# Research Advances in Rapidly Progressive (Crescentic) Glomerulonephritis

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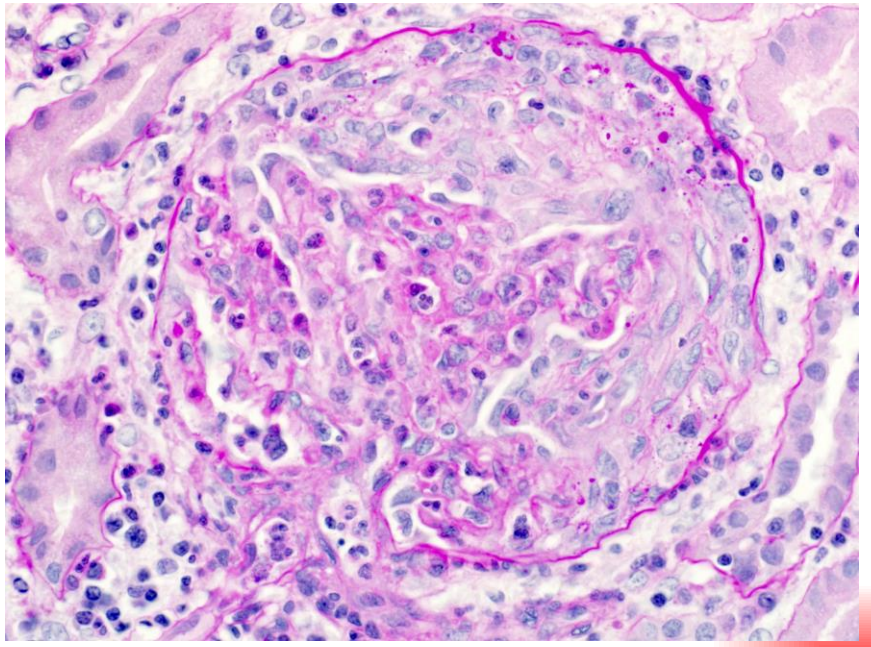


# Rapidly Progressive GN: Introduction

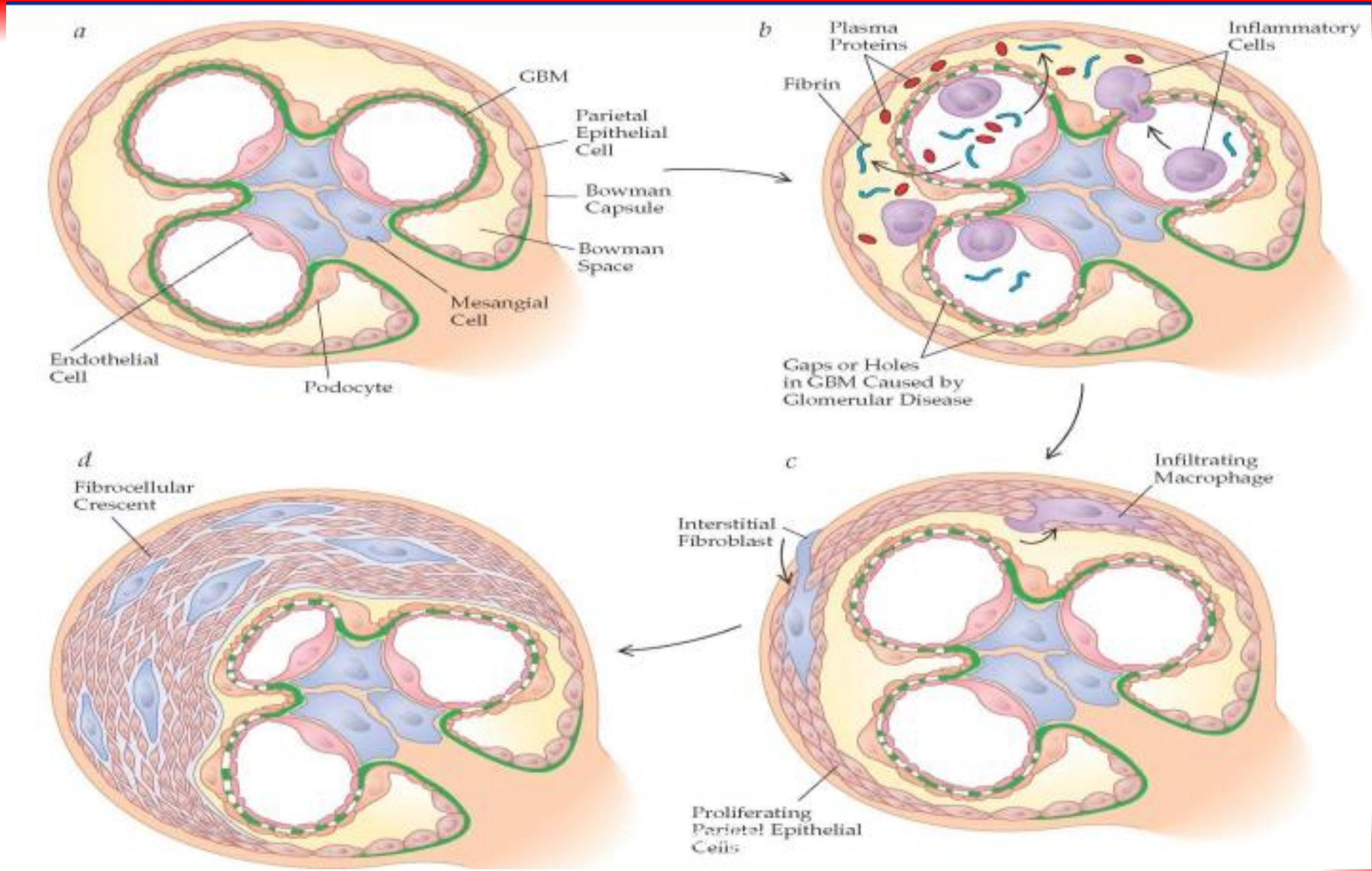
- Progressive loss of kidney function over a comparatively short period of time (days, weeks, or a few months).
- Extensive crescent formation (extracapillary proliferation in Bowman's space).
- Common in the older adult presenting with acute nephritis, but in any age group.
- Crescents in > 80 % of the glomeruli: advanced kidney failure that may not respond well to therapy.
- Crescents in < 50 % of the glomeruli, a more indolent course and may even undergo a remission.

