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Review Article

Internal Medicine Section

A Review of Hyperuricaemia Management with Febuxostat: Dosage Titration, Monitoring and Maintenance

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ABSTRACT

The burden of hyperuricaemia has been steadily increasing both globally and in India. The increasing number of hyperuricaemia-associated co-morbidities, such as Chronic Kidney Disease (CKD), Type 2 Diabetes Mellitus (T2DM), Cardiovascular Diseases (CVD), and hypertension, implies that hyperuricaemia is associated with an increased risk of other chronic conditions or diseases. Despite the availability of several guidelines on hyperuricaemia, recommendations for appropriate titration of Urate Lowering Therapy (ULT) to achieve and maintain appropriate serum Uric Acid (sUA) levels in the Indian context are unclear. Another important challenge is the diagnosis and management of asymptomatic hyperuricaemia with ULT. This review summarises evidence-based discussion and review of literature by expert panellists on hyperuricaemia management with ULT, particularly with Xanthine Oxidase (XO) inhibitors. Based on the discussion, the experts developed a dose-titration algorithm for initiation and long-term management of hyperuricaemia with ULT, comprising febuxostat. The review also highlights some of the current challenges in hyperuricaemia management, which when addressed would benefit primary care physicians across the country for early screening and timely management of hyperuricaemia.

Keywords: Allopurinol, Awareness, Renal impairment, Serum uric acid, Urate lowering therapy

INTRODUCTION

The burden of hyperuricaemia has been on the rise both globally and in India [1]. Hyperuricaemia or increased serum Uric Acid (sUA) levels results from either overproduction of uric acid (an end product of purine metabolism) or its underexcretion [2]. Hyperuricaemia is defined as sUA levels >7 mg/dL in men and >6 mg/dL in women [1]. In the intracellular setting, uric acid has proinflammatory effects, whereas it acts as a strong antioxidant in the plasma. Prolonged duration of hyperuricaemia leads to a chronic phase of microvascular injury, which contributes to afferent arteriolopathy. This results in elevated blood pressure and unresponsiveness to Urate Lowering Therapy (ULT) over time [3]. Besides hypertension, increased levels of sUA have been associated with an increased risk of multiple disorders, including hypertension, Chronic Kidney Disease (CKD), Type 2 Diabetes Mellitus (T2DM), stroke, Congestive Heart Failure (CHF), Coronary Artery Disease (CAD), metabolic syndrome, dyslipidaemia, atherosclerosis, and obesity [2].

Additionally, hyperuricaemia is an independent risk factor for renal disorders and CVDs [4]. Hyperuricaemia can be symptomatic or asymptomatic. In asymptomatic hyperuricaemia, the sUA level is elevated without any symptoms, while in symptomatic patients elevated sUA levels are accompanied by gout, acute urate nephropathy, or urolithiasis [5]. Despite the association between hyperuricaemia and multiple co-morbidities, there still exist considerable gaps in the approach toward hyperuricaemia screening and management. Common gaps included entifying the threshold sUA level for initiating ULT, management of asymptomatic patients, routine screening for sUA, and use of sUA as a prognostic tool in clinical screening [5]. With this background, a series of multidisciplinary advisory board meetings were conducted with experts from different specialities across four zones of India to gain expert insights on hyperuricaemia management with ULT, understand the prevailing practices on titration of ULT in India, develop a simplified algorithm for treatment initiation, titration and maintenance with ULT, and address the current gaps and challenges in hyperuricaemia management.

BURDEN OF HYPERURICAEMIA

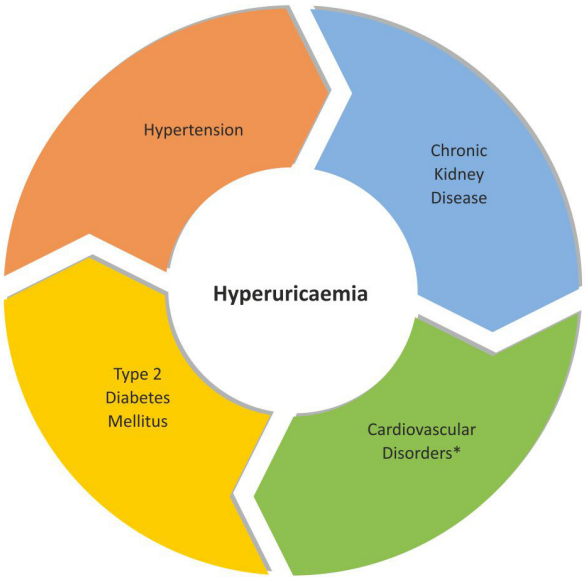
Epidemiology of Hyperuricaemia

The prevalence of hyperuricaemia is higher in Asian countries, including India (25.8%), when compared with that in western countries like the United States of America (USA) (21-22%), Italy (9-12%), and Brazil (13%) [1]. In India, as compared to healthy individuals, higher prevalence of hyperuricaemia has been noted in patients with co-morbidities, such as hypertension (37.3%), T2DM (25.3%), obesity (44.6%), and metabolic syndrome (47.1%) [2]. High sUA levels have also been reported in 38.4% of individuals with CKD [6]. Further, as compared to patients with T2DM (5.6%) or hypertension (4.2%) alone, the incidence of hyperuricaemia is higher in patients with both T2DM and hypertension (7.4%) [1]. In the Indian population, the prevalence of hyperuricaemia increases with age and duration of co-morbidity and is higher in men as compared to women [1]. Furthermore, compared to urban areas, sUA levels are higher in the rural areas [7].

