POST INFECTION Glomerulonephritis

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What can I say
More !


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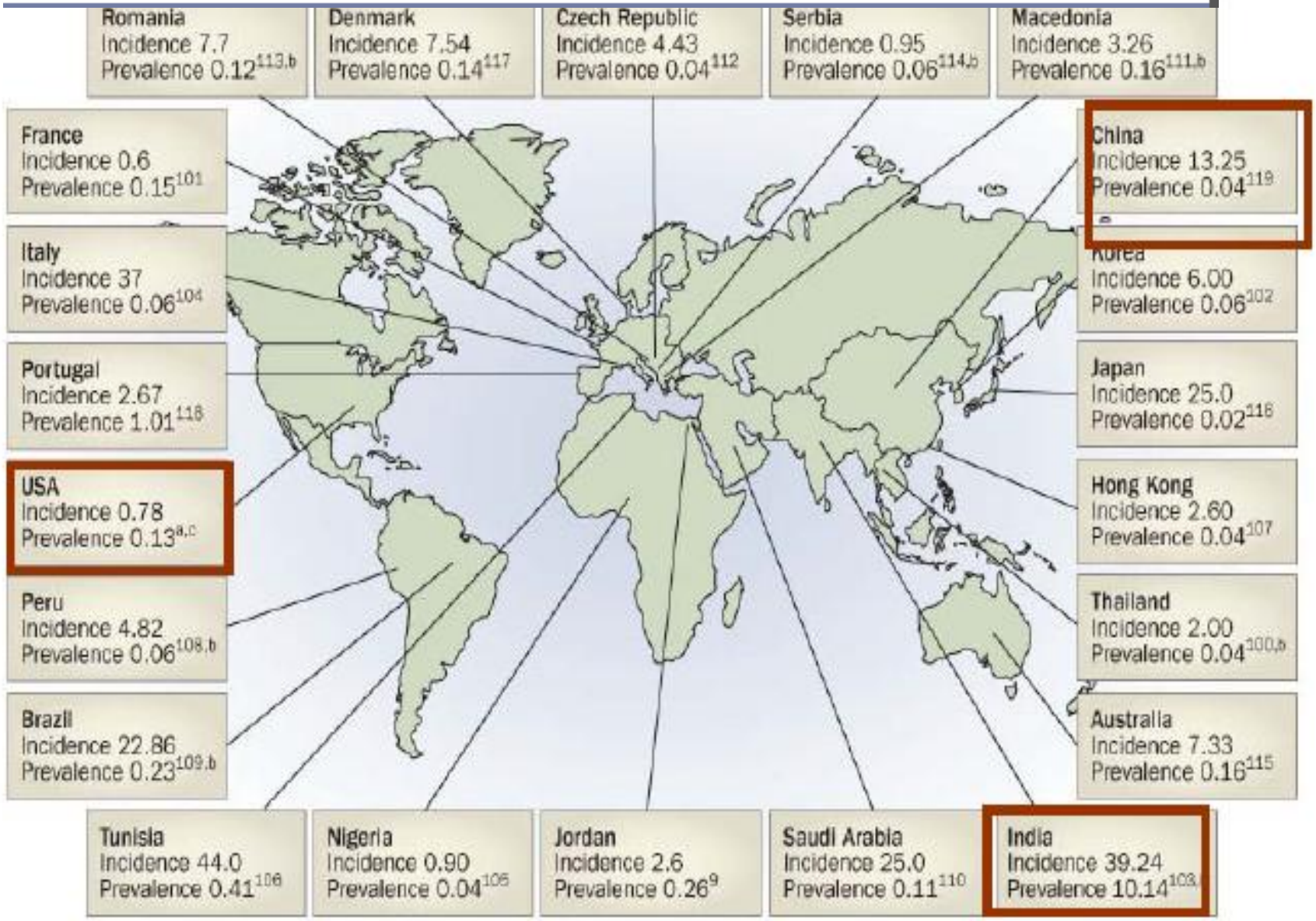
PIGN

IAGN

IRGN

Because adult infections are often ongoing at the time of diagnosis, the term IRGN appears more appropriate

Incidence of PIGn in different Geographic Locations



EPIDEMIOLOGY

On the basis of a review of 11 population-based studies published between 1988 and 2000

0.3 casesper 100,000 person-years adult

6 cases per100,000 person-years in children

The renal biopsy incidence of adult IRGN in thedeveloped countries ranges from 0.6 to 4.6%,

lower than that of adult IgA nephropathy,
focal segmental glomerulosclerosis
membranous glomerulopathy
MPGN

