 70%).

Both losartan (434) (with approved indication for the treatment of hypertension) and fenofibrate (435) (with approved indication for the treatment of hypertriglyceridaemia and mixed hyperlipidaemia) are drugs with a low uricosuric effect that have shown modest clinical utility in open-label studies at doses of 50 mg qd and 300 mg qd (equivalent to 200 mg of micronized fenofibrate), respectively. These studies, with sequential or cross-over treatment design, including a small number of patients and short follow-up, which limits conclusions about effectiveness and long-term safety (434, 435).

Recommendation 65: From a clinical standpoint, the effect of fenofibrate and losartan is marginal, but both compounds could be useful in selected cases. Both probenecid and sulfinpyrazone are not available in Spain, so they must be requested as special drugs (LE 3a; GR C; DA 100%).

XI.H. OFF-LABEL TREATMENTS OR TREATMENTS IN ADVANCED CLINICAL DEVELOPMENT

Royal Decree 1015/2009 of 19 June, regulating the availability of drugs in special situations, defines three of these situations:

1. Compassionate use of investigational drugs: use of a drug, prior to its authorization in Spain, in patients with a chronic or severely debilitating disease or one that could be considered life threatening and cannot be treated satisfactorily by a licensed medicinal product. The drug in question should be subject to an application for marketing authorization or must be undergoing clinical trials.
2. Use of drugs for conditions other than those licensed: drug use in conditions other than those included in the authorized summary of product characteristics.
3. Access to drugs not licensed in Spain: use of drugs approved in other countries but not licensed in Spain when they do not comply with the definition of compassionate use of investigational drugs.

This chapter focuses on drugs that may fall under any of these three categories: either because they are being subjected to trials on gout, or because they have another indication approved in Spain, or because they have other approved indication in another country. However, this does not include tetracosactide, used for the treatment of acute episodes of inflammation in gout, since among its licensed indications are "rheumatic processes amenable to treatment with corticosteroids" nor vitamin C, since it is not considered a drug but a dietary supplement.

XI.H.1. Acute episodes of inflammation

XI.H.1.1. IL-1 inhibitors: Anakinra, Canakinumab and Rilonacept

Recommendation 66: Canakinumab, rilonacept and anakinra may be effective in the treatment and prevention of acute episodes of inflammation. They could be considered in conditions other than those authorized – canakinumab and anakinra – or as a drug not licensed in Spain – rilonacept – in acute episodes of refractory inflammation or for prophylaxis when other approved therapeutic options cannot be used in patients with severe gout, specifically with chronic inflammation or very frequent acute episodes of inflammation (LE 1b; GR B; DA 78%).

In microcrystal arthritis, especially in the case of gout, acute and chronic inflammation appears to be mediated primarily by IL-1 (436).

Anakinra (Kineret®) is approved by the FDA, the EMA and the AEMPS (437) for rheumatoid arthritis in a dose of 100 mg qd SC (subcutaneously) as a drug for hospital use. This compound is an analogue of IL-1 receptor antagonist (anti-IL-1-R1), with a half life of between 4 and 6 hours. In addition to case reports and retrospective series, there has only been an open-label,

non-comparative trial of 10 patients treated with 100 mg/day SC for 3 days, due to intolerance or failure to "standard treatment", with a response in 100% of cases (218). However, the results of two retrospective series in patients with pre-treatment failure have shown that the complete response rate is between 60 and 70%, recurrence is frequent (90% between 3 and 45 days) and some patients (anakinra-dependent) may require continuous treatment (218, 438, 439).

Canakinumab (Ilaris®) is approved by the FDA, the EMA and the AEMPS (440) as a drug for hospital use for treatment of CAPS (Cryopirin Associated Periodic Syndrome) in doses of 150 mg every 8 weeks. In January 2013 the EMA and the AEMPS extended the indications to treatment in single 150 mg dose for acute episodes of inflammation to a restricted population of patients: adults with at least three episodes of acute inflammation in the previous year, with contraindication or intolerance to NSAID and colchicine and for whom repeated courses of corticosteroids are not considered medically acceptable. This recent indication extension has not been evaluated by the expert panel.