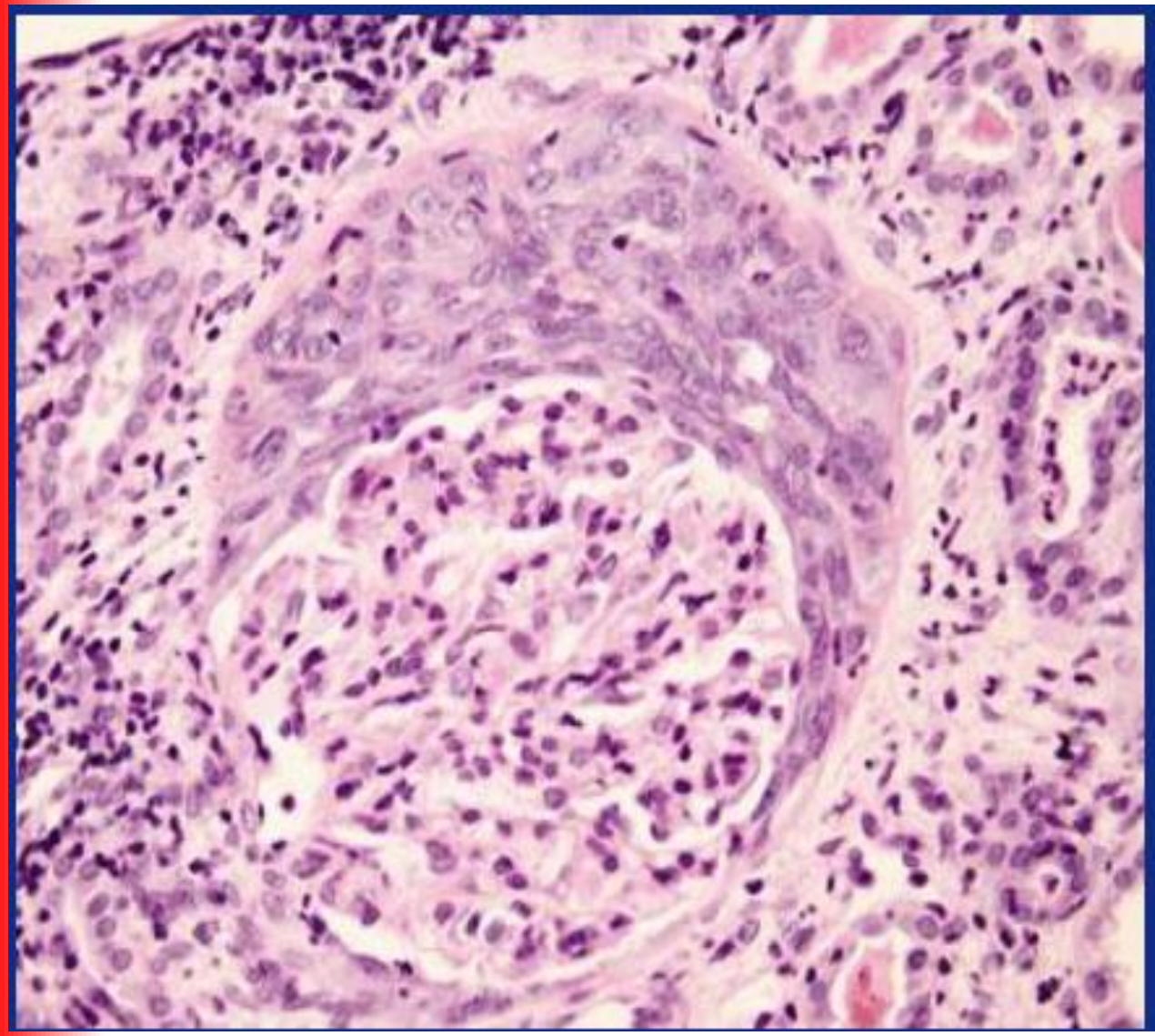
# Crescentic GN: Definition

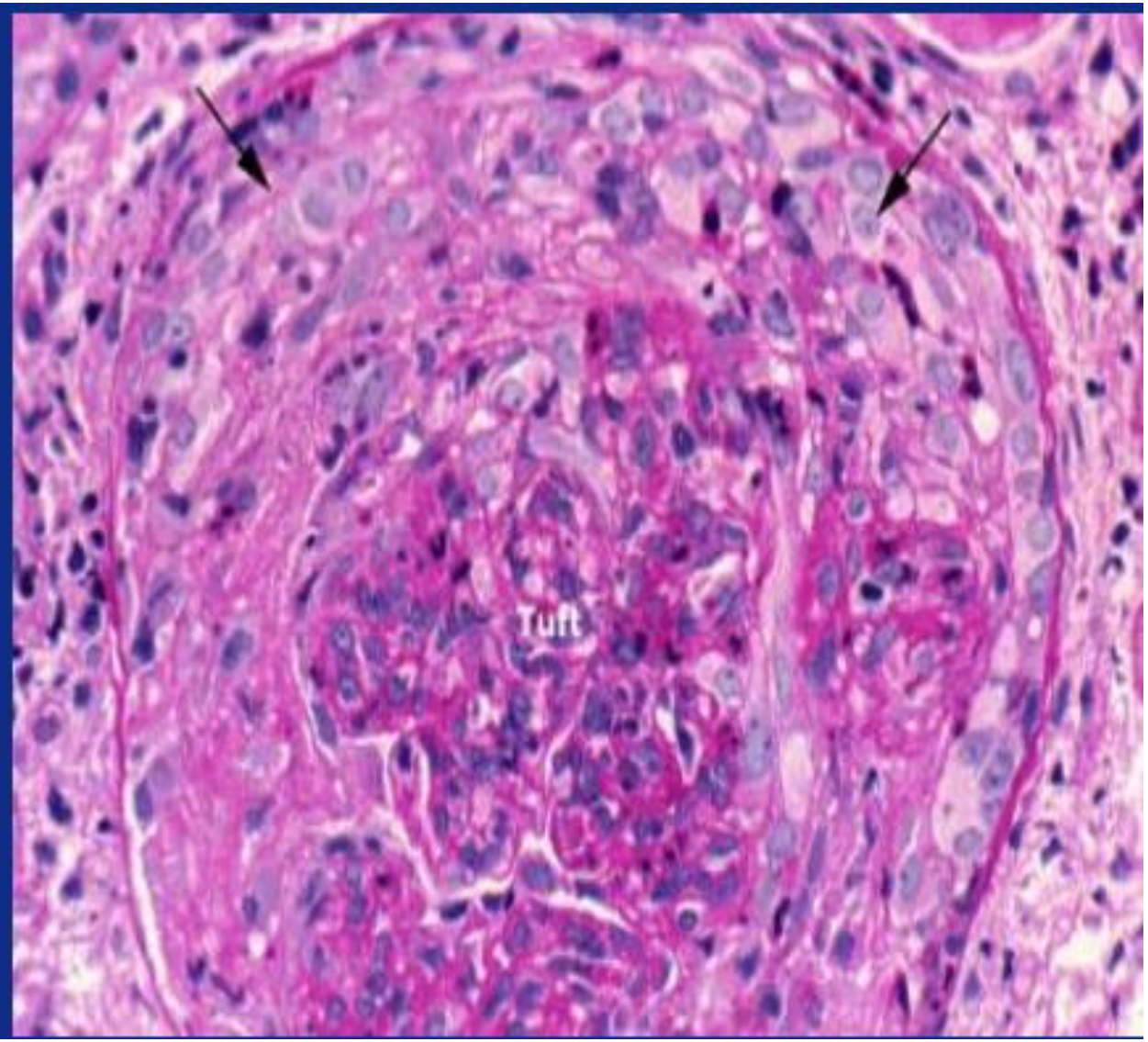
- ✓Over 50 percent crescents called crescentic
- ✓10 to 50 percent crescents called crescentic
- ○Less than 10 percent crescents are not called crescentic

# PATHOGENESIS OF CRESCENT FORMATION

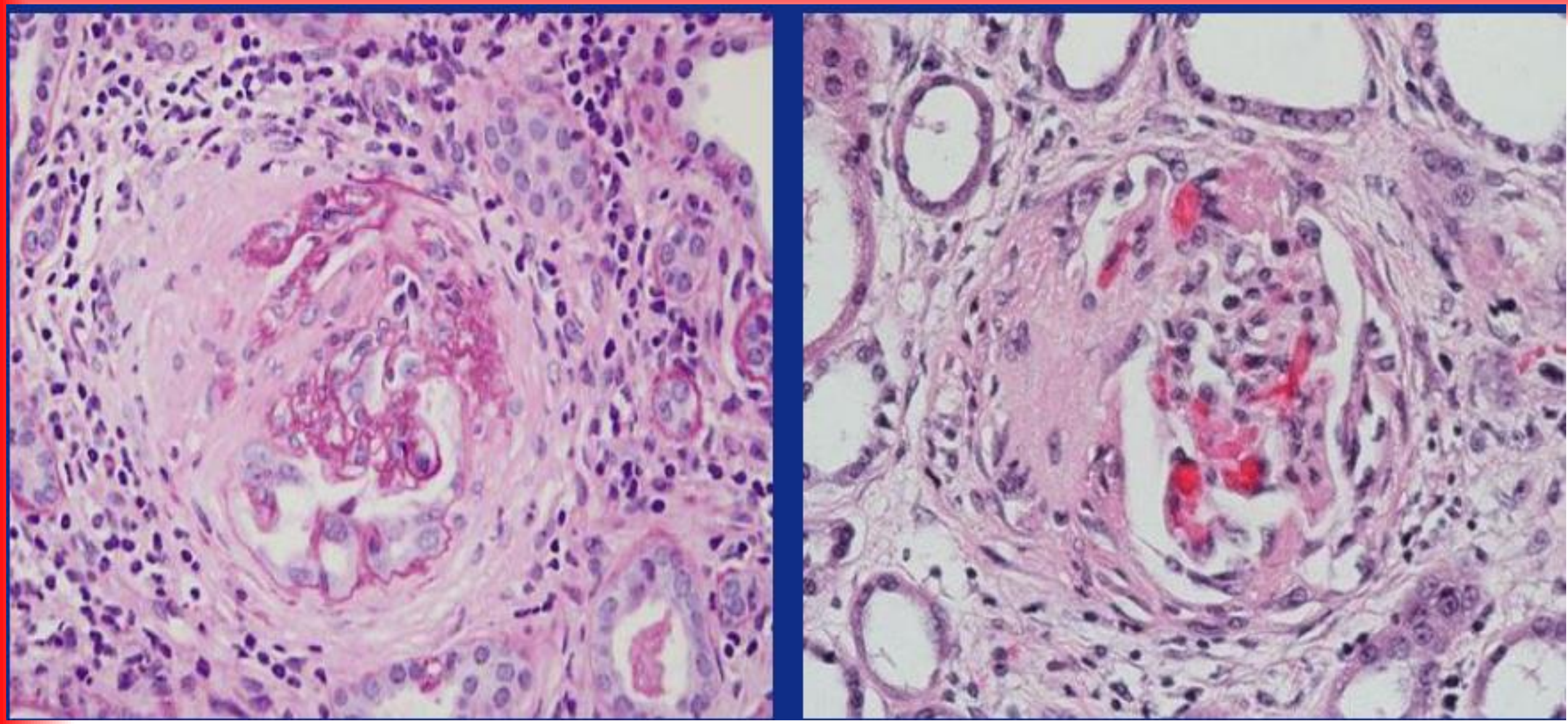
- Focal gaps of the capillary wall resulting in the movement of fibrinogen, into Bowman's space with subsequent fibrin formation, the influx of macrophages and T cells and the release of pro-inflammatory cytokines, such as interleukin-1 and tumor necrosis factor-alpha and procoagulant and fibrinolytic inhibitory factors.
- The early stage followed by the development of fibrocellular and fibrous crescents in Bowman's space.
- Collagen deposition is due to fibroblast proliferation
- This transition is important because fibrous crescents is not likely to respond to immunosuppressive therapy


a
GBM
Parietal Epithelial Cell
Bowman Capsule
Bowman Space
Mesangial Cell
Endothelial Cell
Podocyte
b
Plasma Proteins
Inflammatory Cells
Fibrin
Gaps or Holes in GBM Caused by Glomerular Disease
c
Infiltrating Macrophage
Interstitial Fibroblast
Proliferating Parietal Epithelial Cells
d
Fibrocellular Crescent






Cellular crescents



Fibrocellular and fibrous crescent

# TYPES OF CRESCENTIC GN

Three broad mechanisms of glomerular injury:

1. Anti-GBM disease (15%)
2. Immune complex-mediated injury (24%)
3. Pauci-immune necrotizing and crescentic GN (ANCA positive) (60%).
4. Idiopathic pauci-immune disease that is ANCA negative (<5%).

# Immune complex-mediated injury

Presence of immune deposits in the glomeruli, the serologic and histologic findings point to the underlying disease:

- IgA nephropathy and IgA vasculitis;
- Postinfectious GN
- Lupus nephritis
- Mixed cryoglobulinemia

# CLINICAL PRESENTATION

- Severe nephritic syndrome : the acute onset of gross hematuria, decreased urine output, hypertension, and edema.
- More commonly, an insidious onset with the initial symptoms being fatigue or edema.
- Kidney function impairment is present at diagnosis in almost all cases, plasma creatinine often exceeding 3 mg/dL.

