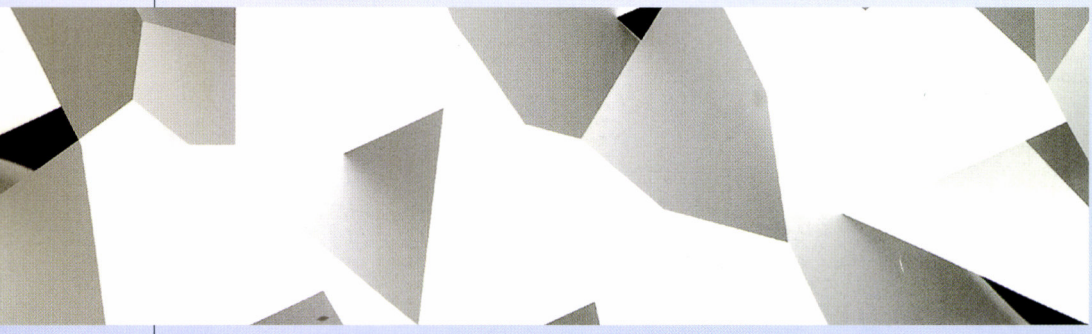
Guidelines for the Management of Hyperuricemia and Gout

Abridged Edition



Committee for the Preparation of Guidelines for the Management of Hyperuricemia and Gout
Japanese Society of Gout and Nucleic Acid Metabolism

Chapter I. Introduction

1. Current status of gout and hyperuricemia in Japan

Gout was a rare disease in Japan prior to 1960. However, with the Westernization of the Japanese diet and increased alcohol consumption, the incidence of gout has been increasing every year. At present, the estimated number of patients with gout is 300,000 to 600,000 and the incidence continues to increase. Hyperuricemia, which is the disease underlying gout, also is on the increase. Furthermore, this disease was formerly seen in patients from their ages of 50s and now has a trend to shift their morbidity peaks forward to younger patients with 30s of ages.

Although hyperuricemia has become a common lifestyle-related disease, there have been no large-scale prospective studies in Japan to investigate whether untreated hyperuricemia can lead to gouty arthritis, renal disorder, urolithiasis, or cardiovascular disease. There are also no worldwide efforts to conduct intervention studies of urate-lowering agents.

Treatment guidelines based on sufficient consensus on the treatment of hyperuricemia and gout has not been available due to the lack of such studies. Thus, to address this current situation and to meet the needs of the clinician, the Japanese Society of Gout and Nucleic Acid Metabolism has prepared the "Guidelines for the Management of Hyperuricemia and Gout" employing the evidence-based method as much as possible.

This publication is the abridged edition of the Guidelines.

In this publication, statements that are "highly recommended (based on sufficient evidence)" are shown in **bold red letters** and those that are "recommended (based on consensus)" are shown in **bold blue letters** for easy reference.

Chapter II. Definitions and Evaluations

1. Epidemiology of gout and hyperuricemia in Japan

Gout was previously considered a rare disease, but the number of patients increased dramatically during the era of rapid economic growth in the 1960s and 1970s, and today it is considered to be a common illness. Based on the "Comprehensive Survey of Living Conditions of the People on Health and Welfare "conducted by the Ministry of Health, Labour and Welfare, there were 590,000 patients with gout in 1998, which was double the number in 1989. Accompanying this increase is the recent phenomenon of a rapid rise in the morbidity of gout among people between 20-30 years of age.

For hyperuricemia, which underlies gout, the incidence rate has also increased from about 5% of adult men in the 1960s to about 15% in the 1970s to early 1980s and about 20% in the late 1980s to 1990s. For women, the incidence rate is about 1% in premenopausal women and 3-5% in postmenopausal women.

Symptoms of gout, as manifestations of the urate crystal deposition syndrome, are epitomized as arthritis (gouty attack), gouty tophus, and renal disorder including urinary calculus. However, in addition, **gout patients often concurrently have obesity, hypertension, hyperlipidemia, glucose intolerance, etc., and the cumulative effects of these complications are thought to affect the prognosis of gout patients.** Insulin resistance is also considered to be involved in the cumulative effects of complications. Among hyperuricemic patients, about 80% have some concurrent lifestyle-related disease.

It is known that high serum urate level is a risk factor for ischemic heart disease, and two large cohort studies conducted in Japan have shown that hyperuricemia is an independent risk factor for cardiovascular and cerebrovascular disease. Many epidemiological studies have shown that hyperuricemia is an independent predictive factor for cardiovascular and cerebrovascular events, but there has been controversy over whether hyperuricemia is indeed a risk factor. It is therefore necessary to await the results of further intervention studies in this area.

2. Diagnosis of gout and definition of hyperuricemia

A. Diagnosis of gout

(1) Clinical picture

The arthritis of gout is called a gouty attack and is often seen in the joints of the lower extremities, such as the first metatarsophalangeal joint. The patient experiences pain, swelling, and redness, with difficulty in walking, but the symptoms improve in 7-10 days. The patient is then completely asymptomatic until the next attack. If the patient is left untreated without adequate control of the serum urate level, repeated episodes of gouty arthritis lead to chronic arthritis. In addition, granulomatous tissue with urate called gouty tophus may also develop.

Persistent hyperuricemia can also lead to interstitial nephritis in the renal medulla, resulting in gout nephropathy appearing as a complication. Such progression to uremia from that stage was formerly responsible for the majority of deaths in patients with gouty arthritis, but uremia has greatly decreased due to systematic treatment of hyperuricemia.

Table 1 Standards for the diagnosis of gouty arthritis

1. The presence of characteristic urate crystals in the joint fluid
2. A tophus proved to contain urate crystals by chemical means or polarized light microscopy
3. The presence of 6 of the following 11 clinical, laboratory, and x-ray phenomena listed below:
   a) More than one attack of acute arthritis
   b) Maximum inflammation developed within 1 day
   c) Attack of monoarticular arthritis
   d) Joint redness observed
   e) First metatarsophalangeal joint painful or swollen
   f) Unilateral attack involving first metatarsophalangeal joint
   g) Unilateral attack involving tarsal joint
   h) Suspected tophus
   i) Hyperuricemia
   j) Asymmetric swelling within a joint (roentogenogram)
   k) Complete remission of arthritis

Table 2 Important reminders in the diagnosis of gouty arthritis

1. Serum urate level during a gouty attack may be low and thus is of low diagnostic value.
2. Upon obtaining joint fluid, submit it immediately for microscopic examination and identify whether urate crystals are present.
3. Gouty tophus has diagnostic value but is uncommon.

Table 3 Classification of hyperuricemia by urinary urate excretion(E_{UA}) and urate clearance (C_{UA})

Disease type	E_{UA} (mg/kg/hr)		C_{UA} (mL/min)
Over-producer type of urate	> 0.51	and	≥ 6.2
Under-excretor type of urate	< 0.48	or	< 6.2
Mixed type	> 0.51	and	< 6.2

(2) Diagnosis

Gout is a crystal-induced arthritis caused by urate that has deposited into the joint space from persistent hyperuricemia, and is therefore clearly distinct from

hyperuricemia. The diagnosis of gouty arthritis is made when acute arthritis appears in a patient with hyperuricemia, in which acute arthritis with redness and swelling often develops in the first metatarsophalangeal joint or other joint in the foot.

The diagnostic standards based on the American College of Rheumatology are used in Japan**(Table 1)**. Whenever possible, it is recommended that the joint fluid from a patient with acute arthritis be examined by polarized light microscopy for the presence of needle-like monosodium urate crystals phagocytized by neutrophils to confirm the diagnosis **(Table 2).**

(3) Differential diagnosis

Since various rheumatic diseases cause acute arthritis, it is necessary to differentiate gout from such diseases as chronic rheumatoid arthritis, pseudogout, etc. It is often necessary to differentiate gout from other causes of pain or swelling developing in the lower extremities such as hallux valgus, paronychia, cellulitis, sprain, bursitis, etc.

B. Definition of hyperuricemia

Regardless of age or sex, a plasma uric acid solubility of 7.0 mg/dL is considered to be the upper limit of the normal range, and patients with a value exceeding this limit are defined to be hyperuricemia.

