RPGN

GP CME

19 August 2019

GLMS

MRS G

- 35 F warehouse worker, mother of 2
- 3 days of headache, abdo pain, arthralgia and vomiting
- Preceded by few weeks history of sinusitis and intermittent fever
- 4:30am severe upper abdominal pain then loss of sensation and power below upper aabdomen
- PMHx: RHD with severe MR = MVR and Tricuspid Annuloplasty 2017 on warfarin

MRS G

O/E:

- Very unwell looking, febrile
- Haemodynamically stable

- Acute cord syndrome - no lower limb power or sensation, and absent reflexes, loss of sensation T6 downwards

Ix:

- Cr 530 (143 Feb 2017) INR 4.0
- Active urinary sediment (AlCR 27, rbc 470)
- CTH: extensive sinus disease but no intracranial pathology
- CTKUB: no renal tract obstruction normal size kidneys
- CT Thoracic: Multiple nodular/patchy lung infiltrations, signs of pulmonary HTN.
- No evidence of acute spinal fracture or epidural haematoma.

ADMISSION DIAGNOSIS AND PLAN

- Acute cord syndrome
- AKI with active urinary sediments

- Transverse myelitis
- D/D – Vasculitis, embolic, hematoma

ADMISSION DIAGNOSIS AND PLAN

- Neurology review
- Renal review
- Vasculitic screen, Reverse warfarin
- Lumbar puncture, renal biopsy when appropriate
- Fluid balance chart

MRS G

- Renal team involved on day 1
- **PR3 antibodies 498** (<20)
- Working diagnosis:
- ANCA-associated Vasculitis (Granulomatosis with polyangiitis)
- Spinal cord syndrome due to ? Infarction vs haemorrhage vs inflammation (Transverse myelitis)
- Initial Management:
- Pulsed Methylpred on day 1
- Reverse INR
- IDC insertion due to neurogenic bladder and AKI
- Plasma exchange the next day => indications: severe AKI and spinal cord syndrome

RENAL BIOPSY

- 5 glomeruli show older fibrous crescents,
- Another 4 glomeruli show more cellular crescents, although these also appear to be undergoing fibrosis.
- Two possible small early necrotising lesions are seen.
- Immunoflorescence – negative
- Diagnosis – Pauci-immune GN cocsistent with ANCA associated GN with crescent formation

MRS G

- The cause of Spinal cord syndrome:

- Ortho /Neurology involved
- MRI contraindicated due to retained incompatible pacing wires
- - Cardiologists and Radiologists confirmed absolute contraindication – burning myocardium by induced current
- Spinal artery angiogram difficult to do to rule out/in bleeding
- AAV usually involves spinal cord by causing subacute myelopathy with gradual onset
- LP did not suggest haemorrhage but consistent with a bloody tap

- Most likely spinal cord infarction (AAV as the underlying cause)
- - Most likely irreversible

MRS G PROGRESS: THE FIRST FEW DAYS

- 2nd dose of methylpred was not given on day 2
- = medication charted (Medchart transition)
- = Night OCHS contacted and advised to give it mane
- = Gen med–renal transition – no formal ward round notes or specific plan to continue methylpred
- = completed 3 doses on day 4

- Renal Bx = pauci-immune glomerulonephritis with crescent formation.
- Cyclophosphomide 1st dose started Day 5
- Renal function started to improve at day 7
- No signs of improvement of neurology

MRS G PROGRESS: SPINAL CORD SYNDROME MX

- Contacted Inpatient spinal unit on day 3 re bowel care
- advised: Laxsol 2 nocte
- Bisacodyl suppository mane
- Phosphate enema PRN
- Lax sachets nocte until good BM
- Movical Bomb if constipated
- Early referral to spinal unit doctor and nurse specialist to support nursing needs

- Reviewed by spinal Rehab SMO on day 6 with full assessment
- Addition: needs **manual evacuation 2x daily** due to no anal tone

MRS G PROGRESS: BOWEL COMPLICATIONS

- Developed E Coli urosepsis on day 13
- CT Abdo: distended rectum with faeces
- inflammatory stranding of rectal wall
- locules of gas + perineum fat stranding
- = **Stercoral Colitis**
- Surgeical review – recommended **Manual evacuation**

- **777 MET Call day 18**
- Larger PR bleed BP 70/34 Hb 76 (90-100) INR 3.7
- RBC transfusion, reversed INR = patient stablised
- Surgical review – no surgical intervention, embolization if further haemodynamically significant blood loss.

