CRESCENTIC GLOMERULONEPHRITIS

Prof. Ashraf M A Bakr

Prof. of pediatrics, Mansoura Faculty of Medicine,

Vice president for students affairs, Mansoura University,

Consultant, Pediatric Nephrology, Mansoura University Children's Hospital

CASE PRESENTATION

- A twelve-year old boy presented to ER by 4 days history of dark-colored urine, oliguria. His blood pressure is 150/100. UA reveals R**Acute nephritic syndrome**ar cast. Serum creatinine is 3mg/dL. Over the next 10 days, he becomes anuric and serum creatinine rises to **Rapidly progressive**

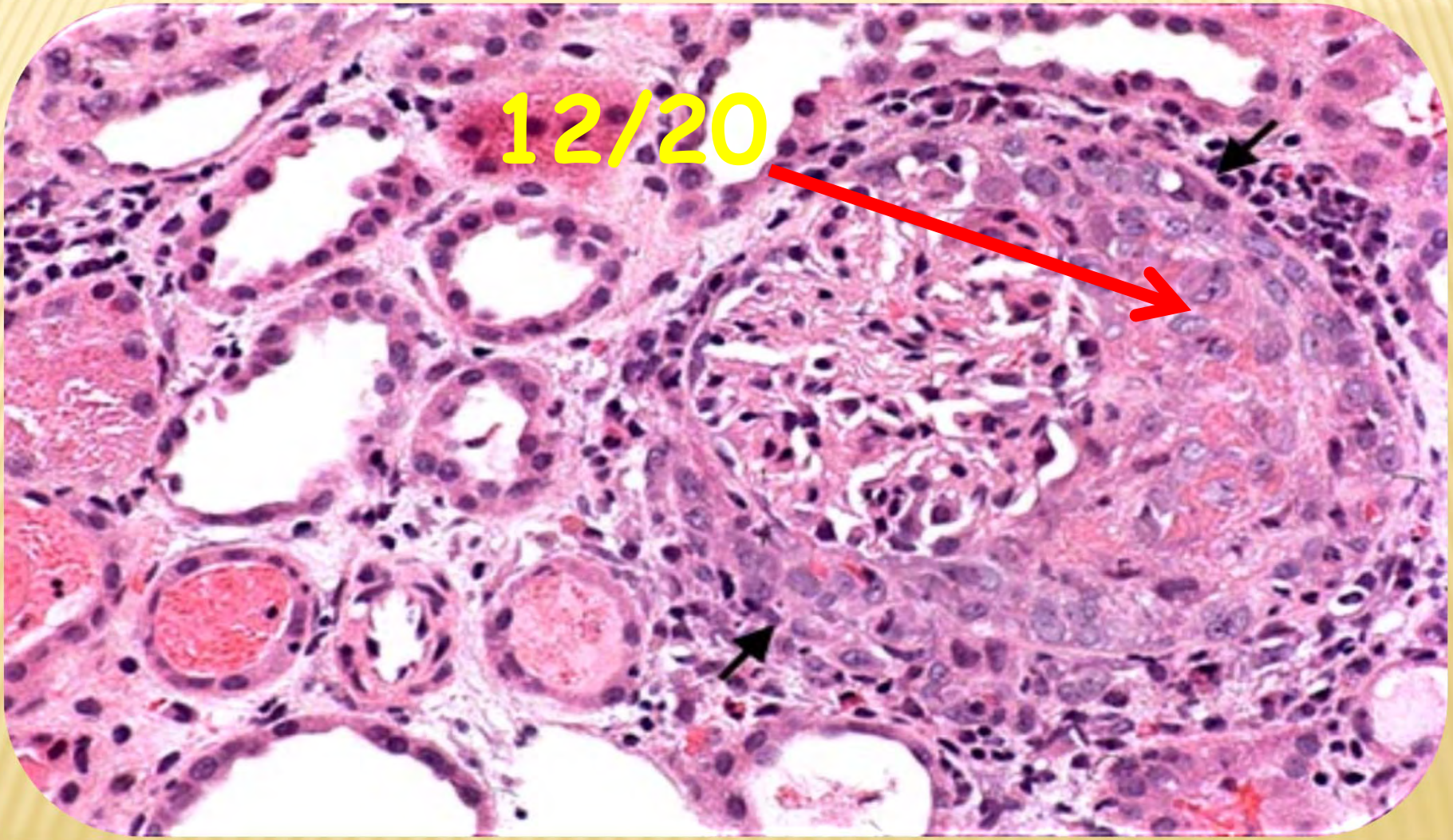
WHAT IS YOUR DIAGNOSIS?

Rapidly progressive glomerulonephritis

WHAT IS THE SUGGESTED INVESTIGATION?