3. Measurement of uric acid

Uric acid can be measured by various analytical methods such as the reduction method based on the reducing ability of urate, the enzymatic method using the uricase, and high-performance liquid chromatography (HPLC).

In Japan, the reduction method was the most popular method until the 1970s, then the use of enzymatic method increased from the 1980s. Currently, at most institutions, uric acid is measured by the uricase peroxidase method using an auto analyzer. Differences between institutions have improved, and this method is considered to be reliable.

The timing of the blood drawing may be flexible independently from meals, but establishing the diagnosis of chronic hyperuricemia requires several repeated measurements in consideration of the physiological variations in serum urate levels.

4. Disease classification

Hyperuricemia can be classified into the overproduction type of urate

(increased production of urate), the underexcretion type of urate (decreased urinary excretion of urate), and the mixed type involving a combination of both.

The disease classification can be definitively established by measuring the urinary excretion of urate (E_{UA}) and urate clearance (C_{UA}) under fasting, water loading, and restriction from purine-rich diet as well as the creatinine clearance (C_{cr}) to correct for renal function. $E_{UA} > 0.51$ mg/kg/hr means the overproduction type of urate, while $C_{UA} < 6.2$ mL/min means the underexcretion type of urate **(Table 3).**

Chapter III. Treatment

1. Treatment objective and treatment strategy

The treatment objective of hyperuricemia and gout is primarily to prevent onset of gouty arthritis. The available data indicate that serum urate control to 4.6-6.6 mg/mL offers the lowest incidence. In particular, it is important to prevent the onset or progression of complications such as renal disorder (gouty kidney) and urolithiasis caused by urate precipitation.

Furthermore, hyperuricemia and gout are known to often complicate with lifestyle-related diseases such as hyperlipidemia, hypertension, glucose intolerance, and obesity, and it has been suggested that these complications for hyperuricemia lead to increased incidence of ischemic heart diseases and cerebrovascular disorders. Thus, the physician must not only control the serum urate level but also take sufficient considerations for these complications.

Based on these considerations, it is desirable to maintain serum urate at a level of not more than 6 mg/dL.

Clinically, once the gouty arthritis has been treated and the clinical course is under control, a urate-lowering agent is selected based on the disease type and complications. The urate-lowering agent is started at a low dose, and the dose is gradually escalated over the course of 3-6 months while monitoring the serum urate level and urinary urate excretion to determine the appropriate maintenance dose. If a gouty arthritis recurs during this period, the dose of the urate-lowering agent is kept constant until the arthritis regresses.

At the same time, additional measures should be taken such as lifestyle guidance, dietary therapy, and urologic management, for the treatment of lifestyle-related diseases and any complications such as renal disorder and urolithiasis **(Figure 1).**

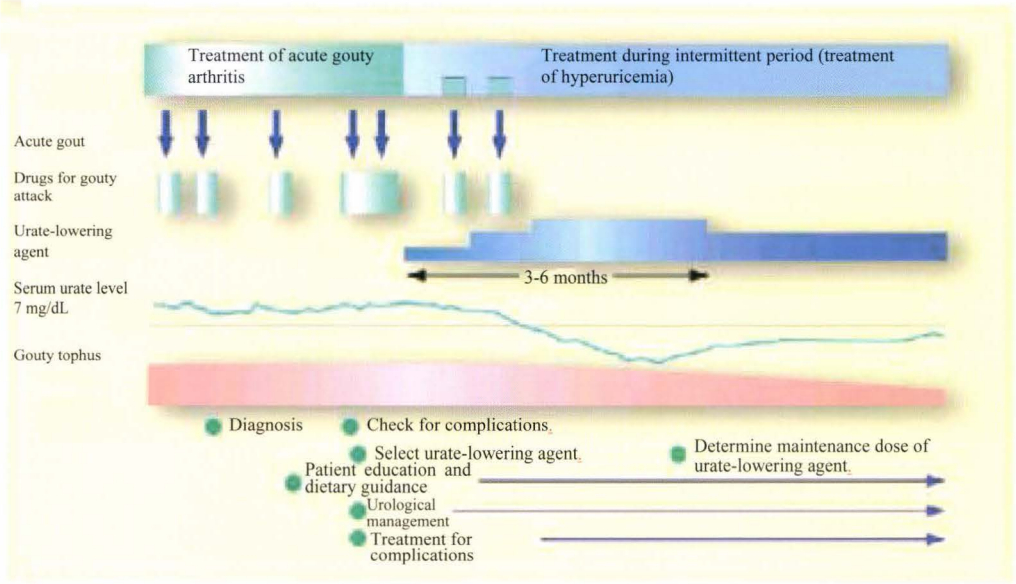


Figure 1 Treatment strategy for a patient with gouty arthritis

2. Treatment of gouty arthritis

Gouty arthritis is generally characterized by intense pain, and while short lived, extremely reduces the quality of life (QOL) of the patient. Thus, the aim of acute treatment is to eliminate pain and improve QOL. In addition, because the patient's own experience of the gouty arthritis is important in introducing long-term management of the underlying hyperuricemia, the treatment cannot be considered completed once the pain of arthritis has subsided.

Three therapeutic options available are colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids. All have been demonstrated to have clinical efficacy. One general approach is to give one tablet of colchicine at the aura phase of the gouty flare and then give high doses of NSAIDs during the advanced stage for a short period to subside the inflammation. Steroids are also effective and have advantages in which they can be selected by various administration routes such as —oral, intramuscular, or direct injection into the joint—to meet the needs of the patient conditions.

A. Colchicine

Administration in the aura phase of gouty attacks

In contrast to the U.S. and Europe, the general approach in Japan is to use small

doses of colchicine in the aura phase of gouty attacks. **The administration of one tablet of colchicine (0.5 mg) during the aura phase of gouty attacks can abort the attacks.** For this reason, patients are prescribed colchicine and instructed to have it with them.

Colchicine shows insufficient efficacy when started at the advanced stage of the attack, even when given at high doses. At high doses, patients may experience adverse reactions such as abdominal pain or diarrhea, and followed by others such as vomiting and muscle spasms.

Careful attention is also needed for the concomitant use of colchicine, with cimetidine, erythromycin, and nifedipine, since it may cause drug-interactions.

Table 4 List of NSAIDs indicated for gouty arthritis

Indication	Generic name	Brand name	Drug formulations	Dosage and administration for gouty attack
Inflammatory diseases including gouty attack	indomethacin	Indacin, etc.	25 mg, 37.5 mg and 50 mg tablets, slow-release capsules, suppositories	25 mg per dose, 1-3 times a day
	naproxen	Naixan	100 mg tablets, 300 mg capsules	Initial dose of 400-600 mg on the first day, then 200 mg per dose 3 times a day; or 300 mg every 3 hours up to 3 times a day.
	fenbufen	Napanol	100 mg and 200 mg tablets	Initial dose of 600-1,000 mg on the first day, and be followed 200 mg per dose 3 times a day
	pranoprofen	Niflan	75 mg tablets	Initially 150 - 225 mg per dose 3 times on the first day, and be followed 75 mg per dose 3 times a day
	oxaprozin	Alvo	200 mg tablets	Normally 400 mg per day, to a maximum of 600 mg

Aspirin at low doses increases serum urate level and decreases at high doses.
Because aspirin at analgesic doses decreases urate level and may worsen or prolong the attack, it should not be used to during gouty attacks. Similarly aspirin derivatives and diflunisal should not be used during attacks.

B. NSAIDs

NSAIDs are the mainstay for the treatment of acute inflammation of gouty arthritis. In the advanced stage of the gouty attack, a general rule is to administer relatively give higher doses for a short period of time (pulse NSAIDs treatment). For naproxen, 300 mg is given every 3 hours in 3 doses only for a single treatment. Often this is sufficient to improve the symptoms. **If the symptoms improve, naproxen is discontinued.**

In the case that the residual arthritic pain continues to affect the activities of daily life after the intense pain has improved, the conventional dose of NSAIDs may be continued. **When the symptoms improve, it is then discontinued.**

In Japan, there are only a few NSAIDs approved for National Health Insurance reimbursement for gouty attacks (**Table 4**). The doses for attacks are generally higher than those used for chronic rheumatoid arthritis.

