Recent advances in the classification and management of pulmonary small vessel vasculitides

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5/8/11

- The vasculitides are a set of related disorders characterized by blood vessel inflammation leading to tissue or end-organ injury

- Differentiated from other vascular disorders by the presence of inflammation of the vessel wall as compared to bland vasculopathy

The vasculitides	
Primary vasculitis	Small-vessel vasculitis
	Wegener granulomatosis
	Microscopic polyangiitis
	Churg-Strauss vasculitis
	Medium-vessel vasculitis
	Polyarteritis nodosa
	Kawasaki disease
	Larger-vessel vasculitis
	Takayasu arteritis
	Giant cell arteritis
Immune complex–mediated vasculitis	Goodpasture syndrome
	Henoch-Schönlein purpura
Secondary vasculitis	Infection
	Malignancy (paraneoplastic)
	Drug-induced vasculitis
	Connective tissue diseases
	Antiphospholipid antibody syndrome
	Inflammatory bowel disease
	Essential cryoglobulinemia

Frankel SK, Jayne D. The Pulmonary Vasculitides. *Clin Chest Med 31 (2010) 519–536*

Classification

To understand a name you must be acquainted with the particular of which it is a name

- Bertrand Russel

Explanation of terminology used for naming, defining classifying, and diagnosing diseases

Term	Explanation	Example
Diagnostic term	The name of a disease	Wegener's granulomatosis
Definition of disease	Abnormalities in a patient that warrant assignment of the diagnostic term	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries)
Classification criteria	Observations that classify a patient into a standardized category for study	Two or more of the following criteria: 1) nasal or oral inflammation, 2) chest radiograph showing nodules, fixed infiltrates, or cavities, 3) hematuria or red cell casts in urine sediment, 4) granulomatous inflammation on biopsy (ACR Committee criteria [9])
Diagnostic criteria	Observations that demonstrate or confidently predict the presence of the defining features of the disease in a patient	Not yet documented. This would need to be determined by analysis of larger numbers of patients in whom the defining features are unequivocally present

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ACR classification criteria

WG	Nasal or oral inflammation
	Abnormal chest radiograph
	Active urinary sediment
	Granulomatous inflammation on biopsy
	≥2 of 4 criteria to meet classification as WG
CSV	Asthma
	Eosinophilia
	Mono- or polyneuropathy
	Pulmonary infiltrates
	Paranasal sinus abnormality
	Extravascular eosinophils
	≥4 criteria to meet classification as CSV
MPA	No separate classification from classic polyarteritis nodosa

Sensitivity →71·0% - 95·3%
Specificity →78·7% - 99·7%

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Limitations

1. ANCA → developed afterwards

2. No distinction made between poly arteritis nodosa and MPA

3. Evolving diagnostic techniques and pathophysiology has made distinction easier

4. Not intended to be used as diagnostic but as classification criteria

Chapel Hill Consensus Conference (CHCC)

- Held at Chapel Hill, North Carolina

- Goals
  - To reach consensus on the names for some of the most common forms of noninfectious systemic vasculitis

  - To construct root *definitions* for the vasculitides so named

    - Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum 1994;37:187*

Large vessel vasculitis	
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. *Often involves the temporal artery. Usually occurs in patients older than 50 and often is associated with polymyalgia rheumatica.*
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. *Usually occurs in patients younger than 50.*
Medium-sized vessel vasculitis	
Polyarteritis nodosa† (classic polyarteritis nodosa)	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.
Kawasaki disease	Arteritis involving large, medium-sized, and small arteries, and associated with mucocutaneous lymph node syndrome. *Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.*
Small vessel vasculitis	
Wegener's granulomatosis‡	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). *Necrotizing glomerulonephritis is common.*
Churg-Strauss syndrome‡	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia.
Microscopic polyangiitis† (microscopic polyarteritis)‡	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). *Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.*
Henoch-Schönlein purpura	Vasculitis, with IgA-dominant immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). *Typically involves skin, gut, and glomeruli, and is associated with arthralgias or arthritis.*
Essential cryoglobulinemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles), and associated with cryoglobulins in serum. *Skin and glomeruli are often involved.*
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum 1994;37:187*

- Wegener's granulomatosis
  - Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries)
  - *Necrotizing glomerulonephritis is common*
- Churg-Strauss syndrome
  - Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia.

