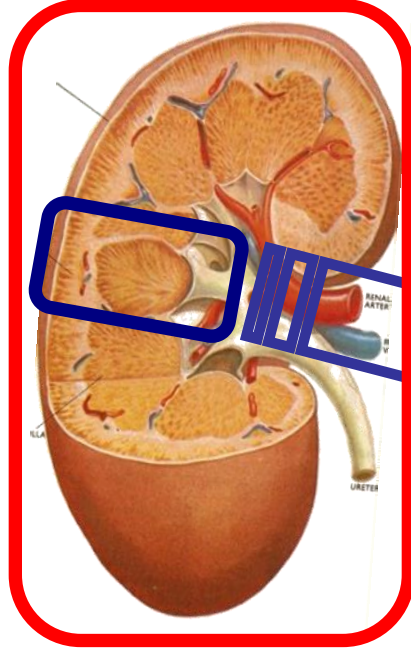


# Tubulointerstisyel Hastalıklara Klinik Yaklaşım

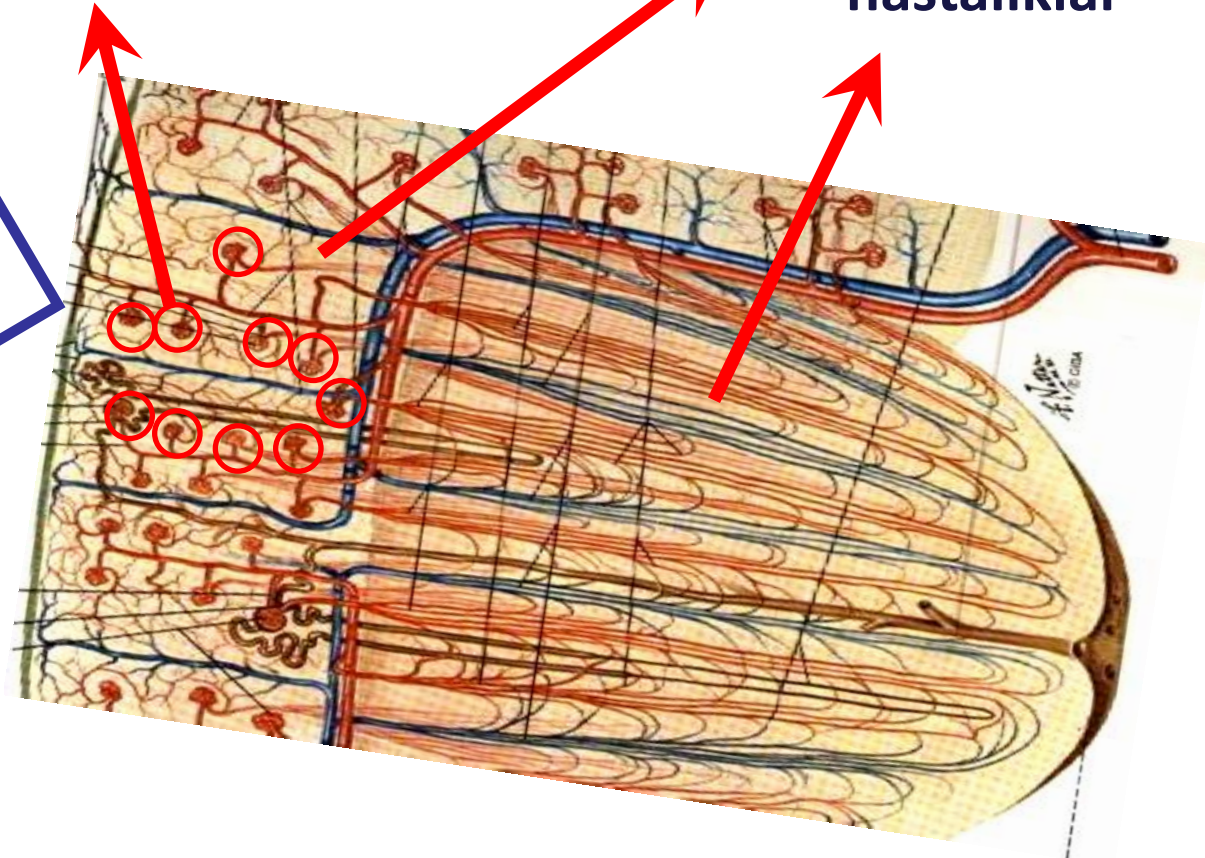
**Prof. Dr. Tefik Ecdar**  
İstinye Üniversitesi Tıp Fakültesi

# Böbrek Hastalıkları



Glomerüler hastalıklar

Tubulointerstisyel hastalıklar

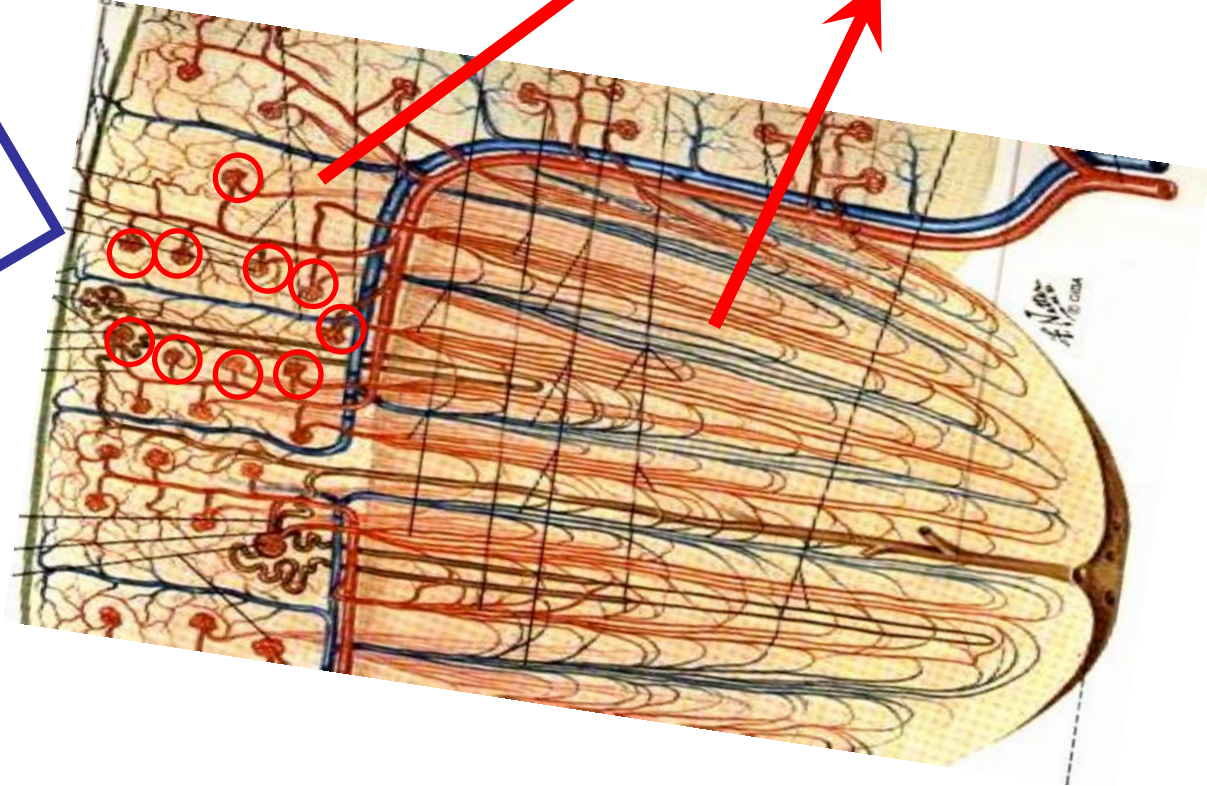
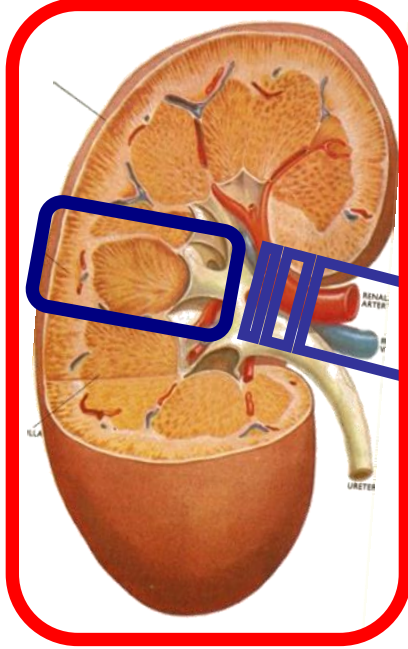


Böbrek yetersizliği:

- Akut
- Kronik

# Tubulointerstisyel Hastalıklar

- Primer
- Sekonder



**Böbrek yetersizliği:**

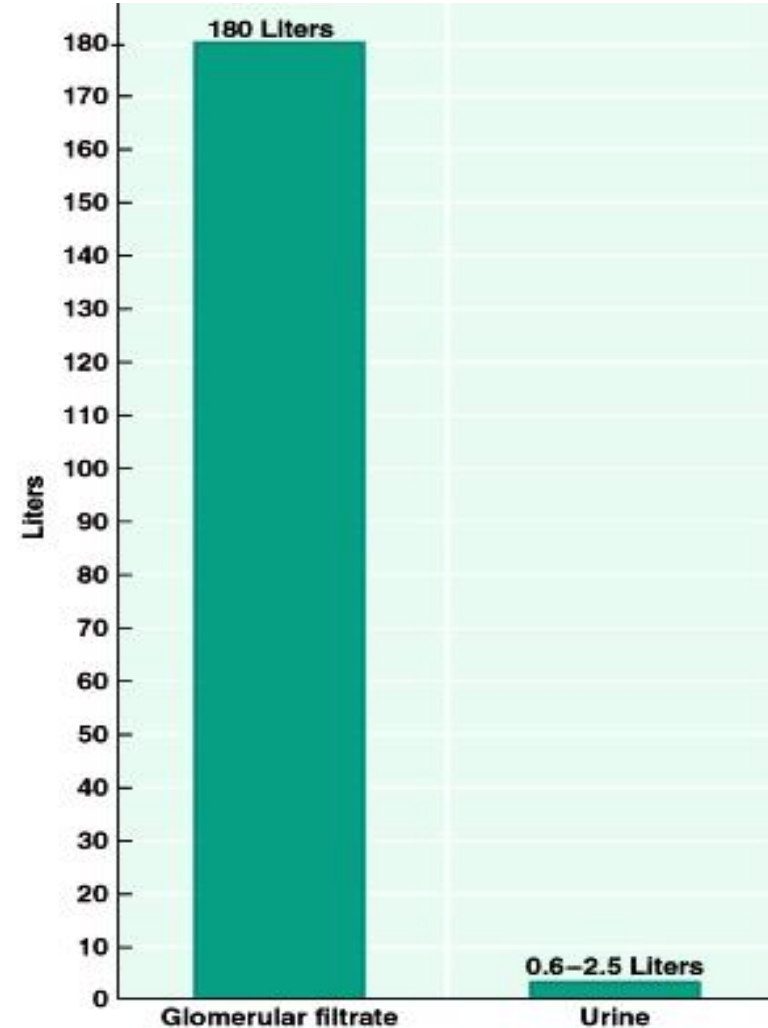
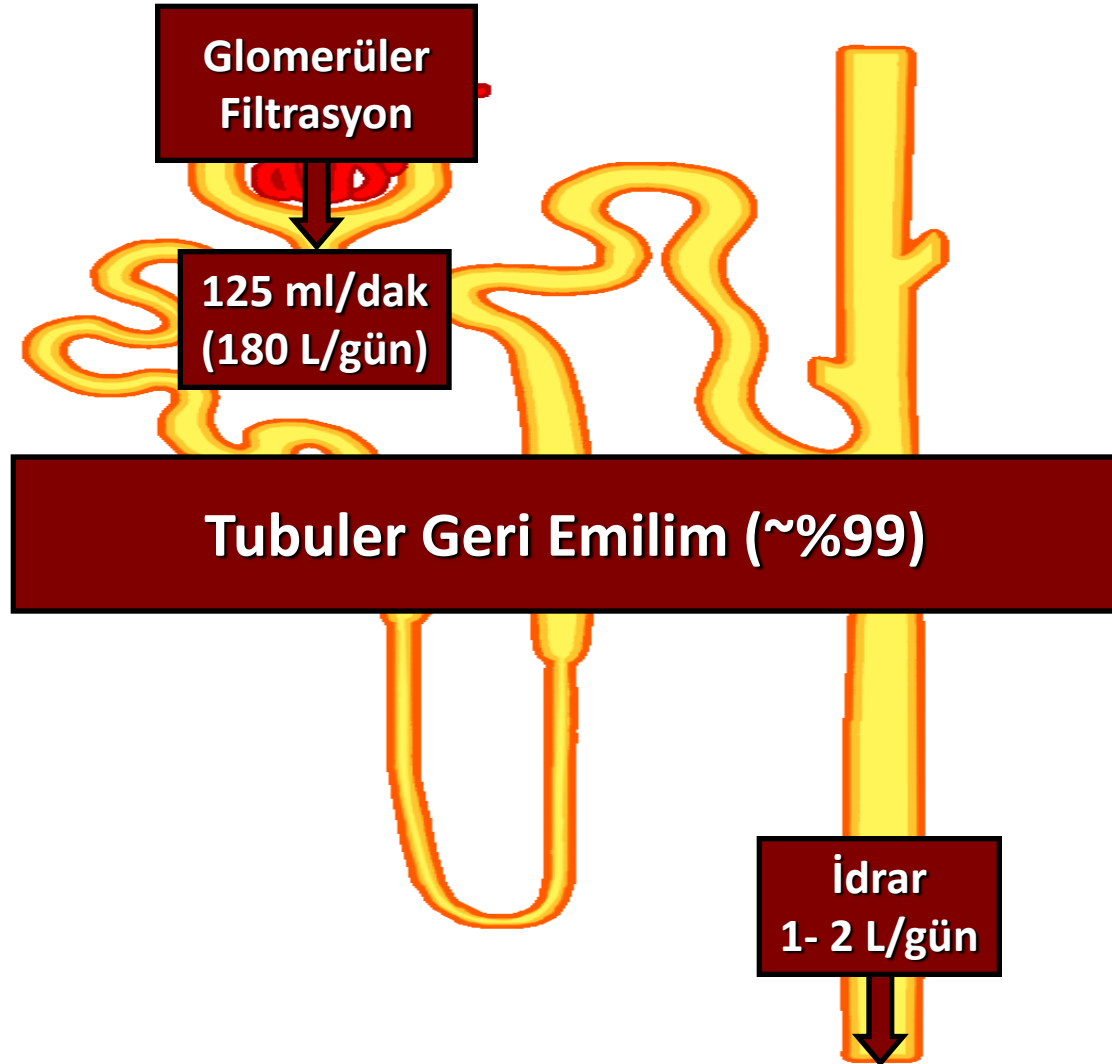
- Akut
- Kronik

# Tubulointerstisyel Nefropatiler (TİN)

- **Primer TİN**: Ön planda tubuluslarda ve interstisyumda hasara yol açan bir klinikopatolojik tablodur. Hastalığın ilerlemesi ile glomerüller ve damarlar da etkilenebilir.
- **Sekonder TİN**: Ön planda glomerülleri ve damarları etkileyen bir hastalığın seyri sırasında gelişen tubulointerstisyel hasara bağlı bir klinikopatolojik tablodur.