Common problems in administration include induction or exacerbation of lesions in the gastric mucosa (especially gastric ulcer), exacerbation of renal disorder, and interaction with warfarin, so **the patient should be carefully monitored for these adverse reactions.** In patients with renal disorder or edema, it is preferable to use NSAIDs with lower renal toxicity or to use steroids rather than NSAIDs. For patients on warfarin treatment, steroids rather than NSAIDs should be used.

C. Steroids

In those cases that NSAIDs cannot be used, their administration is ineffective, or there observed multiple arthritis, oral steroids should be used. For example, 15-30 mg of prednisolone is to be administered to control the arthritis, with the dose being tapered by 1/3 every week and stopped after 3 weeks. In severe cases, a low dose (about 5 mg/day) may need to be maintained for several months.

In arthritis patients with edema in the knee or elbow joint, sterile puncture is made into the joint space and, after removing as much of the joint fluid as possible, steroids can be injected into the joint. The joint fluid must be examined for the presence of sodium urate crystals. If there is any suspicion of suppurative arthritis, the joint fluid should be tested for bacterial culture. In such cases, the steroid should not be injected into the joint.

Note

• During the gouty attack period, the patient should be instructed to take rest and cool the affected joint and to avoid alcohol intake. In principle, changes in the serum urate

level at the time of attacks can often exacerbate the attack, so a urate-lowering agent should not be started during the attacks. However, if the patient is already on a urate-lowering agent, the patient should continue at the same dose of the agent with the addition of colchicine, NSAIDs, or steroids.

3. Treatment of hyperuricemia

A. Treatment objectives

For the hyperuricemic patient, the narrowly defined treatment objectives are to eliminate the deposition of urate deposits into tissues caused by the persistence of hyperuricemia and to avoid gouty arthritis and renal disorder. **In addition, it is also important to note that the ultimate goal is to improve the long-term prognosis of hyperuricemia and gout by taking into considerations to the complications such as obesity, hypertension, and glucose and lipid metabolism abnormalities, with the concomitant need for improvement in lifestyle.** Undesirable lifestyles, such as excessive intake and preference for purine-rich, lipid-rich, or protein-rich diet; drinking habit; and lack of exercise, are not only a cause of hyperuricemia but also deeply related to obesity, hypertension, and glucose and lipid metabolism abnormalities, etc. Thus, it is of primary importance to provide guidance for improving these aspects of the patient's lifestyle.

Patients who have recurrent episodes of gouty arthritis or patients with gouty tophus should be subjected to medical treatment (with urate-lowering agents) regardless of the serum urate level. Patients who have a history or presence of urinary calculus should be treated with allopurinol to reduce urate excretion into urine as well as to control serum urate.

The optimum serum urate level to be achieved by treatment has not been established yet in large-scale prospective studies. The current recommendation is to maintain the urate level at not more than 6.0mg/dL that is a level below the theoretical solubility for uric acid in human serum, as recommended by the Japanese Society for Purine and Pyrimidine Metabolism (now the Japanese Society of Gout and Nucleic Acid Metabolism).

Patients with asymptomatic hyperuricemia without gouty arthritis should be considered for the subjects for medication if the serum urate level is 8 mg/dL or greater, but in case that the patient has no complications such as obesity, hypertension, or glucose or lipid metabolism abnormalities, then the criteria for introducing the medication may be applied flexibly **(Figure 2).**

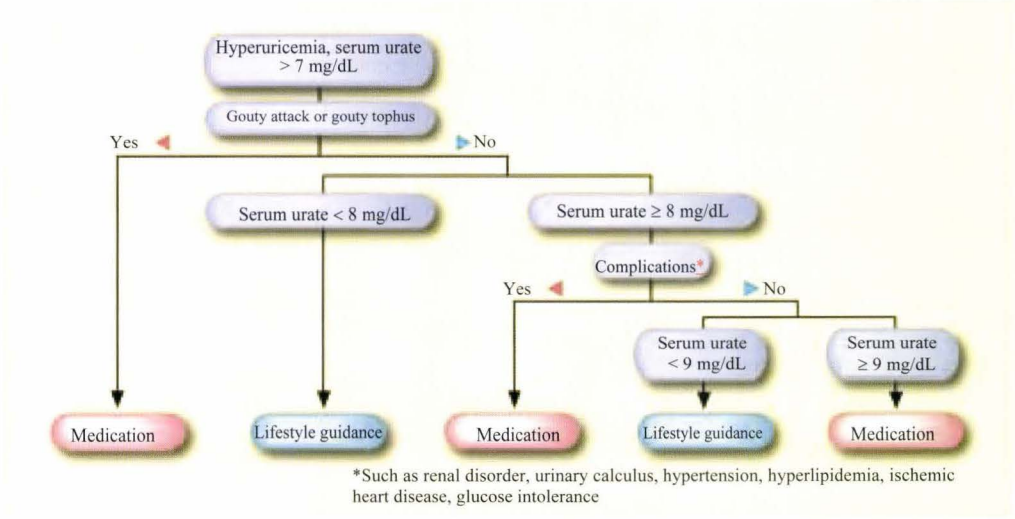


Figure 2 Algorithms for the treatment of hyperuricemia

B. Types of urate-lowering drugs and their adverse reactions

Urate-lowering drugs are classified to two categories based on their mechanism of action, which promote urate excretion or those that inhibit uric acid production. In Japan, there are three drugs on the market that promote urate excretion (uricosuric). Allopurinol is the only available inhibitor of uric acid production **(Table 5)**.

(1) Uricosuric drugs

Uricosuric drugs enhance the urinary excretion of urate by inhibiting the renal reabsorption of urate at renal tubules, resulting in decreased serum urate levels. At the start of drug administration, though the patient may show a transient increase in urinary excretion of urate, after that once the pool of urate in the body has normalized, the urinary excretion does not increase except the case on excessive purine loading. **It is important to take careful attentions to the formation of urinary calculus in the treatment.**

(a) Probenecid

Probenecid enabled a treatment for basic remedy of gout in the former period of time when only symptomatic treatment could be applied and has been used since 1951 as a major drug for gout treatment.

In addition to the effect on urate level, it also affects on the pharmacokinetics of other drugs. It inhibits the renal excretion of sulfinpyrazone, salicylic acid,

indomethacin, penicillin, etc., and also inhibits hepatic uptake and reduces biliary excretion of rifampicin and methotrexate. Low-dose salicylic acid reduces the uricosuric effect of probenecid.

Incidence of adverse reaction is low, and in most patients long-term administration is possible.

(b) Bucolome

This drug, initially developed as an NSAID in Japan, has a uricosuric action. Concomitant use with low-dose aspirin decreases the blood concentration of bucolome and reduces the uricosuric effect. Gastrointestinal disorders, headache and dizziness are seen as infrequent adverse reactions.

(c) Benzbromarone

Among the uricosuric drugs available at present, this drug has the most potent uricosuric action. The uricosuric effect is achieved by inhibiting the post-secretory reabsorption of urate in the renal tubules.

It does not interact much with other drugs and the reduction of its uricosuric effect by concomitant use with salicylic acid is small. It may cause severe hepatic disorder in patients with idiosyncrasy, but the incidence of adverse reactions is low, and currently this drug is the most frequently used uricosuric agent in Japan.