Hyperuricaemia and Associated Co-morbidities

Previously, hyperuricaemia was considered as an independent condition or a consequence of the co-morbidities in persons with T2DM, Heart failure (HF), hypertension, obesity, or CVD. However, accumulating evidence suggests that rather than being just an inducer of gout, hyperuricaemia might have different clinical implications in individuals with these co-morbidities [8]. Apart from these co-morbidities, high sUA levels are also associated with male sex, smoking, old age, dyslipidaemia, obesity, increased waist-hip ratio, hypertriglyceridaemia, and metabolic syndrome [9]. [Table/Fig-1] depicts the different co-morbidities for which hyperuricaemia is proposed to be a predictive factor [10].

1. Chronic Kidney Disease (CKD): In individuals with CKD, sUA levels are elevated owing to decreased estimated Glomerular Filtration Rate (eGFR) [8]. Several studies have elucidated a close association between hyperuricaemia and kidney diseases [4]. In fact, hyperuricaemia is considered to be an independent risk factor for the development of CKD, diabetic nephropathy, Acute Kidney



[Table/Fig-1]: Various co-morbidities where hyperuricaemia is proposed to have a predictive role.
*Includes atrial fibrillation, stroke, coronary artery disease, left ventricular hypertrophy, myocardial infarction, and heart failure

Injury (AKI), and End-Stage Kidney Disease (ESKD). The existing findings on the role of sUA in CKD progression are inconsistent, there is insufficient evidence to suggest that lowering sUA levels prevents CKD progression [4,11-14], and the causal relationship is yet to be proven with longitudinal studies [4]. A few observational studies support the association of hyperuricaemia with the risk of CKD development or progression in persons with T2DM [15,16]. A meta-analysis of 24 studies, involving 25,453 CKD patients, found a significant association between high sUA levels and risk of mortality [17]. In patients with ESKD undergoing haemodialysis, hyperuricaemia was a predictor of higher mortality risk [18].

A study from South India reported a significantly higher prevalence of hyperuricaemia in patients with CKD versus those without CKD (mean sUA levels 8.0 mg/dL and 5.03 mg/dL in CKD and non CKD groups, p-value <0.001). Among CKD patients, sUA levels were higher in diabetic and hypertensive patients, and prevalence of CAD was also higher in CKD patients with high sUA levels [19].

Hyperuricaemia is also frequently observed in renal transplant patients. Lower eGFR levels following transplantation are associated with increased sUA levels. Reportedly, hyperuricaemia does not cause increased mortality or graft loss in renal transplant patients [8].

2. Diabetes: Hyperuricaemia has emerged as an independent risk factor for the development of T2DM [20]. Multiple meta-analyses have revealed that 1 mg/dL increase in sUA level was associated with 6-17% increase in the risk of T2DM [21,22]. Higher concentrations of serum insulin cause increased renal reabsorption of uric acid, thereby increasing sUA levels [23]. While several studies have provided observational evidence that elevated sUA levels lead to the development of diabetes [22,24], some conflicting studies suggest inverse association between diabetes and sUA levels [25]. In individuals with normoglycaemia, higher sUA levels have been associated with a higher risk of incident prediabetes [26,27].

Patients with T2DM and hyperuricaemia, with decreased urinary excretion of uric acid, are reportedly at higher risk of developing CKD; the prevalence is as high as 47.8% [28]. However, the causal relationship between diabetes and hyperuricaemia is still inconclusive [29]. A recent study in a mouse model demonstrated that hyperuricaemia does not induce diabetes but predisposes to diabetes by disrupting beta-cell function. The study showed that hyperuricaemia-induced inhibition of islet beta cell survival accelerates diabetes [29].

3. Hypertension: A plethora of clinical studies have demonstrated that sUA is an independent predictor of hypertension [30]. Among untreated hypertensive patients, approximately 25-40% have concomitant hyperuricaemia [31]. The findings of a hyperuricaemia screening program from India revealed that 35.1% of hyperuricaemic patients were hypertensive [2]. A retrospective study from North India reported hyperuricaemia prevalence of 35.3% among patients with hypertension and/or T2DM [32].

A study showed that in the general population untreated for both hypertension and hyperuricaemia, every 1 mg/dL increase in sUA level contributed to 20% increase in the prevalence of hypertension [31,33]. Asymptomatic hyperuricaemia in the absence of any co-morbidities can also predict the development of hypertension [34].

Several antihypertensive medications also affect sUA levels. While antihypertensive agents like beta-blockers, thiazide diuretics, angiotensin II receptor antagonists, and angiotensin-converting enzyme inhibitors often increase sUA levels, long-acting calcium antagonists and losartan have been shown to decrease sUA levels [31].

