PYNEH Rheumatology
Dr KYMa , 16/12/2014

RHEUMATOLOGY CRITICAL CARE

Rheumatology and critical care

- Rheumatologists – “skeptical”, “pan-”, “indecisive”
- Patients – “psy”, “long-winded”, “mental”
- Clinic – “worst medical clinic”, “life-span reducing”
- Case – “steroided”, “immunocompromised”, “big firepan”

- Rheumatology – “difficult but boring”

epidemiology

- Approximately 10% to 25% of all patients with rheumatologic disorders visiting the A&E require hospital admission [1–3]
- up to **one third** of the hospitalized patients need ICU care
- They Form only a small percentage of all intensive care unit (ICU) admissions
- **MR very high**

[1] Rojas-Serrano J, Cardiel MH. Lupus patients in an emergency unit. Causes of consultation, hospitalization and outcome. A cohort study. Lupus 2000;9:601 – 6.
[2] Sharma M, Leirisalo-Repo M. Arthritis patient as an emergency case at a university hospital. Scand J Rheumatol 1997;26:30 – 6.
[3] Smith EC, Berry H, Scott DL. The clinical need for an acute rheumatology referral service. Br JRheumatol 1996;35:389– 91.

Major causes of ICU referral

- Sepsis due to immunosuppression

- Exacerbation (flare-up) of the disease
- Development of new vital organ involvement
  Usually respiratory failure or SE

- for monitoring post procedures

The intensivist role

- In about 20% of patients the diagnosis of the rheumatologic disorder was made for the first time during the ICU admission.
- the intensivist should be able to recognize the various manifestations ,complications and the management of rheumatologic diseases.

Bouachour G, Roy PM, Tirot P, et al. Prognosis of systemic diseases diagnosed in intensive care units. Presse Med 1996;25:837– 41.

Case 1

- F23 university student; good past health
- Admitted to psy ward for anxiety depression

- Upon admission
- Dyspnoea; bilateral pedal oedema
- Malar rash, synovitis and low grade temp

- Thrombocytopenia; anaemia
- ESR 70 mm/hr; CRP <5 IU/L
- Serum alb 23; Cr 188 umol/L; urinalysis protein +++ rbc ++ cast +

SLICC† Classification Criteria for Systemic Lupus Erythematosus

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Petri M, et al. Arthritis and Rheumatism. Aug 2012

Lupus nephritis

- Management of LN evolved consistently
- Joint EULAR / ERA-EDTA recommendations 2013

  (european league againsy rheumatism / european renal association / european dialysis and transplantation association)
- ACR guideline 2012
- KDIGO guideline 2012 (kidney disease improving global outcomes)

- ALNN (asian lupus nephritis network) steering group 2014

Lupus nephritis III/IV

- Severity and rate of progression varies
- Prompt ablation of disease activity and inflammation of cruical importance
- Early phrase immunosuppressant – INDUCTION therapy

- Combination of high dose steroid + CYC/MMF (level 1b)
-
- IV pulse Methylprednisolone (500mg-1g/day) x3 days (level 5)
- followed by high dose oral prednisolone (0.5-1mg/kg/day) (level 2b)

- IV CYC (0.5-1gm/m2 *initial dose ~750mg) x6 months (we DON'T recommend Euro-lupus regimen) (level 2b)
- Oral CYC (0.5-1.5mg/kg/day) (level 2b)
- MMF (up to 3g/day) (level 2b)

Table 2 KDIGO recommended regimens for initial therapy of class III/IV Lupus Nephritis[4]

Regimen	A. NIH	B. Euro-Lupus	C. Oral CYC	D. MMF
CYC	i.v. CYC 0.5–1 g/m^2, monthly for 6 months	i.v. CYC 500 mg every 2 weeks for 3 months	Oral CYC 1–1.5 mg/kg/day (maximum dose 150 mg/day) for 3–4 months	–
MMF	–	–	–	MMF up to 3 g/day for 6 months
Benefits shown by RCT in proliferative LN	Yes	Yes	Yes	Yes
Benefit shown by RCT in severe LN	Yes	Untested	Untested	Untested
Comments	Effective in Whites, Blacks, Hispanics and Chinese	Effective in Whites, untested in Blacks, Hispanics and Chinese	Effective in Whites, Blacks and Chinese Easy to administer and lower cost than oral CYC	Effective in Whites, Blacks, Hispanics and Chinese; high cost

CYC = cyclophosphamide; LN = Lupus nephritis; MMF = mycophenolate mofetil; RCT = randomized controlled trial

All regimens include corticosteroids:

- Oral prednisone, 0.5–1 mg/kg/day; tapered over 6–12 months according to clinical response
- i.v. methylprednisolone sometimes added initially for severe disease

Lupus neprhitis treatment

- Maintenance immunosuppression
- ACR, KDIGO, EULAR – low dose steroid and AZA (2mg/kg/day) or MMF (1.5-2g/day)
- ALMS data – MMF preferred over AZA if MMF as induction
- Total duration no less than 3years

- Don't forget anti-malarial – Hydroxychloroquine (level 2b)

- Other alternatives
- Low dose MMF + tacrolimus + steroid
- Rituximab
- Leflunomide