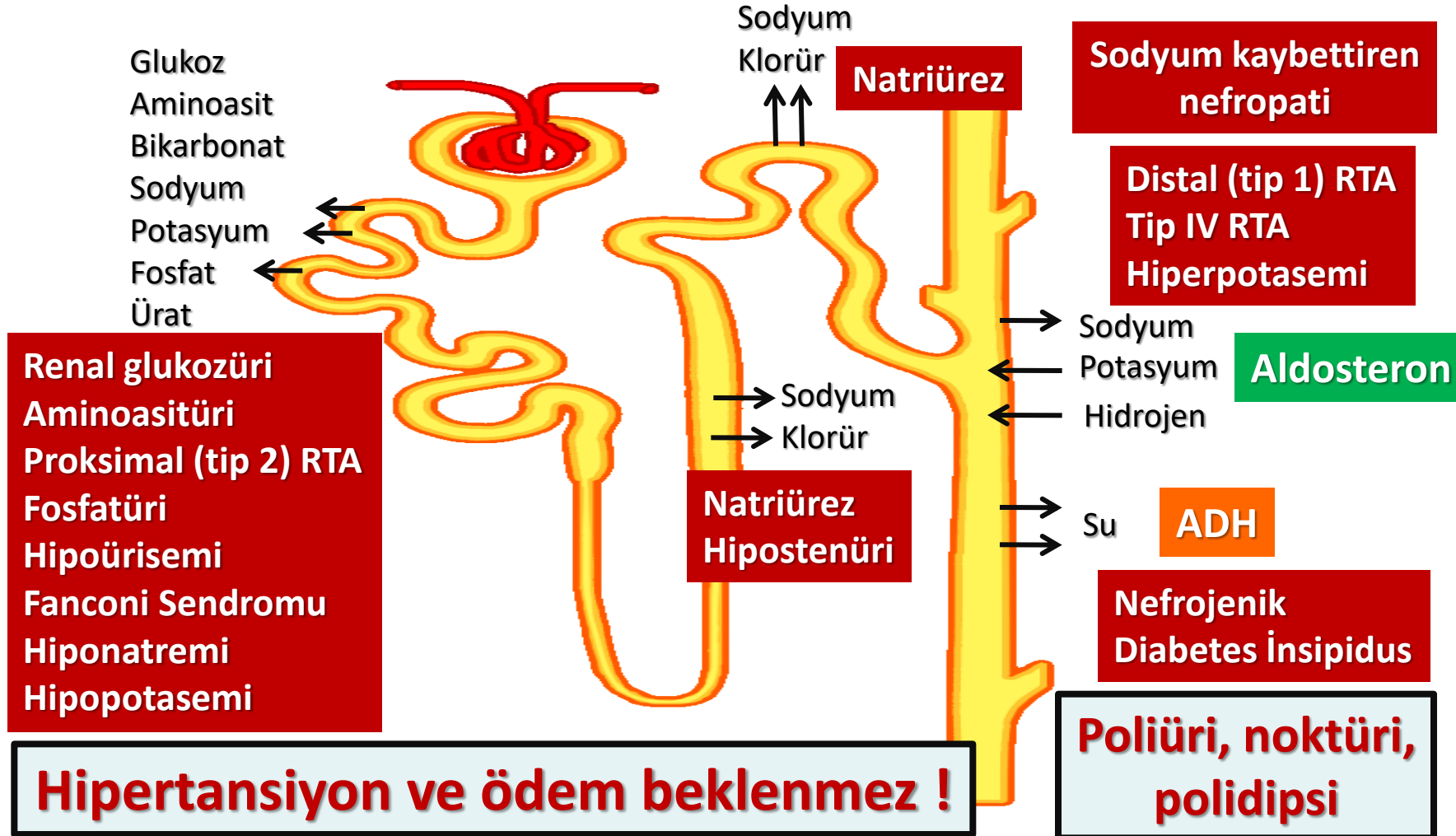


# Glomerüler Filtrasyon ve Tubuler Transport



# Tubulointerstisyel Hastalıklarda Klinik Bulgular

## Tubulus fonksiyon bozuklukları



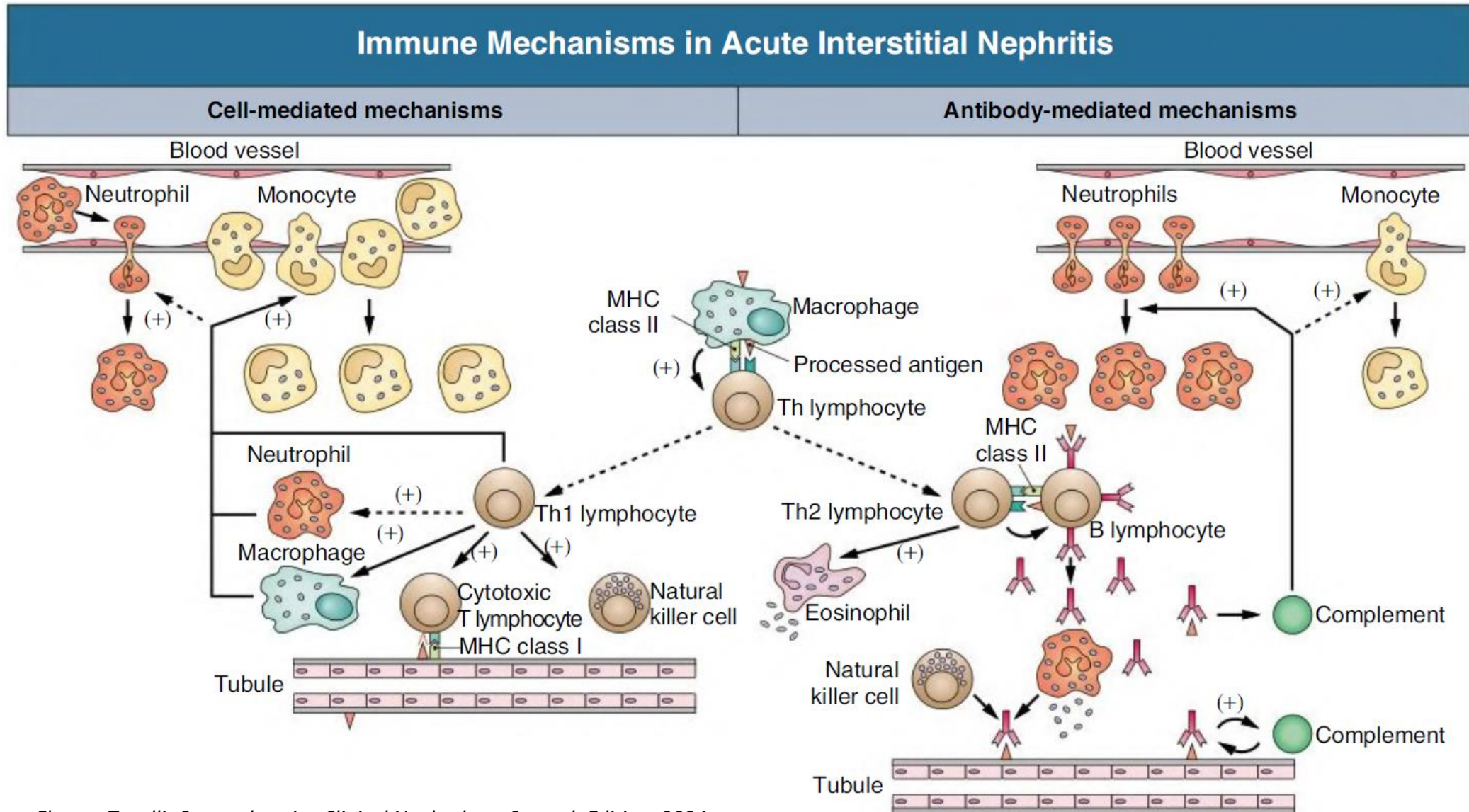
# Akut İnterstisyel Nefrit

## Etyoloji

- İlaçlar
- İnfeksiyonlar
- Sistemik Hastalıklar
- Neoplaziler
- İdyopatik
- Akut rejeksiyon

**Akut interstisyel nefritlerin %70 – 90'ında sebep ilaçlardır!**

# Akut İnterstisyel Nefrit





# Akut İnterstisyel Nefrite Yol Açabilen İlaçlar

<b>Antimicrobial Agents</b>	Minocycline	<b>Phenylbutazone</b>	Cytosine arabinoside
<b>Penicillins</b>	Nitrofurantoin <sup>a</sup>	Sulfasalazine	Gemcitabine
Amoxicillin	Piromidic acid	<b>Tolmetin</b>	Ifosfamide
<b>Ampicillin<sup>a</sup></b>	Polymyxin B <sup>a</sup>		Interleukin-2
Aztreonam	Quinine	<b>Antalgics</b>	Lenalidomide
Carbenicillin	<b>Rifampin<sup>a</sup> (rifampicin<sup>a</sup>)</b>	Aminopyrine	Methotrexate
Cloxacillin	Spiramycin <sup>a</sup>	Antipyrine	Pemetrexed
Flucloxacillin	<b>Sulfonamides<sup>a</sup></b>		Sorafenib
<b>Methicillin<sup>a</sup></b>	Teicoplanin	<b>Anticonvulsants</b>	Sunitinib
Mezlocillin	Telithromycin	Carbamazepine <sup>a</sup>	
Nafcillin	Tetracycline	Diazepam	<b>Others</b>
Oxacillin <sup>a</sup>	Vancomycin <sup>a</sup>	Lamotrigine <sup>a</sup>	<b>Allopurinol<sup>a</sup></b>
<b>Benzylpenicillin<sup>a</sup></b>		Levetiracetam	α-Methyldopa
Piperacillin		Phenobarbital (phenobarbitone)	Amlodipine
		<b>Phenytoin<sup>a</sup></b>	Azathioprine
<b>Cephalosporins</b>	<b>NSAIDs, Including Salicylates</b>	Valproic acid (valproate sodium)	Betanidine (bethanidine) <sup>a</sup>
Cefaclor	<b>Salicylates and Derivatives</b>		Bismuth salts
	<b>Acetylsalicylic acid (aspirin)</b>		
	Diflunisal <sup>a</sup>		
		<b>Diuretics</b>	

Açıklanamayan akut böbrek hasarı olan her hastada akut interstisyel nefrit düşünülmelidir.

<b>Ciprofloxacin</b>			
Levofloxacin <sup>a</sup>	Alclofenac	Famotidine	Exenatide
Moxifloxacin	Diclofenac	Ranitidine	Fenofibrate <sup>a</sup>
Norfloxacin	Fenclofenac		Fluindione
	Sulindac	<b>Proton Pump Inhibitors</b>	Gold salts
<b>Other</b>	<b>Zomepirac</b>	Esomeprazole	Griseofulvin
Acyclovir		Lansoprazole	Interferon
Azithromycin	<b>Enolic Acid Derivatives</b>	<b>Omeprazole</b>	Isotretinoin
Clarithromycin	Meloxicam	Pantoprazole	Liraglutide
Colistin	<b>Piroxicam<sup>a</sup></b>	Rabeprazole	Nifedipine <sup>a</sup>
<b>Cotrimoxazole<sup>a</sup></b>			<b>Phenindione<sup>a</sup></b>
Erythromycin <sup>a</sup>	<b>Fenamic Acid Derivatives</b>	<b>Immune Checkpoint Inhibitors</b>	Phenothiazine
Ethambutol	<b>Mefenamic acid</b>	Ipilimumab <sup>a</sup>	Phenylpropanolamine
Flurithromycin		Nivolumab	Probenecid
Foscarnet	<b>Coxibs</b>	Pembrolizumab	Propranolol
Gentamicin	Celecoxib		Propylthiouracil
Indinavir	Rofecoxib	<b>Other Anticancer Agents</b>	Sirolimus
Interferon		Adriamycin	Streptokinase
Isoniazid	<b>Other</b>	Bevacizumab	Sulfipyrazone
Lincomycin	Azapropazone	Bortezomib	Warfarin
Linezolid	Mesalamine (mesalazine, 5-ASA)	Carboplatin	Zopiclone
	Phenazone		

\*Granülomatöz AİN'e yol açarlar

# İlaca Bağlı Akut İnterstisyel Nefritin Klinik Bulguları

- Bir hipersensitivite reaksiyonudur. Bu nedenle *akut allerjik interstisyel nefrit* adı da verilmiştir.
- Doza bağımlı değildir.
- Tedavinin başlamasından sonraki 2 – 40 gün içinde gelişebilir.
- Eşlik eden başka hipersensitivite bulguları olmayabilir.

