Treatment of Renal Involvement in ANCA– associated Vasculitis

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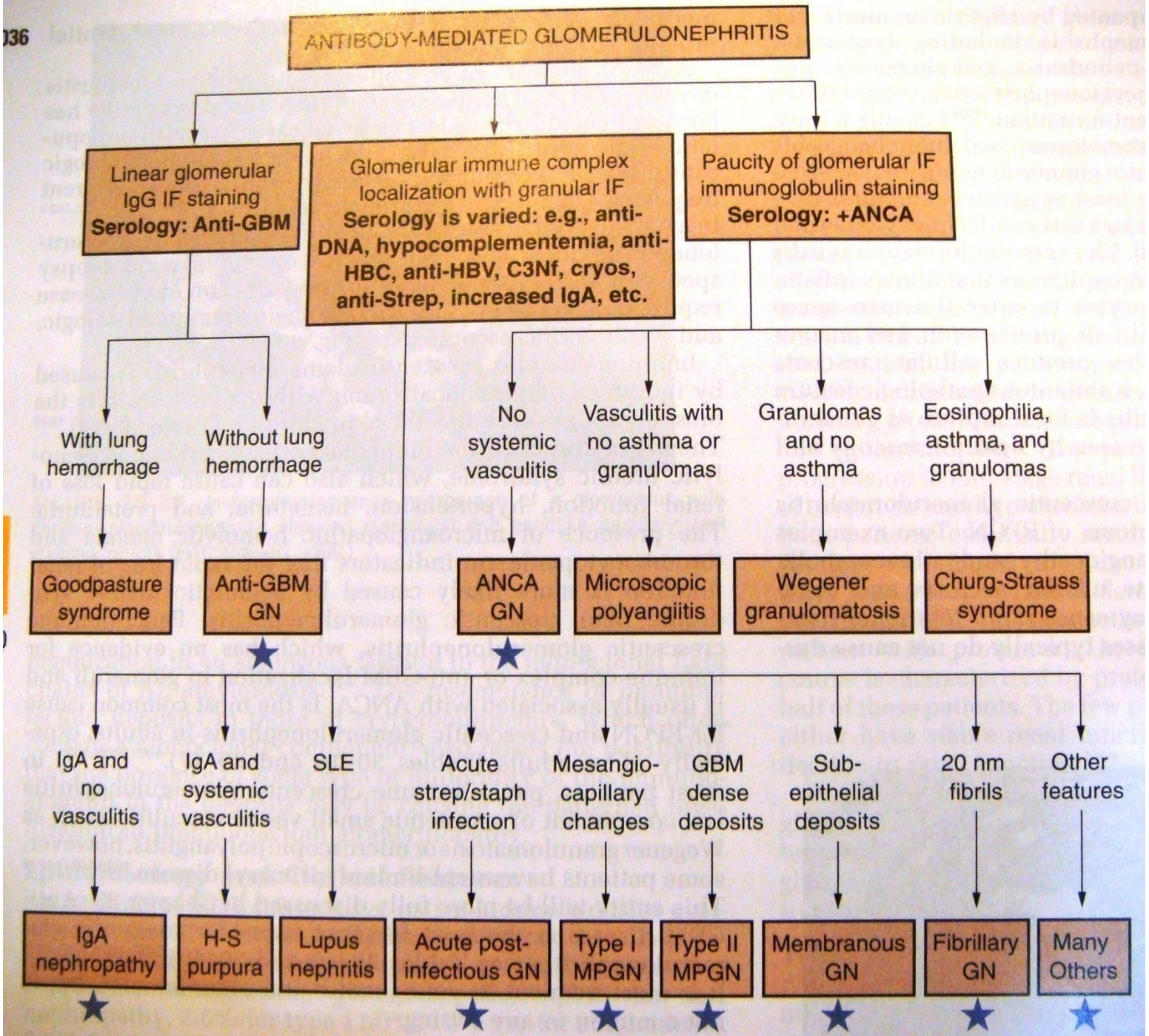
SUPPLEMENT TO
kidney® INTERNATIONAL

KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

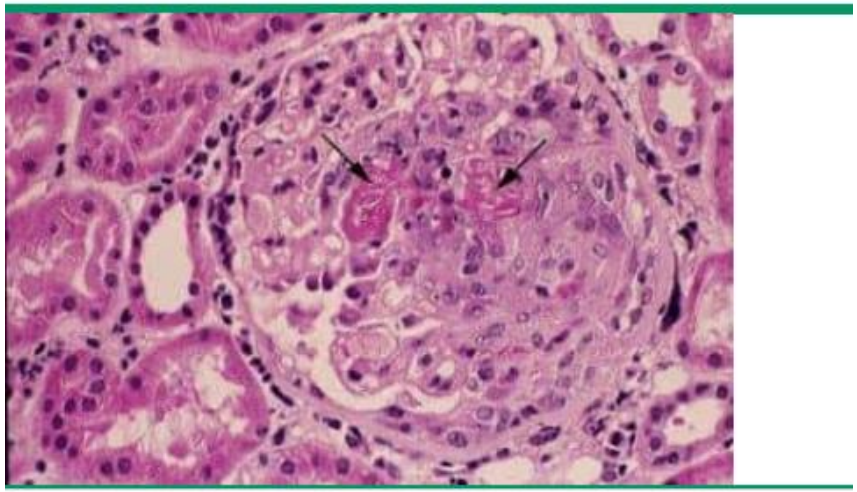
Antineutrophil cytoplasmic antibody (ANCA)– associated vasculitis

Pauci-immune small-vessel vasculitides

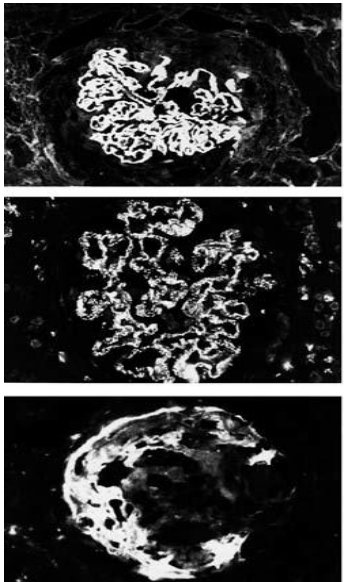
- **Polyangiitis (GPA)**
- **Microscopic polyangiitis (MPA)**
- **Renal-limited vasculitis**
- **Eosinophilic granulomatosis with polyangiitis (EGPA)**
- **ANCA-negative pauci-immune crescentic glomerulonephritis**


ANTIBODY-MEDIATED GLOMERULONEPHRITIS
Linear glomerular IgG IF staining
Serology: Anti-GBM
Glomerular immune complex localization with granular IF
Serology is varied: e.g., anti-DNA, hypocomplementemia, anti-HBC, anti-HBV, C3Nf, cryos, anti-Strep, increased IgA, etc.
Paucity of glomerular IF immunoglobulin staining
Serology: +ANCA
With lung hemorrhage
Without lung hemorrhage
No systemic vasculitis
Vasculitis with no asthma or granulomas
Granulomas and no asthma
Eosinophilia, asthma, and granulomas
Goodpasture syndrome
Anti-GBM GN
ANCA GN
Microscopic polyangiitis
Wegener granulomatosis
Churg-Strauss syndrome
IgA and no vasculitis
IgA and systemic vasculitis
SLE
Acute strep/staph infection
Mesangio-capillary changes
GBM dense deposits
Sub-epithelial deposits
20 nm fibrils
Other features
IgA nephropathy
H-S purpura
Lupus nephritis
Acute post-infectious GN
Type I MPGN
Type II MPGN
Membranous GN
Fibrillary GN
Many Others