Table 5 Types, doses, and adverse reactions of urate-lowering drugs

	Generic name	Brand name(s)	Daily dose and administration	Adverse reactions
Uricosuric agents	probenecid	Benecid	500-2,000 mg in 2-4 divided doses	Gastrointestinal disorder, nephrotic syndrome, aplastic anemia, rash, urinary calculus
	bucolome	Paramidin	300-900 mg in 1-3 divided doses	Gastrointestinal disorder, rash, leukopenia, urinary calculus
	benzbromarone	Urinorm Narcaricin Benzmarone others	25-100 mg in 1-2 divided doses	Fulminant hepatitis, gastrointestinal disorder, urinary calculus
Uric acid production inhibitor	allopurinol	Zyloric Alositol Salobel others	100-300 mg in 1-3 divided doses	Toxic syndrome (hypersensitivity angiitis), Stevens-Johnson syndrome, exfoliative dermatitis, rash, aplastic anemia, hepatic dysfunction

Table 6 Selection of urate-lowering drug

Indication of uricosuric agent	Indication of uric acid production inhibitor (allopurinol)
• Under-excretor type of urate • The case suffered from adverse reactions by allopurinol	• Over-producer type of urate • History or presence of urinary calculus • Moderate or severe renal dysfunction • The case suffered from adverse reactions by uricosuric agents

(2) Uric acid production inhibitor

The only drug available that inhibits the uric acid production is allopurinol. Allopurinol inhibits xanthine oxidase, which involves in the final steps of purine metabolism. It was first introduced in 1964 for the treatment of gout and is widely used today. Allopurinol lowers the serum urate level and also reduces the urinary excretion of urate. The oxidative metabolite of allopurinol, oxypurinol, has a strong inhibitory action on xanthine oxidase and has a long half-life in the blood in the range of 18-30 hr, so allopurinol has a relatively long-lasting inhibiting effect on uric acid production.

Conventional dosing **in renal failure patients** can result in the accumulation of oxypurinol in the body, and may cause lethal toxic syndrome. **Thus, it is recommended that the dosage is adjusted based on the degree of renal dysfunction.**

As an inhibitor of xanthine oxidase, it increases the blood concentrations of 6-mercaptopurine (6-MP), azathioprine, and theophylline; affects hapatic drug-metabolizing enzymes; and prolongs the physiological half-life of antipyrine, probenecid, and warfarin. In addition, although the mechanism is unknown, it increases the incidence of ampicillin-induced rash and has various other drug-drug interactions.

Note

• It is recommended that urate-lowering drugs is started at the minimal dose to avoid the induction of gouty arthritis.

C Selection of urate-lowering drug

A general rule is to use a uricosuric drug in patients with under-excretor type of urate and to use a uric acid production inhibition (allopurinol) in patients with over-producer type of urate (Table 6). In the use of uricosuric drug, concomitant use of an agent for urine alkalization should be recommended to prevent urinary calculus.

In the cases of renal disorder with a moderate degree or more (creatinine clearance of 30 mL/min or less, or serum creatinine of 2 mg/dL or greater) or a history of urinary calculus, allopurinol should be used. In patients with renal failure, it is recommended the careful administration of allopurinol.

If adverse reactions prevent the use of a urate-lowering drug, the optional use of another drug is permitted even though it is out of the general rule. **However, when using a drug incompatible with the disease type, the physician should particularly take careful attentions to adverse reactions and start at as low a dose as possible, and periodical hematology tests and urinalysis should be needed.**

D. Treatment of hyperuricemia without gouty arthritis or gouty tophus (so-called asymptomatic hyperuricemia)

Hyperuricemia (serum urate level of 7.0 mg/dL or more) without clinical manifestations such as gouty arthritis or gouty tophus is called asymptomatic hyperuricemia. At this stage, it is important to prevent the progression to renal disorder and the onset of urinary calculus and gouty arthritis, and to improve the risks of atherosclerosis that may often associate with hyperuricemia.

Aggressive measures should be taken at this point to incorporate lifestyle management that can reduce the serum urate level. Furthermore, any complications must be properly controlled and treated, and urologic management is also important.

In hyperuricemia patients with serum urate levels of 9.0mg/dL or more showed a significantly higher prognostic incidence of gouty arthritis and urinary calculus compared to those with lower values.

In patients with a family history of hyperuricemia or gout, or complications (renal disorder, urinary calculus or a history thereof, hypertension, hyperlipidemia, ischemic heart disease, diabetes and obesity), the urate lowering treatment should be considered if the serum urate is 8.0 mg/dL or more. In addition to nonpharmacologic therapy, introductions of medication should also be considered. In patients without complications, introduction of medication should be considered if the serum urate is 9.0 mg/dL or more.

Note

- A rapid decrease in serum urate level can elicit gouty arthritis, urinary calculus, or adverse drug reactions, so it is preferable to reduce the urate levels gradually.
- The physician should list all drugs for prescriptions and carefully consider potential drug-drug interactions, with particular attention to those of cardiovascular drugs.

E. Treatment during a gouty attack (arthritis) and during the intermittent period

In the treatment of hyperuricemia, it is important to reduce the serum urate level without inducing acute arthritis, renal complications, or urinary calculus.

During a gouty attack (acute arthritis), changes in serum urate level will deteriorate the attack, so urate-lowering drugs should not be started. Rather, remission of the attack should be awaited through the administration of anti-inflammatory drugs. About 2 weeks after the remission, the urate-lowering drug should be started at a low dose (1/2-1/3 of the standard dose) and **the dose should be gradually increased over a period of 3-6 months to achieve the serum urate level of 6 mg/dL or lower.**

If an episode of acute arthritis occurs in the patient taking the urate-lowering drugs, the dosage of the drug should be maintained without change. At about 2 weeks after remission, the dosage should be gradually increased again to achieve a serum urate level of 6 mg/dL or lower.

Thereafter, the drug should be given at a maintenance dose to sustain a serum urate level of 6 mg/dL or lower.

Specifically, the patient is given a starting dose of allopurinol (at 50-100 mg/day), benzbromarone (25 mg/day), or probenecid (250 mg/day) once a day, and then given a maintenance dose to achieve a serum urate level of 6 mg/dL or lower with allopurinol (at 100-300 mg/day, 1-3 times/day), benzbromarone (25-100 mg/day, 1-3 times/day), or

probenecid (250-2,000 mg/day, 1-4 times/day).

When administering a uricosuric agent, the formation of urate calculus can be prevented by maintaining the urine pH at 6.0-7.0 using a combination drug containing potassium citrate and sodium citrate (a drug for urine alkalization, 3-6 g/day, 3-4 times/day). Daily water intakes should be maintained with the daily urine volume of 2,000 mL or more.

Note

• In order to find adverse reactions in the early stage, the patient should be periodically monitored by laboratory tests for hepatic function or peripheral blood. For benzbromarone, the Safety Information of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare mandates monthly laboratory tests for hepatic function for 6 months after the start of administration.

Table 7 Suggested allopurinol doses for renal functions

$C_{cr} > 50$ mL/min	100-300 mg/day
30 mL/min $< C_{cr} \leq 50$ mL/min	100 mg/day
$C_{cr} \leq 30$ mL/min	50 mg/day
Hemodialysis	100 mg at end of dialysis session
Peritoneal dialysis	50 mg/day

F. Use of urate-lowering drugs in patients with complication of renal disorder

In many patients, hyperuricemia must be treated in the setting of renal disorder. When renal function decreases, the effect of uricosuric drugs is blunted, so patients with renal dysfunction are often treated with allopurinol, a drug that decreases the production of uric acid.

However, it has been reported that allopurinol can cause serious adverse reactions in patients with renal failure. For this reason, **in patients with renal disorder, the dose of allopurinol should be adjusted for the degree of renal functions, as shown in Table 7.**

In patients with a moderate degree of renal failure with a creatinine clearance (C_{cr}) of 30 mL/min or greater, **it is effective and safe to use concomitantly of small doses of benzbromarone (25-50 mg/day) and allopurinol (50-100 mg/day).**

Note

• As to the serious adverse reactions on the renal dysfunctions, careful attentions should

be taken for bone marrow suppression (pancytopenia, aplastic anemia), dermal hypersensitivity reaction, and hepatic disorder.

G. Use of urate-lowering drugs in patients with complications of hepatic dysfunction

In patients with hepatic dysfunction, it is important to treat the complicated hepatic disorders to treat the hyperuricemia without exacerbating the hepatic dysfunction.