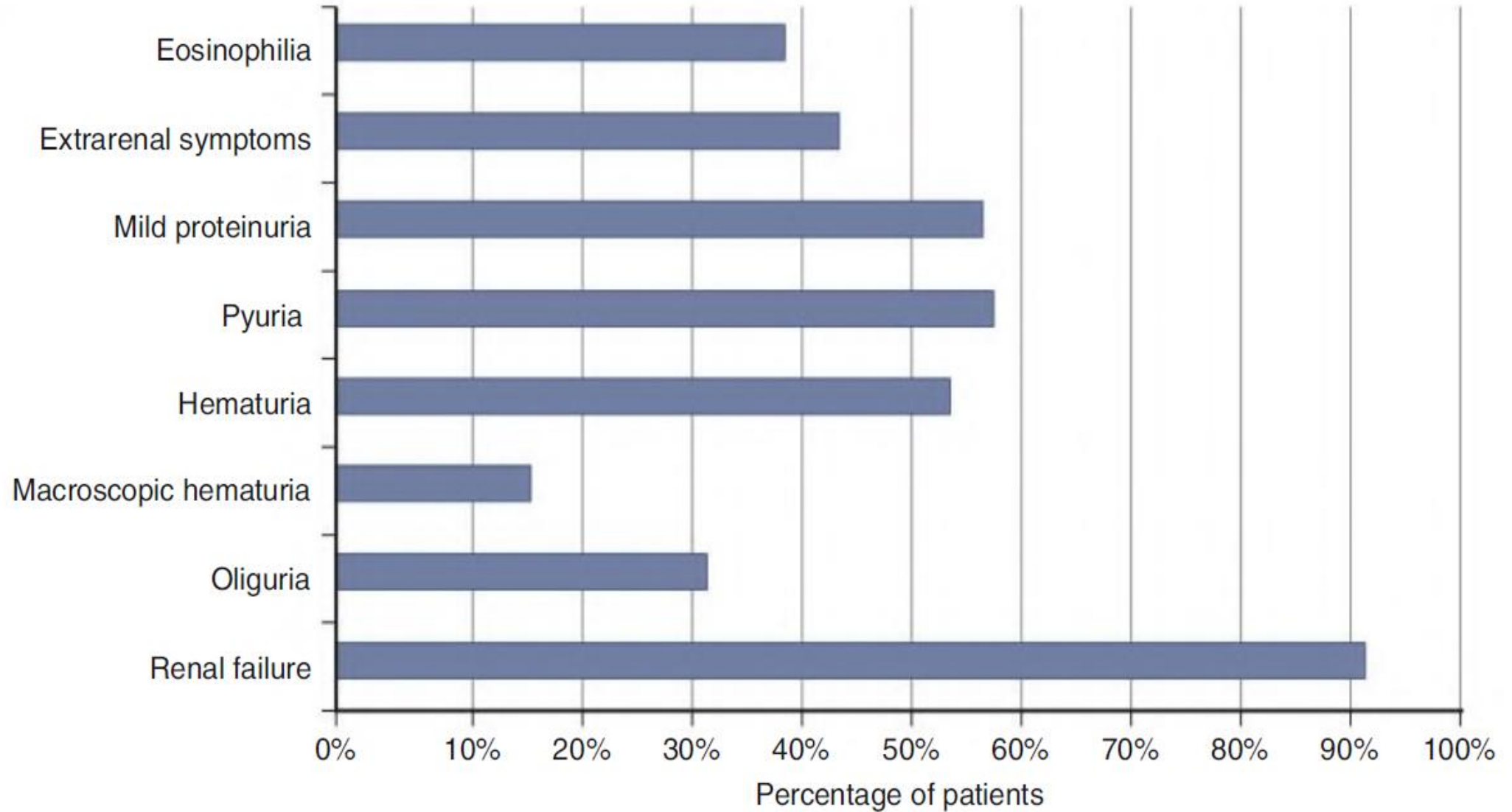


# İlaca Bağlı Akut İnterstisyel Nefritin Klinik Bulguları

- Böbrek yetersizliği  
(oligürik, nonoligürik, poliürik olabilir!)
- Böğür ağrısı
- Ateş (%60-100)
- Makulopapüler döküntü (%30-50)
- Eozinofili (%30-60)
- Ateş, döküntü ve eozinofili triadı (%10)
- İdrar tahlili:
  - Proteinüri <1 g/gün
  - Hematüri ve piyüri
  - Nadiren eozinofilüri

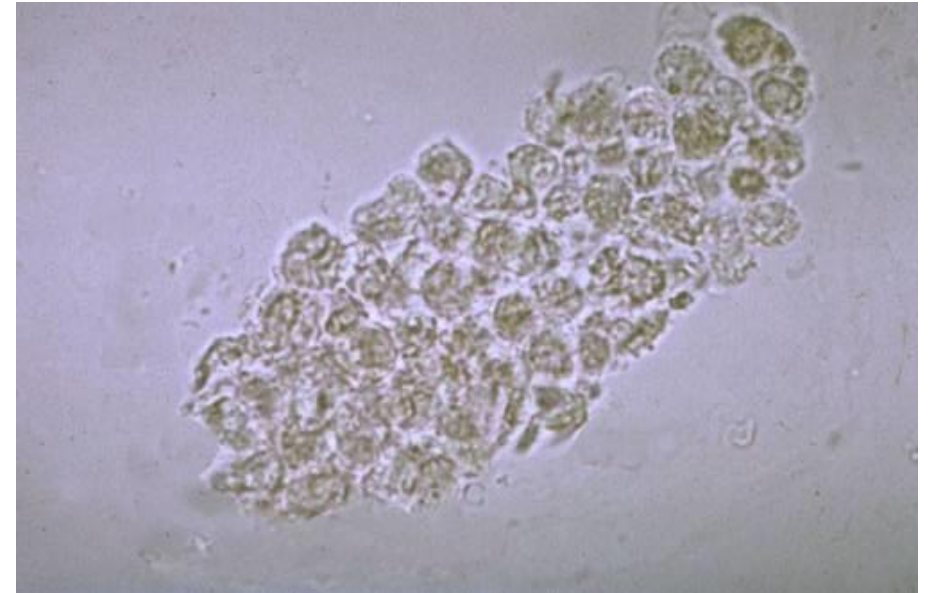
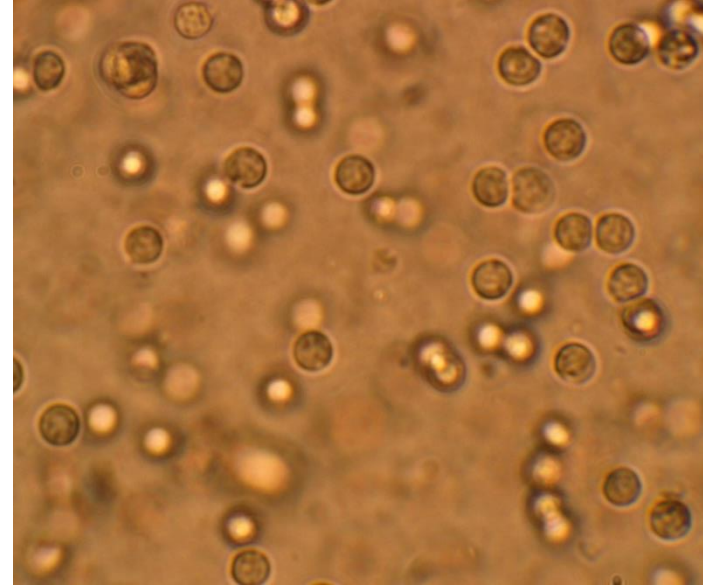
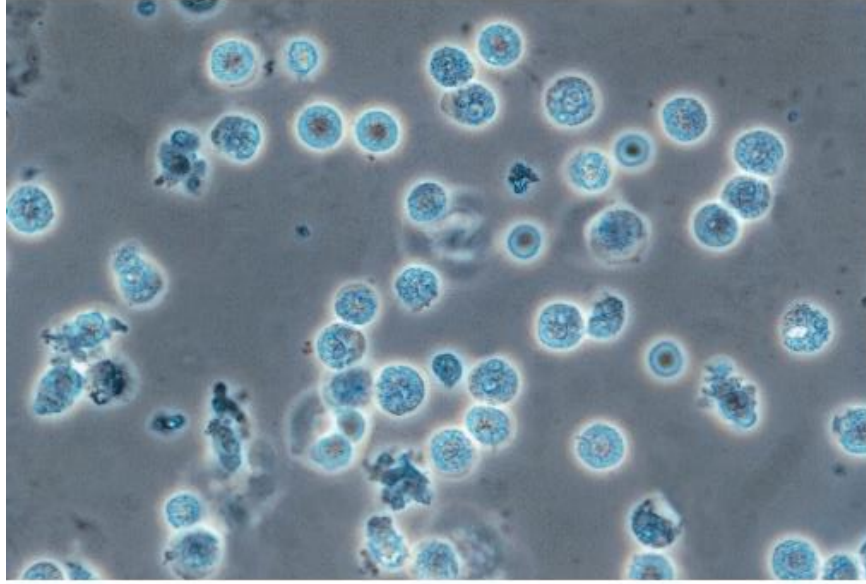