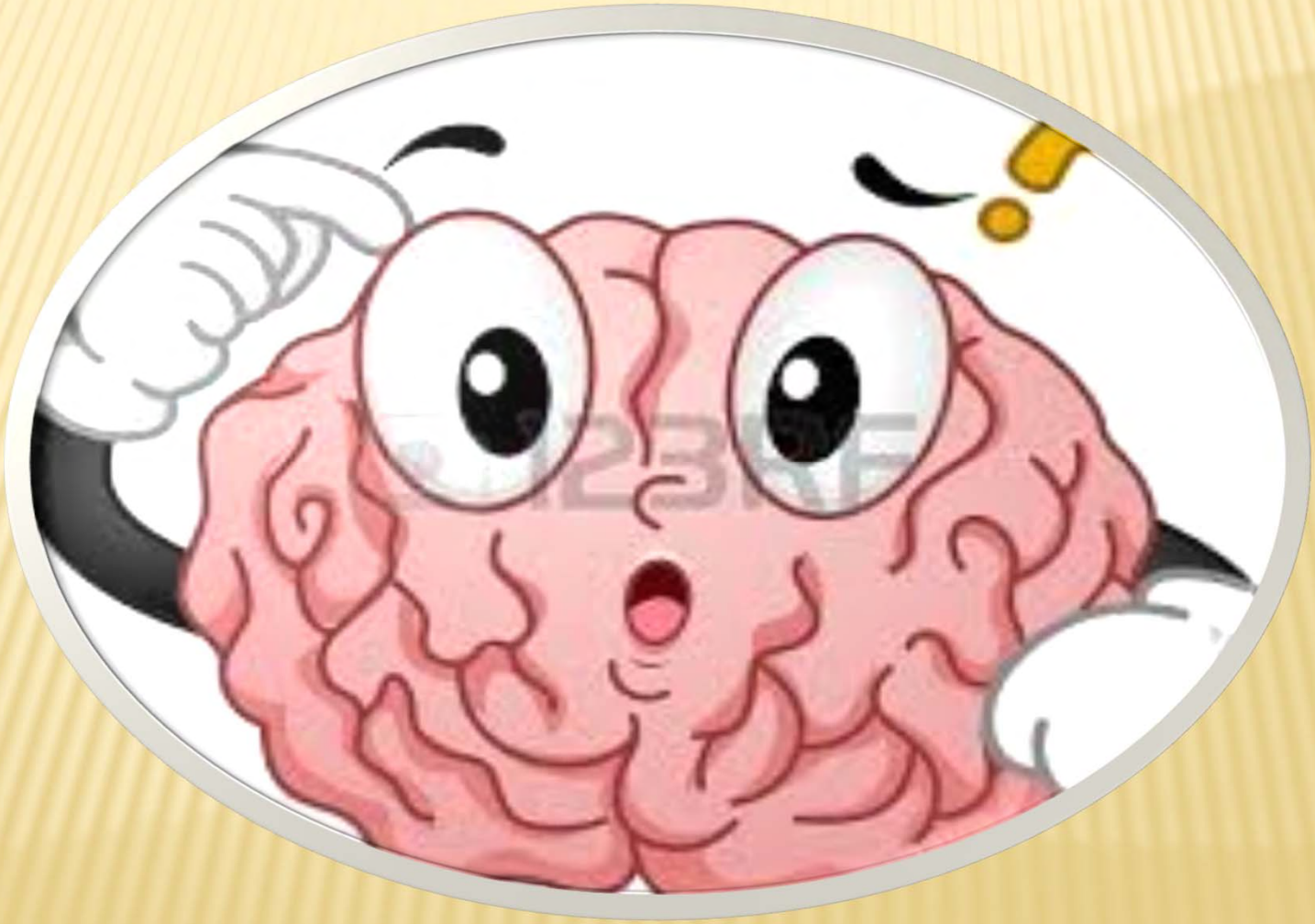
Renal Biopsy

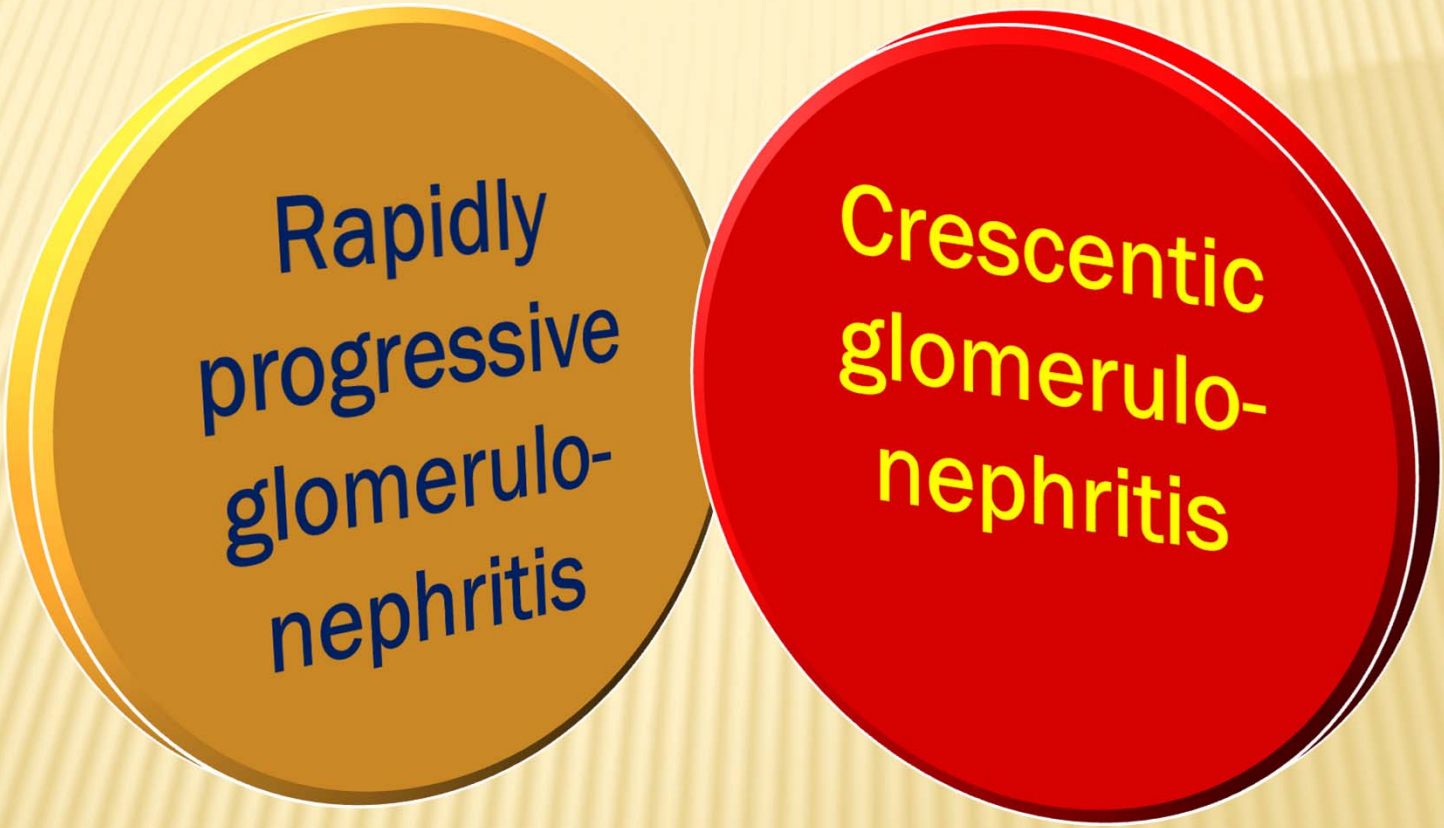
RENAL BIOPSY



WHAT IS YOUR DIAGNOSIS?

Crescentic glomerulonephritis




Rapidly progressive glomerulo-nephritis
Crescentic glomerulo-nephritis

AGENDA

- What is meant by crescentic GN…?
- Pathogenesis
- Classification and causes
- Pathology
- Causes
- Epidemiology
- Work up
- Treatment
- Outcome
- Take home Messages

WHAT IS MEANT BY CRESCENTIC GN….?

