IgA (Henoch-Schönlein) Vasküliti

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Ege Üniversitesi Tıp Fakültesi

Romatoloji Bilim Dalı

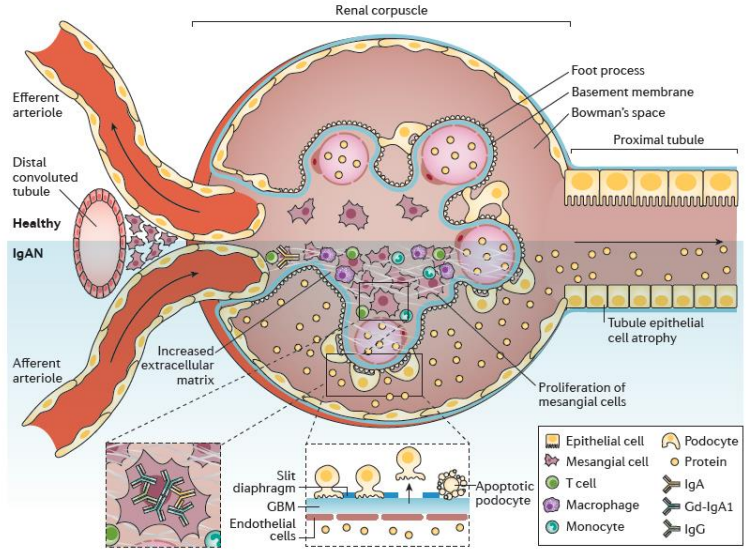
Tanım

- Dr. William Heberden – 1802 – olgu; artrit, GİS. böbrek tutulumu,purpura
- Johann Schoenlein - 1837, purpura,artralji
- Eduard Henoch - 1874, GİS ve renal semptomlar

- Küçük damar vasküliti
- Lökositoklastik
- İmmün kompleks aracılı
- IgA1-dominant immün birikimler
- Kendi kendini sınırlar
- Spesifik semptomlara yönelik tedavi
- Agresif seyir-agresif tedavi
- Alevlenmeler (%22-erişkinlerde), kronik hastalık (%33-erişkinlerde)
- Çocukluk çağındaki en sık vaskülit (3-26/100,000 yıllık insidans))
- Ortalama başlangıç yaşı 6
- Erişkinlerde daha az sıklıkta (0.1–1.8/100,000 yıllık insidans)

Ortalama başlangıç yaşı 50

E/K: 10:2



Pillebaut E, 2021

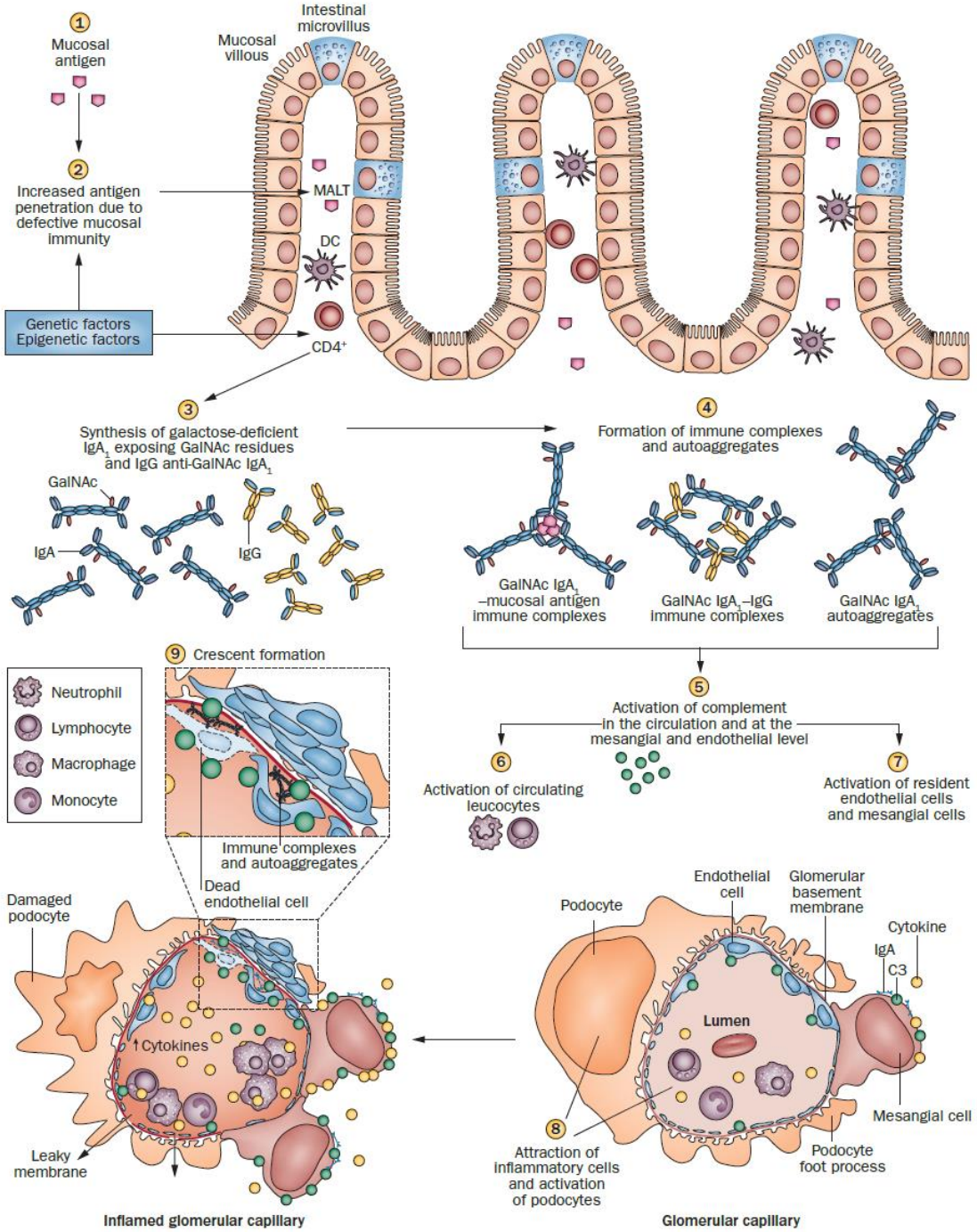
Yaseen K,2021

Table 1 Comparison between ACR 1990 and EULAR/PRINTO 2010 classification criteria for IgAV

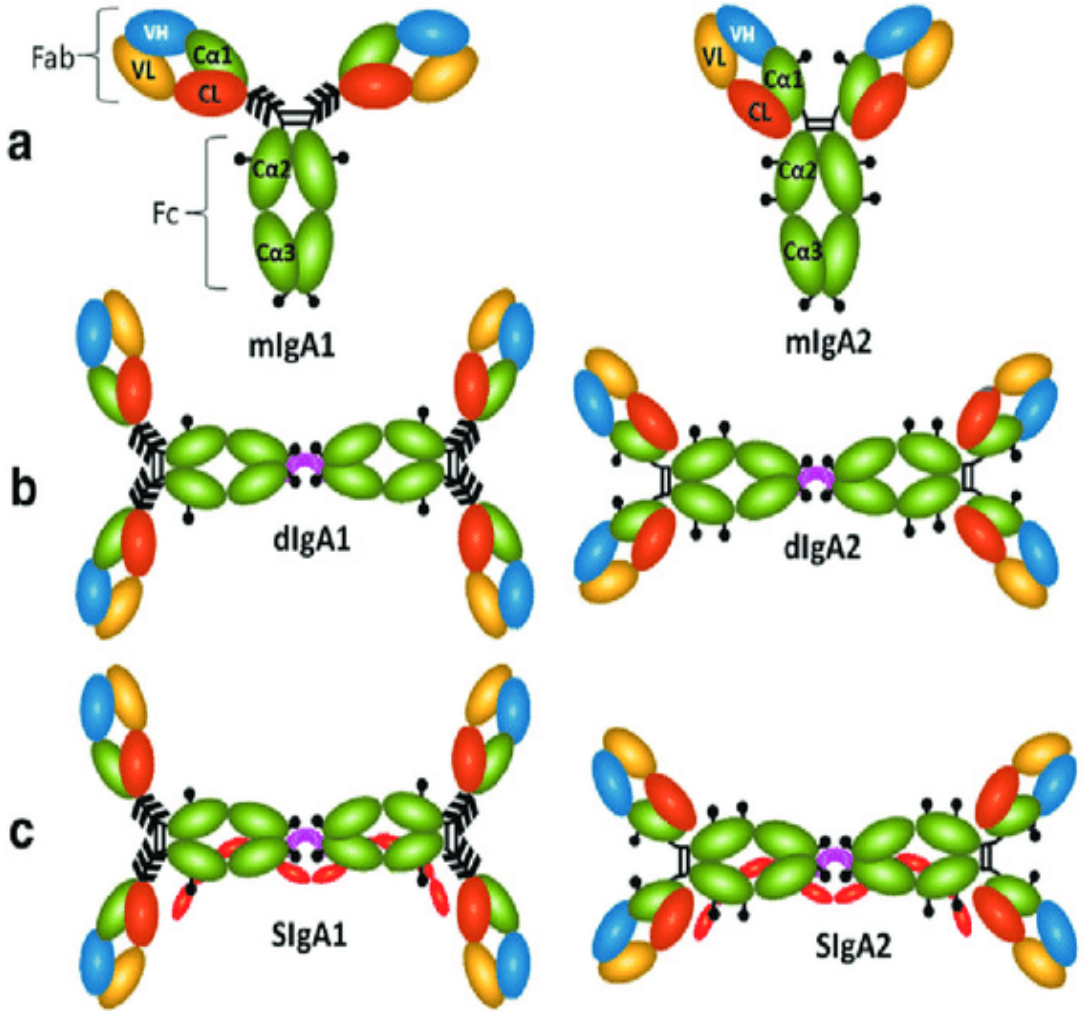
ACR classification criteria (1990) [8]	EULAR/PRINTO/PRES classification criteria (2010) [11]
Two of the following criteria	Purpura or petechiae and one of the following four criteria
1. Age < 20 years	1. Abdominal pain
2. Palpable purpura	2. Arthritis or arthralgia
3. Acute abdominal pain	3. Renal involvement
4. Biopsy showing granulocytes in the walls of the small arterioles or venules	4. Leukocytoclastic vasculitis with predominant IgA deposits or proliferative glomerulonephritis with predominant IgA deposits
Sensitivity 87.1%; specificity 87.7%	Sensitivity 100%; specificity 87%

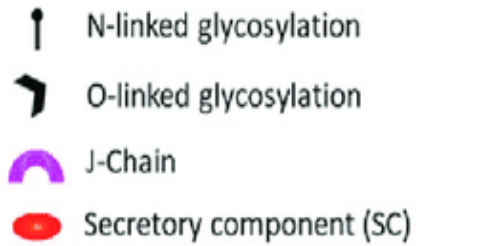
ACR 1990 ;
IgA dominant immün birikimler dahil edilmemiş
IgAV diğer küçük damar vaskülitlerinden ayıracak kadar spesifik değil
Chapel Hill 1994;
IgA dominant immün birikimlerin olduğu küçük damar vasküliti
Chapel Hill 2012 Revise;
Henoch-Schönlein purpura – IgAV
EULAR/ PRINTO/PRESS 2010 ;
Yaş kaldırılıyor, IgA birikimi, eklem ve renal tutulumu
Daha sensitif

Patogenez


1
Mucosal antigen
2
Increased antigen penetration due to defective mucosal immunity
Genetic factors
Epigenetic factors
Intestinal microvillus
Mucosal villous
MALT
DC
CD4+
3
Synthesis of galactose-deficient IgA1 exposing GalNAc residues and IgG anti-GalNAc IgA1
GalNAc
IgA
IgG
4
Formation of immune complexes and autoaggregates
GalNAc IgA1 –mucosal antigen immune complexes
GalNAc IgA1–IgG immune complexes
GalNAc IgA1 autoaggregates
5
Activation of complement in the circulation and at the mesangial and endothelial level
6
Activation of circulating leucocytes
7
Activation of resident endothelial cells and mesangial cells
9
Crescent formation
Neutrophil
Lymphocyte
Macrophage
Monocyte
Immune complexes and autoaggregates
Dead endothelial cell
Damaged podocyte
Cytokines
Leaky membrane
Inflamed glomerular capillary
Endothelial cell
Glomerular basement membrane
Podocyte
Cytokine
IgA
C3
Lumen
Mesangial cell
8
Attraction of inflammatory cells and activation of podocytes
Podocyte foot process
Glomerular capillary

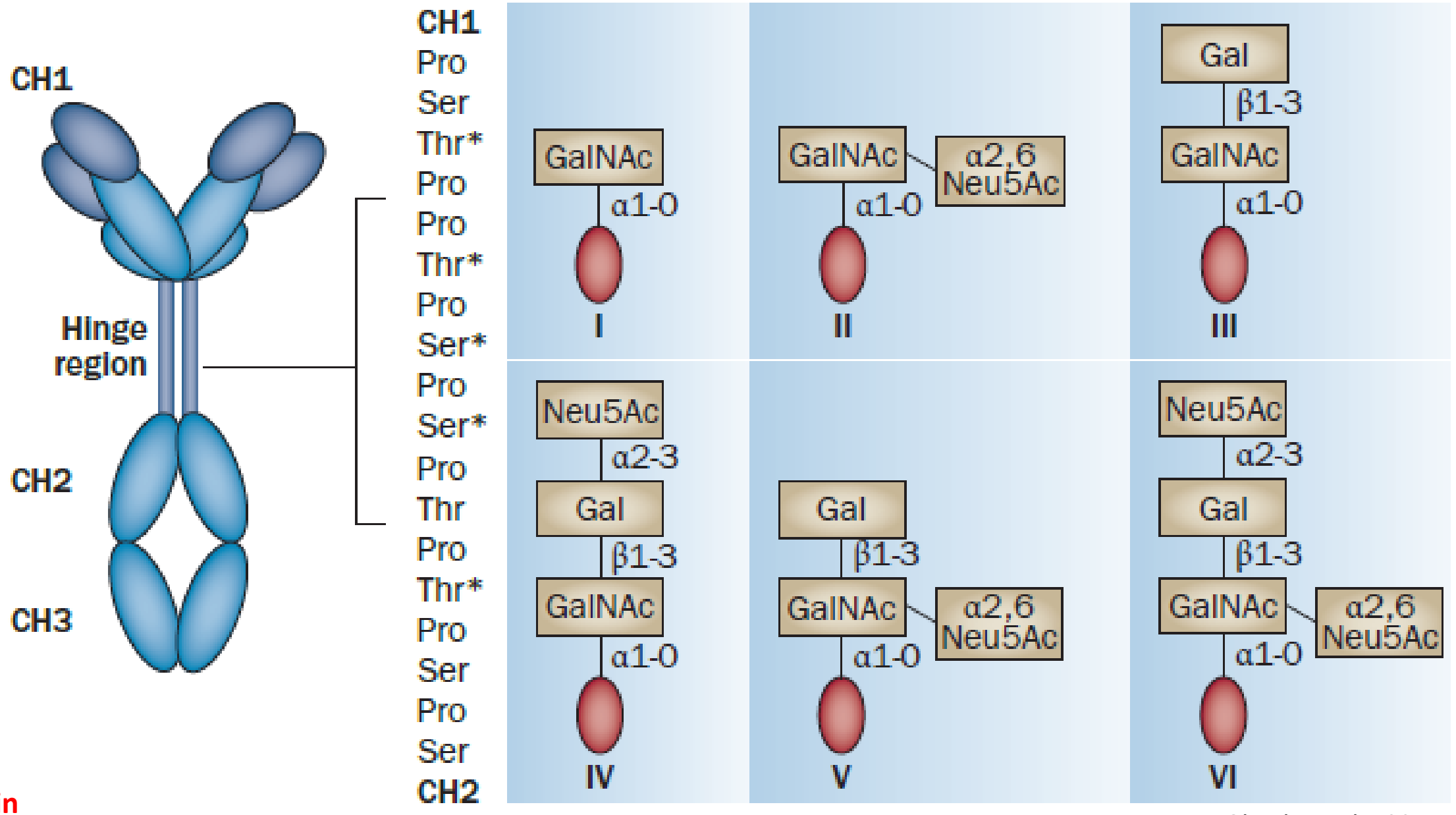
- Solunum ve GİS mukozası
- Plazma hücreleri-Kİ
- IgA1, IgA2
- Periferik kanda IgA1 dominant





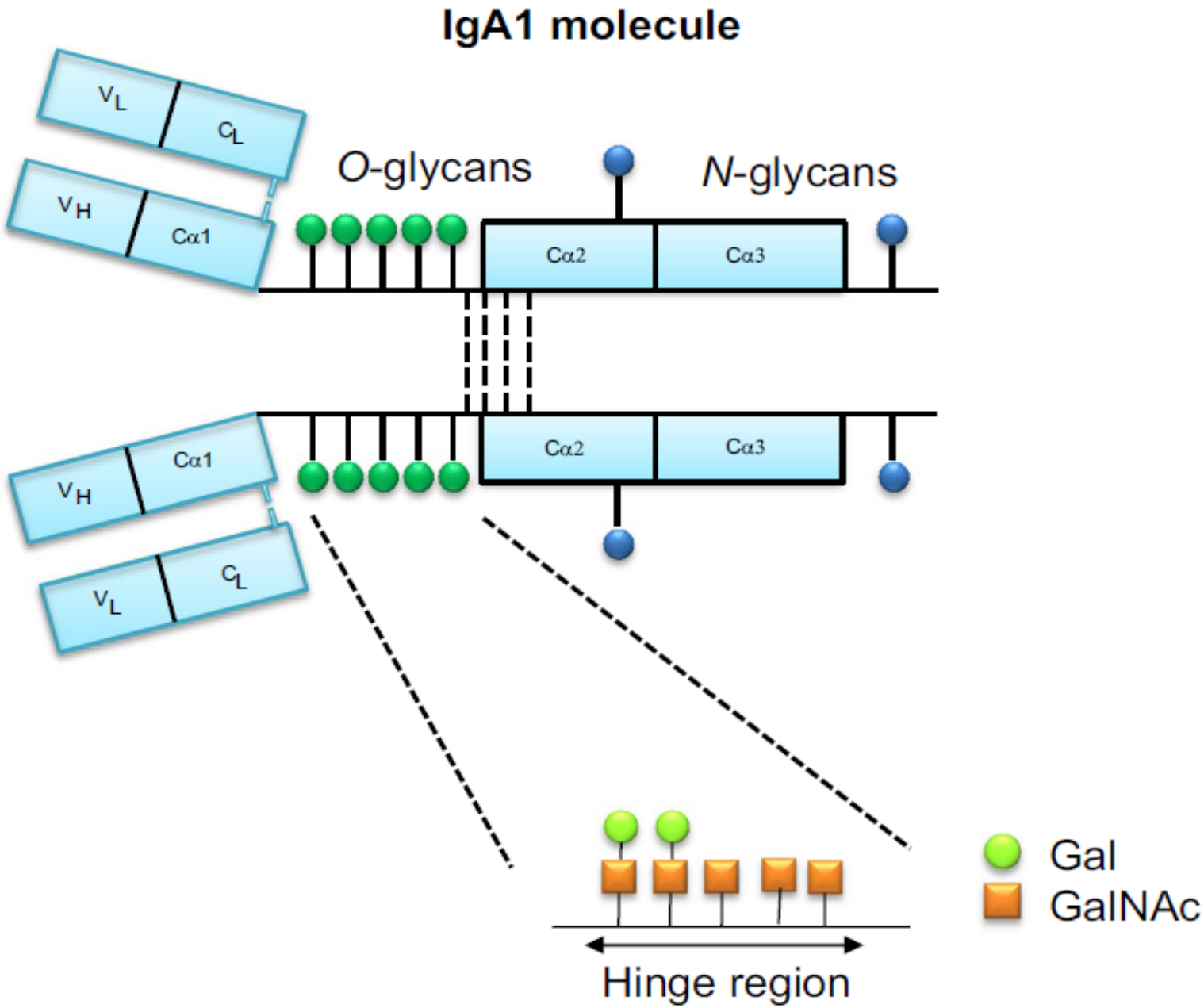
	mIgA	dIgA	SIgA
Molecular mass	~150 kDa	~320 kDa (dimer)	~390 kDa (dimer)
		~620 kDa (tetramer)	~690 kDa (tetramer)