Kidney involvement

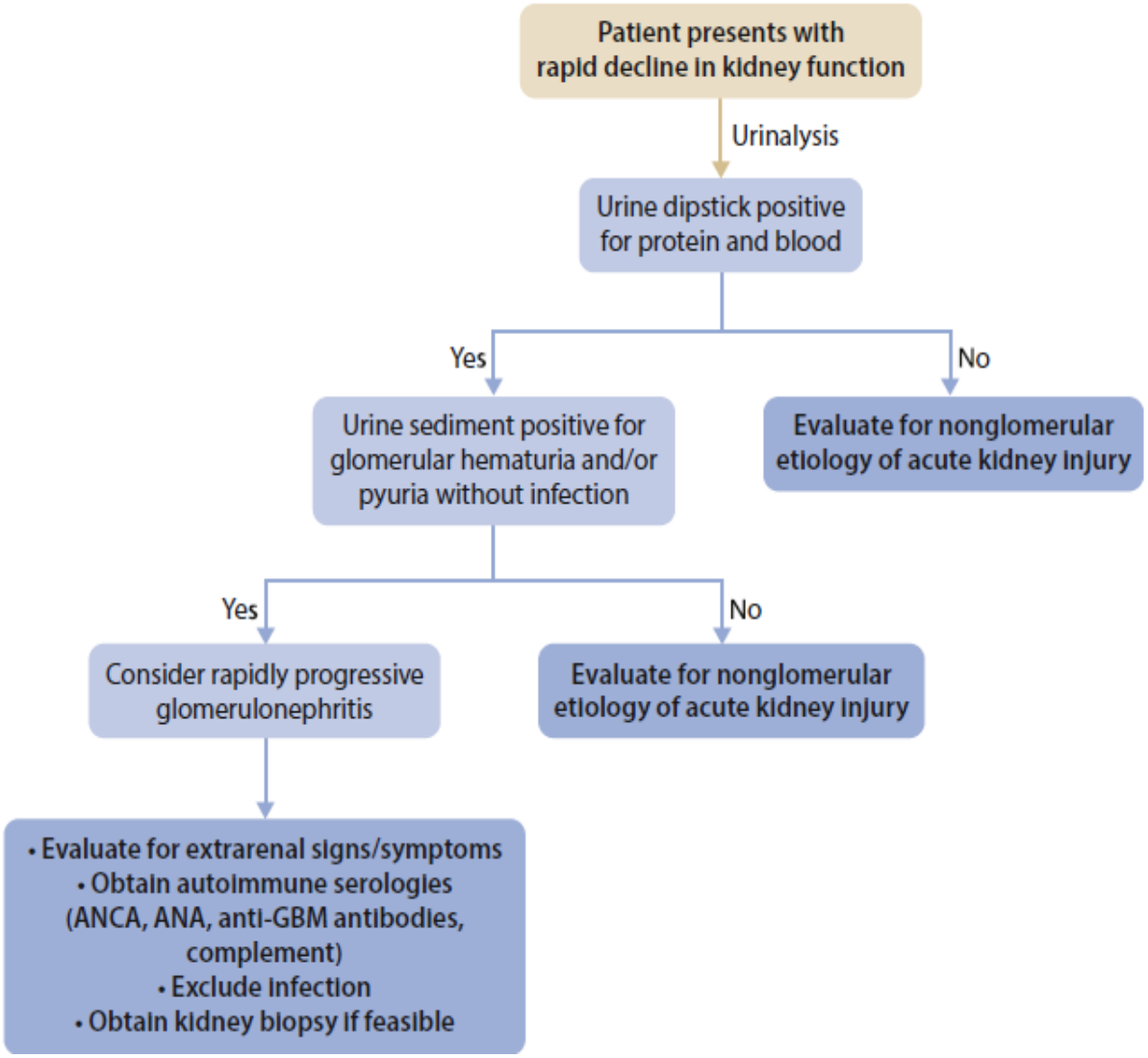


- focal and segmental glomerulonephritis
- diffuse necrotizing and crescentic Gn

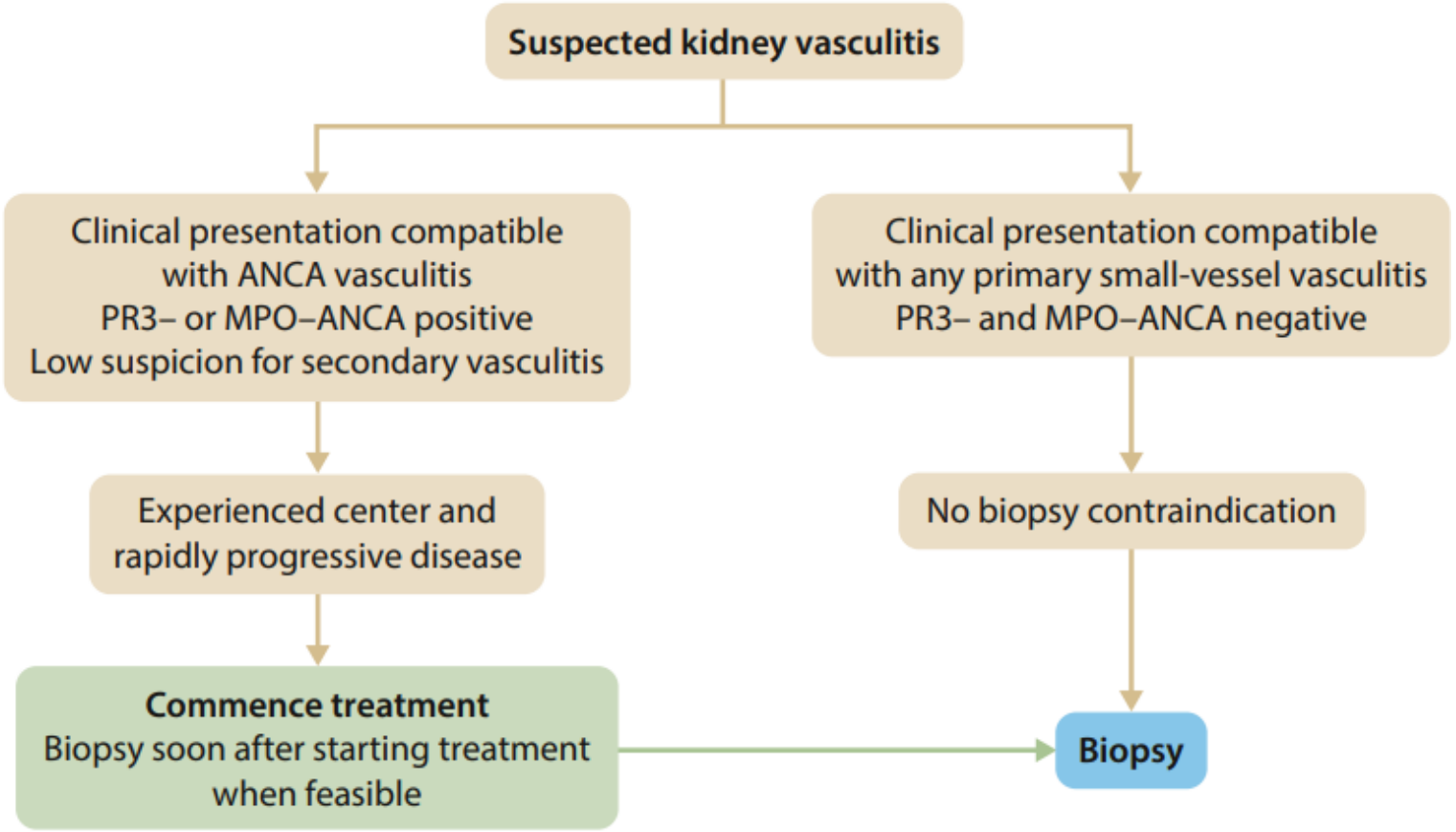


Spectrum of acute GN, RPGN and asymptomatic urinary abnormality

Diagnostic strategy in rapidly progressive glomerulonephritis.



Biopsy strategy in suspected kidney vasculitis



ANCA negative, an important point to note is that several non vasculitic diseases may closely mimic small-vessel vasculitis.(systemic rheumatic diseases, such as SLE, infections, and malignancies)

Histopathologic classification of ANCA-associated glomerulonephritis contributes to the ability to predict kidney outcomes .

- **Focal** – At least 50 percent of glomeruli are normal (ie, without vasculitic lesions or global sclerosis
- **Crescentic** – At least 50 percent of glomeruli have cellular crescents that are either cellular or fibrotic.
- **Sclerotic** – At least 50 percent of glomeruli are globally sclerotic (defined as more than 80 percent sclerosis of the glomerulus).
- **Mixed** – Less than 50 percent of glomeruli are normal, less than 50 percent are crescentic, and less than 50 percent are globally sclerotic.

Definition of disease activity, remission, relapse, and treatment-resistant disease in AAV

Disease activity of ANCA-associated vasculitis represents signs or symptoms attributable to active disease in any organ system.