ü *All reported series of adult IRGN after 1990*

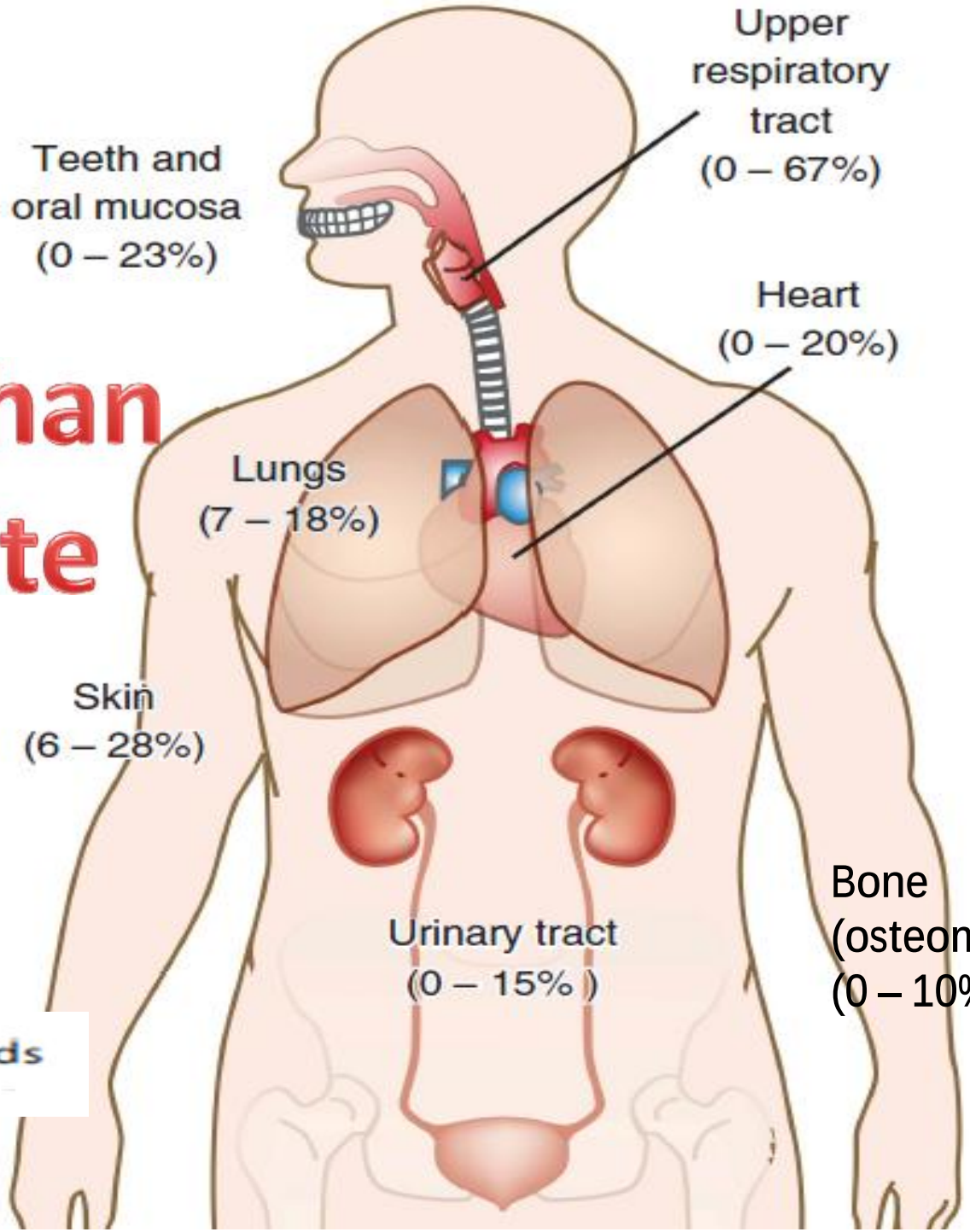
✓ ***There has been also a recent change in the age predominance in IRGN***

In studies reported 4 decades ago,
o6% of affected adults were elderly
compared with 34%in a recent report

ü *immunocompromised background is present in* Diabetes

ü *The sites of infection in adult IRGN are more heterogeneous than in children*

two series of adult IRGN from Europe



more than one site

Staphylococcus
S. aureus
MRSA

Gram-negative rods
Escherichia coli

Bone (osteomyelitis) (0 – 10%)

CLINICAL FEATURES OF ADULT IRGN

Nonspecific fever is absent in 20–30% of patients, contributing to delays in diagnosis

proteinuria varies

Almost all patients have microhematuria

Gross hematuria occurs in 17–56% of patients

Serum creatinine at presentation is elevated

Hypocomplementemia is present in 35–80%

PATHOLOGIC FEATURES OF ADULT IRGN

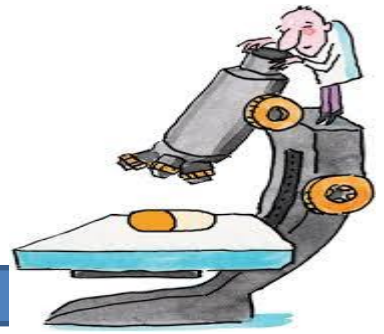
- The most common histological pattern of injury is diffuse endocapillary proliferative and exudative GN

- **focal endocapillary proliferative GN**
- **Mesangial proliferative GN**
- **In patients with infectious endocarditis crescentic and necrotizing glomerulonephritis is the most frequent pattern**
- **MPGN MPGN is the most common pattern in patients with shunt nephritis**

Immunofluorescence microscopy

- *C3-dominant or codominant*
- *glomerular staining starry sky pattern garlandpattern more often there is co-deposition of one or more immunereactants (IgG, IgM, IgA, C1q)*
- *IgG is usually the most PSGN.*
- *In shunt nephritis, IgM staining*
- *infectious endocarditis–associated typically a paucity paradoxically, 'full-house' staining*

Electron microscopy



Electron microscopy shows scattered large subepithelial electron-dense deposits, which exhibit a characteristic 'hump-shaped'

IgA-DOMINANT IRGN

In 2003 reported five cases

more than 60 cases have been reported in the English literatur

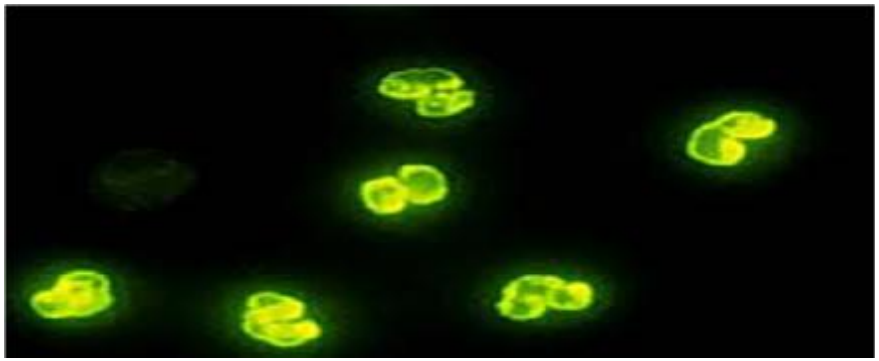
increasingly recognized morphologic variant of IRGN is most common in the elderly, where it accounts for 17% of cases

All cases were associated with staphylococcal infection, hypocomplementemia, and underlying diabetic nephropathy.