https://www.researchgate.net/



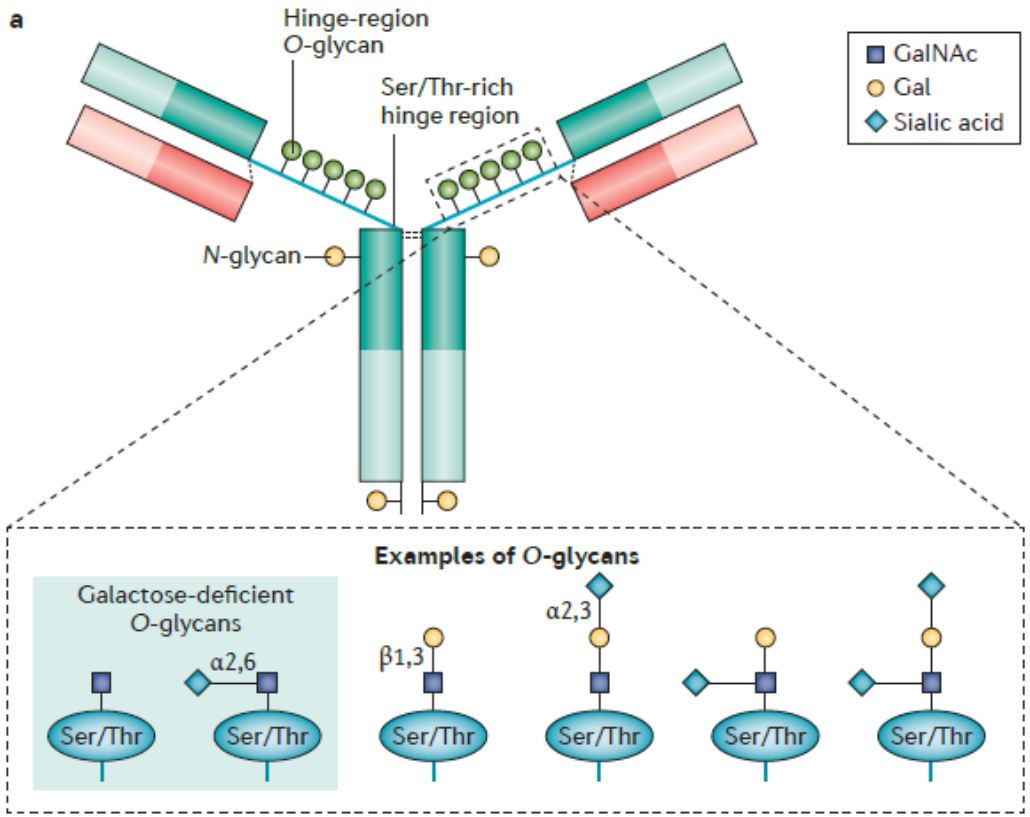
Proline
Serin
threonin

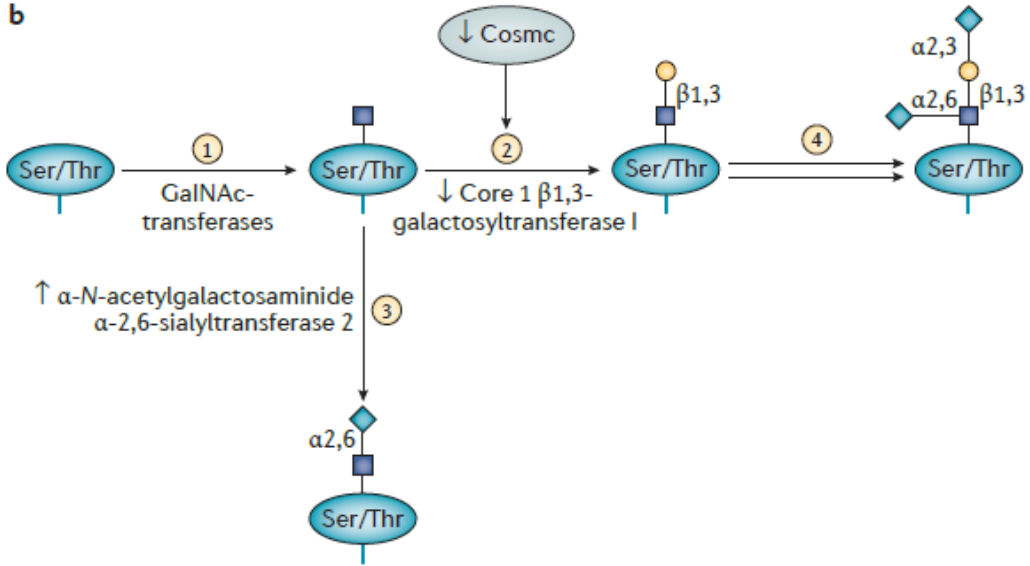
Jean-Claude Davin, 2014



Example of a Gal-deficient hinge-region glycopeptide

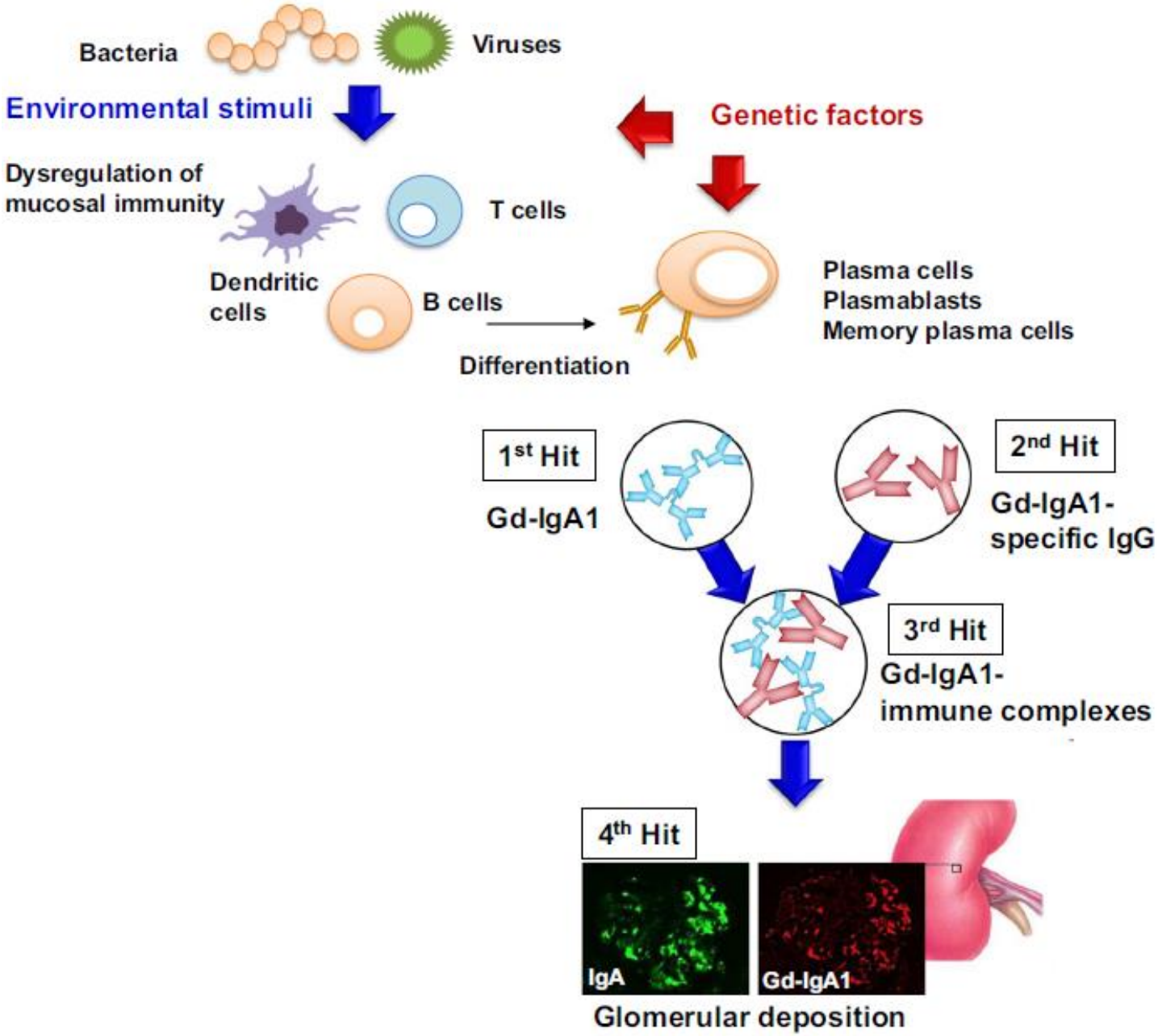
Suziki H, Novak J, 2021



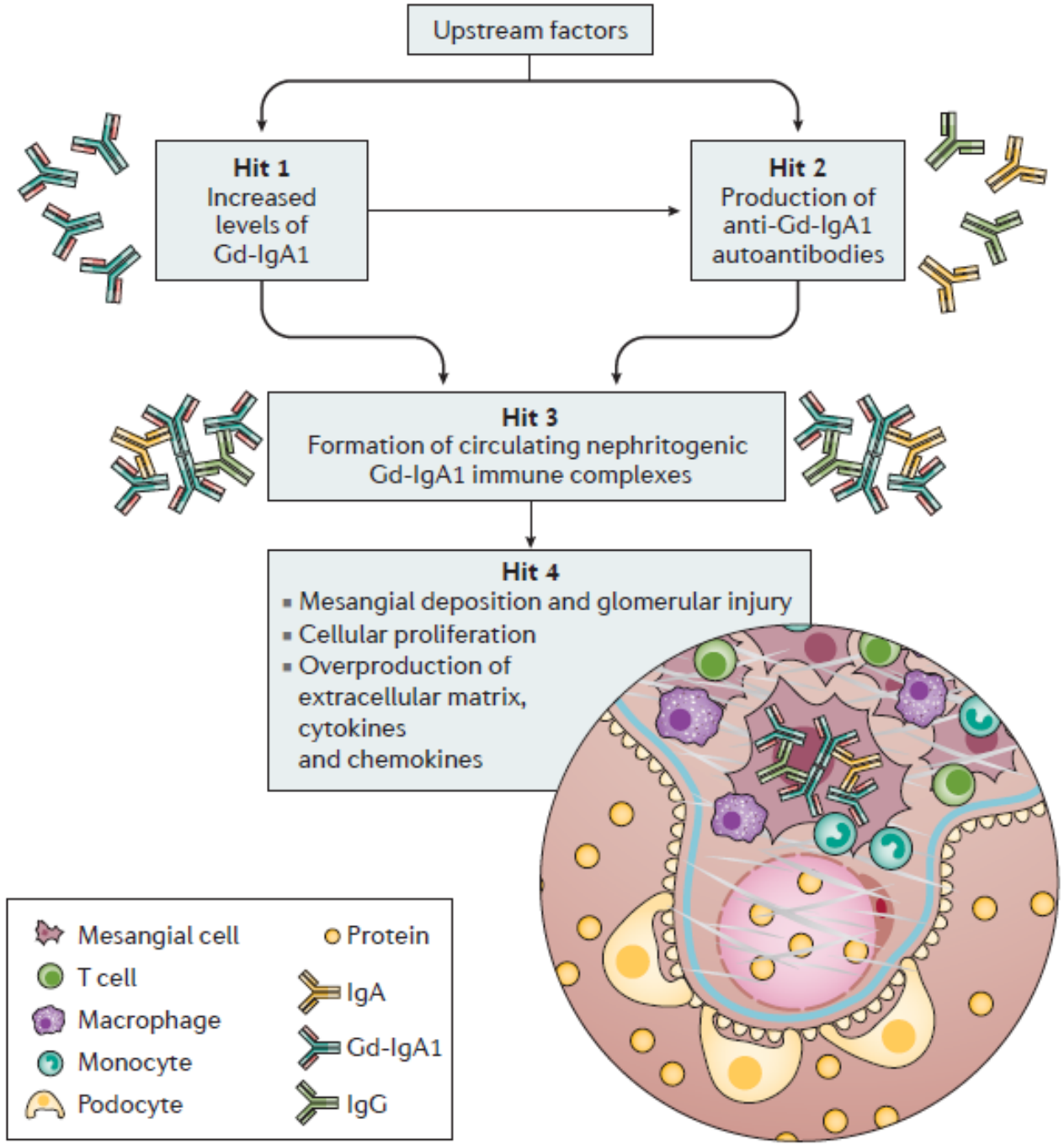


Self agregasyon
Antijenik yapı
IgG antikorların oluşumu
Gd-IgA1-IgG immun kompleks oluşumu
Dolaşım ----- böbrek
Mezenjial hücre aktivasyonu
Glomerüler zararlanma