Day post admission	Nursing Documentation re bowel care
14	-
15	Blood in stool
16	2x BM blood noted
17	-

Heparin infusion stopped day 16 as INR

MRS G PROGRESS:

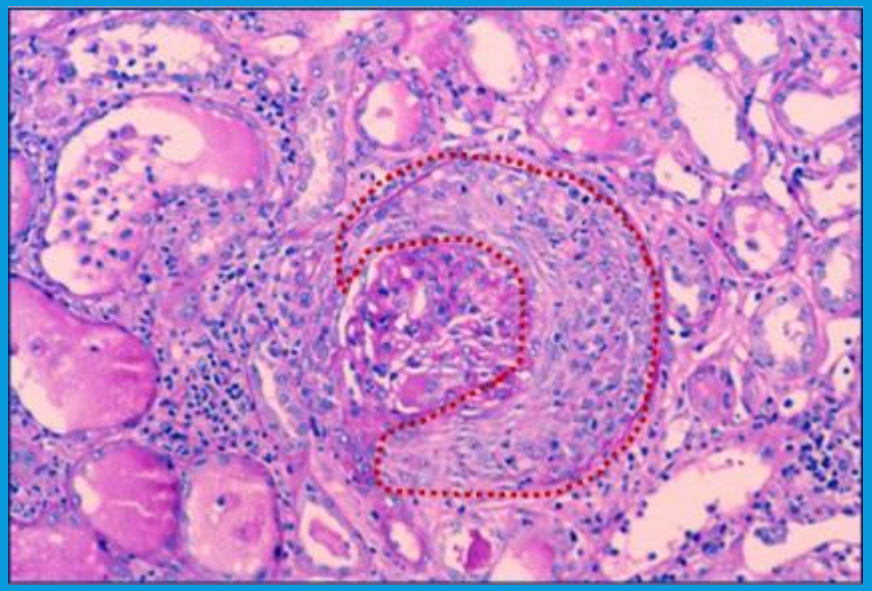
- Transferred to ASRU on day 32
- Markedly improved renal function Cr 108 – now 85
- Received 4 doses of cyclophos
- No functional improvement
- Received full MDT input
- Optimal bowel care with 2x manual evacuation + laxatives
- Discharge plan to home in early July with carer in charge of bowel / bladder care

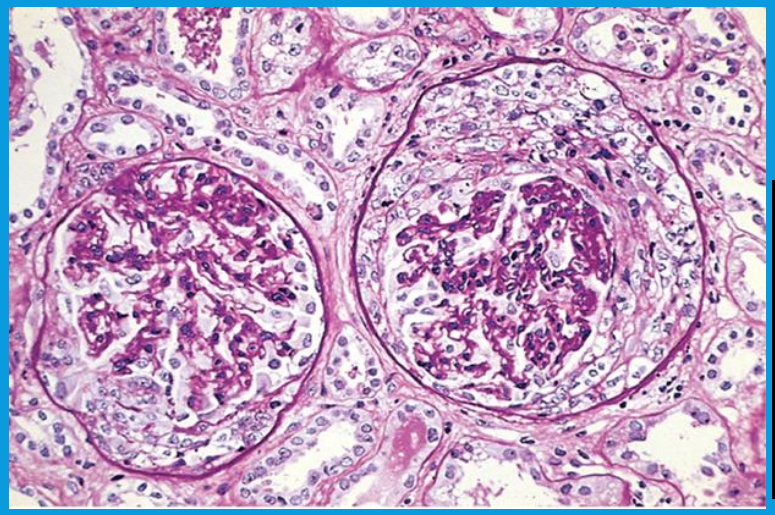
RPGN

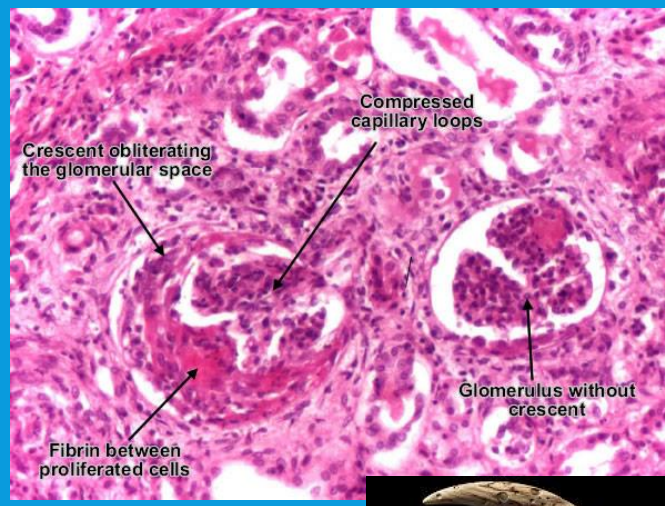
- clinical syndrome manifested by features of glomerular disease in the urine and by progressive loss of renal function over a comparatively short period of time
- characterized morphologically by extensive crescent formation

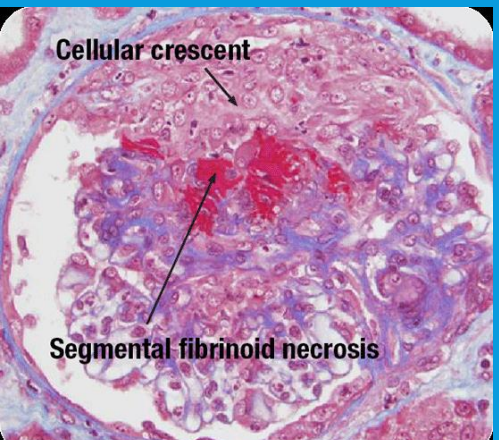
CRESCENTS

- nonspecific response to severe injury to the glomerular capillary wall
- Pathogenesis
  - initiating event development of gaps in glomerular capillary wall, glomerular basement membrane and Bowmans capsule
  - movement of plasma products, including coagulation factors and inflammatory cells, into Bowman's space
  - fibrin formation, the influx of macrophages and T cells, and the release of proinflammatory cytokines, such as interleukin-1 and tumor necrosis factor-alpha
- Active phase followed by fibrocellular and fibrous crescent formation