IgA nephropathy and HSP

- ü initial presentation in older age
- ü acute renal failure
- ü intercurrent infection
- ü Hypocomplementemia
- ü prominent glomerular neutrophil infiltration on light microscop
- ü stronger staining for C3 than IgA on immunofluorescence

anca

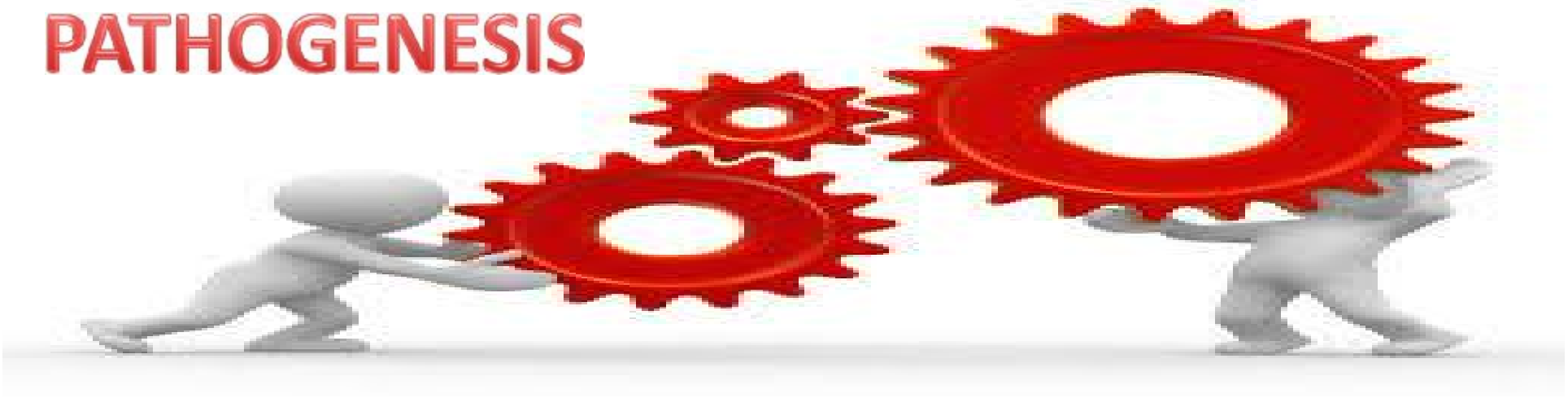


Anti-neutrophil cytoplasmic antibody (ANCA) seropositivity (directed against MPO or PR3)

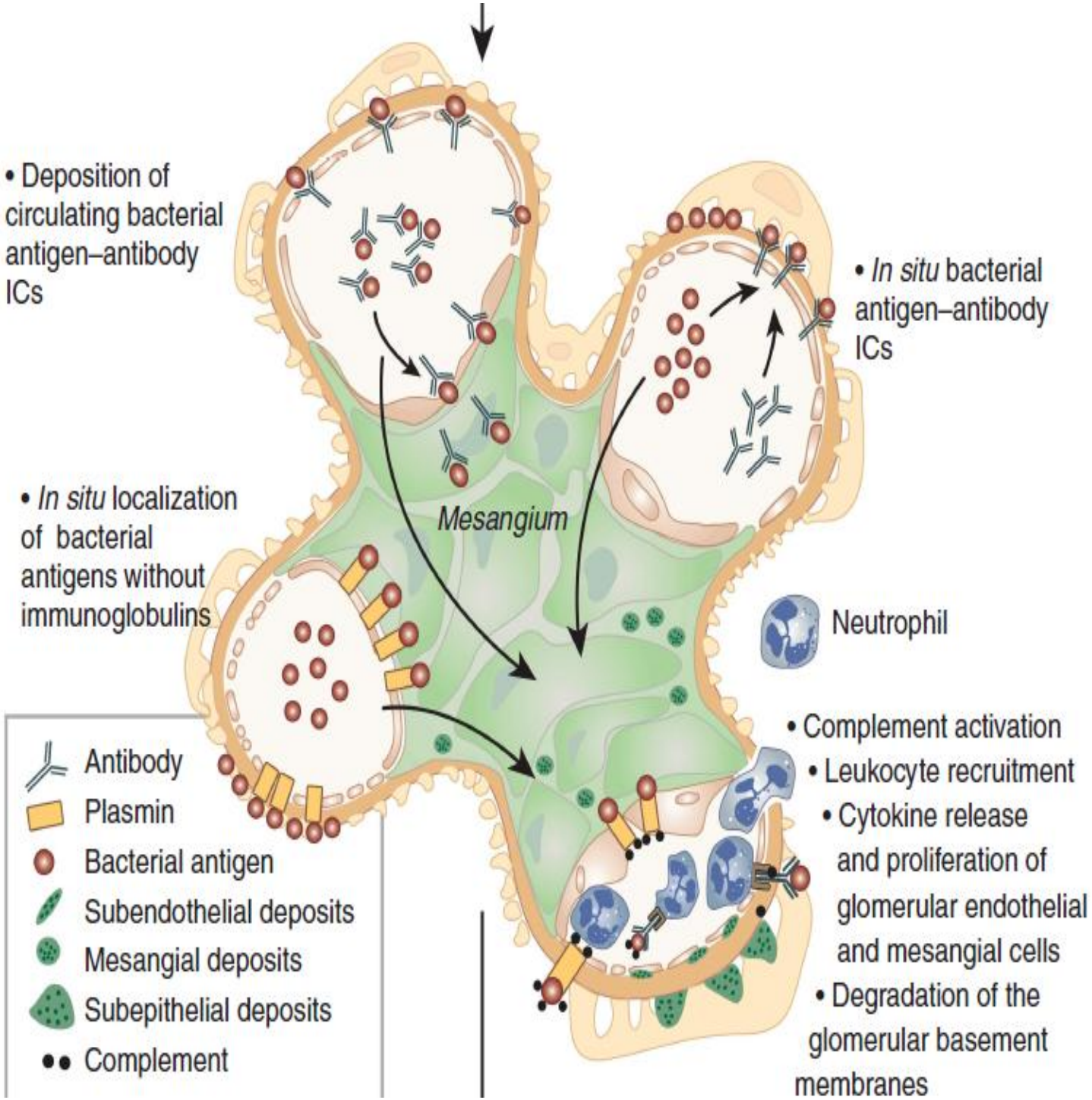
- ✓ occurs in 8% of elderly patients with IRGN overall1
- ✓ in 25% of patients with infectious endocarditis–associated GN

where it may contribute to the development of characteristic diffuse crescentic and necrotizing GN.