- Microscopic polyangiitis

  - Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles)

  - *Necrotizing arteritis involving small and medium sized arteries may be present*
  - *Necrotizing glomerulonephritis is very common*
  - *Pulmonary capillaritis often occurs*

- Recognised that histological samples would not be always available

- Introduced concept of surrogate markers and ANCA

Limitations

- Neither diagnostic nor classification criteria

- Sorensen etal tested the CHCC for diagnosis and found that only 8 of 27 patients were diagnosed with Wegener's granulomatosis, and 3 of 12 cases with microscopic polyangiitis

Surrogate parameters for vasculitis

- New diagnostic criteria:

  - Wegener's granulomatosis

    1. Biopsy or surrogate parameter for granulomatous inflammation in the respiratory system

    2. Biopsy verified necrotising vasculitis in small to medium sized vessels or biopsy/surrogate parameter for glomerulonephritis or positive PR3-ANCA test

    3. Lack of eosinophilia in blood and biopsy samples

– Microscopic polyangiitis

1. Biopsy verified necrotising vasculitis in small vessels and/or glomerulonephritis with few or no immune deposits

2. Involvement of more than one organ system as indicated by biopsy verified vasculitis in small to medium sized vessels or surrogate parameter for glomerulonephritis

3. Lack of biopsy and surrogate parameter for granulomatous inflammation in the respiratory system

    - Sorensen SF, Slot O, Tvede N, Petersen J. A prospective study of vasculitis patients collected in 5-year period: evaluation of the Chapel Hill nomenclature. *Ann Rheum Dis 2000;59:478–82.*

- Lane etal → evaluated the Sorensen criteria and found that
  - They were not useful for MPA
  - The exclusion of eosinophilia limited the usefulness of the criteria for WG

- Lane SE, Watts RA, Barker THW, Scott DGI. Evaluation of the Sorensen diagnostic criteria in the classification of systemic vasculitis. *Rheumatology 2002;41:1138–41.*

- An algorithm to classify ANCA associated vasculitis for epidemiological studies was developed that included MPA and incorporated ANCA

- Known as the **EMEA (European Medicine Agency)** algorithm

- However, this was too cumbersome to use in individual patients

  - Watts R, Lane S, Hanslik T et al. Development and validation of a consensus methodology for the classification of the ANCA associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis 2007; 66:222–7*

Recent revision of the classification scheme based on

1. The traditional approach of classifying vasculitis by size of predominant vessel involved

2. Diagnostic auto-antibodies (ANCA)

3. Current understanding of pathogenesis

» Watts RA, Suppiah R,Merkel PA, Luqmani R. Systemic vasculitis – is it time to reclassify? *Rheumatology 2011;50:643-645*

Diagnostic and Classification criteria in Vasculitis (DCVAS)

- A major international effort to use data-driven methods to develop
  - A revised single classification system for the vasculitides
  - A validated set of diagnostic criteria for the vasculitides in accordance with standards established by the ACR and the European League Against Rheumatism (EULAR)

- NCT01066208

- Started in Feburary 2010 and expected to be complete by July 2012

Granulomatosis with polyangiitis (Wegener's)

- The term *Wegener's granulomatosis w*as introduced into the English-language literature by Drs Godman and Churg in 1954
  - Godman GC, Churg J. Wegener's gra ulomatosis: pathology and review of the literature. *AMA Arch Pathol 1954;58:533–53*.
- The name change was triggered by evidence that Dr Friedrich Wegener was a memberof the Nazi party before and during World War II
  - Woywodt A, Haubitz M, Haller H, *et al. Wegener's granulomatosis.* Lancet 2006; 367:1362–6
- The parenthetical reference to Wegener's will be phased out after several years as the new usage becomes more widely known
  - Falk RJ, Jennette JC. ANCA disease: where is this fi eld heading? *J Am Soc Nephrol 2010;21:745–52*
  - Falk RJ, Gross WL, Guillevin L et al. Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis. A joint proposal of the American College of Rheumatology, the American Society of Nephrology, and the European League against Rheumatism. *Ann Rheum Dis 2011 70: 704*

Management

- Treatment protocols have changed in the last two decades after the first wave of the EUVAS (European vasculitis study group) trials

- EUVAS criteria are objective disease classification instruments that have been developed to assist the clinician in categorizing disease severity so that therapies may be appropriately titrated to disease activity and the associated risk of end-organ injury and/or mortality.