CRESCENTIC

GLO

PATHOGENESIS

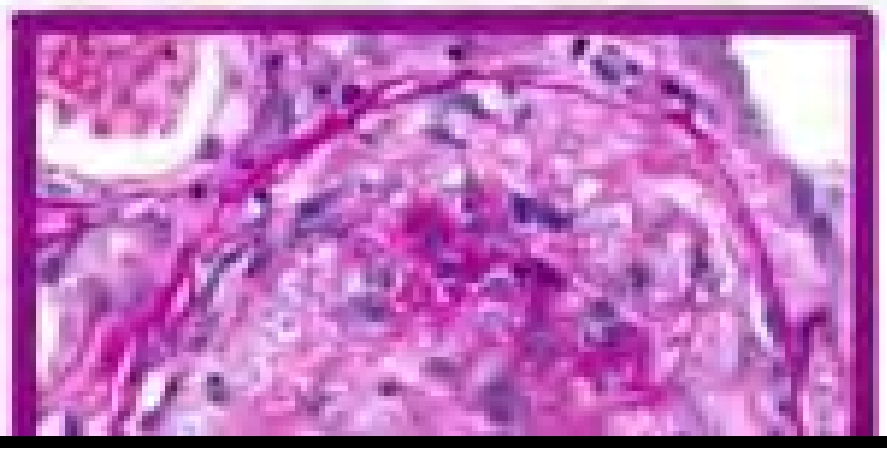
CLASSIFICATION AND CAUSES

CLASSIFICATION AND CAUSES

PATHOLOGY

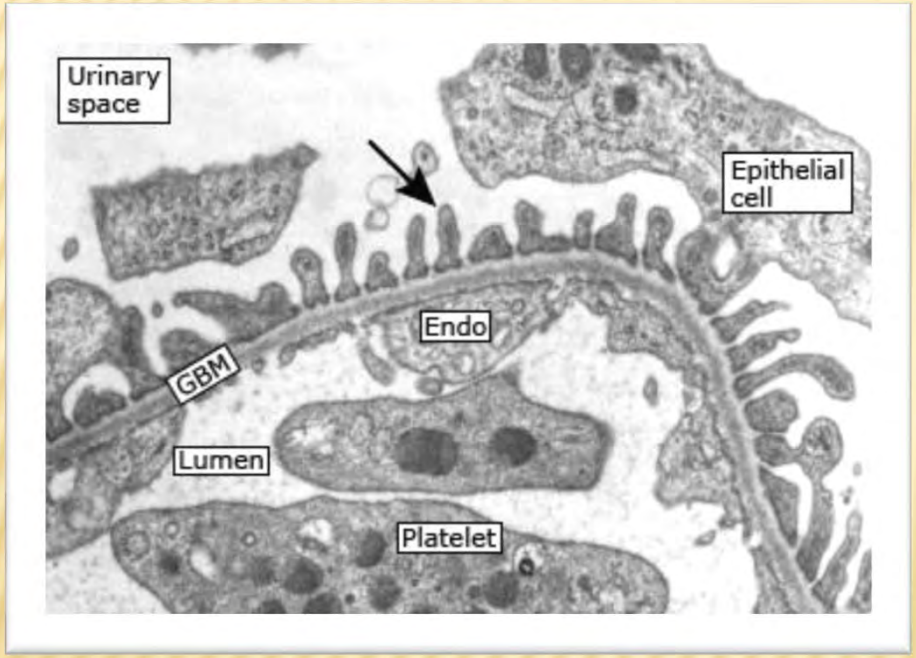
PATHOLOGY

L

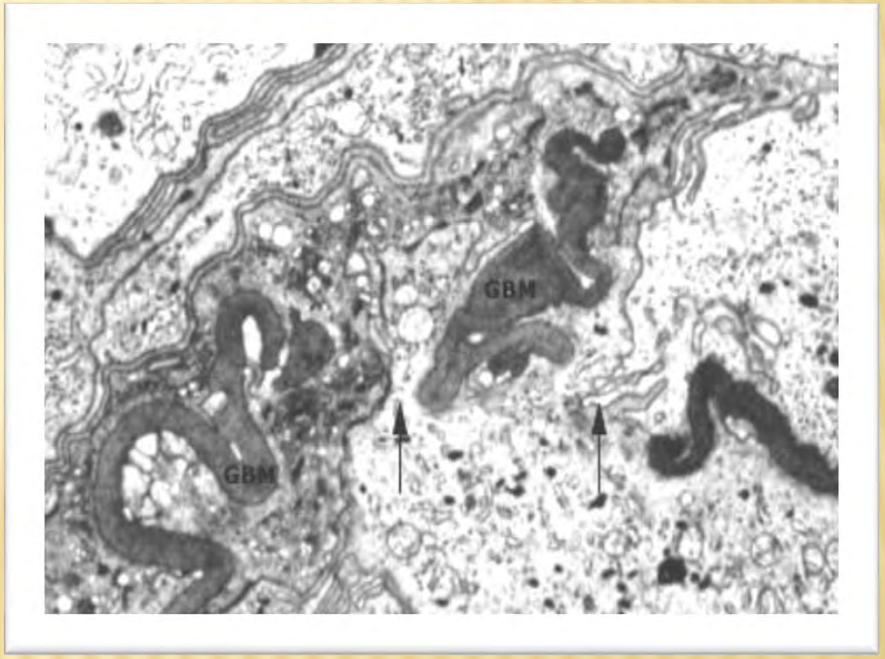


PATHOLOGY

EM



Normal glomerulus



Active hypercellular crescent (Gaps in glomerular basement membrane)

CAUSES

CAUSES

Immune complex GN

- Post infectious GN. Poststreptococcal nephritis, infective endocarditis, shunt nephritis, visceral abscesses, Staphylococcus aureus sepsis, other infections: human immunodeficiency virus, hepatitis B and C, syphilis, legionella, mycoplasma, tuberculosis, leprosy
- Systemic disease. SLE, HSP, cryoglobulinemia, mixed connective tissue disorder, juvenile rheumatoid arthritis, Behcet's syndrome, relapsing polychondritis, mixed connective tissue disease, dermatomyositis
- Primary GN. IgA nephropathy, membranoproliferative GN, membranous nephropathy, C1q nephropathy

Pauci-immune crescentic GN

- Microscopic polyangiitis, Wegener's granulomatosis, renal limited vasculitis, Churg Strauss syndrome
- Medications: penicillamine, hydralazine, hydrocarbons, propylthiouracil

Anti glomerular basement membrane (GBM) GN

- Anti-GBM nephritis, Goodpasture's syndrome, postrenal transplantation in Alport syndrome

