IN THE NAME OF GOD

Hyperuricemia and gout in kidney transplant recipients

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Objectives

- ❑ Definition
- ❑ Hyperuricemia Epidemiology & Risk factors
- ❑ Serum Uric Acid Levels and Kidney Transplant Outcomes
- ❑ Clinical Features
- ❑ Diagnosis
- ❑ Treatment

Definition

- Hyperuricemia is a common complication after kidney transplantation, and may adversely affect graft survival.

- Hyperuricemia was defined as a serum uric acid concentration of **at least 7.0 mg/dL in men and 6.0 mg/dL in women.**

Curr Med Res Opin. 2018 Jul;34(7):1193-1199

EPIDEMIOLOGY

- The prevalence of hyperuricemia in recipients of a renal allograft has been shown to range **from 19% to 55%** in patients whose immunosuppressive regimen did **not include CsA** and from **30% to 84%** in patients treated **with CsA.**

- In the same series, **incident gout** was not observed in non-CsA treated patients, whereas it ranged from 2.0% to 28% following CsA therapy.

Emphasis

- Hyperuricemia is associated with **increased BMI** and **decreased eGFR**.
- **In women**, was also associated with a **worse lipid profile**.
- Hyperuricemia can be a further factor for the occurrence of cardiovascular complications in this population.

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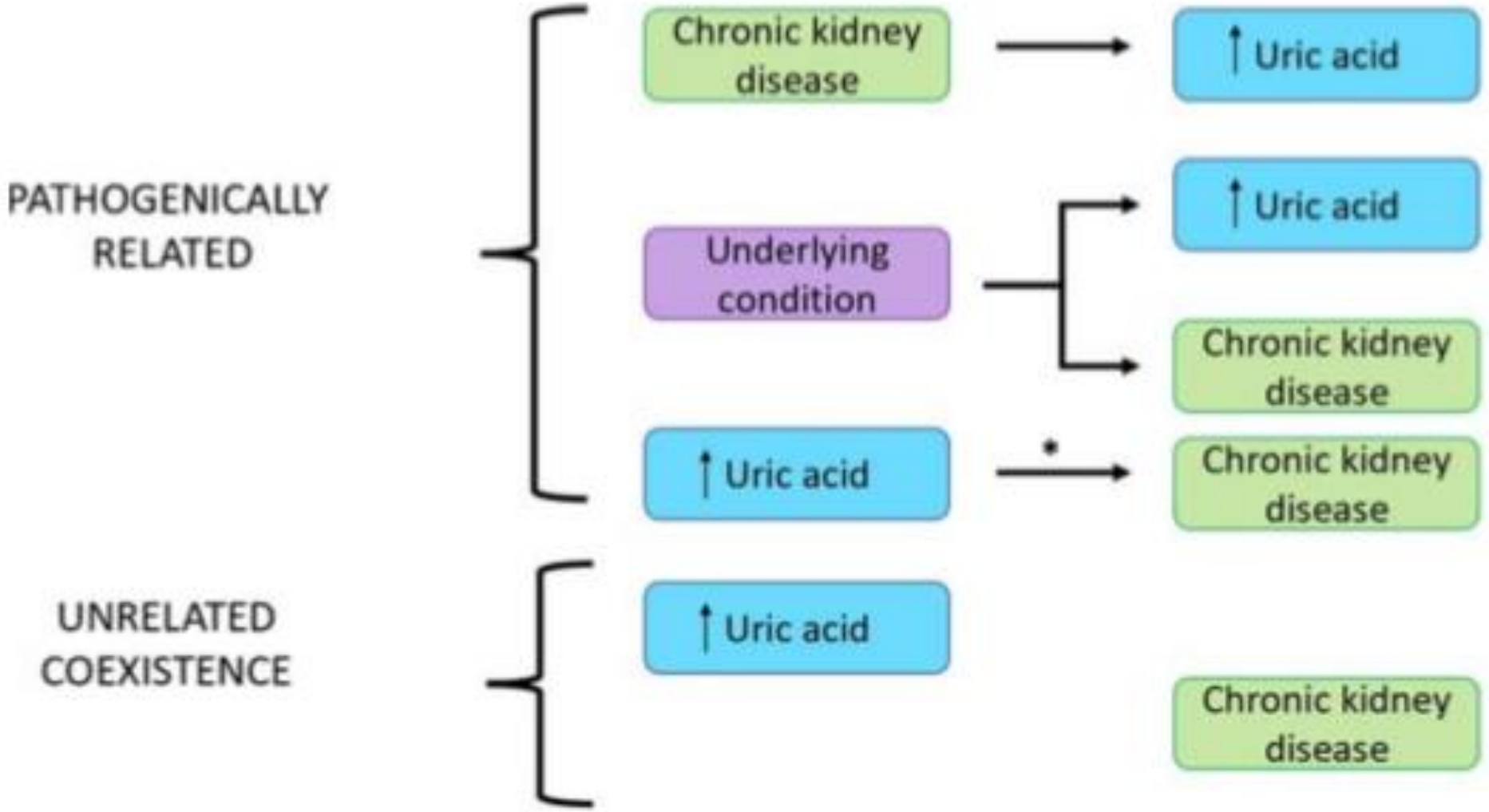
Possible relations between serum uric acid and chronic kidney disease