4. Cardiovascular disorders: Hyperuricaemia directly or indirectly promotes the progression of cardiometabolic risk factors involved in the pathogenesis of CVD, including HF. Baseline sUA levels serve as a predictor of Cardiovascular (CV) mortality [35]. The development and progression of cardiovascular disorders, such as Coronary Heart Disease (CHD), stroke, myocardial infarction, HF, hypertension, and CVD, have been associated with elevated sUA levels [35,36]. Elevated sUA levels are also a predictor of all-cause mortality among HF patients. In the general population, higher sUA levels are a predictor of all-cause or CV mortality [35]. Hyperuricaemia is proposed to an independent risk factor or a significant marker for ischaemic heart disease [37]. An observational cross-sectional study from East India reported 42.7% prevalence of hyperuricaemia among 82 patients with CAD [38]. Another study from South India reported 46.5% prevalence of hyperuricaemia among 520 patients with stable CAD [9].

PATHOPHYSIOLOGICAL MECHANISMS OF HYPERURICAEMIA AND VARIOUS CO-MORBIDITIES

Hyperuricaemia and Hypertension

Two phases are involved in the pathophysiology of hyperuricaemia and hypertension: an initial acute phase involving endothelial dysfunction, inflammation, oxidative stress, and activation of the renin-angiotensin-aldosterone system; and a later chronic phase involving arterial wall hypertrophy, which causes interstitial inflammation and renal microvascular changes [30].

Hyperuricaemia and CKD

High intracellular uric acid levels induce a pro-oxidant environment that activates profibrotic, proinflammatory, proliferative and senescence pathways. It causes endothelial dysfunction and secretion of vasoconstrictors. These mechanisms lead to systemic hypertension and CKD [39].

Hyperuricaemia and Diabetes

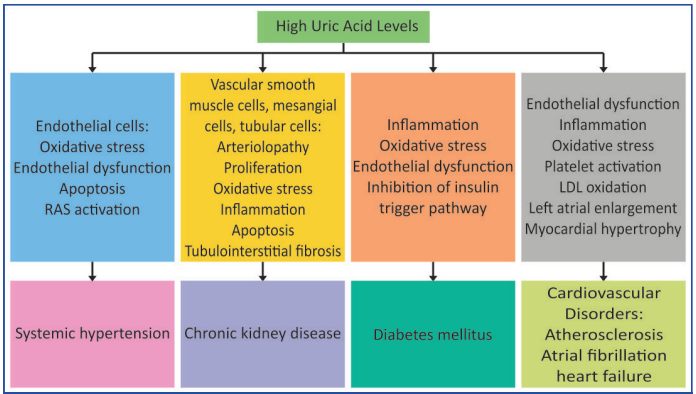
The pathological mechanisms include inflammation with increased levels of Tumour Necrosis Factor-α (TNF-α), Nuclear Factor Kappa light chain enhancer of activated B cells (NF-kB), C-Reactive Protein (CRP) and Interleukin-6 (IL-6); oxidative stress involving increased Reactive Oxygen Species (ROS) production; endothelial dysfunction involving reduced bioavailability of Nitric Oxide (NO); and inhibition of the trigger of the insulin signalling pathway involving Ectonucleotide Pyrophosphatase Phosphodiesterase-1 (ENPP1) recruitment at the receptor level. The mechanisms associated with the chronic

complications of diabetes include promoting vascular thrombosis by triggering platelet adhesion and aggregation; and activation of the Renin-Angiotensin-Aldosterone System (RAAS) via increased production of juxtaglomerular renin and plasma angiotensin II induced aldosterone release (which is mediated by hyperuricaemia-induced ROS). The activation of RAAS leads to inflammation, vascular dysfunction, renal and cardiovascular complications, and high intraglomerular pressure [40].

Hyperuricaemia and Cardiovascular Disorders

Atherosclerosis causes CHD. High uric acid levels cause atherosclerosis via endothelial dysfunction, platelet activation, ROS production, and low-density lipoprotein oxidation. Atrial fibrillation is caused by hyperuricaemia-induced inflammation and oxidative stress. High uric acid levels are directly associated with increase in left atrial diameter, which leads to atrial fibrillation and thrombosis. High uric acid-induced oxidative stress, inflammation and myocardial hypertrophy are the key mediators in development and progression of HF [41].

The proposed pathophysiological mechanisms underlying high uric acid-induced co-morbidities are delineated in [Table/Fig-2].



[Table/Fig-2]: Possible pathophysiological mechanisms associating hyperuricaemia with various co-morbidities.
LDL: Low-density lipoprotein; RAS: Renin angiotensin system

SCREENING FOR HYPERURICAEMIA

Early screening of sUA levels has been advised by the Indian Forum of Hyperuricaemia (IFH), even in asymptomatic patients to prevent or manage the complications of hyperuricaemia in patients with co-morbidities such as T2DM, prediabetes, CVD, and metabolic syndrome [42]. The British Society for Rheumatology 2017 guidelines recommend that all patients with gout should be screened for co-morbid conditions, such as diabetes, hypertension, dyslipidaemia, renal disease, obesity, cigarette smoking, and CV risk factors, due to the association of these co-morbidities with gout [43].