Idiopathic crescentic GN

EPIDEMIOLOGY

EPIDEMIOLOGY

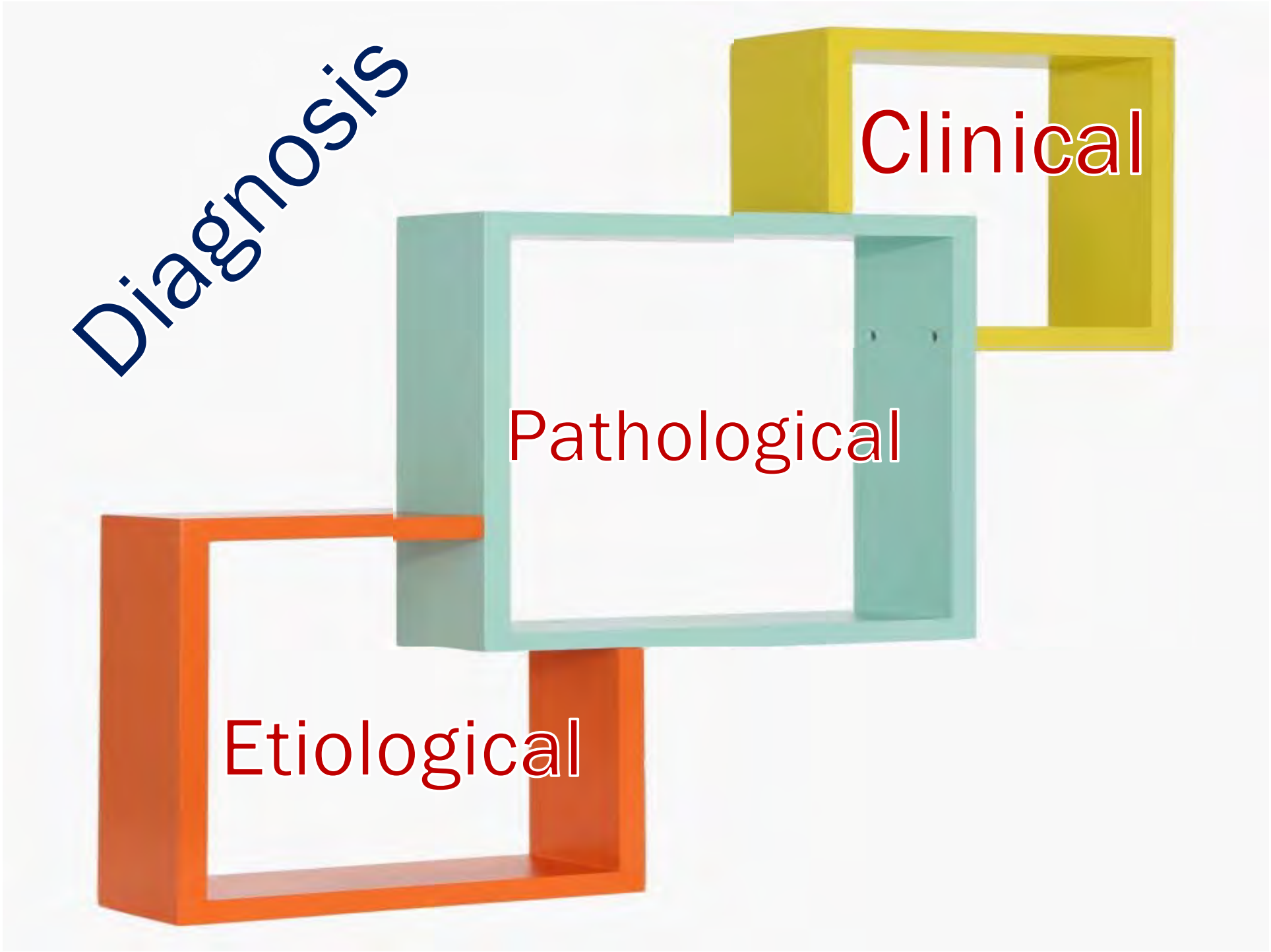
TABLE 31-16 Relative Frequency of Immunopathologic Categories of Crescentic Glomerulonephritis (CGN) in Different Age Groups (in Percent)*

IMMUNOPATHOLOGIC CATEGORY	AGE IN YEARS			
	ALL AGES (n = 632)	1-20 (n = 73)	21-60 (n = 303)	>60 (n = 256)
Anti–glomerular basement membrane CGN	15	12	15	15
Immune complex CGN	24	45	35	6
Pauci-immune CGN†	60	42	48	79
Other	1	0	3	0

EPIDEMIOLOGY

	SPNSG (n=50)	Srivastava et al (n=43)	Niaudet Levy (n=41)	Jardim et al (n=30)
Immune complex disease				
Unspecified	26	-	4.8	-
Systemic lupus erythematous	18	2.3	2.4	3.3
Poststreptococcal GN	12	25.5	12.1	6.6
Henoch-Schonlein purpura	14	6.9	34.1	30
Membranoproliferative GN	4	-	21.9	23.3
Vasculitis	6	-	7.3	16.6
Idiopathic crescentic GN	14	60.4	7.3	13.3
Antiglomerulor basement disease	6	2.3	7.3	6.6
Others	-	2.3	2.4	-

WORK UP


Diagnosis
Clinical
Pathological
Etiological

Diagnosis

Clinical

- Blood levels of urea, creatinine, electrolytes, calcium, phosphate
- Urinalysis: proteinuria; microscopy for erythrocytes and leukocytes, casts

Diagnosis

Pathological

Renal biopsy (light microscopy, immunofluorescence, electron microscopy)