# İlaca Bağlı Akut İnterstisyel Nefritin Klinik Bulguları





# Lökositler ve Lökosit Silindirleri



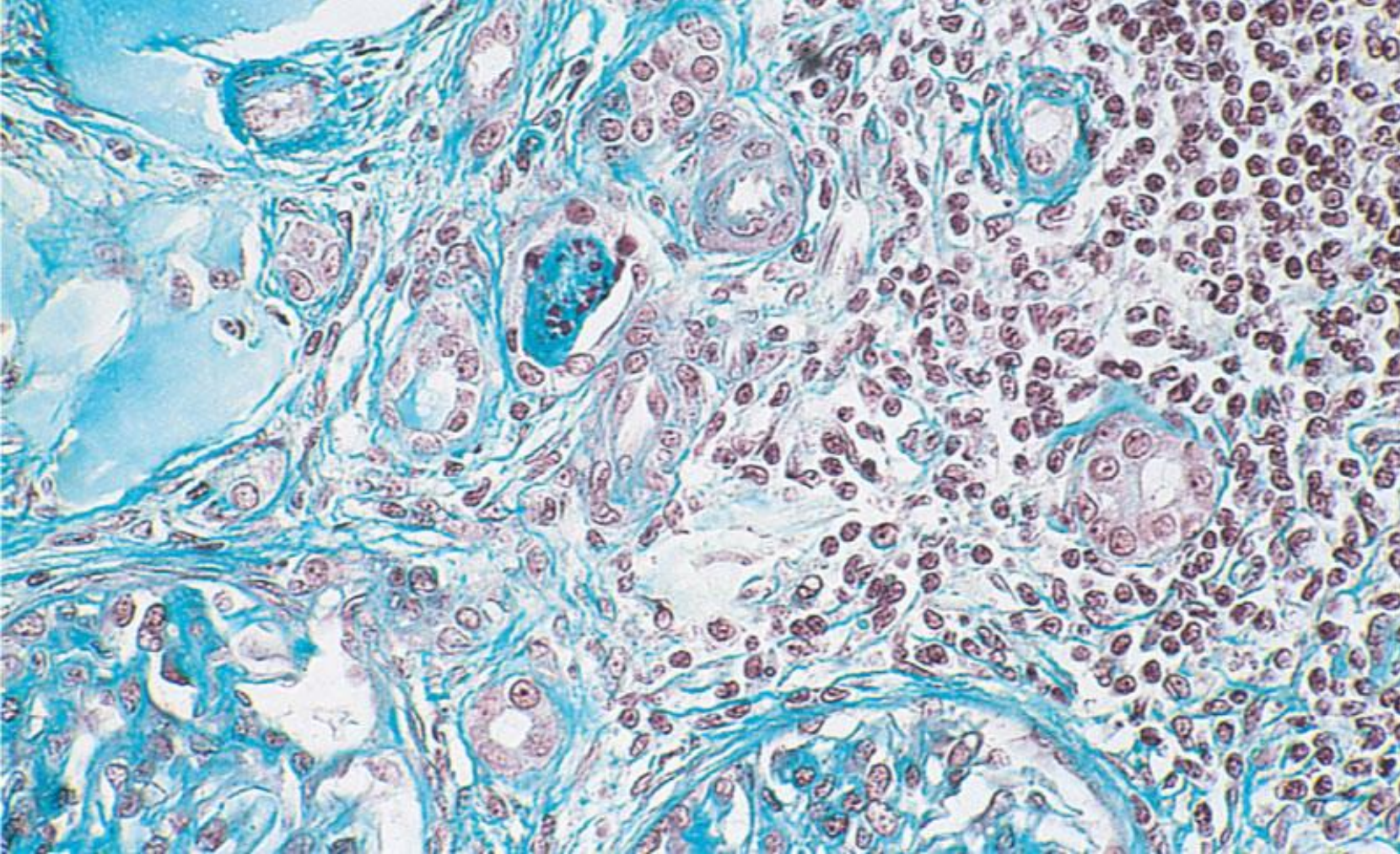


# İlaca Bağlı Akut İnterstisyel Nefrit

## Tanı

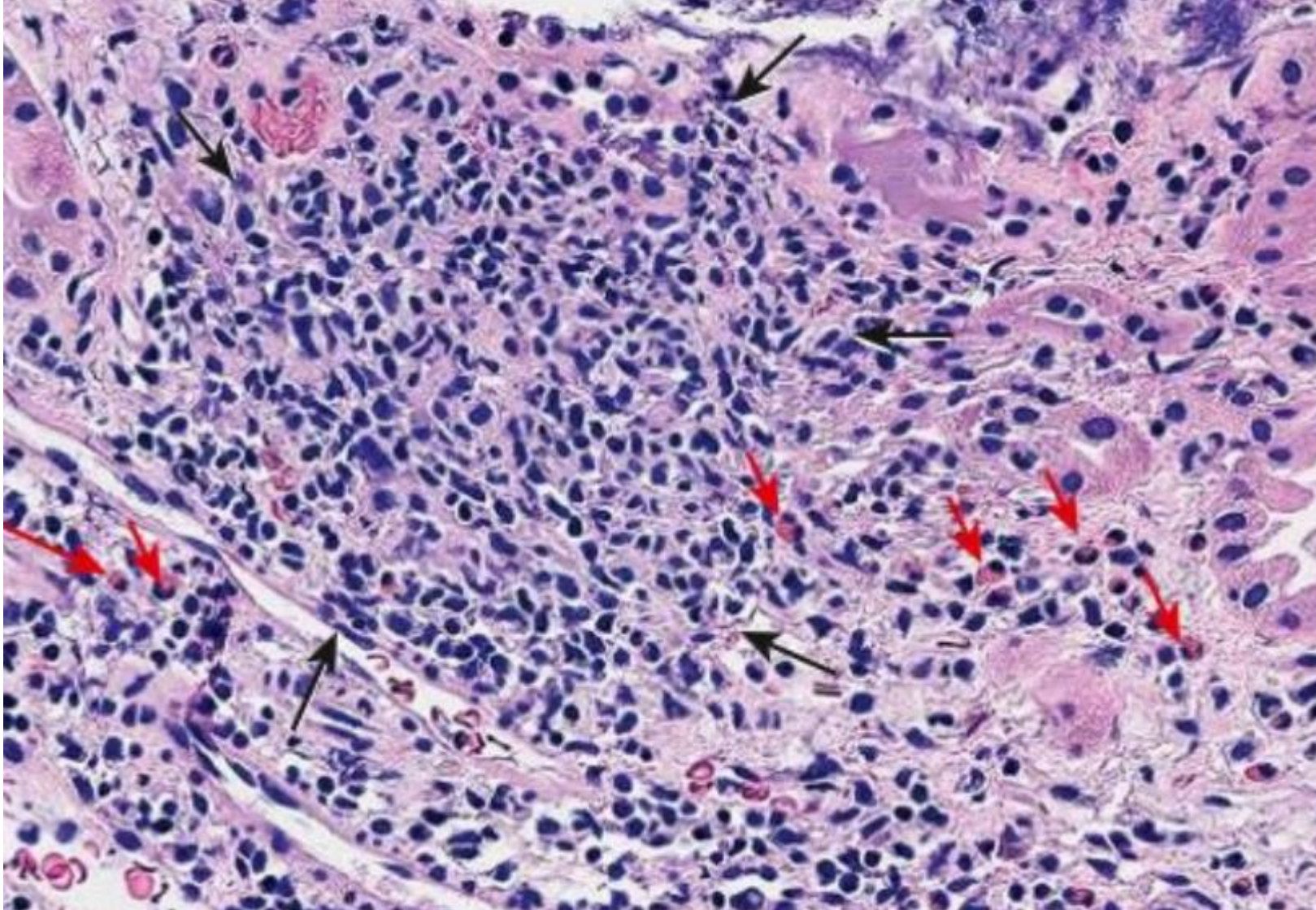
- Anamnez, klinik ve laboratuvar bulguları
- Ultrasonografi: Böbrekler normal veya hafif derecede büyümüş olabilir (interstisyel ödeme bağlı)
- Böbrek biyopsisi

# İlaca Bağlı Akut İnterstisyel Nefrit



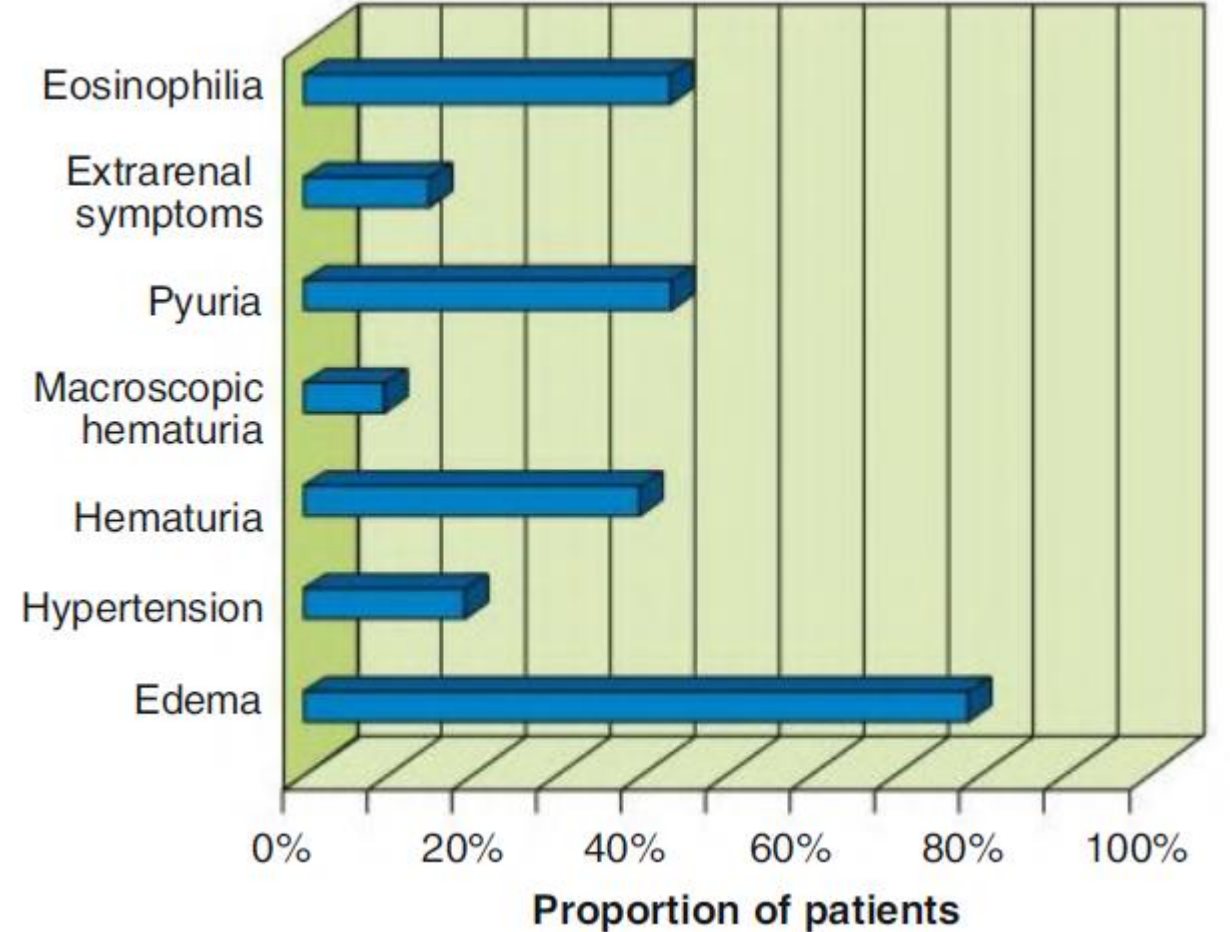


# İlaca Bağlı Granülomatöz Akut İnterstisyel Nefrit



# NSAİ İlaçlara Bağlı Nefrotik Sendrom ve Akut İnterstisyel Nefrit

- Nefrotik sendrom tablosu görülür
- Biyopsi: Minimal değişiklik hastalığı veya membranöz nefropati saptanır.
- Hipersensitivite reaksiyonu (ateş, döküntü, eozinofili) görülmez.
- Genellikle ilaca uzun süreli maruz kalma sonucu gelişir.



# İlaca Bağlı Akut İnterstisyel Nefrit

## Tedavi

- Sorumlu ilacın kesilmesi  
*Erken fark edilmesi önemli!*
- Böbrek yetersizliğinin tedavisi:  
Destek tedavisi  
Diyaliz tedavisi
- Kortikosteroid tedavi  
1 mg/kg prednizolon ile başlanır. 4 – 6 hafta



# Akut interstisyel Nefrite Neden Olabilen infeksiyonlar

## **Bacteria**

*Brucella* spp.  
*Campylobacter jejuni*  
*Corynebacterium diphtheriae*  
*Escherichia coli*  
*Legionella* spp.  
*Leptospira* spp.  
*Mycobacterium tuberculosis*<sup>a</sup>  
*Salmonella* spp.<sup>a</sup>  
*Staphylococcus* spp.  
*Streptococcus* spp.  
*Yersinia pseudotuberculosis*

## **Viruses**

Adenovirus  
Cytomegalovirus  
Epstein-Barr virus<sup>a</sup>

Hantavirus  
Hepatitis A virus  
Hepatitis B virus  
Herpes simplex virus  
Human immunodeficiency virus  
Measles virus  
Polyomavirus  
Rickettsia

## **Parasites**

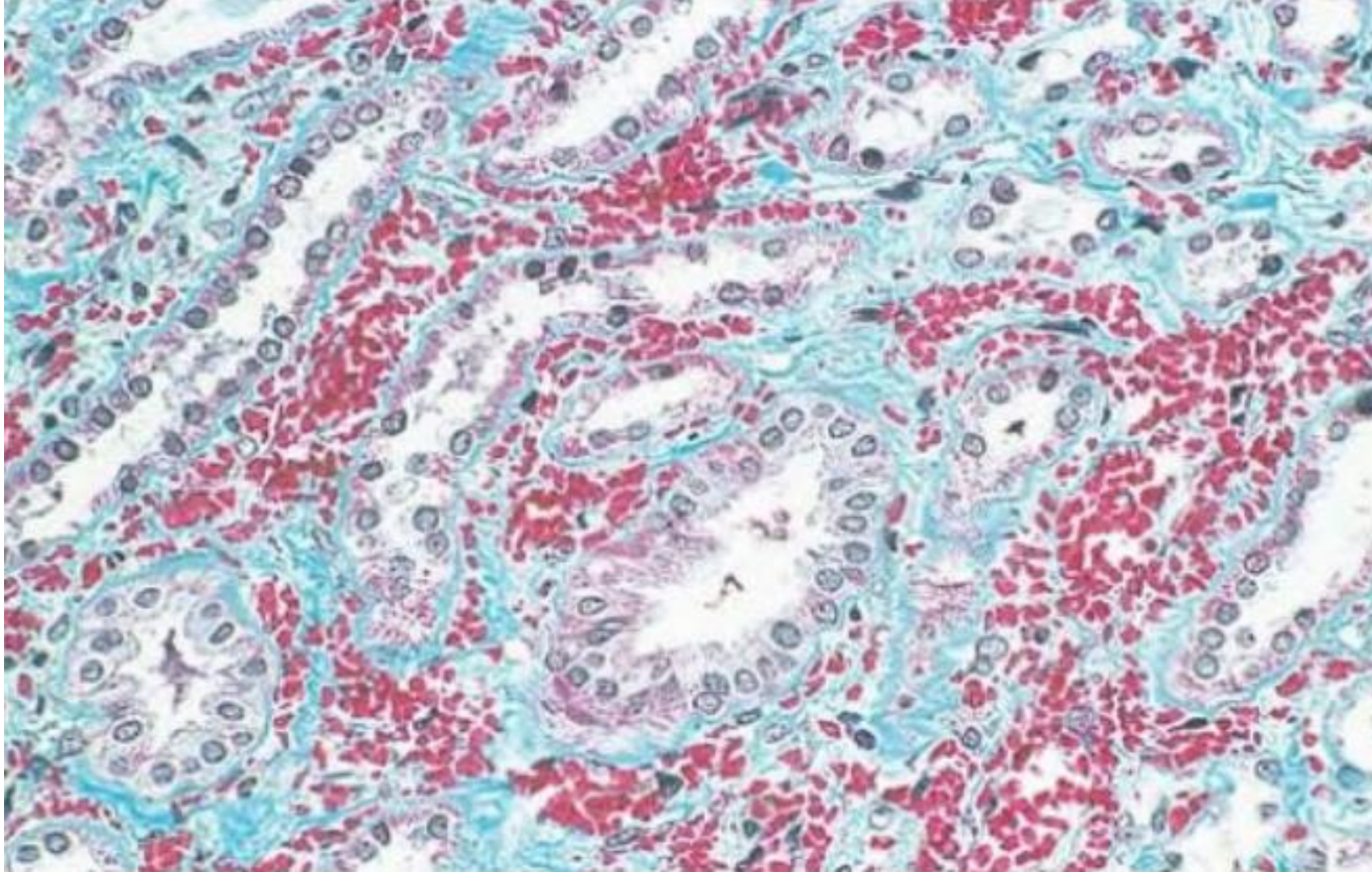
*Toxoplasma* spp.<sup>a</sup>  
*Leishmania donovani*

## **Other**

*Chlamydia* spp.  
*Mycoplasma* spp.

<sup>a</sup> Infections that can induce granulomatous acute interstitial nephritis.