Category	Definition
Localised	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms
Early systemic	Any, without organ-threatening or life-threatening disease
Generalised	Renal or other organ threatening disease, serum creatinine <500 µmol/litre (5.6 mg/dl)
Severe	Renal or other vital organ failure, serum creatinine >500 µmol/litre (5.6 mg/dl)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

Mukhtyar C etal. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis 2009;68:310–317.*

A. Localised disease

- Refers to isolated upper or lower airway disease and a complete absence of other end organ involvement or constitutional symptoms

- Managed with topical therapy, corticosteroids, and/or a single moderate potency cytotoxic agent such as methotrexate or azathioprine

B. Early generalised disease

- Presence of constitutional symptoms and active vasculitis but without any specific threat to organ function
- Standard therpay → Cylophosphamide + steroids

- NORAM (Non-Renal Alternative with Methotrexate) trial
  - Compared methotrexate with cyclophosphamide for the induction of remission in early disease
  - Time to remission (5 m vs 3 m)
  - Relapse rate (74% vs 42%) favored cyclophosphamide

- Methotrexate was better tolerated and had less side affects
  - de Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum 2005;52:2461*

- MYCYC (Mycophenolate Mofetil Versus Cyclophosphamide for Remission Induction ANCA Associated Vasculitis) trial
  - EUVAS sponsored randomised contolled trial
  - Compares mycophenolate mofetil with cyclophosphamide for the induction of remission
  - Currently underway

C. Generalised active disease

- Presence of constitutional symptoms and threatened organ function caused by vasculitic activity
- Oral cyclophosphamide plus steroids → standard therapy since the 1970s

- CYCLOPS (Daily Oral Versus Pulse Cyclophosphamide for Renal Vasculitis) trial
  - 149 patients with newly diagnosed generalized active AAV were randomized to pulse intravenous cyclophosphamide (15 mg/kg every 2–3 weeks) or daily oral cyclophosphamide (2 mg/kg/d) plus prednisolone

- No difference in time to remission or proportion of patients who achieved remission (88.1% vs 87.7% at 9 months)

- Pulse group had a lower rate of leukopenia and received a lower total cumulative dose of cyclophosphamide

  - de Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med 2009;150:670*

D. Severe disease

- Presence or threat of immediate organ failure and/or death
  - Rapidly progressive glomerulonephritis and renal failure (creatinine >5.7 mg/dL)
  - Alveolar hemorrhage associated with respiratory failure
  - Cardiomyopathy with heart failure
  - Life-threatening arrhythmias
  - Central nervous system disease
  - Gastrointestinal disease with bowel schemia or life-threatening hemorrhage

- Standard treatment → Plasma exchange + i/v cyclophophamide + steroids

- MEPEX (Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis)

  - EUVAS sponsored randomised controlled trial
  - 137 patients with a new diagnosis of AAV and a serum creatinine level greater than 500 mmol/L (5.8 mg/dL) were included
  - All patients received standard therapy with oral cyclophosphamide and oral prednisolone and were then randomized to either 7 plasma exchanges or 3000 mg of intravenous methylprednisolone

- At 3m → 69% of patients treated with plasma exchange were alive and independent of dialysis compared with only 49% in the methylprednisolone group
    - Jayne DRW, Gaskin G, Rasmussen N, et al. Randomised trial of plasma exchange or high dose methyl prednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol 2007; 18:2180*

- A 20 patient case series showed the efficacy of this treatment strategy in alveolar hemorrhage also
    - Klemmer PJ, Chalermskulrat W, Reif MS, et al. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small vessel vasculitis. *Am J Kidney Dis 2003;42:1149*

- PEXIVAS (Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis)

  - EUVAS sponsored
  - Largest international multicenter trial in vasculitis to date
  - Will include 500 patients with ANCA-associated vasculitis with glomerular filtration rate of less than 50ml/min or lung hemorrhage
  - Started in June 2010
    - www.pexivas.bham.ac.uk, http://clinicaltrials.gov/ct2/show/NCT00987389

E. Refractory disease

- Disease that does not respond to conventional accepted therapy
- Investigational or unproven therapies are used

1. Rituximab
   - Targets the CD20 antigen on the surface of B cells and clears circulating B cells from the circulation
   - Evaluated in two recent trials