However, as per the Integrated Diabetes and Endocrine Academy (IDEA) consensus statement on the management of asymptomatic hyperuricaemia, routine screening for hyperuricaemia is not recommended because the natural course of asymptomatic hyperuricaemia is not well understood [44]. Therefore, screening for hyperuricaemia has been recommended by IDEA only for patients with:

- CVD
- Metabolic syndrome
- CKD (eGFR ≤60 mL/min/1.73 m^2)
- Malignancy, particularly when receiving chemotherapy
- History of medications that induce hyperuricaemia, such as diuretics (loop and thiazide diuretics), antitubercular drugs (pyrazinamide and ethambutol), low-dose aspirin (≤325 mg/day), immunosuppressants (cyclosporine and tacrolimus), chemotherapeutic agents for tumour lysis syndrome, nicotinic acid, testosterone, and levodopa
- History of acute monoarthritis suggestive of gout
- Urolithiasis
- History of chronic gout or tophi

In addition to the above-mentioned patient populations, the experts opined that screening for hyperuricaemia among pre-hypertensive individuals is also important because hyperuricaemia is a strong risk predictor of development of hypertension in these patients. All the global and national guidelines univocally and strongly recommend screening for hyperuricaemia in individuals with co-morbidities [45].

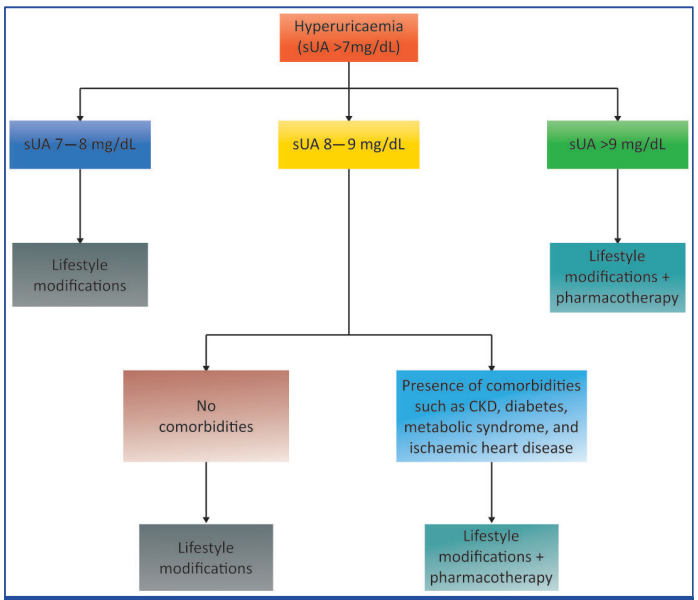
MANAGEMENT

Indian Guidelines on Hyperuricaemia Management

Persistent untreated asymptomatic hyperuricaemia may lead to complications like nephrolithiasis, urate nephropathy, and gout. Asymptomatic hyperuricaemia is also noted in patients with CKD, hypertension, CVD, and metabolic syndrome [42]. Previously, there were no specific guidelines on hyperuricaemia in India, especially for the management of asymptomatic hyperuricaemia [44].

Global societies such as the American College of Rheumatology (ACR) and the British Society for Rheumatology (BSR) do not have guidelines providing specific recommendations for the management of asymptomatic hyperuricaemia [43,46]. In order to fill these lacunae, IDEA developed consensus recommendations for the management of asymptomatic hyperuricaemia in 2020 [44].

The IFH was formed to provide a clear definition of hyperuricaemia, delineate treatment options for hyperuricaemic patients, and to establish hyperuricaemia as a risk factor for the development of various co-morbidities [42]. A simplified algorithm on hyperuricaemia management, based on IFH [42] and IDEA [44] recommendations is presented in [Table/Fig-3].



[Table/Fig-3]: A simplified algorithm on hyperuricaemia management.
sUA: Serum uric acid

Management of chronic hyperuricaemia involves long-term maintenance of uric acid level below <6 mg/dL, whereby the formation of new urate crystals is prevented, and the existing crystals are dissolved. Besides lifestyle modifications and pharmacotherapy, chronic hyperuricaemia management should encompass multiple steps as presented in [Table/Fig-4] [42].

Although hyperuricaemia screening and treatment can be carried out at a low cost, indiscriminate hyperuricaemia screening should be avoided, while ULT therapy should be individualised for each patient [44].

Hyperuricaemia Management with ULT

Dosage titration, monitoring, and maintenance: Xanthine oxidase (XO) inhibitors (allopurinol and febuxostat), uricosurics (probenecid

and benzbromarone), and uricase or urate oxidase (pegloticase, rasburicase) are some of the urate-lowering drugs commonly advised for the management of hyperuricaemia [42].