# CLINICAL PRESENTATION…

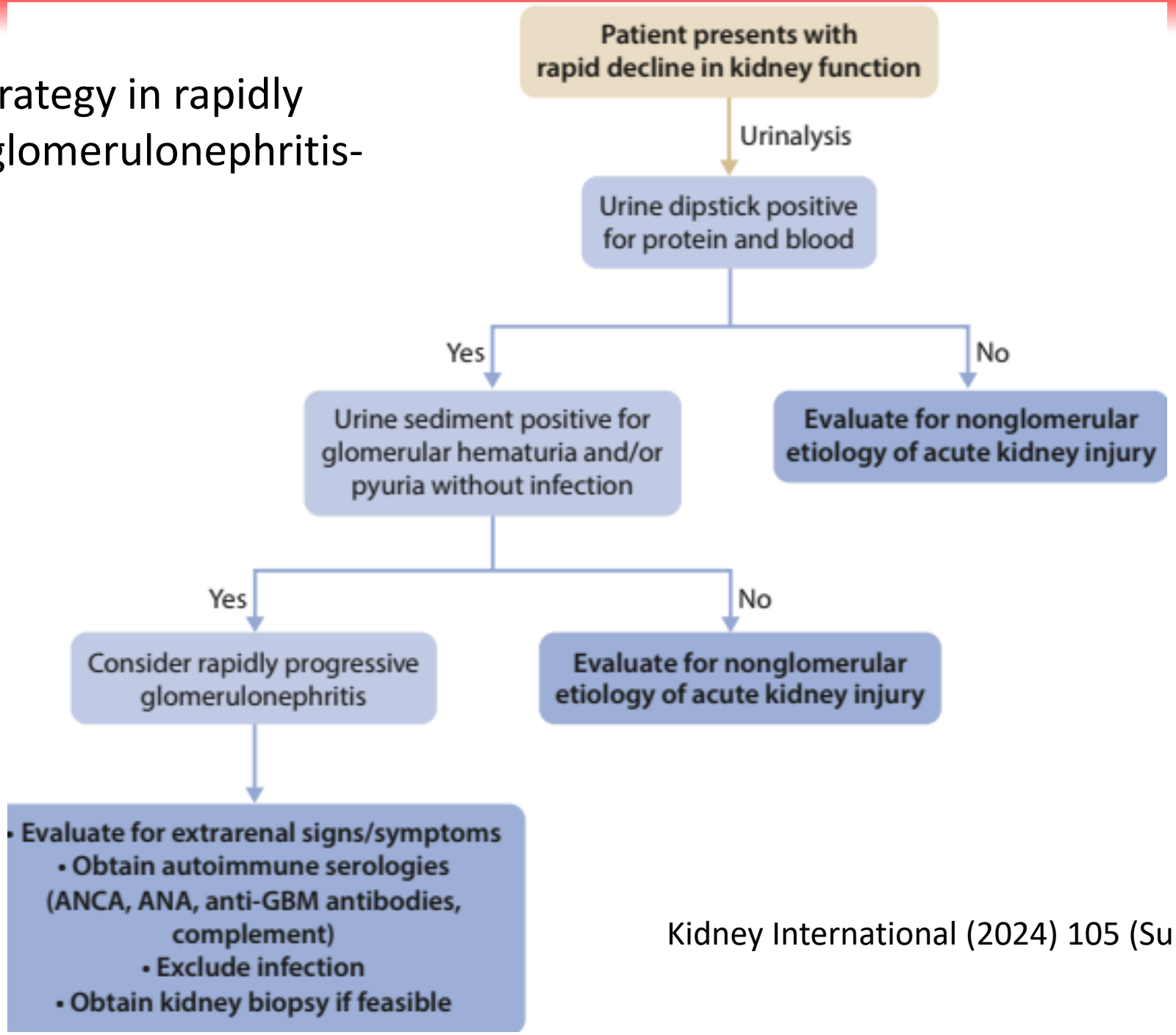
- Higher incidence of upper airway disease in ANCA-positive.
- Similar percentage of ANCA-negative and -positive patients presented with involvement of the lower airway, musculoskeletal system, skin, and/or nervous system.
- Anti-GBM disease may have pulmonary hemorrhage and hemoptysis, leading to anemia and iron deficiency.

# EVALUATION AND DIAGNOSIS

Serologic tests:

- ANCA,
- Anti-GBM antibodies,
- Complement component assays,
- Antinuclear antibodies,
- Cryoglobulins,
- Kidney biopsy, unless contraindicated.

# Diagnostic strategy in rapidly progressive glomerulonephritis- KDIGO- 2024

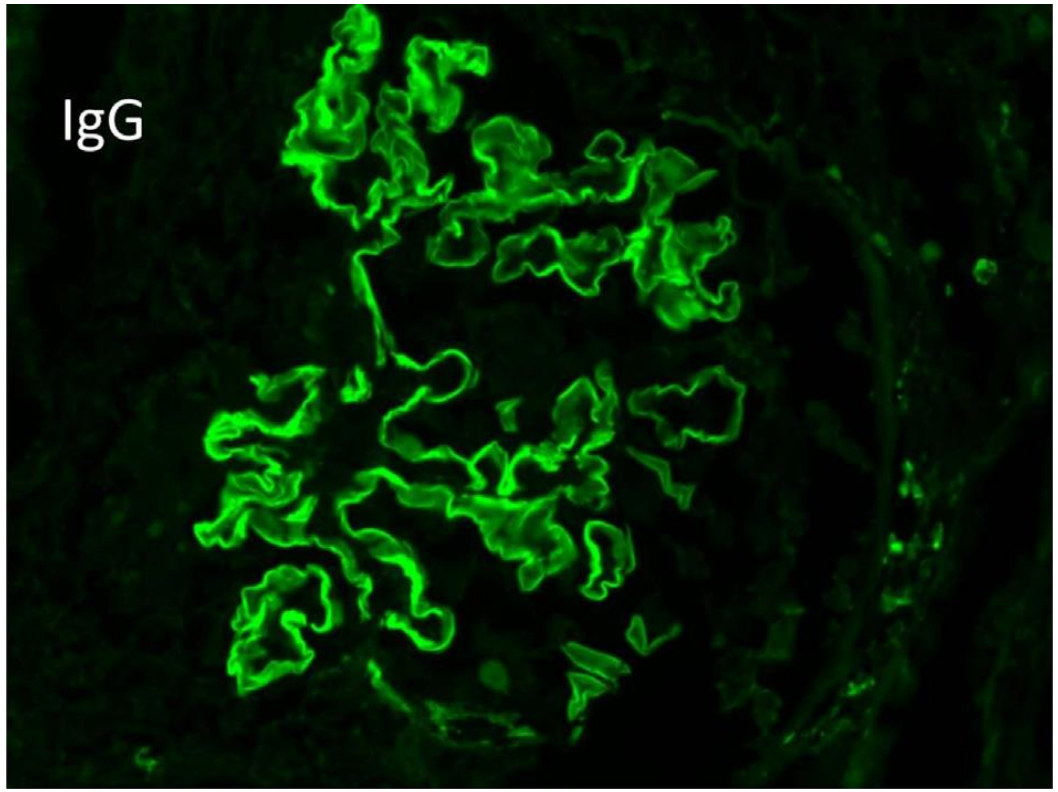



Kidney International (2024) 105 (Suppl 3S), S71–S116

# DIAGNOSIS and TREATMENT

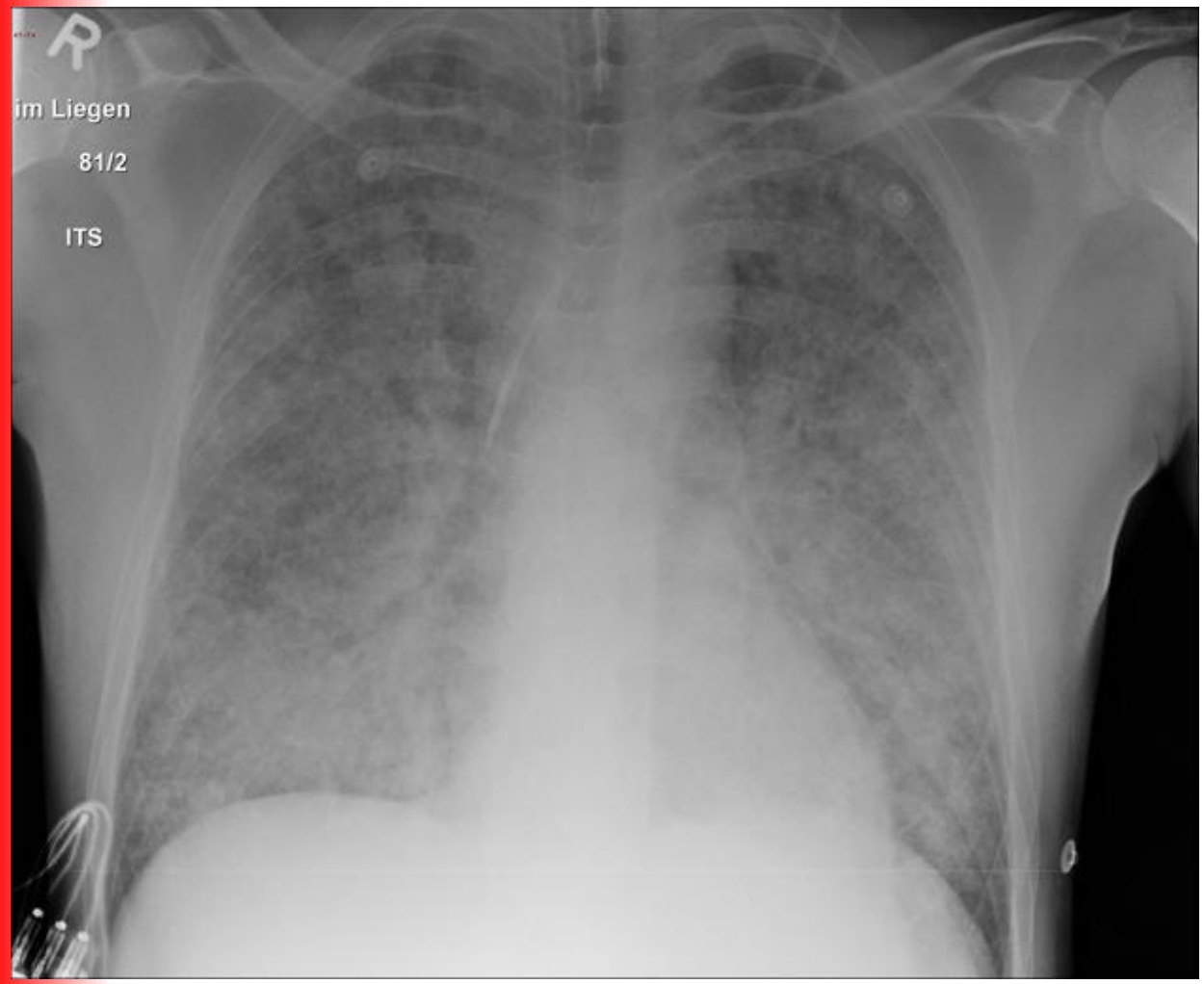
- Early diagnosis with kidney biopsy and serologic testing and early initiation of appropriate therapy is essential to minimize the degree of irreversible kidney injury.
- Empiric therapy should be initiated in patients with severe disease, particularly if either kidney biopsy or interpretation of the biopsy will be delayed.
- Iv pulse methylprednisolone (500 to 1000 mg/day, 3 days) and plasmapheresis, especially in hemoptysis.
- Histologic abnormalities will not alter if kidney biopsy performed soon after initiating empiric therapy.