# Hantavirus İnfeksiyonuna Bağlı Akut İnterstisyel Nefrit

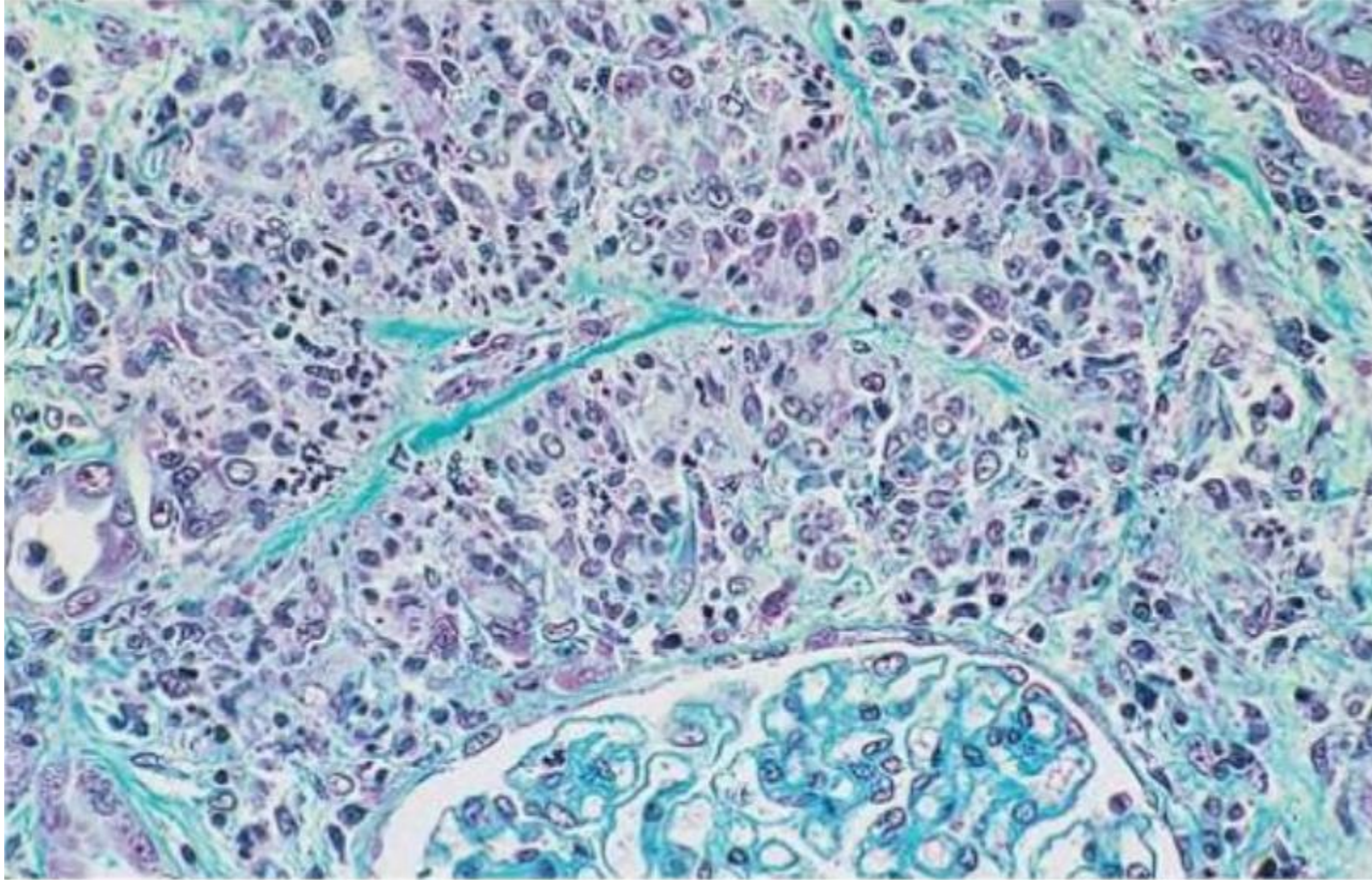


# Sistemik Hastalıklara Bağlı Akut İnterstisyel Nefrit

- Sarkoidoz
- Sjögren sendromu
- Sistemik lupus eritematozus
- Kriyoglobulinemi
- IgG4 ile ilişkili hastalık



# Sarkoidoza Bağlı Granüloamatöz Akut İnterstisyel Nefrit



# Kronik Tubulointerstisyel Nefritlerin Nedenleri

## Böbreklerin Makroskopik Olarak Normal Olduđu Hastalıklar

- **İlaçlar ve toksinler:** Aristoloşik asit, lityum, siklosporin, takrolimus, indinavir, sisplatin, proton pompa inhibitörleri
- **Metabolik:** Hiperürisemi, hipokalemi, hiperkalsemi, hiperoksalüri, sistinozis
- **Ağır metaller:** Kurşun, kadmium, arsenik, cıva, altın, uranyum
- **Radyasyon**
- **Balkan nefropatisi**
- **Mezoamerikan nefropatisi**
- **İmmünite ile ilişkili durumlar:** SLE, Sjögren sendromu, sarkoidozis, granümatöz polianjiitis, diğer vaskülitler
- **Vasküler hastalıklar** (aterosklerotik böbrek hastalıkları)
  - Transplantasyon (kronik transplant rejeksiyonu)
  - Hematolojik hastalıklar (multipl miyelom, hafif zincir depolanma hastalığı, orak hücreli anemi, paroksizmal nokturnal hemoglobinüri)
- **Progresif glomerüler hastalıklar** (glomerulonefrit, diyabet, hipertansiyon)
- **İdyopatik**



# Kronik Tubulointerstisyel Nefritlerin Nedenleri

## Böbreklerin Makroskopik Olarak Anormal Olduğu Hastalıklar

- **Analjezik nefropatisi**
- **Kronik obstrüksiyon**
- **Hereditör** (nefronofitizi, medüller kistik böbrek hastalığı, ailevi juvenil hiperürisemik nefropati, otozomal dominant polikistik böbrek hastalığı, otozomal resesif polikistik böbrek hastalığı)
- **İnfeksiyon** (kronik piyelonefrit, malakoplaki, ksantogranülomatöz piyelonefrit)

# Kronik Tubulointerstisyel Nefritler

## Klinik ve Laboratuvar Bulguları

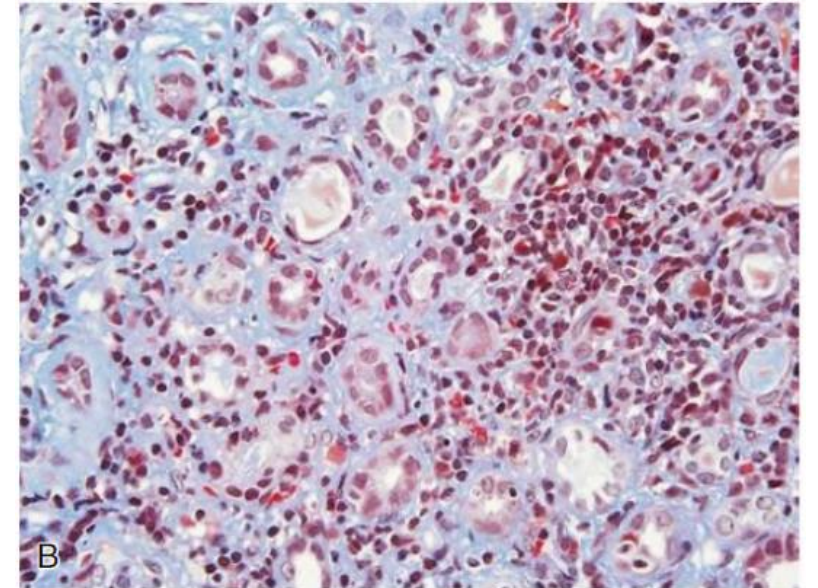
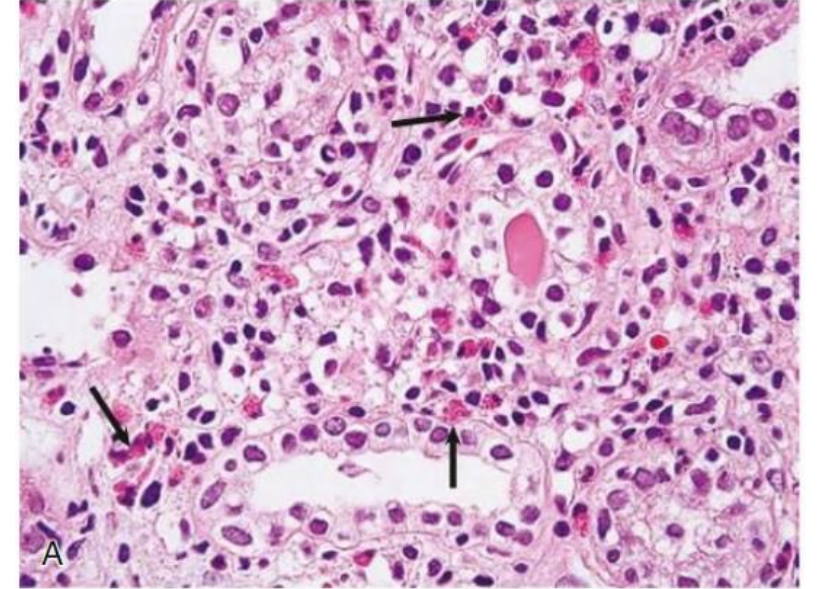
- Primer olay ile ilişkili bulgular
- GFR'de azalma (sinsi ve yavaş bir süreç)
- Tubuler proteinüri (< 1 g/gün)
- İnaktif idrar sedimenti
- Erken dönemlerden itibaren anemi
- Proksimal tubulus fonksiyon bozuklukları (aminoasidüri, fosfatüri, proksimal renal tubuler asidoz, Fanconi sendromu)
- Distal tubulus fonksiyon bozuklukları (tip 4 renal tubuler asidoz)
- Medüller fonksiyon bozukluğu (konsantrasyon defektleri)
- Tuz kaybettiren nefropati
- Tuza duyarlı hipertansiyon

# Kronik Tubulointerstisyel Nefritler

Feature	Symptom, Sign, or Historical Clue	Potential Diagnosis
Occupational history	Exposure to heavy metals (e.g., batteries, alloys)	Lead or cadmium nephropathy
Alcohol	History of moonshine ingestion	Lead nephropathy
Social history	Country of origin	Balkan nephropathy
Past history	Systemic lupus erythematosus	Disease-associated chronic interstitial nephritis
	Sjögren syndrome	
	Sarcoidosis	
	Inflammatory bowel disease	
	Autoimmune pancreatitis	
	Chronic pain syndrome	Analgesic nephropathy
	Gouty attack	Lead nephropathy
Medication	Prescribed	Drug-induced chronic interstitial nephritis
	OTC (NSAIDs, PPIs)	Analgesic
	Herbal	Aristolochic acid-associated nephropathy
	Indinavir	Crystal nephropathy
Physical examination	Dry eyes	Sjögren syndrome
	Uveitis	TINU syndrome
Laboratory examination	Hyperuricemia	Chronic uric acid nephropathy
	Hypokalemia	Hypokalemic nephropathy
	Hypercalcemia	Hypercalcemic nephropathy
	High serum IgG4 levels	IgG4-related sclerosing disease
Radiologic examination	Decreased volume, bumpy contours, and papillary calcification on CT	Analgesic nephropathy
	Microcysts on MRI or ultrasound	Lithium nephropathy
	Nephrocalcinosis on CT	Hypercalcemic nephropathy

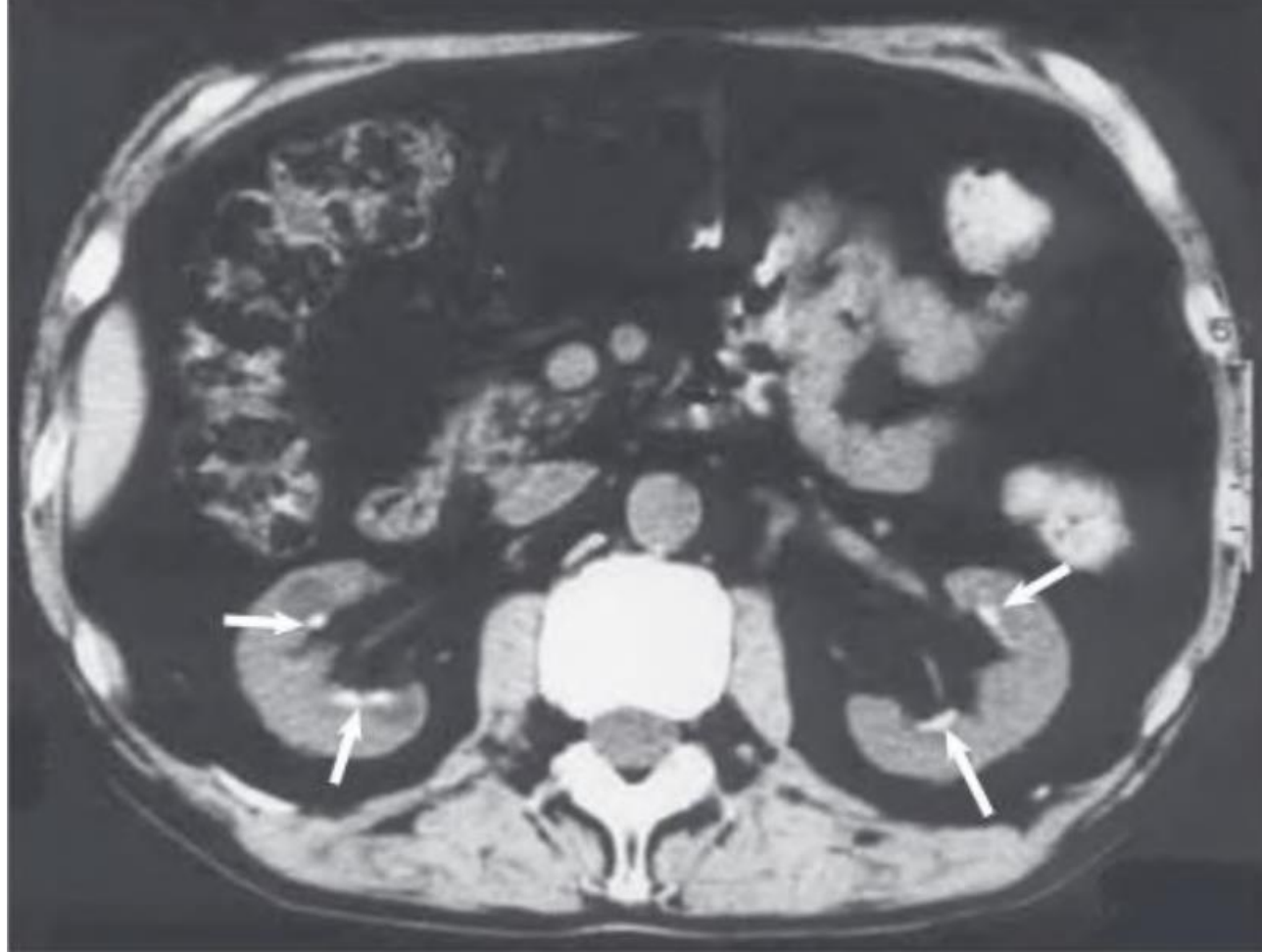
# Analjezik Nefropatisi

- Yoğun analjezik kullanımı hikayesi
  - Fenasetin (*günümüzde yasaklanmıştır*) ile birlikte asetaminofen ve aspirin kombinasyonu
- Medullada iskemi
  - ↓
  - Vaza rektalarda hasar
    - ↓
    - İnterstisyel inflamasyon
      - ↓
      - Papiller iskemi
        - ↓
        - Papiller nekroz (*papilla koparsa renal kolik olabilir*)
        - İnterstisyel fibrozis
        - Kalsifikasyonlar