Remission is defined as the absence of manifestations of vasculitis and GN (BVAS=0). For GN, it is defined as a stable or improved glomerular filtration rate. While hematuria and proteinuria are present at times of active disease and can resolve completely, their persistence does not necessarily imply active disease.

Relapse is defined as the occurrence of increased disease activity after a period of partial or complete remission. A return or increase of hematuria with proteinuria may indicate a kidney relapse. Relapse can be divided into major or minor, with major relapses defined as life- or organ-threatening. Examples of major relapse include diffuse alveolar hemorrhage, subglottic stenosis, GN or vasculitis threatening vision.

Treatment-resistant disease is defined as the persistence of or appearance of kidney and/or systemic manifestations of vasculitis, while receiving treatment equal in intensity to initial immunosuppressive therapy.

Treatment

Treatment of AAV is generally divided into

- Initial phase, commonly termed “induction,”

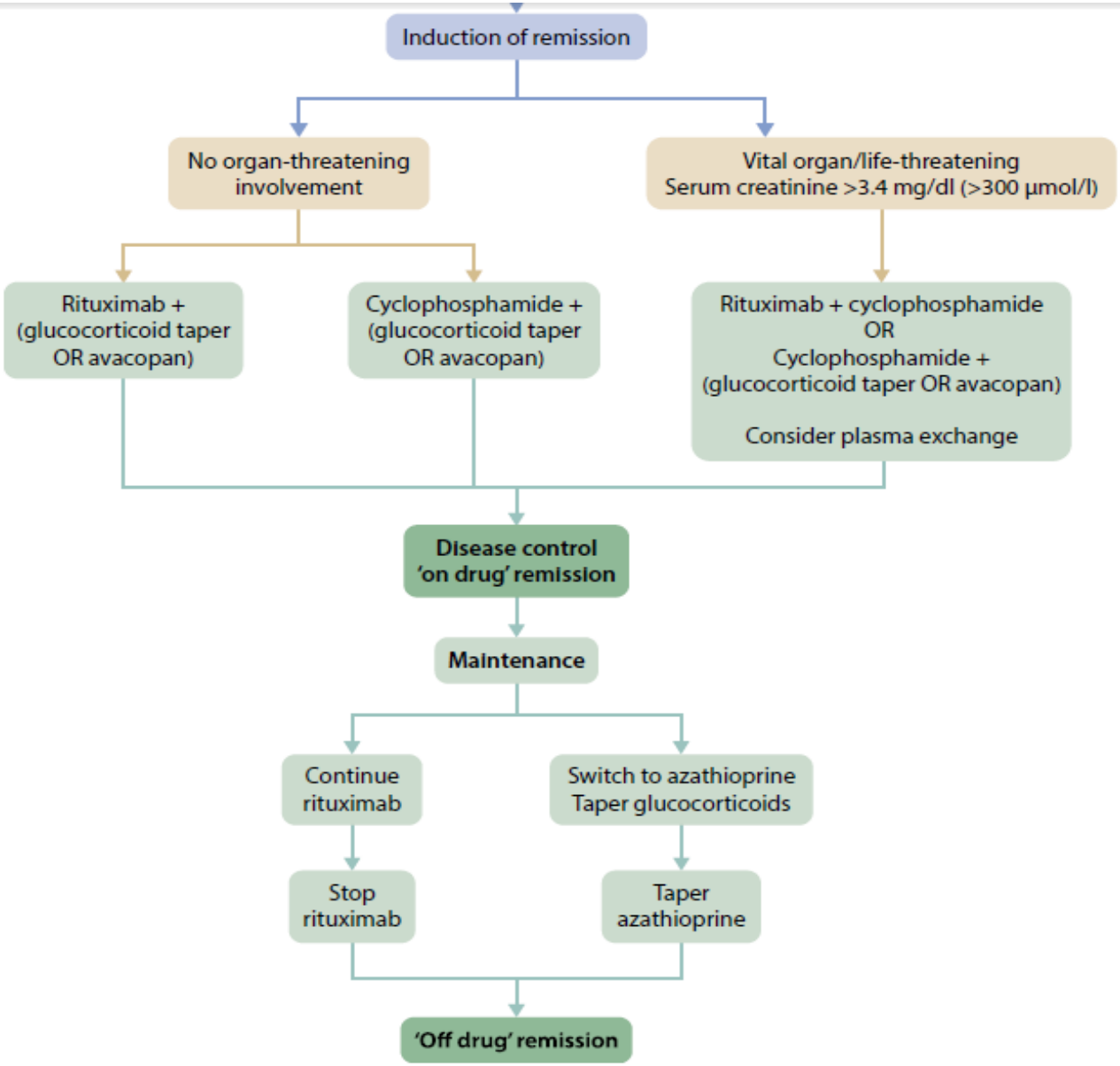
- Maintenance phase.