Urate-lowering drugs can sometimes cause hepatic dysfunction as an adverse reaction, so careful administration is needed in patients with hepatic dysfunction. In particular, **benzbromarone is contraindicated in patients with hepatic dysfunction, and thus other urate-lowering drugs must be used.**

When treating a patient with a urate-lowering drug, it is important to monitor hepatic functions periodically. In general, urate-lowering drugs, except for benzbromarone, can be started at a low dose and the dose gradually increased, to lower the serum urate to a stable level. Benzbromarone requires monthly laboratory tests for hepatic functions for 6 months after the start of drug administration.

4. Management of patients with hyperuricemia or gout

Aside from the serum urate level, patients with hyperuricemia or gout should be managed as follows.

A Urologic management

This Guideline differs from current clinical practices, in which urologic management is not a part of the urate-lowering therapy but is considered to be an independent component of the therapeutic programs.

In patients with hyperuricemia or gout, concurrent urinary calculus is common. It is thought that acidic urine (pH less than 6.0) may be the reason. The urinary pH greatly affects urate solubility. Maintaining urinary pH at the appropriate level serves also to prevent the formation of other urinary calculus induced by urate calculus and urate crystallization.

The first morning void of urine is tested to determine whether the urine pH is less than 6.0. If the pH reading persistently confirms acidic urine, urine alkalization is necessary.

For this purpose, a combination drug with potassium citrate and sodium citrate is often used.

In patients with hyperuricemia, even if the serum urate level is 7.0-8.0 mg/dL during the observation period, **it is necessary to use urine alkalizing drug if the urine pH is consistently less than 6.0. A persistent urine pH of less than 5.5 is an essential indication for treatment in patients with urinary calculus or a history thereof. When using uricosuric drugs, a urine alkalizing drug should be used concomitantly.**

B. Lifestyle management

It is important to address hyperuricemia as a lifestyle-related disease from the viewpoint of a cardiovascular risk factor. Management of the lifestyle has priority over urate-lowering therapy using drugs.

The increase in the incidence of obesity following Westernization of the Japanese diet and the trend toward overeating have been the focus of attention as underlying factors of lifestyle-related diseases, and this in turn emphasizes the importance of dietary therapy, restriction of excessive alcohol consumption, and appropriate exercise therapy. The physician should counsel the patient to correct the aspects of lifestyle that can be corrected and instruct the patient to prevent obesity. However, since such lifestyle guidance can be excessive and decrease the patient's quality of life, the physician should undertake only practical aspects. Hyperuricemia that is not affected by the patient's lifestyle should be primarily subjected to urate-lowering therapy.

C. General health maintenance

Patients with hyperuricemia often have other complication with lifestyle-related diseases, so the physician should understand that the hyperuricemia is a part of multiple risk factor syndromes along with such diseases as obesity (visceral fat obesity), hyperlipidemia, glucose intolerance, and hypertension. **It is currently unclear whether measures to lower the urate level reduce the cardiovascular risk. The physician should endeavor to reduce the serum urate level in the patient in the context of generally improving the multiple risk factors by lifestyle management.**

For this reason, other lifestyle-related diseases, especially complication with cardiovascular diseases, should be monitored periodically by ECG as well as tests for blood glucose and serum lipids. To monitor adverse drug reactions, tests for peripheral blood, hepatic function, and renal function should also be periodically performed.

Chapter IV. Treatment of Complications or Concurrent Diseases

1. Renal disorder and urolithiasis

Hyperuricemia and gout are frequently complicated by renal disorder and urolithiasis. For these complications, control of serum urate is known to be effective. The major cause of the renal disorder and urolithiasis is thought to be oversaturation of urate in the urine, resulting in deposition. The deposition can be effectively prevented by decreasing the amount of urinary urate as a solute, and increasing the volume of urine as the solvent.

For patients with concurrent renal disorder, presence of urolithiasis, or a history of urolithiasis, allopurinol, the inhibitor of uric acid production, is to be used. For patients with extent to a moderate degree of renal disorder, co-administration of low doses of allopurinol (50-100 mg/day) and benzbromarone (25-50 mg/day) may be effective. For patients with renal dysfunction, the dose of allopurinol should be adjusted based on the degree of renal dysfunction (see Chapter III).

The urologic management for the reduction of urinary urate excretion is performed by a low-purine diet and allopurinol treatment. Larger urine volume increases the amount of urate dissolved in the urine, but can also affect the patient's quality of life. Thus, the patient should be instructed to intake water to maintain a urine volume of 2,000 mL or greater per day. Water intake before sleeping and during the night is especially important. Water intake should involve beverages that do not contain alcohol or sugar.

The solubility of urate in the urine decreases with acidification urine, and the urine of gout patient often tends to be acidic. Correction of acidic urine is achieved through **dietary therapy or urine alkalizing agents.** **Table 8** shows a food that tends to alkalize the urine. Urine alkalizing agents are the preparations of sodium bicarbonate or the citrate agents; such agents should be taken at 1-6 g/day in 1-6 divided doses to maintain a urine pH of 6.0-7.0 **(Table 9).**

2. Hypertension and cardiovascular disorders

Elevated serum urate, from the standpoint of primary prevention and secondary prevention, could be a risk factor for cerebrovascular and cardiovascular events. **In hypertensive patients, even after proper control of the blood pressure, elevated serum urate level is likely to be a risk factor for cerebrovascular and cardiovascular events.** In hyperuricemic patients with hypertension, the serum urate

levels thought to increase the risk of cardiovascular disease are > 7.5 mg/dL in men and > 6.2 mg/dL in women.

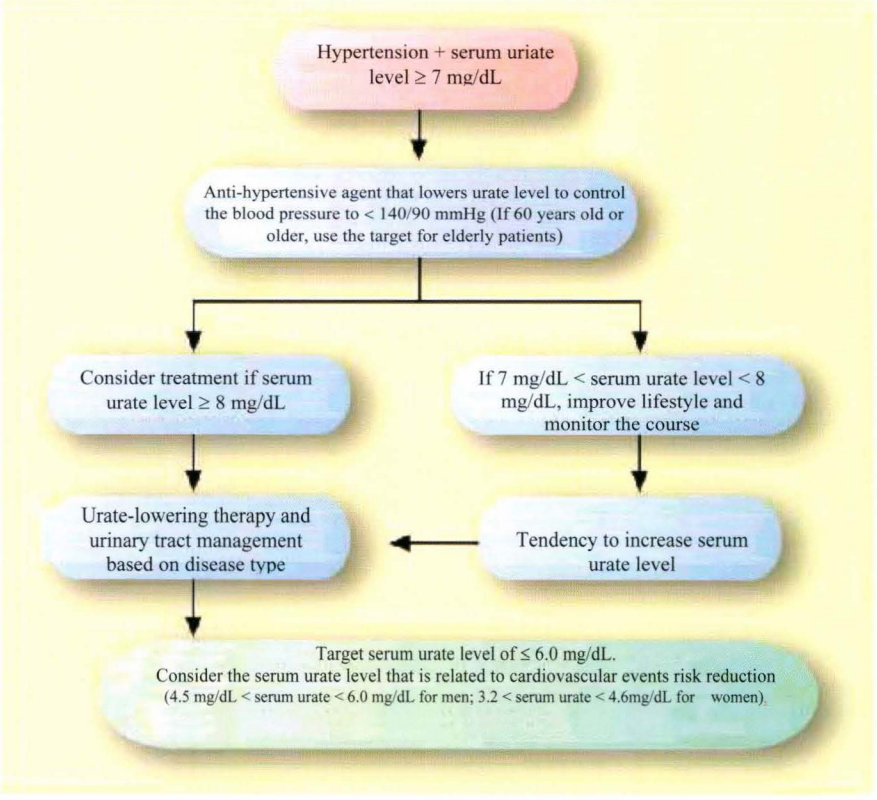


Figure 3 Treatment algorithms for hyperuricemia and concurrent hypertension

Table 8 Foods that tend to alkalize or acidify urine

Foods that tend to alkalize urine	Alkalinity Acidity	Foods that tend to acidify urine
	High	
Seaweed (*hijiki, wakame*)		Eggs, pork, mackerel
Seaweed (sea tangle), dried Chinese mushrooms,		Beef, trough shell
Soybeans, Spinach		Bonito, scallop
Burdock, sweet potato		White rice, yellowtail
Carrot		Tuna, saury
Banana, aroid		Horse mackerel, saury-pike
Cabbage, melon		Sardine, flounder
Japanese radish, turnip, eggplant		Conger eel, Shiba shrimp
Potato, grapefruit	Low	Oriental shrimp