Steps	Reasons for assessment
Physical examination and ultrasonography	To identify urate deposits in the kidney, joints, or skin.
Detailed patient history	To assess the presence of any co-morbidities along with their treatments.
Identify evitable causes of hyperuricaemia	Evaluation and eradication of causes like alcohol consumption or drugs that increase urate levels. Evitable causes should be removed if possible, and such drugs should be discontinued.
Laboratory tests	To evaluate routine parameters such as glycated haemoglobin (HbA1c) levels, complete blood count, lipid profile, liver function test, and phosphate and calcium levels, to monitor complications or co-morbidities.
Additional steps	To monitor the dissolution or formation of new urate crystals by using methods like urine sediment analysis, and musculoskeletal ultrasound.

[Table/Fig-4]: Steps to be followed in chronic hyperuricaemia management.

Allopurinol is the relatively older XO inhibitor. The usual initiation dose of allopurinol is ≤100 mg/day. It has been associated with hypersensitivity reactions including potentially life-threatening drug reactions, Stevens-Johnson syndrome, rash, cytopenia, pruritus, and toxic epidermolysis [5]. In patients with pre-existing renal insufficiency, allopurinol may cause progression of renal failure because it undergoes renal clearance. To prevent life-threatening toxicity, allopurinol should be used in reduced doses in patients with eGFR <60 mL/min/1.73m^2 [5,47].

Febuxostat is the newer XO inhibitor with better efficacy than allopurinol. It is primarily cleared by the liver and bile and is associated with lesser risk of hypersensitivity as compared to allopurinol [47]. The recommended starting dose of febuxostat is 40-80 mg/day [5]. Febuxostat can be used without dose reduction in CKD patients with eGFR ≥30 mL/min/1.73 m^2, and hence is preferred in patients with renal insufficiency [5,46]. Although allopurinol has been the cornerstone ULT for decades, febuxostat has emerged as the more potent ULT [48].

Uricosurics like benzbromarone and probenecid lower sUA levels by increasing urate excretion. However, benzbromarone has been withdrawn from several countries because of abnormal liver function or mortality from liver failure associated with its use [42]. Uricases, such as pegloticase and rasburicase, lower sUA by converting it to allantoin, which is 5-10 times more urine-soluble than uric acid. Although these agents have significant urate-lowering efficacy, pegloticase has been associated with cardiovascular side effects. Rasburicase is associated with significant adverse effects, including anaphylactic reactions, skin rashes, and methemoglobinaemia [42].

A comparison of different types of ULT has been presented in [Table/Fig-5] [42].

Initiation of ULT: Before initiating ULT, the effects of lifestyle or sUA elevating drugs should be ruled out [42,43]. In case of presence of renal stones or CKD stage ≥3 (or eGFR is <60 mL/min/1.73 m^2), ULT should be initiated when sUA levels are >7 mg/dL [44]. In global guidelines, allopurinol is the commonly recommended first-line ULT. The initiation dose for allopurinol is 50-100 mg once daily [43]. It is strongly recommended for all patients by the ACR guidelines, even in those with moderate-to-severe CKD (stage 3 or higher) [46]. Use of febuxostat is recommended as an alternative ULT when allopurinol is not tolerated or it is added to allopurinol when dose escalation is contraindicated due to presence of renal impairment [43,49]. The IDEA consensus guidelines recommend using febuxostat as first-line therapy in patients with CKD [44]. The BSR recommends initiating febuxostat at a dose of 80 mg once daily, while ACR recommends ≤40 mg dose for initiation [43,46]. The efficacy of 40-120 mg of febuxostat is similar to that of 300 mg dose of allopurinol [42].

Name of drug	Type	Standard daily dose	Remarks
Allopurinol	Xanthine oxidase inhibitors (oral)	300 mg (range: 100 mg-900 mg)	• Causes several adverse effects such as Stevens-Johnson syndrome, rash, and gastrointestinal effects • Allopurinol hypersensitivity syndrome rarely occurs which could be potentially lethal • Increases risk of complication in patients with renal insufficiency, thereby requires dosage adjustment based on renal function
Febuxostat	Xanthine oxidase inhibitors (oral)	80 mg (range: 40 mg-120 mg)	• Dosage adjustment not required in patients with mild or moderate renal impairment • Side effects reported are nausea, diarrhoea, and elevated liver enzymes • No increase in side effects reported with impaired liver or renal function, or with increased age • Safe and well-tolerated alternative to allopurinol • Very few drug interactions reported, principally interacts with azathioprine
Probenecid	Uricosuric agent (oral)	1000 mg (range: 500 mg-2000 mg)	• Used as an alternative for those patients who cannot reach target sUA levels with monotherapy of xanthine oxidase inhibitors, or cannot tolerate allopurinol • Has significant drug interactions with multiple drugs (NSAIDs, beta-lactams, and heparin) • Poor efficacy in patients with moderate-to-severely impaired renal function
Benzbromarone	Uricosuric agent (oral)	100 mg (range: 50 mg-200 mg)	• More potent than probenecid when used as an add-on to allopurinol • Reported to be efficacious in patients with eGFR as low as 20 mL/min/1.73 m^2 • Withdrawn from several countries owing to postmarketing concerns over abnormal liver function and hepatic failure-related deaths
Pegloticase	Uricase (urate oxidase) (IV)	8 mg every 2-4 week	• Infusion reactions involving dyspnoea, flushing, and chest discomfort have been reported in 20-40% of patients • Associated with higher frequency of cardiovascular side-effects
Rasburicase	Uricase (urate oxidase) (IV)	IV infusion given over a duration of 4 to 24 hours prior to initiating cancer chemotherapy over 30 minutes at a dose of 0.15 to 0.2 mg/kg.	• Used in children and adults with tumour lysis syndrome for treatment or prevention of hyperuricaemia • Significant adverse effects reported including anaphylactic reactions, skin rashes, and methemoglobinaemia • Contraindicated in patients with history of hypersensitivity or hemolytic reactions with rasburicase, and in those with glucose-6-phosphate dehydrogenase deficiency