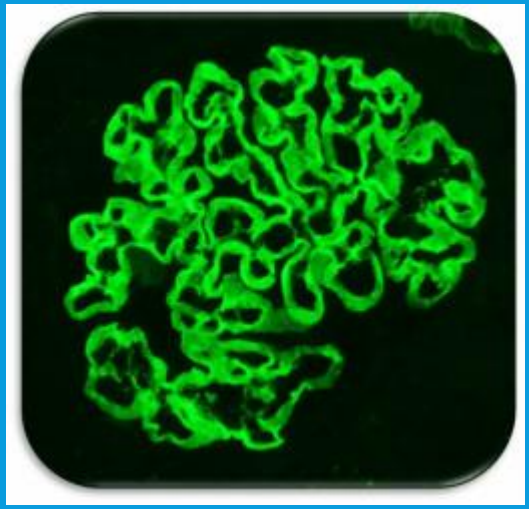

Compressed capillary loops
Crescent obliterating the glomerular space
Glomerulus without crescent
Fibrin between proliferated cells


Cellular crescent
Segmental fibrinoid necrosis


Collapsed capillary
escent

RPGN

- Crescentic GN due to 1 of 3 mechanisms of glomerular injury
- Anti GBM disease (Good Pasture)
- Immune complex GN (Lupus)
- Pauci immune (ANCA associated)



VASCULITIS

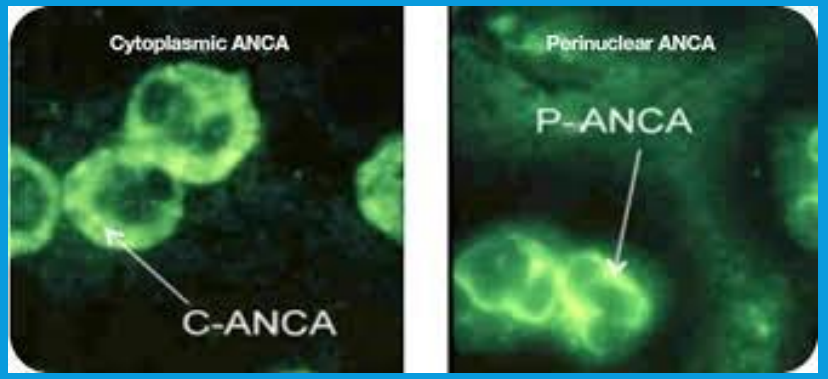
- Inflammation on the blood vessels
- Divided by size of vessel affected
- Renal involvement-small vessel vasculitis-AAV
  - MPA (microscopic polyangiitis)
  - GPA (granulomatis with polyangiitis)/ Wegeners
  - EGPA (eosinophilic GPA) / Churg Strauss

Table 1. Classification of vasculitis according to the 2012 Chapel Hill Consensus Conference nomenclature of vasculitis

Large-vessel vasculitis
Takayasu arteritis
Giant cell arteritis
Medium-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Small-vessel vasculitis
AAV
MPA
GPA (Wegener's granulomatosis)
EGPA (Churg-Strauss syndrome)
Immune complex small-vessel vasculitis
Anti-glomerular basement membrane disease
Cryoglobulinemic vasculitis
IgA vasculitis (Henoch-Schönlein purpura)
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
Variable-vessel vasculitis
Behçet's disease
Cogan's syndrome
Single-organ vasculitis
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis
Others
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others
Vasculitis associated with probable etiology
Hepatitis C virus-associated cryoglobulinemic vasculitis
Hepatitis B virus-associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Drug-associated AAV
Cancer-associated vasculitis
Others

ANTI NEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA)

- Predominantly IgG class autoantibodies directed against constituents of granules of neutrophils and lysosomes of monocytes
- Indirect immunofluorescence (IIF) 2 staining patterns cytoplasmic (cANCA) and perinuclear pANCA
- Antigen specific ELISA 2 different target antigens – Myeloperoxidase(MPO) and PR3



EPIDEMIOLOGY

- Incidence: 20 cases per million
- Incidence increasing until 2000 then plateaued - ?real increase v increased awareness of disease and availability of ANCA testing
- Prevalence increased last 2 decades - greater survival
- M > F in 1 study, others genders equally affected
- 65 – 74. rare in childhood
- MPA predominant subtype in japan, china, southern Europe
- 90 % pauci immune GN ANCA positive

PATHOGENESIS

- ? ANCA
  - Administer MPO-ANCA to wild type mice consistently causes disease
  - Propylthiouracil, MPO inhibitor, develop MPO – ANCAs and AAV - like syndrome
  - Activation of complement system via alternative pathway primary mechanism by which ANCA mediates disease
  - Animal models – C5 or factor b KO mice don't develop disease, anti MPO abs mice treated with c5 inhibitor prevents disease, C4 knockout mice develop vasculitis
  - Human case-control studies found factor Bb, C3a, C5a and final common pathway factors were increased relative to controls