PATHOGENESIS



- ✓ glomerular deposition of preformed circulating ICs
- ✓ in situ localization of circulating cationic bacterial antigens
- ✓ molecular mimicry between bacterial antigens and glomerular constituents in the pathogenesis of PSGN


• Deposition of circulating bacterial antigen–antibody ICs
• *In situ* bacterial antigen–antibody ICs
• *In situ* localization of bacterial antigens without immunoglobulins
Mesangium
Neutrophil
• Complement activation
• Leukocyte recruitment
• Cytokine release and proliferation of glomerular endothelial and mesangial cells
• Degradation of the glomerular basement membranes
Antibody
Plasmin
Bacterial antigen
Subendothelial deposits
Mesangial deposits
Subepithelial deposits
Complement

DIAGNOSTIC CRITERIA

At least three of the following criteria were required

for study entry in two studies from our group:

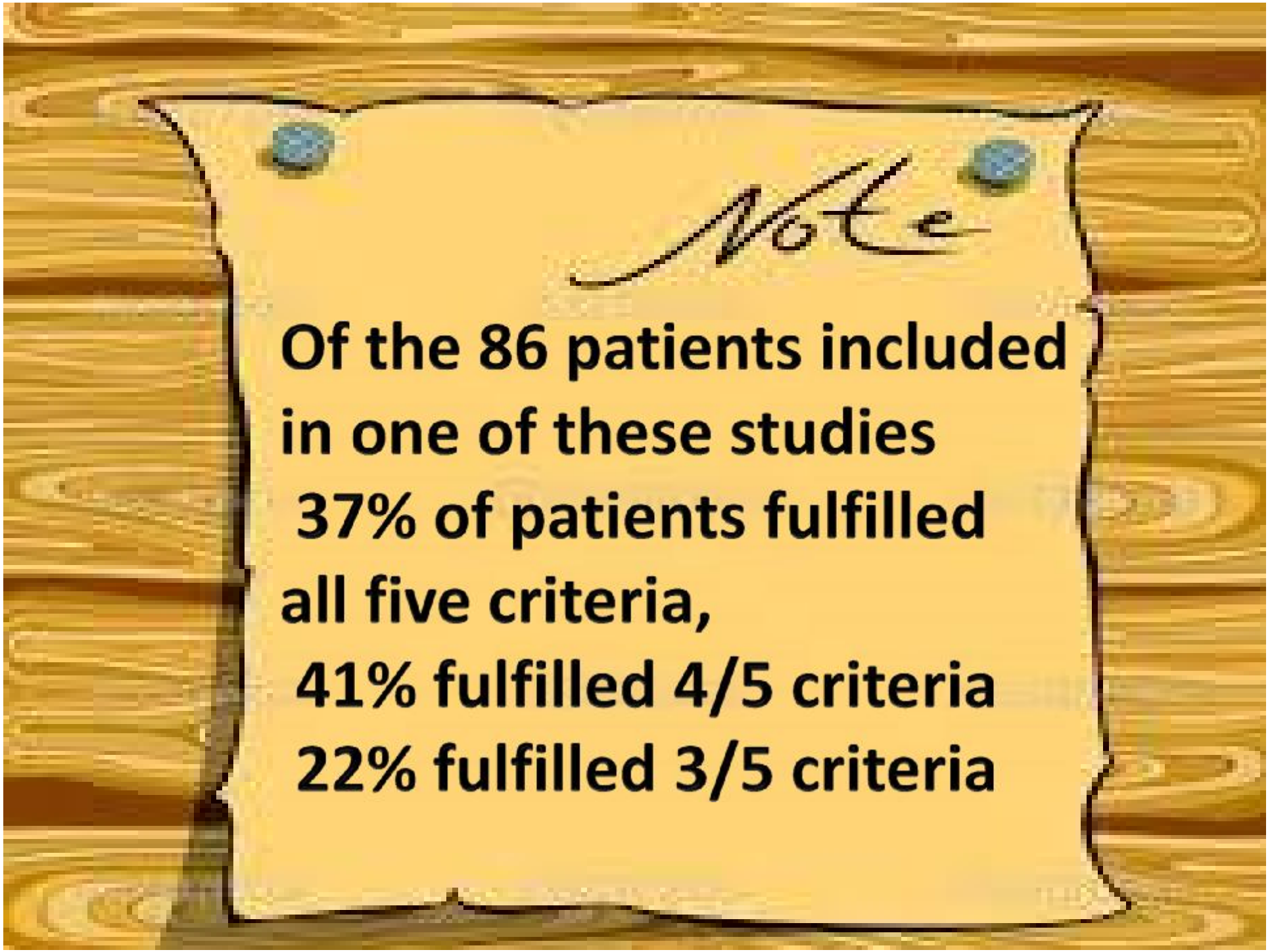
(1) clinical or laboratory evidence of infection preceding or at the onset of glomerulonephritis

(2) depressed serum complement

(3)endocapillary proliferative and exudative glomerulonephritis

(4) C3-dominant or co-dominant glomerular immunofluorescence staining

(5) hump-shaped subepithelial deposits on electron microscopy


Note
Of the 86 patients included in one of these studies
37% of patients fulfilled all five criteria,
41% fulfilled 4/5 criteria
22% fulfilled 3/5 criteria

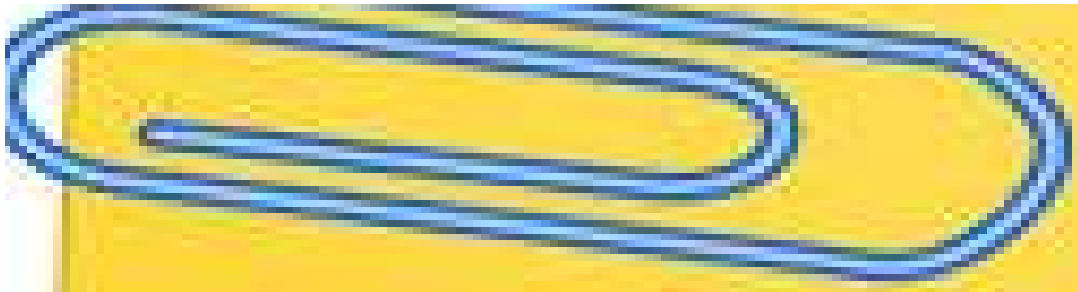
INDICATIONS FOR RENAL BIOPSY

recommended in most adults suspected of having IRGN to confirm the diagnosis and rule out other glomerulonephritides that have similar clinical presentations and may require prompt aggressive immunosuppressive therapy.