# Analjezik Nefropatisi



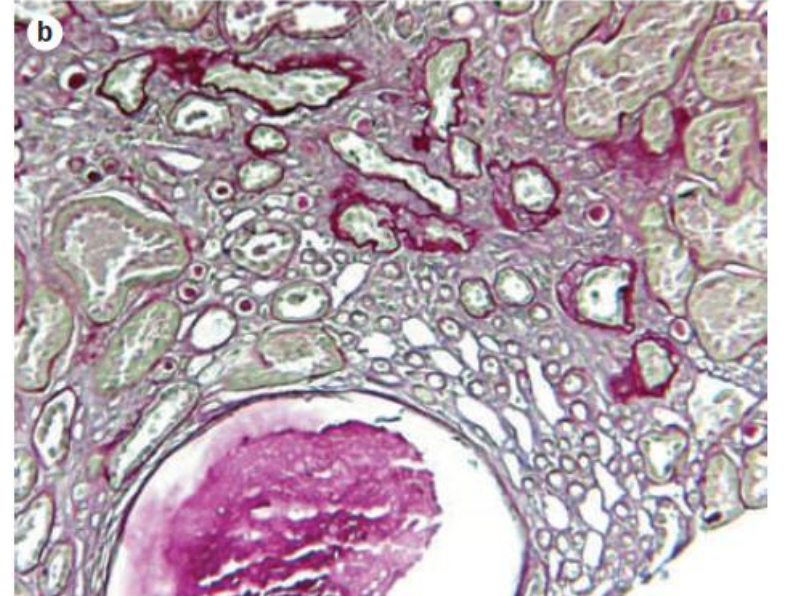
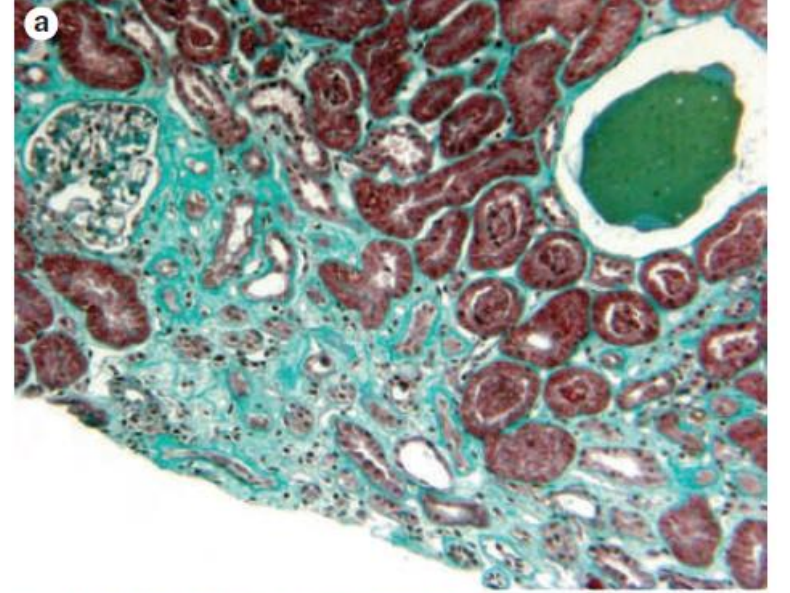
Böbrek parenkiminde incelme, papiller kalsifikasyonlar

# Analjezik Nefropatisi

- Hematüri, steril piyüri, hipostenüri, izostenüri
- Distal tipte RTA → Nefrokalsinozis
- Anemi
- Böbrek yetersizliği
- Böbrek boyutlarında küçülme, konturlarda düzensizlik
- Geç dönemde pelvis veya üreterde değişici epitel hücreli karsinom gelişebilir.

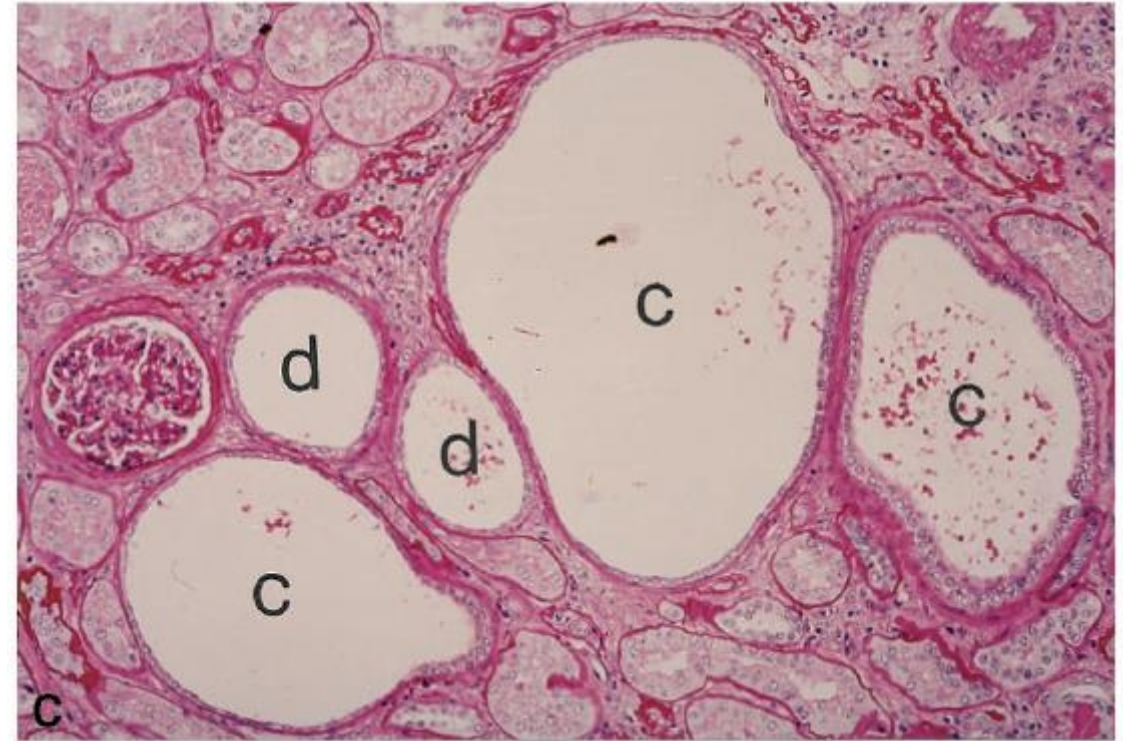
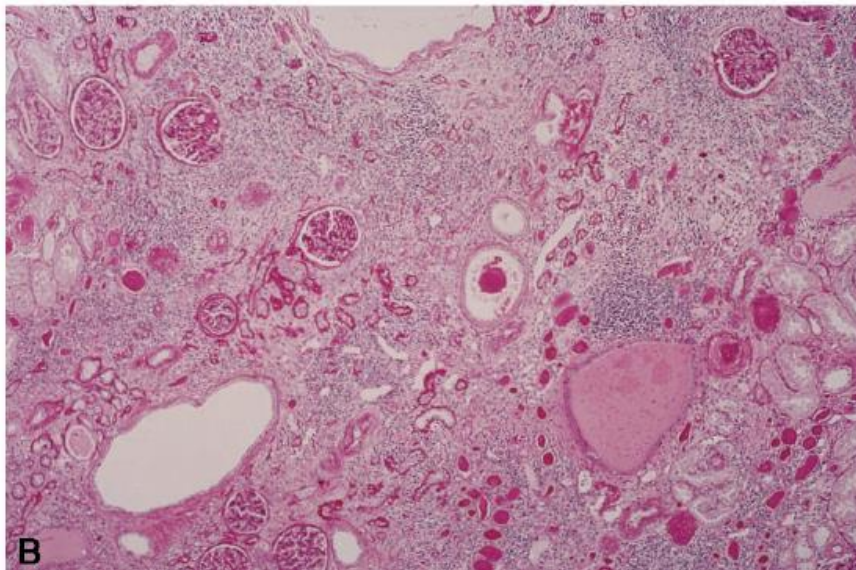
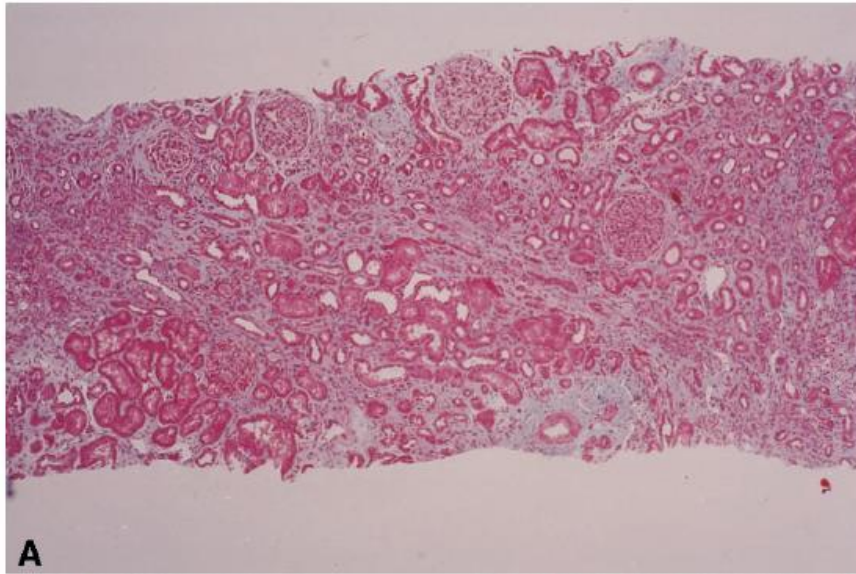
# Lityum Nefropatisi

- Lityum tedavisinin en sık görülen yan etkisi nefrojenik diabetes insipidustur.
- Lityumun uzun süreli kullanımında kronik tubulointerstisyel nefrit gelişebilir.
- Lityumun sitotoksik etkileri ön planda toplayıcı kanallardaki esas hücrelere yöneliktir.
- Esas hücrelerdeki epitelyal sodyum kanalları (eNaC) etkilenir.
- Tedavide amilorid yararlı olabilir.





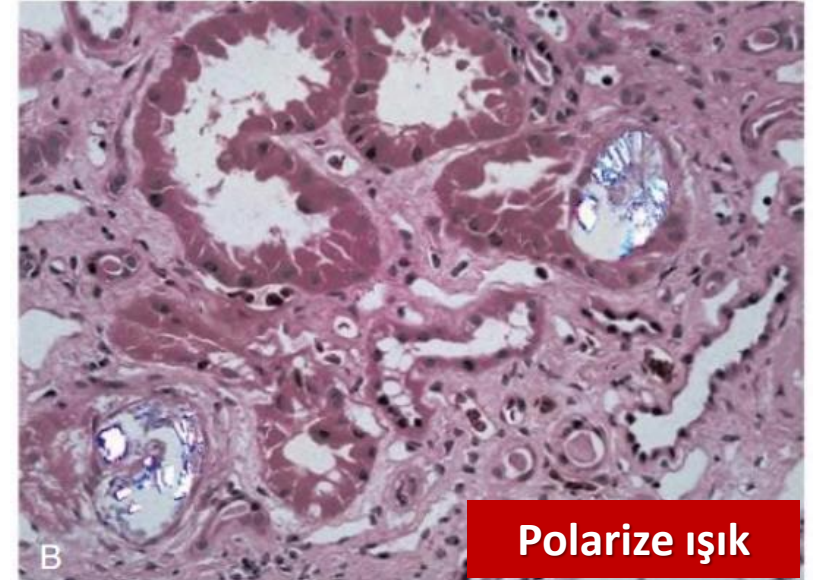
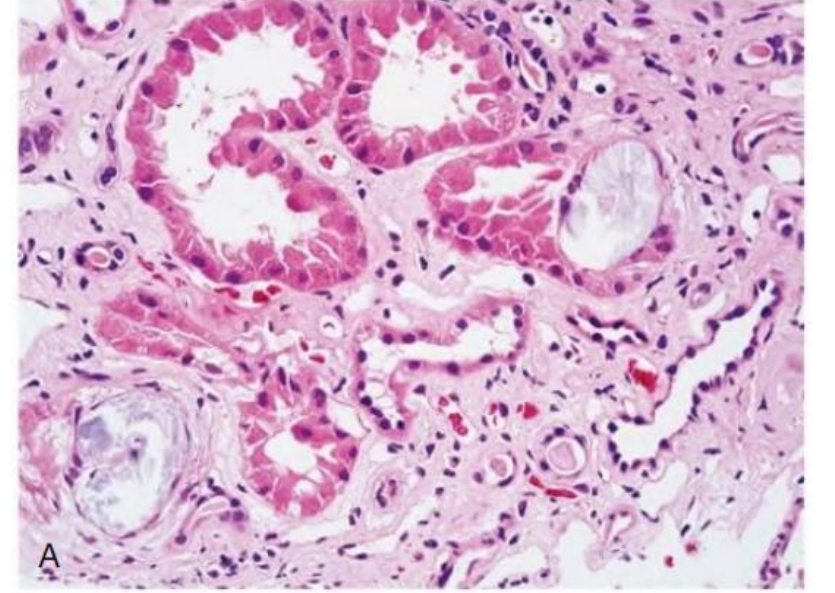
# Lityum Nefropatisi