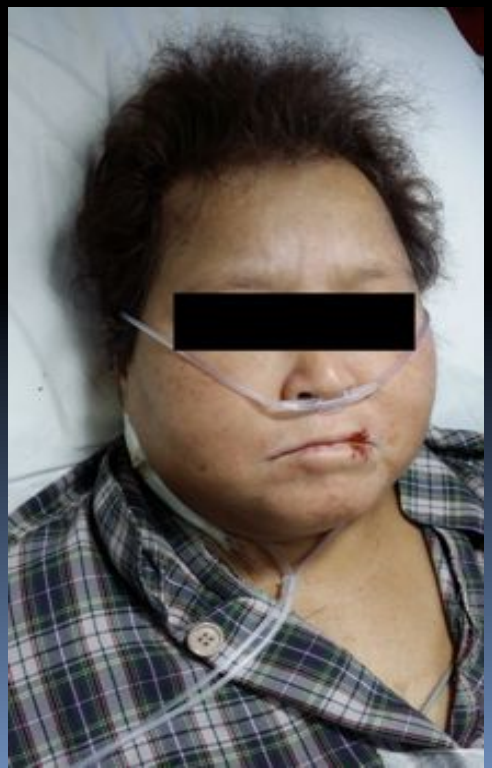
Case 2

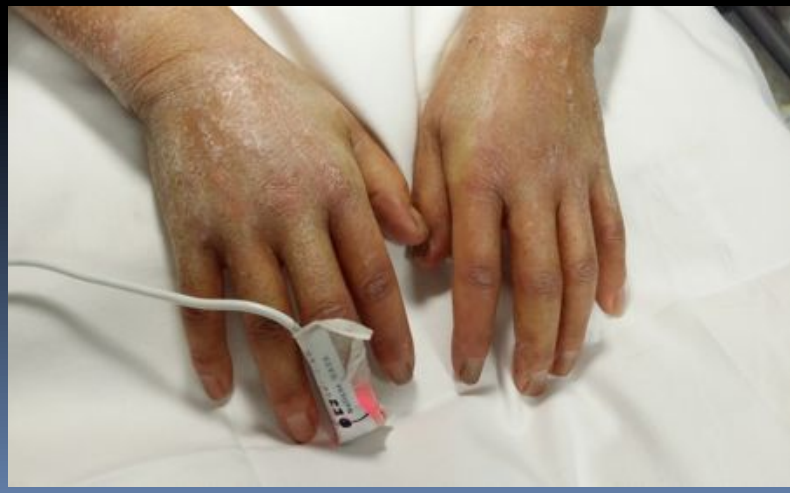
- 47yo retired fisherwomen
- Progressive dyspnoea and pleuritic chest pain
- Newly dx lupus with arthritis, positive ANA, depressed C3 and serositis
- Started on steroid 0.5mg/kg + MTX + HCQ

- CXR and HRCT – c/w fluid overload; not suggestive of infection / ILD
- BP 155/85
- RFT impaired ~ 200umol/L (baseline 54umol/L); urinalysis rbc ++ wbc + protein +
- Mild NcNc anaemia; thrombocytopenia
- Urgent USG kidneys; normal sized kidneys
- Oliguria

Case 2

- Serology panel
- ANA 1:1250 [s]; dsDNA <12.5 IU/L; C3 depressed
- Anti-ENA (Ro/La/Sm/RNP/Scl70) negative; ANCA negative





Case 2

- Complicated by resp distress and high O2 req
- Put on HD support; out of fluid overload
- Steroid tailed down gradually
- Plasma exchange given a few courses
- Acertil was switched to Captopril; stepped up gradually
- Remained dialysis dependent for the time being

Table 1: The ACR/EULAR Criteria for the Classification of SSc*

Item	Sub-item(s)	Weight/ score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (*sufficient criterion*)	-	9
Skin thickening of the fingers (*only count the higher score*)	Puffy fingers Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesions (*only count the higher score*)	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/ or interstitial lung disease (*maximum score is 2*)	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	-	3
Scleroderma-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) (*maximum score is 3*)	Anticentromere Anti–topoisomerase I Anti–RNA polymerase III	3

* These criteria are applicable to any patient considered for inclusion in a systemic sclerosis study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiropathy).

† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of >9 are classified as having definite systemic sclerosis.

Credit: Arthritis Rheum. 2013;65:2737-2747.

Scleroderma renal crisis

- First described in 1863; major cause of death in SSc in 1960s

  Moore & Sheehan

- Caucasian population: 5-10% SSc (~12% dcSSc; ~2% lcSSc *Penn H, 2007*)

  Denton CP scleroderma – clinical and pathological advances. Best Pract Res Clin Rheumat 2004; 18:271-90

- Taiwan: ~2.5%

  Chan KH et al, scleroderma renal crisis in central taiwan

- Historical mortality at 1yr very high up to 50-80%
- ACEI: improved to 76% at 1yr

  Steen VP, Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme inhibitors. Ann Inttern Med 1990; 113:352-7