Assessment of disease severity for type of treatment

- **Organ- or life-threatening disease**: ***Active glomerulonephritis***, Pulmonary hemorrhage, Cerebral vasculitis, Progressive peripheral or cranial neuropathy, Orbital pseudotumor, Scleritis, Gastrointestinal bleeding due to vasculitis, pericarditis, myocarditis

- **Non-organ-threatening and non-life-threatening disease:** rhinosinusitis, arthritis, and/or pulmonary nodules.

A practical treatment algorithm for AAV with kidney



Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Premenopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l]), combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered

Low-dose TMP-SMX, is advised for pneumocystis pneumonia pro-phylaxis for the duration of the cyclophosphamide course or for 6 months following rituximab induction.

Considerations for the route of administration of cyclophosphamide

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Ready access to an infusion center • Adherence may be an issue	• Cost is an important factor • Access to an infusion center difficult • Adherence is not an issue

Prednisolone tapering regimen for AAV

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		

Plasma exchange dosing and frequency for AAV

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

Consider plasma exchange for patients with SCr >3.4, patients requiring dialysis .

A single infusion of IV immune globulin (100 to 400 mg/kg) for replenish antibody levels. This benefit was greatest for patients at high risk of ESKD or requiring dialysis.

Immunosuppressive drug dosing for AAV.

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/m^2/week × 4 weeks OR 1 g at weeks 0 and 2	Rituximab 375 mg/m^2/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2 OR Rituximab 1 g at 0 and 2 weeks with i.v. 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: • 60 yr, 1.5 mg/kg/d • 70 yr, 1.0 mg/kg/d Reduce by 0.5 mg/kg/day for GFR <30 ml/min/1.73 m^2	Reduction for age: • 60 yr 12.5 mg/kg • 70 yr, 10 mg/kg Reduce by 2.5 mg/kg for GFR <30 ml/min/1.73 m^2				

Avacopan

- C5a receptor inhibition is a potential alternative to glucocorticoid treatment
- Patient subgroups those at increased risk of glucocorticoid toxicity, including those with high infection risk, preexisting diabetes mellitus, psychiatric disorders, and osteoporosis.
- Regarding avacopan, high cost, limited availability, and lack of long-term safety data are currently barriers to its widerapplication.

Maintenance therapy

- **When to start**
- **Choice of maintenance therapy**

✓ Rituximab

✓ Azathioprine

✓ Mycophenolat

✓ Methotrexate: should not be used for patients with a GFR<60 ml/min

- **Dosing**
- **Duration**

- **KDIGO** recommends **maintenance therapy with either rituximab, or azathioprine and low-dose glucocorticoids after induction of remission (1C).**

Considerations for using rituximab or azathioprine for AAV maintenance therapy

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

Recommendations for dosing and duration of maintenance therapy

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: **1.** 500 mg × 2 at complete remission, and 500 mg at mo 6, 12, and 18 thereafter (MAINRITSAN scheme) OR **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	

Patients with relapsing disease (life- or organ-threatening)

- **Re-induction: cyclophosphamide-based or a rituximab-based regimen: preferably with rituximab.**
- **Maintenance therapy after re-induction**

✓ **Relapse *during* maintenance therapy:** using a different drug for maintenance therapy

✓ **Relapse *after* maintenance therapy:** using the same drug for maintenance therapy

There is some evidence that trimethoprim-sulfamethoxazole is an effective maintenance drug for the prevention of relapses limited to the upper respiratory tract

Factors that increase relapse risk for AAV.