A biopsy may be deferred only among selected patients who have a strongly suggestive history of preceding or concurrent bacterial infection together with low C3 and Spontaneous resolution of signs and symptoms

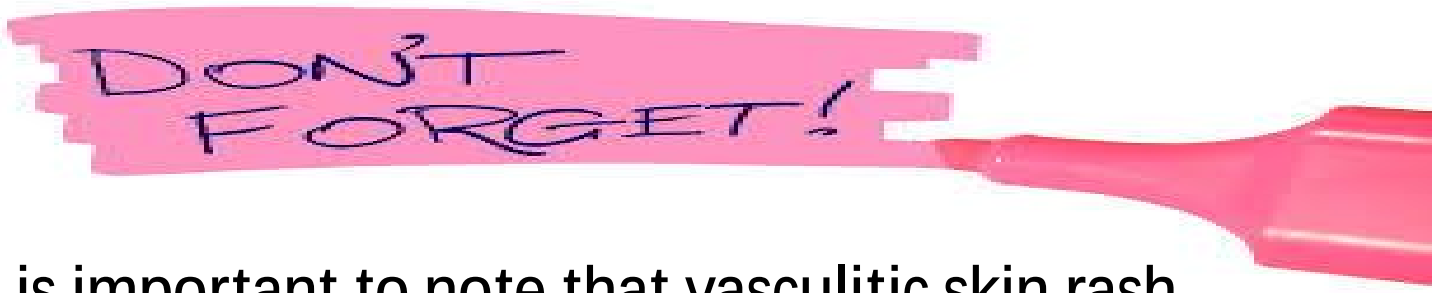
DIFFERENTIAL DIAGNOSIS

- ✓ lupus nephritis
- ✓ cryoglobulinemic glomerulonephritis
- ✓ C3 glomerulopathy
- ✓ diseases that may be triggered by infection such as IgAnephropathy
- ✓ ANCA-associated pauci-immune glomerulonephritis.



necrotizing and crescentic glomerulonephritis.

infectious endocarditis should be excluded in patients presumed to have ANCA-associated glomerulonephritis because of the attendant risks of immunosuppression



It is important to note that vasculitic skin rash (with or without IgA deposition incutaneous small vessels) can be seen in IgA-dominant Staphylococcus-related GN, mimicking HSP

underlying staphylococcal infection must be excluded in adults with skin rash and IgA-dominant IRGN before committing the patient to immunosuppressive therapy

- ✓ **Active infection should be eradicated**

with antibiotic if needed, with surgery

- ✓ **Treatment of acute nephritic syndrome includes**

antihypertensive drugs
diuretics
dietary salt restriction

- ✓ **persistent moderate or heavy proteinuria**

renin–angiotensin system

One small randomized controlled study Children enalapril

role of immunosuppressive therapy

been tested in a randomized prospective clinical trial

based on observations from retrospective studies.

the studies in which statistical analysis was performed beneficial effect of steroids on outcome

A small randomized controlled study inchildren with crescenticPSGN found no benefit of aggressive immunosuppressive therapy (prednisone, azathioprine, and cyclophosphamide) compared with supportive care only.

immunosuppressive therapy in adult crescentic IRGN

steroids with or without cyclophosphamide in adult crescentic IRGN is largely anecdota

Immunosuppressive therapy is not recommended in most adults with IRGN

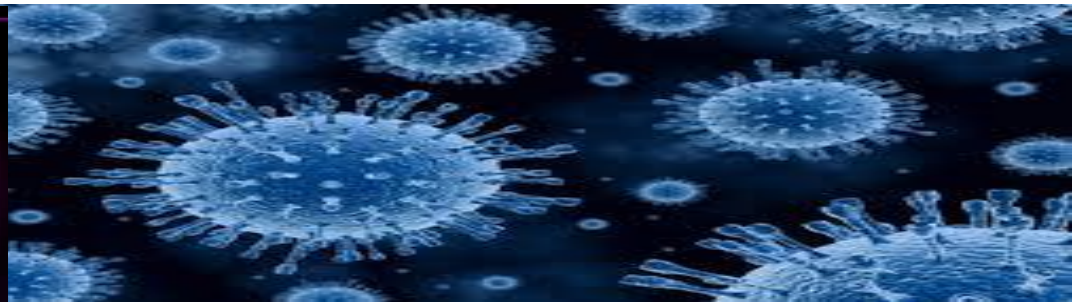
adult patients with diffuse crescentic and necrotizing IRGN(particularly those with positive ANCA titers), a course of pulse steroids with or without cyclophosphamide can be offered (based on extrapolation from other etiologies of rapidly progressive glomerulonephritis), provided that there is no active infection or contraindication related to the immunocompromised state.

The decision to treat adults with immunosuppressive therapy is more challenging than in children

THE INFECTION IS FREQUENTLY ACTIVE AT THE TIME OF RENAL PRESENTATION

underlying immunocompromised state such as diabetes

Hepatitis C virus (HCV) has an estimated prevalence of 3% worldwide (around 170 million infected individuals all over the world) and remains a major global health burden.



The most common type of HCV-related glomerulonephritis is type I MPGN in the context of typII cryoglobulinemia

less common

- ✓ MPGN without cryoglobulinemia
- ✓ membranous nephropathy
- ✓ focal segmental sclerosis
- ✓ Mesangial glomerulonephritiS
- ✓ fibrillaryimmunotactoid glomerulopathies

IgA nephropathy, cryoglobulinemic thrombotic microangiopathy

Roccatello et al.

included 146 patients with cryoglobulinemic nephritis, of whom 87% (n = 127) were HCV positive.

Type II cryoglobulins (IgG/IgMk) occurred in 74.4% of cases. The remainder had type III cryoglobulins.

A diffuse MPGN was the most common histological pattern (83%).

Cox regression model showed that

age

serum creatinine

proteinuria at onset of kidney disease

associated ***independently*** with a risk for developing severe renal failure at followup

Roccatello et al.

Survival at 10 years was about 30% and cardiovascular disease was the cause of death in more than 60% of patients