(Excerpted from *The Japanese Food Composition Table,* 4th edition)

Table 9 Indications of urine alkalization drugs for primary gout patients

I : relative indication
I plus one of 1-6 in II: mandatory indication

I Acidic urine (urine pH < 6.0) and not improved by with dietary therapy

II
1. Patients with increased urate excretion in urine (≥ 800 mg of urate excreted in urine per day)
2. Over-producers of urate
3. Patients estimated to have marked increase in urate pool in the body
4. Patients on uricosuric agents
5. Patients with current or history of urolithiasis
6. Patients suspected of urate nephropathy (except renal failure)

Excessive alkalization of the urine can lead to lessen the solubility of calcium phosphate; thus, careful attention is needed. Sodium bicarbonate can lead to sodium load, so careful attention should be required for patients with heart failure, hypertension or renal dysfunction. Citrates have lower sodium load than sodium bicarbonate but contain potassium, and thus should be used with caution in patients with renal dysfunction.

Table 10 Effects of anti-hypertensives on serum uric acid level

Anti-hypertensives	Effect on serum urate level
Thiazide diuretics	Increase
β-blocker	Increase
α_1-blocker	Decrease
α/β-blocker	Increase
ACE inhibitor	Decrease
α-methyldopa	No change
Calcium antagonist	Decrease
Losartan	Decrease
Other angiotensin II (AII) receptor inhibitors	No change

Table 11 Treatment of hyperlipidemia in patients without complication other than hyperuricemia

	Target serum lipid level
Serum total cholesterol	< 220 mg/dL
Serum triglycerides	< 150 mg/dL
Serum HDL-cholesterol	≥ 40 mg/dL

The objective of blood pressure control in hyperuricemic patients complicated with hypertension is a blood pressure less than 140 mmHg/90 mmHg for patients aged under 60 years, and a systolic blood pressure less than 150 (or less than 160 mmHg) for patients aged 60 years or older (see The Guidelines of the Japanese Society of Hypertension) **(Figure 3)**. **In selecting the hypertensive agent, it is preferable to use antihypertensive drugs that also have urate-lowering actions (Table 10), such as losartan, angiotensin converting enzyme (ACE) inhibitors, long-acting calcium (Ca) antagonists, and α_1-blockers.**

The criteria of serum urate levels to be considered to start anti-hyperuricemic treatment and target control levels follow the 6, 7, and 8 rules specified by the Consensus Conference of the Society. These rules involve evidence-based considerations for serum urate levels that represent a risk for cerebrovascular or cardiovascular events, and the condition of serum urate levels that reduce the development of those events.

In hypertensive patients, the major cause of hyperuricemia is based on their under-excretor type of urate, so uricosuric agents are primarily used. However, it is also effective to concurrently use small amounts of uric acid production inhibitor (allopurinol).

It is important to select drug and determine the dosage, paying attention to dose reduction of allopurinol based on the degree of renal dysfunction, and to the precautions in the use of benzbromarone in patients with hepatic dysfunction.

3. Hyperlipidemia

Greater importance is being placed on atherosclerosis as a factor in the prognosis of hyperuricemic patients. For this reason, it is important to treat and control hyperlipidemia.

However, although it is strongly suggested that higher urate level is an independent risk factor for atherosclerosis, this has not yet been clearly established. **Thus, at this point, it is preferable that hyperlipidemia be treated according to the Guidelines for Diagnosis and Treatment of Atherosclerosis Cardiovascular diseases of the Japan Atherosclerosis Society (Table 11)** without considering the serum urate level. It is effective to use nictitate drugs in patients with complication of hyperlipoproteinemia (a) (Lap(a)).

Some drugs for the treatment of hyperlipidemia can also affect the serum urate level, so these effects also need to be taken into account **(Table 12)**. Among these drugs, fenofibrate used to treat hypertriglyceridemia have a strong uricosuric action and can

reduce the serum urate levels. Thus, this drug is especially effective for hyperuricemic patients with under-excretor type of urate.

In order to identify any adverse drug reactions caused by anti-hyperlipidemic drugs at the earliest stage, the patient should be periodically monitored by the tests for hepatic function, and peripheral blood together with the creatine phosphokinase (CPK) assay.

Table 12 Drugs used in the treatment of hyperlipidemia

Generic name	Dose	Effect on serum urate level
HMG-CoA reductase inhibitor		
pravastatin sodium	10-20 mg	None
simvastatin	5-10 mg	None
fluvastatin sodium	20-60 mg	None
atorvastatin	10-20 mg	None
Anion exchange resins		
cholestimid	3 g	None
cholestyramine	8-12 g	None
Probucol	500-1,000 mg	None
Nicotinic acids		
niceritrol	750-1,500 mg	Essentially none or slight increase
nicomol	600-1,200 mg	Essentially none or slight increase
Fibrates		
fenofibrate	200-300 mg	Decrease
bezafibrate	400 mg	None
clinofibrate	600 mg	Essentially none or slight decrease
clofibrate	750-1,500 mg	Essentially none or slight decrease
Eicosapentaenoic acid		
ethyl icosapentate	1,800-2,700 mg	None

4. Glucose intolerance and obesity

It is not negligible in the effects of obesity on the cause or exacerbation factor of hyperuricemia. In Japan, there has been an increase in obese patients due to overnutrition, overeating, or unbalanced diet. Obesity has also led to the simultaneous development of hypertension, hyperlipidemia, glucose intolerance or insulin resistance being involved with hyperuricemia, thus leading to the accumulation of multiple risk

factors.

A. Glucose intolerance

It is known that insulin resistance is observed in the early stages of obesity and that the increase in serum urate is associated with hyperinsulinemia.

In diagnosing glucose intolerance, plasma insulins are advised to measure simultaneously in the oral glucose tolerance test. The disease type of diabetes is determined by the blood glucose levels based on the Classification and Diagnostic Criteria of Diabetes Mellitus of the Japan Diabetes Society. There is no guidance for insulin level, so the following considerations are given as an example.

(1) Patients without hyperinsulinemia

If the fasting insulin level is less than 10 μU/mL and does not exceed a peak of 100 μU/mL after glucose loading, there is no complication with severe insulin resistance. This includes patients without hyperinsulinemia and accumulation of visceral fat.

In such patients, glucose intolerance is not a cause of the increased serum urate level, and dietary guidance for diabetes is given to correct the glucose intolerance. The hyperuricemia is treated as usual.

(2) Patients with hyperinsulinemia

Insulin resistance can be diagnosed if the fasting plasma insulin level is greater than 10 μU/mL or the insulin level after glucose loading is greater than 100 μU/mL. Many of these patients are also obese and can be observed by accumulation of visceral fat.

In such patients, dietary therapy is instituted as well as a program of exercise therapy. Weight reduction can lower or normalize the serum urate level, so it may not be necessary to institute urate-lowering therapy. If the rate of urate excretion does not improve, then the primary underlying type is the under-excretor of urate. If the rate of urate excretion normalizes but hyperuricemia still remains, then the underlying type is the over-producer of urate. Urate lowering therapy being matched for the classification of hyperuricemia is to be conducted.

For the treatment of diabetes mellitus, the appropriate treatment guidelines are consulted.

If the glucose intolerance deteriorates and develops to the diabetic condition with overt glucosuria, then the renal excretion of urate increases and the serum urate level

begins to fall. In such patients, if the underlying type of hyperuricemia is the over-producer of urate, then the urinary concentration of urate increases, so treatment with a urine alkalizing agent alone may be preferable. If the patient already has complication with urinary calculus, a small dose of uric acid production inhibitor is used.

It is often difficult to differentiate whether the hyperuricemia has developed as a result of glucose intolerance or that of primary hyperuricemia modified by glucose intolerance. In such patients, the glucose intolerance should be treated first and then the hyperuricemia be corrected; the application of urate-lowering therapy alone should be avoided.