Canakinumab is a human monoclonal antibody with specificity to IL-1β (IL-1β Mab) and a half-life of 3 to 4 weeks. Three randomized, active comparator (triamcinolone acetonide), parallel-group, double-blind trials, have evaluated the efficacy of canakinumab in the treatment of acute episodes of inflammation in gout patients with a history of lack of efficacy or tolerability to NSAIDs or colchicine. The results of two phase III trials (β-Relieved (441) and β-Relieved II (442)) with 150 mg SC as a single dose, showed a faster response (24 h) and a greater reduction in pain (72 h) than administration of a single IM (intramuscular) dose of triamcinolone acetonide 40 mg. In selected cases, off-label prescription may be requested.

Rilonacept (Arcalyst®) is an IL-1 (IL-1α, IL-1β, IL-Ra Trap) blocker approved by the FDA and the EMA (443) for the treatment of CAPS in doses of 320 mg SC as a loading dose followed by 160 mg SC each week as a maintenance dose. There is no record that it has been approved by the AEMPS. The results of a comparison test of indomethacin plus placebo versus indomethacin plus rilonacept in acute episodes of inflammation showed no additional beneficial effects with rilonacept compared to indomethacin (444). In select cases, it may be requested as foreign medication if it is available in any country in the EU, although this is a more complex procedure than obtaining off-label approval.

XI.H.2. Prevention of acute inflammation episodes

XI.H.2.1. Non-steroidal anti-inflammatory drugs (NSAIDs) and steroids

NSAIDs are drugs indicated for treatment of signs and symptoms of inflammation. In Information Note 2006/07 the AEMPS states that "NSAIDs should be used at the lowest possible effective dose for the shortest duration necessary to control symptoms according to the established therapeutic goal" (445). Also, in Information Note 2006/10, it insists that "NSAIDs are drugs with a relevant value for the symptomatic relief of patients, particularly those with chronic inflammatory rheumatic processes" (446). Both documents indicate that "the prescription of NSAIDs should still be performed on the basis of the overall safety profiles of each of the drugs, according to the information provided in the summaries of product characteristics, and depending on cardiovascular and gastrointestinal risk factors in each patient".

Despite these official statements, it is not uncommon for experts to recommend NSAIDs as drugs for the prevention of acute episodes of gout (149). However, these recommendations do not take into account some important facts such as the following: 1) the particulars of the public documents of National Agencies for Medicines, 2) prevention includes mostly asymptomatic patients with frequent comorbidity and cardiovascular risk factors; 3) prevention treatment is prolonged (at least 6 months), and 4) the lowest effective doses for each of NSAIDs are unknown, due to lack of evidence.

In general terms, these considerations also apply to corticosteroids. Since, according to the SmPC, prednisone is indicated for "acute and chronic rheumatic joint and muscle processes", the use of these compounds could be justified only in acute episodes of inflammation or in “chronic polyarthritis: highly active inflammatory phases and special forms, e.g., forms quickly taking a destructive course and/or presenting visceral manifestations” (447).

XI.H.2.2. IL-1 inhibitors: Anakinra, Canakinumab and Rilonacept

There have been isolated cases of corticosteroid-sparing effect in patients with persistent inflammation or tophi treated with varying doses of anakinra, mainly in regimens of 100 mg SC administered daily or every 3 days (448, 449). Few data are available about obtaining acceptable results with a fixed dosage of anakinra (100 mg every 7 days and optional rescue dose for 3 months) in patients with repeated episodes of acute inflammation and elevated corticosteroid requirements (450).

The results of two trials to assess the utility of canakinumab (150 mg single dose) for the prevention of acute inflammation episodes (441, 442) have shown delays in time to onset of a new episode and risk of a new episode of 55%-68% and 73%-54%, respectively.

Rilonacept was evaluated in two clinical trials for the prevention of acute inflammatory episodes in patients initiating urate-lowering treatment (451, 452), comparing doses of 80 and 160 mg SC weekly with placebo for a period of 16 weeks. Both trials showed an 80% reduction in both the number of episodes of acute inflammation per patient – primary objective – as well as in repeated episodes and days with inflammatory manifestations – secondary objectives – with the dose of 160 mg.

XI.H.2.3. Serum uric acid reduction

Other drugs such as losartan, fenofibrate, atorvastatin or leflunomide approved in other indications have a slight urate-lowering effect.

XI.H.2.3.1. Rasburicase

Recommendation 67: Rasburicase may be an alternative for off-label use in patients unresponsive or intolerant to all approved urate-lowering compounds. Pegloticase could be requested for use as a drug not licensed in Spain (LE 4; GR C; DA 78%).