# Anti-GBM (Goodpasture) Disease



# Anti GBM disease

- Goodpasture disease or goodpasture syndrome are older terms.
- Pulmonary hemorrhage: <30 years
- Isolated GN: >50 years
- 90 % clinical features of RPGN.
- Malaise, weight loss, fever, or arthralgia, only for a few weeks,
- Complement: normal.
- **Kidney manifestations**
  Non-nephrotic proteinuria and a nephritic sediment, macroscopic hematuria, mild degree of kidney involvement
- **Pulmonary manifestations**
  shortness of breath, cough, hemoptysis, pulmonary infiltrates on CXR, CT: ground glass or consolidative opacities in a diffuse and bilateral distribution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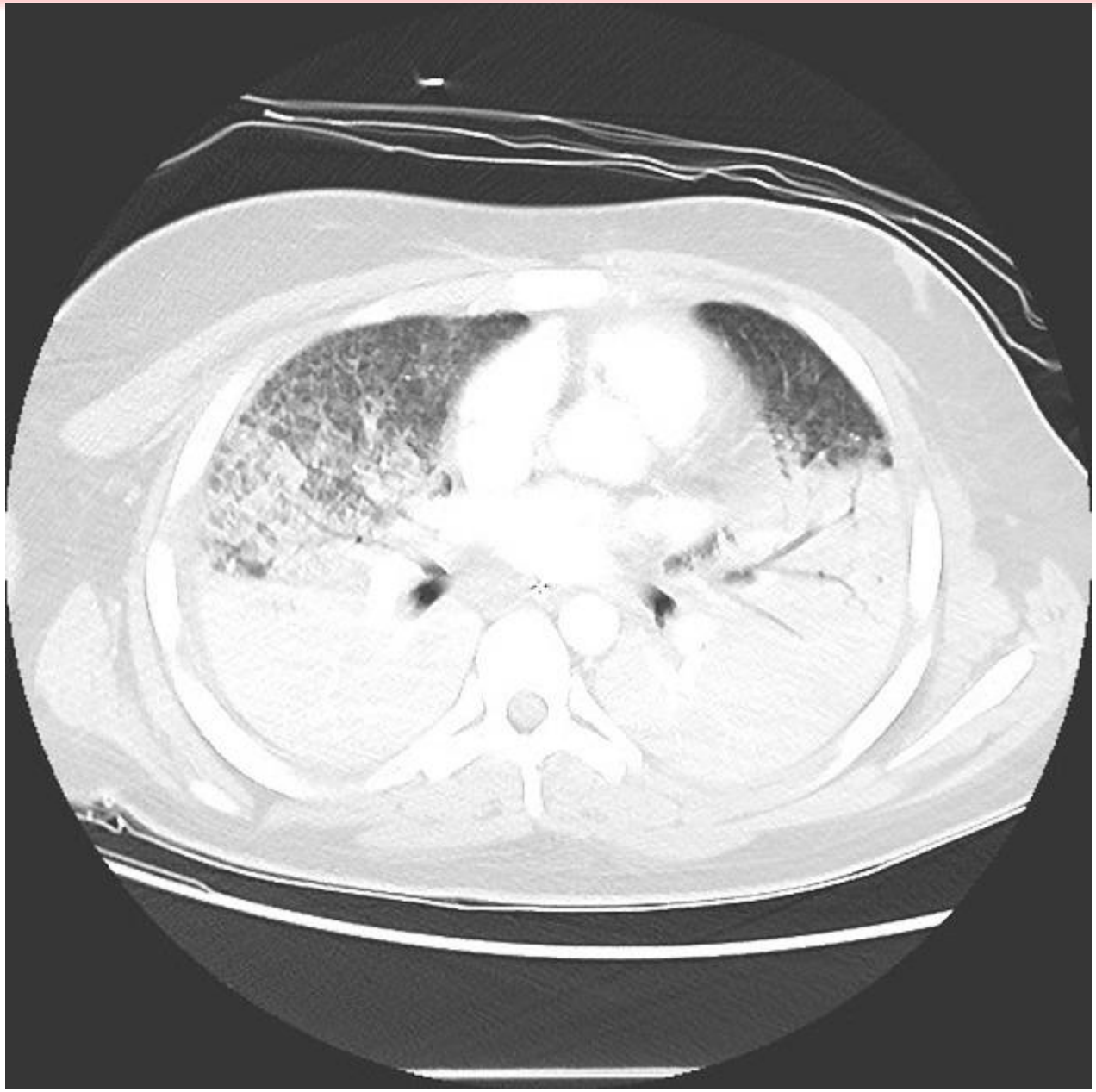


# Anti GBM (Goodpasture) disease

**When to suspect anti-GBM disease**

- Acute or subacute nephritic syndrome, rapid progression and/or alveolar hemorrhage or alveolar hemorrhage alone.

Less common variants:

- Nephrotic syndrome with a rapid decline in kidney function
- Kidney transplant recipients with Alport syndrome present with acute GN or graft failure

# Anti GBM (Goodpasture) disease

**Establishing the diagnosis**

**Kidney biopsy:**

**without delay** in all unless contraindicated, LM: crescent formation

IF: pathognomonic, linear deposition of IgG along GBM.

**Serological testing**:

When kidney biopsy cannot be performed or delayed, anti-GBM antibodies by ELISA with or by indirect IF.

All patients with suspected anti-GBM disease should also be tested for ANCA.

# Anti-GBM disease WHOM TO TREAT

**Plasmapheresis (PP) combined with prednisone and cyclophosphamide:**

- All patients with pulmonary hemorrhage (hemoptysis).
- All patients with kidney involvement not require immediate dialysis
- Dialysis patients [a **short** trial (two to three weeks) of plasmapheresis and immunosuppressive therapy]:
  - Patients with very acute disease
  - Younger patients able to tolerate aggressive immunosuppression.
  - Biopsy, focal crescentic glomerular damage associated with acute tubular injury.
  - Anti-GBM disease with both ANCA and clinical signs of a systemic vasculitis (purpuric rash and arthralgias )

# Anti-GBM disease

## INITIAL THERAPY: Plasmapheresis plus immunosuppressive (IS) therapy

**Plasmapheresis (PP) regimen:**

- Daily 4 liter exchanges for two to three weeks
- Centrifugal or membrane separation equally efficacious.
- **Albumin** is given as the **replacement fluid**.
- **Recent kidney biopsy or pulmonary hemorrhage**, one to two liters of **FFP** should be substituted for albumin at the **end of the procedure**.

# Anti-GBM disease

## INITIAL THERAPY (Plasmapheresis (PP) plus IS therapy)

- **Continued plasmapheresis if**:

  Active pulmonary disease (eg, hemoptysis),

  Antibody titers not declining substantially,

  Antibody titers rebound after stopping PP.

  Alternate day, after the initial two weeks of treatment.

- Severe infection, a single infusion of IVIG; 100 to 400 mg/kg after plasmapheresis session.

# Anti-GBM disease Immunosuppressive therapy (Glucocorticoids plus cyclophosphamide)

**Glucocorticoids:**

Methylprednisolone iv (15 to 30 mg/kg to a maximum dose of 1000 mg over 20 minutes) daily for three doses

followed by daily oral prednisone (1 mg/kg per day to a maximum of 60 to 80 mg/day), tapered once remission is induced.

Prednisone after plasmapheresis.

Glucocorticoids continued for up to six months.

**Plasmapheresis must be accompanied by glucocorticoids and immunosuppressive**

# Anti-GBM disease Immunosuppressive therapy (Glucocorticoids plus cyclophosphamide)

**Cyclophosphamide:**

Initial dose: 2 mg/kg per day orally. age >60 years and frail patients, reduce by 25 %

impaired kidney function, adjust the dose.

Time: after plasmapheresis.

Duration: three months, If anti-GBM not reduced by 3 months, continue up to 6 month

- IV therapy, if cannot take oral.

Anti-GBM and ANCA, higher risk of relapse, maintenance therapy similar to ANCA-AV.

# Anti-GBM disease (Alternatives to cyclophosphamide)

- **Rituximab:**

1 g for two doses

If on plasmapheresis, rituximab after the initial 7 consecutive days of PP and glucocorticoids, and 48-hour should be elapsed to resume PP.