Uric acid levels & Renal transplantation

- There was no difference in graft loss, general mortality, and cardiovascular events between normo-uricemic and hyperuricemic groups. *are still controversial*

- Increased uric acid levels contribute to eGFR decline in patients with renal transplantation.

- There are no randomized clinical trials showing a real benefit in reducing uric acid in these patients.

World J Nephrol. 2015 Jul 6; 4(3): 324–329.

Uric acid levels & Renal transplantation…

Hyperuricaemia causes graft dysfunction through the activation of proinflammatory mediators, which eventually elicit endothelial and renal microvasculature damage.

Medicina 2020 , 56 , 95 ; doi: 10.3390 /medicina 56030095

Hyperuricemia & Endothelial dysfunction

- smooth muscle cell proliferation and inflammation → this occurs through increased production of:
  - Growth factors (PDGF)
  - Vasoconstrictive substances (cyclooxygenase-2 induced thromboxane and angiotensin II)
  - Proinflammatory molecules (C-reactive protein and monocyte chemoattractant protein).
- HU can induce oxidative stress and endothelial dysfunction, resulting in the development of systemic and glomerular hypertension; reduced renal blood flow and gradual decline in kidney function.

Medicina 2020 , 56 , 95 ; doi: 10.3390 /medicina 56030095

Hyperuricemia risk factors

- ❑ Decreased GFR & tubular damage
- ❑ Use of diuretics
- ❑ Male gender
- ❑ Diabetes mellitus
- ❑ Hypercalcemia
- ❑ Higher body weight
- ❑ Treatment with calcineurin inhibitors

Medicina 2020 , 56 , 95 ; doi: 10.3390 /medicina 5603009

Post-transplant serum UA levels & KT Outcomes

- The mean serum uric acid level **during the first 6 months after transplantation** has been reported to be an independent predictor of long-term graft survival and short-term graft function.

- Early-onset hyperuricemia **at 3 months after KT** showed an increased risk for graft failure.

PLoS ONE 2018 , 13 (12): e 0209156 . https:// doi.org/ 10.1371 /journal.pone. 0209156

Serum Uric Acid Levels and KT Outcomes…

The association of uric acid with human diseases beyond **kidney stones** was initially described in patients with **gouty arthritis**, but has since extended to **other conditions** such as**:**

- ❑ Hypertension
- ❑ Cardiovascular disease
- ❑ Cerebrovascular disease
- ❑ Metabolic syndrome
- ❑ Preeclampsia
- ❑ Kidney Disease

Am J Kidney Dis. 2017;70(6):752-753

Uric acid and various disease states

Uric acid's potential role in:

- ❑ endothelial dysfunction (by nitric oxide depletion)
- ❑ vascular smooth muscle proliferation
- ❑ inflammation
- ❑ oxidative stress
- ❑ activation of the renin-angiotensin system

Am J Kidney Dis. 2017;70(6):752-75

Post-transplant uric acid level and renal allograft fibrosis

These changes lead to progressive renal fibrosis:

- inhibition of endothelial nitric oxide
- activation of the renin angiotensin system
- inducing vasoconstriction
- vascular smooth muscle cell proliferation

- **By comparing Banff pathologic scores from renal biopsies:**

higher uric acid was associated with more severe fibrosis in transplanted kidneys.