Rasburicase (Fasturtec®) is a uricase, a recombinant urate oxidase enzyme obtained from a strain of genetically modified *Saccharomyces cerevisiae*, authorized by the EMA and the AEMPS (453) for the treatment and prevention of tumour lysis syndrome in doses of

0.20 mg/kg/day in IV infusion of >30 min. Its half-life is 20 hours. The prescription of uricase – any of them – is contraindicated in patients with glucose-6-phosphate dehydrogenase (GPDH) or catalase deficiency due to risk of inducing haemolytic anaemia crisis. Therefore, GPDH must be determined prior to its administration. Uricase has *ex vivo* activity, so that the samples to assess its effect on uric acid levels should be refrigerated after collection and during handling (453).

In rare cases it has been used off-label in Spain and in Europe, but only one 10-patient series has been published, comparing two regimens of 5 doses, daily or monthly, with uneven results (454). Limitations for use must take into account a reduced half-life and the appearance of anti-rasburicase antibodies with repeated administration.

XI.H.2.3.2. Pegloticase

Pegloticase (Krystexxa®) was approved by the FDA (455) for the treatment of hyperuricaemia in patients with chronic gout refractory to standard therapy at a dose of 8 mg every 2 weeks intravenously. In January 2013 the EMA approved marketing authorization of pegloticase in Europe, with the following indication: treatment of severe disabling chronic tophaceous gout in adults who may also have erosive joint involvement and in whom the uric acid serum level has not normalized with xanthine oxidase inhibitors at the maximum clinically appropriate dose or for those for whom these drugs are contraindicated. It also proposes that the decision to prescribe be based on an ongoing assessment of the risks and benefits for each individual patient. The treatment must be administered under the supervision and monitoring of a physician experienced in the diagnosis and treatment of severe refractory chronic gout (http://www.ema.europa/eu).

This compound is a quasi-swine tetrameric urate oxidase obtained by recombination (contains some baboon residues). Conjugation with 9 polyethylene glycol chains per subunit reduces immunogenicity against uricase and increases the plasma half-life (456).

In the two Phase III clinical trials conducted with the registered dose of pegloticase in patients refractory to conventional therapy (378), serum uric acid control was obtained at 3 and 6 months in 38% and 47% of patients, respectively. The most common side effects consisted of acute episodes of inflammation (76%) and infusion reactions (26%). Loss of response and infusion reactions were associated with the appearance of anti-pegloticase antibodies; in 91% of cases, the loss of efficacy preceded adverse reactions to infusion (378). The presence of pre-infusion uric acid over 6 mg/dL is a marker of unresponsiveness and infusion reaction risk. It is therefore recommended to verify serum uric acid levels prior to infusion, avoid concomitant administration of other urate-lowering drugs and discontinue treatment if uric acid >6 mg/dL on two consecutive measurements is observed.

An open-label 3-year study was published in which the profile and safety was maintained (457). Association with urate-lowering drugs is contraindicated in order not to mask the risk of infusion reaction of poor serum uric acid control.

XI.H.2.3.3. Lesinurad

Lesinurad (RDEA594) is the active metabolite of RDEA604, a reverse transcriptase inhibitor that acts on renal urate transporters (uricosuric), mainly hURAT1, which is currently in phase III. Although using Lesinurad can be used as monotherapy in patients intolerant to other drugs,

greater effectiveness has been observed in trials in combination with allopurinol (458) or febuxostat (429).

XI.H.2.3.4. BCX4208

Ulodesin (BCX4208) is an inhibitor of purine nucleoside phosphorylase (PNP), whose greatest effectiveness was observed in Phase II clinical trials in combination with allopurinol (428). Although PNP inhibition is associated with a decrease in lymphocytes (PNP deficiency is associated with severe combined immunodeficiency), trials have not shown increased risk of infections.

XI.H.2.3.5. Losartan

See combination treatments.

XI.H.2.3.6. Atorvastatin

In clinical trials to reduce cholesterol levels and ischaemic cardiomyopathy events (459) atorvastatin (generic) has been shown to reduce uric acid levels by approximately 10%. This effect seems to be mediated by increased renal excretion of urate, a property not possessed by other statins (347).

XI.H.2.3.7. Fenofibrate

See combination treatments.