[Table/Fig-5]: Comparison of different types of urate-lowering therapies [42].
eGFR: Estimated glomerular filtration rate; IV: Intravenous; NSAID: Nonsteroidal anti-inflammatory drugs; sUA: Serum uric acid

Owing to the increased risk of adverse reactions with allopurinol and the subsequent requirement of dose modification, febuxostat may be preferred for stage 3-4 CKD patients [44].

Dose titration for ULT: For all patients receiving ULT, achieving and maintaining a target sUA level of <6 mg/dL is strongly recommended

by the ACR [46]. While sUA levels should be maintained below the target, dose titration involves both up- and down- titration of ULT doses because severe decline in sUA levels (to <3 mg/dL) is also not advisable [44]. After initiation with low-dose (50-100 mg) allopurinol, the dose should be uptitrated in increments of 100 mg approximately once every four weeks till the target sUA level is reached [43]. Up-titration of allopurinol can be done up to the FDA-approved maximum dose of 800 mg daily [43,46]. The increments should be smaller for patients with renal impairment (about 50 mg) [43]. In case of febuxostat, up-titration is recommended after four weeks to a maximum dose of 120 mg daily till target sUA levels are reached [43]. Clinical studies that evaluated different titration doses of febuxostat have reported that the dose of febuxostat can be down-titrated from 80 mg/day to 60 mg/day, 40 mg/day or 20 mg/day as per the requirement [50-55].

Monitoring of patients on ULT: After dose titration of ULT, sUA levels should be monitored monthly or once in two months [42,56]. Sustained low levels of sUA are necessary for some important physiological roles, such as neuroprotection. Hence, the sUA levels should be closely monitored to avoid decline below the targeted range (<3 mg/dL) [5]. Patients should be monitored till target sUA levels are maintained, and stable condition is achieved [42,55,56]. ULT can be temporarily discontinued if sUA level drops below 3 mg/dL [57].

Maintenance therapy with urate lowering agents: There is no clarity in the existing guidelines regarding the maintenance of sUA levels within the desired range (3-6 mg/dL) with ULT in symptomatic hyperuricaemia patients. Once the target sUA levels are reached, a low and constant maintenance dose could be used to maintain sUA levels within a desired range. Maintenance therapy with urate-lowering agents would be beneficial because to avoid gout flares, discontinuation of ULT is not recommended after target sUA levels are achieved [46]. After target sUA levels and stable disease status are achieved, the patient should be continued on the same dose of ULT or maintained on low-dose therapy and reviewed once in 6 to 12 months [42,55,56]. If target sUA level is not maintained, dose of the ULT should be adjusted [42]. ULT should be continued indefinitely at the maintenance dose, unless modifiable risk factors are successfully addressed, and clinical cure is achieved [43,46,55].

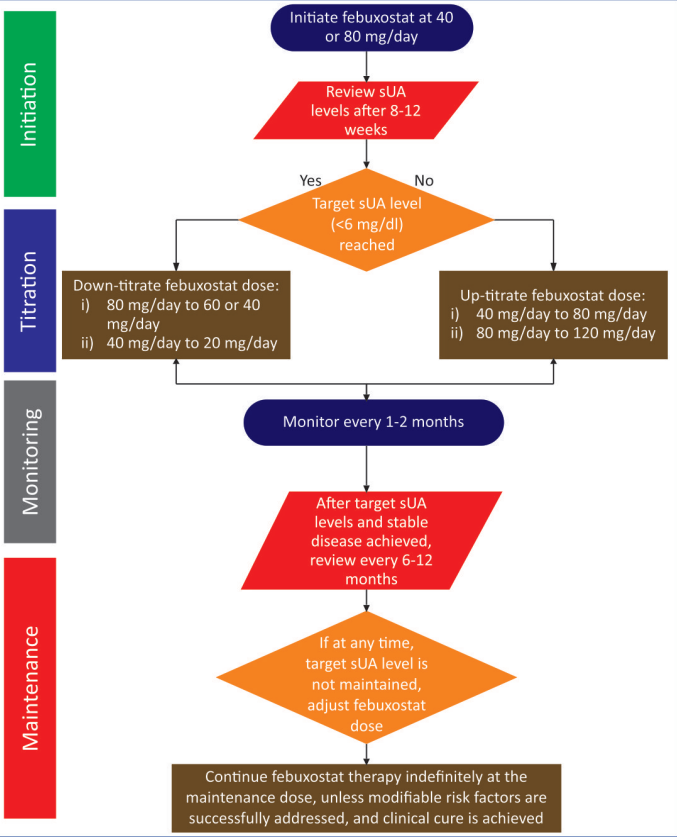
Simplified algorithm for dosage titration, monitoring and long-term maintenance of hyperuricaemia with ULT: For allopurinol, the treatment algorithm is nearly consistent across all global and national guidelines suggesting initiation of allopurinol at a dose of 100 mg/day. Periodic monitoring (once every 2-4 weeks) is recommended, and the dosage can be increased by 50-100 mg/day, to achieve target sUA levels [42]. In case of febuxostat, the IFH recommends treatment initiation with 40 mg/day, which can be up-titrated to 120 mg/day, if necessary [42]. However, there is lack of clarity on the down-titration with febuxostat after target sUA level is reached. Temporary discontinuation of ULT is not advisable since because it increases the likelihood of flares [46], while continuation of unaltered therapy might lower the sUA levels below the physiological range (<3 mg/dL), which is not desirable [5].