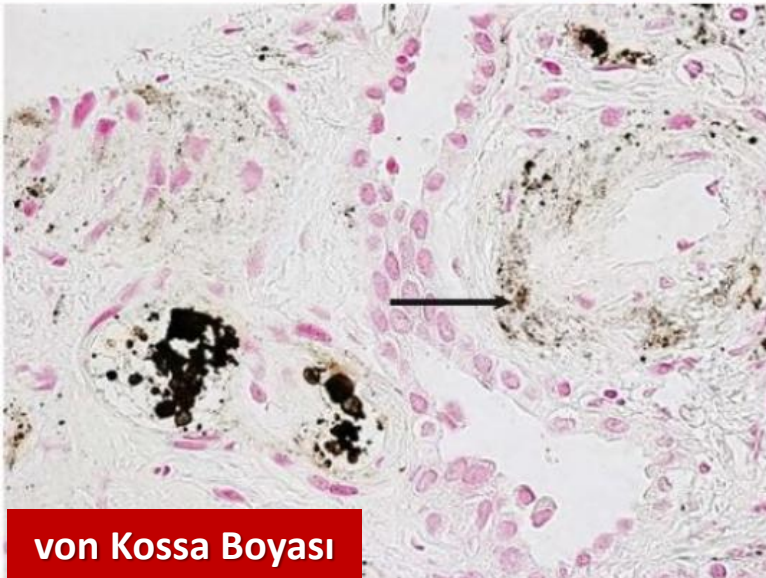
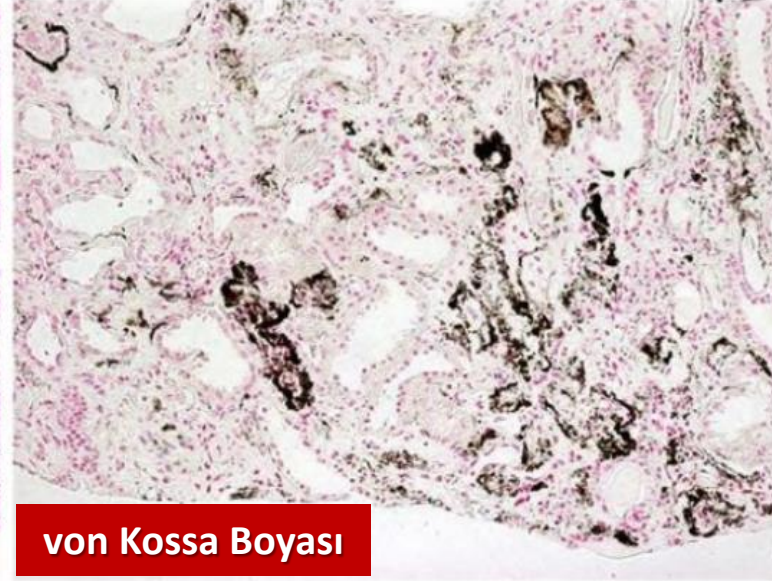
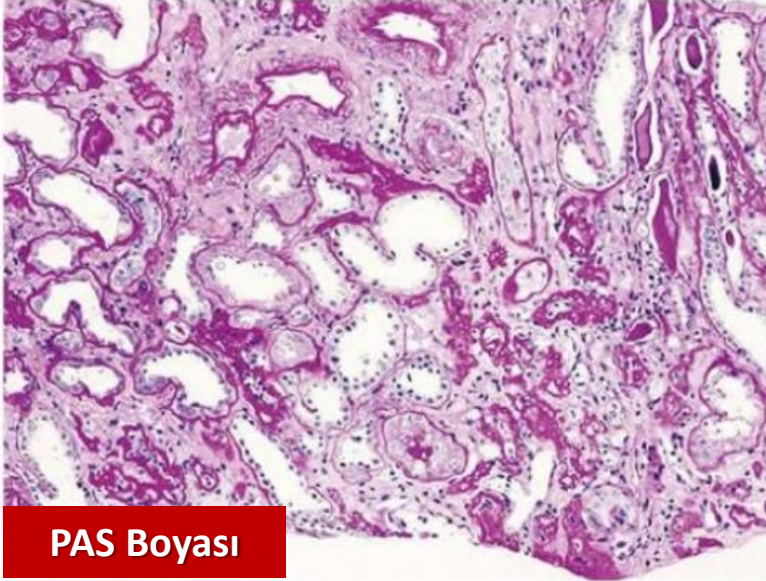


# Kronik Ürik Asit Nefropatisi

- Ürik asit taşları hikayesi
- Yıllar süren gut hikayesi
- Ürik asit ve monosodyum urat tuzlarının böbrek parenkiminde birikmesi → Obstrüksiyon, inflamasyon, fibrozis
- Çoğunlukla hipertansiyon ve hiperlipidemi de eşlik eder.
- Tedavi: Allopurinol, febüksostat



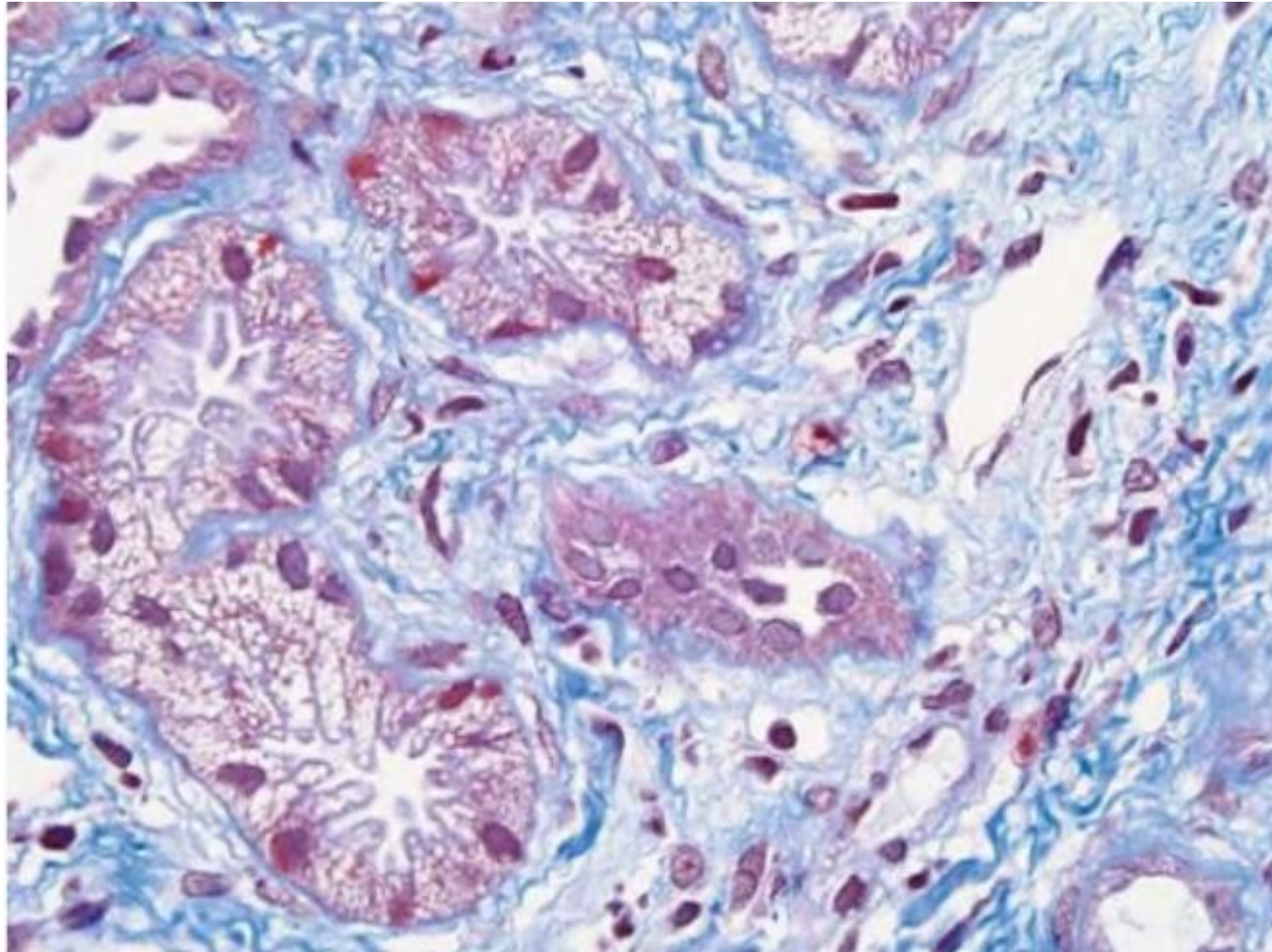
# Hiperkalsemi Nefropatisi



- Glomerüllerde, tubulustalarda, damarlarda ve interstisyumda kalsiyum çökmeleri (nefrokalzinosis)
- Nefrojenik diabetes insipidus



# Hipokalemi Nefropatisi



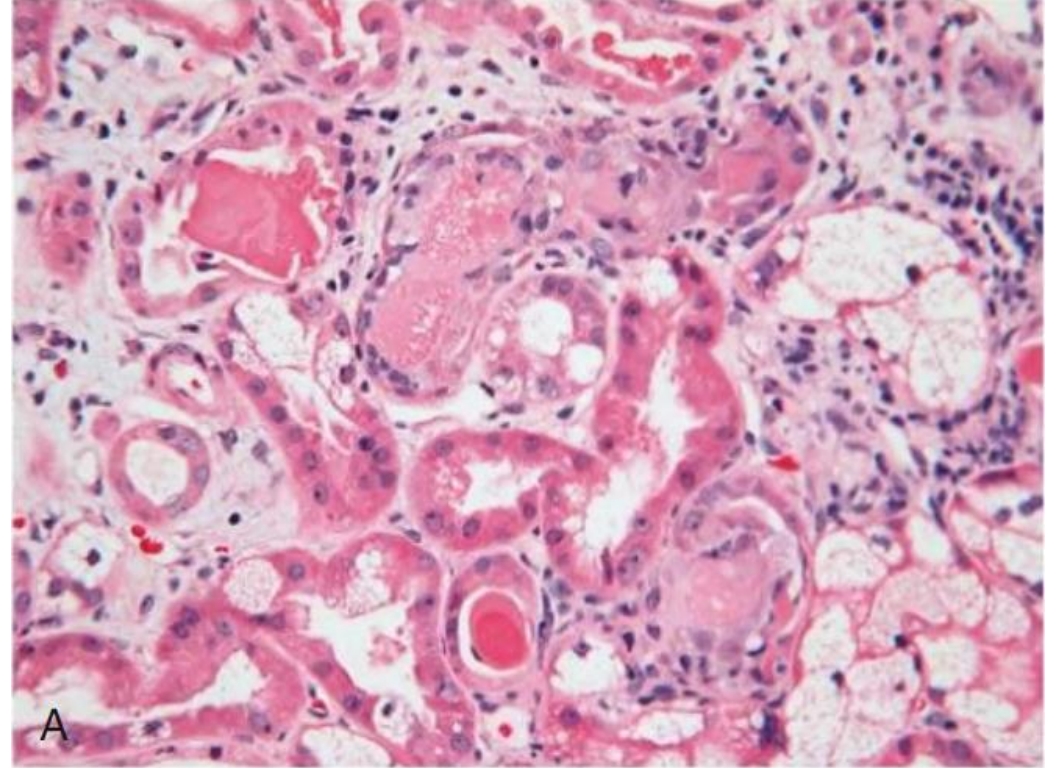
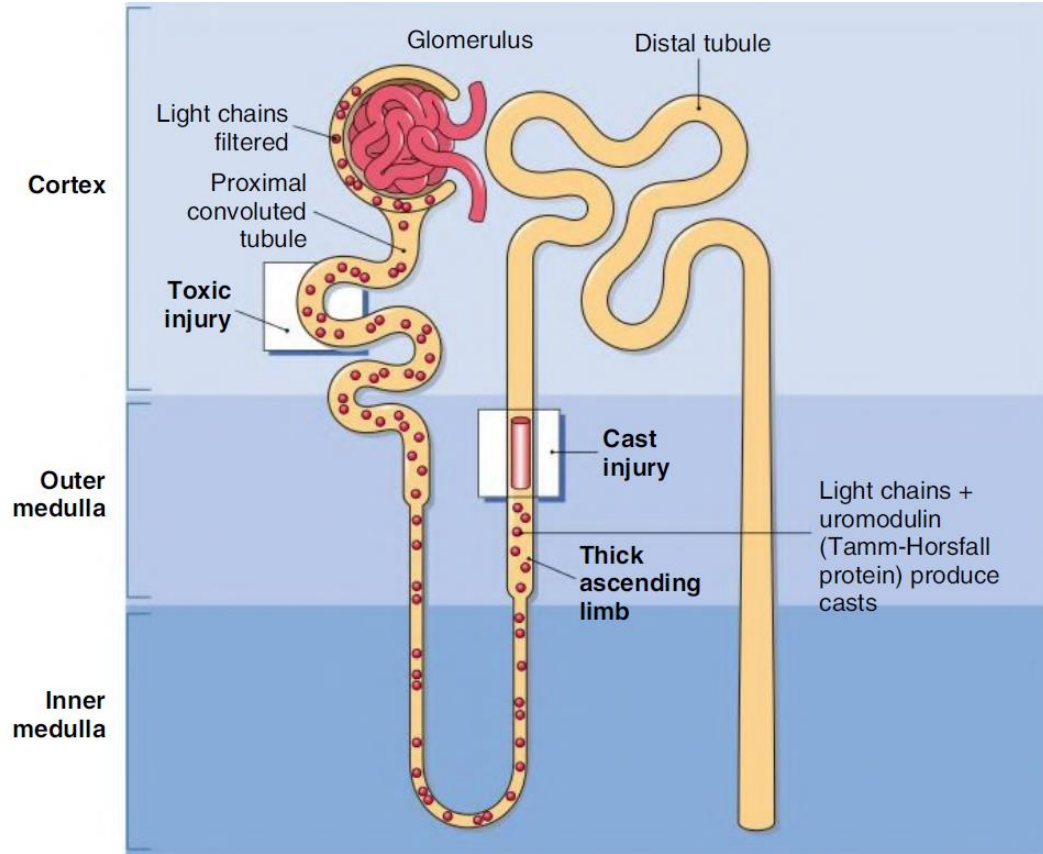


# Multipl Miyelomda Nefrolojik Sorunlar

- Silindir nefropatisi
- Hiperkalsemi nefropatisi
- Hiperürisemi nefropatisi
- Proksimal tubulus fonksiyon bozuklukları
- AL amiloidoz gelişimi
- Plazma hücrelerinin infiltrasyonu

# Multipl Miyelomda Nefrolojik Sorunlar

## Miyelom Böbreği (Silindir Nefropatisi)



İnatubuler eozinofilik silindirler, dev hücre reaksiyonu ve inflamatuvar hücresel infiltrasyon. Tubulus hücrelerinde vakuolizasyon ve tubuluslarda dejenerasyon (Hematoksilen ve eozin boyası; ×160).