- **Mycophenolate mofetil** (MMF):

500 mg twice daily and as tolerated to 1000 mg twice daily.

Dose reduction with leukopenia or significant GI side effects.

# Anti-GBM disease **Monitoring the response to therapy**

**Clinical status**:

Creatinine, CBC, and urine output daily: first two to three weeks
Follow up visits: weekly for two to four weeks, then every two to four weeks

**Anti-GBM antibody level:** weekly for the first six weeks until they are undetectable on two consecutive occasions, every other week for four weeks then once monthly for six months.

Avoid smoking and hydrocarbon exposures (higher recurrence).

| Intervention | Dosing | Duration of treatment |
|---|---|---|
| Plasma exchange | • 40–50 ml/kg ideal body weight exchange daily against 5% albumin<br>• Add fresh frozen plasma at the end of plasma exchange in patients with alveolar hemorrhage and/or after kidney biopsy | Until circulating anti-GBM antibodies can no longer be detected; usually 14 days |
| Cyclophosphamide | • 2–3 mg/kg orally (reduce to 2 mg/kg in patients >55 years); experience with pulse intravenous cyclophosphamide is limited and efficacy is uncertain<br>• Cyclophosphamide dosing should be reduced (or treatment interrupted) in cases of leukopenia<br>• In patients not tolerating (or not responding to) cyclophosphamide, rituximab or mycophenolate mofetil may be tried but experience is limited and efficacy uncertain | 3 months |
| Glucocorticoids | • Pulse methylprednisolone may be given initially up to 1000 mg/d on 3 consecutive days<br>• Prednisone 1 mg/kg orally<br>• Reduce to 20 mg/d by 6 weeks | 6 months |

**Treatment of anti-GBM disease**, KDIGO 2021, Kidney International (2021) 100, S1–S276

# PERSISTENT ANTI-GBM ANTIBODIES after therapy

Anti-GBM:

- ≥ 3 the ULN for at least two to three weeks of therapy
  - Ongoing disease activity (hemoptysis or active GN) : RTX 1 g first and 14 days later
  - On dialysis, no activity, presence of diffuse crescents or glomerulosclerosis and interstitial fibrosis: taper off treatment and continue to monitor anti-GBM antibody levels.
- 1-3 times the ULN after 3-4 months of CYC. therapy, recovered kidney function and overall doing well
  - Switch to RTX ((1 g initially and 14 days later).
  - If RTX not available, AZA (1 to 2 mg/kg per day) or MMF 1000 mg twice daily, continue treatment for 6-9 months.

# INVESTIGATIONAL THERAPIES –anti GBM disease

- **Immunoadsorption:** as part of the plasmapheresis procedure, may be effective in some patients with anti-GBM disease, even in those who are dialysis dependent.
- **Imlifidase:** enzyme from *Streptococcus pyogenes* that cleaves human IgG, inhibiting complement-dependent and antibody-dependent cellular cytotoxicity.

Endopeptidase Cleavage of Anti-Glomerular Basement Membrane Antibodies in Severe Kidney Disease. J Am Soc Nephrol 2022; 33:829.

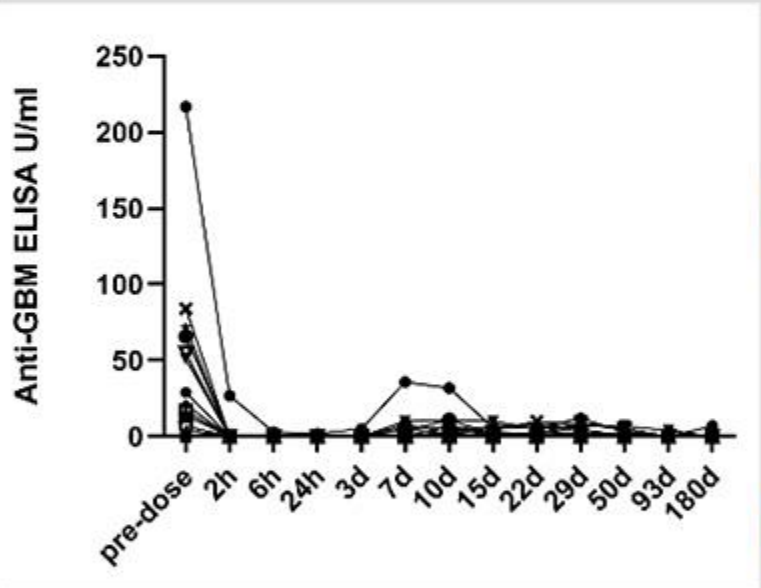
# Endopeptidase Cleavage of Anti-Glomerular Basement Membrane Antibodies *in vivo* in Severe Kidney Disease: An Open Label Phase IIa Study

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

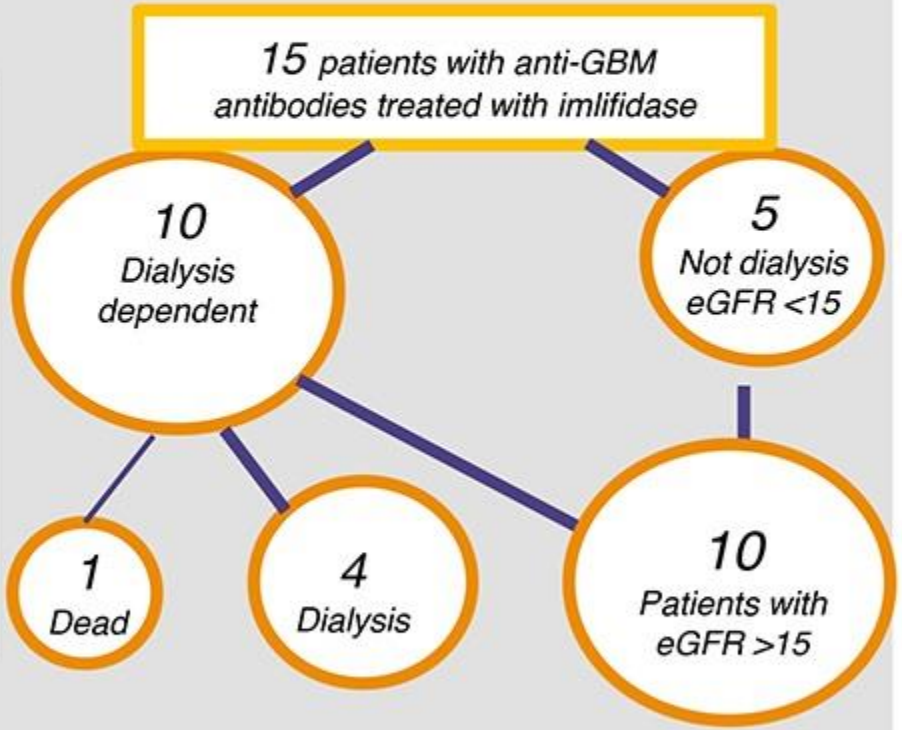
## METHODS

- 15 patients with circulating anti-GBM antibodies
- eGFR <15 ml/min/1.73m$^2$
- To all:
  - Imlifidase 0.25 mg/kg
  - Cyclophosphamide
  - Corticosteroids
- If rebound of anti-GBM
  - Plasma exchange

**Primary outcome:**
Dialysis independency at 6 months




## OUTCOME




**Conclusion**
Cleavage of IgG *in vivo* with the endopeptidase imlifidase caused rapid clearance of anti-GBM antibodies and was in this one arm pilot study associated with renal survival in 10 out of 15 patients.

doi: 10.1681/ASN.2021111460

# Top 5 Takeaways for Clinicians for the Management of Anti-GBM Glomerulonephritis

1. **Diagnosis**
   In all with a RPGN, a diagnosis should be made as quickly as possible, but if anti-GBM disease is suspected, **treatment should be started without delay, even if diagnosis has not been confirmed**
2. **Treatment**
   Immunosuppression with CYC and glucocorticoids plus PEx should be initiated in all patients with anti-GBM except dialysis at presentation, 100% crescents or >50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary hemorrhage.
3. **Length of treatment**
   PEx until anti-GBM antibodies in serum are no longer detectable. CYC for 2–3 months and glucocorticoids tapered over 6 months. No maintenance therapy except who are also ANCA-positive.
4. **Refractory disease**: rituximab may be tried.
5. **Kidney transplantation:** should be postponed until anti-GBM antibodies remain undetectable for at least 6 months.

**KDIGO- 2025**

# Case 1

- An 82-y/o man with a history of HTN and CAD presents with significant fatigue, lethargy, and BP=150/90.
- Lab tests: increase in creatinine from 1.2 to 8.0 mg/dL, significant hematuria (too numerous to count/HPF), proteinuria (0.8 gms/gm of creatinine), Hb: 12 g/dL, and positive anti-GBM antibodies. C XR: mild pulmonary congestion but no lung infiltrates.
- Hemodialysis for hyperkalemia in the setting of oliguria.
- A kidney biopsy: extensive necrotizing and crescentic GN with 95% cellular crescents with linear IgG deposits, indicating anti-GBM disease with 30-40% interstitial fibrosis and tubular atrophy.
- What is the next best step in management?

A. Initiate plasma exchange, pulse methylprednisolone, and oral cyclophosphamide
B. Initiate plasma exchange, pulse methylprednisolone, and rituximab
C. Initiate pulse methylprednisolone only
D. Do not initiate plasma exchange or any immunosuppression.