XI.H.2.3.8. Leflunomide

Leflunomide (generic) is a drug approved for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis. In a clinical RA trial, decreased serum uric acid was recorded in patients treated with leflunomide, while there were increases in those receiving methotrexate (460). At approved doses this effect seems to be related to an increase in the renal excretion of urate and phosphate (461), presumably mediated by the ABCG2/BCRP renal transporter (ATP Binding Cassette, subfamily G, type 2) (462), a ubiquitous urate transporter not limited to kidney tissue (463). The percentage serum uric acid reduction effect was similar to that observed with losartan or fenofibrate.

XII. IMAGING TESTS FOR MONITORING TREATMENT RESPONSE

XII.A. IMAGING TESTS

Assessment of response to urate-lowering treatment can be accomplished by various indicators such as: frequency of acute attacks, serum uric acid levels, presence and number of MSU crystals obtained from intraarticular synovial fluid aspiration, identified by compensated polarized light microscopy, and number and size of tophi. During the acute attack of gout assessing the response to treatment is essentially clinical (resolution of pain and inflammation). However, appropriate imaging techniques can also be used to assess joint inflammation, such as MRI or ultrasound. In addition, joint damage due to gout can be monitored by plain x-ray, MRI, ultrasound or CT.

The use of imaging techniques may include plain x-ray, high-resolution ultrasound, CT, dual-energy CT, and MRI. At present tophi can only be measured by ultrasound and MRI (119, 120) fulfilling the OMERACT filter for measuring outcomes of urate-lowering treatment.

There are no studies on the sensitivity to change of measurement of tophi with CT, dual-energy CT, or plain x-ray during urate-lowering treatment, although dual-energy CT seems initially to be a highly reproducible technique. Finally, the diagnostic utility of PET in patients with gout has not been evaluated.

The measurement of tophi, both visible subcutaneous and/or palpable as well as superficial or localized in musculoskeletal structures, can be performed by different imaging techniques such as MRI, ultrasound, CT or dual-energy CT (130, 464).

Visualization and measurement of tophi by imaging techniques is used as a criterion for monitoring response to treatment, thus avoiding repeated aspiration of a joint with prior urate deposits.

Radiographic evaluation by the modified Sharp/van der Heijde method has high reliability. However, there are no published studies on sensitivity to change in patients undergoing urate-lowering treatment. The results of a retrospective review showed that in patients with inadequate control of uric acid, radiographic progression is more pronounced in the presence of higher serum uric acid levels (124). Another retrospective study found that control of uric acid is associated with regression of bone erosions, but not of joint space narrowing (465). However, both studies are severely limited by their retrospective nature and because they use an inadequate systematization of radiographic findings.

Conventional CT facilitates manual delineation of tophi and any subsequent volumetric calculations. The method is reproducible, but no data are available on its sensitivity to change. Moreover, the results of a study comparing the extent of subcutaneous tophi with CT and with callipers showed no differences in reliability between the two procedures (466). In clinical practice measurement by callipers is more feasible (367), and it has also proven to be sensitive to change during urate-lowering treatment (130).

Dual-energy CT presents high specificity, even higher than clinical assessment, and it allows automatic volumetric quantification with minor interobserver variability. Therefore, this

method might be sensitive to small changes, which would, if it were shown, document treatment response (131-133). However, as yet there are no studies in this area.

MRI provides a highly reproducible measurement of the size of tophi, is sensitive to change and reduction of measurements has an inverse correlation with serum uric acid levels during treatment. It also allows monitoring of the degree of gadolinium (Gd) uptake due to the presence of vascularisation in tophi and synovial membrane before and during urate-lowering treatment (383).

XII.B. ULTRASOUND

Recommendation 68: Ultrasound measurement of the size of monosodium urate tophaceous deposits could be used as an outcome measure in evaluating the response to treatment of gout (LE 3a; GR B; DA 90%).

High-frequency ultrasound allows high resolution imaging of peripheral musculoskeletal structures. It is a non-invasive technique, well accepted by the patient, and can sometimes be repeated during the medical visit.

Various descriptive case studies (467, 468) and case-control studies (122, 143, 145, 146, 469) have reported typical ultrasound findings or very specific findings of gout in knees, ankles, wrists, elbows, shoulders, and joints of the feet (metatarsophalangeal), and hands. These findings consist mainly of formations of varying size and morphology, of irregular hyperechoic material and intra-articular or periarticular location (intratendinous, intrasheath synovial tendon, intrabursal). These can show areas of calcification, irregular hyperreflective thickening of the margin of the articular cartilage surface (double contour sign), linear hyperechoic intratendinous materials and bone erosions adjacent to the intra-articular materials already mentioned.