- Long term survival remains poor: mortality at 5yr 40% despite ACEi

  DeMarcos PJ A&R 2002; 46:2983-9; Penn H, QJ Med 2007; 100:485-94

SRC – clinical features

- 2 major cardinal features

  1) a new onset of systemic HT

     >150/85mmHg x2 over a consecutive 24h

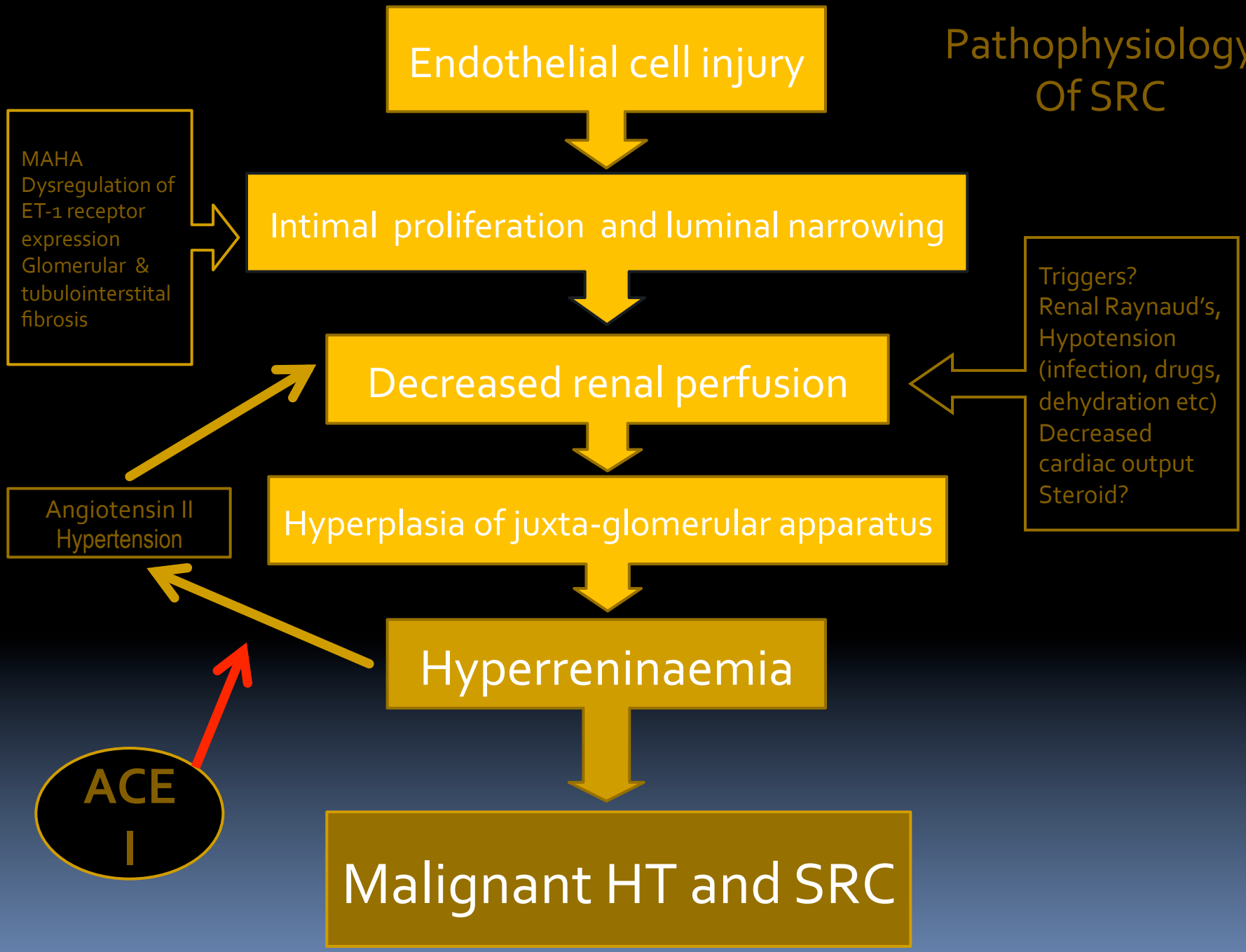
  2) a decrement in renal function

     ≥30% reduction in eGFR

- Other manifestations

- Headache, hypertensive retinopathy / encephalopathy
- Flash pulmonary oedema
- Oliguria / anuria (mild proteinuria and microscopic hematuria)
- MAHA (60%), thrombocytopenia (50%)
- Typical renal biopsy findings

Pathophysiology Of SRC



SRC - risk factors

- dcSSc 12% (vs lcSSc 2%)

  Penn H, 2007.

- Rapid, progressive skin disease

  DeMarcos, 2002

  - Median duration of SSc = 8mth
  - 66% SRC within 1yr of dx; 86% at 4yrs

- Corticosteroid therapy

  Steen and Medsger

  - Recent history of high-dose corticoid steroid use ie prednisolone ≥15mg/day
  - No additional risk with chronic low dose; no causal effect found
  - Confounding? early and active ds patients

- Other risk factors
  - * Ab to RNA polymerases
  - Cardiac involvement: pericardial effusion, cardiac insufficiency
  - High skin score (mRSS ≥20); large joint contractures
  - Anaemia, HRT

SRC – renal outcome and mortality

- ~40% req dialysis
- 35-60% might have renal recovery
- Median time to recovery ~1yr
- Recovery unlikely after 3yrs
- Implies renal vascular remodeling

- Predictors of poor outcomes
- dcSSc; skin scores ≥20 and evidence of cardiac involvement

Treatment - ACEI

- Early aggressive control of BP by ACEI (even if Cr increases)
- Prevent irreversible vascular injury
- Captopril mostly researched; no significant outcome vs other ACEIs
- Significant improvement in 1yr survival 76% (vs controls 15%)
- Use of statins : endothelial protection
- Plasma exchange : substantial thombotic microangiopathy
- Renal replacement therapy
- Renal transplant should be considered if no renal recovery after 18-24mths

Medical management of Scleroderma, Cannon, NEJM 1978
Successful Medical treatment of SRC, Wasner et al, Nejm 1978
Scleroderma renal crisis, Steen, 2009