Diagnosis

Etiological

Diagnosis

Etiological

Diagnosis

Etiological

Diagnosis

Etiological

Diagnosis

Etiological

Diagnosis

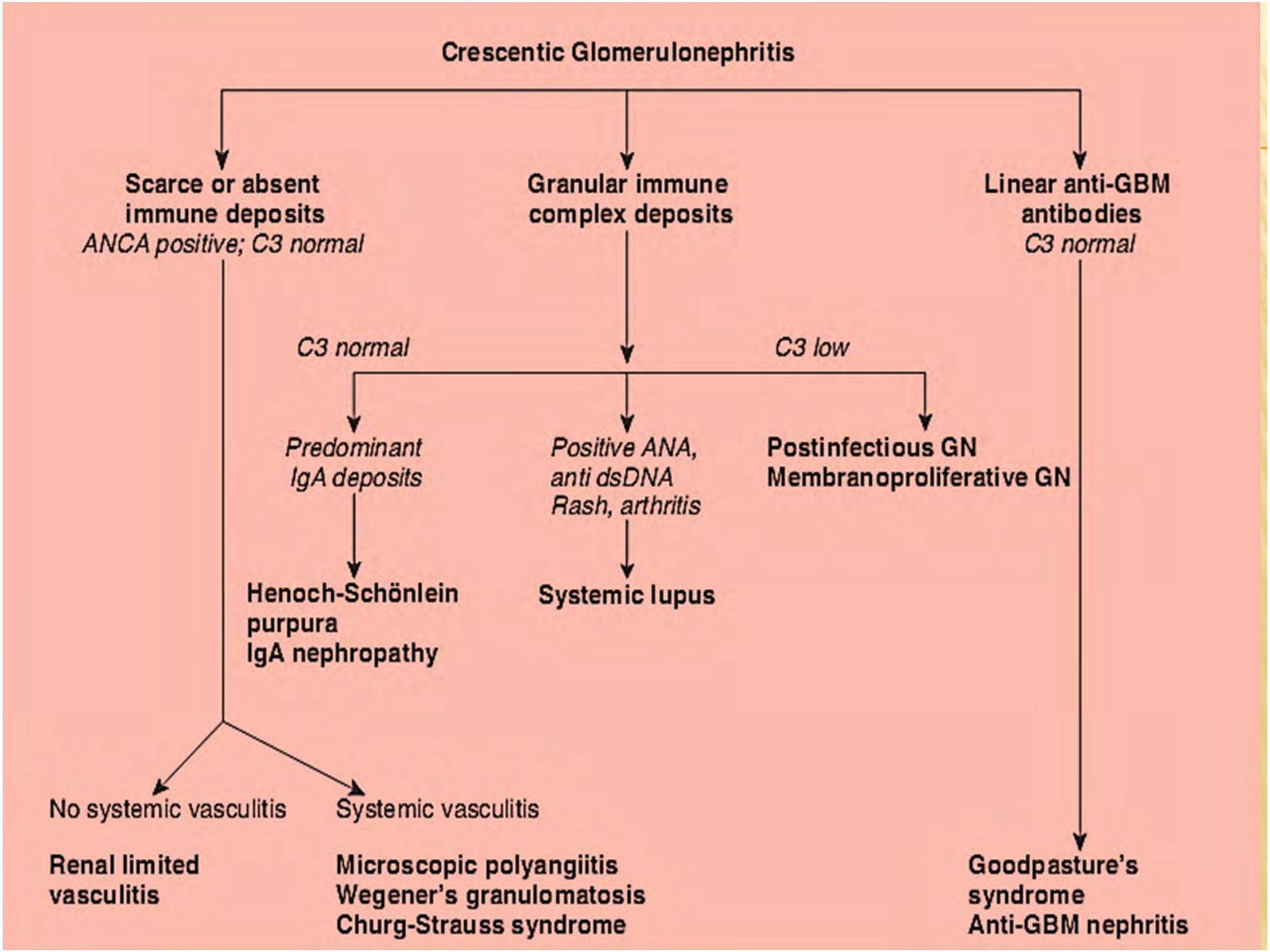
Etiological

- Blood levels of cryoglobulin, hepatitis serology

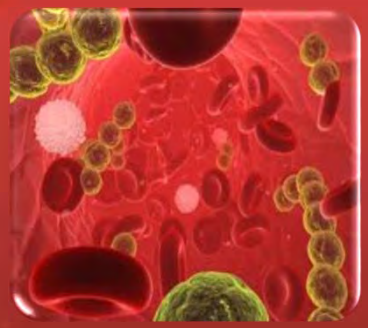
Diagnosis

Etiological

- Radiographs, CT scan for chest, sinuses (patients with Goodpasture's syndrome, Wegener's granulomatosis)


Crescentic Glomerulonephritis
Scarce or absent immune deposits
ANCA positive; C3 normal
Granular immune complex deposits
Linear anti-GBM antibodies
C3 normal
C3 normal
C3 low
Predominant IgA deposits
Positive ANA, anti dsDNA Rash, arthritis
Postinfectious GN
Membranoproliferative GN
Henoch-Schönlein purpura
IgA nephropathy
Systemic lupus
No systemic vasculitis
Systemic vasculitis
Renal limited vasculitis
Microscopic polyangiitis
Wegener's granulomatosis
Churg-Strauss syndrome
Goodpasture's syndrome
Anti-GBM nephritis

TREATMENT



PSAGN Vs other causes

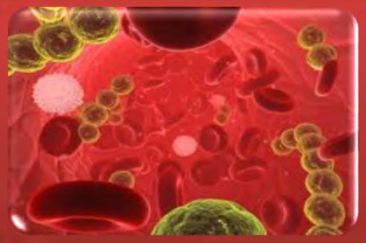
- Are there differences between APSGN and other causes?
- When to start the specific treatment?

Induction phase

- What is the duration of induction phase ?
- What is the suggested protocol to be used?

Maintenance Phase

- When to shift?
- What is the suggested protocol to be used?



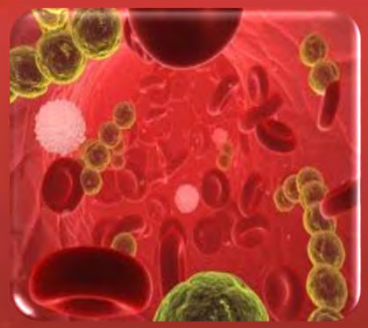
PSAGN Vs other causes

- Are there differences between APSGN and other causes?
- When to start the specific treatment?