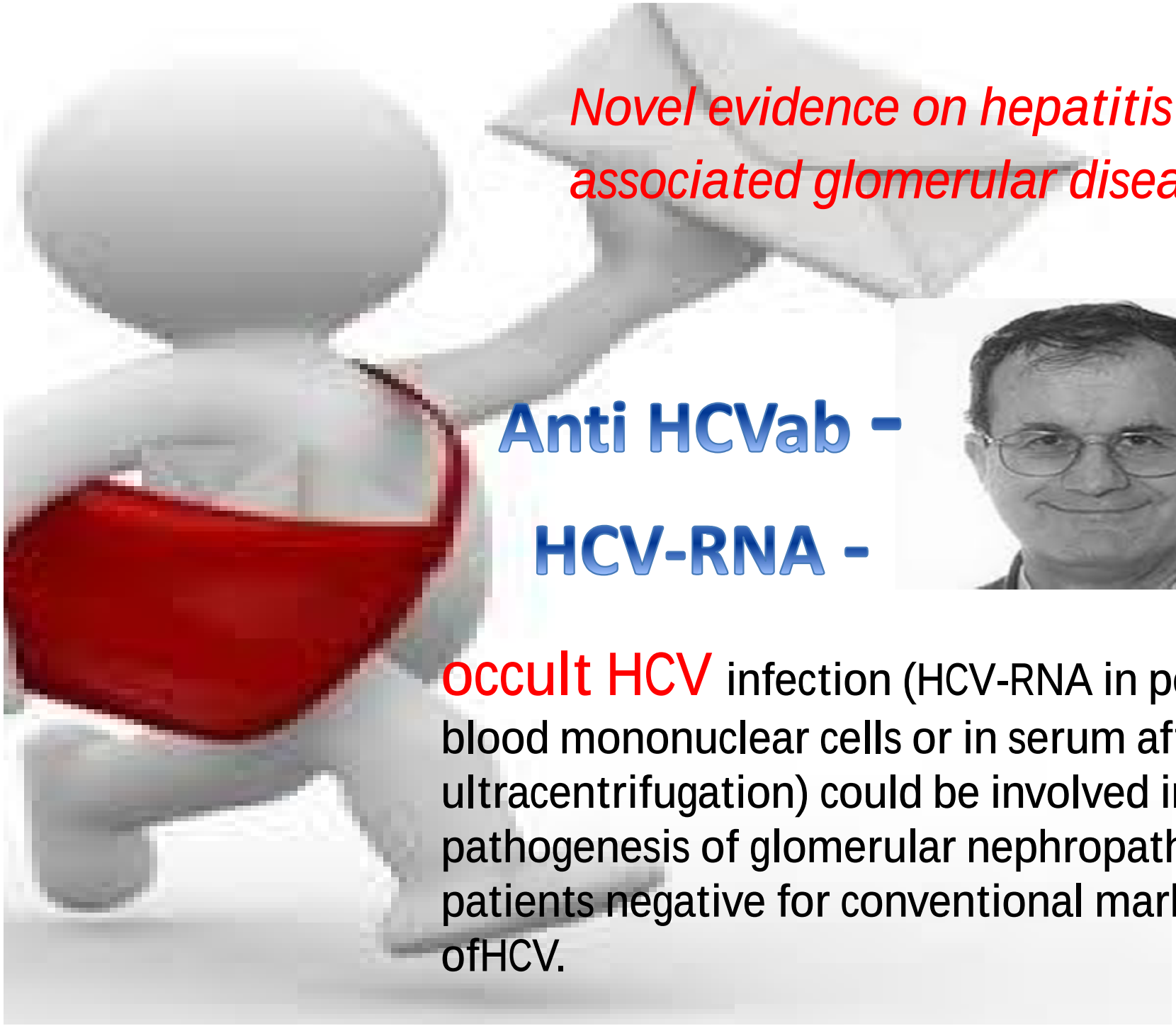
additional causes of death included infections (10%), hepatic failure (19%), and neoplasia (3%).

Conflicting results

an older study by Tarantino et al. who enrolled 105 patients and showed that the number of deaths caused by infections (21%) and hepatic failure (19%) approached the number of deaths caused by cardiovascular diseases (29%).

These opposite findings have been attributed to different use of antibiotics, antiviral agents, or immunosuppressive drugs

Kaplan Meier survival curves were worsened by baseline serum creatinine greater than 1.5 mg/d