Treatment

- ARB alone are less effective than ACEI

  Caskey, 1997; Cheung 2005

- Worsening HT and renal failure including the need of dialysis s

  Steen VD, Rheum Dis Clin N,Amer, 2009

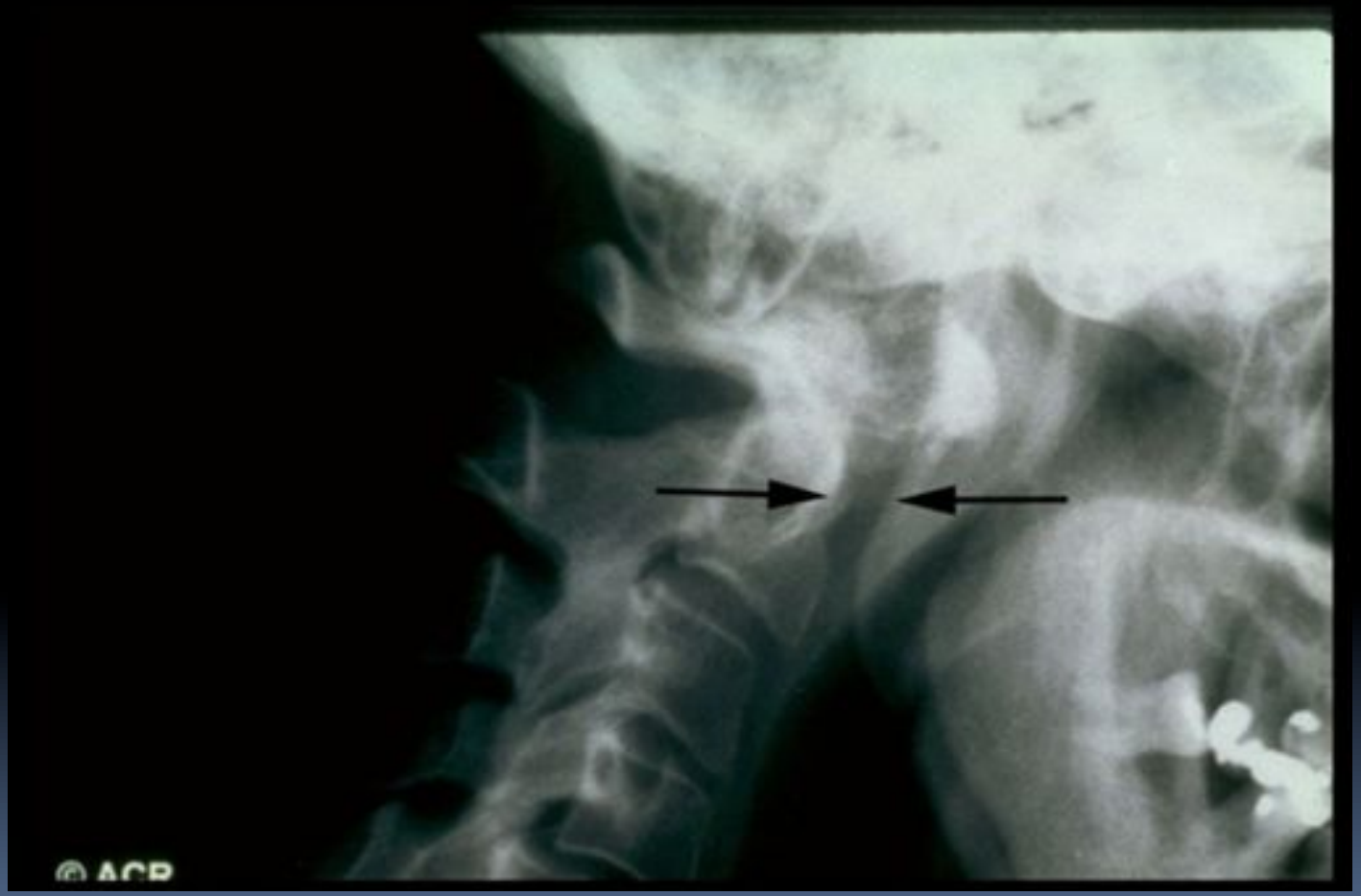
- Endothelin receptor antagonist
- High levels of ET-1 at time of SRC; increase receptor expression
- Study on Bosentan on-going

Case 3

- 64yo female with 30yr history of refractory RA
- In disease remission after Infliximab therapy for 1yr

- C admitted for cholecystectomy 2days later
- C/o occasional 4 limb numbness over extremities
- O/e full limb power; gait normal; no sensory deficit
- Reflexes abit brisk

Case 3



Atlanto-axial (C1/2) subluxation

- Prevalence; unknown (depends on classification criteria)
- Overall: NOT Uncommon
- 194 RA patients awaiting orthopedic surgery, up to 67% had Xray evidence of cervical subluxation
- 31% of them recalled NO neck pain
- Ann Rheum Dis 2006

Risk Factors

Spine 1998;23(19):2052 & Ann Rheum Dis 2006;65:884-888

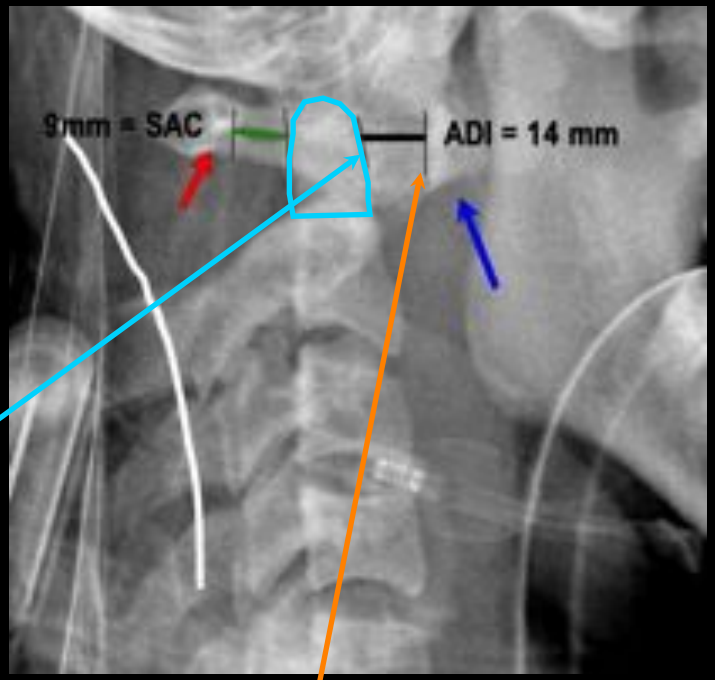
- Who had longer disease duration (with a mean of 6.5 years)
- More radiological progression of peripheral joints
- The presence of positive rheumatoid factor or an elevated C-reactive protein