- **Whom to treat?**
  1. Crescents involving ≥50% glomeruli.
  2. Acute kidney injury

- **Medication?**
  1. Methylprednisolone
     - 3 to 6 IV pulses of methylprednisolone followed by tapering doses of oral steroids for 6 months.
  2. Cyclophosphamide?????
     - Orally for 3 months.
     - or by IV monthly for 6 months.

lack of evidence-based data.



PSAGN Vs other causes

- Are there differences between APSGN and other causes?
- When to start the specific treatment?

Induction phase

- What is the duration of induction phase ?
- What is the suggested protocol to be used?

Maintenance Phase

- When to start ?
- What is the suggested protocol to be used?

Induction phase

- What is the duration of induction phase ?
- What is the suggested protocol to be

Duration: 3–6 months

Protocol:

1. **Prednisone:**
   - Methylprednisolone 15–20 mg/kg (maximum 1 g) IV daily for 3–6 doses
   - Prednisone 1.5–2 mg/kg/day PO for 4 weeks; taper to 0.5 mg/kg daily by 3 months; 0.5–1 mg/kg on alternate day for 3 months

2. **Cyclophosphamide**
   - IV: 500–750 mg/m2 every 3–4 weeks for 6 pulses **OR**
   - Oral: 2 mg/kg/day

3. **Plasmapheresis (double volume) on alternate days for 2-weeks**

4. **Agents for refractory disease: Intravenous immunoglobulin, TNF-a antibody (infliximab), anti CD20 (rituximab)**

Maintenance Phase

- When to start ?
- What is the suggested protocol to be used?

Duration: 2–5 years

Protocol:

1. Prednisone 0.5–1 mg/kg on alternate days; later taper
2. Azathioprine 1.5–2 mg/kg/day for 12–18 months
3. Consider mycophenolate mofetil (1,000–1,200 mg/m^2/day), if disease activity is not controlled

Treatment of crescentic glomerulonephritis

Induction phase (3–6 months)	Maintenance phase (2–5 year)
Methylprednisolone 15–20 mg/kg (maximum 1 g) IV daily for 3–6 doses	Azathioprine 1.5–2 mg/kg/day for 12–18 months
Prednisone 1.5–2 mg/kg/day PO for 4 weeks; taper to 0.5 mg/kg daily by 3 months; 0.5–1 mg/kg on alternate day for 3 months	Prednisone 0.5–1 mg/kg on alternate days; later taper
[a]Cyclophosphamide 500–750 mg/m^2 IV every 3–4 weeks for 6 pulses	Consider mycophenolate mofetil (1,000–1,200 mg/m^2/day), if disease activity is not controlled
[b]Plasmapheresis (double volume) on alternate days for 2-weeks	
Agents for refractory disease	
Intravenous immunoglobulin, TNF-α antibody (infliximab), anti CD20 (rituximab)	

- Evidence-based data are limited and specific treatment guidelines for children are based on data from case series and prospective studies in adults mainly.

Clin Exp Nephrol (2016) 20:322–341
DOI 10.1007/s10157-015-1218-8

GUIDELINE

Evidence-based clinical practice guidelines for rapidly progressive glomerulonephritis 2014

Yoshihiro Arimura[1] · Eri Muso[2] · Shoichi Fujimoto[3] · Midori Hasegawa[4] · Shinya Kaname[1] · Joichi Usui[5] · Toshiko Ihara[6] · Masaki Kobayashi[7] · Mitsuyo Itabashi[8] · Kiyoki Kitagawa[9] · Junichi Hirahashi[10] · Kenjiro Kimura[11] · Seiichi Matsuo[12]

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Is renal biopsy useful in determining the treatment strategy for RPGN?

C1

Renal biopsy is useful in determining the treatment strategy for RPGN. It is important to evaluate and examine the histological parameters that determine the response to therapy and affect the renal prognosis.

Is initial therapy with corticosteroids alone recommended for improving renal function and survival in patients with RPGN?

CQ 8. Is initial therapy with corticosteroids alone recommended for improving renal function and survival in patients with RPGN?

C1

- Corticosteroid alone → effective
- Corticosteroid + immunosuppressive → more effective
- Initial therapy with corticosteroids alone is recommended only in cases in which the use of immunosuppressive agents is not desirable.

Recommendation grade: C1

In patients with anti-GBM antibody glomerulonephritis presenting with RPGN, high doses of corticosteroids may improve renal function and survival. However, the combined use of immunosuppressive agents is more effective; therefore, initial therapy with corticosteroids alone is recommended, in combination with plasmapheresis, in cases in which the use of immunosuppressive agents is not desirable.

Which of oral corticosteroid or intravenous pulse corticosteroid is recommended as an initial corticosteroid therapy for improving renal function and survival in patients with RPGN?

CQ 9. Which of oral corticosteroid or intravenous pulse corticosteroid is recommended as an initial corticosteroid therapy for improving renal function and survival in patients with RPGN?

C1

- Adding intravenous pulse corticosteroid therapy to oral corticosteroids is recommended when the decline of renal function is very rapid, or when severe systemic complications are present.