Scientific Reports 2018 , 8:11601 . https:// doi.org/ 10.1038 /s 41598 - 018 – 29948-9 - 9

سوال ۱

نحوه مانیتور سطح اسید اوریک سرم بعد از گذشت یک سال از پیوند کلیه به چه صورت است؟

A. هر ۳ماه تا یک سال وسپس هر ۶ماه
B.هر ۶ماه تادوسال وسپس سالانه
C.هر ۳ماه تا دو سال وسپس هر ۶ ماه
D. هر ۶ ماه تا یک سال وسپس سالانه

Monitoring

❖ **Serum urate levels should be monitored:**

- at the time of routine laboratory monitoring in the first year after transplantation
- every six months for the next two years
- then annually

❖ **Serum urate levels should also be monitored:**

after changes in comorbid disorders and their treatments (especially diuretics or other medications that may alter urate levels)

Table 72.3 Routine Surveillance Laboratory Testing After Transplantation

	<6 Months After Transplantation		>6 Months After Transplantation	
Test	**q 2 wk**	**q mo**	**q 2 mo**	**q 12 mo**
CBC	x	x	x	
Electrolytes, glucose, BUN	x	x	x	
Creatinine	x	x	x	
Drug level*	x	x	x	
Albumin, calcium, phosphate, uric acid†	x	x	x	
Liver enzymes	x	x	x	
Urinalysis	x	x	x	
Lipid profile				
BK virus‡				x§

Brenner 2016

CLINICAL FEATURES

- The clinical manifestation of gout, even if de novo, can occur **within months after transplantation**.

- Sometimes characterized by greater severity than is usual in nontransplanted.

DIAGNOSIS

❖ new-onset symptoms and signs suggestive of a first gout flare:

Arthrocentesis and synovial fluid analysis and culture should be performed to establish the diagnosis of gout and to exclude alternative diagnoses, including joint infection.

Ruling out septic arthritis is especially important in transplant patients who are receiving chronic immunosuppression therapy.

diagnosis of septic arthritis **must always** be excluded prior to the administration of intraarticular glucocorticoids

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DIAGNOSIS…

- **prior documented gout flares who are experiencing a recurrence of acute joint inflammation:**

initiate flare treatment without a preceding arthrocentesis if the patient's symptoms and signs are the same as those encountered in prior gout flares and do not include fever, chills, or other symptoms/signs of local or regional infection.

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TREATMENT OF GOUT FLARES

- Patients receiving ongoing urate-lowering therapy for prevention of recurrent gout flares **should not discontinue** this therapy if a gout flare occurs, since there is no apparent benefit in temporary discontinuation, and later re-initiation may predispose the patient to another flare.

- If a gout flare is accompanied by **AKI** in a patient who is receiving urate-lowering therapy, this agent **should be discontinued** until an accurate and stable GFR can be reestablished.

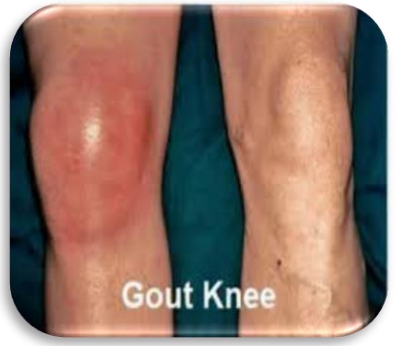
Up to date2021

سوال ۲

آقای ۶۳ ساله که ۶ماه قبل تحت پیوند کلیه قرار گرفته است وبدون سابقه قبلی نقرس به علت درد والتهاب فعال در ۳ مفصل اندام تحتانی از سه روز قبل مراجعه کرده است . در معاینه شواهدی به نفع عفونت مفاصل ندارد .
کدامیک از درمانهای زیر را برای بیمار فوق انتخاب می کنید؟

A.تریامسینولون داخل مفصلی
B.قرص پردنیزولون
C.کلشی سین
D. ناپروکسن

TREATMENT OF GOUT FLARES
Patients with new-onset gout



In patients with a **first gout flare who have one or two actively inflamed joints** arthrocentesis with joint fluid aspiration followed by intra-articular injection of glucocorticoids:

- ✓ **Triamcinolone acetonide** (40 mg for a large joint [eg, knee], 30 mg for a medium joint [wrist, elbow, or ankle], and 10 mg for a small joint)
- ✓ **or equivalent doses of methylprednisolone acetate**.

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Patients with new-onset gout…

- In patients who have **more than two actively inflamed joints or who have one or two actively inflamed joints but are unable to receive intra-articular glucocorticoids,** suggested **oral anti-inflammatory agents:**

(eg, prednisone or prednisolone) **doses of 30 to 40 mg once daily and continue this dose for five days.**

- **In patients with glucocorticoid intolerance: low-dose colchicine and NSAIDs are alternative options.**

Suggested low-dose colchicine in patients initiating antiinflammatory treatment **within 24 hours of symptom onset**.