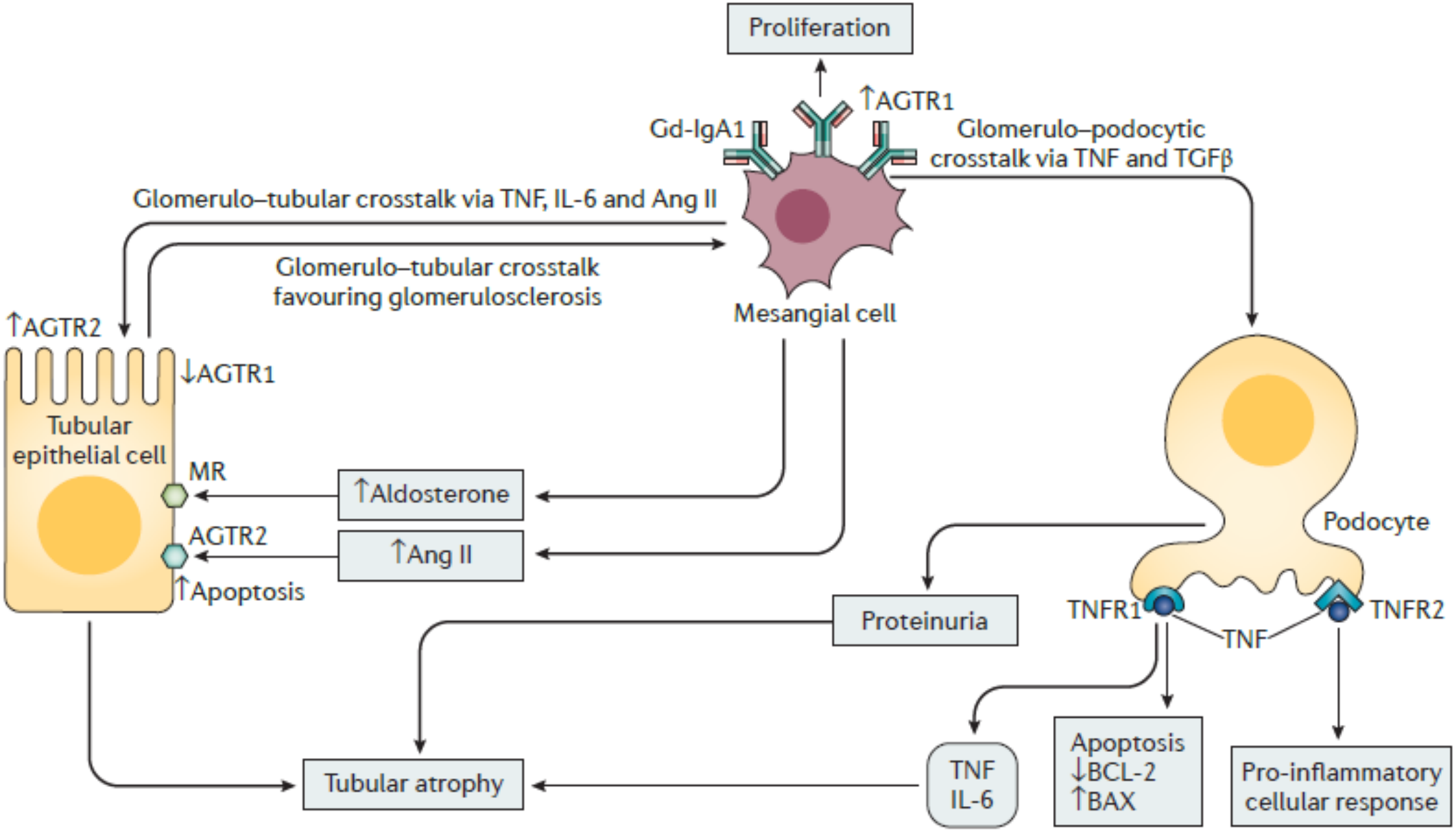
Kar Neng Lai, Sydney C, 2016



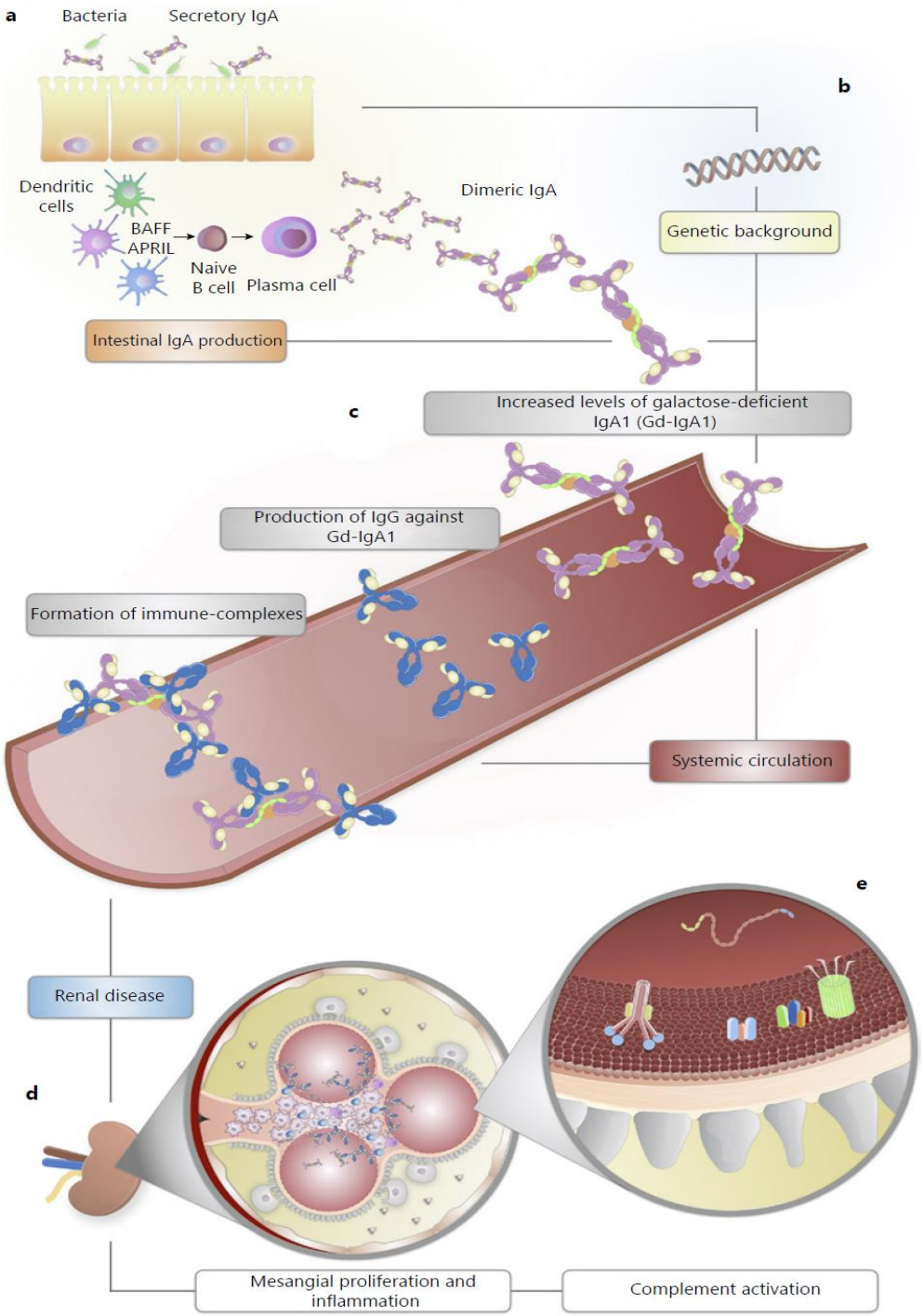
Suziki H, Novak J, 2021

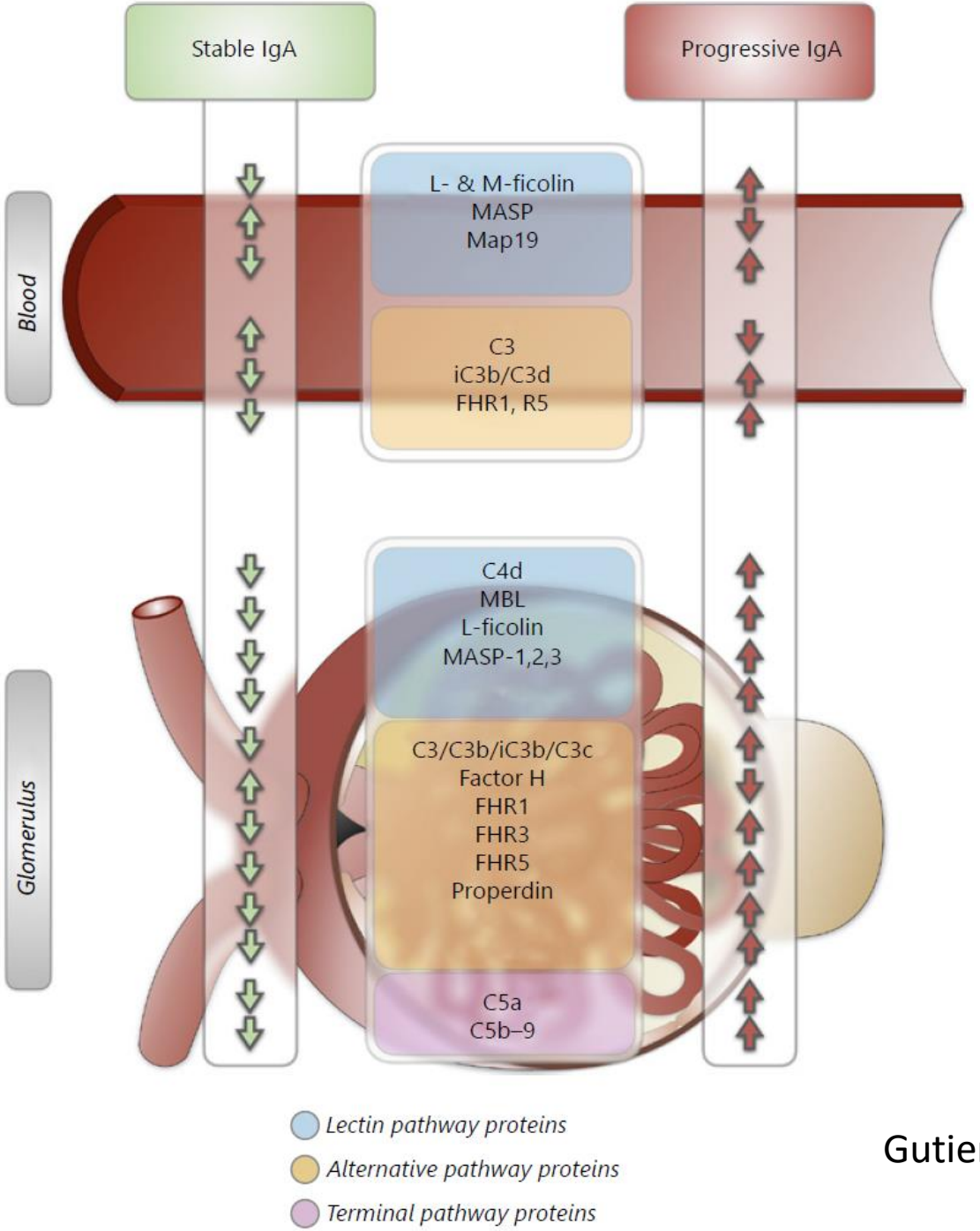


Kar Neng Lai, Sydney C, 2016

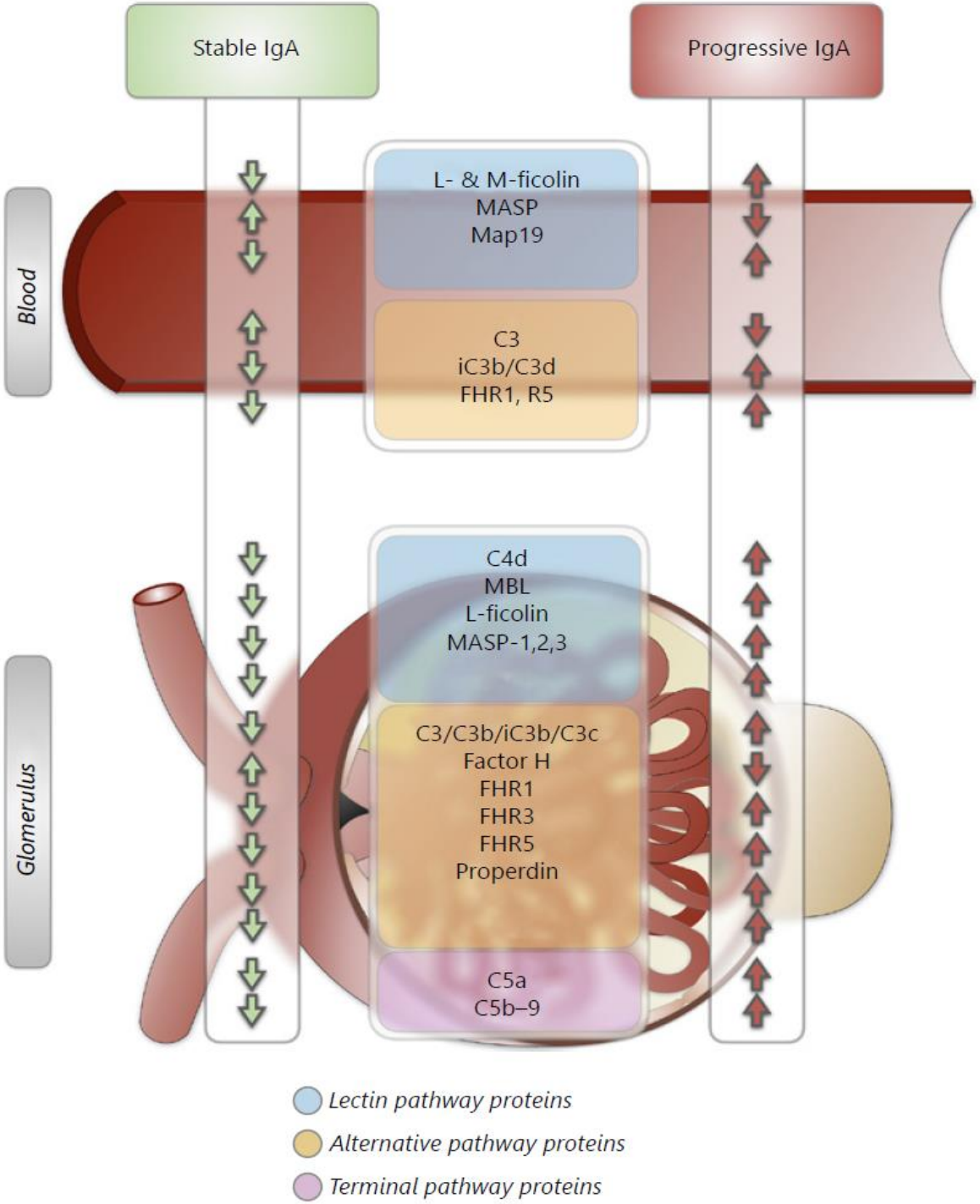


Kar Neng Lai, Sydney C, 2016





Gutierrez E, 2020



Alternatif yolak

- C3 birikimi
- FHR1
- FHR5
- Renal biyopsi

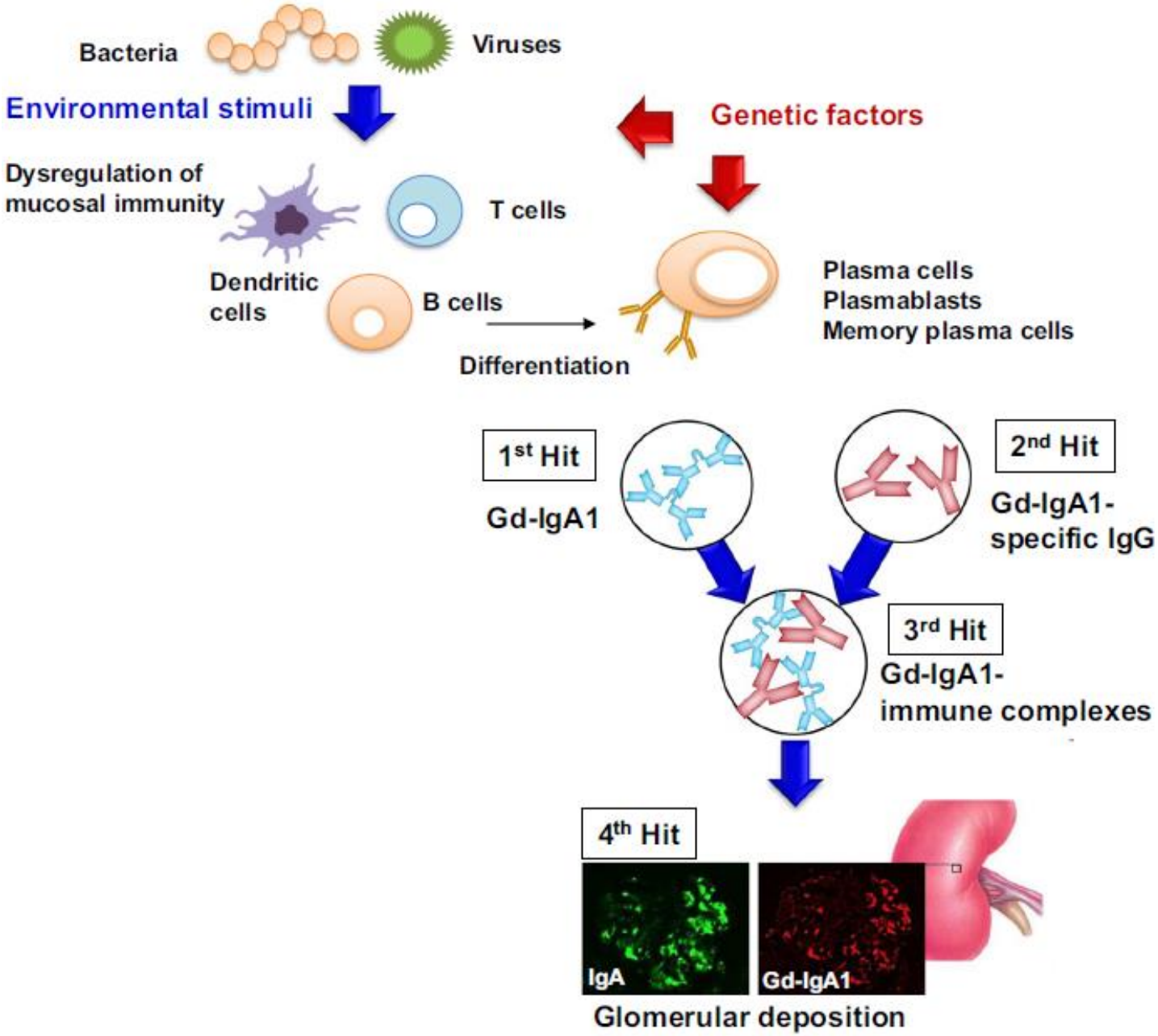
Lektin yollağı

- **C4d**

Terminal kompleman yolağı

- C5b-9

Gutierrez E, 2020



Kompleman yolakları

Suziki H, Novak J, 2021

İlişkili klinik durumlar

- İnfeksiyon

Üst solunum yolu

GİS

Diğer infeksiyonlar

Staf, strep, parvo, H pilori, hepatit B

- İlaçlar

Kinolon

Klaritromisin

Furosemid

Varfarin

- Malignite; Solid tm (AC , prostat, renal), hematolojik
- Romatolojik ; FMF, İBH, SPA

Klinik Belirtiler

- Deri
- Eklem
- Gastrointestinal sistem
- Renal
- Diğer

Palpabl purpura

Artrit/artralji

Karın ağrısı

Renal hastalık

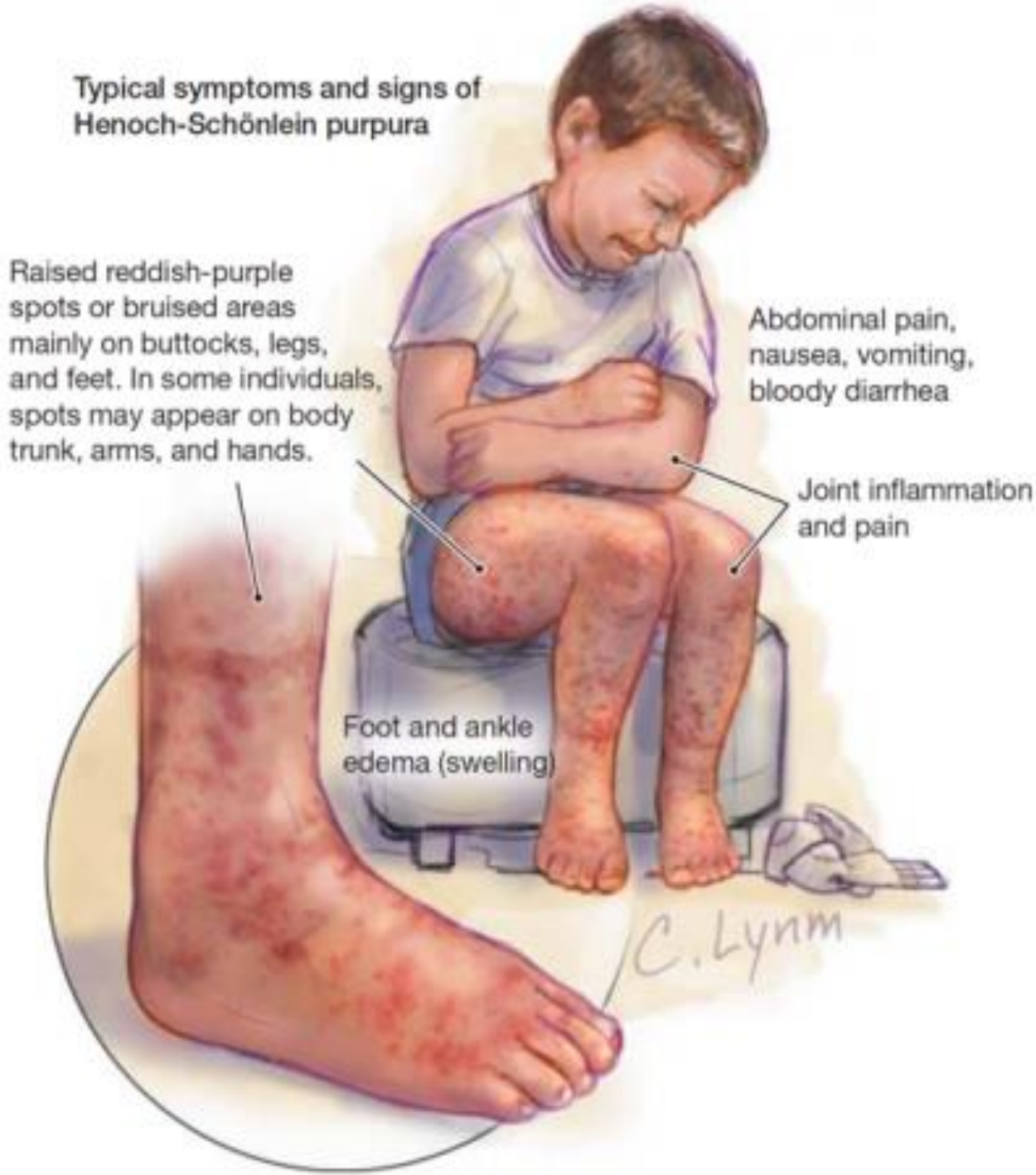
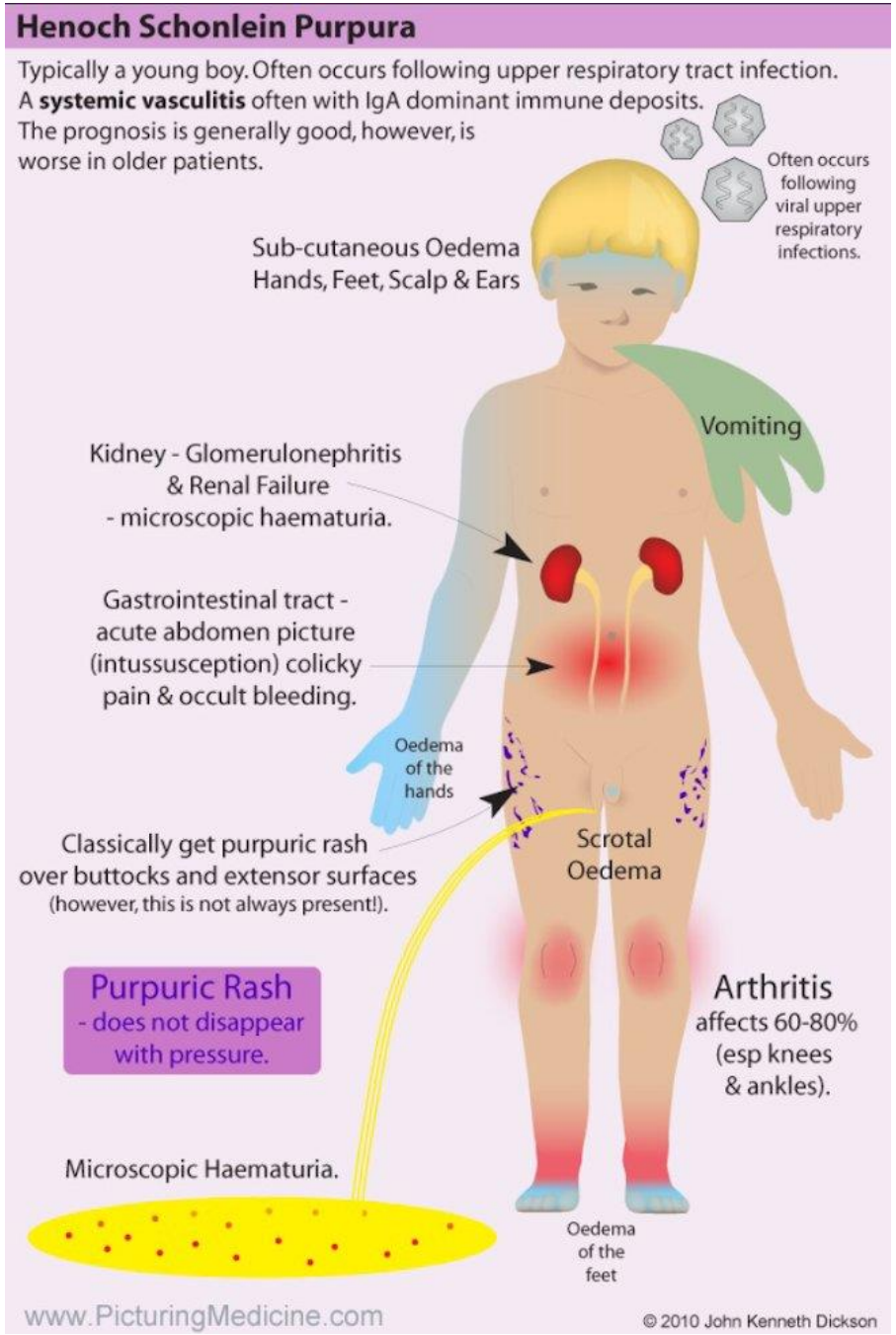


Table 2 Comparison of clinical manifestations and disease outcomes between adults and children

	Adults	Children
Incidence	0.1–1.8 per 100,000 individuals [2]	3–26 per 100,000 individuals [1]
Seasonal pattern	Less seasonal	Typically seasonal
	Common in summer	Common in fall and winter
Clinical association	Malignancy and drugs are more common triggers	
	Infection is less common [15–17]	Infections are common
Skin manifestations	Severe lesions are common	Mild lesions are common
Rash	Necrotic, bullous lesions are frequent [7, 14]	Purpura in most patients [7, 14]
Affected distribution	Lesions are frequently resistant to treatment	Lesions are frequently self-limited and do not require treatment
	Frequently reported in upper extremities and trunk [15]	Usually limited to lower extremities [15]
Joint manifestations	Common [16]	Common [16]
	High incidence at disease onset	Less reported at disease onset
Gastrointestinal manifestations		
Abdominal pain, diarrhea , hematochezia, & nausea	Common 56% [15]	Common 62% [15]
Intussusception	Rare	Common up to 13.6% [20]
Renal disease	Common [21]	Uncommon
	Severe renal disease in 30% (nephrotic syndrome and renal failure) [15, 21]	Severe renal disease in 1% (nephrotic syndrome and renal failure) [15, 21]
Renal outcome	At 2-year follow up, chronic disease in 80% [7, 15]	At 2-year follow up, self-limited in > 95% [15, 16]
	Frequent relapses: 20% [15]	Relapses are rare