   - RAVE (Rituximab in ANCA-Associated Vasculitis) trial
     - Multicenter, randomized, double-blind, double-dummy, noninferiority trial
     - Compared rituximab with standard cytotoxic therapy for the induction of complete remission by 6 months in patients with severe ANCA-associated vasculitis

- 64% of the patients achieved complete remission compared to 53% in the cyclophosphamide control arm

- More efficacious than the cyclophosphamide-based regimen for inducing remission of relapsing disease; 34 of 51 patients in the rituximab group (67%) as compared with 21 of 50 patients in the control group (42%) (P = 0.01)

- As effective as cyclophosphamide in the treatment of patients with major renal disease or alveolar hemorrhage

- No significant differences between the treatment groups with respect to rates of adverse events

    - Stone JH, Merkel PA, Spiera R *et al*. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med 2010; 363:221–32*

- RITUXVAS (rituximab versus cyclophosphamide in ANCA associated vasculitis) trial
  - 44 patients with newly diagnosed ANCA-associated vasculitis and renal involvement were randomly assigned, in a 3:1 ratio, to a standard glucocorticoid regimen plus
    - either rituximab at a dose of 375 mg per square meter of body-surface area per week for 4 weeks, with two intravenous cyclophosphamide pulses (33 patients, the rituximab group)
    - or intravenous cyclophosphamide for 3 to 6 months followed by azathioprine (11 patients, the control group)
  - 76% patients in the rituximab group and 82% patients in the control group had a sustained remission (P = 0.68)
  - Severe adverse events occurred in 14 patients in the rituximab group (42%) and 4 patients in the control group (36%) (P = 0.77)

- Rituximab-based regimen was not superior to standard intravenous cyclophosphamide for severe ANCA-associated vasculitis
- Sustained-remission rates were high in both groups
- Rituximab-based regimen was not associated with reductions in early severe adverse events
    - Jones RB, Tervaert JW,Hauser T et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med 2010; 363:211–20*

– Further work is still needed before rituximab is integrated into the standardised mangement of vasculitis

2. Other agents

a. Infliximab - chimeric IgGk monoclonal antibody against soluble and membrane-bound TNF

- Has given positive benefit in small trials

b. Anti thymocyte globulin

- Studied in the EUVAS sponsored SOLUTION trial
- 15 patients received ATG for refractory vasculitis
- Partial disease remission was induced in 9/15 and complete disease remission in 4/15
- 2 patients died after drug administration
- 1 of pulmonary hemorrhage
- 1 of infection
- Serum sickness and nonfatal infections were among the notable complications
    - Schmitt WH etal. Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients. *Kidney Int. 2004 Apr;65(4):1440-8*

c. Intravenous immunoglobulin (IVIg)

- Studied in small clinical trials
- Effect is generally short-lived
- Most appropriate in acute situations where conventional therapy is contraindicated especially if severe infection is present

d. WEGENT (Wegener's Granulomatosis-Entretien) trial

- 32 induction-refractory (24 WG and 8 MPA) patients were treated with oral CYC in 20 patients, combined with infliximab in 1
- 15 (75%) achieved remission or low disease activity state, 3 subsequently died of uncontrolled disease and 2 entered remission using several other agents including biological agents
    - Seror R, Pagnoux C, Ruivard M, et al. Treatment strategies and outcome of induction-refractory Wegener's granulomatosis or microscopic polyangiitis: analysis of 32 patients with first-line induction-refractory disease in the WEGENT trial. *Ann Rheum Dis 2010;69:2125–2130*

e. Alemtuzumab

f. Deoxyspergualin

F. Remission maintenance

- Less aggressive regimens are used for maintenance of disease remission

- CYCAZAREM (Cyclophosphamide versus Azathioprine for Remission in Generalized Vasculitis) trial
  - EUVAS sponsored randomised controlled trial
  - Patients were initially treated with oral cyclophosphamide and oral prednisolone for induction
  - They were then randomised to
    - Either oral cylophosphamide for 12 m followed by azathioprine
    - Or directly to azathioprine

- No difference in relapse rates (15.5% in the AZA group and 13.7% in the CYC group) [P 0.65; 95% confidence interval (CI) -9.9 to+13.0%] up to the end of the study at 18 months after treatment outset

  - Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med 2003; 349:36.*

- IMPROVE (International Mycophenolate Mofetil to Reduce Outbreaks of Vasculitides trial
  - EUVAS sponsored Open-label randomized controlled trial
  - Directly compared mycophenolate mofetil with azathioprine for the maintenance of remission in renal vasculitis