# Balkan Nefropatisi

review

<http://www.kidney-international.org>

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## Aristolochic acid nephropathy: A worldwide problem

Frédéric D. Debelle<sup>1,2</sup>, Jean-Louis Vanherweghem<sup>1</sup> and Joëlle L. Nortier<sup>1,2</sup>

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*Aristolochik asit içeren  
“Aristolochia clematitis” bitkisi  
(Hırvatistan’da bir buğday tarlası)*



# Chronic Interstitial Nephritis in Agricultural Communities

## Observational and Mechanistic Evidence Supporting the Role of Nephrotoxic Agrochemicals

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### Abstract

Chronic interstitial nephritis in agricultural communities (CINAC) is an epidemic of kidney disease affecting specific tropical and subtropical regions worldwide and is characterized by progressive CKD in the absence of traditional risk factors, such as hypertension and diabetes. CINAC prevalence is higher among young, male agricultural workers, but it also affects women, children, and nonagricultural workers in affected areas. Biopsies from patients with CINAC across regions commonly demonstrate tubular injury with lysosomal aggregates, tubulointerstitial inflammation, and fibrosis and variable glomerular changes. Each endemic area holds environmental risk factors and patient/genetic milieus, resulting in uncertainty about the cause(s) of the disease. Currently, there is no specific treatment available for CINAC. We highlight survey findings of Houston-based migrant workers with CINAC and draw similarities between kidney injury phenotype of patients with CINAC and mice treated chronically with paraquat, an herbicide used worldwide. We propose potential pathways and mechanisms for kidney injury in patients with CINAC, which may offer clues for potential therapies.



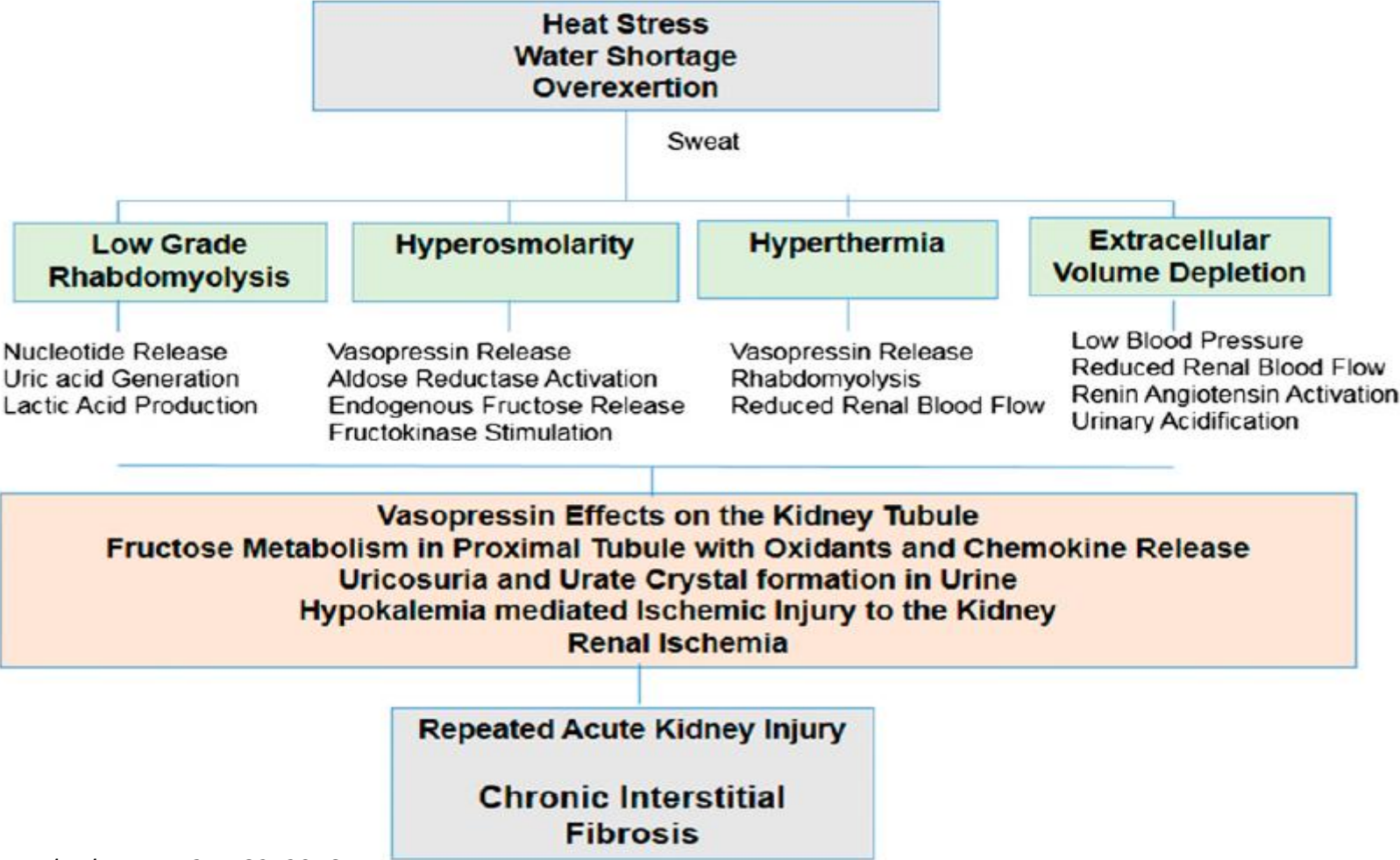
# Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural Communities: The Case for Heat Stress Nephropathy

*Jason Glaser, Jay Lemery, Balaji Rajagopalan, Henry F. Diaz, Ramón García-Trabanino, Gangadhar Taduri, Magdalena Madero, Mala Amarasinghe, Georgi Abraham, Sirirat Anutrakulchai, Vivekanand Jha, Peter Stenvinkel, Carlos Roncal-Jimenez, Miguel A. Lanaspa, Ricardo Correa-Rotter, David Sheikh-Hamad, Emmanuel A. Burdmann, Ana Andres-Hernando, Tamara Milagres, Ilana Weiss, Mehmet Kanbay, Catharina Wesseling, Laura Gabriela Sánchez-Lozada, and Richard J. Johnson*

## **Abstract**

Climate change has led to significant rise of 0.8°C–0.9°C in global mean temperature over the last century and has been linked with significant increases in the frequency and severity of heat waves (extreme heat events). Climate change has also been increasingly connected to detrimental human health. One of the consequences of climate-related extreme heat exposure is dehydration and volume loss, leading to acute mortality from exacerbations of pre-existing chronic disease, as well as from outright heat exhaustion and heat stroke. Recent studies have also shown that recurrent heat exposure with physical exertion and inadequate hydration can lead to CKD that is distinct from that caused by diabetes, hypertension, or GN. Epidemics of CKD consistent with heat stress nephropathy are now occurring across the world. Here, we describe this disease, discuss the locations where it appears to be manifesting, link it with increasing temperatures, and discuss ongoing attempts to prevent the disease. Heat stress nephropathy may represent one of the first epidemics due to global warming. Government, industry, and health policy makers in the impacted regions should place greater emphasis on occupational and community interventions.

# Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural Communities: The Case for Heat Stress Nephropathy

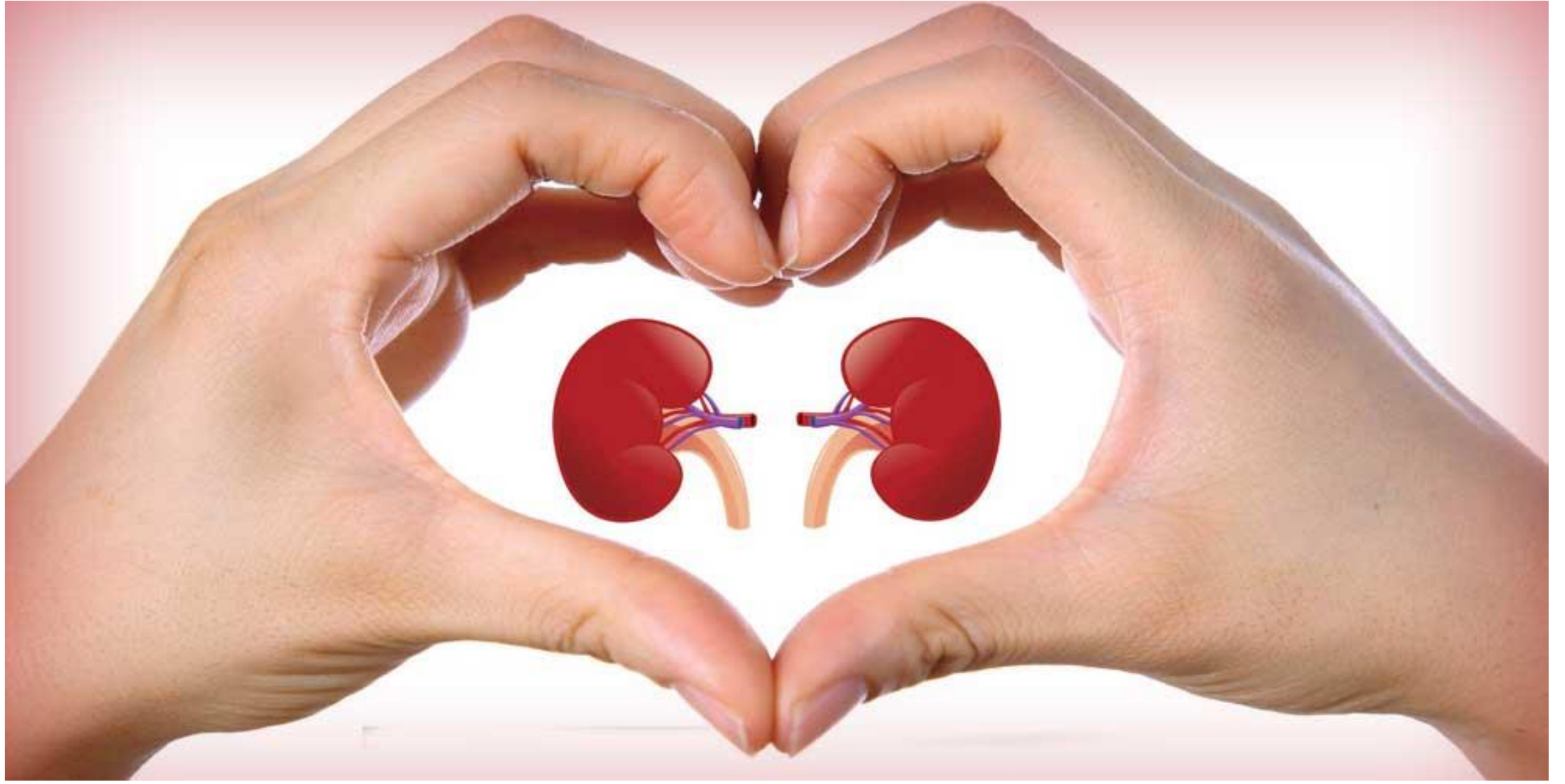


Glaser et al: Clin J Am Soc Nephrol 11: 1472-1483, 2016

# Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural Communities: The Case for Heat Stress Nephropathy

Country	Region	Reference
<b>Confirmed Sites</b>		
Central America		
<i>Costa Rica</i>	Guanacaste	Wesseling <i>et al.</i> (39)
<i>El Salvador</i>	Bajo Lempa	Orantes <i>et al.</i> (45)
<i>Guatemala</i>	Southwest Region	Laux <i>et al.</i> (105)
<i>Nicaragua</i>	León and Chinandega	Torres <i>et al.</i> (36)
South Asia		
<i>India</i>	Andhra Pradesh	Reddy and Gunasekar (79), Abraham <i>et al.</i> (30)
<i>Sri Lanka</i>	North Central Region	Jayatilake <i>et al.</i> (72) Jayasumana <i>et al.</i> (106)
<b>Possible Sites</b>		
South Asia		
<i>India</i>	Goa, Odisha, and Maharashtra	Rajapurkar <i>et al.</i> (107)
<i>Thailand</i>	Northeast (Isan Region)	Sirirat Anutrakulchai (personal communication)
Middle East		
<i>Saudi Arabia</i>	Tabuk region	El Minshawy <i>et al.</i> (108)
Africa		
<i>Egypt</i>	El-Minia, Upper Egypt	El Minshawy <i>et al.</i> (96)
<i>Sudan</i>	Southern Sudan	Elamin <i>et al.</i> (109)
North America		
<i>Mexico</i>	Tierra Blanco, Veracruz	Mendoza-González <i>et al.</i> (90)
<i>United States</i>	California Central Valley	Moyce <i>et al.</i> (93)





***Sabrınız için teşekkür ederim...***