Yaseen K,2021

Deri

- **Palpabl purpura**

%75

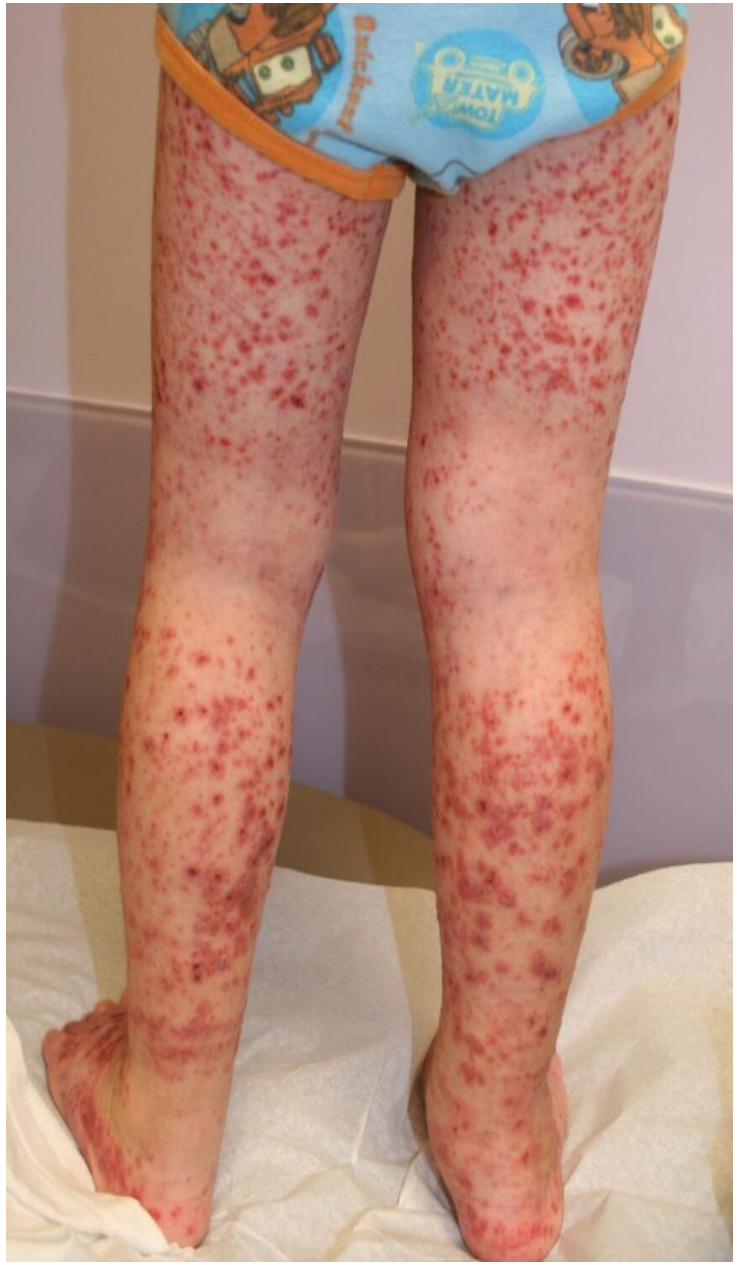
Simetrik

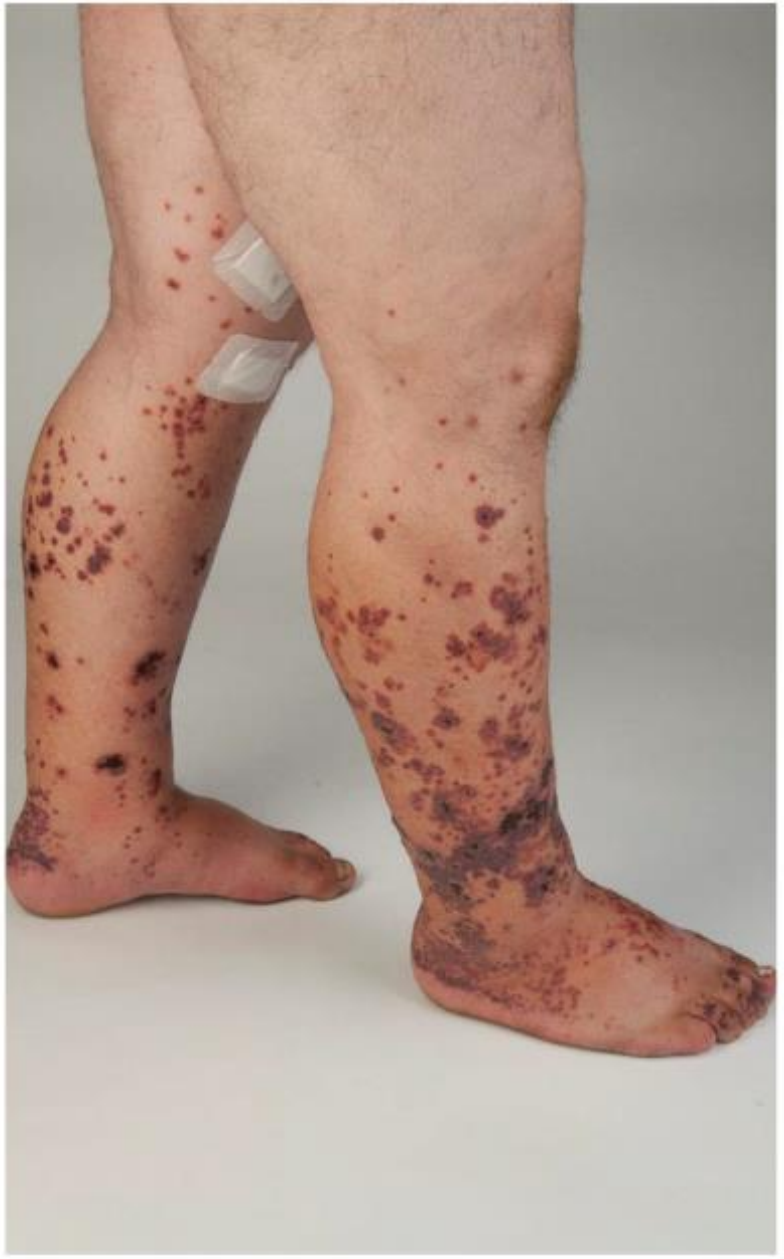
Kalçalar ve alt ekstremite

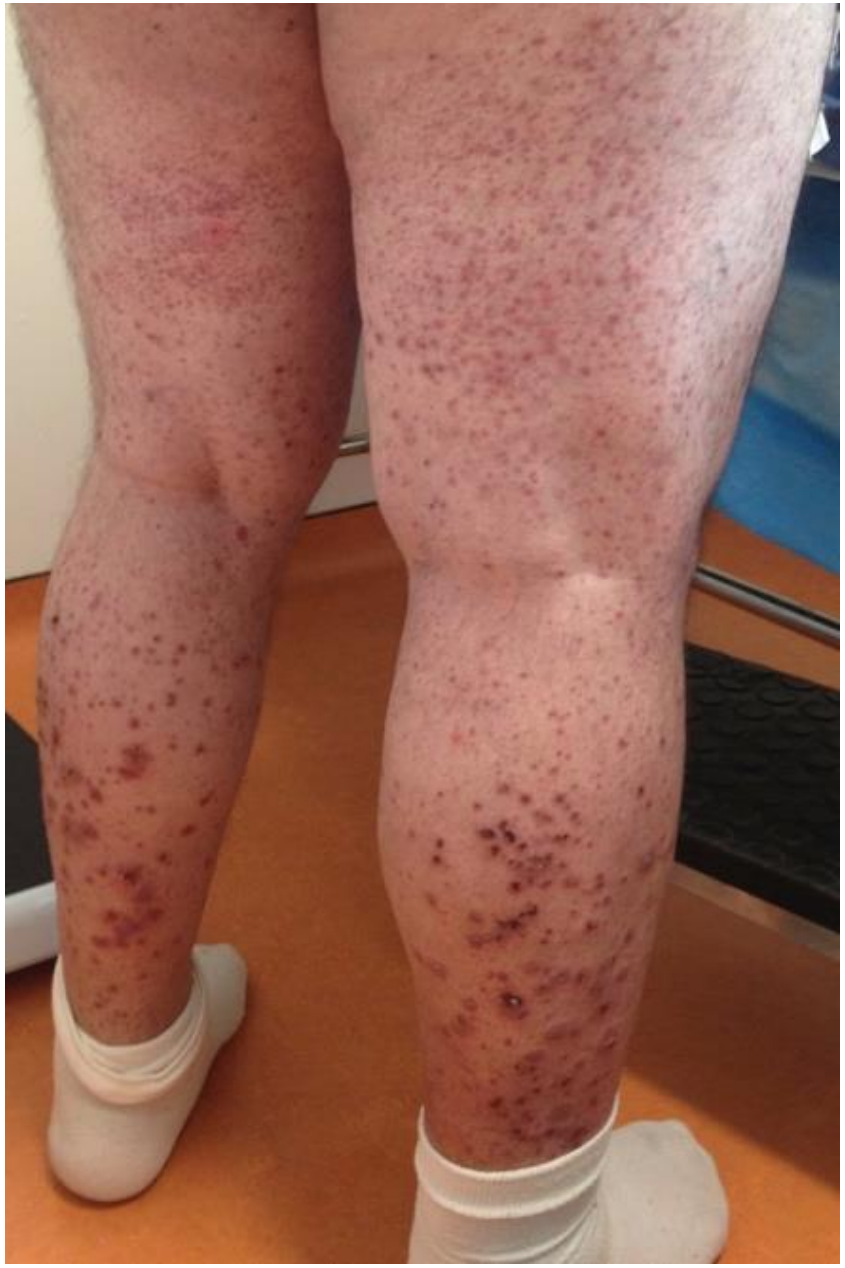
Bacaklar ve ayaklar

Kaşıntılı olabilir ama nadiren ağrılı

- lokalize subkutan ödem
- Nekrotik veya hemorajik purpura
- Bül ve püstül







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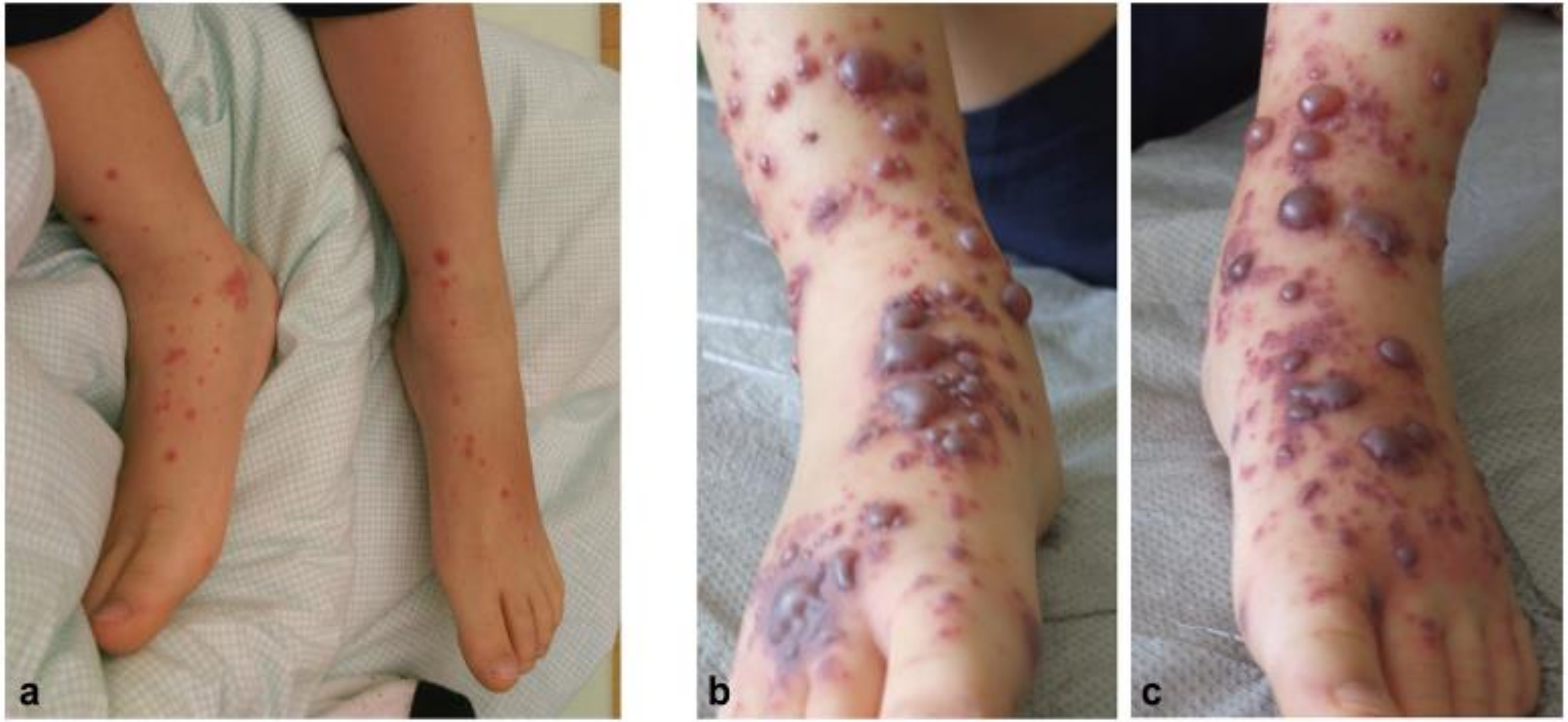
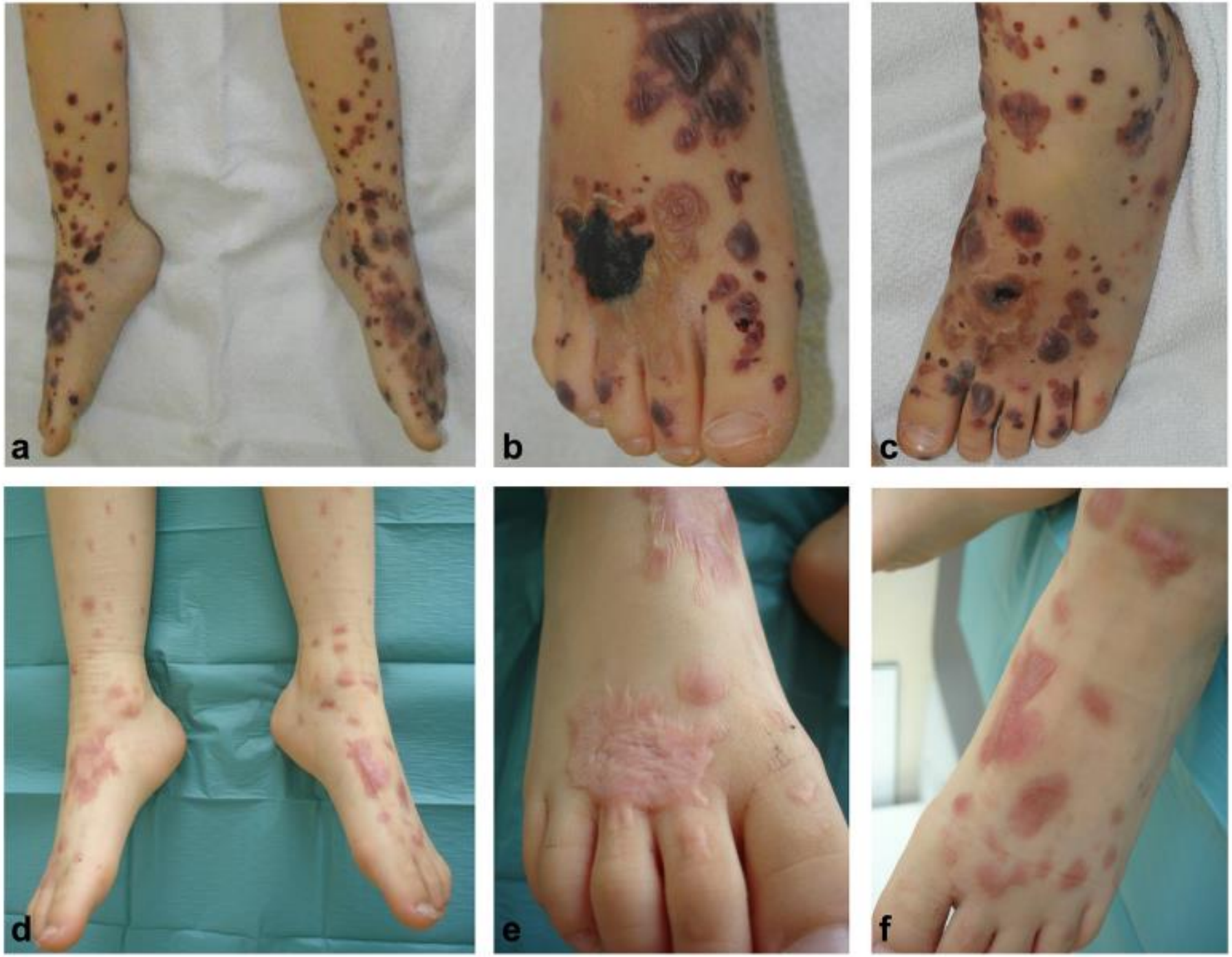
https://www.researchgate.net

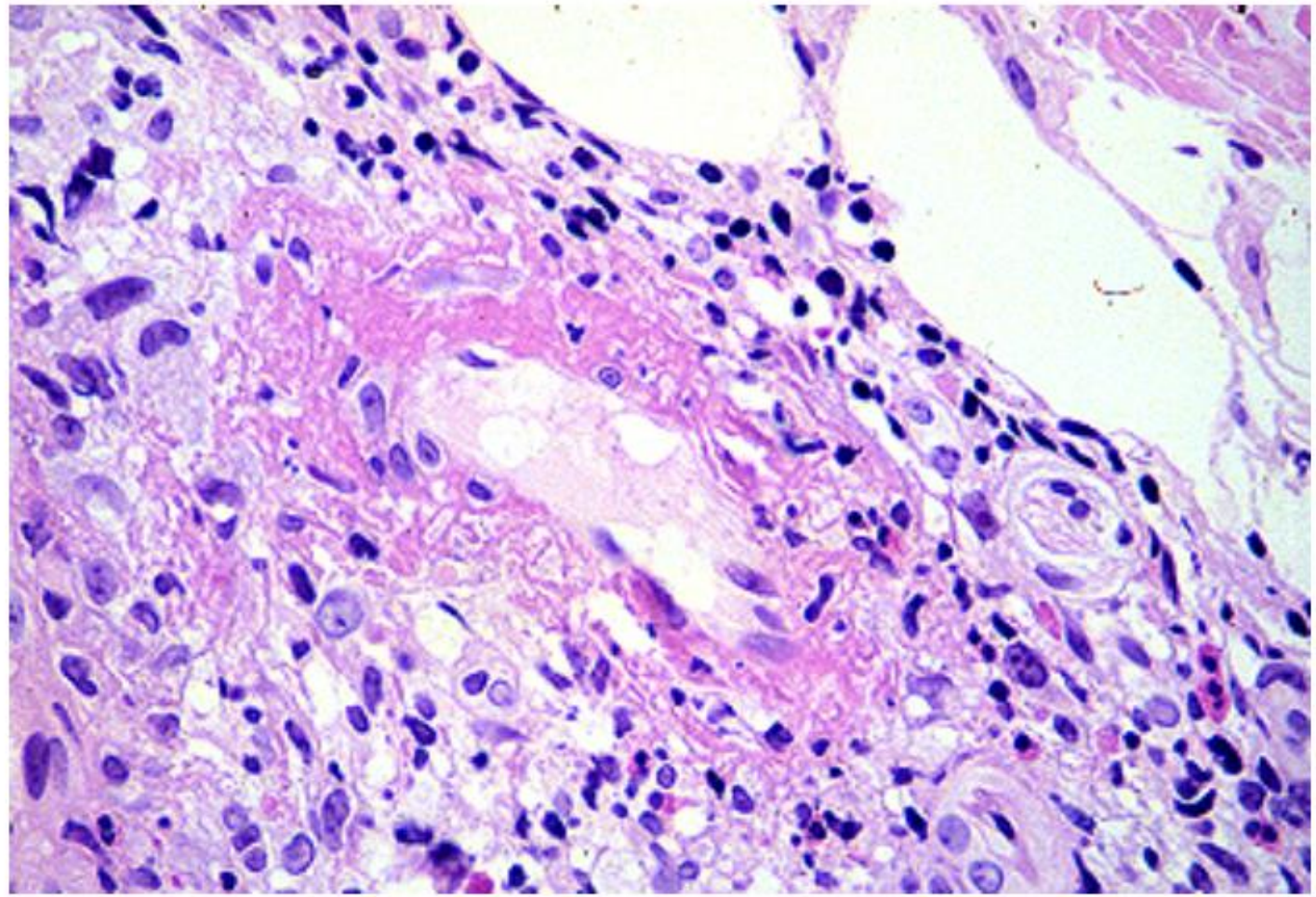


Matthias Nothhaft, 2019



Matthias Nothhaft, 2019

Leukocytoclastic vasculitis histology



Eklem

- **Artralji**, ayak bileği ve diz
- Periartiküler yumuşak doku şişliği
- Efüzyon sık değil
- Artrit