PATHOGENESIS

- Some people circulating ANCAs without disease phenotype
- PR3 abs stimulate leucocyte activation in vitro but don't produce reliable animal model
- 2nd hit - eg inflammatory response secondary to LRTI
- Stimulate neutrophils with cytokines eg TNF a will stimulate them to express autoantigens mpo and pr3 on surface
- Series of 11 ANCA -, pauci immune GN had autiantibodies to human lysosome-associated membrane protein2(LAMP2)

PATHOGENESIS

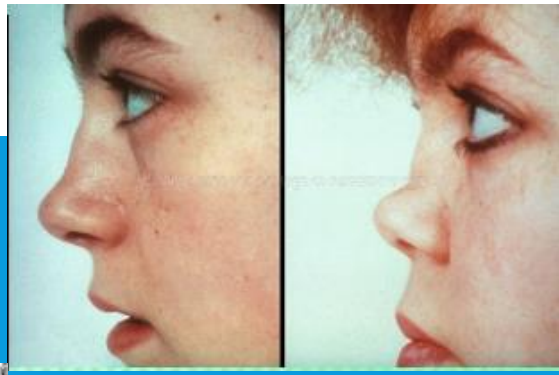
- 1st degree relative GPA 1.6x
- Lots genes, associated with immune function, slightly increase risk
- Chromatin modification(a measure of epigenetic modification) is depleted in ANCA patients
- Chronic occupational exposure to environmental toxins RF – silica. Intense inflammation may promote neutrophil migration and formation on abs agains neutrophil components(MPA)
- Infections- seasonal fluctuation
- 67% GPA nasal SA carriers, colonisation increases risk of relapse between 1.6 and 31 x
- Co- trimoxazole effective means of introducing remission

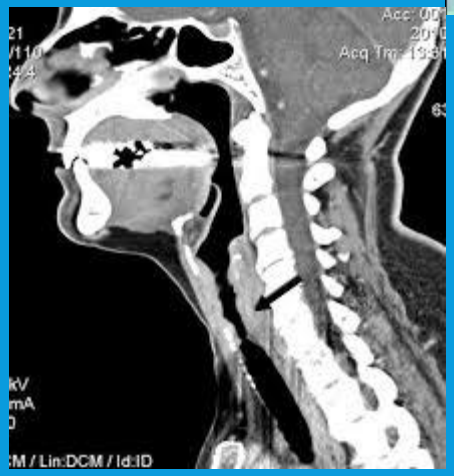
PRESENTATION - RENAL

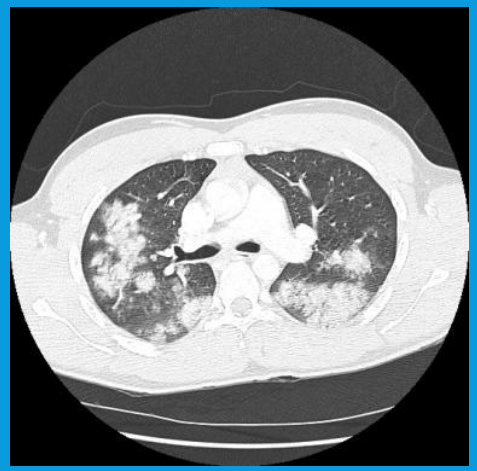
- Spectrum
- Active urine sediment- haematuria, dysmorphic red cells, red cell casts, proteinuria
- Raised creatinine
- Prospective study 70 pts- haematuria and proteinuria common, mean protein 2.5 g/24h, mean entry creatinine 5.5+/- 4.1 (486)
- General sx - low grade fever, fatigue, weight loss, myalgias
- 94% - flu like illness preceding vasculitis
- 75% pauci immune GN evidence small vessel systemic vasculitis
- Study 350 ANCA + patients with pauci immune GN-58% MPA, 25% renal limited, 17% GPA

EXTRA RENAL MANIFESTATIONS

- URT disease – 90% patients with GPA
- Nasal crusting + obstruction, epistaxis, mucosal ulceration, sinus pain and drainage, otitis media, hearing loss.
- Involvement of vessels to cartilage may lead to septal perforation or destructive bone disease +/- granulomas
- Saddle nose deformity, facial paralysis, subglottic stenosis
- Pulmonary involvement- 53% necrotising granulomatous inflammation or alveolar capillaritis. May cause haemoptysis or massive pulmonary haemorrhage