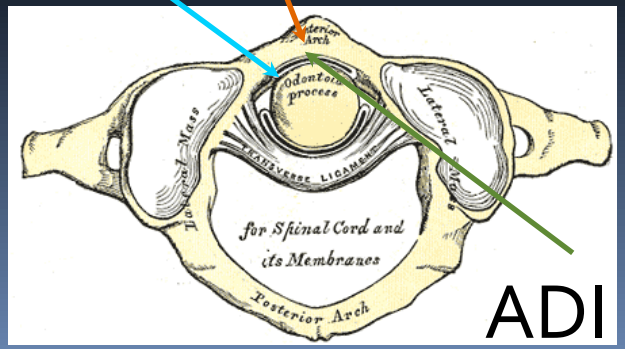
- But NOT HLA-DR4 or B27 positivity

imaging Findings

J Bone Joint Surg. Am Sept 1993

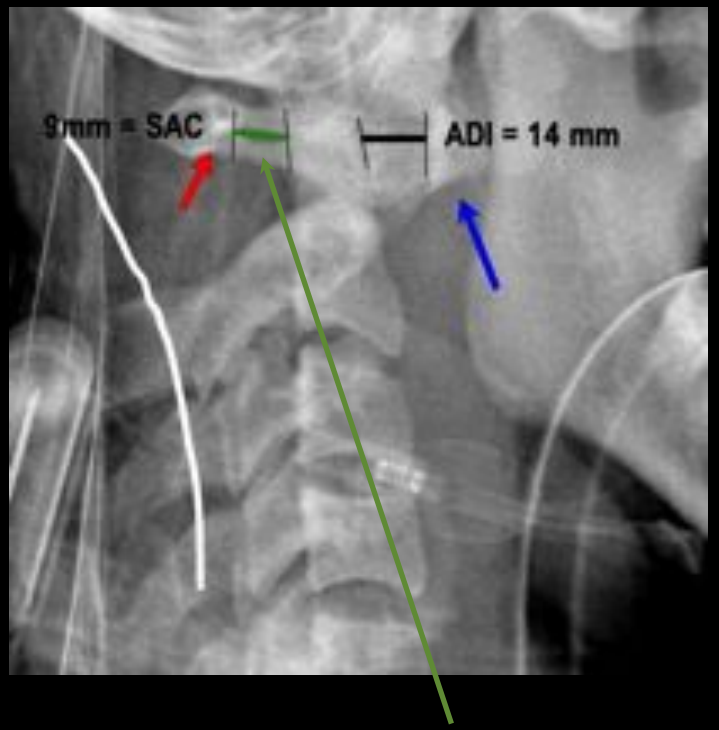
- Traditionally, the anterior atlantodental interval (AADI/ ADI) is used to monitor CS
- AADI >3mm is abnormal, >= 9mm increased risk of cord compression (sensitivity 41% specificity 77%)
- However, C-spine is a 3-dimensional structure. It measures the anterior compartment only, not reflect real space for cord

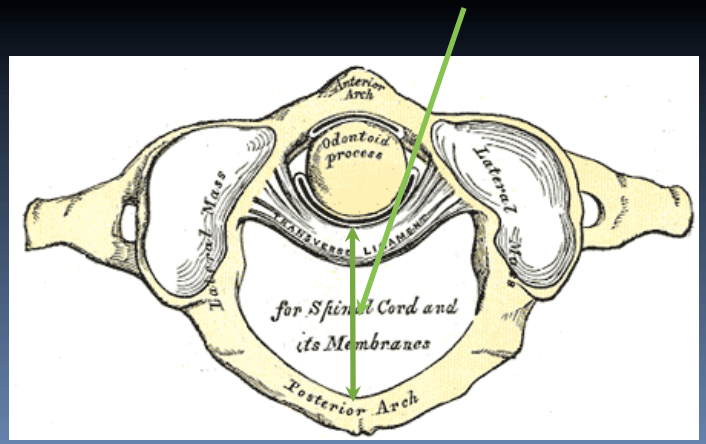




PADI (posterior atlantodental interval) / SAC (space available for cord)

- Recently, PADI recommended as a more reliable predictor of whether neurologic compromise will develop
- PADI <= 14 mm resulted in a sensitivity 97% to detect paralysis in 7 years period, negative predictive value (will not develop paralysis) up to 94%
- Pitfall: synovial pannus may occupy 1-3 mm of retro-odontoid space, this interval does not represent the true space available for the cord





Treatment (medical)

- High-impact exercise and spinal manipulation are contraindicated
- Soft collars/ brace give reassurance to both physician and patient, but provide little structural support
- Rigid/ stiff cervical collars limit neck extension, decrease neck pain but will not prevent further subluxation Br J Rheumatol 1996;35(8):771-4
- Compliance & skin sensitivity is a problem