Geçici

Oligoartiküler

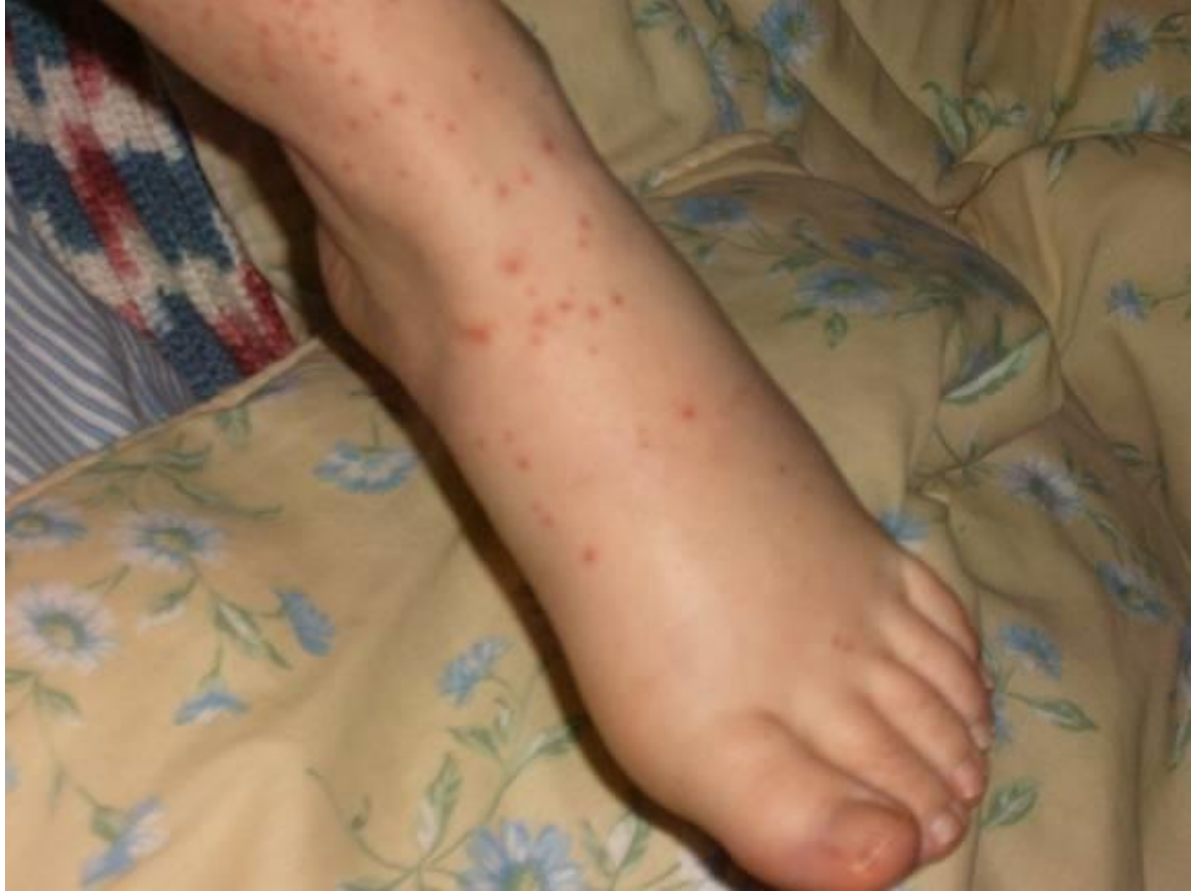
Deformitesiz

Alt ekstremite

Eritem ve sıcaklık artışı genellikle yok

- Myalji,

Kreatinin kinaz yüksekliği yok



https://www.hopkinsvasculitis.org

Gastrointestinal sistem

Submukozal hemoraji, duvar ödemi, ince ve kalın barsak vasküliti

- **Karın ağrısı,** %50

Çocuklarda; difüz karın ağrısı

Erişkinlerde;

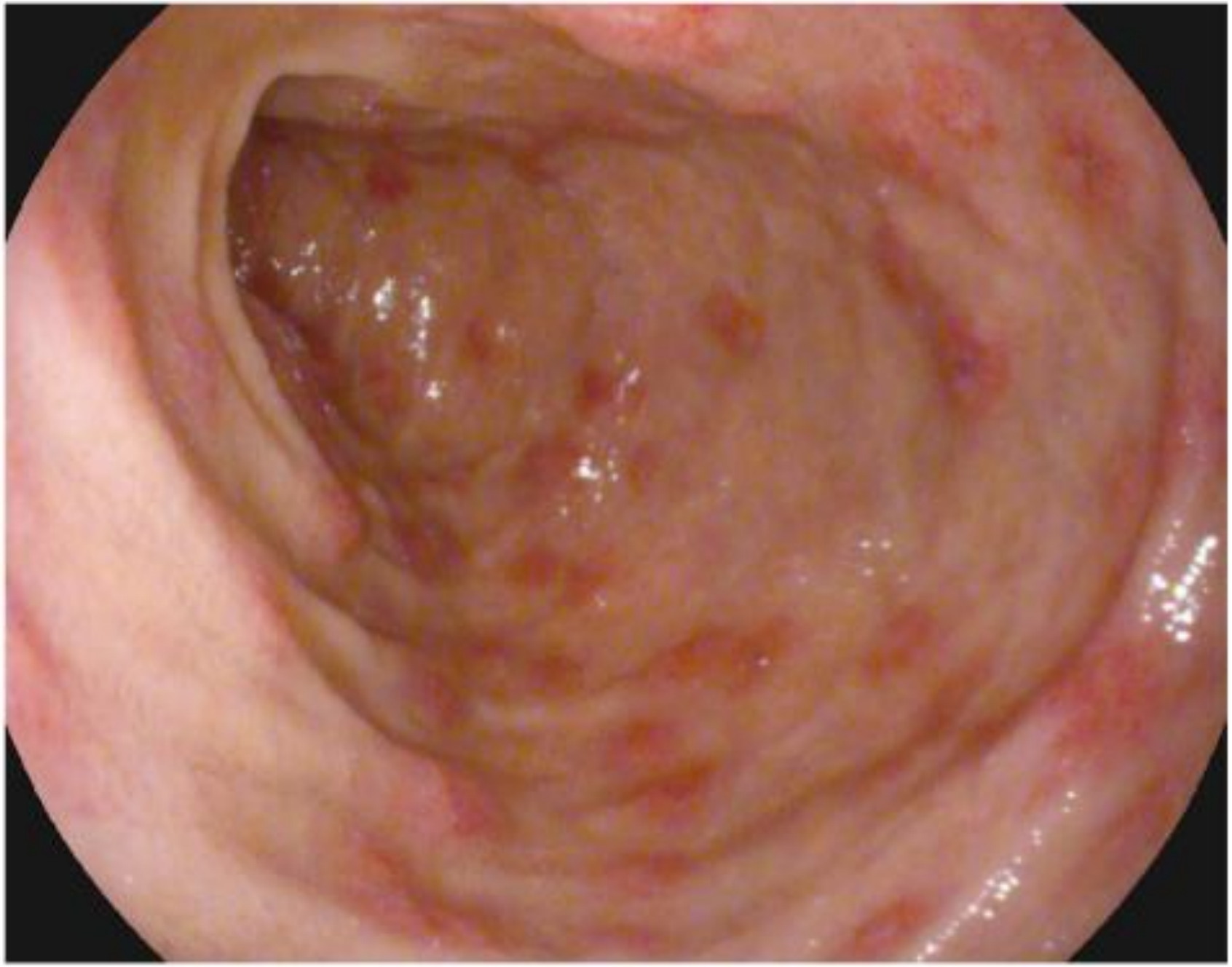
Epigastrik, sağ alt karın lokalizasyonlu

Yemeklerden sonra artış

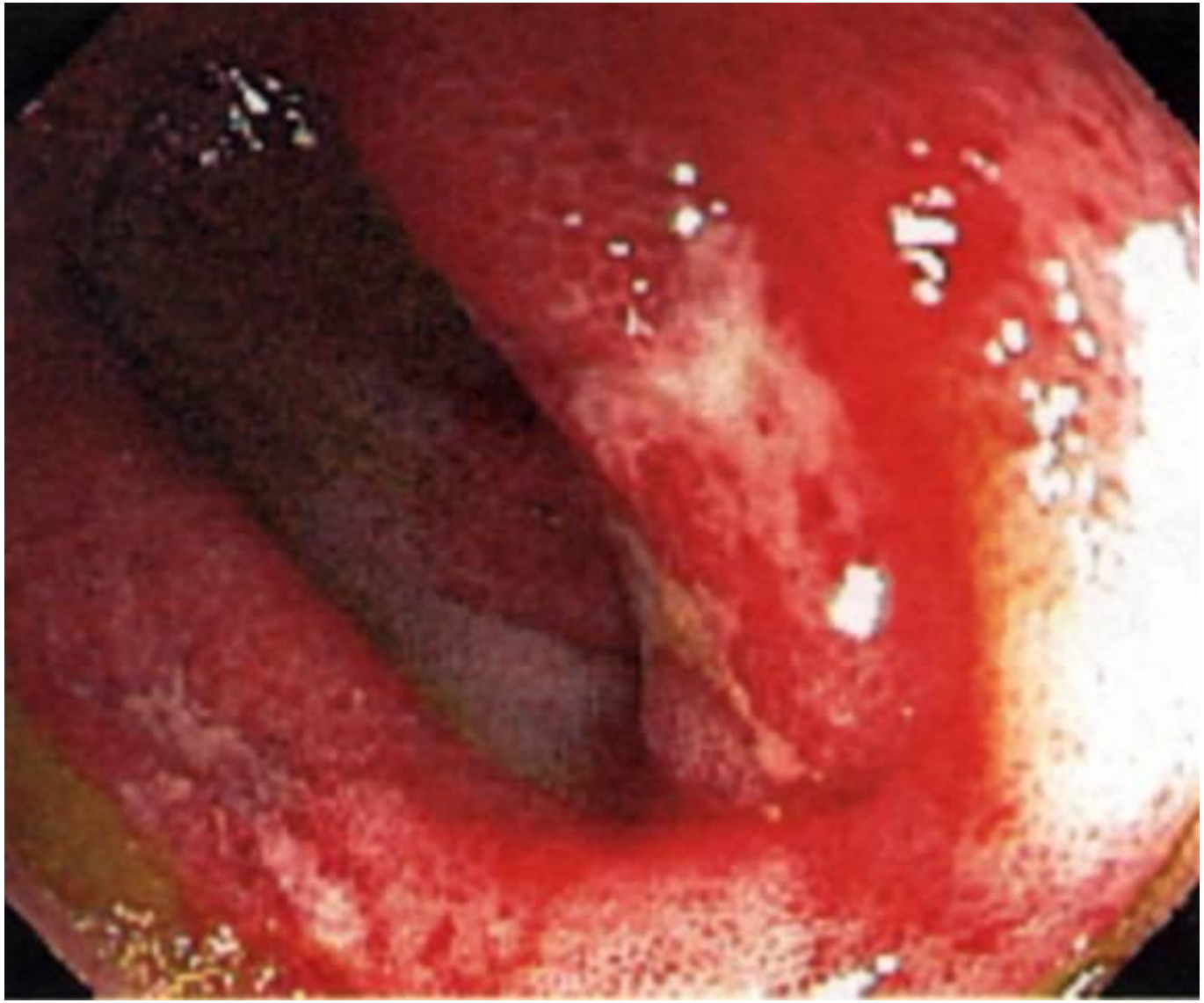
Barsak iskemisine benzer yakınmalar

- Bulantı
- Diare
- Gaitada kan
- GİS kanaması, %20-30
- İntussepsiyon; en sık **ileoileal**, ileokolik
- Perforasyon; ince barsak özellikle **ileum**
- Pankreato-hepatobilier tutulum; pankreatit kolesistit

Lina Du,2021



Chiara Rubino, 2018



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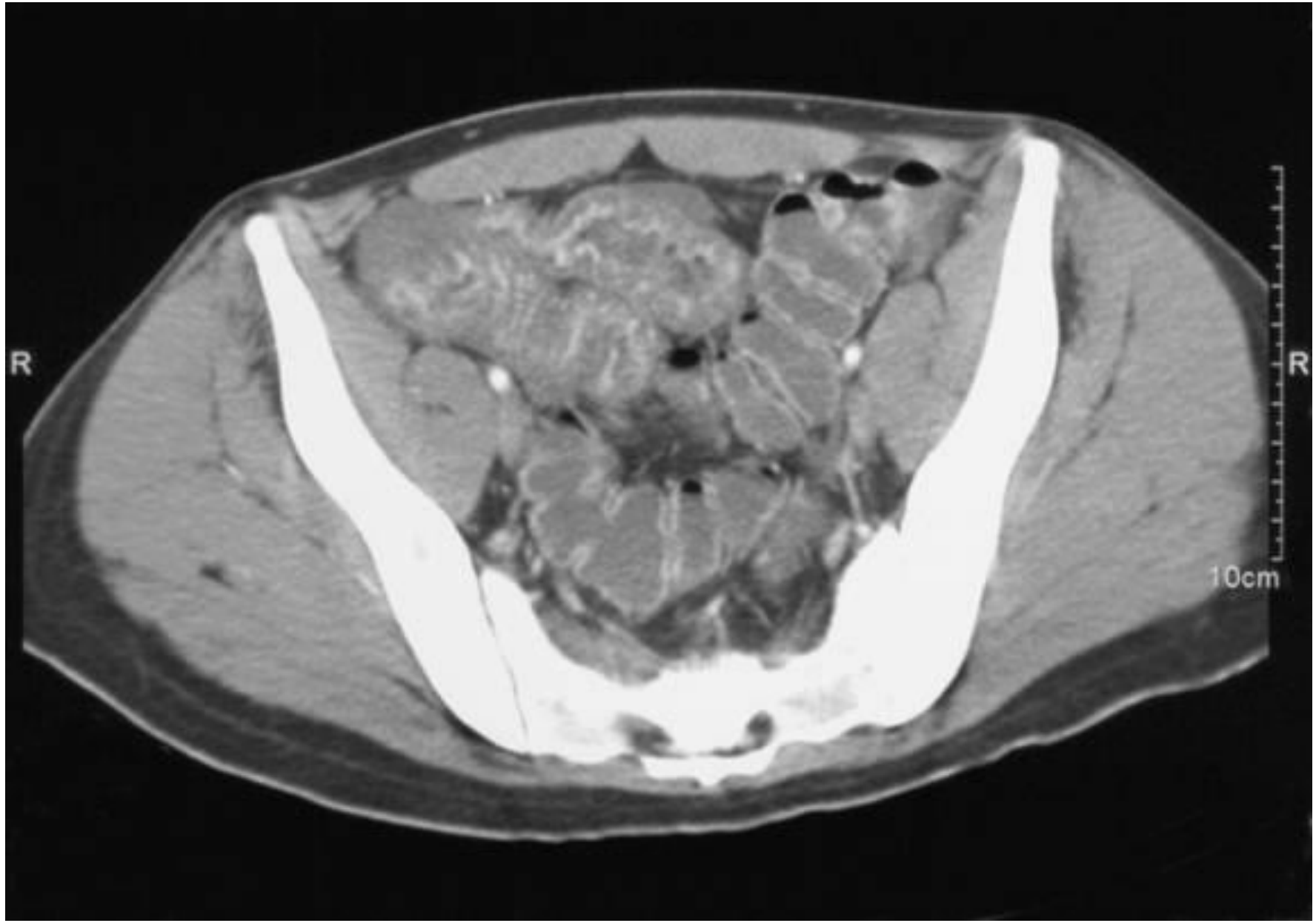


https://www.hopkinsvasculitis.org

Renal

- Gross hematüri, bir ya da daha fazla atak - %40-50
- Mikroskopik hematüri, orta derecede proteinüri - %30-40
- Nefrotik sendrom, akut hızlı ilerleyen glomerulonefrit