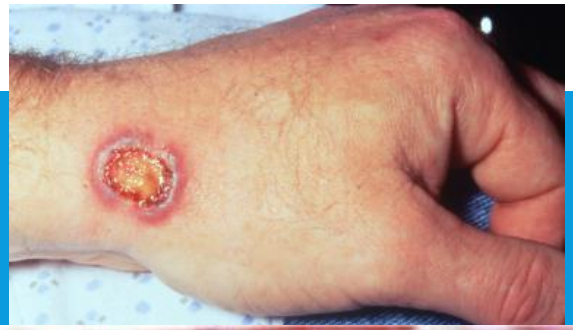


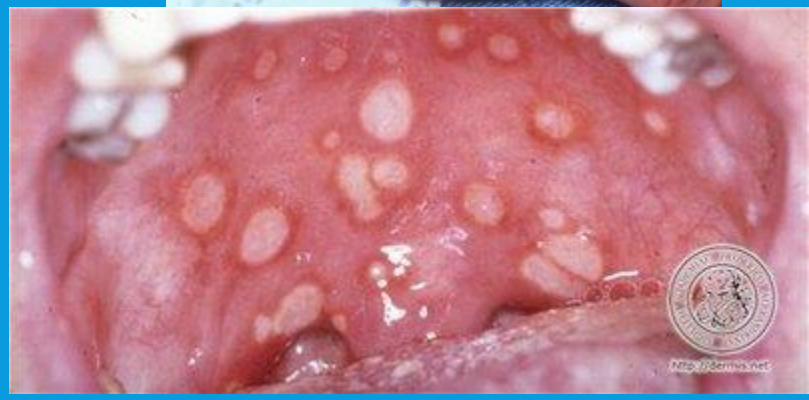


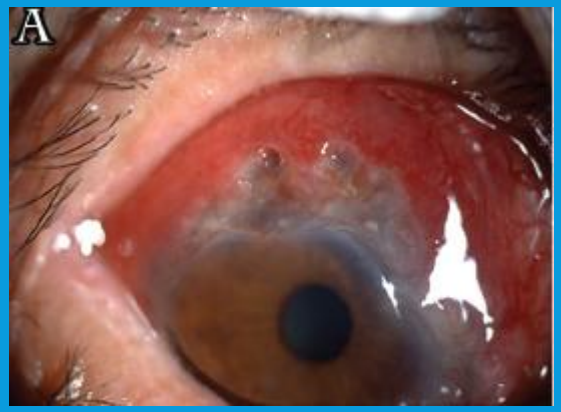


EXTRA RENAL MANIFESTATIONS

- Cutaneous involvement (25%) – palpable purpura and nodules
- Mucous membranes – ulcers
- Ophthalmologic - conjunctivitis, blepharitis, keratitis, acute visual loss, orbital mass
- 30% GI symptoms - abdo pain, gastritis, ischemic colitis, pancreatitis
- Peripheral neuropathy 30%







TREATMENT

- Aim: induce remission , defined as stabilisation or improvement of kidney function, resolution of haematuria and all other organ-specific vascultitic manifestations
- Inadequate or no response = treatment resistance. Progressive decline in kidney function, persistence active urine sediment.\, new extra renal manifestations
- Some patients initially respond, avoid life threatening/advanced organ damage – left with grumbling disease
- Achieve remission - relapses
- Induction – get control of disease
- Maintenance - stay in control of disease

INDUCTION THERAPY

- Combination of high dose steroids and cyclophosphamide standard of therapy for 30 years
- RCT 149 pts pulsed IV v oral. IV lower cumulative dose , no difference in time to remission, increased risk of relapse, mortlity and ESRD no difference
- Steroids: iv pulse methylpred 7mg/kg 3 days, oral pred 1mg/kg 1st 4 weeks and tapered

CTX: iv 0.5-1 g/m2 or oral 2mg/kg.

- 6-12 moths

- Trial 197 pts found rituximab non inferior to ctx incl 102 pts with renal involvement
- Adverse effects not reduced at 6m and 1y. More cancers rtx
- Most centres reserve rtx for refractory cases

PLASMA EXCHANGE

- 2 clear indications: severe renal disease at presentation and pulmonary haemorrhage
- MEPEX - plasma exchange beneficial in creat >500, on dialysis at diagnosis . Provides additional benefit reduce progression to dialysis severe renal vasculitis
- PEXIVAS - trial ongoing . Evaluate mortality outcomes

- Tacrolimus, IVIG, anti TNF agents trialled - current evidence limited. Unlikely to be adopted as first line therapy

INDUCTION THERAPY TRIALS : SUMMARY

Study	Subjects	Therapy	Endpoint	Comment
CYCLOPS[45]	149 patients with newly diagnosed AAV and renal involvement	IV-CYC vs. oral CYC	Time to remission	IV-CYC non-inferior to oral CYC and is associated with reduced cumulative exposure and leukopenia. Subsequent long-term follow up (4.3 years) of participants demonstrated relapse rates are higher with IV regimen[47]
RITUXIVAS[40]	44 patients with newly diagnosed AAV and renal involvement	Rituximab + 2 IV-CYC pulses vs. IV-CYC	Remission at 12 months	Rituximab non-inferior to IV-CYC for remission induction
RAVE[38]	197 patients with newly diagnosed or relapsing AAV. Dialysis dependent patients excluded	Rituximab vs. oral CYC	Remission at 6 months	Rituximab non-inferior to oral CYC for remission induction and based on subsequent *post-hoc* analysis of patients with renal involvement, there is no demonstrable difference in renal outcomes[39]
MEPEX[48]	137 patients with newly diagnosed AAV and severe renal involvement	Plasmapheresis vs. methylprednisolone as adjunct therapy to oral CYC and oral prednisolone	Dialysis independence at 3 months	Plasma exchange superior to methylprednisolone for preventing dialysis dependence at 3 and 12 months, but not for survival at 12 months
PEXIVAS[50]	500 patients with newly diagnosed severe AAV	Plasmapheresis vs. no plasmapheresis as adjunct therapy to high vs. low dose glucocorticoids	Time to all-cause mortality or ESRD	Currently in recruiting phase