Novel evidence on hepatitis C virus–associated glomerular disease

Anti HCVab –

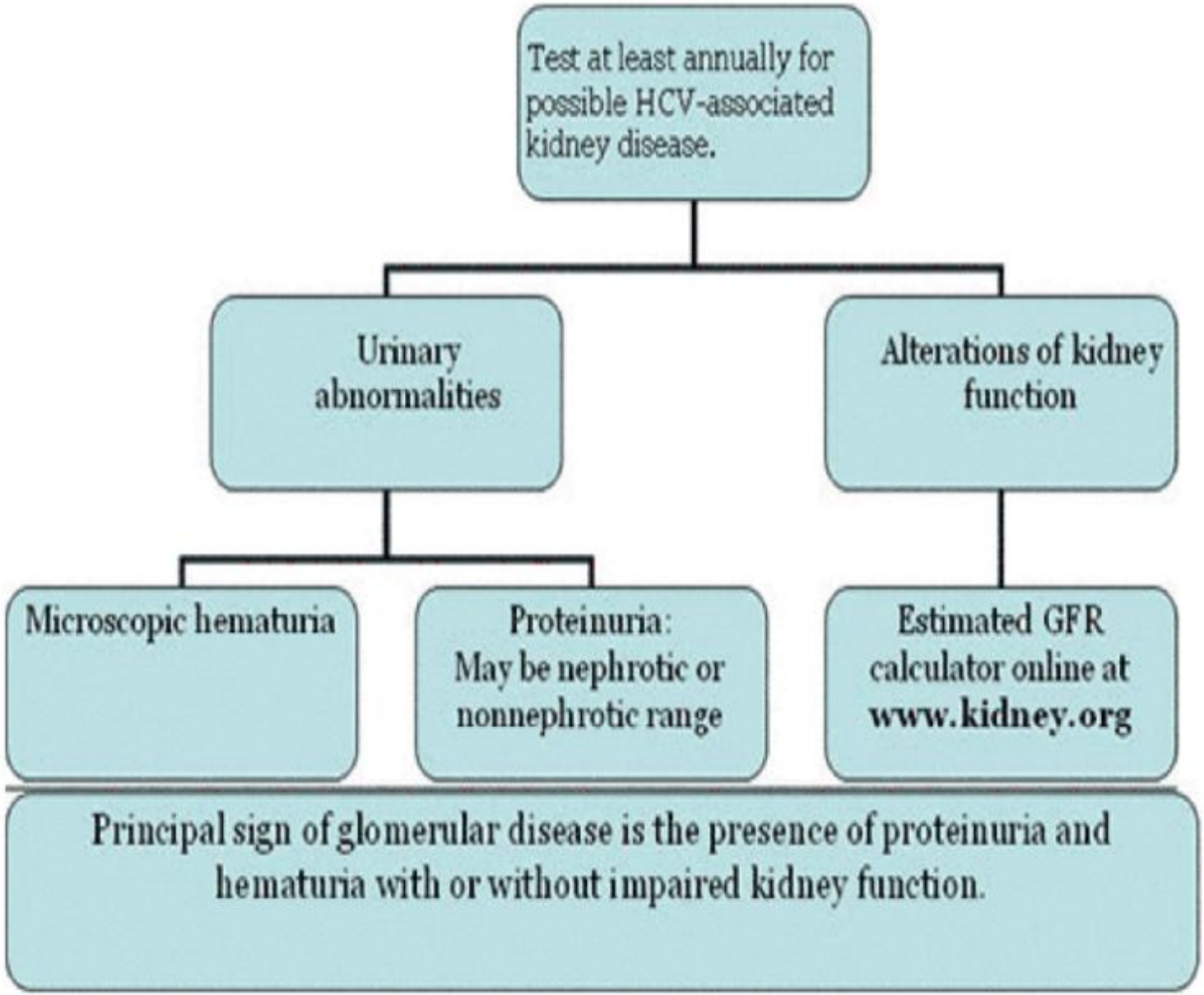
HCV-RNA –

occult HCV infection (HCV-RNA in peripheral blood mononuclear cells or in serum after ultracentrifugation) could be involved in the pathogenesis of glomerular nephropathy among patients negative for conventional markers ofHCV.

- patients infected with HCV be tested at least annually for proteinuria, hematuria, and estimated glomerular filtration rate (eGFR) weak evidevce

HCV-infected patients with clinical evidence of glomerulonephritis should undergo kidney biopsy weak

CKD SCREENING for HCV-Infected Patients



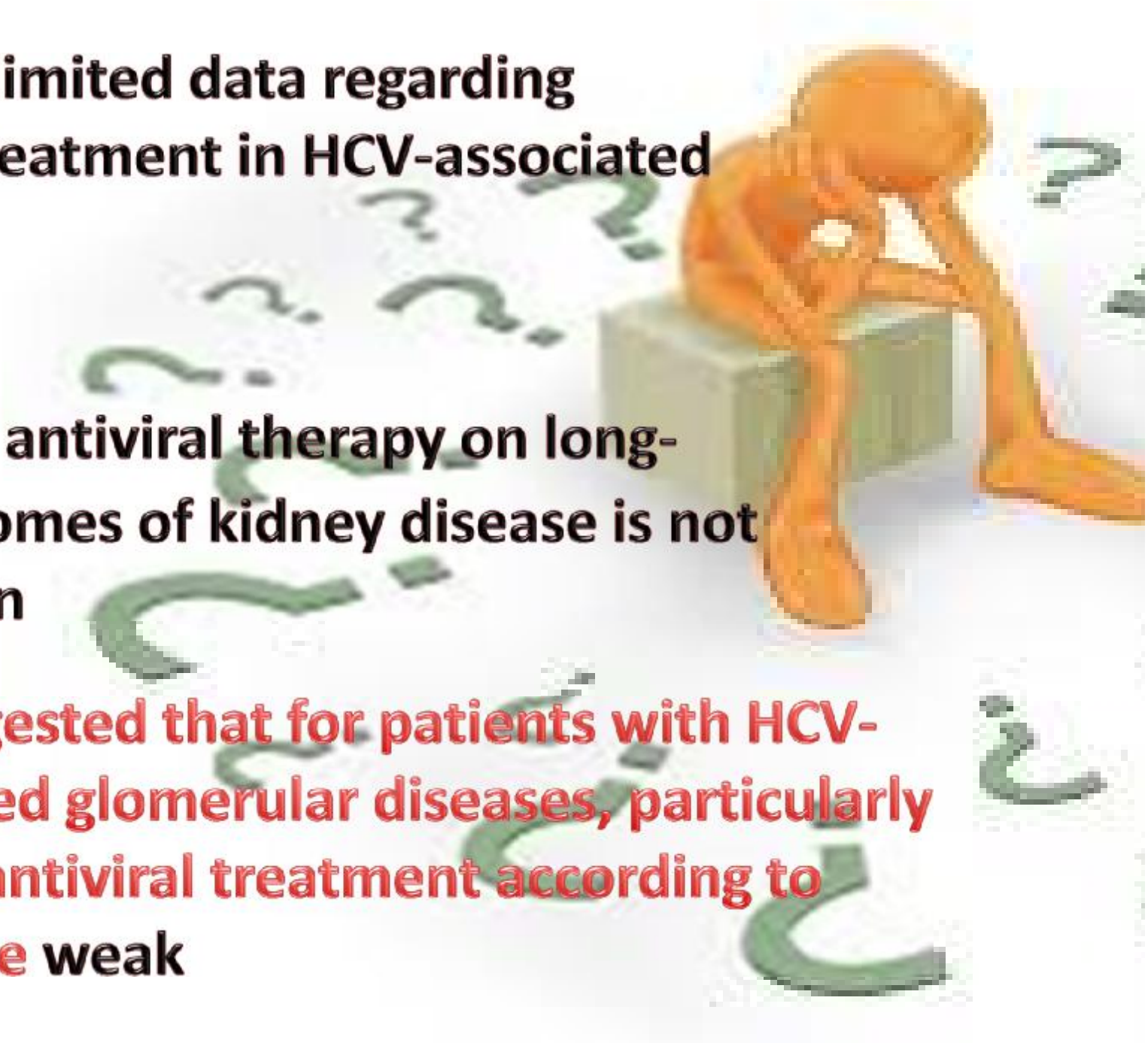
B-Cell Depletion Therapy

ANTIVIRAL THERAPY

NONSPECIFIC IMMUNOSUPPRESSIE AGENTS

ACE/ARB

There are limited data regarding antiviral treatment in HCV-associated GN



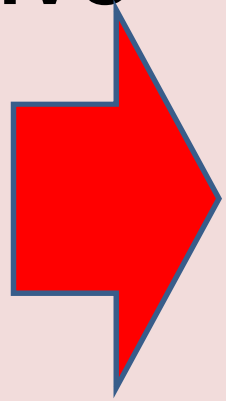
impact of antiviral therapy on long-term outcomes of kidney disease is not well known

It is suggested that for patients with HCV-associated glomerular diseases, particularly MPGN, antiviral treatment according to Guideline weak