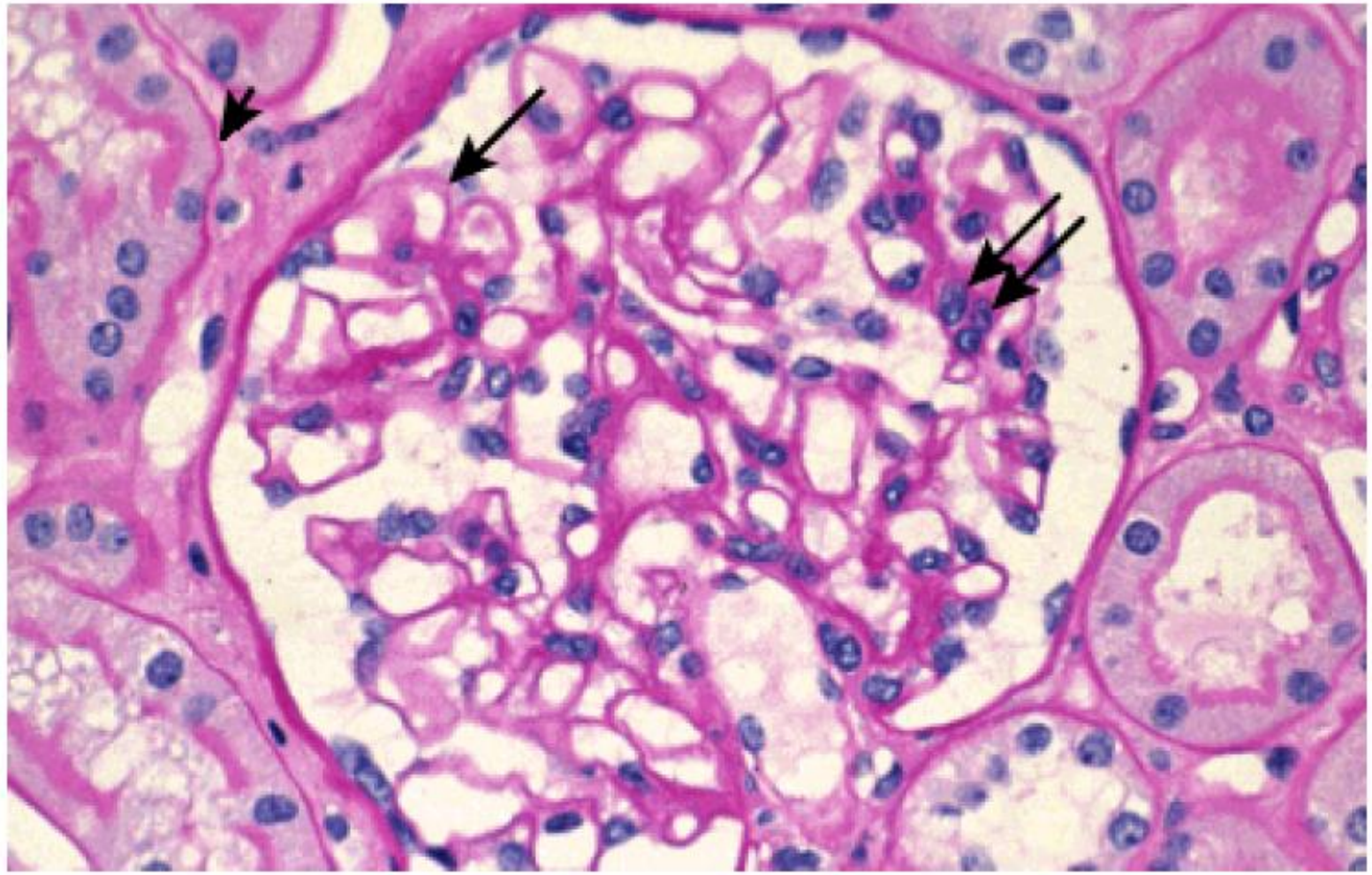
Ödem

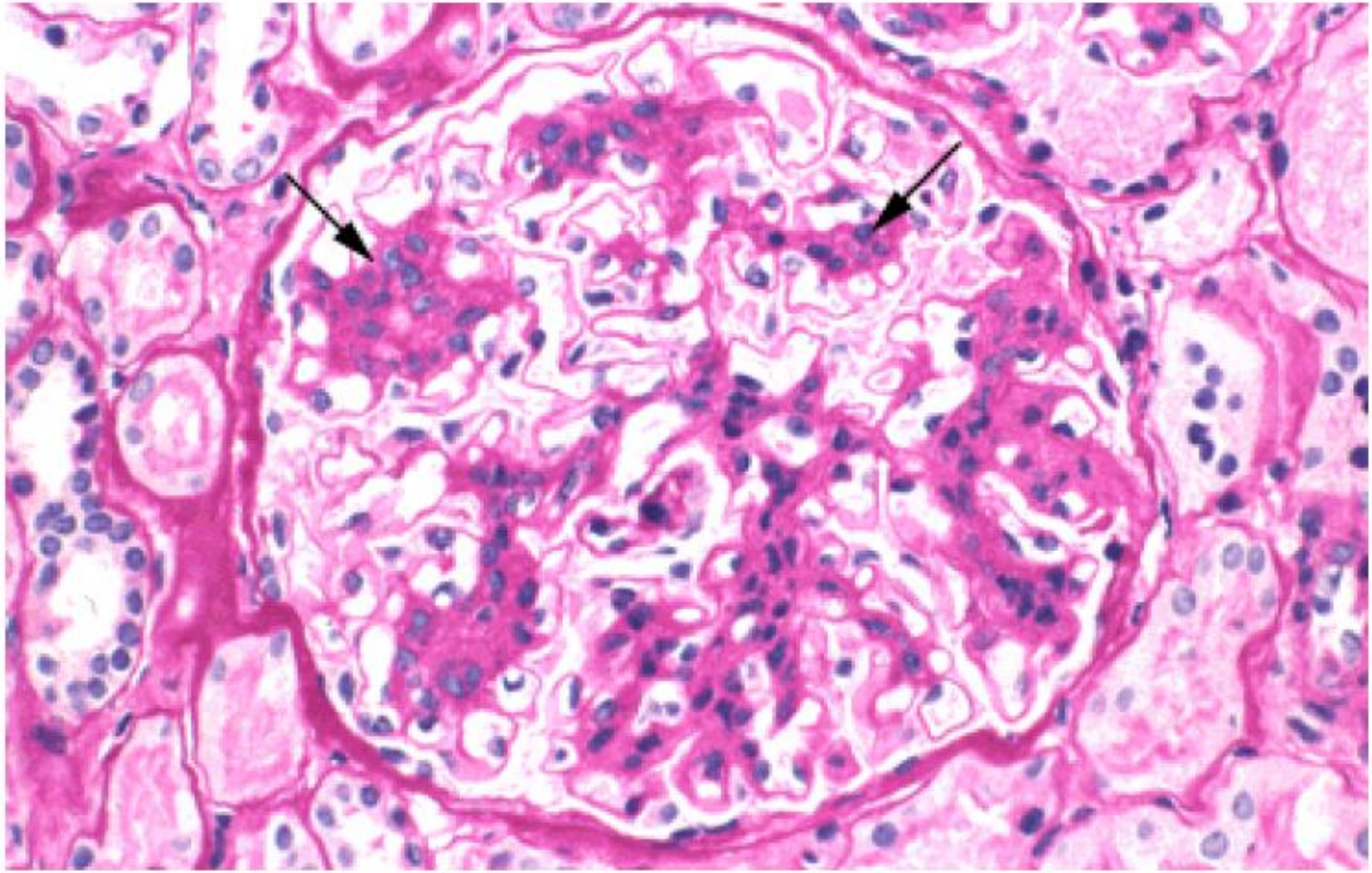
Hipertansiyon

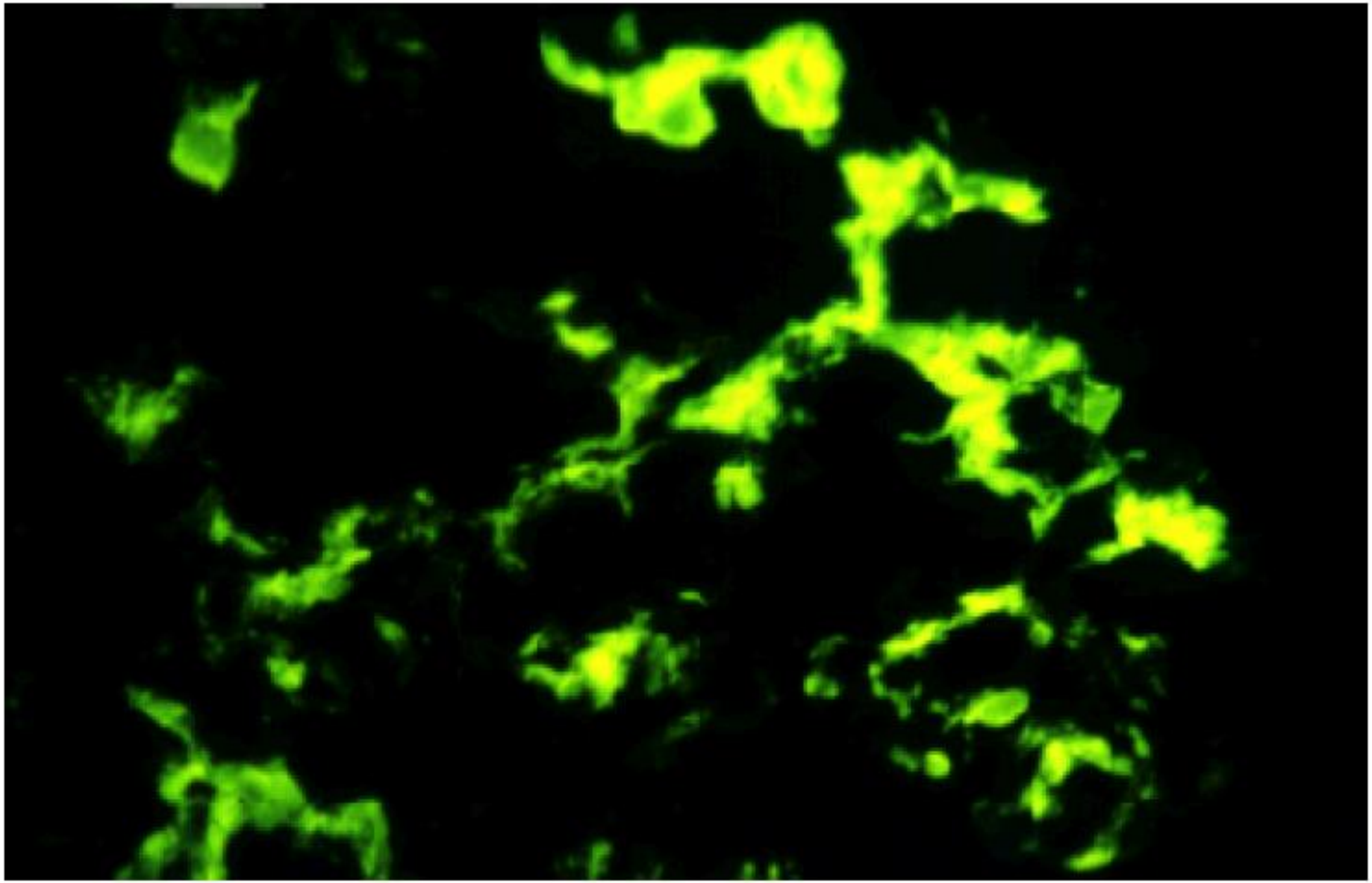
Böbrek yetmezliği

- Malign hipertansiyon

Chee Kay Cheung, 2021







MEST-C IgA nefropatisi

- **M**esangial hypercellularite
- **E**ndocapillary hypercellularite
- **S**egmental glomerulosclerosis
- **T**ubular atrophy/interstitial fibrosis
- **C**rescents

Table 1 | **MEST-C criteria in the updated Oxford Classification of IgA Nephropathy**[3]

Histological variable	Definition	Score
Mesangial hypercellularity	More than four mesangial cells in any mesangial area of a glomerulus	• M0: <50% of glomeruli showing mesangial hypercellularity • M1: >50% of glomeruli showing mesangial hypercellularity
Endocapillary hypercellularity	Hypercellularity due to an increased number of cells within glomerular capillary lumina	• E0: no endocapillary hypercellularity • E1: any glomeruli showing endocapillary hypercellularity
Segmental glomerulosclerosis	Adhesion or sclerosis (obliteration of capillary lumina by matrix) in part but not the whole glomerular tuft	• S0: absent • S1: present in any glomeruli
Tubular atrophy/ interstitial fibrosis	Estimated percentage of cortical area showing tubular atrophy or interstitial fibrosis, whichever is greater	• T0: 0–25% of cortical area • T1: 26–50% of cortical area • T2: >50% of cortical area
Cellular or fibrocellular crescents	Percentage of glomeruli with cellular or fibrocellular crescents	• C0: absent • C1: 0–25% of glomeruli • C2: ≥25% of glomeruli

IgA vaskülitli erişkin hastalarda validasyonu yoktur

Markowitz G, 2017

Prognoz

Box 3 | **Markers of poor prognosis in IgA nephropathy**

Demographic

Male sex[143,144]
Older age at diagnosis (>60 years)[145,146]
Obesity[147]

Clinical

No history of macroscopic haematuria[148]
Persistent microscopic haematuria[149,150]
Persistent hypertension[151,152]
Increased serum creatinine levels at presentation[149,153]

Laboratory

Persistent proteinuria (>1,000 mg per day)[81,154]
Hyperuricaemia[155,156]
Hypertriglyceridaemia[157]
Angiotensin-converting enzyme DD genotype[145]

Histological — light microscopy

Glomerular sclerosis[150,154]
Endocapillary cellular proliferation[158]
Capillaritis[159]
Interstitial fibrosis[152,160,161]
Thrombotic microangiopathy[162]
Loss of podocytes[163]
Collectively increased Oxford-MEST scores[164]

Histological — immunofluorescence microscopy

Mesangial IgG co-staining[165,166]

Kısa dönem prognoz GİS semptomlarının ciddiyetine, Uzun dönem prognoz nefrite bağlıdır

Kar Neng Lai, Sydney C, 2016

Diğer

- Alt üriner sistem; üreter obstrüksüyonu, üretrit, hemorajik sistit
- Üreme sistemi; skrotum ve testislerde ödem ve ağrı,epididimit, orşit, testisde hematom
- Dolaşım sistemi; DLCO azalma
- Difüz alveolar hemoraji
- Myokardial tutulum; iletim anomalisi, KKY, myokardial nekroz
- Kalp kapağı tutulumu
- Tromboz; venöz , arteryel, portal,mezenterik, iliofemoral ven, koroner arter
- Santral sinir sistemi tutulumu; ensefalopati
- Serebral vaskülit
- Serebral hemoraji
- Posterior reversibl ensefalopati sendromu
- Nöbet; jeneralize
- Periferik sinir sistemi zararlanması; fasial paralizi, GBS, akut motor sensori aksonal nöropati
- Oküler tutulum, Ant iskemik optik nöropati, bilateral santral retinal arter oklüzyonu,sklerit
- Şilotoraks, şiloasit, adrenal hemoraji

Lina Du,2021

Tanı

- Klinik belirtiler, bulgular
- Histopatolojik değişiklikler
- Spesifik tanısal lab testi yok
- ESH, CRP
- Böbrek fonksiyon testleri
- İdrar
- Kompleman düzeyleri
- IgA

Adult IgA-vasculitis Diagnosis algorithm

HISTORY:
- Skin lesions/rash
- Joint pain
- Abdominal pain
- Lower extremity edema

PHYSICAL EXAM:
- Skin lesions/rash
- Joint tenderness and/or swelling
- Abdominal tenderness
- Lower extremity edema

LABORATORY TESTS:
- Complete blood cell count
- WSR and CRP
- Urinalysis & 24 hour urine protein
- Serum creatinine

IF ABDOMINAL PAIN PRESENT:
- Obtain abdominal ultrasound or CT (to rule out other disorders): may show lymphadenopathy in IgA-vasculitis

IF RASH PRESENT:
- Obtain skin biopsy with direct immunofluorescence

IF URINE DIPSTICK POSITIVE FOR BLOOD:
- Exam fresh urine sediment for the presence of RBC casts and/or dysmorphic RBCs

If skin biopsy shows leukocytoclastic vasculitis with deposits of IgA and C3, urine sediment shows RBC casts and the kidney function is normal, a kidney biopsy may not be necessary for diagnosis.

Kidney biopsy may be necessary if:
- Impaired kidney function
- Nephrotic or nephritic syndrome
- Persistent proteinuria > 1g/day at 6 months
- Diagnostic uncertainty

Yaseen K,2021

Tedavi

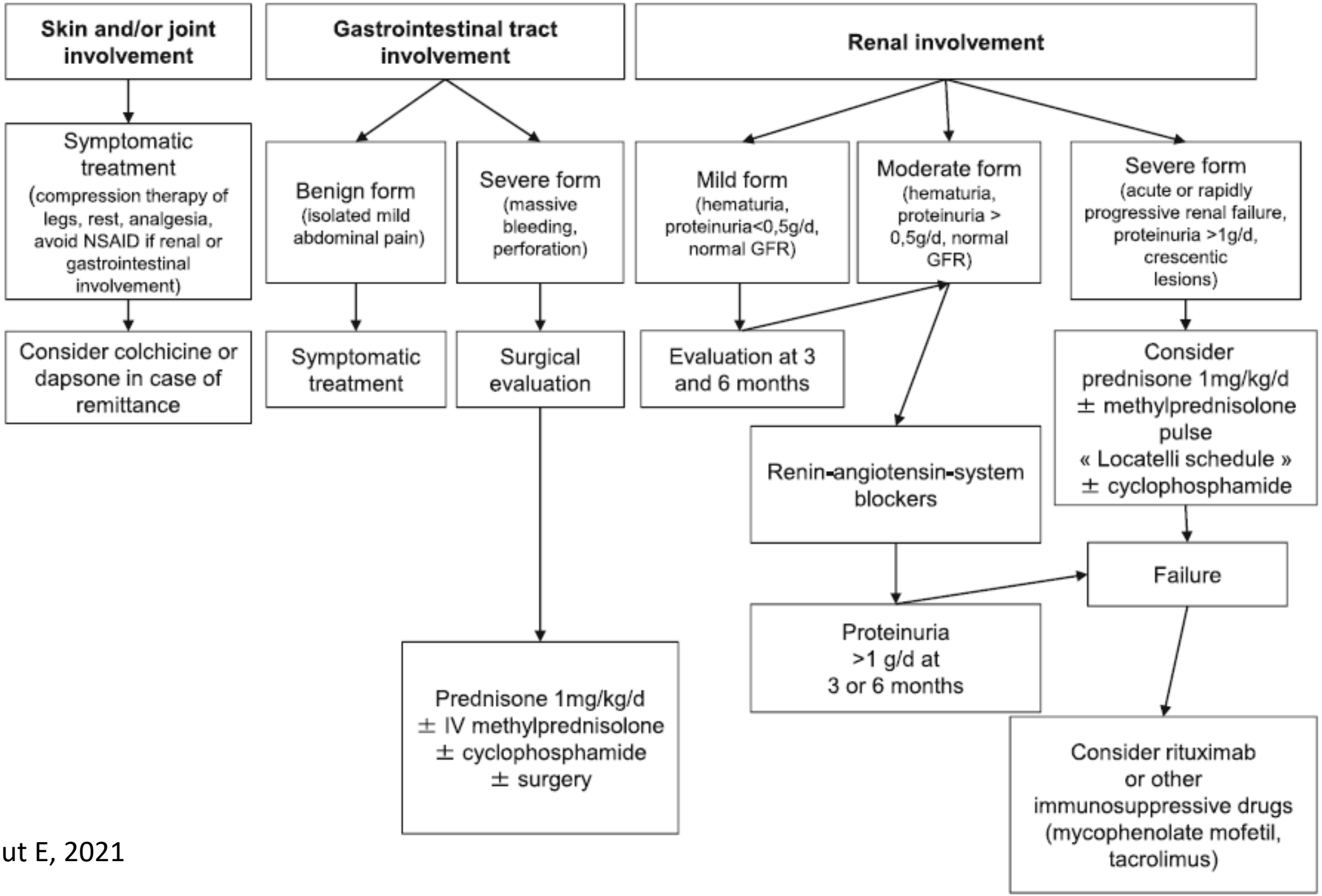
- Semptomatik; parasetamol NSAİİ !, antispasmodikler
- Steroid;

Artrit,orta şiddette karın ağrısı, purpura

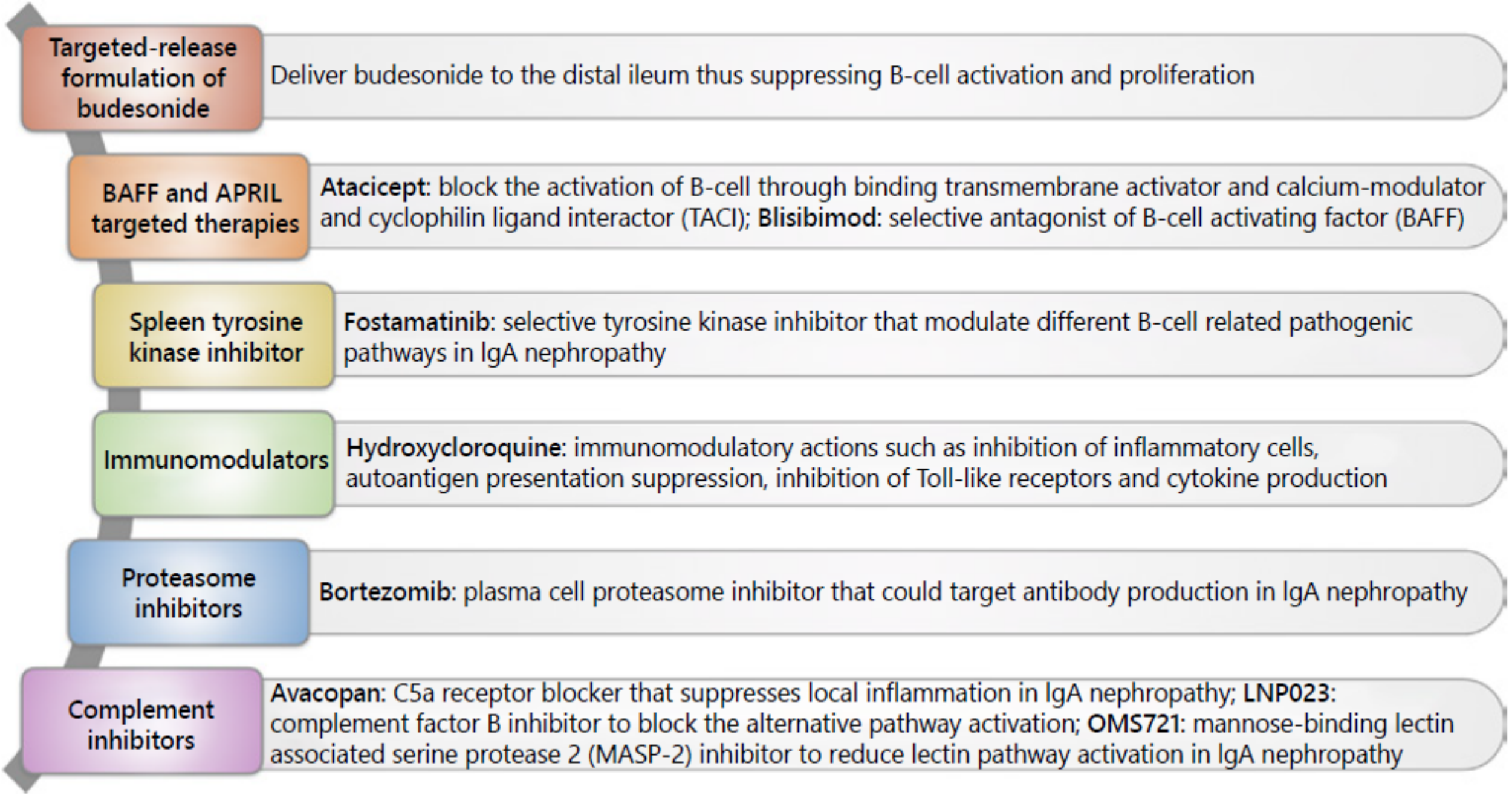
ESRD önler mi?