Several studies with lower doses of febuxostat showed similar efficacy and safety as allopurinol [Table/Fig-6] [51-54,58,59]. Down-titration of febuxostat to low doses, such as 20 mg/day, might aid maintenance of therapy without the concern of undesired lowering of sUA levels or flares. Based on the review of current literature and

Author and year of publication	Study design	Patient population	Intervention and dose	Results
Kamatani N et al., 2011 [51]	Multicentre, open-label 52-week dosing trial involving dose escalation. Safety and efficacy of febuxostat were evaluated.	172 hyperuricaemia and gout patients aged >20 years	Febuxostat at initial dosage of 10 mg/day followed by 20 mg/day after 2 weeks, and 40 mg/day from 6 weeks. Ten weeks onward 60 mg/day if sUA levels >6 mg/dL, or else 40 mg/day	At 52 weeks, 84.5% and 85.0% of patients in the 40- and 60-mg groups, respectively, achieved target sUA levels (≤6 mg/dL). No differences were observed in safety and efficacy of different doses up to a dose of 60 mg/day among patients with normal renal function or mild to moderate renal dysfunction.
Shibagaki Y et al., 2014 [52]	A prospective, open-label, non controlled study to evaluate the safety, efficacy, and renal effect of febuxostat	70 hyperuricaemia patients with CKD stages 3b, 4, and 5	Febuxostat initial dose of 10 mg/day, titrated after 4 weeks to 20 mg/day, followed by maintenance dose of 40 mg/day at week 8 (or 60 mg/day in 12 weeks, if required) and continued till 24 weeks, even if the target sUA level (≤6.0 mg/dL) was achieved with a lower dose.	By 24 weeks, reduction in sUA levels was <40% in CKD stage 3b and >50% in CKD stages 4 and 5. More than 70% of patients achieved target sUA levels.
Kamatani N et al., 2011 [53]	A multicentre randomised, placebo-controlled, double-blind phase 3 trial to evaluate safety and efficacy of febuxostat	103 hyperuricaemia and gout patients aged >20 years	Febuxostat (20 or 40 mg/day) vs placebo for 8 weeks	91.2% patients in the febuxostat 40 mg/day group, 45.7% in the 20 mg/day group, and 0 in the placebo group achieved sUA levels ≤6 mg/dL after 8 weeks. No severe or significant adverse reactions were noted.
Zhang F et al., 2019 [54]	A phase 3, multicentre, randomised, active-controlled, three-arm, parallel-group, double-blind, non inferiority study comparing the efficacy and safety of febuxostat with allopurinol, using uptitration method	472 hyperuricaemic subjects with or without gout and with or without complications (abnormal glucose tolerance, lithangiuria, hypertension, or hyperlipidaemia)	20 mg/day dose of febuxostat was uptitrated to 40 mg/day and 80 mg/day up to 16 weeks, which was then maintained till 24 weeks. Allopurinol was initiated with 100 mg/day and uptitrated to 300 mg/day.	Non inferiority was not reached for allopurinol 300 mg/day vs febuxostat 40 mg/day. Superiority was observed at 16 weeks for 60 mg/day febuxostat vs 300 mg/day allopurinol and at 24 weeks for 80 mg/day febuxostat vs 300 mg/day allopurinol.
Tojimbara T et al., 2014 [58]	A single-centre, prospective study evaluating the safety and efficacy of febuxostat	22 renal transplant recipients with hyperuricaemia	Febuxostat at 10-20 mg/day	sUA levels were significantly lowered after treatment as compared to before treatment (5.7±0.7 mg/mL vs 8.0±0.8 mg/mL; p-value <0.001). Target sUA levels (<6 mg/dL) were achieved by 73% of patients.
Liu X et al., 2019 [59]	A single-centre, prospective cohort study to assess the efficacy and safety of febuxostat vs allopurinol	208 (n=112 on febuxostat and n=96 on allopurinol) subjects with symptomatic hyperuricaemia and CKD stages 3-5 who had not undergone renal replacement therapy.	Febuxostat 40 mg/day, treatment and 20 mg/day maintenance dose, or allopurinol 100 mg/day	Target sUA levels (<360 µmol/L) were achieved by 96.4% of participants in the febuxostat group and 37.5% in the allopurinol group, at 6 months. At 6 months, eGFR increased in the febuxostat group from 28.45 to 30.65 mL/min/1.73 m^2 and decreased in the allopurinol group from 28.06 to 24.39 mL/min/1.73 m^2. With 20 mg/day dose of febuxostat, 83% of patients remained below target sUA levels.