ANCA: Anti-neutrophil cytoplasmic antibody, AAV: ANCA associated vasculitis, IV: Intravenous, CYC: Cyclophosphamide, ESRD: End-stage renal disease

INDUCTION THERAPY

- Bone: Vitamin D ? DEXA and bisphosphonates
- GI ulcers: PPI
- Infections : Co-trimoxazole
- Check for TB, hepatitis

MAINTENANCE THERAPY

- Azathioprine established as maintenance drug of choice in CYCAZAREM trial found introducing AZA 3 m after clinical remission did not result in more early relapses that continuing CTX 12m
- Head to head trials AZA v MMF and MTX, no evidence to support alternative agents
- 2mg/kg
- Longterm follow up CYCAZAREM – AZA group trend towards higher rates relapse, ESRD, Death after 5 y
- MAINRITSAN 115pts AZA v RTX, superiority of RTX at 28 months

Optimal duration of AZA unclear

Optimal duration of steroid tx unclear

MAINTENANCE THERAPY

- 30 – 50% relapse after completion induction therapy
- Majority achieve remission with one or more relapses over time
- Similar rate of remission those off and on immunosuppressive therapy
- Irreversible SE and comparable relapse rates -optimal duration individualised
- Predictors of relapse - PR3 +, pulmonary/ ENT involvement
- Relapses 73% pts all risk factors, 23% none

- co- trimoxazole reduces risk of relapses in GPA

MAINTENANCE THERAPY

Study	Subjects	Therapy	Endpoint	Comment
CYCAZAREM[54]	115 patients with newly diagnosed AAV and renal involvement	AZA vs. oral CYC, both in combination with prednisolone, after achieving remission with oral CYC and steroids	Relapse at 18 months	AZA and CYC associated with similar rates of relapse. Cumulative exposure to CYC is reduced
IMPROVE[55]	156 patients with newly diagnosed AAV	AZA vs. MMF after achieving remission with CYC and steroids	Relapse free survival at 39 months	AZA superior to MMF at maintaining disease remission with similar rates of adverse events
WEGENT[56]	159 patients with newly diagnosed AAV	AZA vs. MTX after achieving remission with IV-CYC and steroids	Adverse event requiring drug discontinuation or causing death. Relapse as secondary end point. Mean follow up 29 months	AZA and MTX associated with similar rates of adverse events and relapse
MAINRITSAN[58]	115 patients with newly diagnosed or relapsing AAV	Rituximab vs. AZA after achieving remission with CYC and steroids	Rate of major relapse at 28 months	Rituximab superior to AZA at maintaining remission and not associated with increased severe adverse events
RITAZAREM[62]	160 patients with relapsing AAV	Rituximab vs. AZA after achieving remission with Rituximab and steroids	Rate of relapse	Currently in recruiting phase
BREVAS[66] NCT01663623	400 patients with AAV following standard therapy	Belimumab plus Azathioprine vs Placebo plus Azathioprine	Time to First Relapse	Currently in Recruitment phase
ABROGATE[67] NCT02108860	150 patients with AAV following standard therapy	Abatacept vs plaacebo	Treatment failure after 12 months	Recruitment phase
TAPIR[64]	60 patients with GPA who are in remission	Low dose (5mg) Prednisone vs No dose (0mg) Prednisone	Proportion requiring increased dose relapse	Recruitment phase

ANCA: Anti-neutrophil cytoplasmic antibody, AAV: ANCA associated vasculitis, IV: Intravenous, AZA: Azathioprine, CYC: Cyclophosphamide, MMF: Mycophenolate mofetil, MTX: Methotrexate

PERSISTENT, REFRACTORY AND RELAPSING DISEASE

- Methotrexate with steroids - remission 60 – 90%, higher rates of remission. Experience limited extra renal manifestations
- MMF option non life threatening recurrent or resistant disease
- MMG with CSA effective small series with relapsing/remitting disease
- RTX with steroids or with CT X

COMPLICATIONS AND PROGNOSIS

- Without treatment- median survival 5 months
- With treatment 88% 1 year survival, 78% 5y survival
- Mortality 1st y 2x controls and 30% higher in subsequent yrs

- 1st year 50% deaths infection, 20% disease related complications
- Sunsequent years CVD and cancers major cause death
- AAV and treatments are independent risk factors for CVD and malignancy

RENAL PROGNOSIS

- Renal involvement independent predictor of mortality and progression to ESRD (6% progressing)
- Risk progression 2x MPO
- Requirement for dialysis at presentation v poor prognosis 23% die 6 months, 29% don't regain function, 15% temporarlily regain function but require dialysis within 13-63 months
- Relapse rates lower among those on dialysis
- Histologic analysis aids predicting renal outcomes: focal, mixed, crescentic, sclerosed. Focal best sclerosed worst
- %normal glomeruli and degree tubulointerstitial fibrosis and atrophy also predicts renal survival