Adv in Kidney Disease and Health 2024;31(6):485-495

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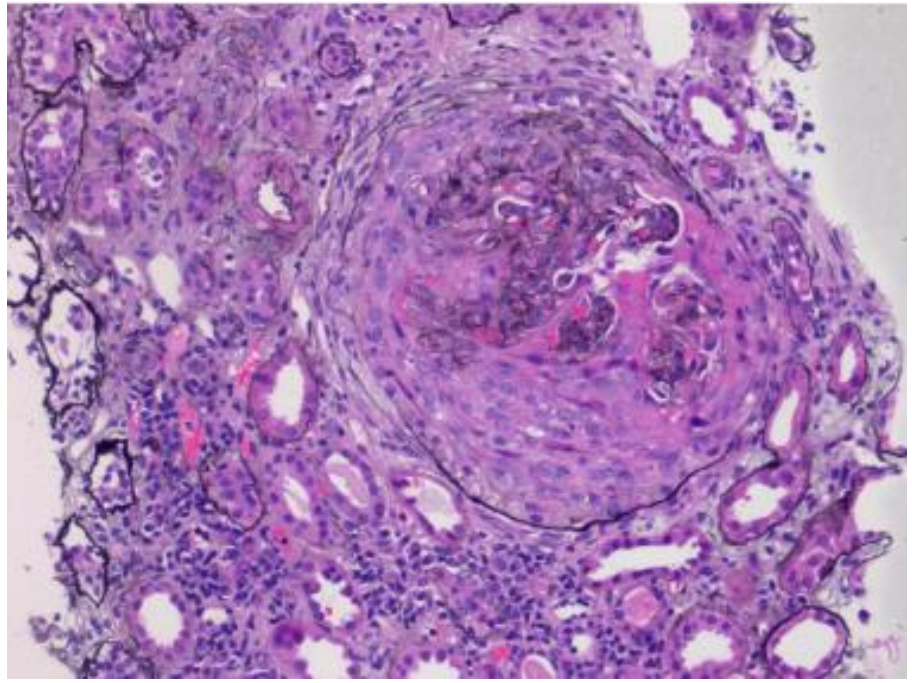
- The correct answer is D.

Adv in Kidney Disease and Health 2024;31(6):485-495

# Pauci-immune Necrotizing and Crescentic GN



# Pauci-immune necrotizing and crescentic GN

Few or no immune deposits by immunofluorescence or electron microscopy.

**Causes:**

1. Renal-limited vasculitis (The majority are ANCA positive).
2. Granulomatosis with polyangiitis (GPA)
3. Microscopic polyangiitis (MPA)
4. ANCA-negative, pauci-immune crescentic GN limited to the kidney (renal-limited vasculitis), similar clinical features, kidney biopsy findings, and prognosis.
5. Drugs (propylthiouracil, hydralazine, allopurinol, penicillamine, minocycline, rifampicin, levamisole) ANCA-positive disease.

# Pauci-immune necrotizing and crescentic GN..

- Drugs most MPO ANCA antibodies, but some both MPO and PR3 ANCA antibodies.
- Both ANCA-positive RPGN and anti-GBM disease, called "double-antibody" positive disease.
- ANCA-positive crescentic GN and positive ANA or other positive lupus serology.
- ANCA negative-disease:

  Part of GPA/ MPA spectrum, treated with the same regimens for ANCA-positive disease.
- Immunosuppressive therapy: in almost all patients with GPA or MPA.

# KDIGO guideline 2024- ANCA associated vasculitis (AAV)

- Clinical presentation compatible with small-vessel vasculitis with MPO- or PR3-ANCA serology, waiting for a kidney biopsy to be performed or reported should not delay starting immunosuppressive therapy, especially in patients who are rapidly deteriorating.
- Patients with AAV should be treated at centers with experience in AAV management.
- The persistence of ANCA positivity, an increase in ANCA levels, or a change in ANCA from negative to positive may be predictive of future disease relapse.

# Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)-induction therapy

**Definitions:**

- **Complete remission:** the systemic symptoms and signs resolve and the urine sediment becomes inactive, **even if** persistent proteinuria or persistent or even slowly worsening kidney function impairment.
- **Incomplete remission:** Persistent dysmorphic (ie, glomerular) hematuria in patients who have a stable serum creatinine and no other evidence of disease activity.
- **Relapse:** the recurrence of signs or symptoms of active vasculitis in any organ system after remission.

# **TREATMENT** (ANCA-positive pauci-immune crescentic disease)- Induction therapy

**Organ-threatening or life-threatening disease:**

- Active glomerulonephritis
- Pulmonary hemorrhage
- Cerebral vasculitis
- Progressive peripheral or cranial neuropathy
- Orbital pseudotumor
- Scleritis
- Gastrointestinal bleeding due to vasculitis
- Cardiac disease due to vasculitis (pericarditis, myocarditis)

| Oral cyclophosphamide | Intravenous cyclophosphamide | Rituximab | Rituximab and i.v. cyclophosphamide | MMF | Avacopan |
|---|---|---|---|---|---|
| 2 mg/kg/d for 3 months, continue for ongoing activity to a maximum of 6 months | 15 mg/kg at weeks 0, 2, 4, 7, 10, 13 (16, 19, 21, 24 if required) | 375 mg/m²/week × 4 weeks<br>OR<br>1 g at weeks 0 and 2 | Rituximab 375 mg/m²/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2<br>OR<br>Rituximab 1 g at 0 and 2 weeks with cyclophosphamide 500 mg/2 weeks × 6 | 2000 mg/d (divided doses), may be increased to 3000 mg/d for poor treatment response | 30 mg twice daily as alternative to glucocorticoids, in combination with rituximab or cyclophosphamide induction |
| Reduction for age:<br>• 60 yr, 1.5 mg/kg/d<br>• 70 yr, 1.0 mg/kg/d<br>Reduce by 0.5 mg/kg/day for GFR <30 ml/min/1.73 m² | Reduction for age:<br>• 60 yr 12.5 mg/kg<br>• 70 yr, 10 mg/kg<br>Reduce by 2.5 mg/kg for GFR <30 ml/min/1.73 m² | | | | |

Immunosuppressive drug dosing for AAV- KDIGO-2024

# **TREATMENT** (ANCA-positive pauci-immune crescentic disease)- Induction therapy…

- Glucocorticoids in combination with **either** rituximab or cyclophosphamide or
- Glucocorticoids in combination with **both** rituximab and cyclophosphamide (organ-threatening or life-threatening GPA or MPA or Cr>4 mg/dl [KDIGO 2024])

✓WBC > should 3500/microL, and the absolute PMN should > 1500/microL

- Comparison of pulse cyclophosphamide V.S. daily oral cyclophosphamide:

less leukopenia, more relapse, lower accumulation, Incidence of ESKD similar

✓Some administer mercaptoethane sulfonate (MESNA) to prevent cystitis

| Rituximab preferred | Cyclophosphamide preferred |
| --- | --- |
| • Children and adolescents<br>• Pre-menopausal women and men concerned about their fertility<br>• Frail older adults, **alopecia, malignancy**<br>• Glucocorticoid-sparing especially important<br>• Relapsing disease<br>• PR3–ANCA disease | • Rituximab difficult to access<br>• Severe GN (SCr >4 mg/dl [354 µmol/l]), combination of two intravenous pulses of cyclophosphamide with rituximab can be considered |

**Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV-** KDIGO-2024

# TREATMENT (ANCA-positive pauci-immune crescentic disease)-Induction therapy..

**Glucocorticoid dosing and taper**:

- Pulse IV: methylprednisone 7 to 15 mg/kg to maximum 1 g/day for three.
- Oral:1 mg/kg per day (maximum of 60 to 80 mg of prednisone after the IV therapy.
- Concomitant treatment with avacopan may facilitate the use of an even shorter, reduced-dose glucocorticoid.

# **TREATMENT** (ANCA-positive pauci-immune crescentic disease)- Induction therapy…

**Avacopan**:

- Complement c5a receptor inhibitor
- As alternative glucocorticoids to **OR** an adjunctive agent to limit the use of glucocorticoids, in combination with rituximab or cyclophosphamide.
- 30 mg orally twice daily,
- Glucocorticoids are tapered over four to six weeks
- Avoided: chronic liver disease and moderate to strong CYP3A4 inducers.
- Liver function tests during therapy.

ANCA–associated vasculitis, KDIGO-2024, Uptodate® 2025

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CLINICAL RESEARCH

# Avacopan or Glucocorticoids for Severe Antineutrophil Cytoplasmic Autoantibody–Associated Rapidly Progressive Glomerulonephritis

Stanislas Faguer[1,2,3], Charlotte Gabilan[1,2], Magali Colombat[2,3,4], Alexis Cassard[1], Clément Kounde[1], Juliette Pellegrini[1,4], Antoine Huart[1], Julie Belliere[1,2,3] and David Ribes[1]

[1]Department of Nephrology and Organ Transplantation - Referral Center for Rare Kidney Diseases, University Hospital of Toulouse, Toulouse, France; [2]Faculty of Health, Toulouse University, Toulouse, France; [3]Institute of Metabolic and Cardiovascular Diseases, UMR 1297, National Institute for Health and Medical Research, Toulouse, France; and [4]Department of Pathology, Toulouse University Institute of Cancer - Oncopole, Toulouse, France

- Severe ANCA-RPGN (eGFR: 0–30 ml/min per 1.73 m2), compared kidney outcomes at month 6 and 12 according to induction regimen (avacopan- vs. glucocorticoid [GC]-based). 50 patients received GC regimen combined with cyclophosphamide (CYC) (30%), rituximab (RTX, 54%) or a combination of both (16%), whereas 20 patients received avacopan combined with RTX (90%) or RTX plus CYC (10%).
- **Conclusion:** At months 6 and 12, patients with severe forms of ANCA-RPGN and receiving avacopan plus a short course of GCs have similar kidney recovery rates to patients receiving GC regimen.