Indication x OT (Ant. Subluxation)

- General indications: 1) refractory pain, 2) clearly evident neurologic compromise & 3) intrinsic spinal cord signal changes on MRI
- Controversy surrounds treatment for patients with little or no pain and no neural deficit
- General opinion - Measure posterior atlantodental interval (PADI)/ SAC on lateral X-ray, PADI/SAC <= 14 mm should have MRI study to determine the true space available for the spinal cord
- MRI < 13 mm of space available for the spinal cord are generally indications for surgical stabilization

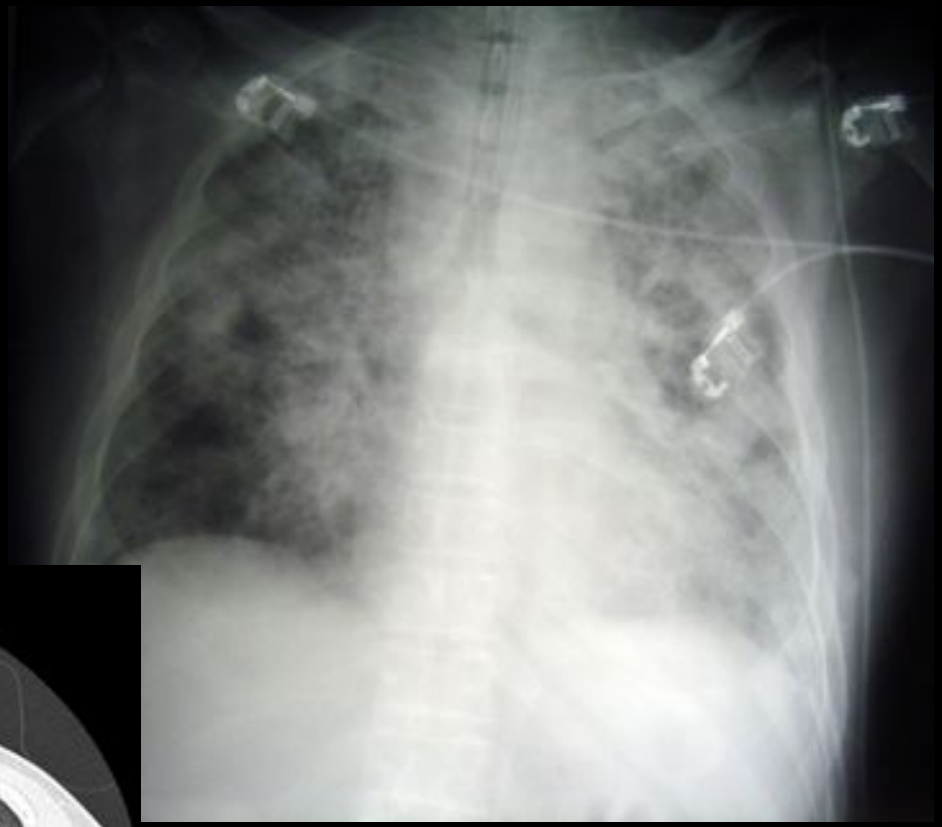
Case 4

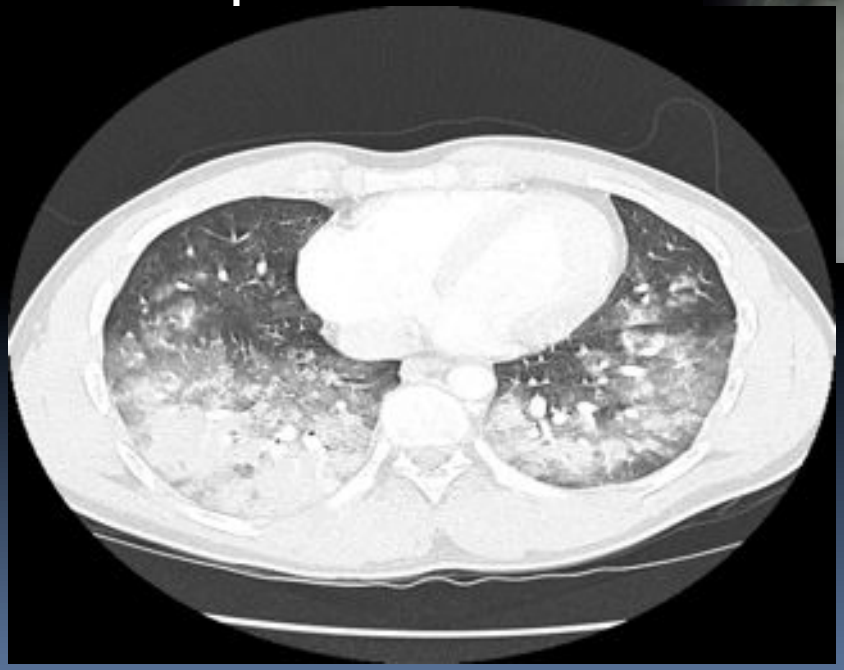
- M/50, driver, smoker
- Hx of bilateral LL rash treated in GP