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Colchicine

Colchicine should generally **not be given** to patients if treatment is initiated **more than 36 hours after symptom onset**.

In addition, colchicine **should not be given** to **kidney transplant recipients** with the following:

- ✓ **Concomitant use of cyclosporine or another medication that strongly inhibits the cytochrome P450 system component.**
- ✓ **eGFR <30 mL/min.**
- ✓ **Moderate to severe hepatic impairment.**
- ✓ **Concomitant renal and hepatic impairment of any degree.**

In transplant recipients who are receiving tacrolimus (rather than cyclosporine), approach to dosing colchicine:

- In patients with an **eGFR of 45 to <60** mL/min per 1.73 m2, start colchicine on **day 1** at an initial dose not to exceed **0.6 mg** (given as 0.3 mg at time 0 and 0.3 mg in 6 to 8 hours), followed by **0.3 mg on day 2 and then 0.3 mg every 2 days**.

- Thereafter until flare symptoms abate: The colchicine dose can then be reduced to no more than 0.15 mg every 2 days and withdrawn within 48 hours of complete flare resolution.

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In transplant recipients who are receiving tacrolimus (rather than cyclosporine), approach to dosing colchicine:

- In patients with an **eGFR of 30 to <45 mL/min per 1.73 m^2**, we start colchicine on **day 1** at an initial dose not to exceed **0.3 mg** (given as 0.15 mg at time 0 and 0.15 mg in 6 to 8 hours), followed **by 0.15 mg on day 3 and 0.15 mg every 3 days.**

- thereafter until flare symptoms abate:

The colchicine dose can then be reduced to no more than 0.075 mg given every 3 days, and can be withdrawn within 48 hours of complete flare resolution.

In patients who cannot receive colchicine

- Treat with a potent oral NSAID, such as **naproxen** (500 mg twice daily) or **indomethacin** (50 mg three times daily).

- **A short course of NSAIDs** (**five to seven days**) can usually be administered in kidney transplant recipients without significant adverse consequences

- NSAIDs are **most effective** when treatment is initiated **within 48 hours of symptom onset.**

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NSAIDS

The NSAID can be **discontinued within <u>two days after complete resolution of the flare</u>**.

The use of NSAIDs should be avoided in:

- ✓ older patients **(>60 years old**)
- ✓ those with active peptic ulcer disease
- ✓ eGFR <50 mL/min per 1.73 m^2
- ✓ active cardiovascular disease
- ✓ NSAID allergy

NSAIDs should not be used for gout flare prophylaxis in kidney transplant recipients.

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In patients who are unable to take oral medications and are not candidates for intra-articular glucocorticoids:

1. Parenteral (intravenous or intramuscular) glucocorticoids.

2. An alternative therapeutic approach is the off-label use of anakinra, a short-acting IL-1 receptor antagonist, given as three or more, as required by clinical response daily subcutaneous injections of 100 mg each.

Patients with a prior history of gout

- The use of **oral glucocorticoids** should be accompanied by a **more prolonged taper over 10 to 21 days.**

- In a patient who is **receiving** colchicine **or** who has been treated with colchicine for a gout flare **within the past 14 days, discontinue colchicine and treat the gout flare with oral or intraarticular glucocorticoids.** resume gout flare prophylaxis with colchicine **after complete resolution** of the flare.

- In patients who are not receiving oral prednisone as part of their maintenance immunosuppression regimen, **switch from colchicine to low-dose prednisone (2.5 to 7.5 mg daily) for gout flare prophylaxis if repeated flares indicate failure of colchicine prophylaxis at an acceptable colchicine dose.**

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Pharmacologic urate-lowering therapy

Indicated in patients with frequently recurrent flares or those who develop tophi or joint injury.

- **Xanthine oxidase inhibitors (XOIs):** allopurinol and febuxostat.
- **Uricosuric agents:** probenecid in patients with eGFR ≥50, benzbromarone, losartan, and lesinurad.
- **Uricase:** pegloticase and rasburicase.

Asymptomatic hyperuricemia is not an indication for urate-lowering therapy in kidney transplant patients.