*Kidney Int Rep* (2025) ■, ■–■; https://doi.org/10.1016/j.ekir.2025.08.008

# TREATMENT (ANCA-positive pauci-immune crescentic disease)- Induction therapy…

**Plasma exchange**:

**Indications:**

- Double-positive anti-GBM and ANCA-associated disease
- Severe kidney disease (creatinine >4.0 mg/dL or need dialysis )
- Pulmonary hemorrhage

**Replacement fluid**:

- Albumin
- Risk of bleeding or a recent kidney biopsy: FFP 1 to 2liters at the end of the procedure to reverse pheresis-induced depletion of coagulation.
- Exclusively FFP: Active hemorrhage,
- IV IG: Severe infection, a single infusion (100 to 400 mg/kg) to partially replenish antibody levels.

# KDIGO guideline 2024
# ANCA associated vasculitis (AAV)

- **Plasma exchange**
- SCr >3.4 mg/dl (>300 mmol/l),
- Requiring dialysis
- Rapidly increasing SCr,
- Diffuse alveolar hemorrhage who have hypoxemia.
- Overlap syndrome of AAV and anti GBM disease.

# KDIGO guideline 2024 ANCA associated vasculitis (AAV)-
# Plasma exchange dosing and frequency

| ANCA vasculitis with severe kidney disease | Vasculitis with diffuse pulmonary hemorrhage | Vasculitis in association with anti-GBM antibodies |
|---|---|---|
| Seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution | Daily until bleeding stops, replace albumin with fresh, frozen plasma | Daily for 14 days or until anti-GBM antibodies are undetectable |

# TREATMENT (ANCA-positive pauci-immune crescentic disease)- Maintenance therapy-1

**Timing of initiation of maintenance therapy:**

Between 3-6 months after the initiation of induction therapy in the majority of patients.

- If Rituximab for induction: four to six months after the last induction dose
- If IV cyclophosphamide: two to four weeks after the last dose of cyclophosphamide if white blood cell count is >350/mm³ and absolute PMN count is >1500/mm³
- If Oral cyclophosphamide: as soon as the above white blood cell criteria are met.

After approximately three to six months, cyclophosphamide is replaced

# TREATMENT (ANCA-positive pauci-immune crescentic disease)- Maintenance therapy-2

**Choice of maintenance therapy:**

Rituximab, Azathioprine, Methotrexate (MTX), and Mycophenolate (MMF).

- **MTX** should **not** be used in eGFR <60 mL/min/1.73 m2 and pregnancy.
- Rituximab should be avoided, or used in conjunction with anti-hepatitis B virus therapy, in $HBsAg^+$ or $anti\text{-}HBc^+$ patients.
- Azathioprine is preferred in patients become pregnant.
- Etanercept: may increase the risk for malignancy; should **not** be used.

# KDIGO guideline 2024-ANCA associated vasculitis (AAV)- Immunosuppressive dosing and duration of maintenance therapy

| Rituximab | Azathioprine | MMF |
|---|---|---|
| **Scheduled dosing protocol:**<br>**1. 500 mg × 2 at complete remission, and 500 mg at mo 6, 12, and 18 thereafter (MAINRITSAN scheme) OR**<br>**2. 1000 mg infusion after induction of remission, and at mo 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)** | **1.5–2 mg/kg/d at complete remission until 1 yr after diagnosis then decrease by 25 mg every 3 mo** | **2000 mg/d (divided doses) at complete remission for 2 yr** |
| | **Extend azathioprine at complete remission until 4 yr after diagnosis; start at 1.5–2 mg/kg/d for 18–24 mo, then decrease to a dose of 1 mg/kg/d until 4 yr after diagnosis, then taper by 25 mg every 3 mo. Glucocorticoids should also be continued at 5–7.5 mg/d for 2 yr and then slowly reduced by 1 mg every 2 mo** | |

# TREATMENT (ANCA-positive pauci-immune crescentic disease)- Maintenance therapy-3

**Dosing of maintenance therapy**:

**Rituximab**: 500 to 1000 mg every four or six months,

Reduce the dose if hypogammaglobulinemia, monitor serum immunoglobulin levels if frequent infections.

**Azathioprine**: 50 mg/day and gradually increased over several weeks to 2 mg/kg per day.

**MTX:** 15 mg/week, increases every 2 to 8 weeks of 5 mg/week up to 25 mg/week.

folic acid (1 to 2 mg per day), or folinic acid (5 to 10 mg per week), 24 hours after MTX given.

**MMF** is typically between 1.5 and 3 g daily

# TREATMENT (ANCA-positive pauci-immune crescentic disease)- maintenance therapy

**Avacopan:**

- An alternative to glucocorticoids.
- In case of Increased risk of glucocorticoids toxicity
- Lower GFR may benefit from greater GFR recovery.

**Prednisolon:**

Prednisolone tapering regimen

| Week | 'Reduced-corticosteroid dose' in PEXIVAS trial | | |
|---|---|---|---|
| | <50 kg | 50–75 kg | >75 kg |
| 1 | 50 | 60 | 75 |
| 2 | 25 | 30 | 40 |
| 3–4 | 20 | 25 | 30 |
| 5–6 | 15 | 20 | 25 |
| 7–8 | 12.5 | 15 | 20 |
| 9–10 | 10 | 12.5 | 15 |
| 11–12 | 7.5 | 10 | 12.5 |
| 13–14 | 6 | 7.5 | 10 |
| 15–16 | 5 | 5 | 7.5 |
| 17–18 | 5 | 5 | 7.5 |
| 19–20 | 5 | 5 | 5 |
| 21–22 | 5 | 5 | 5 |
| 23–52 | 5 | 5 | 5 |
| >52 | Investigators' local practice | | |

Week 1: 1mg/kg, Week 2: dose ½
Each 2 wks: reduce 5 mg untill week 6
Each 2 wks: reduce 2.5 mg untill week 12 -16
Then 5 mg/ d

Kidney International (2024) 105 (Suppl 3S), S71–S116, KDIGO-2024

# ANCA associated vasculitis (AAV)-
# **Choosing rituximab or azathioprine** for maintenance therapy-
# KDIGO guideline 2024

| Rituximab preferred | Azathioprine preferred |
|---|---|
| • Relapsing disease<br>• PR3–ANCA disease<br>• Frail older adults<br>• Glucocorticoid-sparing especially important<br>• Azathioprine allergy | • Low baseline IgG <300 mg/dl<br>• Limited availability of rituximab |

Kidney International (2024) 105 (Suppl 3S), S71–S116

# **TREATMENT** (ANCA-positive pauci-immune crescentic disease)- maintenance therapy

**Duration of maintenance therapy:**

- 12 to 24 months after stable remission has been induced.
- 24 to 36 months multiple risk factors for relapse (eg, PR3-ANCA seropositivity, pulmonary involvement, and upper respiratory tract involvement).
- Indefinitely prior relapse, severe organ damage (limited residual kidney function) and a relapse would be poorly tolerated.
- 6 to 12 months low relapse risk (MPO-ANCA seropositivity and no respiratory tract involvement prior to remission)

# KDIGO guideline 2024-ANCA associated vasculitis (AAV) Maintenance therapy- Duration of remission therapy

- The optimal duration between 18 months and 4 years after induction of remission.
- Maintenance therapy with either rituximab, or azathioprine and low dose glucocorticoids after induction of remission (1C).
- Mycophenolate mofetil (MMF) or methotrexate (MTX) as alternatives to azathioprine in patients intolerant of azathioprine.
- MTX should not be used in GFR <60 ml/min per 1.73 m2

Kidney International (2024) 105 (Suppl 3S), S71–S116

# KDIGO guideline 2024
# ANCA associated vasculitis (AAV)

**Discontinuation of immunosuppressive therapy**

- After 3 months on dialysis and not have any extrarenal manifestations

Kidney International (2024) 105 (Suppl 3S), S71–S116

# Factors that increase relapse risk for AAV- KDIGO-2024

| Baseline factors | Factors after diagnosis | Treatment factors |
|---|---|---|
| • Diagnosis of granulomatosis with polyangiitis<br>• PR3–ANCA subgroup<br>• Higher serum creatinine<br>• More extensive disease<br>• Ear, nose, and throat disease | • History of relapse<br>• ANCA positive at the end of induction<br>• Rise in ANCA | • Lower cyclophosphamide exposure<br>• Immunosuppressive withdrawal<br>• Glucocorticoid withdrawal |

Kidney International (2024) 105 (Suppl 3S), S71–S116

# **TREATMENT** (ANCA-positive pauci-immune crescentic disease)-

**Monitoring the response to therapy**:

Follow-up visits:

Every two to four weeks for the first 3 months then be extended to every two to three months

- History and physical examination
- Assessment of blood pressure
- serum creatinine and electrolytes
- U/A with microscopic examination of the urinary sediment
- CBC
- ESR and/or C-reactive protein level

# **TREATMENT** (ANCA-positive pauci-immune crescentic disease)

**INVESTIGATIONAL APPROACHES**

Belimumab,

Vilobelimab,

B cell-targeted immunotherapy, and

Gene editing to eliminate the proteinase 3 (PR3) autoantigen

# **TREATMENT** (ANCA plus anti-GBM disease)

- Crescents are usually present in >75 % of glomeruli when the plasma creatinine concentration is above 5 mg/dL.
- Avoidance of maintenance dialysis is uncommon in patients who require dialysis within 72 hours of presentation, particularly in those who have crescents involving all glomeruli.
- Do **not** delay therapy in these patients and initiate therapy within 24 hours of a presumptive diagnosis.