SUMMARY

- ANCA vasculitis common cause RPGN
- Suspect – high creatinine, active urinary sediment, insidious or multi system disease
- 65-74 years ago
- Complex pathogenesis - ANCA implicated
- Gold standard - rapid instigation of induction treatment with high dose steroids and cyclophosphamide +/- PLEX
- Transition to maintenance therapy after induction of remission
- Monitor for relapses and complications of disease and treatment

REFERENCES

- Recent advances in anti-neutrophil cytoplasmic antibody-associated vasculitis B. Lazarus,G. T. John, C. O'Callaghan, and D. Ranganathan
- The Prevalence and Management of Pauci-Immune Glomerulonephritis and Vasculitis in Western Countries Sophia Lionaki, John N. Boletis
- The Prevalence and Management of Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis in China

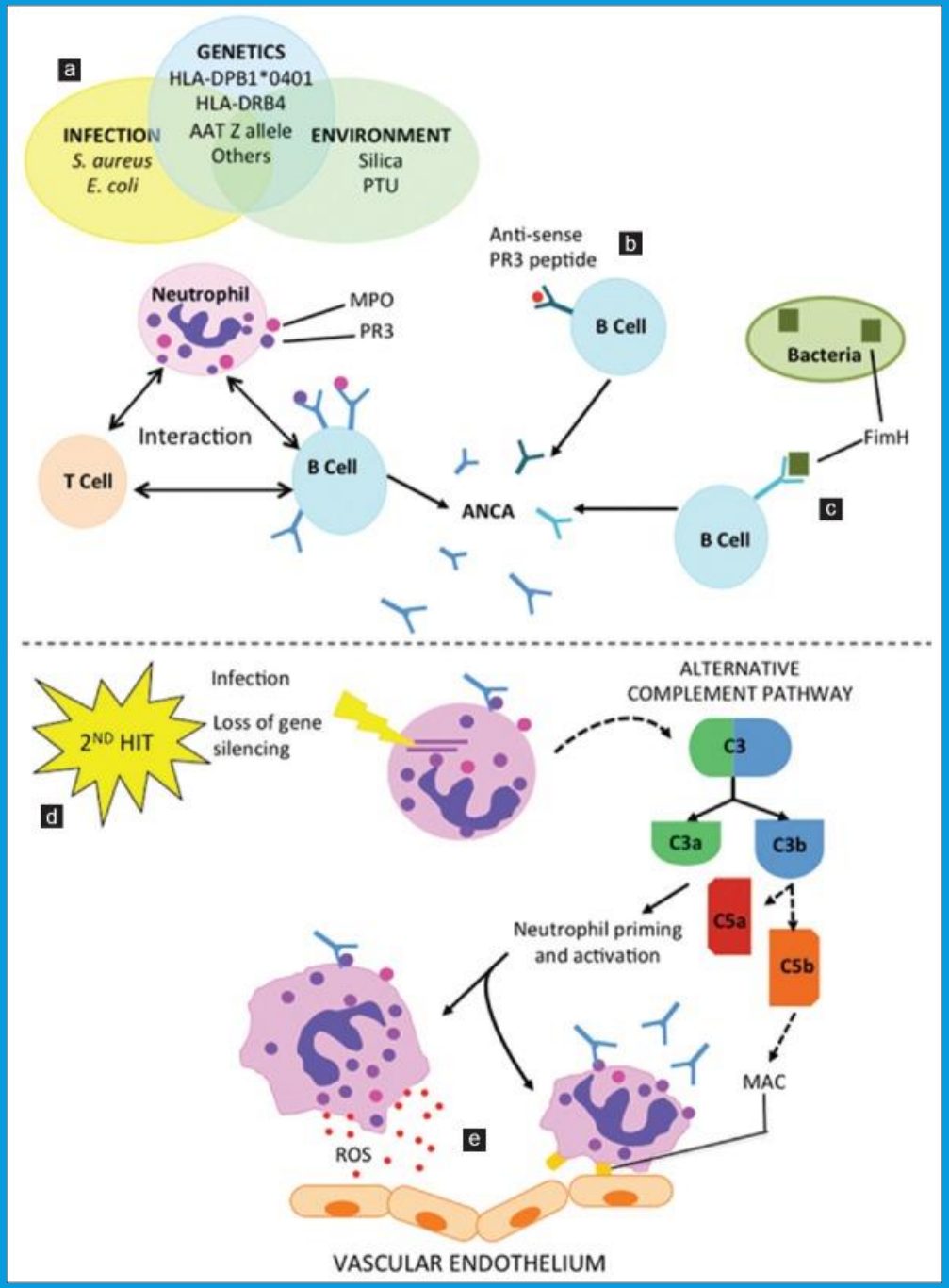
hi-Ying Li , Tian-Tian Ma , Min Chen, Ming-Hui Zhao

TAKE HOME MESSAGE

- Consider RPGN in patients with AKI once pre and post renal ruled out
- Ask general constitutional symptoms
- Urine microscopy for active sediments (blood and protein)
- Refer early