- Dyspnoea and hemoptysis
- Bil pedal oedema and elevated BP
- Hypoxemia

- Urinalysis proteinuria + rbc ++

- Hb 8; Cr 400 umol/L
- ANA 1:80
- ANCA positive

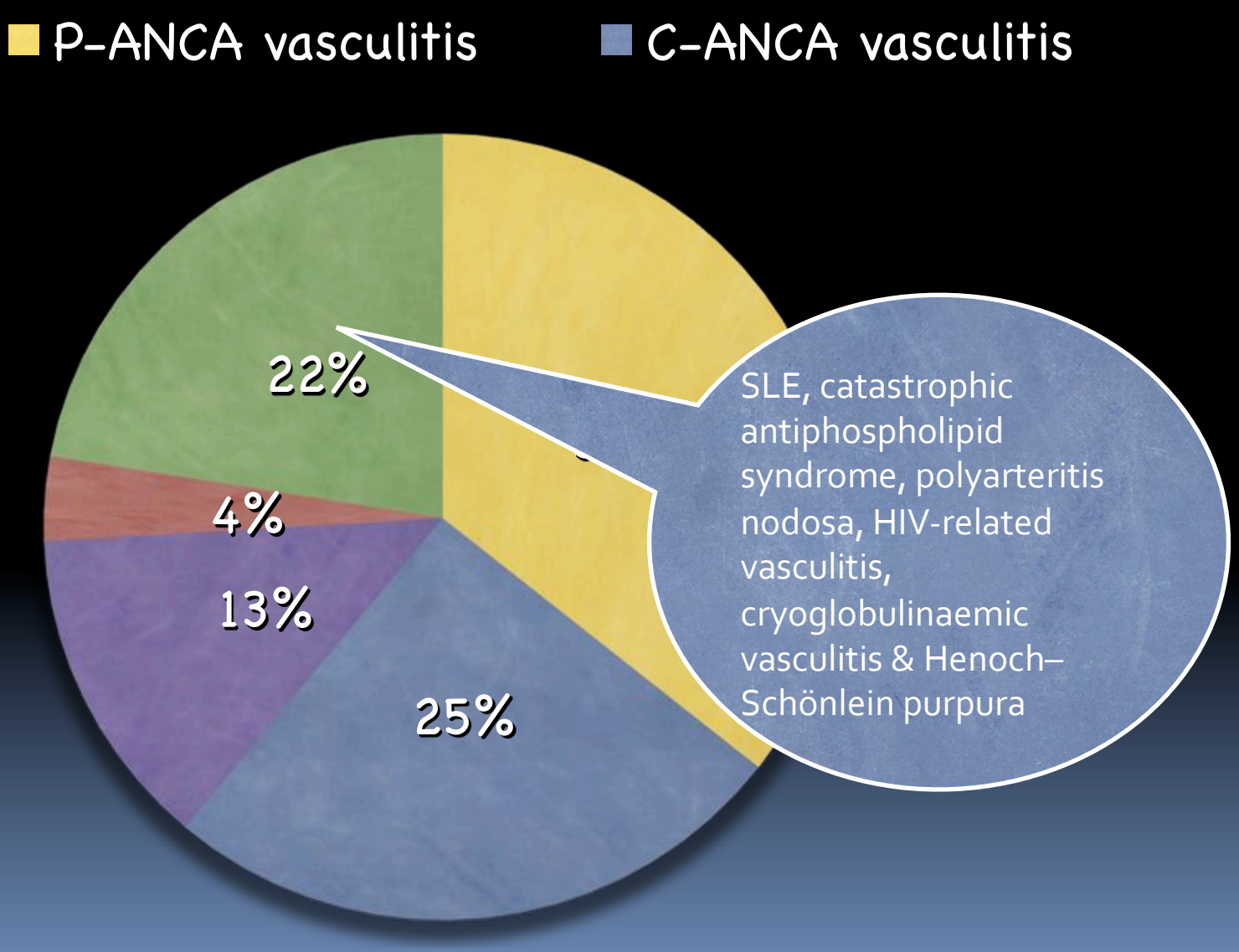




Pulmonary Renal syndrome in vasculitis

- Pulmonary-renal syndrome (PRS) is diffuse alveolar hemorrhage and glomerulonephritis occurring simultaneously
- It is a hetergenous syndrome with multiple causes
- Small vessel vasculitis / capillaritis a common cause for PRS J Crit Care. 2010 Jun;25(2):230-5
- Majority (80%) of these vasculitis cases are due to Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV)

Relative frequencies of conditions contributing to pulmonary-renal syndrome in ICU
Adapted from Papiris et al. Critical Care 2007, 11:213



ANCA associated vasculitis (AAV)

FEATURE	WEGENER'S GRANULOMATOSIS (GPA)	MICROSCOPIC POLYANGIITIS	CHURG-STRAUSS SYNDROME (eGPA)
ACNA +ve	80-90%	70%	50%
ANCA antigen specificity	PR3 > MPO	MPO > PR3	MPO > PR3
Histology	Necrotizing, granulomatous inflammation	Leukocytoclastic vasculitis	Eosinophilic tissue infiltrates & vasculitis
ENT	Nasal septal perforation, saddle-nose, hearing loss, subglottic stenosis	Absent or mild	Nasal polyps, allergic rhinitis
Eye	Orbital pseudotumor, scleritis, episcleritis	Occ.	Occ.
Lung	Nodules, infiltrates, cavities, alveolar hemorrhage	Alveolar hemorrhage	Asthma, infiltrates, alveolar hemorrhage
Kidney	Necrotizing GN	Necrotizing GN	Rare
Heart	Occ. Valvular	Rare	Heart failure
Peripheral nerve	10%	58%	78%
Esoinophilia	Occ. Mild	None	All

ANCA associated disease

Disease	pANCA	cANCA
WG	10%	85%
MPA	45-80%	15-45%
PAN	15%	5%
CSS	60%	10%
SLE	20% (atypical)	
RA	25% (atypical)	
IBD	30-70% (atypical)	
Autoimmune liver disease	up to 70% (atypical)	
idopathic cresentic GN	65%	25%