# KDIGO guideline 2024
# ANCA associated vasculitis (AAV)

- **Relapsing** disease (life- or organ-threatening) should be reinduced, preferably with rituximab.
- **Refractory** disease: *increase* in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction had been used previously, or vice versa. Plasma exchange can be considered.
- In **diffuse alveolar bleeding** with hypoxemia, *plasma exchange* can be considered in addition to *glucocorticoids* with either *cyclophosphamide or rituximab.*
- **Delay transplantation** until complete clinical remission for **≥6 months**. The persistence of ANCA should not delay transplantation.

letters to the editor

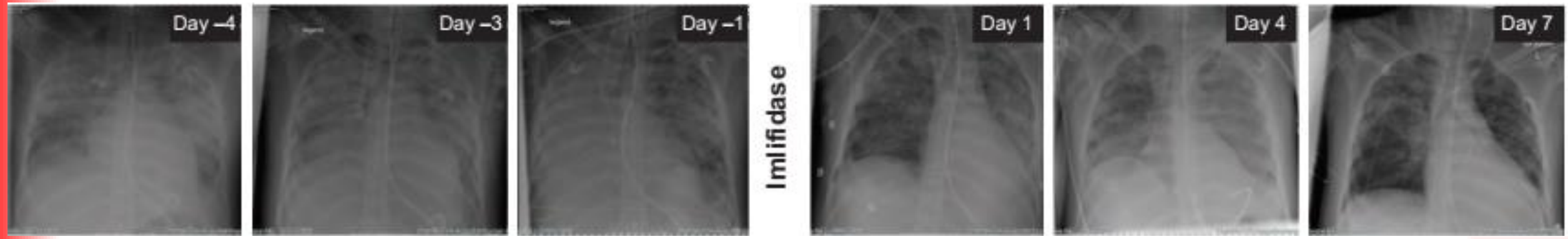
# Imlifidase as novel treatment strategy in anti-neutrophil cytoplasmic antibody-induced pulmonary renal syndrome

A 35-y/o man with clinically evident granulomatosis with polyangiitis (dyspnea, hemoptysis, skin vasculitis, and elevated proteinase 3–ANCA) developed severe ARDS, requiring venovenous extracorporeal membrane oxygenation.

Despite prednisolone, rituximab, cyclophosphamide, and plasma exchange, disease was active.

Imlifidase resulted in cessation of hemoptysis and proteinase 3–ANCA clearance hours after an infusion.

The patient was weaned from extracorporeal membrane oxygenation within a week.

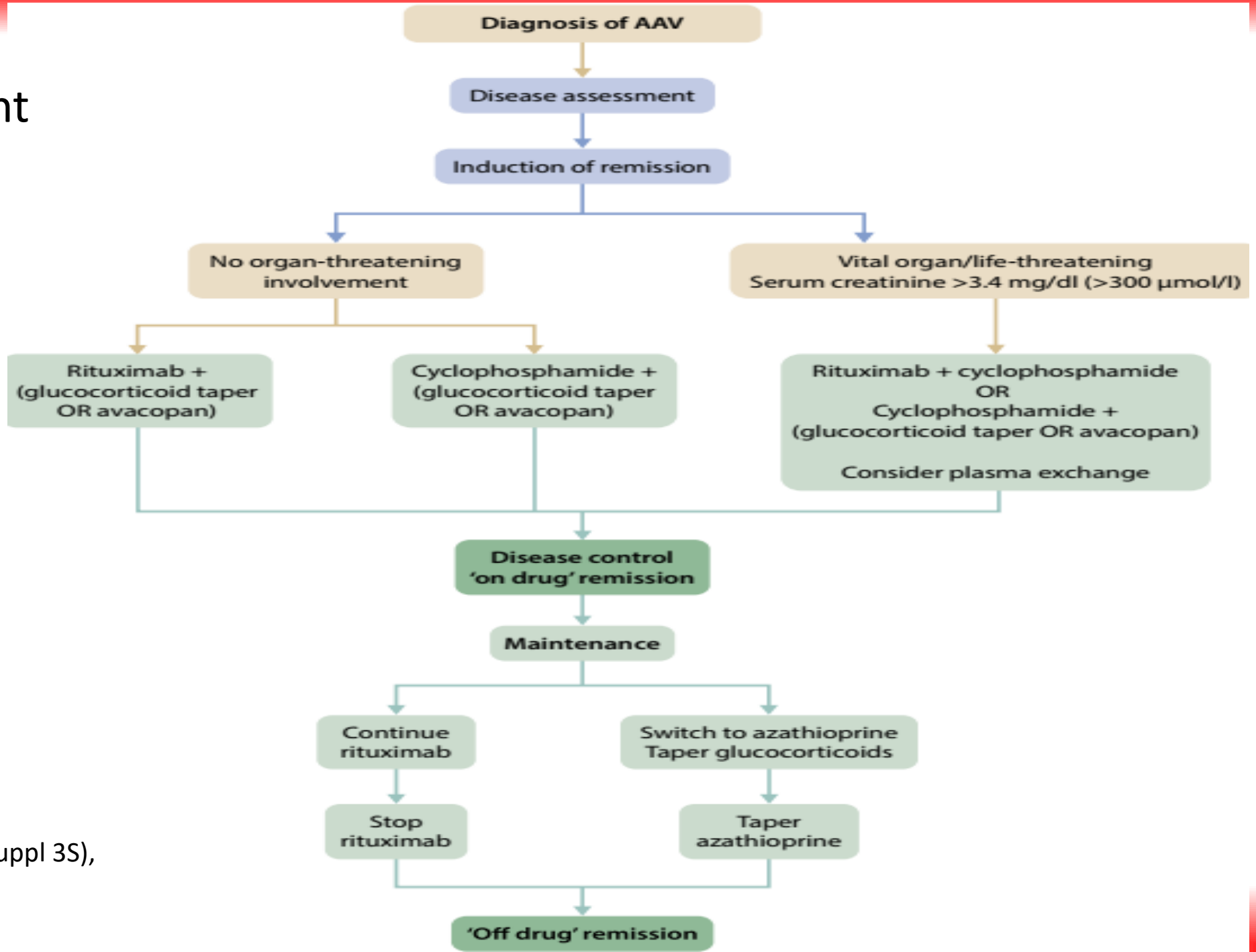



Kidney International (2021) 100, 1344–1345; https://doi.org/10.1016/j.kint.2021.09.020

# Prevention of opportunistic infections and vaccinations

- ***Pneumocystis jirovecii*** pneumonia: all patients receiving cyclophosphamide or rituximab in combination with prednisone at a dose ≥20 mg/day: TMP-SMX 80 mg/400 mg tablet daily, especially in six months after initiation of treatment,
- Discontinue prophylaxis when the dose of prednisone is tapered to less than 5 to 10 mg/day
- **Vaccinations**: pneumococcus, influenza, and herpes zoster

# Practical treatment regimen for AAV -KDIGO-2024




Kidney International (2024) 105 (Suppl 3S), S71–S116

# Case 2

A 69-y/o female with DM and osteoporosis, with 2 months of fatigue, worsening dyspnea, and a recent lower extremity skin rash.

PE: palpable purpura on her legs and bilateral lung crackles.

Laboratory tests: creatinine (3.2 mg/dL), Hb (5.7 g/dL), proteinuria (1500 mg/gram), and dysmorphic hematuria with RBC casts. Serologies: high MPO-ANCA titer (91 units/ml), normal C3, C4, and negative PR3-ANCA, ANA, and anti-GBM titers.

CT chest: bilateral perihilar ground glass opacities.

Renal biopsy: pauci-immune necrotizing and crescentic GN with cellular crescents in most glomeruli. There was minimal interstitial fibrosis and tubular atrophy.

She was given iv methylprednisolone 500 mg daily for 3 days and transitioned to oral prednisone 60 mg daily and rituximab 375 mg/m2/week. She was discharged on day 5 with a serum creatinine of 2.8 mg/dL with plans to taper prednisone per reduced dose and complete 3 weekly doses of rituximab.

# Case 2..

Three days after her third weekly rituximab infusion, she experienced a flare in skin rash, emotional lability, sleep disturbances, a significant rise in serum creatinine (6.3 mg/dL), worsening of the inflammatory markers (ESR 110, C reactive protein 24), and persistence of dysmorphic hematuria and RBC casts.

Which of the following would be the next best step in management?

A. Give IV methylprednisolone 500 mg daily for 3 days and complete his 4th weekly dose of rituximab and continue steroid taper.
B. Switch from rituximab to cyclophosphamide.
C. Administer IV methylprednisolone 500 mg daily for 3 days and transition to prednisone 60 mg daily, switch to cyclophosphamide, and start PLEX.
D. Start avacopan, continue to taper prednisone, switch to cyclophosphamide, and start PLEX.

Adv in Kidney Disease and Health 2024;31(6):485-495

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D. Start avacopan, continue to taper prednisone, switch to cyclophosphamide, and start PLEX.

The correct answer is D

Adv in Kidney Disease and Health 2024;31(6):485-495

# Case 3

- A 63-y/o man with type 2 DM, HTN, and HLP, on metformin, lisinopril, and atorvastatin, presented with shortness of breath, a skin rash, dark urine, and decreased urination. He reported using marijuana and heroin occasionally.
- PE: purpuric rash, an early diastolic murmur, BP 142/84 mmHg, and a HR of 92 bpm.
- Labs: increase in creatinine from 1.3 to 6 mg/dL over 4 days and potassium of 5.4 mEq/L.
- Serological tests: positive PR3-ANCA and MPO-ANCA, with negative anti-GBM, ASO, cryoglobulins, hepatitis serologies, and HIV. Blood cultures were positive for Staphylococcus aureus.
- Echocardiogram: vegetations on the aortic leaflet.
- Skin biopsy: leukocytoclastic vasculitis.
- Kidney biopsy: pauci-immune necrotizing crescentic GN with 40% cellular crescents. Only mild interstitial fibrosis and tubular atrophy (10%).

Adv in Kidney Disease and Health 2024;31(6):485-495

# Case 3..

- What would be the BEST next step in the management of this patient?
  A. Intravenous immunoglobulin (IVIG)
  B. Corticosteroids and cyclophosphamide
  C. Corticosteroids and Rituximab
  D. Intravenous antibiotics
  E. Plasmapheresis

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  A. Intravenous immunoglobulin (IVIG)
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  C. Corticosteroids and Rituximab
  D. Intravenous antibiotics
  E. Plasmapheresis

- The correct answer is D.

Adv in Kidney Disease and Health 2024;31(6):485-495


Thank you for
your support and
patience


ANY
QUESTION?