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

Relapsing glomerulonephritis versus nonimmunologic progression of chronic kidney disease

- **Two nonimmunologic mechanisms may be important in the absence of relapsing glomerulonephritis:**

- Glomerular ischemia and subsequent glomerulosclerosis

- Secondary hemodynamic and metabolic factors induced by nephron loss, such as intraglomerular hypertension

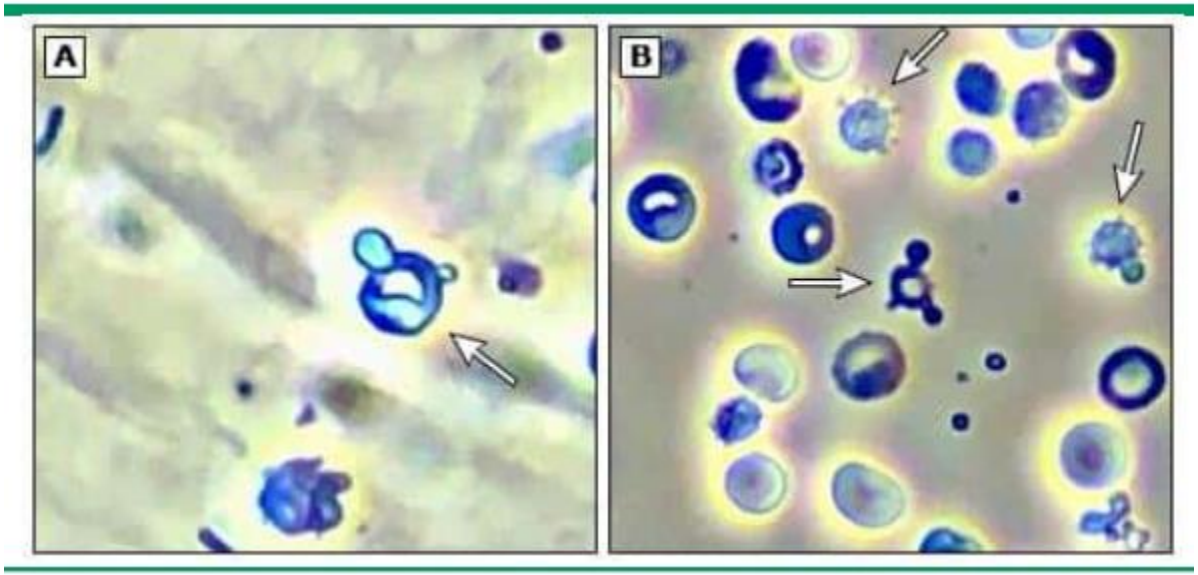
Patients with nonimmunologic progression have

slowly progressive disease: gradual increases in the serum creatinine concentration and proteinuria, which is usually subnephrotic but can reach the nephrotic range

not have an active urinary sediment (dysmorphic hematuria with or without red cell casts)

an example, an elevated serum creatinine (with or without proteinuria of any degree) can reflect chronic injury with scarring and is not considered a sign of active kidney disease in ***the absence of dysmorphic (glomerular) hematuria***.

Phase-contrast micrograph showing dysmorphic red blood cells in urine sediment



Resistant Disease

- **Definition: no response to initial treatment (usually six months, or three months in a patient who is dialysis dependent)**

- **Treatment:** 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.

The causes of refractory disease include drug intolerance, nonadherence, concomitant morbidities complicating treatment, a secondary drive for vasculitis, such as malignancy, drugs, or infection, and true treatment failure

Management of patients with GPA or MPA on Maintenance dialysis

- **No active disease:** **discontinuation of immunosuppressive therapy after 3 months in patients who remain on dialysis and who do not have any extrarenal manifestations of disease**
- **Active kidney but not extrarenal disease**
- **Active extrarenal disease** –

  Methotrexate should **not** be given
  and cyclophosphamide should be used cautiously
  with careful monitoring.

- **Kidney transplantation:** At a minimum, transplantation should be delayed for at least six months from the time of initial presentation or most recent relapse

persistence of an isolated positive ANCA titer is **not** a contraindication to kidney transplantation.

Conclusion

- Induction treatment of new-onset AAV With glucocorticoids in combination with rituximab or cyclophosphamide
- Recommendation for maintenance therapy with either rituximab, or azathioprine and low dose glucocorticoids
- Patients with relapsing disease (life- or organ-threatening) should be reinduced preferably with rituximab.
- Distinguish between nonimmunologic mechanisms of kidney injury with relapsing glomerulonephritis

Thanks for your attention