Among these findings the double contour sign was almost exclusively found in patients with gout and in virtually none of the controls including patients with calcium pyrophosphate deposits; therefore, it can be considered very specific to gout (122, 143, 145-147). Furthermore, the results of a recent cross-sectional study have shown an association between the presence of the double contour sign and serum uric acid levels in patients with gout (467). However, concurrent validity of the double contour sign so far not been demonstrated against a reference standard such as the microscopic study of the articular cartilage, nor the construct validity versus microscopic study of monosodium urate crystals in the synovial fluid of the joint.

Moreover, the results of an observational cohort study showed the concurrent validity of ultrasound for the detection of tophi. Analysis with polarized light microscopy of synovial fluid obtained by ultrasound-guided needle aspiration, of 12 intra and periarticular hyperechogenic nodules similar to those previously described in patients with gout, showed presence of MSU crystals in 10 of them (147). This study evaluated the construct validity of ultrasound compared to MRI obtaining a good agreement in detection (>80%) and an acceptable correlation in the measurement of the maximum diameter (r = 0.659) of lesions compatible with tophi in 22 patients with gout (147).

On the other hand, according to data from a case-control study which included 39 patients with gout, ultrasound detects more bone erosions than plain x-ray in the first metatarsophalangeal joint (122).

In an acute attack, the use of Doppler facilitates the identification of effusion with floating hyperechoic foci in the synovial fluid and synovial thickening with abnormal vascular flow (122, 143). However, it should be noted that these joint inflammation findings have also been described in asymptomatic joints of patients with gout (464).

The validity of appearance and content of ultrasound for the detection of pathological phenomena present in the musculoskeletal system in gout seem theoretically acceptable if we rely on homogeneous results of published descriptive studies and case-control studies (122, 143, 145-147, 467, 468).

XII.B.1. Assessment of therapeutic response

Recommendation 69: At present there are no data to support the evaluation or quantification of other ultrasound features of gout as an outcome measure in the assessment of response to gout treatment (LE 3a; GR B; DA 100%).

A prospective observational uncontrolled cohort study analyzed metric properties of ultrasound (intraobserver reliability and sensitivity to change) as a method for assessing the therapeutic response of 14 patients with gout and tophi presence in knee and ankle that had been treated with allopurinol (119). The intraobserver reliability analysis was performed by scanning the same joint and measuring the diameters of 27 tophi repeated on 2 occasions during the interval of one week. The intraclass correlation coefficient was 0.96 (95% CI: 0.93-0.98) for the maximum diameter, 0.95 (95% CI: 0.88-0.97) for the minimum diameter, and 0.98 (95% CI: 0.96 to 0.99) for the volume. These results showed very good reproducibility of ultrasound tophi measurement. The minimum detectable difference (MDD), defined as the smallest change that can be attributed to real change and not measurement error, was 5.5 mm for the maximum diameter, 3.5 mm for the minimum diameter, and 1.27 cc for volume. Sensitivity to change of the ultrasound measurement was assessed at 12 months of treatment with allopurinol on 38 tophi. The results showed that the mean serum uric acid level during treatment was significantly lower in patients with decreased maximum diameter and volume of tophi, MDD higher than in those who did not present any change in size. Similarly, a significant correlation was observed, and a negative sign, between the reduction of the maximum diameter and volume of tophi and average serum uric acid (r2 = 0.47 and r2 = 0.41, respectively). The size of the Guyatt effect (quantification of sensitivity to change) was 1.7 for the change in the maximum diameter and 1.93 for the change in tophi volume.

On the other hand, in an observational cohort study (470) double contour signs in ultrasound were evaluated in 7 joints (2 metacarpophalangeals, 3 knees and 2 first metatarsophalangeals) of 5 patients with gout at 7 and 18 months of urate-lowering therapy (3 allopurinol, 1 probenecid) or colchicine (1 patient). During follow-up there was a disappearance of the ultrasound sign in patients who achieved and maintained serum uric acid levels <6 mg/dL (3 patients) versus persistence of the same in patients with serum uric acid ≥7 mg/dL (470). However, so far the disappearance of the double contour sign has not been studied compared

to the construct of disappearance of synovial fluid crystals in the joints themselves or intraobserver reliability and sensitivity to change.