Selection of urate-lowering therapy

- First-line therapy (allopurinol monotherapy)
- Second-line therapy (uricosuric agent monotherapy)
- Third-line therapy (combination of allopurinol and uricosuric agent)
- Fourth-line therapy (febuxostat monotherapy)

Pharmacologic urate-lowering therapy…

- In most kidney transplant recipients, suggested: Allopurinol as **first-line urate-lowering therapy.**

- **Febuxostat** especially, concerns about a greater frequency of adverse cardiovascular events (particularly cardiovascular death) with febuxostat compared with allopurinol.

- **Allopurinol and febuxostat should be avoided in patients treated with azathioprine**. if an XOI must be used, reduce the azathioprine dose (**by at least 50 percent**) and carefully monitor the WBC count.

Up to date2021
N Engl J Med 2018; 378:1200

Allopurinol

- In patients with an **eGFR of >60** mL/min per 1.73 m^2, initiate allopurinol treatment at 100 mg daily and titrate the dose upward by 100 mg **every two to four weeks** to the minimum dose required to achieve and **maintain the goal range of serum urate-lowering of <6 mg/dL or, in patients with tophaceous gout, <5 mg/dL.**

- In patients with an **eGFR of 30 to <60** mL/min per 1.73 m^2, initiate allopurinol at a dose of 50 mg once daily and titrate the dose upward in 50 mg increments **every three to four weeks** to the minimum dose needed to achieve and maintain the urate-lowering goal range.

- In patients with an **eGFR of <30** mL/min per 1.73 m^2, we initiate allopurinol at a dose equivalent to ≤1.5 mg/day per mL/min eGFR

Ann Rheum Dis 2017; 76:1522

Antiinflammatory prophylaxis during initiation of urate-lowering therapy

- Gout flares are common early in the course of urate-lowering therapy.

- administer either **colchicine or oral glucocorticoids** for **gout flare prophylaxis**
  - **colchicine 0.15 to 0.6 mg daily or every other day**
  - **prednisone 2.5 to 7.5 mg once daily**

- **The duration of flare prophylaxis** :**3-6 months after the target serum urate level** is achieved and confirmed in patients without tophi and for the same duration after the resolution of tophi in patients with more advanced gout.

Up to date2021
Arthritis Care Res (Hoboken) 2012; 64:1447

Antiinflammatory prophylaxis during initiation of urate-lowering therapy…

Do **not** use NSAIDs for gout flare prophylaxis in kidney transplant recipients.

- NSAIDs can usually be used for the **short-term treatment** of a gout flare without significant adverse consequences.

- **longer-term prophylaxis** with NSAIDs is a potential concern since **reduction in GFR** and **worsening calcineurin inhibitor nephrotoxicity**.

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Monitoring the response to urate-lowering therapy

- In **all kidney transplant** recipients, **monitor serum urate levels monthly**

- **Once the serum urate target is achieved: monitor serum urate levels every three months for the first year** and **every six months thereafter**.

- In kidney transplant recipients receiving **allopurinol or febuxostat**, monitor **liver function tests (serum aminotransaminases and serum bilirubin) three months after initiation and then every 6 to 12 months.**

- In kidney transplant recipients receiving **colchicine** during initiation of urate-lowering therapy, **monitor serum creatine kinase levels once or twice yearly**, especially in patients receiving interacting drugs, **such as statins**.

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clinical benefits of urate-lowering pharmacotherapy

- The clinical benefits is usually demonstrable within **two to three weeks of initiation or dose titration.**

- Reductions in flare frequency or severity are often not apparent until after **6 to 18 months** of urate-lowering therapy (even longer in the case of tophus resolution).

- appear to depend upon the extent of baseline urate crystal burden and magnitude of serum urate reduction achieved.

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SUMMARY

- ✓ Reduced uric acid excretion can occur after kidney transplantation and more common among patients treated with calcineurin inhibitors (especially cyclosporine)
- ✓ serum urate levels should be monitored at the time of routine laboratory monitoring in the first year after transplantation, every six months for the next two years, and then annually.
- ✓ clinical manifestation of gout, even if de novo, can occur within months after transplantation and is sometimes characterized by greater severity than is usual in nontransplanted patients.
- ✓ Asymptomatic hyperuricemia is not an indication for urate-lowering therapy.
- ✓ the recommended target serum urate level with urate-lowering therapy is <6 mg/dL in most patients and <5 mg/dL in patients with tophi and/or joint damage.
- ✓ Do **not** use NSAIDs for gout flare prophylaxis in kidney transplant recipients.
- ✓ Monitoring serum urate levels in response to urate-lowering therapy is critical.


Thanks
be happy