Sign & Symptoms of PRS

- Hemoptysis happens in 1/3 of patients
- Cough & SOB, esp. with a drop in hemoglobin, should raise suspicion for alveolar hemorrhage
- Rarely, recurrent subclinical AH give rise to interstitial pulmonary fibrosis > chronic cough with SOB
- Renal S/S: 1) subtle proteinuria/hematuria with normal RFT, 2) explosive oliguria ARF with RBC casts 3) CRF with proteinuria-hematuria & RBC casts, 4) intermittent protenuria/hematuria mimicking IgA nephropathy
- Most patients have advance renal failure at time of presentation (Cr >400umol/dL)

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Making Diagnosis of AAV

- Suggestive clinical picture
- Positive c-ANCA/p-ANCA (not obligatory)
- Histological
- Always difficult to distinguish WG & MPA due to similar clinical features/histopathologic/serologic findings

Investigations for PRS

- Radiological imaging (CXR/ CT thorax) reveals bilateral airspace infiltrates
- Pulmonary function tests - increased (>100%) diffusion capacity for DLCO, but are difficult to carry out in critically ill patients

- Bronchoscopy is a valuable tool - BAL
  - document alveolar hemorrhage
  - exclude airway source of bleeding
  - exclude associated infection

Treatment for Severe PRS

- Supportive - ABC, ventilation & dialysis
- Glucocorticoids - IV methylprednisolone (500-3000 mg) are widely used for severe PRS > oral steroid
- Cyclophosphamide - continuous daily dose or intermittent IV as induction
- Plasma exchange (PLEX) - exact mechanism unclear ? due to removal of ANCA, coagulation factors, cytokine and chemokines

Plasma Exchange in Severe PRS

- MEPEX trial 2007 - plasma exchange (PLEX) 7 cycles over 7-14 days vs IV methylprednisolone (MP) 3g x 3 days to treat 137 ANCA associated vasculitis patients with renal failure (Cr > 500) J Am Soc Nephro July 2007
- Both groups received oral cyclophosphamide & oral prednisolone
- At 3 mo, IV MP 49% & PLEX 69% were independent of dialysis
- At 12 mo, PLEX 19% vs IV MP 43% had ESRF
- Patient survival & severe adverse event rates were similar in both groups

However

- Some retrospective studies showed PLEX did not impact beneficially on patient survival Am J Kidney Dis 2002;39(1);42-47 & J Clin Apher 2005;20(4):244-251
- These conflicting outcomes are partially explained by the differences in FU periods, the severity of AH and renal impairment between the studies

PEXIVAS

Design of a Randomised Controlled Trial of Plasma Exchange and Glucocorticoid Dosing in Severe ANCA Associated Vasculitis

- A similar protocol with MEPEX trial is now undergoing
- 500 patients with new or relapsing severe AAV (renal vasculitis with GFR< 50 ml/min or/and pulmonary hemorrhage), from 60 centres in 15 countries are recruited over 5 years & FU for a maximum of 7, minimum 2 years
- 4 groups: 1) PLEX + standard dose GC, 2) PLEX+ reduced dose GC, 3) no PLEX + standard dose GC, 4) no PLEX + reduced dose GC
- To determine the death & ESRF

Rituximab versus Cyclophosphamide in ANCA-Associated Renal vasculitis NEJM July 15, 2010

- Open labelled, randomized trial of 44 AAV patients with renal involvement
- Median CrCl in Rituximab group 20ml/min vs 12ml/min in cycylophosphamide group
- 33 patients with Rituximab 375mg/m2 weekly x 4 wks (+ IV cyc at 1st & 3rd Rituximab infusion) vs 11 patients with IV cyclophosphamide (15mg/kg) monthly x 3-6 months -> AZA
- Conclusion: Rituximab based regimen was NOT superior to cyc, remission rate at 12mth (76% Rit. vs 82% cyc.) & similar serious adverse events

In Conclusion

- Most of rheumatological disorders are insidious in onset
- But we do sometimes encounter emergencies in rheumatological practice
- Management has to be individualized depending upon the organ involved
- Therapy should not be deferred pending confirmation of diagnosis by laboratory tests

Table 2: Rheumatological emergencies - disease-wise.

Rheumatoid arthritis
- Atlanto-axial dislocation
- Scleromalacia perforans
- Vasculitis
- Acute exacerbation of synovitis
- Infections

Seronegative sponyloarthropathy
- Iridocyclitis

Systemic lupus erythematosus
- Seizures, psychosis, encephalopathy
- Pericarditis, myocarditis, endocarditis
- Pneumonitis, ARDS
- Acute glomerulonephritis
- Vasculitis
- Hypertensive crisis
- Acute pancreatitis
- Polyserositis
- Infections

Antiphospholipid antibody syndrome
- Stroke
- Acute myocardial infarction
- Retinal vessel thrombosis
- Pulmonary embolism and infarction
- Thrombocytopenia
- Placental ischaemia and foetal loss
- Catastrophic APL syndrome

Vasculitis
- Cerebral vasculitis
- Optic neuritis
- Uveitis
- Mesenteric vasculitis
- Acute nephritis
- Hypertensive crisis

Systemic sclerosis and mixed connective tissue disease • Digital vasculitis and ischaemia
- Scleroderma renal crisis

Inflammatory myositis (poly / dermatomyositis)
- Respiratory failure

Crystal-induced arthropathies
- Acute gout
- Acute interstitial nephritis

Arthritis related to infections
- Septic arthritis
- Reactive arthritis

Osteoporosis
- Fracture

Miscellaneous disorders
- Haemophilic arthropathy
- Rupture of Baker's cyst

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