There are no studies on the therapeutic response of other sonographic findings such as the presence of intra-articular or periarticular inflammation in acute attack or asymptomatic phases, except for anecdotal description of a case (469), or bone erosions.

In conclusion, although there have been promising solid data on the ability of ultrasound to evaluate the therapeutic response in gout, in particular the reduction of microcrystalline tophaceous deposits, it is necessary to conduct further studies with different observers in order to confirm these results. It is also necessary to investigate the reproducibility and sensitivity to change of other ultrasound findings, such as the double contour sign of cartilage, synovitis and bone erosions.

Other aspects that should be subject of analysis are joint regions and ultrasound findings to be included in the assessment and quantification of therapeutic response in clinical practice based on metric properties and feasibility. It is also important to check whether the reduction and disappearance of the various ultrasound findings, as indicators of therapeutic response, are homogeneous with respect to time and tissue and anatomical location. Finally, there is no evidence at present of the added value or benefits of ultrasound monitoring of therapeutic response over serum uric acid monitoring with respect to feasibility, cost effectiveness, and outcome measures.

Image 4. Simple anteroposterior x-ray of the hand.

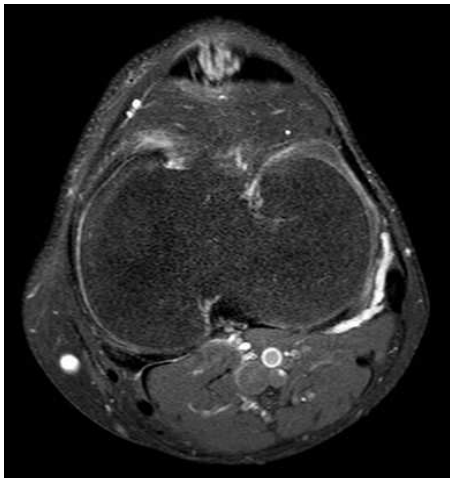
Foci of increased nodular density in periarticular soft tissue, both in the ulnar and radial side of the 2nd, 3rd, 4th and 5th proximal interphalangeal joints, and 2nd, 3rd and 4th distal interphalangeal secondary to the presence of tophi. Underlying pararticular erosions are seen with an over-hanging edge and sclerotic border. Preserving joint space and bone density.

Image 5. MRI of knee: Coronal sequence FSE-T2.

Digging into the popliteal fossa occupied by a nodular intermediate signal, in relation to tophus. Associated image of oblique lateral meniscus tear.

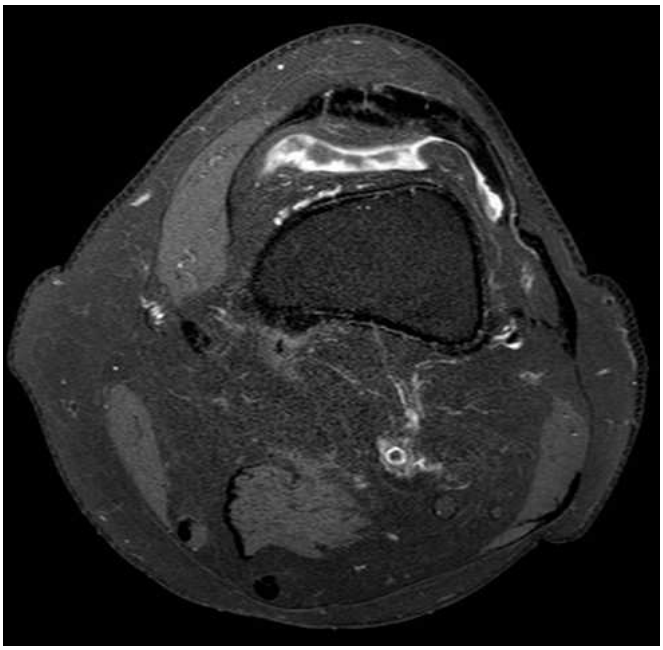
Image 6. MRI of knee.

a) a) Sagittal T1 sequence. Intermediate signal node and swelling occupying the popliteal tendon prior to patellar insertion, in relation to tophus at said location.



b) Axial T1 sequence with fat suppression and intravenous gadolinium. Intense tophus enhancement after IV contrast.

Image 7. Synovitis. MRI T1 sequence with fat suppression after administration of IV gadolinium.



Marked diffuse thickening of the synovial membrane of nodular aspect with intense enhancement after intravenous contrast administration.

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