[Table/Fig-6]: Clinical studies showing efficacy of dose titration with febuxostat or febuxostat as low-dose maintenance therapy [51-54,58,59].
CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; sUA: Serum uric acid

existing guidelines, the experts developed the following algorithm on hyperuricaemia management with febuxostat, delineating the details of frequency of monitoring, titration doses and maintenance therapy [Table/Fig-7].



[Table/Fig-7]: Algorithm for initiation, management, and maintenance of hyperuricaemia with febuxostat.
sUA: Serum uric acid

Safety of urate-lowering drugs: The active metabolite of allopurinol, oxypurinol, undergoes renal excretion and gets accumulated in patients with renal impairment leading to complications, thereby necessitating dose reductions [42]. Although several clinical studies have demonstrated the benefits of allopurinol in patients with co-morbidities [44], allopurinol therapy is associated with serious adverse effects including rash, gastrointestinal effects, and Stevens-Johnson syndrome. Another rare and potentially lethal adverse effect of allopurinol is allopurinol hypersensitivity syndrome (AHS). Further, allopurinol interacts with multiple drugs including amoxicillin and ampicillin, which can cause skin rashes [42]. Use of allopurinol is known to be problematic in the elderly population and in those with HLA-B*5801 antigen thatprimarily comprise the Asian population [48].

The common side-effects associated with febuxostat are nausea, diarrhoea, and elevated levels of liver enzymes. However, the incidence of side effects with febuxostat has been found to be low even at high doses (≥120 mg). Notably, the sides effects associated with febuxostat are not affected by age and impaired liver or renal function. Very few medications are known to interact with febuxostat, such as azathioprine [42].

Cardiovascular safety of febuxostat versus allopurinol: The findings of the cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular morbidities (CARES) trial showed numerically higher all-cause and CV mortality with febuxostat as compared to allopurinol [60]. These findings resulted in the issue of a "black box" warning by the FDA on the risk of CV death with febuxostat use in patients with pre-existing CVD [48]. Subsequently, a population-based cohort study showed that there was no difference in the risk of all-cause mortality and CV events between gout patients (aged ≥65 years) initiated on febuxostat versus allopurinol [61]. A meta-analysis, involving 10 RCTs and 14,402 subjects, evaluated the risk of Major Adverse Cardiovascular Events (MACE) in gout and hyperuricaemia patients using febuxostat. Nine out of these ten RCTs included subjects with a prior history of either CAD and HF, or hypertension. The findings revealed that febuxostat did not affect the risk of MACE but increased the risk of CV death (p-value=0.03) [62].

Recently published results of the randomised non inferiority Febuxostat versus Allopurinol Streamlined Trial (FAST) trial involving 6128 gout patients with previous CVD established that febuxostat (80-120 mg once daily) was non inferior to allopurinol (100-900 mg once daily) in terms of primary CV endpoints. Further, long-term use of febuxostat was not associated with serious adverse events or an increased risk of death compared to allopurinol [63]. The regulatory warnings may need to be relooked into based on these recent findings about febuxostat use in patients with CVD [63].

Duration of Urate Lowering Therapy (ULT): Hyperuricaemia is termed as primary if it is associated with any underlying cause and secondary if no underlying cause leading to hyperuricaemia can be identified [64]. Duration of ULT is markedly different for primary and secondary hyperuricaemia. While for primary hyperuricaemia, ULT should be continued indefinitely, in case of secondary hyperuricaemia, ULT may be discontinued once stable sUA level is achieved and the underlying risk factor for hyperuricaemia is addressed [43].

HYPERURICAEMIA AWARENESS

There is a need for strong awareness about hyperuricaemia, especially among primary care physicians regarding when to treat and when not to treat hyperuricaemia. Further, awareness is needed on the target sUA levels to be achieved, and about all the co-morbidities that are associated with hyperuricaemia. Hyperuricaemia screening could be included in the annual general health check-up plans, as hyperuricaemia is often asymptomatic. Adherence to therapy is a challenge in hyperuricaemia management. Repeated patient counselling on the importance of treatment adherence in improving the quality of life is of utmost importance. Management of asymptomatic hyperuricaemia is challenging as it is difficult to convince asymptomatic patients to undergo routine evaluation and therapy if necessary.

CONCLUSION(S)

The prevalence of hyperuricaemia is increasing, both globally and in India. The major challenge is related to initiation of therapy in asymptomatic hyperuricaemia patients. There is a need for enhanced awareness among physicians in India about the importance of lowering sUA levels and optimal management of hyperuricaemia. Physicians should be guided on carefully analysing patient condition and lifestyle before initiating ULT. Early diagnosis and streamlined management practices would aid in lowering the growing burden of hyperuricaemia in the country.

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