- 156 patients were assigned to azathioprine (n=80) or mycophenolate mofetil (n=76) and followed up for a median of 39 months
- Relapses were more common in the mycophenolate mofetil group (42/76 patients) compared with the azathioprine group (30/80 patients), with an unadjusted hazard ratio (HR) for mycophenolate mofetil of 1.69 (95% confidence interval [CI], 1.06-2.70; P=.03)
- Severe adverse events did not differ significantly between groups

- Hiemstra TF, Walsh M, Mahr A, et al; European Vasculitis Study Group (EUVAS). Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA 2010;304(21):2381–2388*

- WGET (Wegener Granulomatosis Etanercept Trial)
  - Concluded that Etanercept has no role
    - Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med 2005;352(4): 351–361*

- REMAIN (Randomized Trial of Prolonged Remission Maintenance Therapy in Systemic Vasculitis)
  - Ongoing EUVAS trial
  - Will compare 24 months of therapy with 48 months of therapy

- Leflunomide
  - A small trial compared leflunomide with methotrexate
  - Showed superiority in the leflunomide arm
    - Metzler C, Miehle N, Manger K, et al. Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. Rheumatology (Oxford) 2007;46:1087

EUVAS disease classification criteria and recommended first-line therapy options

Disease Severity	Constitutional Symptoms	Renal Function	Threatened Organ Function	Treatment Options for Induction
Limited	No	Serum creatinine <120 μmol/L (1.4 mg/dL)	No	Corticosteroids or methotrexate or azathioprine +/– topical therapies
Early generalized	Yes	Serum creatinine <120 μmol/L (1.4 mg/dL)	No	Cyclophosphamide + corticosteroids or methotrexate + corticosteroids (mycophenolate + corticosteroids is currently under investigation)
Active generalized	Yes	Serum creatinine <500 μmol/L (5.7 mg/dL)	Yes	Cyclophosphamide + corticosteroids
Severe	Yes	Serum creatinine >500 μmol/L (5.7 mg/dL)	Yes	Cyclophosphamide + corticosteroids + plasma exchange
Refractory	Yes	Any	Yes	Consider investigational or compassionate use agents (eg, rituximab)
Remission	No	Serum creatinine <120 μmol/L (1.4 mg/dL)	No	Azathioprine +/– low-dose corticosteroids Mycophenolate +/– low-dose corticosteroids Leflunomide +/– low-dose corticosteroids

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EULAR recommendations for the management of primary small and medium vessel vasculitis

1. Patients with primary small and medium vessel vasculitis should be managed in collaboration with, or at centres of expertise

2. ANCA testing (including indirect immunofluorescence and ELISA) should be performed in the appropriate clinical context

3. A positive biopsy is strongly supportive of vasculitis and the procedure is recommended to assist diagnosis and further evaluate patients suspected of having vasculitis

4. A structured clinical assessment, urine analysis and other basic laboratory tests at each clinical visit for patients with vasculitis should be done

5. Patients with ANCA-associated vasculitis should be categorised according to different levels of severity to assist treatment decisions

6. A combination of cyclophosphamide (intravenous or oral) and glucocorticoids is recommended for remission induction of generalised primary small and medium vessel vasculitis

7. A combination of methotrexate (oral or parenteral) and glucocorticoid as a less toxic alternative to cyclophosphamide for the induction of remission in non-organ threatening or non-life threatening ANCA-associated vasculitis is recommended

8. The use of high-dose glucocorticoids as an important part of remission induction therapy is recommended

9. Plasma exchange for selected patients with rapidly progressive severe renal disease in order to improve renal survival is recommended

10. Remission-maintenance therapy with a combination of low-dose glucocorticoid therapy and, either azathioprine, leflunomide or methotrexate is recommended

11. Alternative immunomodulatory therapy choices should be considered for patients who do not achieve remission or relapse on maximal doses of standard therapy: these patients should be referred to an expert centre for further management and enrolment in clinical trials

- Mukhtyar C etal. EULAR recommendations for the management of primary small and medium vessel vasculitis*. Ann Rheum Dis 2009;68:310–317*

Additional points

- Dosage and schedule of cyclophosphamide
  - 15 mg/kg (maximum 1.2 g) iv infusion every 2 weeks for first three doses f/b every 3 weeks for next 3 – 6 doses
  - Dose adjustment can be made based on creatinine levels