Yan etkiler – kar zarar oranı

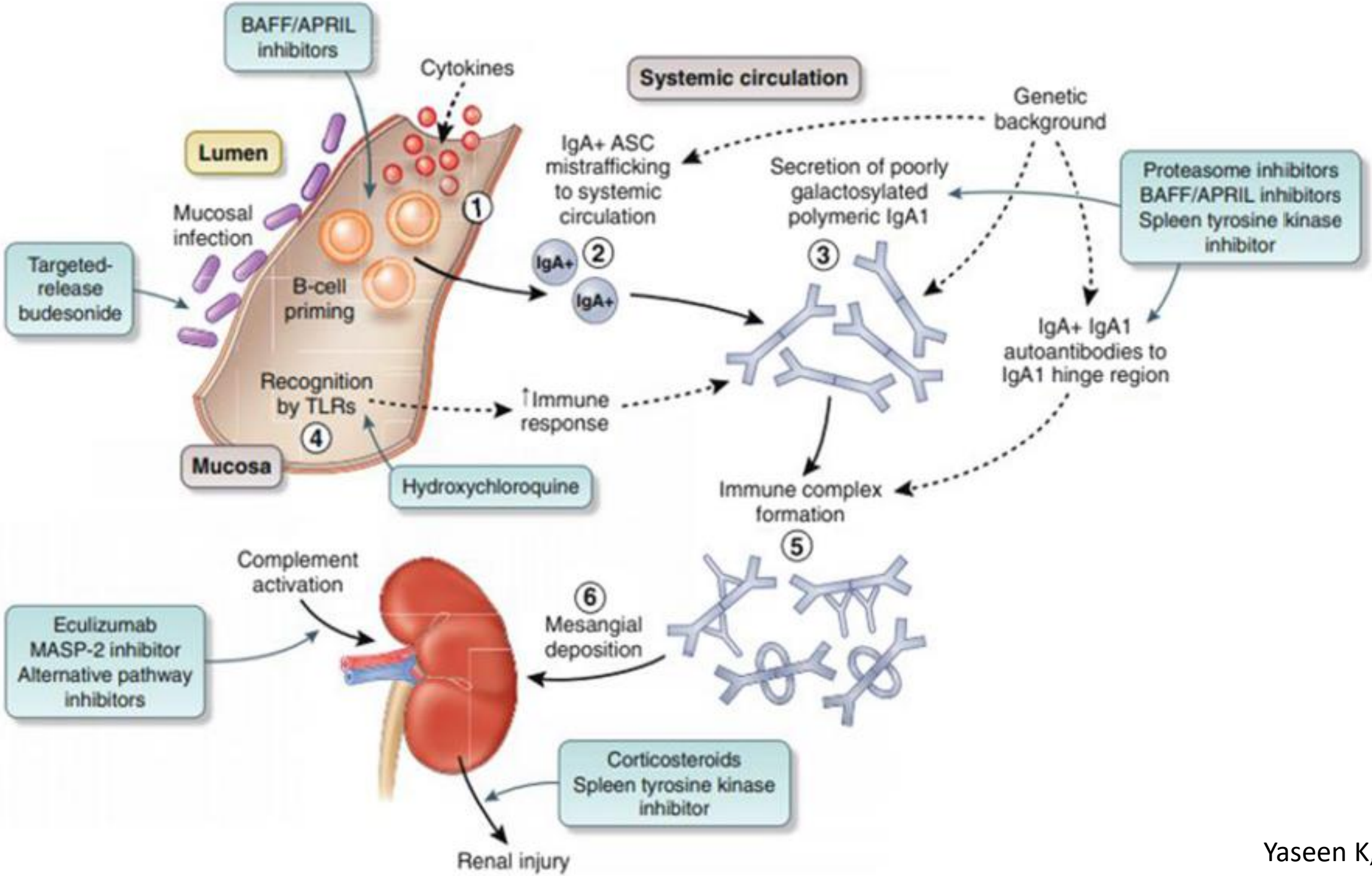
- Siklofosfamid
- MMF
- Azatipyrin
- Kalsinörin inhibitörleri
- Rituximab



Pillebout E, 2021



Gutierrez E, 2020



Yaseen K,2021

Sorular

- Klinik semptom ve bulgular

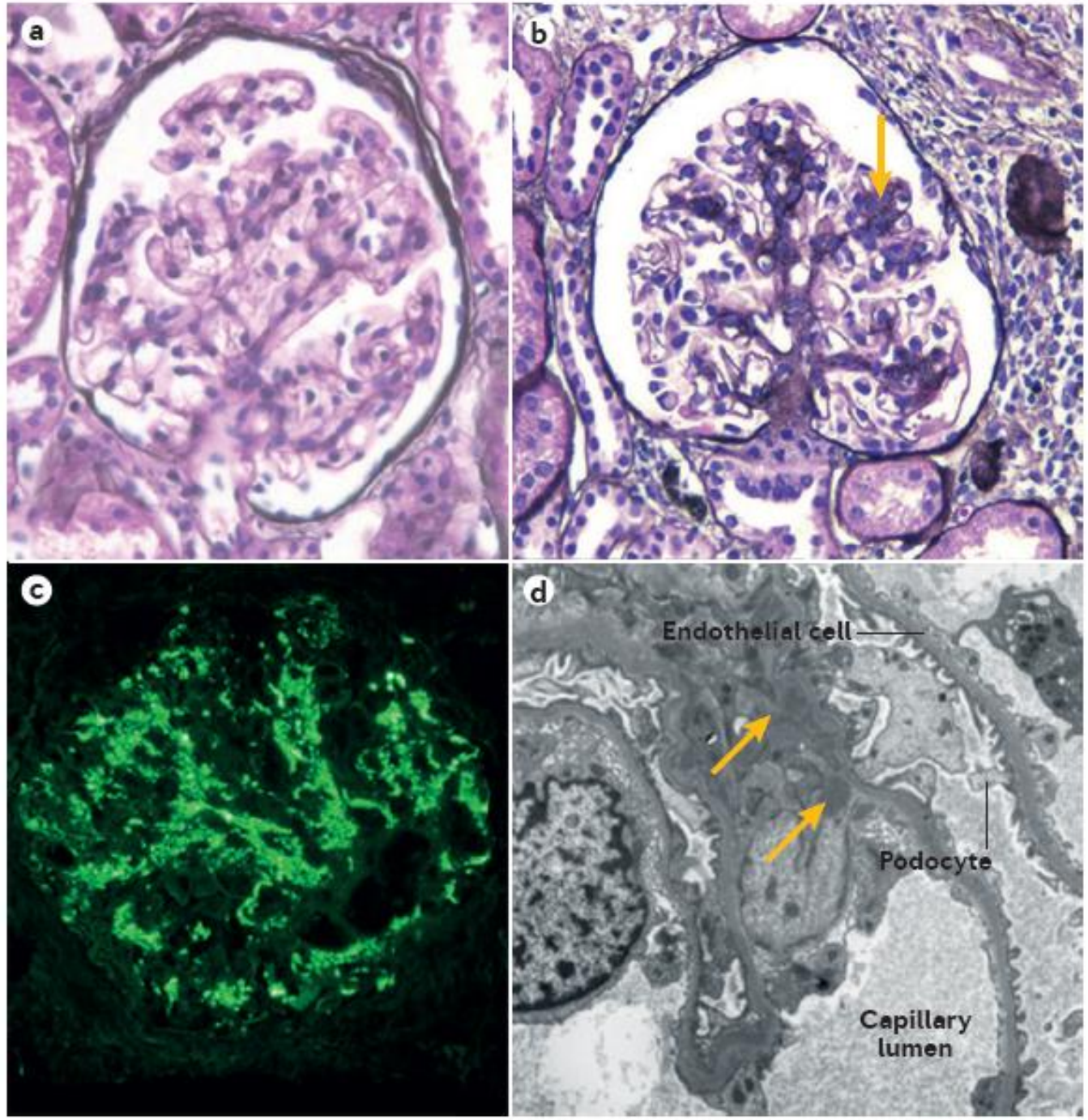
Tipik olanların dışındaki semptom ve bulguların varlığı

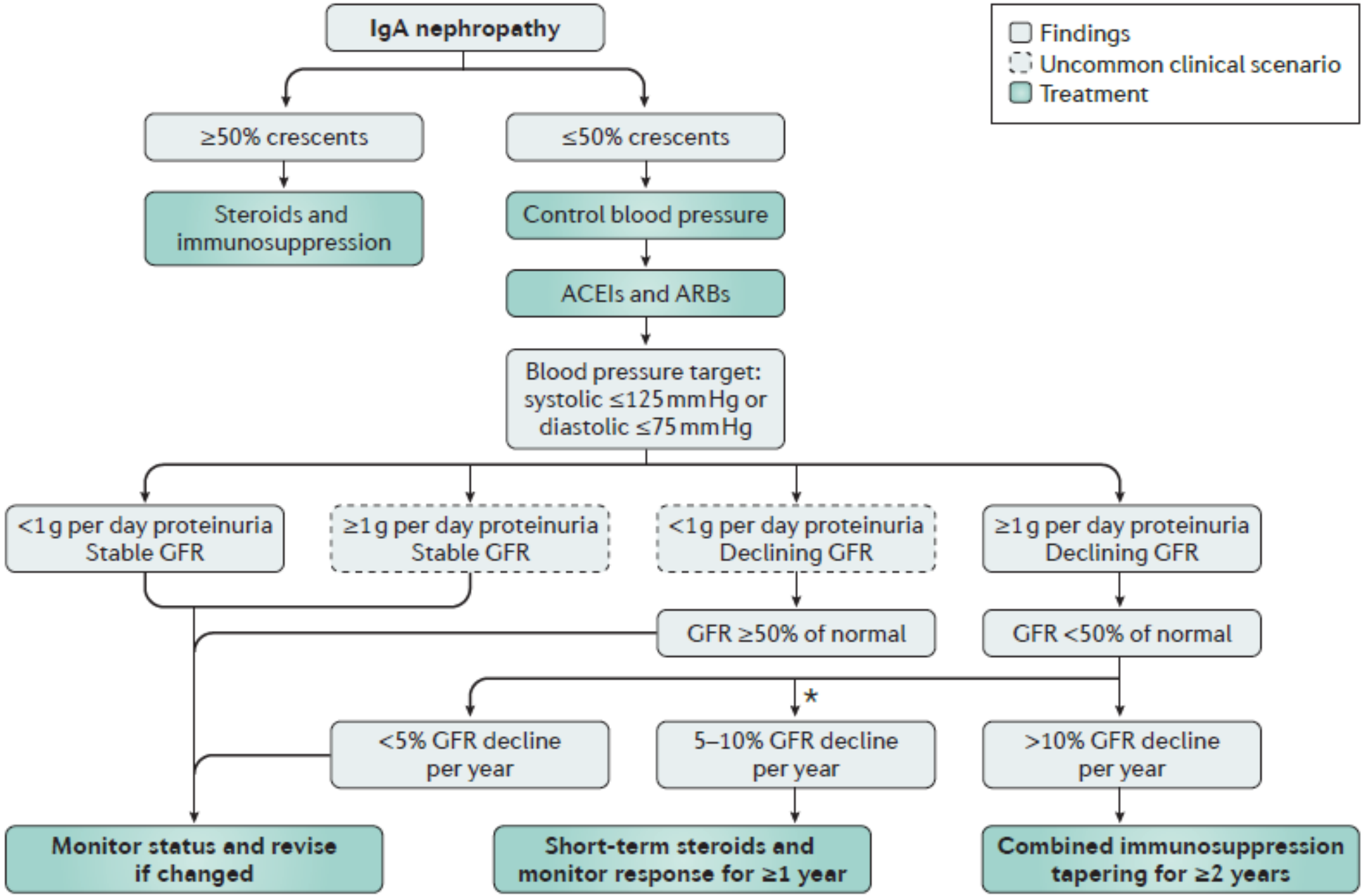
- Nefropatide tedavi için GFR nin alt sınırı nedir?
- ‘Point of no return’ tanımlaması
- Tam remisyon tanımlamasının klinik pratiğe yansıtılması
- İmmünsupresif tedavi ne zaman gereksiz?
- İmmünsupresif tedavi verilecek en uygun doz nedir?
- Gelecek çalışmalar;

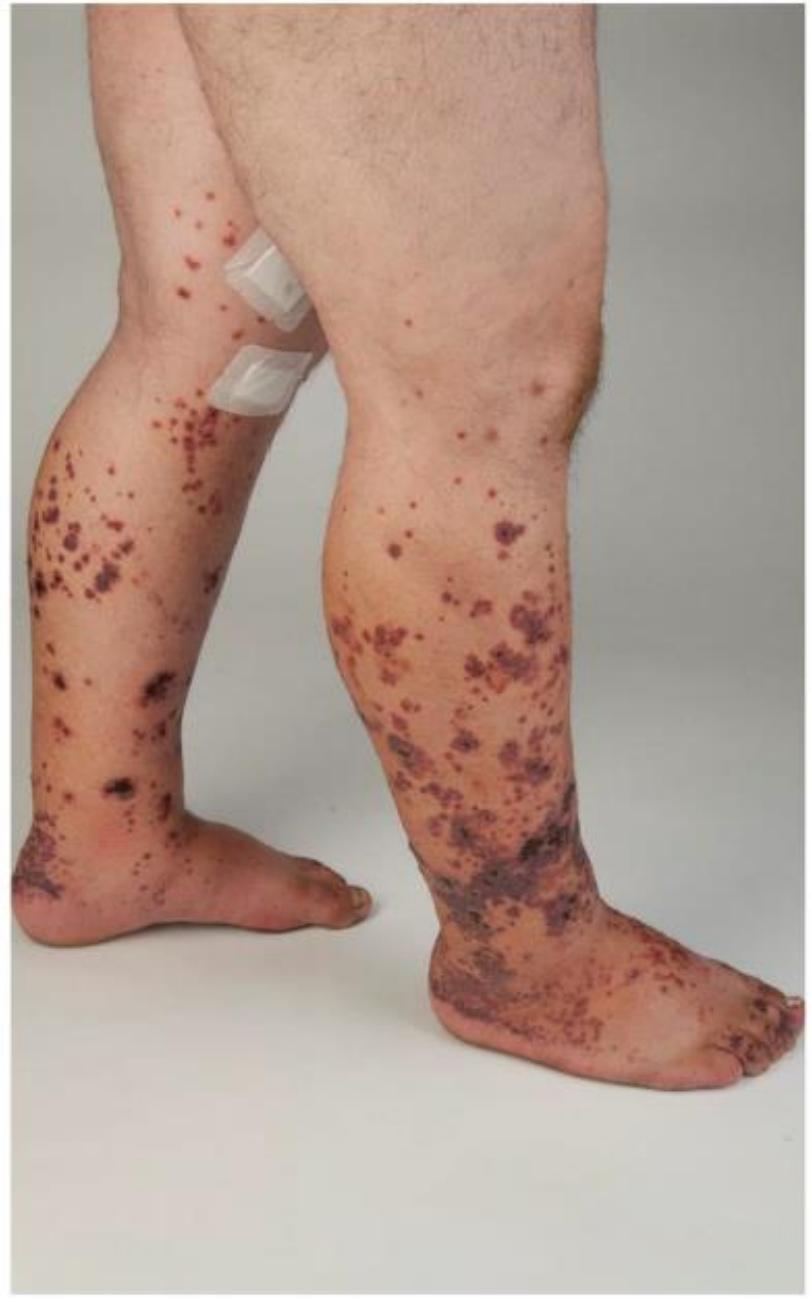
Mukozal immun yanıtın supresyonu

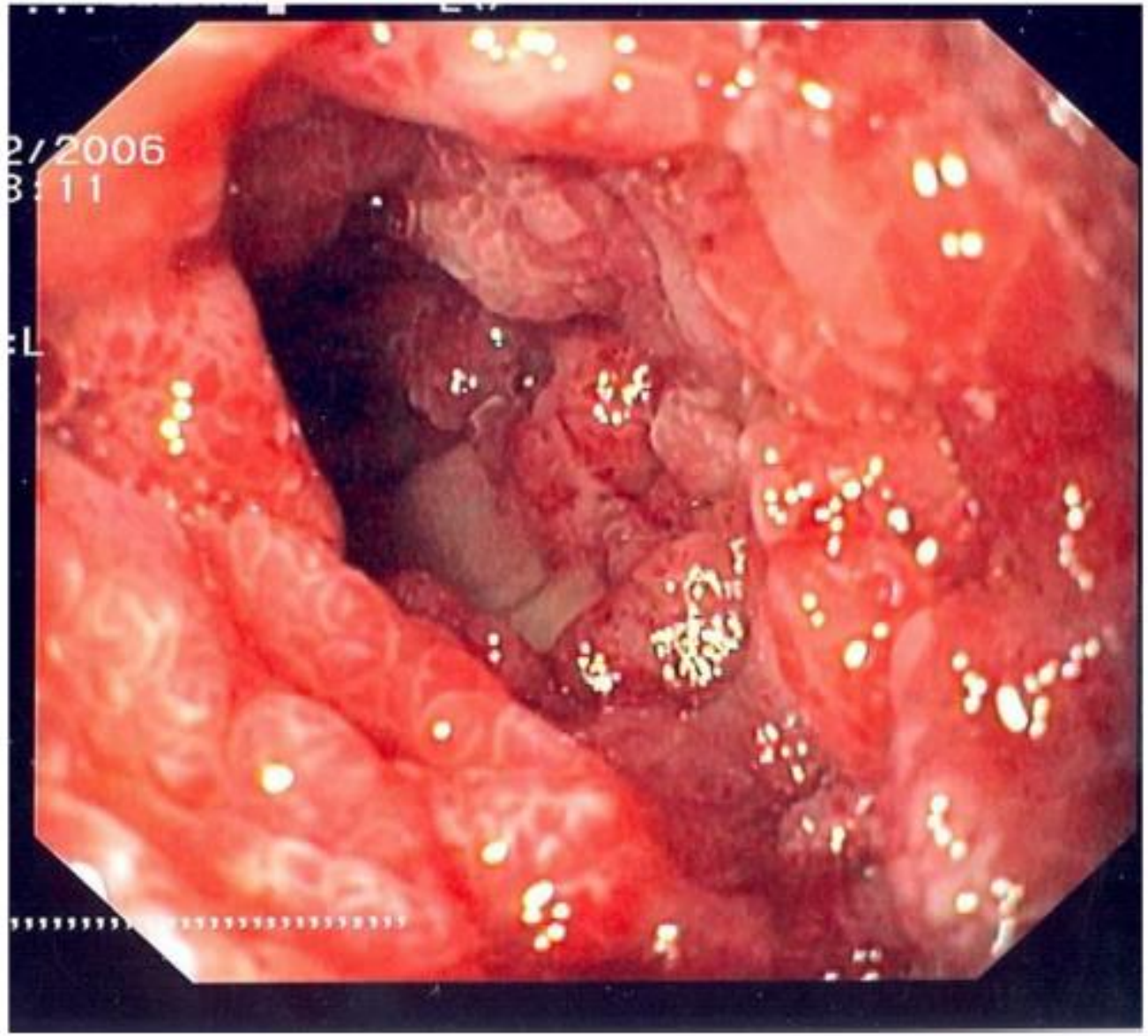
Kompleman yollaklarının baskılanması

Tirozin kinaz inhibisyonu


a
b
c
d
Endothelial cell
Podocyte
Capillary lumen

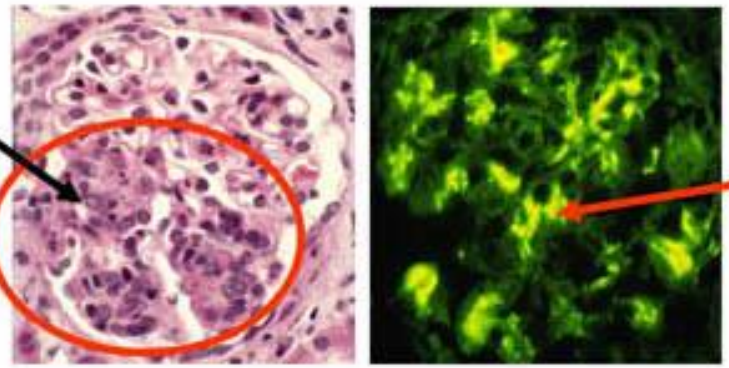

IgA nephropathy
Findings
Uncommon clinical scenario
Treatment
≥50% crescents
≤50% crescents
Steroids and immunosuppression
Control blood pressure
ACEIs and ARBs
Blood pressure target: systolic ≤125 mmHg or diastolic ≤75 mmHg
<1 g per day proteinuria Stable GFR
≥1 g per day proteinuria Stable GFR
<1 g per day proteinuria Declining GFR
≥1 g per day proteinuria Declining GFR
GFR ≥50% of normal
GFR <50% of normal
*
<5% GFR decline per year
5–10% GFR decline per year
>10% GFR decline per year
Monitor status and revise if changed
Short-term steroids and monitor response for ≥1 year
Combined immunosuppression tapering for ≥2 years