B. Obesity

It has shown that the complication with hyperuricemia developed with the elvevation of body mass index (BMI). In both subcutaneous-fat obesity and visceral-fat obesity the incidence of hyperuricemia is high, at about 70%. It has been reported that most patients with visceral-fat obesity are the under-excretor type of urate, while in the case of visceral-fat obesity, 31% of patients are the under-excretor type of urate and 56% are the over-producer type of urate.

As with glucose intolerance, treatment is initiated after evaluating the contribution of obesity to the development of hyperuricemia in the patient. In some patients the hyperuricemia improves with weight reduction alone. Obesity treatment should be conducted after proper classification and diagnosis based on the guidelines of the Japanese Society for the Study of Obesity, and the treatment directed at the removal of cause should be initiated.

Rapid weight reduction can lead to cause hyperuricemia of over-producer type of urate, which can deteriorate existing hyperuricemia and may cause a gouty attack. Thus, it is sometimes necessary to use a uric acid production inhibitor.

In contrast to glucose intolerance, it is often difficult to correct obesity. In particular, those with severe obesity have much difficulty in weight reduction. As a measure against gouty attack and renal disorder, it is often necessary to conduct urate-lowering therapy along with weight reduction.

V. Secondary Hyperuricemia and Its Treatment

1. Over-producer type of urate in secondary hyperuricemia

Secondary gout constitutes about 5% of all gout patients. As with the primary type, patients can be classified into the over-producer type, under-excretor type and mixed

type of urate.

Table 13 shows the various types of secondary hyperuricemia of the overproduction type of urate.

A. Treatment of underlying disease

It is most important to treat the underlying disease, or eliminate or reduce the dose of the offending drug. **In the diagnosis of hyperuricemia, one must always look for possible underlying causes**, and it is important to search for them through medical history, physical examination and general laboratory tests.

Table 13 Over-producer type of urate in secondary hyperuricemia

1. Hereditary metabolic diseases
   Lesch-Nyhan syndrome (hypoxanthine phosphoribosyltransferase[HPRT] deficiency)
   5-phosphoribosyl-1-pyrophosphatase (PRPPase) overactivity
   Congenital myogenic hyperuricemia
2. Increased cell proliferation
   Hematologic malignancies
   - Acute: Acute leukemia, malignant lymphoma
   - Chronic: Chronic myeloproliferative syndromes
     - Chronic myelogenous leukemia in chronic phase
     - Polycythemia vera
     - Essential thrombocythemia
     - Idiopathic myelofibrosis
   - Myelodysplastic syndromes
   - Solid tumors: Sarcoma, Wilms' tumor, small cell lung cancer, breast cancer, seminoma, others

   Acute tumor lysis syndrome
   Non-neoplastic diseases: Psoriasis vulgaris
3. Increased tissue destruction
   Hemolytic anemia
   Hypothyroidism
   Rhabdomyolysis
   Obesity
   Exercise loading
4. Exogenous factors
   High-purine diet
5. Drug induced
   Anti-tumor agents
   Mizoribine
   Theophylline
   Fructose, xylitol

B. Treatment of hyperuricemia

The major component of treatment is the uric acid production inhibitor allopurinol. Until the serum urate (crucial), urine volume, and urinary pH could be controlled, treatment should be conducted along the lines of primary hyperuricemia and gout.

Depending on the status of the underlying disease, it may be necessary to **adjust the therapeutic regimen** including dose modifications. Once the underlying disease has improved, allopurinol should not be administered irresponsibly.

When allopurinol is used concomitantly with anti-tumor drugs, one should take into account the possible drug-drug interactions. Careful attention should be taken when allopurinol is used with agents that cause myelosuppression such as 6-mercaptopurine (reduce dose to about 1/3) and cyclophosphamide (use with caution), and with pentostatin, which carries a risk of severe vasculitis.

C. Treatment of gouty flare

Proceed as in the treatment of primary gout.

Note

- Acute uric acid nephropathy and acute tumor lysis syndrome are diseases with medical emergencies, where the physician needs not only to adjust the serum urate level but also to institute systemic control.

Table 14 Mechanisms of mixed-type secondary hyperuricemia

	Mechanism of over-production of urate	Mechanism of under-excretion of urate
Type I glycogenosis	ATP deficiency	Hyperlactacidemia
Obesity	Increased lipid synthesis	Hyperinsulinemia
Toxemia of pregnancy	Tissue destruction of placenta etc.	Increased reabsorption in proximal tubules
Alcohol consumption	Increased ATP degradation and purine intake	Hyperlactacidemia
Nicotinic acid, nicotinamide	Increased PRPP synthesis	Inhibition of urate excretion

2. Mixed-type secondary hyperuricemia

Table 14 shows the various types of **mixed-type secondary hyperuricemia. Treatment should be similar to that for primary hyperuricemia, taking into account the features of both the over-producer type and the under-excretor type of urate.**

Table 15 Diseases(or pathophysiology) that induce hyperuricemia of the under-excretion type of urate

1. Primary	Cause unknown (idiopathic) Familial juvenile gouty nephropathy
2. Secondary	Chronic renal disease (renal dysfunction) Polycystic kidney Toxemia of pregnancy Lead nephropathy Hyperlactacidemia Down's syndrome Sarcoidosis Type I glycogenosis (due to hyperlactacidemia) Dehydration Drugs Diuretics (furosemide, thiazide, D-mannitol), low-dose salicylate, pyrazinamide, ethambutol, nicotinic acid, ethanol (mediates hyperlactacidmia), cyclosporin

3. Under-excretion type of urate in secondary hyperuricemia

It is necessary to be versed in the diseases that can induce secondary hyperuricemia with the under-excretion type of urate and their pathophysiology (Table 15).

Secondary hyperuricemia associated with renal failure has been reported to have a low incidence of gouty arthritis. In addition, there have been no consensuses on whether hyperuricemia associated with renal failure promotes renal dysfunction or whether hyperuricemia should be corrected from the viewpoint to preserve renal function. For this reason, urate-lowering therapy is currently considered for renal failure patients as follows:

1 Uric acid over-production states (nucleotide synthetase deficiency etc.)
2 Familial renal disease associated with gout and renal failure
3 History of gout
4 Patients with a persistently elevated serum urate level of 9 mg/dL or greater.

In the treatment, uricosuric drugs such as probenecid and benzbromarone **are generally used**. It is known that probenecid affects the metabolism of antibiotics and many other drugs, so it is difficult to use this drug as a uricosuric agent. Thus, **in daily clinical practice, benzbromarone is used.**

For the mixed type of over-producer and under-excretor of urate, it is often useful to use benzbromarone concomitantly with the uric acid production inhibitor allopurinol.

However, as renal function declines, benzbromarone becomes less effective and is completely ineffective in patients with renal failure at a creatinine clearance of 30 mL/min or less. Thus, in patients with renal dysfunction, allopurinol is indicated.

When allopurinol is used in patients with renal dysfunction, the blood concentration of oxypurinol, an active metabolite with a long half-life in blood, increases, and serious adverse reactions of allopurinol may be seen in patients with renal failure. For this reason, **it is necessary to reduce the dose depending on the degree of renal dysfunction** (see Chapter 3).

Chapter VI. Lifestyle guidance

1. Lifestyle guidance

With the realization that hyperuricemia and gout are representative lifestyle-related diseases, the role of lifestyle guidance becomes greatly expanded in a non-pharmacological treatment aimed at improvement of lifestyles and habits. In the setting of good patient-physician communication, the physician should counsel the patient to identify problems of lifestyles that attribute to hyperuricemia so that the patient positively incorporates the lifestyle guidance as a strategy of self-maganged care of hyperuricemia as a long-lasting chronic illness.

Table 16 shows the specific details of lifestyle guidance. **Major objectives in lifestyle guidance for hyperuricemia are dietary therapy, restriction of alcohol consumption, and recommendation of exercise.**

A. Dietary therapy

For the hyperuricemic patient with a tendency toward obesity, the primary objective of dietary therapy is the restriction of caloric intake along the lines suitable for diabetes treatment. Reduction of obesity also leads to the improvement of visceral fat accumulation and insulin resistance and improves the long-term prognosis of the

patient.