- Oral prednisolone or prednisone at 1 mg/kg/day is started alongside and maintained for 1 month, and should not be reduced to less than 15 mg/day for the first 3 months →then tapered to a maintenance dose of 10 mg/day or less during remission

- When a rapid effect is needed, intravenous pulsed methylprednisolone may be used in addition to the oral prednisolone as part of remission induction therapy

- Remission maintenance therapy should be continued for at least 18 months

- The addition of trimethoprim/sulphamethoxazole (800/160 mg twice daily) to standard remission maintenance can reduce the risk of relapse in WG

- Prophylaxis against Pneumocystis jiroveci in all patients being treated with cyclophosphamide; with trimethoprim/sulphamethoxazole (800/160 mg on alternate days or 400/80 mg daily) is recommended

- Thromboembolic disease in the setting of AAV

  - The Wegener's Clinical Occurrence of Thrombosis (WeCLOT) study identified that the incidence of thromboembolic disease in patients with WG was 7.0 per 100 person-years, which is the same rate of venous thromboembolic (VTE) disease as for patients with a known prior history of VTE

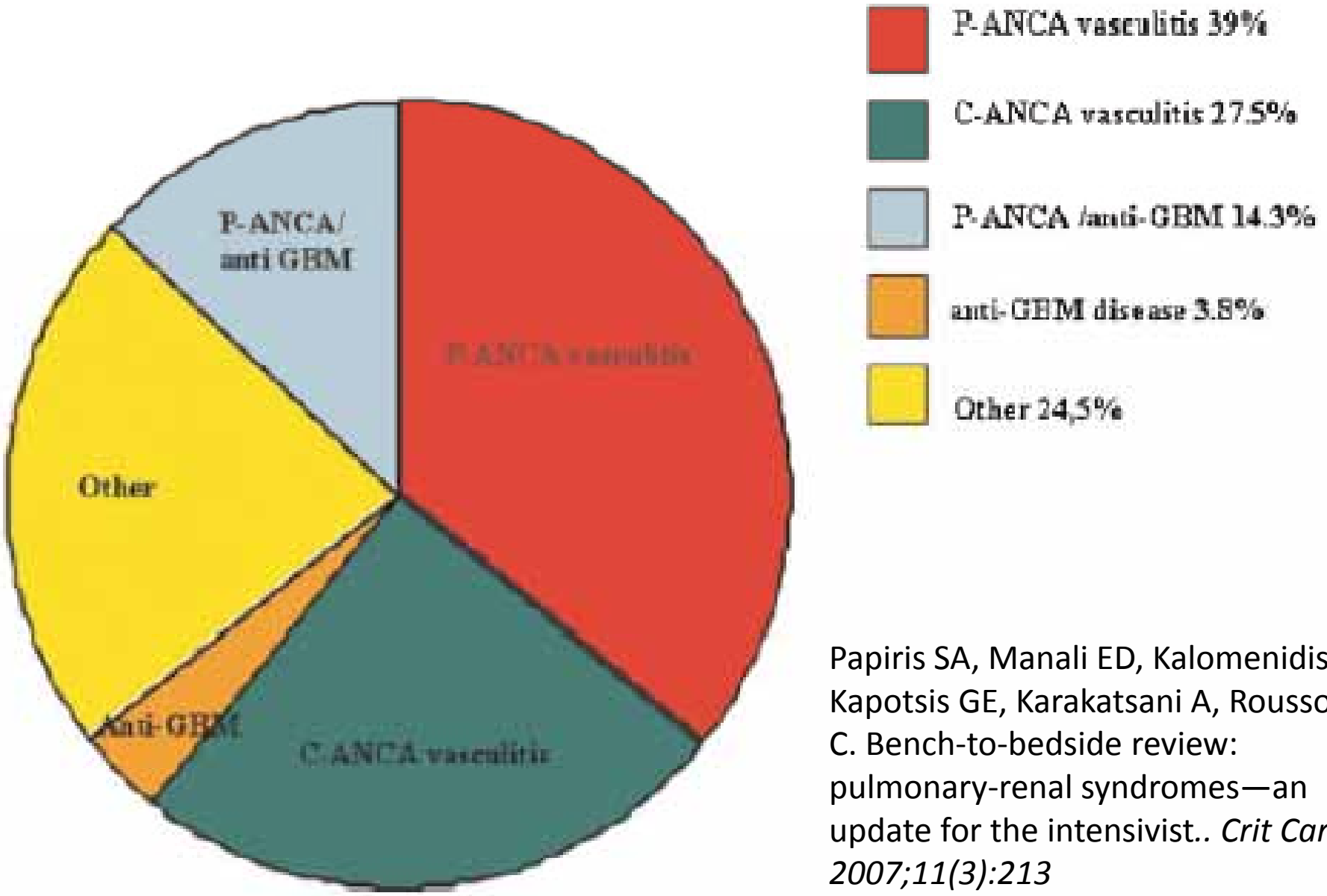
  - Clinicians should consider patients with AAV to be at higher risk for VTE