Induction		
Induction	Screen for tuberculosis Consider PCP prophylaxis see below Provide a proton-pump inhibitor for gastric protection while on high-dose steroids (e.g., pantoprazole 20 mg od PO) Measure baseline bone density by DEXA scan and consider prophylactic bisphosphonate therapy Consider sperm banking for men and leuprorelin (GnRH analog) therapy for women before starting cyclophosphamide	
Medication	**Dosage**	**Comments**
Methylprednisolone IV then PO prednisolone	MP (7.5 mg/kg/bw; 500 mg if <70 kg and 750 mg if more than 70 kg) × 3 consecutive days then prednisone 1 mg/kg/day not exceeding 75 mg; tapered after a few weeks to lowest effective dose	
Plus		
Cyclophosphamide (first option)	IV: 15 mg/kg/bw; adjust according to eGFR 0, 2, 4 and then every 3 weeks until remission is achieved, up to a maximum of 10 pulses (EUVAS protocol) For IV if significant leukopenia (WCC <4) or thrombocytopenia (<100) occur - delay - next dose (until WCC >4 and/or platelet count >100) and reduce - next dose or cyclophosphamide PO, 2-3 mg/kg, for 3-6 months Measure FBC weekly in patients on PO cyclophosphamide for the first 4 weeks then every 2-4 weeks - withhold therapy if WCC <4 and restart at reduced dose (25-50 mg/day less than previous dose) once WCC >4 for ≥2 days	To minimize toxicity of IV cyclophosphamide to the bladder: Give IV fluids - 500-1000 ml 0.9% saline over 1-2 h precyclophosphamide and 500-1000 ml 0.9% saline over 1-2 h postcyclophosphamide (depending on fluid balance) Give IV sodium-2-mercaptoethane (Mesna) - dose is 60% of cyclophosphamide dose (round up dose to the nearest whole vial) 40% mesna dose given precyclophospamide and 60% mesna dose postcyclophosphamide infusion.[81] Do not administer IV cyclophosphamide within 12 h of hemodialysis or plasma exchange
Rituximab (second option)	IV: 375 mg/m²×4 doses	Use for patients refractory to standard therapy or to preserve fertility
Plus		
Plasma exchange	7 exchanges in 2 weeks Each exchange volume should be at least 60 ml/kg actual body weight (usually not <3 L or more than 6 L) Standard replacement fluid should be 4% albumin Substitute FFP for 50-100% of exchange volume in patients with pulmonary hemorrhage or within 48 h of renal biopsy to reduce the risk of bleeding Avoid plasma exchange on the same day as renal biopsy - risk of bleeding	Pulmonary hemorrhage and or severe renal insufficiency
Maintenance	**Initiate maintenance therapy once the patient has achieved remission**	
Prednisolone	Tapering dose-till 5-7 mg/daily	Usually 18 months since remission
Plus		
Azathioprine (first option)	Check TPMT status prior to initiating azathioprine PO 2.0 mg/kg/day Reduce initial dose to 1.5 mg/kg/day >60 years; 1.0 mg/kg/day in patients >75 years	
Or MMF or MPS (second option)	PO: MMF - 1-1.5 g twice daily or PO: MPS - 720-1080 mg twice daily	
Plus		
Trimethoprim/ sulphamethoxazole	To reduce the risk of PCP in all patients (whether initiated on cyclophosphamide or rituximab) provide Trimethoprim 80 mg/sulfamethoxazole 400mg daily (i.e., ½ a Bactrim DS or Resprim Forte tablet daily) - in patients allergic to or intolerant of trimethoprim/sulfamethoxazole consider desensitization (liaise with immunology) or use alternative options	
Definitions		
Refractory to standard therapy	Unchanged or increased disease activity in acute stage after 4 weeks of treatment with standard therapy using cyclophosphamide No response (defined as <50% reduction in disease BVAS score and lack of improvement in at least one major item on the disease activity score list) after 4-6 weeks of treatment Persistent disease with presence of at least one major or three minor items on the BVAS score despite 8-12 weeks of treatment Intolerance of, or contraindications to, cyclophosphamide	
Remission	BVAS score ≤1 and daily prednisone dose ≤10 mg	
Sustained remission	BVAS score 0 and no flares in the last 6 months	
Relapse	One major or three minor disease activity items on the BVAS score, in patients that have previously achieved remission following induction therapy	

Modified from: A 4 year retrospective renal study from a Lupus Vasculitis Clinic, Singh G, White L, Flynn P *et al.* OJ Neph 2015. ANCA: Anti-neutrophil cytoplasmic antibodies, PCP: *Pneumocystis jiroveci* pneumonia, BVAS: Birmingham Vasculitis Activity Score, DS: Double strength, MMF: Mycophenolate moeftil, MPS: Mycophenolate sodium, TPMT: Thiopurine methyltransferase, FFP: Fresh frozen plasma, IV: Intravenous, EUVAS: European Vasculitis Study Group, WCC:


a
GENETICS
HLA-DPB1*0401
HLA-DRB4
AAT Z allele
Others
INFECTION
S. aureus
E. coli
ENVIRONMENT
Silica
PTU
b
Anti-sense
PR3 peptide
Neutrophil
MPO
PR3
B Cell
Bacteria
Interaction
T Cell
B Cell
FimH
ANCA
B Cell
c
d
Infection
2ND HIT
Loss of gene
silencing
ALTERNATIVE
COMPLEMENT PATHWAY
C3
C3a
C3b
C5a
C5b
Neutrophil priming
and activation
MAC
ROS
e
VASCULAR ENDOTHELIUM