ü Cryoglobulinemia without systemic disease and MPGN ü Noncryoglobulinemic MPGN ü MGN ü In those with moderate proteinuria and slow but progressive loss of kidney function:	Standard IFN or peyglated IFN alfa-2a (135 µg week-1 SQ in those with reduced creatinine clearance) OR Pegylated IFN alpha-2B (1.5 µg kg-1 per week1 SQ plus ribavirin (if GFR is >50) With or without erythropoietin support depending on level of hemoglobin

Therapeutic strategy in patients with nephrotic-range proteinuria and/or rapidly progressive disease:

Nephrotic-range proteinuria and/or rapidly progressive loss of kidney function and an acute flare of cryoglobulinemia and MPGN



Consider either plasma exchange (3 l of plasma thrice weekly for 2–3 weeks), rituximab (375 mg m-2 week-1 for 4 weeks), or cyclophosphamide (2 mg kg-1 day-1 for 2–4 months) plus methylprednisolone pulses 0.5–1 g day-1for 3 days.PLUS
Antiviral therapy as in other patients

Rituximab

- ✓ Patients whose disease manifestations are not controlled by,
- ✓ or are not appropriate for, interferon and ribavirin may be candidates for rituximab

Relapses of systemic cryoglobulinemia and membranoproliferative glomerulonephropathy may be treated with additional doses of rituximab

East Asia

Approximately one-third of the world's population has serological evidence of past or present infection with HBV,

350 million people are chronically infected

HBV-associated patterns of GN

- MN
- MPGN
- FSGS
- IgAN

MN is the most common form ofHBVmediated GN


role for
immunosuppression
and plasmapheresis
Nephrotoxicity of
some of
(adefovir
and tenofovir) can
be of concern
Choice of therapy
Antiviral therapy
interferon alfa-2b
entecavir ,
telbivudine
lamivudine ,
adefovir

In patients with HBV-associated renal disease and both seropositivity for HBeAg and evidence of active viral replication (the HBV DNA test is positive) recommend antiviral therapy (Grade 1B).

TWO OPTIONS FOR ANTIVIRAL THERAPY

: INTERFERON ALFA (USUALLY PEGYLATED INTERFERON ALFA)

NUCLEOSIDE/NUCLEOTIDE ANALOGS, SUCH AS LAMIVUDINE , ENTECAVIR , ADEFOVIR , TENOFOVIR , AND TELBIVUDINE

In children and young adults, suggested initial therapy with interferon alfa (usually pegylated interferon alfa) (Grade 2C).
Interferon is less well-tolerated but is more likely to induce a sustained remission

In older adults and in patients with cirrhosis, suggested initial therapy with nucleoside/nucleotide analogs rather than interferon (Grade 2C

goal of antiviral therapy

In patients who are initially HBeAg seropositive, the therapeutic goal is HBeAg seroconversion to anti-HBe

- ✓ **In patients who are initially HBeAg-negative, suppression of viremia, which requires monitoring of HBV DNA levels to ensure that therapy is effective.**

- ✓ **In patients treated with a nucleoside/nucleotide analog, lifelong therapy may be required.**

immunosuppressive therapy

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BRIEF ARTICLE

Treatment of hepatitis B virus-associated glomerulonephritis: A meta-analysis

Yu Zhang, Jian-Hua Zhou, Xiao-Ling Yin, Feng-Yu Wang

Yu Zhang, Jian-Hua Zhou, Xiao-Ling Yin, Feng-Yu Wang ... group (RR = 1.45, 95% CI: 0.68-3.11). Antiviral therapy

Antiviral but not corticosteroid treatment can decrease proteinuria and promote HBeAg clearance in HBV-GN patients.

immunosuppressive therapy

In patients with RPGN&PAN

Suggested both antiviral medication (preferably a nucleoside/nucleotide analog) and a short course of glucocorticoids with or without an immunosuppressant,

The glucocorticoid regimen consists of intravenous methylprednisolone , 500 to 1000 mg/day for three days, followed by prednisone , 0.7 to 1 mg/kg per day, tapered over four to six months.

cyclophosphamide or rituximab (the latter must be accompanied by antiviral therapy since it may lead to increased viral replication

patients with mild PAN, treat with antiviral

in patients with PAN and severe manifestations (defined by the presence of ulcerative or gangrenous lesions of the extremities,
acute kidney injury,
polyneuropathy,
central nervous system involvement, mesenteric arteritis, or myocardial ischemia)

treat with both glucocorticoids and plasmapheresis in addition to antiviral therapy (preferably a nucleoside/nucleotide analog
Prednisone 0.7 to 1 mg/kg per day, tapered over four to six months
Plasma exchange, 2.5 to 4.0 liters per session for a total of 6 to 10 sessions, daily or on alternate days over two to three weeks

data supporting the use of plasma exchange are weak

entecavir or tenofovir in HBV-associated PAN

addition of cyclophosphamide to glucocorticoids and plasma exchange

Antiviral therapy and monitoring of HBV DNA levels are continued for at least six months after cessation of immunosuppressive therapy or until the therapeutic goal is achieved.

In a patient treated with rituximab , antiviral therapy should be continued for 12 months after the rituximab is discontinued.

Concomitant HCV infection

is complex

The choice of therapy depends upon the state of viral replication of the two viruses.

- ✓ **HBV DNA and HCV RNA levels should be measured to determine which virus is dominant and thus most likely responsible for the underlying renal pathology**

- ✓ **Interferon may be a logical therapeutic choice since it is active against both viruses.**

has infected 59 million persons worldwide

AKI

Causes of CKD in HIV-infected patients

HIV-associated nephropathy HIVAN

Immune complex mediated glomerulonephritis

- ✓ membranous nephropathy
- ✓ membranoproliferative
- ✓ mesangial proliferative
- ✓ "lupus-like" proliferative glomerulonephritis

independent disorders

HAART

is beneficial in both preservation and improvement of kidney function in patients with HIV

it is not effective in other GN associated with HIV infection

Long-term follow-up 

Corticosteroids in combination with HAART 

benefits of RAS blockade are independent of HAART therapy 

All HIV-infected patients should be screened for proteinuria and reduced kidney function

Identification of CKD in a patient with HIV should prompt nephrology referral and initiation of HAART

Medication doses should be adjusted for the level of glomerular filtration rate

Patients with CKD should have at least biannual monitoring of estimated glomerular filtration rate (GFR), with medication dose adjustments as neede


KEY
POINT

WHEN TRERE IS ACHRONIC INFECTION

WHEN YOU HAVE AN ACUTE INFECTION

When you have problems identifying the cause of

When treatment fails

Unusual presentation

IRGN