    - Merkel PA, Lo GH, Holbrook JT, et al. Brief communication: high incidence of venous thrombotic events among patients with Wegener granulomatosis: the Wegener's Clinical Occurrence of Thrombosis (WeCLOT) Study. *Ann Intern Med 2005; 142:620*

Alveolar hemorrhage(AH)

- Defined as bilateral alveolar infiltrates on radiological imaging without an alternative explanation plus at least one of the following
  - Hemoptysis
  - Increased carbon monoxide diffusing capacity
  - Bronchoscopic evidence of hemorrhage
  - Unexplained drop in hemoglobin
    - Casian A, Jayne D. Management of Alveolar Hemorrhage in Lung Vasculitides. *Semin Respir Crit Care Med 2011;32:335–345*
- Vasculitis was the third most common cause of AH requiring intensive care support (19% of patients), after thrombocytopenia (27%) and sepsis (22%)
    - Rabe C, Appenrodt B, Hoff C, et al. Severe respiratory failure due to diffuse alveolar hemorrhage: clinical characteristics and outcome of intensive care. *J Crit Care 2010;25(2): 230–235*

- The majority (80%) of these vasculitis cases with AH are due to ANCA associated vasculitis (AAV)



Papiris SA, Manali ED, Kalomenidis I, Kapotsis GE, Karakatsani A, Roussos C. Bench-to-bedside review: pulmonary-renal syndromes—an update for the intensivist.. *Crit Care 2007;11(3):213*

- AH is the most common respiratory manifestation of AAV, occurring in 24%
- 95% of AH due to pauci immune vasculitis are ANCA +
    - Casian A, Jayne D. Management of Alveolar Hemorrhage in Lung Vasculitides. *Semin Respir Crit Care Med 2011;32:335–345*

- AH appears similar in the PR3-ANCA and MPO ANCA groups with regard to clinical features and severity of respiratory failure

- Mild AH is more common (in 24 to 28% of AAV)

- 28% of patients may retrospectively reportprevious symptoms suggestive of AH for >12 months before diagnosis

Treatment

- Treatment decisions are made based on the EUVAS disease severity grading

- AH may fit into almost any of the categories depending on the disease severity
  - **Mild AH** without impairment of pulmonary function
  - **Moderate AH** resulting in impaired pulmonary function but not requiring mechanical ventilation
  - **Severe AH** requiring respiratory support
  - **Refractory AH**

- Mild – moderate AH
  - Treated in the same way as mentioned earlier
  - Rituximab has been used in this setting
    - Stone JH, Merkel PA, Spiera R, et al; RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCAassociated vasculitis. *N Engl J Med 2010;363(3):221–232*

- Severe AH
  - Cyclophosphamide + glucocorticoids + /- Plasma exchange
  - Recombinant, activated factor VII → useful in case reports in life threatening, uncontrollable AH
    - Henke D, Falk RJ, Gabriel DA. Successful treatment of diffuse alveolar hemorrhage with activated factor VII. *Ann Intern Med 2004;140(6):493–494*
    - Heslet L, Nielsen JD, Levi M, Sengeløv H, Johansson PI. Successful pulmonary administration of activated recombinant factor VII in diffuse alveolar hemorrhage. *Crit Care 2006;10(6):R177*
  - Extracorporeal membrane oxygenation (ECMO)

At the end

- The prognosis of the pulmonary small vessel vasculitides has improved markedly in the last few years provided timely diagnosis is made and adequate treatment instituted

- The results of the various trials going on would probably lead to major changes in the nomenclature, classification and management of these disorders