Purine rich diets are defined as those containing 200 mg or more of purines in 100 g. **Table 17** shows such diets; namely, organ meats, dried fish, and other dried foods. Dietary therapy should also incorporate restriction of excessive intake of purines. However, except for hospitalized patients, it is almost impossible to maintain a low-purine diet on a consistent basis, and it is preferable to instruct simply to avoid purine rich diets. A realistic goal is purines intake of not more than 400 mg per day.

Urologic management is important as well. Purine rich diets also tend to increase the acidity of urine, giving a further reason why dietary therapy should aim to restrict such foods. In addition, to dilute the urinary concentration of urate, the patient should aim to achieve a daily urine output of 2,000 mL per day.

Table 16 Lifestyle guidance in hyperuricemia

- Reduction of obesity
- Dietary therapy
  Restriction of high caloric intake
  Restriction of purines intake
  Intake of foods that tend to alkalize the urine
  Sufficient water intake (to urine output of 2,000 mL/day or more)
- Restriction of alcohol intake
  Japanese sake: 1 *go* (180 mL)
  Beer: 500 mL
  Whisky: 1 double (about 60 mL)
  No alcohol intake in 2 days/week or more
- Adequate exercises
  Aerobic exercise
- Reduction of stresses

Table 17 Foods with high or low purine content

Extremely high (> 300mg/100g)	Chicken liver, dried true sardine, milt of grunt, monkfish liver steamed with Japanese sake, dried bonito flake, dried sardine, dried shinese mushroom
High (200-300 mg/100g)	Pork liver, beef liver, bonito, sardine, oriental shrimp, dried horse mackerel, dried saury
Low (50-100 mg/100g)	Eel, smelt, pork loin, pork ribs, beef sirloin, beef ribs, beef tongue, mutton, ham, pressed ham, bacon, minced fish dumpling, spinach, cauliflower
Very low (< 50 mg/100g)	Corned beef, fish sausage, *kamaboko* (boiled fish paste), *chikuwa* (roasted fish paste), fried fish paste, herring roe, salmon roe, wiener sausage, tofu, milk, cheese, butter, eggs, corn, potato, sweet potato, rice, bread, *udon* (wheat noodles), *soba* (buckwheat noodles), fruits, cabbage, tomato, carrot, Japanese radish, Chinese cabbage, *hijiki* (seaweed), *wakame* (seaweed), sea tangle

(Converted as total purines)

B. Restriction of alcohol intake

Even alcoholic beverages containing less purines affect purine metabolism (by promoting the degradation of endogenous purines and reducing urate excretion via the kidneys) and increase the serum urate level, so excessive intake of any type of alcohol should be restricted. Beer not only contains large amounts of purines but also has relatively high caloric contents compared to other types of alcoholic beverages, and thus promotes obesity. It is considered that the effects of alcohol on serum urate begin to appear with an intake of about 180 mL of Japanese sake, 500 mL of beer, or 60 mL of whiskey.

C. Recommendation of exercise

Counseling in exercise therapy is necessary for obese patients, but cardiac function should be evaluated prior to initiation. Excessive exercise should be avoided. It is desirable to achieve a program of light exercise at least 1 hour after meals every day to the target body weight (BMI of less than 25kg/m^2).

Aerobic exercise has no effect on serum urate level but improves the various physical conditions that are associated with hyperuricemia by reducing body fat, improving mild cases of hypertension, increasing HDL cholesterol, and improving glucose tolerance.

Note

• Patients often strictly follow the prescribed caloric, purine and alcohol restrictions for a short period of time but most of cases result in leading to rebound. The physician should repeatedly explain the patient that obesity, purine rich diet and habitual alcohol intake are harmful, so that the patient becomes motivated to follow the treatment program. This comment also applies to exercise. The initial goal should be to achieve the habit of regular exercise, and after establishing that without stress, then the details of the exercise can be modified through consultations.

Committee for the Preparation of Guidelines for the Management of Hyperuricemia and Gout

Committee for the Preparation of Guidelines for the Management of Hyperuricemia and Gout
Japanese Society of Gout and Nucleic Acid Metabolism

- Committee Chair

Tatsuo Hosoya
Division of Kidney and Hypertension, (Nephrology & Rheumatology), Department of Internal Medicine,
Jikei University School of Medicne

- Committee Members

Takanori Ueda
Department of Internal Medicine I (Hematology & Oncology), Faculty of Medical Sciences, University of Fukui

Naoyuki Kamatani
Institute of Rheumatology,
Tokyo Women's Medical University

Hiromu Nakajima
Department of Clinical Laboratory, (Internal Medicine on Endocrinology & Metabolism)
Osaka Medical Center for Cancer and Cardiovascular Diseases (OMCC)

Ichiro Hisatome
Division of Candiology, Department of Cardiovascular Internal Medicine,
Tottori University Hospital

Shin Fujimori
Department of Internal Medicine,
Teikyo University School of Medicine

Hisashi Yamanaka
Institute of Rheumatology,
Tokyo Women's Medical University

Tetsuya Yamamoto
Department of Internal Medicine,
(Endocrinology & Metabolism),
Hyogo College of Medicine

- Authoring Members

Takanori Ueda
Department of Internal Medicine I (Hematology & Oncology), Faculty of Medical Sciences, University of Fukui

Iwao Ohno
Division of Kidney and Hypertension, (Nephrology and Rheumatology)
Jikei University School of Medicine

Hiromu Nakajima
Department of Clinical Laboratory, (Internal Medicine on Endocrinology & Metabolism)
Osaka Medical Center for Cancer and Cardiovascular Diseases (OMCC)

Ichiro Hisatome
Department of Cardiovascular Internal Medicine Cardiology,
Tottori University Hospital

Shin Fujimori
Department of Internal Medicine Metabolomics,
Teikyo University School of Medicine

Tatsuo Hosoya
Division of Kidney and Hypertension, (Nephrology & Rheumatology), Department of Internal Medicine,
Jikei University School of Medicine

Hisashi Yamanaka
Institute of Rheumatology,
Tokyo Women's Medical University

Tetsuya Yamamoto
Department of Internal Medicine, (Endocrinology & Metabolism),
Hyogo College of Medicine

- Advisor

Takuo Koide
Department of Urology,
Osaka Koseinenkin Hospital

- Secretariat

Iwao Ohno
Division of Kidney and Hypertension, (Nephrology & Rheumatology),
Jikei University School of Medicne

• Evaluation Members

Mitsuo Itakura
Division of Genetic Information,
Institute for Genome Research,
The University of Tokushima

Kazuhiko Ito
Health Care Management Center,
Mitsubishi Electric Corporation

Harutoshi Kizaki
Department of Biochemistry,
Tokyo Dental College

Norio Kohno
School of Allied Health Sciences,
School of Medicine, Osaka University

Masataka Sasada
College of Medical Technology,
Kyoto University

Yohei Tofuku
Ishikawa Saiseikai Kanazawa Hospital

Kusuki Nishioka
Institue of Medical Scienses,
School of Medicine, St. Marianna University

Toshikazu Hada
Department of Internal Medicine,
Hyogo College of Medicine

Yuji Matsuzawa
Department of Internal Medicine and
Molecular Science,
Graduate School of Medicine,
Osaka University

Yoshifuji Matsumoto
Toyokawa City Hospital

Yoshiro Wada
Nagoya City University

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Edited by: Committee for the Preparation of Guidelines for the Management of Hyperuricemia and Gout

Published by: Japanese Society of Gout and Nucleic Acid Metabolism
3rd Floor, Nishi-Shimbashi Fukutoku Bldg., 1-11-5 Nishi-Shimbashi, Minato-ku, Tokyo 105-0003, Japan
Tel: (03) 3597-9394 Fax: (03) 3593-8303

Prepared by: Dentsu, Sudler & Hennessey Inc.
Tsukiji MK Bldg., 2-11-26 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Tel: (03) 3546-6104 Fax: (03) 3546-6575

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