2/2006
3:11
:L

IgA Vasculitis

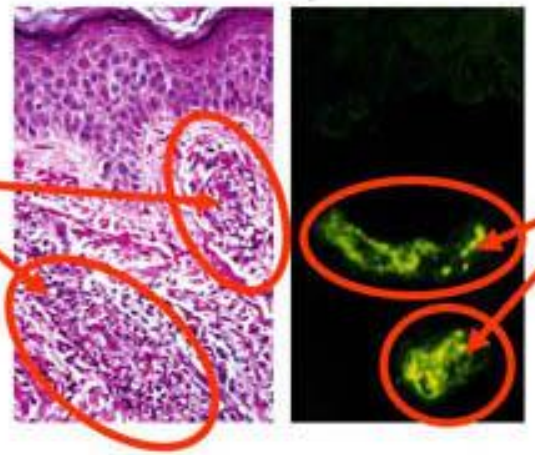
Inflammation of glomerular capillaries



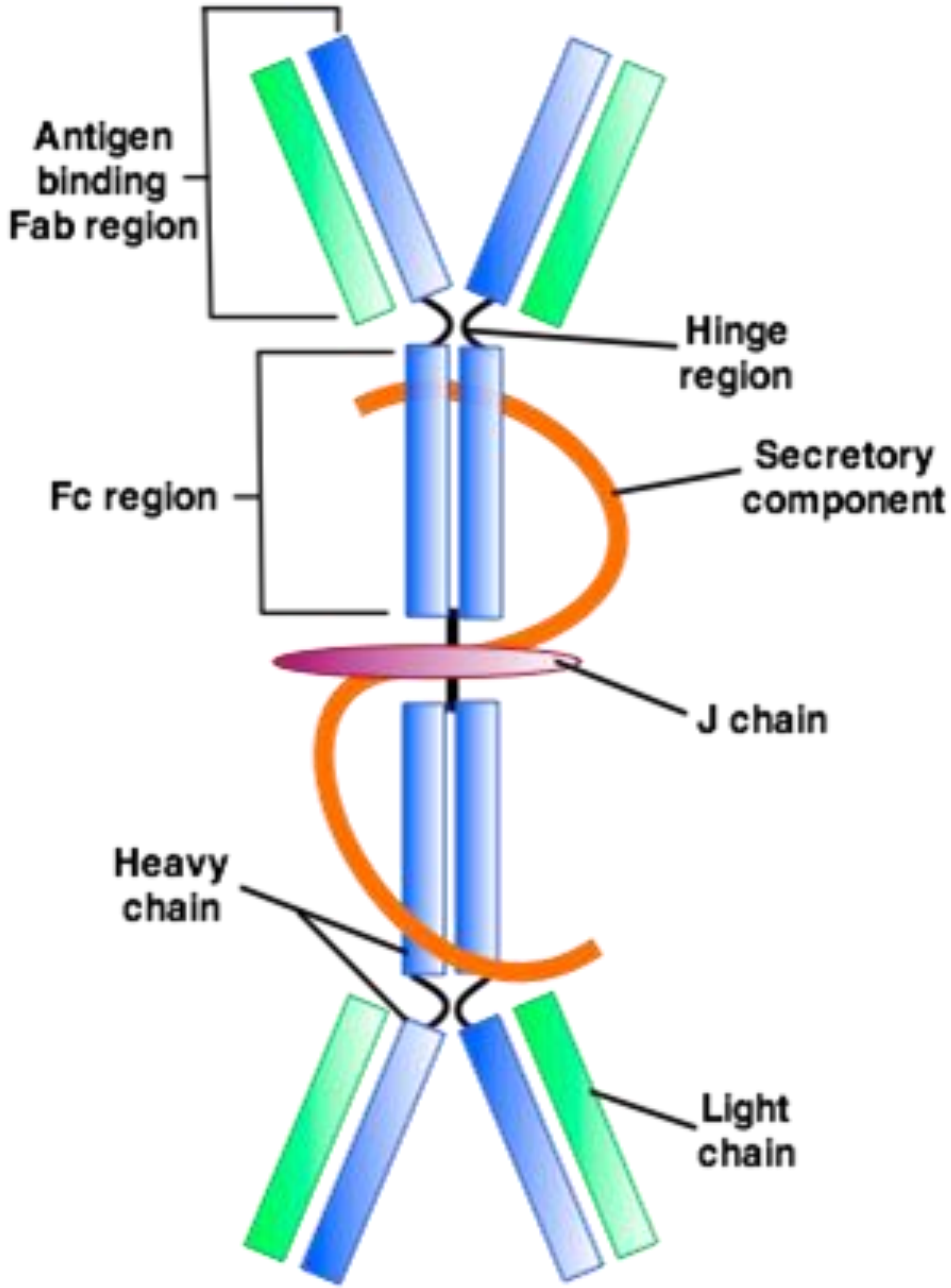
IgA deposits in glomerulus viewed by immunofluorescence microscopy

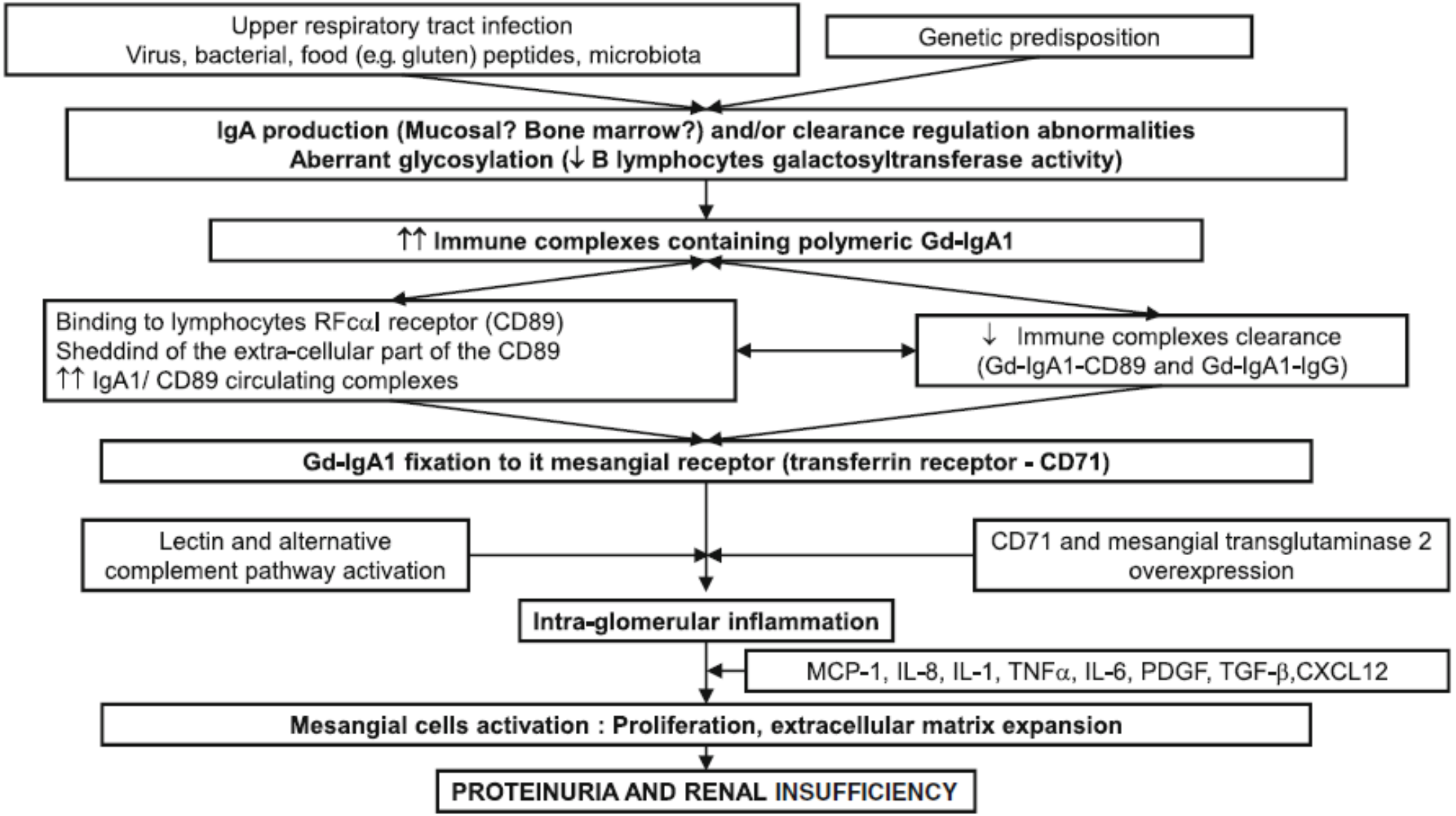
IgA Skin Vasculitis

Inflammation of small vessels in the skin

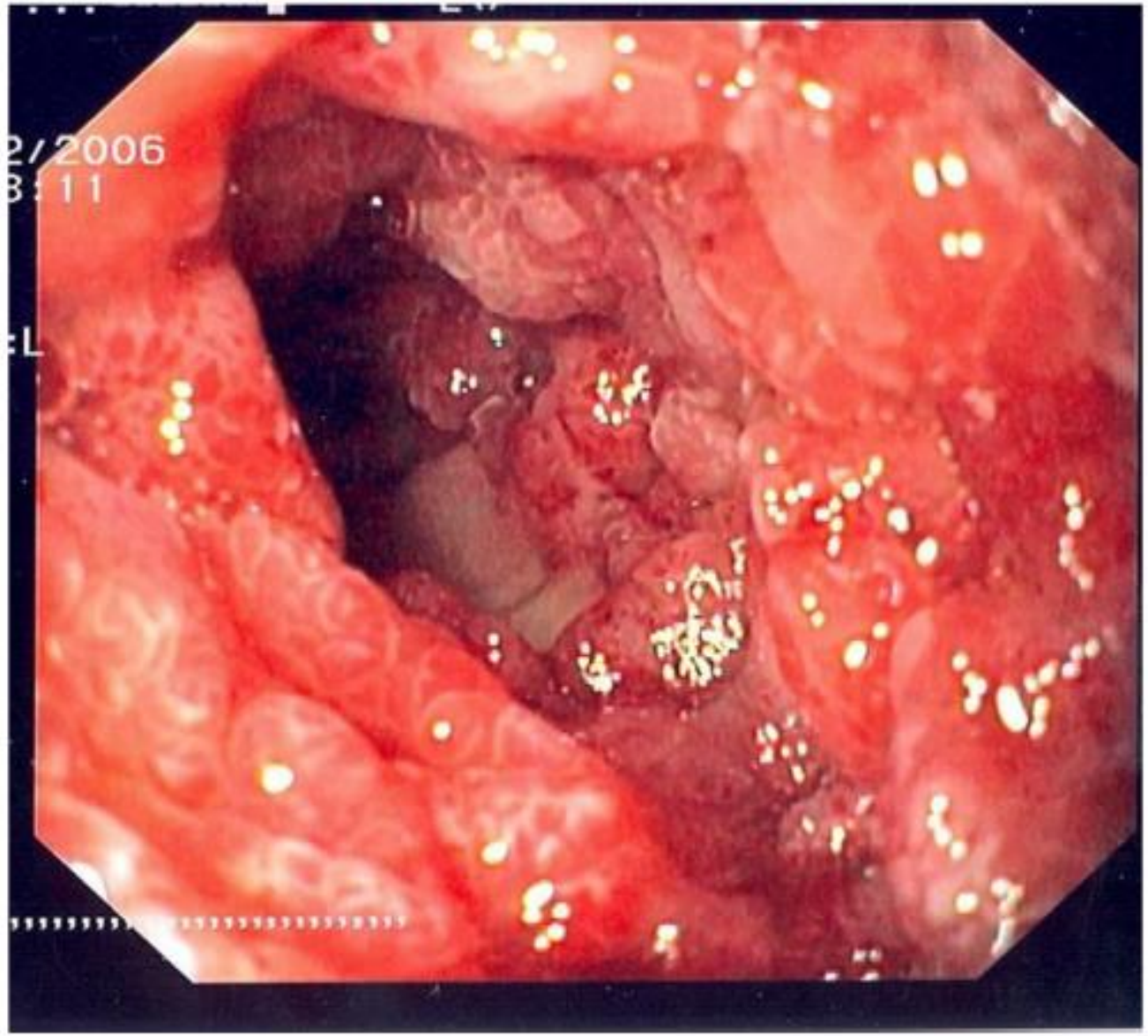


IgA deposits in small vessels in the skin viewed by immunofluorescence microscopy


Antigen
binding
Fab region
Hinge
region
Fc region
Secretory
component
J chain
Heavy
chain
Light
chain



Pillebout E, 2021


2/2006
3:11
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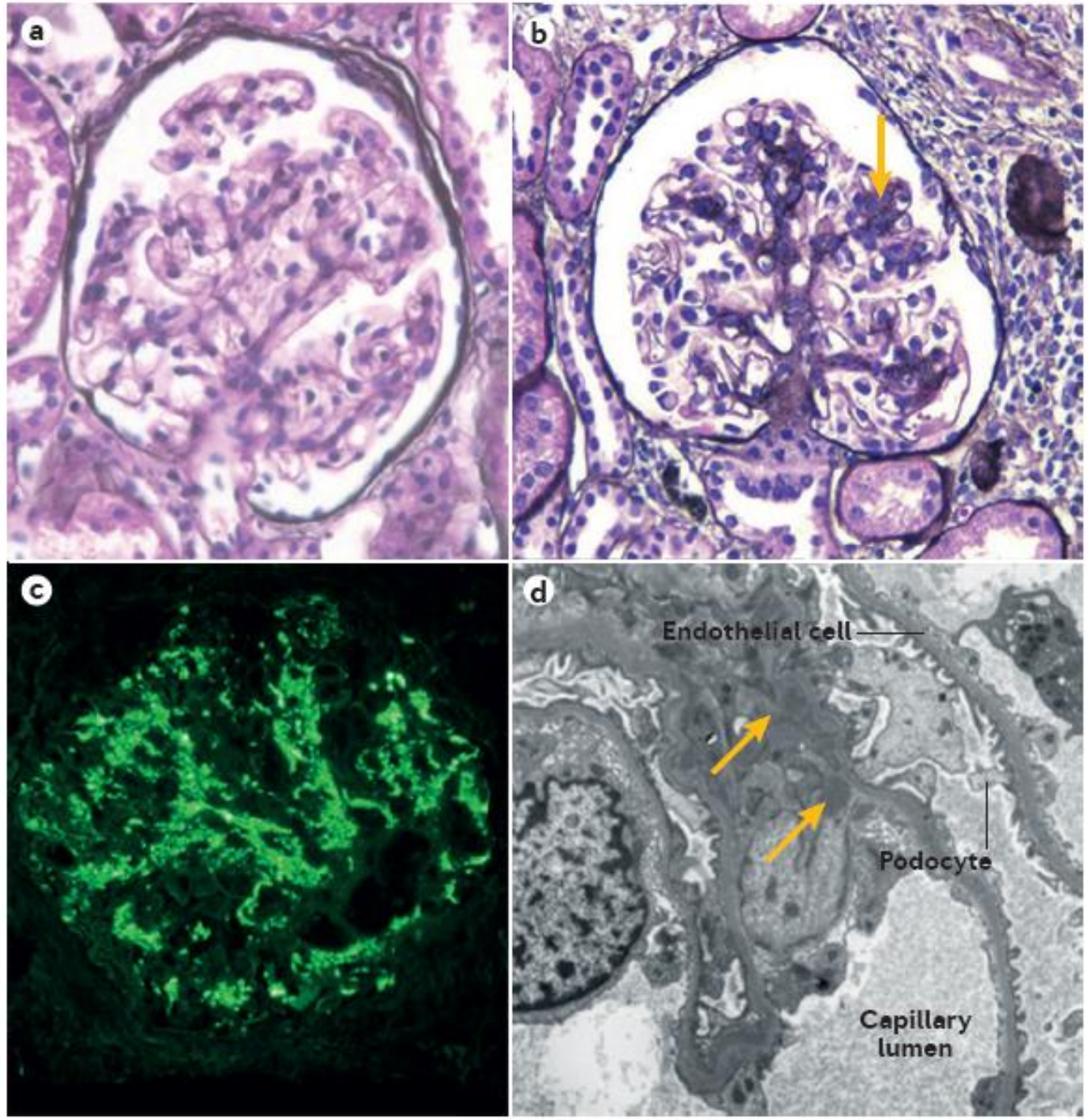
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Endothelial cell
Podocyte
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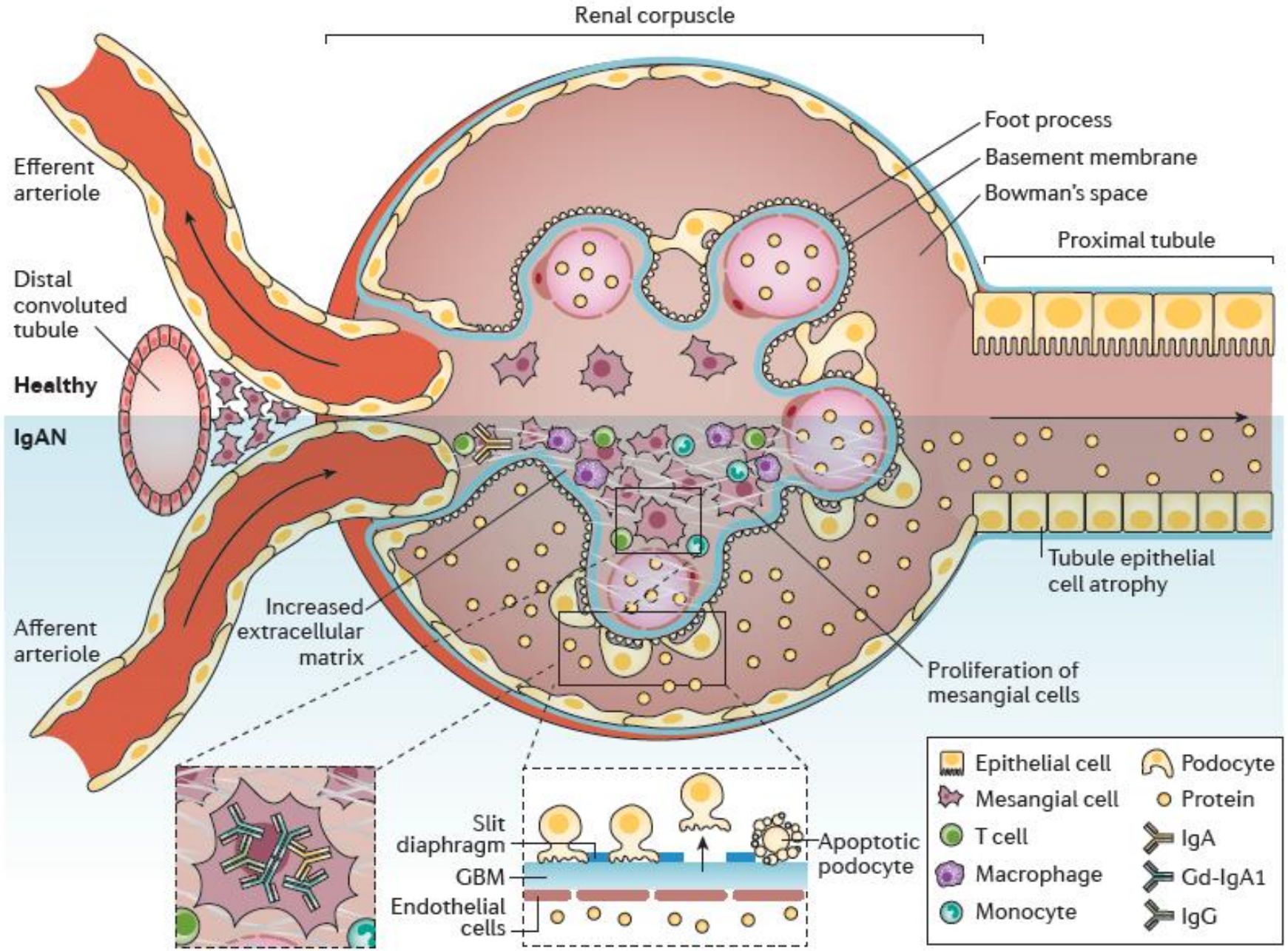
Renal corpuscle
Efferent arteriole
Distal convoluted tubule
Healthy
IgAN
Afferent arteriole
Foot process
Basement membrane
Bowman's space
Proximal tubule
Tubule epithelial cell atrophy
Increased extracellular matrix
Proliferation of mesangial cells
Slit diaphragm
GBM
Endothelial cells
Apoptotic podocyte
Epithelial cell
Mesangial cell
T cell
Macrophage
Monocyte
Podocyte
Protein
IgA
Gd-IgA1
IgG