Recommendation grade: C1

In patients with anti-GBM antibody disease presenting with RPGN, adding intravenous pulse corticosteroid therapy to oral corticosteroids is recommended to improve survival when pulmonary hemorrhage is present (i.e., Goodpasture syndrome). In patients with anti-GBM antibody glomerulonephritis without pulmonary hemorrhage, adding intravenous pulse corticosteroid therapy to oral corticosteroids is recommended to improve renal function, except for those whose renal function is not likely to recover even with aggressive immunosuppressive therapy.

Is initial therapy with immunosuppressive agents recommended for improving renal function and survival in patients with RPGN?

CQ 10. Is initial therapy with immunosuppressive agents recommended for improving renal function and survival in patients with RPGN?

Recommendation grade: B

In patients with ANCA-positive RPGN, the addition

A

The addition of immunosuppressive agents to corticosteroids in the initial therapy has been shown to improve renal function and survival.

pressive agents with corticosteroids as the initial therapy for these patients.

Recommendation grade: C1

In patients with anti-GBM antibody-positive RPGN, the addition of immunosuppressive agents to corticosteroids in the initial therapy may improve renal function and survival. We recommend immunosuppressive agents with corticosteroids as the initial therapy for these patients.

Which is recommended for improving renal and patient survival in RPGN, oral cyclophosphamide or intravenous pulses of cyclophosphamide?

CQ 11. Which is recommended for improving

B

There are no differences in renal and patient survival between oral cyclophosphamide and intravenous pulses of cyclophosphamide.

Is initial therapy with plasmapheresis recommended for improving renal function and survival in patients with RPGN?

CQ 14. Is initial therapy with plasmapheresis recommended for improving renal function and survival in patients with RPGN?

C1

If the standard therapy is insufficient, the addition of plasmapheresis to immunosuppressive therapy as the initial therapy may improve renal function and survival.

Recommendation grade: B

In patients with anti-GBM antibody-positive RPGN, the addition of plasmapheresis to immunosuppressive therapy as the initial therapy has improved renal function and survival. We recommend plasmapheresis for these patients.

Is rituximab recommended for improving renal function and survival in patients with RPGN?

CQ 13. Is rituximab recommended for improving renal function and survival in patients with RPGN?

C1

No evidence to support that treatment with rituximab improves renal function and survival; however, it could be considered if there is no other treatment available

available (not covered by insurance in Japan).

Recommendation grade: not graded
In patients with anti-GBM antibody disease presenting with RPGN, there is no evidence to support that treatment with rituximab improves renal function and survival.

Do intravenous immunoglobulins (IVIg) improve renal and patient survival in RPGN?

CQ 16. Do intravenous immunoglobulins (IVIg) improve renal and patient survival in RPGN?

C1

Limited evidence that IVIg improves renal and patient survival in RPGN, IVIg can be used as an alternative option for patients with concurrent complications such as severe infections when it is advisable to avoid the standard therapy

with high-dose steroids and immunosuppressant (off-label use).

Is maintenance therapy with corticosteroids alone recommended for improving renal function and survival in patients with RPGN?

CQ 17. Is maintenance therapy with corticosteroids alone recommended for improving renal function and survival in patients with RPGN?

A

Low-dose corticosteroids have been shown to improve renal function and survival.

Recommendation grade: B

In patients with anti-GBM antibody glomerulonephritis presenting with RPGN, low-dose corticosteroids have been shown to improve renal function and survival. We recommend corticosteroids as maintenance therapy for these patients.

Is maintenance therapy with immunosuppressive agents recommended for improving renal function and survival in patients with RPGN?

CQ 19. Is maintenance therapy with immunosuppressive agents recommended for improving renal function and survival in patients with RPGN?

A

The addition of immunosuppressive agents to corticosteroids in the maintenance therapy has been shown to improve renal function and survival.

maintenance therapy for these patients.

Recommendation grade: C1

In patients with anti-GBM antibody-positive RPGN, the addition of immunosuppressive agents to corticosteroids in the maintenance therapy may improve renal function and survival. We recommend the use of immunosuppressive agents with corticosteroids as maintenance therapy for these patients.

OUTCOME

Almost to 60-70% recover renal function

Determinates of outcome:

- The severity of renal failure at presentation
- Renal histology
- The promptness of intervention
- The underlying disease

TAKE HOME MESSAGES

TAKE HOME MESSAGES

- RPGN and crescentic GN are two faces of a coin
- The histologic marker is the presence of crescentic, the clinical correlate is RPGN
- Diagnosis of crescentic GN needs the integration of serologic, pathologic and clinical views

TAKE HOME MESSAGES

- It is necessary to make an accurate and rapid diagnosis as treatment strategies vary and delay in instituting treatment results in irreversible disease
- Evidence based data is limited and specific treatment guidelines for children are based on data from case series and prospective studies in adults
- The course is largely determined by the severity of renal failure at presentation, the promptness of intervention, renal histology and the underlying disease.

IN THE TREATMENT OF RPGN:

- Renal biopsy is useful in determining the treatment strategy
- The treatment strategy is similar in ANCA-positive anal ANCA-negative patients
- The addition of immunosuppressive agents to corticosteroids improves renal survival
- All of the above

REGARDING THE HISTOLOGY OF RPGN:

- Patients with circumferential crescents have more indolent course than those with non-circumferential one
- Pauci-immune GN is the most prevalent pathological type in children
- The histological type dose not affect the outcome of the disease
- None of the above


Thank You